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*Editor*

# Prostate Cancer: A Comprehensive Perspective

Springer

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# Foreword

Prostate cancer has become a worldwide problem, not only in the developed world but in developing countries as well. As the population ages worldwide and other diseases become less frequent causes of premature death, prostate cancer, which rapidly increases in frequency with age, will present a growing public health problem. Prostate cancer is a complex and heterogeneous disease. The ratio of deaths to new cases is one of the lowest of any of the major internal organ solid tumors. It is well known that most men die with, rather than of, prostate cancer, a paradox that has long stymied widespread understanding and the easy development of consensus about the management of this disease.

Fortunately, clinical and basic research in the past 20 years have provided important tools that have enormously facilitated our understanding of prostate cancer, the ability to predict the course of the disease and the outcomes of various treatments. Today we can add to the standard clinical factors (stage, grade, PSA and biopsy results) the burgeoning technology of medical imaging (especially magnetic resonance imaging) and the more recent molecular characterizations that could greatly enhance our ability to identify the threat posed by the cancer in any given patient. Further characterization of prostate cancer seems highly likely over the next decade with the expanding use of genomic analysis. The worldwide effort to characterize the prostate cancer genome will prove enormously fruitful and markedly increase our ability to discriminate between potentially lethal and indolent prostate cancers.

The biomarker prostate specific antigen (PSA) has revolutionized our understanding and ability to manage this disease. While PSA testing has proved the source of enormous debate over the last decade, it is clear that PSA is the best biomarker available in oncology. Recent studies have shown that a man's PSA levels in his 40s, 50s, and 60s strongly predict the likelihood that he will ever develop advanced prostate cancer or die of the disease. Nevertheless, controversy swirls around the optimum protocol for PSA testing, the age of onset of testing, and the cost benefit of screening for prostate cancer. Epidemiological data show that in countries where screening has been widely used, mortality from prostate cancer has been declining steadily and rapidly. Today, in the United States, the age-specific mortality rate from prostate cancer has fallen by nearly 50 % over the last 15 years.

The treatment of prostate cancer is also undergoing revolutionary changes. Technology has expanded the surgical options for radical prostatectomy, which now include robotic and free-hand laparoscopic as well as open retropubic and perineal techniques. Radiation therapy has also benefited from a technological advance. Intensity-modulated radiation has allowed us to safely deliver doses as high as 86 Gy to the prostate, and image guidance promises to target the prostate more accurately, improving cancer control. Many centers have developed combinations of interstitial radiation (brachytherapy) with external beam radiation to deliver higher doses. Proponents of proton beam therapy argue that it offers an even greater therapeutic index, although there is little clinical data to support the contention.

For those with metastatic prostate cancer, this is indeed an exciting era. There are over 100 new drugs in the pipeline for commercial development in the United States alone. Phase III clinical trials have shown substantially increased survival with new drugs that target the androgen receptor, such as abiraterone and Medivation 3100. The first immunotherapy approved for use in human cancer was sipuleucel-T, approved for prostate cancer. Other exciting approaches

include immunomodulation with anti-CTLA4 antibodies and with monoclonal antibodies targeting B7x and other immunoinhibitory targets.

These and many other exciting developments in prostate cancer are addressed in detail in this remarkable new book edited by Ashutosh Tewari and an international team of associate editors. Every possible aspect of prostate cancer is covered by a recognized authority in the field. For those deeply interested in understanding this disease, especially clinical and laboratory investigators, and for physicians and surgeons who devote their careers to treating men with prostate cancer, this book is a major new addition to the field.

Peter T. Scardino

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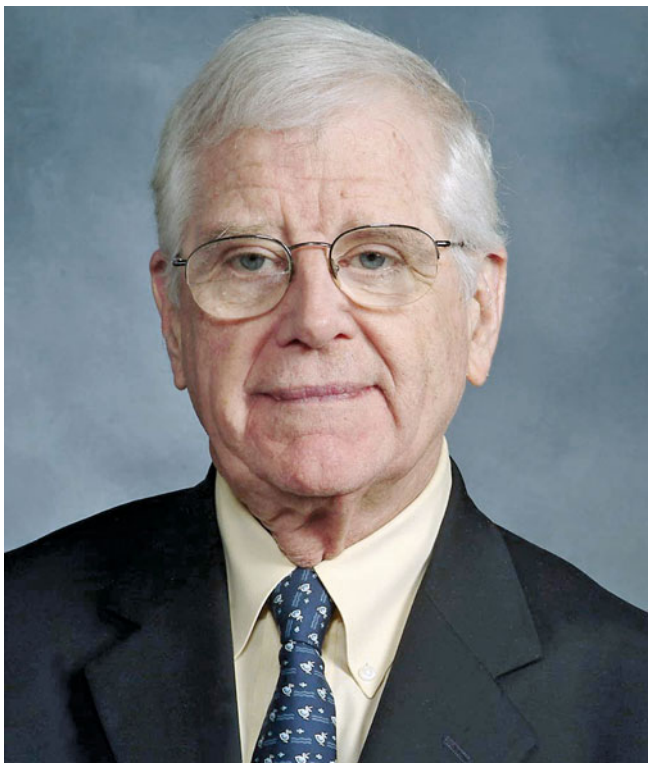

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# Part I

# Basic Scientific Foundation

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# Development, Applied, and Surgical Anatomy of the Prostate

1

Anthony J. Costello and Niall M. Corcoran

## Applied Prostatic Anatomy

### History of Prostatic Anatomy and Radical Prostatectomy

Contemporary anatomical insights beginning in the 1970s have driven the dramatic improvements in outcomes for men treated by surgical removal of the prostate. Before the 1980s, only the very hardy patient was able to tolerate the morbidity of attempted surgical cure of prostate cancer.

The operation was attended often by massive blood loss, certain impotence, and a high likelihood of permanent urinary incontinence. It was preferable therefore to opt for radiation therapy as primary treatment to avoid the morbidity of radical prostatectomy.

## Introduction

Two factors have changed urologists' attitudes to surgery for prostate cancer since 1980. The first was the work of Dr. Patrick Walsh who "discovered" the neurovascular bundle so key in potency preservation at prostatectomy [1, 2]. Walsh also recognized that bleeding occurred due to failure to control Santorini's plexus of dorsal penile veins. These two anatomical insights ushered in three improvements in prostatectomy outcomes [3].

Because the operative field was no longer immersed in blood, greater care in the precise dissection of the striated sphincter was possible. This meant that with care being taken in this step of the operation, most men would maintain urinary continence. The anatomic description of a discrete autonomic neural bundle running in a groove posterolateral to the prostate between rectum and prostate meant potency preservation was a surgical reality. The surgeon's ability to perform the operation now in a mainly bloodless field allowed a better oncological procedure with clean dissection in and around the fascial compartments of the prostate. This led to steady and steep decline in the positive pathological margin rate.

Dr. Whitmore quoted saying that surgery (before 1975) was unlikely to lead to cure and is also less quoted stating "There is no better way to cure prostate cancer that is confined to the prostate than its total removal" [4, 5]. Before the mid-1970s, most men presented with locally very advanced cancer or regularly with metastatic disease. Surgery was most unlikely to cure those men.

The advent in the 1980s of PSA allowed a lead time of around 9 years from localized to metastatic prostate cancer. In 2000, the arrival of telerobotic surgery [6] provided the prostatectomist with an unprecedented ×10 magnified 3-dimensional surgical field. These incremental advances in surgery, underpinned by anatomical insights, enabled urologists to offer a patient presenting with PSA-detected, localized prostate cancer an oncologically sound operation with a high likelihood of continence preservation and retention of erectile function. This is the desired "trifecta" of outcomes.

What was remarkable about Walsh's insights is that they were made not in the anatomy room dissecting cadavers but from observations made in the operating room to be later proven in the dissecting room.

## Contemporary Prostate Anatomy

In the early 2000s at The Royal Melbourne Hospital, we began a series of cadaveric anatomical dissections of the neurovascular bundle (NVB) [7]. Our interest in this subject was spurred by our skepticism of a hypothesis that a nerve graft could be applied to join the severed end of a divided

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nerve [8]. There was no anatomic insight to justify this theory. In spite of this, grafting was undertaken with little long-term success in potency preservation. As we discovered, the neurovascular bundle is a complicated plexus of nerves and blood vessels. There are at least four and up to 16 discrete autonomic sympathetic and parasympathetic nerves in these bundles, contained in three or four separate fascial compartments. It became very clear from these dissections that the hypothesis that a single large somatic nerve would act as a conduit for autonomic nerve recovery was null. Before surgeons were aware of these structures, these nerves were simply excised. As these structures were now recognized, these nerves are injured today by thermal injury (diathermy) and/or traction.

In this chapter we will concentrate on three areas of prostatic anatomy:

1. The neurovascular bundle
2. The fascial layers surround the prostate
3. The urinary sphincter

An understanding of this anatomy will aid the surgeon in performing a surgery that minimizes harm to vital surrounding structures while optimizing chances of a cure of this disease. If urologists empowered by the functional anatomical insights can provide a safe surgery with few or no side effects, then the debilitating debate over treatment for prostate cancer could be moot.

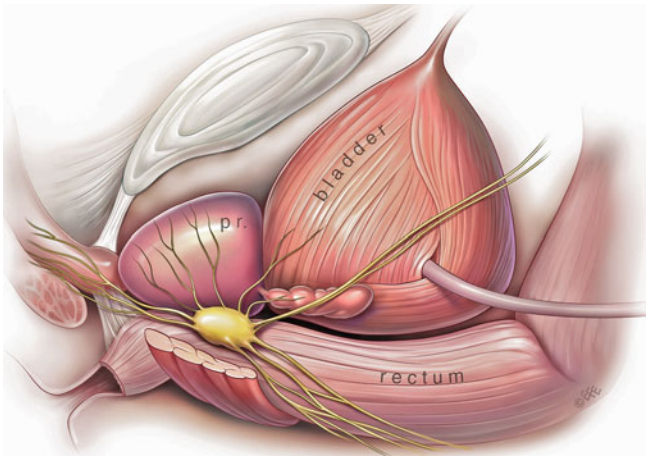



**Fig. 1.1** Pelvic plexus, sympathetic and parasympathetic outflow

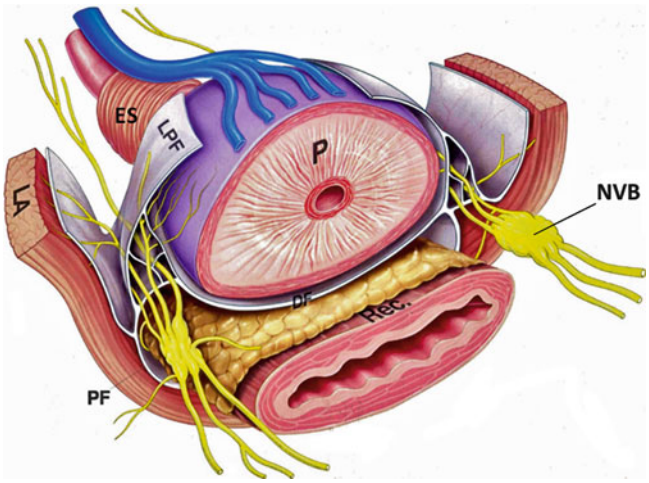



**Fig. 1.2** Prostatic functional anatomy for the radical prostatectomist, highlighting fascial layers, the neurovascular bundle (*NVB*), fascial compartments, the external sphincter, and dorsal vein. *LA* Levator ani, *LPF* Lateral prostatic fascia, *P* Prostate, *DF* Denonvilliers fascia, *PF* Prostatic fascia, *REC* Rectum, *ES* External sphincter

## Neurovascular Bundle Anatomy

In 2003, we performed 12 cadaver dissections of adult male pelves. The age of these cadavers was 56–74 years old. Mathew Brooks, a medical student at the University of Melbourne, performed these dissections using loupes with ×6 magnification [7]. Four specimens were hemisected and eight were dissected en bloc. The original work of Walsh and Doncker [2] was on the fetus where the prostate and surrounds had not developed postpubertally. Most considered that there was a single nerve that ran in the prostatorectal groove. This was partly the thinking behind the sural nerve grafting hypothesis. The components of the NVB were traced from the bladder neck distally to target organs.

What we found was that there were branches to a number of different targets not simply the cavernous tissue. Branches to seminal vesicle, prostate, levator ani muscle, rectum, bladder, and erectile tissue of the penis were identified. The cavernosal nerves were traced as far distal as possible to the level of the prostatic apex and proximal urethra.

The pelvic plexus has two components, the sympathetics via the hypogastric nerve and the parasympathetics via $S_2$, $S_3$, and $S_4$ sacral foraminae (Fig. 1.1). The pelvic plexus is located retroperitoneally on the lateral surface of the rectum. A fascial layer (pararectal fascia) and 1–2 cm of perirectal adipose tissue separate the lateral surface of the rectum from the pelvic plexus. The fenestrated pelvic plexus is situated in a sagittal plane, with moderate variations in its size and position between dissections. It extends as far as 1.5 cm posterior to the dorsal edge of the rectum and 1 cm superior to the rectovesical pouch (pouch of Douglas) (Fig. 1.2). Gauging pelvic plexus size is difficult, with borders between it and its branches hard to define. However, generally, the pelvic plexus ranges from 3 to 5.5 cm long and 2.5 to 5 cm high. There is a quantitative relationship between the size and mass of neural tissue within the pelvic plexus and the number of nerve branches within its projections. The branches of the pelvic plexus form three major projections: (1) anterior, extending across the lateral surface of the seminal vesicle and the inferolateral surface of the bladder; (2) anteroinferior, extending to the prostatovesical junction and obliquely

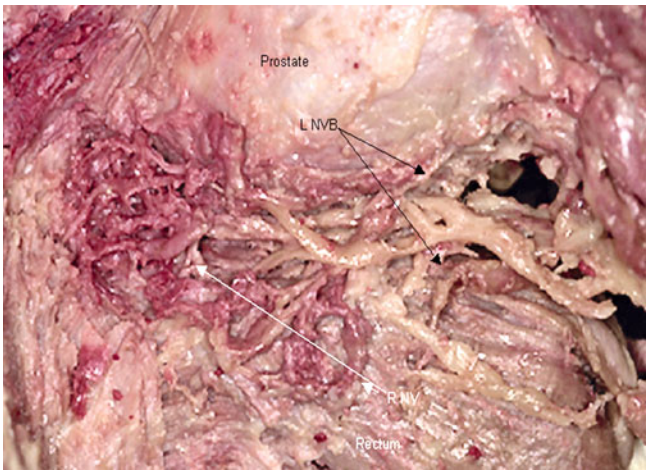



**Fig. 1.3** Left neurovascular bundle midprostate

along the lateral surface of the prostate; and (3) inferior, running between the rectum and the posterolateral surface of the prostate, forming the neural constituents of the NVB (Fig. 1.3).

The pelvic plexus is closely associated with branches of the inferior vesical vein and artery. These large vessels are predominantly in a sagittal plane that is superimposed on the lateral surface of the pelvic plexus. On removing investing adipose and connective tissues, these vascular and neural (pelvic plexus) structures generally lay in distinct separable layers posteriorly, only to converge at the level of the pelvic plexus projections.Illus3

In all 24 dissections, the plexus of nerves running within the NVB branch from the posteroinferior aspect of the pelvic plexus are 0.5–2 cm inferior to the level of the tip of the seminal vesicle. The number of macroscopic nerves present varies, with 6–16 noted. On branching from the pelvic plexus, these nerves are spread significantly, with up to 3 cm separating the anterior- and posterior-most nerves. The nerves located most anteriorly are intimately associated with the seminal vesicle, coursing along the posterolateral surface, while the nerves located posteriorly run dorsal to the posterolateral verge of the seminal vesicle (Fig. 1.4).

Generally, most of the NVB descends posteriorly to the seminal vesicle. The nerves converge en route to the midprostatic level, forming a more condensed NVB, only to diverge once again when approaching the prostatic apex (Fig. 1.5).

The nerves of the NVB are intimately associated with vessels branching from the inferior vesical vein and artery. As these vessels course distally toward the prostatic apex, numerous terminal branches are given off which, in most cases, mimic the course of the nerves.

The nerves running in the NVB innervate the corpora cavernosa, rectum, prostate, and levator ani musculature. The last three also receive a vascular supply from vessels coursing in the NVB. In 20 of the 24 dissections, a large vein

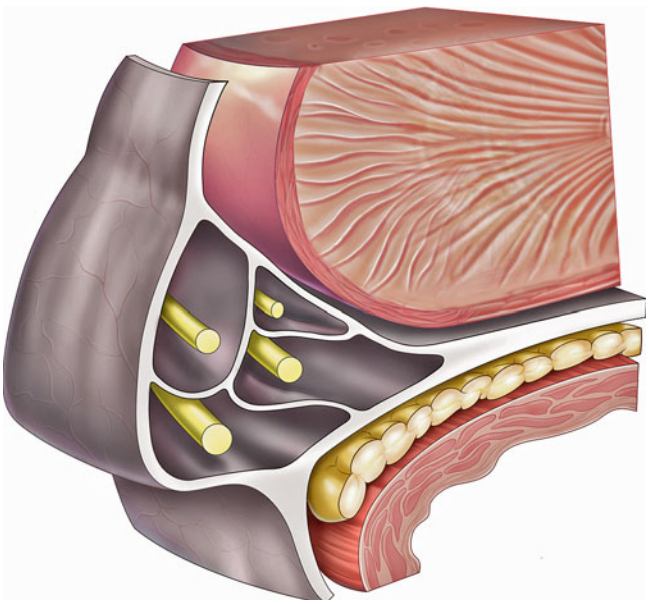


**Fig. 1.4** Fascial compartments of the left neurovascular bundle

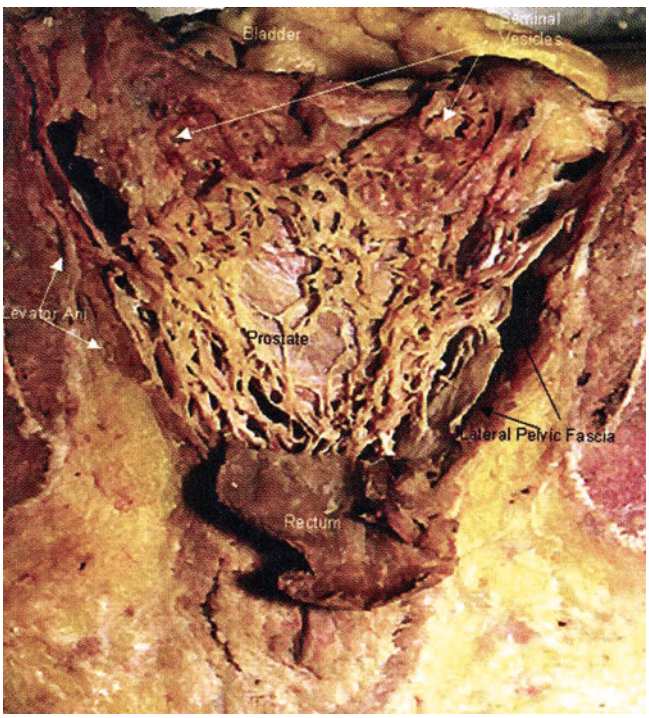
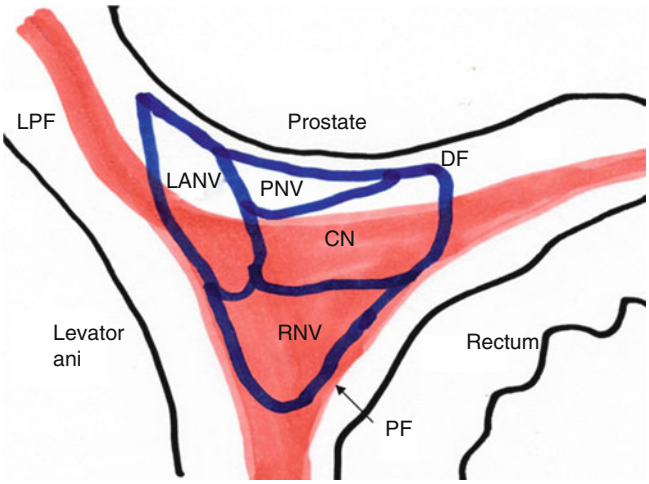



**Fig. 1.5** Posterior view of prostate and neural structures, rectum reflected downwards

drained the rectum, piercing the pararectal fascia and entering the rectal musculature on its anterolateral surface at a variable level, ranging from midprostatic to prostatic apex. Artery and nerve branches supply the anterolateral wall of the rectum from the prostatic apex to midprostate level. Nerves running in the NVB pass through slit-like openings in the lateral pelvic fascia to innervate the superior and




- Rectal nerves posterior + posterolateral
- Levator ani nerves lateral
- Cavernous nerves + prostatic NVB medial

**Fig. 1.6** Functional organization of NVB

middle sections of the levator ani musculature. Many nerve and vascular branches pierce the lateral pelvic fascia distally to supply the inferior portion. The nerves innervating the posterior aspect of the prostate are intimately associated with capsular arteries and veins of the prostate (Fig. 1.5). These structures penetrate the prostatic capsule along its base, midportion, and apex.

The cavernosal nerves and several small vessels pierce the urogenital diaphragm posterolateral to the prostatic apex. At this level, the clearly visible cavernosal nerves divide into numerous small branches that descend along the posterolateral aspect of the membranous urethra before penetrating the posterior aspect of the corpora cavernosa.

The constituents of the NVB are organized into three functional compartments. The neurovascular supply to the rectum is generally in the posterior and posterolateral sections of the NVB, running within the leaves of Denonvilliers' and pararectal fasciae. The levator ani neurovascular supply is in the lateral section of the NVB, descending along and within the lateral pelvic fascia. The cavernosal nerves and the prostatic neurovascular supply descend along the posterolateral surface of the prostate, with the prostatic neurovascular supply most anterior. Part of this anterior compartment runs ventral to Denonvilliers' fascia. The functional organization of the NVB is not absolute and is less pronounced proximally at the levels of the seminal vesicles and the prostatic base (Fig. 1.6).

In addition to the nerves descending within the NVB, a scattering of nerves extends from the medial margin of the NVB to the prostatic midline. The deepest nerves (from an anterior aspect) innervate the anterior surface of the rectum at the level of the prostatic apex. The more superficial nerves descend posterior to the prostatic apex and merge laterally with the NVB.

## Fascial Architecture of the Prostate

We have shown from further dissections by Ben Dowdle et al. [9] and Emma Clarebrough the relevant fascial layers which ensheath the NVB. An understanding of the fascial investments of prostate rectum and levator ani is fundamental to the urologists' ability to perform nerve-sparing radical prostatectomy.

The key fascial layers surrounding the prostate are formed by a fusion or condensation of levator ani fascia, Denonvilliers' fascia, and prostatic fascia. The prostatic fascia varies from fused to the prostatic capsule or separates as a distinct layer.

These fascial layers condense posterior to the prostate where they form distinct fascial compartments. We have identified three or four compartments in which run the neurovascular components of the NVB. There are between 6 and 16 discrete nerves in these layers. Importantly for the surgeon, the neural supply of the cavernous tissue runs in a posteromedial sheath below a conduit supplying nerves to the prostate. Another more lateral and superiorly placed bundle supplies nerves to levator ani. Inferomedial are the rectal nerves. Thus, the nerves in the NVB closest to the prostate are the nerves going directly into the prostate. This means that even when the dissection of the prostate is widened into the NVB, there may not be damage to the nerve supply to cavernous tissue. This gives rise to the possibility of performing an "incremental" nerve-sparing technique. The majority of prostate cancers which penetrate through the capsule do so only by 3 mm. When a cancer truly invades into the NVB (an uncommon occurrence), it is unlikely that that man can be surgically cured of his cancer. There is also a cushion of adipose and fibrous tissue between the prostate and the NVB.

The NVB descends along the posterolateral border of the prostate. It extends laterally to the junction of the lateral pelvic fascia and pararectal fascia and posteriorly to the dorsal layer of Denonvilliers' fascia, which forms a fibrous sheath separating the prostatic capsule from the rectum. Laterally, it becomes continuous with the pararectal fascia posteriorly and the lateral pelvic fascia anteriorly. The pararectal fascia extends along the lateral surface of the rectum, while the lateral pelvic fascia separates the levator ani muscle from the prostate. At the prostatic midline, Denonvilliers' fascia exists as a single sheet and widens laterally to fuse with the fascias of the prostate and levator. This fusion of fascias is compartmentalized into three or four conduits, containing the functional nerves to their target organs. In Dowdle's dissections, 32 blocks of tissue were analyzed. In 18, the NVB had three distinct fascial compartments (Fig. 1.7). This shows staining of the prostate fascia nerves, vessels, muscle, and fat (Fig. 1.7).

Having identified these structures, we conducted further immunohistochemical studies to characterize both the function and the location of these nerves. The precise topography of these nerves has been contentious. There has been debate

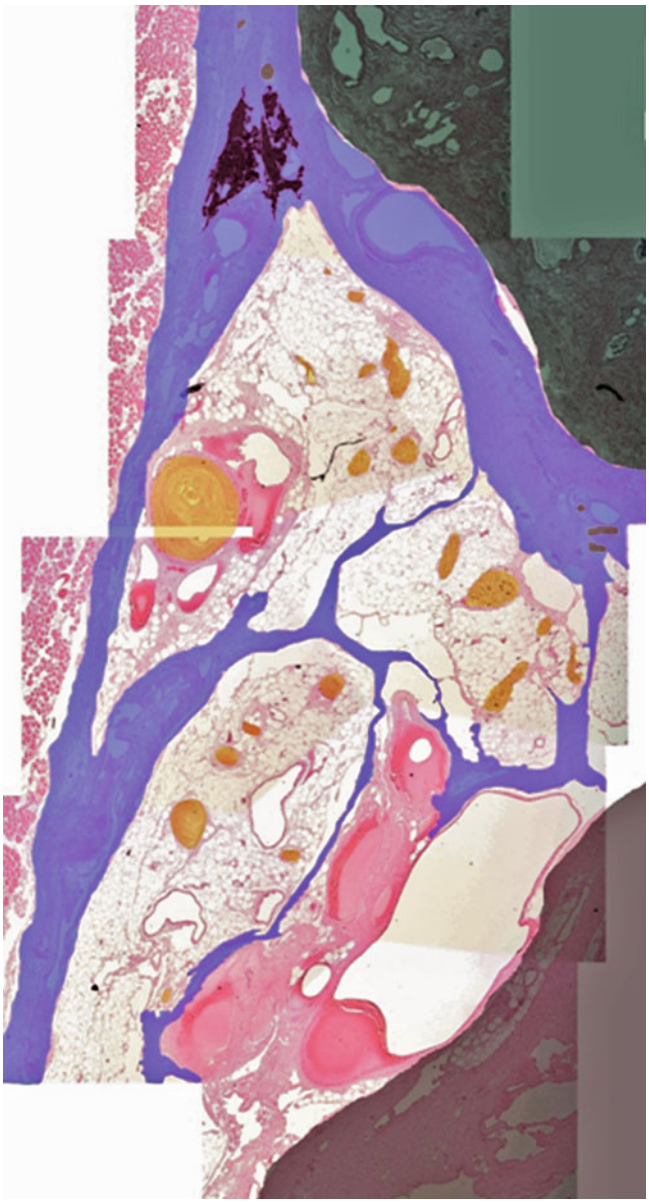


**Fig. 1.7** Connective tissue stain in *blue* of the neurovascular bundle fascial compartments. Prostate superomedial in *green*. Rectum posteromedial

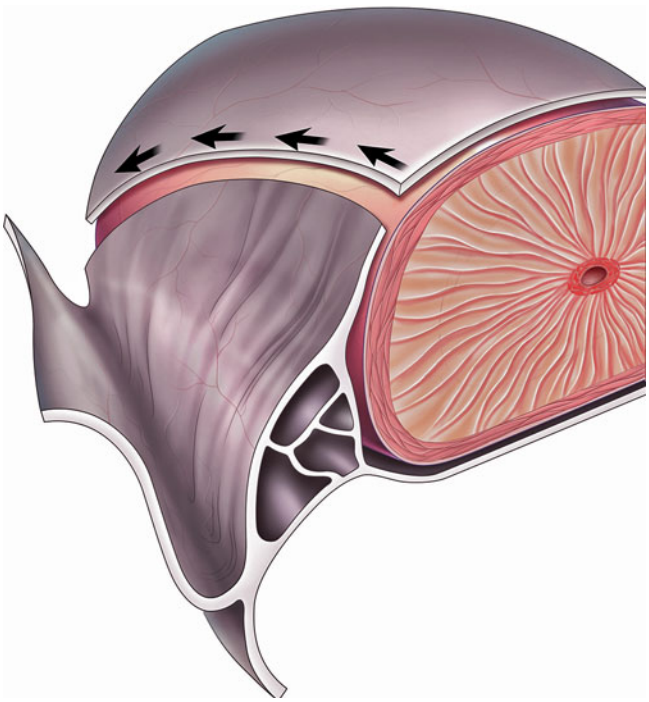


**Fig. 1.8** Line of fascial incision in nerve-sparing prostatectomy

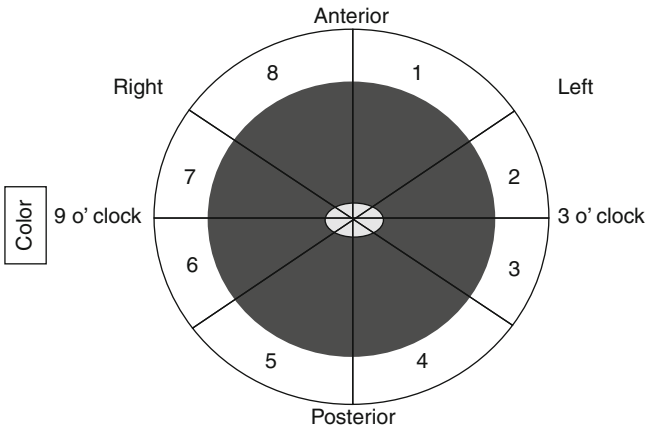



**Fig. 1.9** Distribution of nerve fibers and their positions around the circumference of the prostate

and discussion as to the most efficacious nerve-sparing surgical technique. This has led to the concept of high anterior release [10] (Fig. 1.8) of the anterior levator fascia to improve sexual function after prostatectomy. This hypothesis was proposed by Menon et al. [11–13] who pioneered telerobotic prostatectomy. He described the veil of Aphrodite incision, a high incision into the prostatic fascia to the capsule of the prostate to spare anteriorly placed nerves above the 3 and 9 o'clock position toward the prostatic apex. We have shown however that nerves in this position are nerves to the prostate not cavernous tissue. Nerves to cavernous tissue are predominantly below these o'clock levels. This high-release technique may be relevant in a practical sense. If the fascia is released high, then the effect of traction on these delicate autonomic nerves may be mitigated.

In our studies of the functional architecture of the NVB, we used several stains. To localize the parasympathetics, an antibody against nNos was used. nNos, a 150-kDa protein, is found in parasympathetic nerves and catalyzes the formation of the potent vasodilator nitric oxide (NO). NO is the mediator involved in the physiology of erection. Sympathetic nerves were characterized by tyrosine hydroxylase, an enzyme in the norepinephrine production pathway. Stained slides were analyzed for nerve counts according to fiber number type and position. The analysis allocated nerves in eight around the clock sectors (Fig. 1.9) (Table 1.2). Somatic

**Table 1.1** Distribution of total nerve fibers expressed as number and percentage of total fibers at each level

| Position | Parasympathetic | Sympathetic | Somatic | Combined |
|---|---|---|---|---|
| Base | | | | |
| Total, *n* (%)[a] | 111 (43.3) | 99 (38.7) | 46 (18) | 256 (100) |
| Total above 3–9 o'clock, *n* (%)[a] | 10 (4) | 39 (15.2) | 21 (8.2) | 70 (27.4) |
| Midprostate | | | | |
| Total, *n* (%) | 144 (44.7) | 125 (38.8) | 53 (16.5) | 322 (100) |
| Total above 3–9 o'clock, *n* (%)[a] | 18 (5) | 45 (14) | 24 (7.5) | 87 (26.5) |
| Apex | | | | |
| Total, *n* (%) | 100 (45.5) | 86 (39.1) | 34 (15.5) | 220 (100) |
| Total above 3–9 o'clock, *n* (%)[a] | 15 (6.8) | 34 (15.5) | 16 (7.3) | 65 (29.6) |

[a]Nerve fibers in sectors 1, 2, 7, and 8

**Table 1.2** Functional nerve distribution in anterolateral sectors as a percentage of fibers in sectors 1, 2, 7, and 8

| Position | Parasympathetic | Sympathetic | Somatic |
|---|---|---|---|
| Prostate base | 14.3 | 55.7 | 30 |
| Midprostate | 18.8 | 53 | 28.2 |
| Prostate apex | 23.1 | 52.3 | 18.6 |

nerves were identified on standard hematoxylin and eosin staining. A connective tissue stain was used to differentiate the fascial conduits. The distribution of the nerve fibers is shown in Table 1.1 and their positions around the circumference of the prostate in Table 1.2.

The present study has characterized the periprostatic nerves, including the cavernous nerves, by immunohistochemical analysis of sympathetic and parasympathetic nerves. We confirmed that autonomic nerve fibers were present on the anterolateral aspects of the prostate between the prostate and lateral prostatic fascia; however, only a small proportion of these were parasympathetic nerves likely to be of functional relevance. At the midprostate level, only 18.8 % of the nerves found on the anterior aspect of the prostate were parasympathetic nerves, 68 % being found in the previously defined NVB posterolateral to the prostate. Most of the nerve fibers found on the anterolateral regions examined were sympathetic in nature. The sympathetic nerves contribute significant innervations to the prostatic stroma and are responsible for innervations to the vascular structures in the region. As such, they may extend outside the typical NVB, which is predominantly parasympathetic by immunohistochemical characterization. The external urethral sphincter located immediately distal to prostatic apex receives input from the autonomic sympathetic nerves. The sympathetics may course over the anterior aspects of the prostate to provide innervations to the anterior external urethral sphincter.

At the apex, the absolute number of the parasympathetic fibers above the 3–9 o'clock junction increased slightly. This is consistent with studies that show the cavernous nerves ascending to assume a higher position distal to the apex. Takenaka and Tewari [13, 14] claimed the cavernous nerves assume a higher 2–10 o'clock positioning at the apex. The present study did not confirm these findings. However, careful apical dissection and ligation of the dorsal venous complex are of critical importance for preserving the neural anatomy.

The anteriorly placed parasympathetic nerve fibers are likely to be destined for innervations of the prostatic stroma and not the corpora cavernosa of the penis. This observation is supported by two pieces of evidence. First, the total number of visible nerve fibers was smaller at the prostatic apex as compared to the base. This decrease in the number of fibers has been reported previously and may be related to a significant proportion of nerves penetrating the prostate and other structures, including seminal vesicles, levator ani, and rectum. In the fresh cadavers included in our study, 134 nerve fibers were located at the base compared to 115 at the apex. Of these, the absolute number of parasympathetic nerves found on the anterior half of the prostate at the apex was eight, further supporting this hypothesis. With our connective tissue stains, we have shown the functional conduits of the NVB.

An important contribution to our understanding of the composition of the neurovascular bundle has been made by Takanaka's group [13]. They describe how the parasympathetic contribution joins the pelvic plexus around midprostate similar to our original findings in Brooks' dissections [7]. The major component of the NVB above midprostate is thus sympathetic and may not be as relevant in erectile function. Might it not therefore be more important to concentrate nerve-sparing surgical attention more distally to the apex? There have been suggestions that care in dissection around the tips of the seminal vesicles is mandatory in preservation or erectogenic nerve supply. If parasympathetic nerves make their major contribution to the NVB at midprostate and below, then seminal vesicle tip dissection/preservation seems less relevant.

## Functional Anatomic Characterization of the Neurovascular Bundle

As stated previously in this chapter, the past 20 years have realized remarkable outcome improvements in return of erectile function following radical prostatectomy. These improvements have come as a result of an understanding of the origin and course of the nerves to cavernous tissue. Prior to these anatomic insights, the nerves were mostly cut and left in place. In spite of much greater care in dissection and sparing or absence of heat application via diathermy, some previously potent men lose erectile function after surgery. One of the causes of this complication is excessive traction on these nerves that occurs during dissection occasioning partial or permanent neuropraxia. Alternatively, because the course number and location of these nerves may vary, is there a way of visualizing these nerves in situ to prevent injury to them?

We designed a series of animal experiments using a rat model injecting nerve dye tracers to establish an effective in vivo method of nerve visualization to optimize nerve-sparing surgery. Other technologies such as optical coherence tomography (OCT), transrectal ultrasound, and electrical stimulation have been tried with limited effect.

The discovery of axonal flow by Weiss in 1948 [15] revolutionized neuroanatomical knowledge. Specific effective dye tracers have been developed. We used three different tracers, Fluoro-Gold, Fast Blue, and Alexa Fluor, in this study by Anna Taylor, a medical student at The Royal Melbourne Hospital[16].

Effectiveness of cell labeling and the potential for neurotoxicity were assessed. In total, 63 rats were injected into the penis with three different dye tracers. Immunofluorescence testing in vivo was done as well as in vitro postmortem sectioning of the cavernous nerves and pelvic ganglia stained to assess dye uptake. Potency of the rats to determine toxicity of the dyes on nerve function was assessed.

All dyes successfully demonstrated retrograde nerve tracing in the cavernous nerve and major pelvic ganglion. With an immunofluorescence probe, the cavernous nerves could be visualized in vivo with all three tracers. The Fluoro-Gold tracer was the most easily seen (Fig. 1.10). Nerves could be seen with minimal dissection to remove superficial fat and fascia. Fluoro-Gold was a very sensitive dye labeling specific cavernous nerves clearly and specifically. There was no neurotoxicity evident with any dye.

This immunofluorescence dye injection approach may have surgical utility, allowing a surgeon to identify erectogenic nerves in real time and spare accordingly these functionally relevant nerves.

**Fig. 1.10** Fluoro-Gold staining of cavernous nerve in rat model

Future efforts to improve postoperative erectile function may also include intraoperative cooling as described originally by Ahlering [17] and the use of topical or systemic neuroprotective drugs.

## Anatomy of Male Urinary Continence

### The Prostate and the Urinary Sphincter

There are several reasons why a clear anatomic insight into the composition and physiological function of the male urethral sphincter remained arcane to many practicing urologists. This writer remembers well that whenever this topic was the subject of a tutorial or lecture, a soporific state ensued. Favorite questions of the writer to his urology trainees today are “Why do men develop temporary stress incontinence after radical prostatectomy?” and “What continence components are damaged by the removal of the prostate?”

Kouratim [18] has written a very clear and practical summation of current concepts.

1. The reasons for confusion are several:
2. Poor cadaver gross dissections.
3. Findings from fetal dissections have been applied to the postpubertal adult. The effect of testosterone on prostatic growth produces profound changes to the anatomic relationships of the prostate to its surrounding structures.

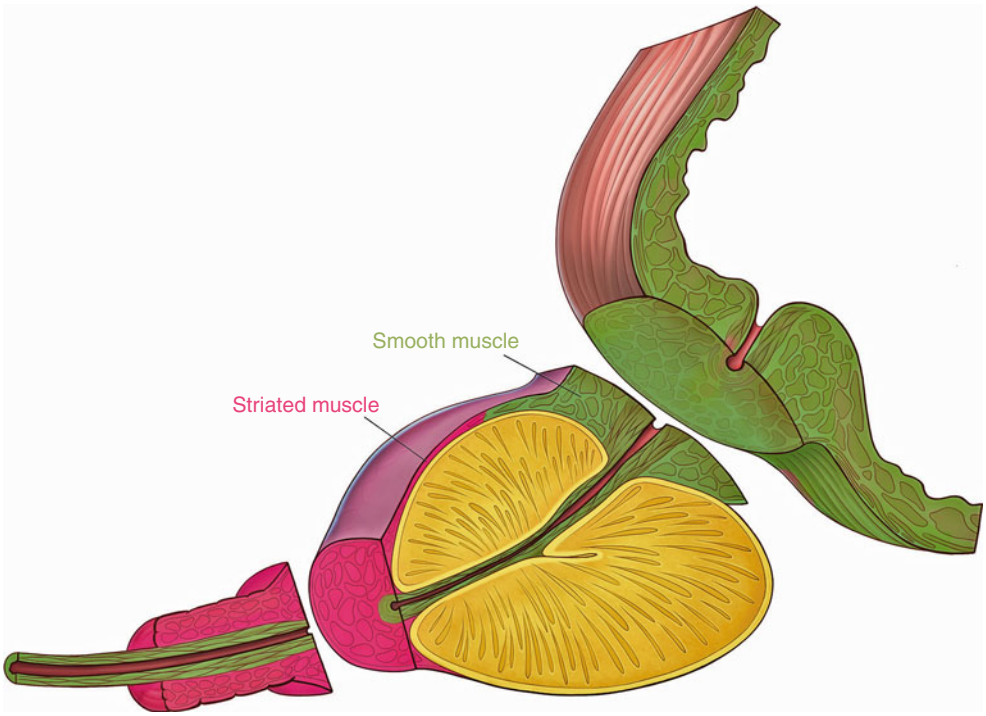



**Fig. 1.11** Smooth muscle (*green*) and striated muscle (*red*) components of the urethral sphincteric mechanism

4. There has been a lack of consensus as to individual anatomic terminology.
5. Many of the original and important anatomic texts were published in German and French and were thus unread by English-speaking surgeons.

The sphincter is composed of two functional muscular components. These are morphologically related but functionally independent.

1. *Smooth muscle*: the inner layer, which runs from bladder neck through the prostate to the membranous urethra and provides "passive" continence
2. *Skeletal muscle*: the outer rhabdo sphincter, which maintains "active" continence

Kouratim describes the urethral sphincter as a complex, in a cylindrical form around the urethra from bladder neck to distal membranous urethra. The outer component is the striated muscle thickest around the membranous urethra. It does not form a complete cylinder around the urethra but is horseshoe shaped. The fibers fold anteriorly around the urethra and unite posteriorly in a central fibrous tendon behind the urethra. The striated muscle extends over the prostate anteriorly and blends proximal to the prostatic apex with the smooth muscle and glands of the anterior zone of the prostate. This finding is sometimes reported by the pathologist following prostatectomy.

## Function of the Smooth Muscle Sphincter

The smooth muscle of the urethra acts to maintain passive continence. No conscious effort is needed for a male to be continent at rest. The smooth muscle is not a sufficient sphincter to maintain continence when intra-abdominal pressure rises with active movement, standing, walking, and coughing.

The smooth muscle of this sphincteric component works by contraction of the circular muscle fibers casing the bladder neck and urethra. Clearly, the entire length of this smooth muscle is not needed to maintain passive control as after both transurethral prostatectomy and radical prostatectomy, a length of this muscle is removed. Generally, men after radical prostatectomy can maintain urinary control at rest, lying in bed, but not when they move. However, as Myers has stated, a certain length of smooth muscle urethral sphincter is required [19]. He cautions great care in apical prostatic dissection for this reason (Fig. 1.11).

## Function of the Striated Sphincter

There has been a recent advocacy for restoration of the posterior urethral plate after prostatectomy [20]. Understanding the anatomy of the posterior prostatic fascial aponeurosis where Denonvilliers' layer fuses with the tendinous junction of the horseshoe striated muscle posterior to the prostatic apex and with muscle, we as surgeons recognize as rectourethralis. Restoration of this plate posteriorly after prostate excision may aid in restoration of continence by proving a platform for contacting circular striated muscle to compress the urethra anteroposteriorly. The attachment of the posterior muscle to the median tendon results in compression of the anterior urethral wall on this fibrous raphe on raising intra-abdominal pressure. Denonvilliers' fascia and rectourethralis form this rigid plate against which the urethral lumen is

flattened. This contraction constitutes active and short-lived voluntary continence mechanism illustrated by the voluntary interruption of the urinary stream. This active and forceful contraction is mediated by fast- and slow-twitch striated muscle fibers. This was originally reported by Denny-Brown who observed that this contraction could only be maintained for a few seconds [21].

As summarized by Kouratim, there are two functionally independent components of sphincteric urinary continence, the inner urethral smooth muscle for passive control and the outer striated skeletal muscle for active control. Finally, the shape of the prostatic apex varies significantly. This has been well described by Myers [22, 23]. "This can influence the length of urethra emerging at the apex. The apex may overlap the urethral sphincter circumferentially, symmetrically bilaterally, asymmetrically unilaterally, anteriorly only, or end above the sphincter." The practical instruction here for the prostatectomist is that great care in each apical dissection is required to maintain the integrity of both muscular sphincteric parts to optimize the likelihood of early return of control. A precise reason for the almost-inevitable short-term stress incontinence followed by a return-to-complete continence later eludes this writer. It may be that the division of the anterior ligamentous supports and some loss of rhabdosphincter muscle proximally that suspend the prostatourethral apical tissue cause this usually temporary surgical side effect.

## Prostate Embryology

### The Prostate Gland

The prostate is part of the accessory sex gland system in human males that synthesizes and secretes both organic and inorganic components of the seminal plasma. Prostatic secretions are believed to be important for spermatozoa survival in the female reproductive tract, although they are not necessary for conception, as sperm retrieved directly from the testis or epididymis can be used to successfully fertilize oocytes. Contraction of the smooth muscle stroma may play a role in semen expulsion during ejaculation, while simultaneous closure of the internal urethral sphincter prevents retrograde flow into the bladder. The internal urethral sphincter may also contribute to male urinary continence. Although the presence of a prostate is universal in mammals, its gross anatomical structure differs markedly between species. In man, it is a compact gland that extends from the bladder neck proximally to the external urethral sphincter complex at its distal apex.

### Gland Structure

Postsexual maturation and in the absence of pathology, the prostate approximates an inverted pyramid in shape, with a broad base, anterior, posterolateral and posterior surfaces, and a tapering apex. The gland is enclosed by a thin capsule, approximately 0.5 mm in diameter that is composed of collagen, elastin, and smooth muscle. At the base of the prostate, the outer longitudinal detrusor fibers of the bladder wall fuse with the fibromusclar fibers of capsule, with no true capsule identifiable separating prostate glands from bladder neck muscle. Similarly, the prostate capsule is deficient at the apex, and normal glands are commonly observed to extend into the sphincter complex. The bulk of the glandular tissue is situated posteriorly and laterally, with the anterior one third being composed of fibromuscular stroma. The urethra, approximately 3 cm in length and lined by transitional epithelium, runs the entire length of the prostate gland, situated closer to the anterior surface. At its midpoint, the urethra angles approximately 35–40° anteriorly, dividing the urethra into proximal (preprostatic) and distal (prostatic) segments. At the bladder neck, the inner longitudinal and middle circular detrusor muscle fibers project distally to surround the preprostatic urethra. Thickening of the circular fibers in this area forms the internal urethral sphincter, which is incomplete anteriorly, with the lateral projections inserting into the anterior fibromuscular stroma on either side. Arising from the posterior wall of the urethra and projecting into the lumen is the urethral crest, which runs the length of the prostatic uretha, giving it a crescentic appearance on cross section. The urethral crest broadens at the point of angulation to form the colliculus seminalis or verumontanum and to taper inferiorly at the prostatic apex. Projecting posteriorly and cephaladly from the verumontanum in the midline is the prostatic utricle, a blind ending pouch measuring approximately 4–7 mm in length that is believed to be a vestigial remnant of the paramesonephric system. The ejaculatory ducts which are formed by the union of the seminal vesicles and the vasa enter the prostate at its base posteriorly and course through the prostate in a plane parallel and slightly posterior to the postprostatic segment of the urethra to open on either side of the utricular opening. On either side of the urethral crest are shallow recesses termed the prostatic sinuses, which receive the ductal openings of glandular elements, 95 % of which lie in the distal urethra.

### Zonal Anatomy

Although the cut surface of a disease-free prostate is fairly homogenous, it has long being recognized that there are distinct regions within the gland that differ in the patterning of their acini and susceptibility to disease. Over the last 100 years, a number of different models of gland organization have been proposed; the most widely accepted model currently is that elaborated by Dr. McNeal based on serial sectioning of a large number of prostates removed at radical

prostatectomy [24]. Four discrete glandular zones are described based on the location of their ductal openings within the urethra with reference to the verumontanum. Most prostatic glands reside in the peripheral zone, which makes up approximately 75 % of glandular elements and occupies most of the posterior and lateral aspects of the gland. Peripheral zone ducts arise in a double row from the floor of the prostatic sinuses bilaterally, extending the whole length of the postprostatic urethra at approximately 2 mm intervals, with main ducts extending posteriolaterally and minor ducts more anteriorly. Subsidiary ducts arise at regular intervals along the course of the main duct, branching at an angle of approximately 15°, and extend only a short distance before giving rise to groups of acini. Ducts of the central zone, which accounts for approximately 25 % of glandular elements, originate circumferentially around the openings of the ejaculatory ducts and the convex surface of the verumontanum. These ducts then branch directly toward the base, parallel to and surrounding the ejaculatory ducts, forming a conical wedge of tissue, separated from the peripheral zone by a narrow band of stroma. Ducts of the transition zone arise at the junction of the proximal and distal urethral segments and course beneath the preprostatic sphincter to arborize on its posterior and lateral surfaces toward the bladder neck, with the most medial fibers penetrating into the internal prostatic sphincter. In the normal prostate, the transition zone accounts for 5–10 % of glandular elements and is separated from other glandular elements by a discrete fibromuscular band. The periurethral glands comprise less than 1 % of glandular elements. These rudimentary glands are scattered along the length of the proximal urethral segment and extend between fibers of the longitudinal smooth muscle to be contained wholly within the preprostatic sphincter. The anterior zone is composed primarily of fibromuscular stroma and extends from the bladder neck to the striated sphincter in direct continuity with the prostatic capsule.

## Microscopic Appearance

The architectural arrangement of the prostate befits its function, with a distensible glandular system capable of acting as a reservoir for secretions embedded in a smooth muscular stroma and capable of expelling those secretions during ejaculation. In the normal prostate, approximately 70 % of the prostate is composed of secretory glands, with the fibromuscular stroma accounting for the remainder. The glands themselves are tubuloalveolar, extend out to the prostatic capsule, and have a relatively simple branching pattern, with acini distributed uniformly along the course of the main duct [25]. Both acini and ducts are secretory and are lined by simple cuboidal or columnar epithelium. These cells are terminally differentiated, with a low proliferative index and contain abundant secretory granules. These cells stain positive for PSA, acid phosphatase, and the androgen receptor, express cytokeratins 8 and 18, and are attached to the underlying basement membrane via integrin receptors. Sandwiched between the basolateral surface of secretory epithelium and the basement membrane are basal cells, which are small and flattened with scant cytoplasm. These cells comprise less than 10 % of prostate epithelial cells and are distinguished immunohistochemically from secretory cells by staining negative for PSA and the androgen receptor, but positive for cytokeratins 4, 14, and 15. In man, the basal cell layer forms a nearly continuous layer between the basement membrane and secretory cells. Although they themselves have a low rate of proliferation, they are believed to be the progenitors of the rapidly dividing transient proliferating cells which replace secretory epithelium lost through attrition. The basal cell layer is also the proposed location of prostate stem cells, a population of single cells that can completely reconstitute all tissue elements of the normal gland. Scattered between secretory epithelium both within acini and ducts are neuroendocrine cells which express neural markers such as chromogranin A, neuron-specific enolase, and synaptophysin. Both the origin and function of these cells remain obscure, although a role in the paracrine regulation of prostate growth, differentiation, and secretory activity has been suggested. The stroma is composed of fibrillar collagen, elastin, and smooth muscle.

The microscopic appearance of glands in the central zone is distinct from that found in the peripheral and transitional zones. Peripheral zone glands are small (0.15–0.3 mm in diameter) with a simple almost rounded contour, with prominent undulations in the acinar wall, and are embedded in a loosely arranged matrix of smooth muscle. Secretory cells have small basal nuclei, pale cytoplasm, and a smooth luminal border. In contrast, central zone glands and ducts measure up to 6 mm in diameter, with polygonal acini arranged in clusters around a central draining duct. Secretory cells have larger nuclei, irregularly arranged in a darker, more granular-appearing cytoplasm. The luminal surface is noticeably irregular, with individual cells projecting into the lumen. The ratio of epithelium to stroma is higher in the central zone compared to the peripheral zone, although the stroma is denser and composed of compact smooth muscle bundles. Transitional zone glands resemble those of the peripheral zone but are embedded in compact, interweaving smooth muscle bundles.

## Embryonic Development

The normal development of the human prostate gland is incompletely understood, with most insights derived from fetal dissections or the study of organ development in other

species, in particular rodents. In man, its development spans almost two decades, from initial organogenesis in the first trimester to maturation during puberty. Its development is intimately related to other organs of the lower genitourinary system, which occurs in two phases, a sexually indifferent stage, which is common to both male and female fetuses, and a sexually determined phase that is dependent upon fetal genotype. In general, three distinct processes are involved in the generation of a branched glandular network – initiation, growth, and termination – which may be independently regulated. In addition, particularly for sexual glands, separate phases of development occur with the generation of rudimentary gland structure during embryonic development, a postnatal quiescent phase, and the reemergence of cell proliferation and branching during puberty to achieve a mature gland structure.

## Sexually Indifferent Development

The prostate gland develops predominantly from the urogenital sinus (UGS), the anterior division of the cloaca, with a small contribution from the mesonephric or Wolffian system [26]. The cloaca itself is formed by expansion of the caudal end of the primitive gut tube and is clearly identifiable during the third week of development. It is separated from the chorionic cavity by the cloacal membrane. During weeks 4–6 of development, the cloaca is divided by the ingrowth of a mesoderm partition in the coronal plane, separating the anterior urogenital sinus that will form the lower genitourinary tract in both sexes from the rectum posteriorly. This urorectal septum is a coalescence of three separate mesodermal folds, the superior fold of Tourneaux which projects caudally from above and the two folds of Rathke which originate laterally and project inwards to fuse in the midline. At its most caudal end, the urorectal septum fuses with the cloacal membrane at the site of the future perineum, similarly dividing it into the anterior urogenital and posterior anal membranes. The UGS is situated in the midline and is composed of two layers, an epithelial layer derived from endoderm and a mesenchymal layer derived from mesoderm. Viewed sagitally, the urogenital sinus assumes a short wine-glass appearance, with an expanded superior portion that will form most of the bladder, a narrow neck at the level of the true pelvis which in males gives rise to the prostatic and membranous urethra, and an inferior expansion termed the definitive urogenital sinus, from which the distal urethra and external genitalia is derived.

The mesonephric ducts first appear as paired condensations within the intermediate mesoderm of the thoracic region, related ventrally and medially to the developing tubules of the intermediate kidney, the mesonephros. Through a combination of cell proliferation and cell migration, the distal tips project caudally to fuse with the lateral aspects of the cloaca and then canalize to form a true duct. On approximately day 28, ureteric buds sprout from the distal portion of the buds, which invade the metanephric blastema to form the definitive kidney. At the same time, as the cloaca is being divided by the urogenital septum, the portion of the mesonephric duct distal to the ureteric buds begins to become incorporated into the presumptive bladder through a process of extrophy which affects the leading superior edge to much greater extent than the trailing inferior edge, which fuses with its contralateral counterpart in the midline. This results in the migration of the narrow mouths of the mesonephric ducts to open into the pelvic urethra at the level of the verumontanum and incorporation of the distal ureters into the bladder wall to attain their normal adult position at the posterolateral corners of the trigone. The mesonephric ducts give rise to the seminal vesicles at the level of the bladder neck in a process that is similar to that regulating prostate gland development, with the more distal ducts continuing as the common ejaculatory ducts that open into the floor of the urethra at the level of the verumontanum. The paramesonephric ducts arise by the growth and invagination of coelomic epithelium just lateral to the mesonephric system during the 6th week of development. Similar to the mesonephric system, the distal tips project caudally to open into the pelvic urethra just medial to the openings of the mesonephric ducts.

## Sexual Determination and Initiation

The primary genetic determinant of male-type patterning is the presence of SRY (Sex-determining region of the Y chromosome), which is usually located on the short arm of the Y chromosome [26]. The gene encodes a HMG-box transcription factor, and its expression in indifferent gonads in the 7th week leads to the differentiation of medullary sex cord cells into pre-Sertoli cells and, ultimately, the formation of a testis. Pre-Sertoli cells secrete anti-Mullerian hormone (AMH), which actively causes rapid regression of the paramesonephric duct system between weeks 8 and 10, with the most distal end persisting in the male fetus as the prostatic utricle. Similarly, in response to SRY expression in pre-Sertoli cells, during weeks 9–10, mesenchymal cells in the gonadal ridge differentiate into Leydig cells. Leydig cells synthesize and secrete testosterone, initially under the influence of chorionic gonadotropin produced by the placenta and later by LHRH secreted by the pituitary. The production of testosterone promotes survival of the mesonephric ducts with persistence of the distal ends as vasa deferentia and ejaculatory ducts.

Initiation begins with the specification of particular cell clusters for tube development, distinguishing them from surrounding cells that are destined to form other tissues.

For prostate organogenesis this involves the commitment of specific epithelial cells of the urogenital sinus to a prostate epithelial cell lineage and is marked by the expression of a specific cassette of androgen-dependent genes. The visible correlate of this molecular-mediated event is the development of solid cords of epithelial cells that will ultimately form glandular ducts that project from the urethra into the surrounding urogenital mesenchyme just caudal to the bladder neck at about the 10th week. Although this may occur in a number of ways, in mammals, invagination appears to be a predominant mechanism, whereby the initial tube forms by the ingrowth of cells perpendicular to the plane of the parent epithelium. These projections are symmetrical bilaterally with buds originating in groups in a ventral, lateral, and dorsal direction from the pelvic UGS, where they are surrounded by compact mesenchyme. These ductal origins remain constant into adult life and are a point of differentiation between zones in contemporary descriptions of gland structure. The distinctive patterning of glands in the central zone has led to the suggestion that precursor buds maybe of Wolffian rather than urogenital sinus epithelial origin. As the fetus develops, these cellular cords elongate and divide in a program of branching morphogenesis to form the rudimentary cellular structure of the glandular system [27]. At approximately the same time, the seminal vesicles bud from the distal mesonephric duct near its attachment to the pelvic uretha, which then comprises the common ejaculatory duct.

## Branching Morphogenesis and Cytodifferentiation

Branching morphogenesis is a fundamental biological program that is responsible for the patterning of tubuloalveolar networks. Although in certain species or organs, particular mechanisms of growth predominate, various aspects of network formation and its regulation are conserved from Drosophila to mammals [28]. The requirement to form an interconnected network of hollow tubes is important to the genesis of many organs, from the bronchoalveolar system of the lungs to the nephrons of the kidney, and is a feature in the formation of many exocrine glands, including salivary, mammary, and prostate glands. Formation of a tubuloalveolar network is advantageous to the function of a gland by providing a greater surface area for secretion of glandular plasma, as well as increasing storage capacity.

In order to understand the processes involved in branching morphogenesis, it is useful to review the end structure that the program is trying to attain. The essential characteristic of a tube is of a hollow lumen surrounded by a circumferential lining or epithelium. Adjacent epithelial cells maintain close cell-cell contact and adhesion through specialized junctions that link cells, provide structural support, and act as barrier function to prevent the movement of ions, fluid, and macromolecules between compartments. In mammalian epithelia, these roles are fulfilled by the tight and adherens junctions, as well as the desmosome. Epithelial cells also have a distinct apicobasal polarity, with the apical surface facing the lumen and the basal surface interacting with a basal layer of epithelium or a basement membrane. Tight junctions are important in the maintenance of cell polarity, as they prevent the diffusion of cell membrane proteins and lipids between compartments.

Depending of the system studied, the network may have a lumen ab initio, in which case cells must maintain their polarity during subsequent development, or grow initially as solid cellular cords that then become canalized. The growth phase is marked by tube elongation and elaboration. Tubes may grow by a number of mechanisms, such as elongation of individual cells or their rearrangement to increase tube length, recruitment of new cells, or by division of existing epithelia. Network elaboration through branching is important to allow the network to maximize the occupancy of a specified three-dimensional space. Although the finally achieved pattern is frequently bewilderingly complex, recent studies in both mammalian lung and kidney indicate that these arrangements are explained by the regular repetition of a small number of simple branch patterns. The final phase of the process is termination, whereby both tube elongation and branching are switched off when the network has achieved the desired size.

Branching morphogenesis begins when the elongating prostate epithelial buds make contact with the condensed urogenital mesenchyme that lies external to the periurethral smooth muscle. Multiple branch points occur at regular intervals, with a pattern that differs between zones. As branching morphogenesis continues proximally, distal ductal cells undergo differentiation to a prostate epithelial phenotype, with similar differentiation of surrounding mesenchymal cells to a smooth muscle. From 20 to 30 weeks, the primitive gland acini are represented by simple, solid cellular buds at the end of ducts, and by as early as week 13, prostate secretory activity may be discerned. Differences in epithelial cell shape are noted in these buds, with columnar-type epithelium noted in the basal region, with more spindle-shaped cells toward the center. Toward term, the acinotubular system becomes more elaborate.

## Regulation of Development

### Molecular Control of Development

A limited repertoire of transcription factors (such as the Hox and NK family of homeobox genes) and secreted signaling molecules (such as SHH, FGF-10, and BMPs) have been identified that have highly conserved roles in cell specification

and developmental patterning [29]. Expression of these factors occurs in a temporally and spatially restricted manner to promote (or inhibit) cell determination, initiation, branching morphogenesis, and differentiation in a number of different branched networks, including the developing prostate gland. For example, one of the first indications of prostate epithelial cell specification in the urogenital sinus epithelium is the expression of the homeobox transcription factor Nkx3.1 in response to circulating androgens [30]. A detailed description of the complex interplay between the various signaling cascades involved is outside the remit of this chapter, and interested readers are referred to an excellent recent review of the subject [31].

### Inductive Role of Urogenital Sinus Mesenchyme

It has been recognized for many years that a specific interaction between primitive stromal cells and corresponding primitive epithelial cells is important in the development of many organ systems. In general, it has been shown that mesenchyme induces and patterns epithelial development in that certain epithelia will only develop in the presence of a specific mesenchyme. In addition, this interaction is reciprocal, and the specified epithelium induces and patterns specific mesenchymal differentiation.

Many of the early insights into the role of stromal-epithelial interactions in prostate development were based on elegant tissue recombination experiments performed by Dr. Cunha and colleagues [32]. In early work, they showed that the presence of both urogenital mesenchyme and sinus epithelium is required for prostate development, as coimplantation of both tissue results in the successful gland formation, whereas implantation of either tissue alone does not. In the same system, they also demonstrated a specific requirement for urogenital mesenchyme, as mesenchymal tissue isolated from other organ sites failed to induce prostate gland development. To demonstrate the inductive power of urogenital mesenchyme in instructing epithelial differentiation, they then showed that coculture with urogenital sinus mesenchyme was sufficient to override the developmental programming of both embryonic and adult bladder epithelial (which is also of urogenital sinus origin) and result in the formation of prostate glandular formation. Confirming the reciprocal nature of this interaction, they have also shown that developing prostate epithelium induces smooth muscle differentiation of primitive urogenital mesenchyme. Overall, these results suggest that prostate development is spatially restricted by the distribution of prostate-inducing urogenital mesenchyme surrounding the urogenital sinus; however, the developmental cues that trigger the formation of the inductive mesenchyme and limit its spatial distribution have yet to be determined. Interestingly, although the factors that mediate the mesenchymal induction of prostate development have yet to be completely elucidated, they appear to be conserved between species, as heterospecific tissue recombination experiments result in successful prostate development.

### Role of Androgens

Testosterone is produced by the fetal testis from about the 8th week and presages male sexual differentiation of the urogenital system. Determination of prostate cell identity and initiation of branching morphogenesis from the prostate anlagen are critically dependent upon the presence of androgens [31]. In the absence of androgens, the urogenital sinus forms the female urethra and lower portion of the vagina. Although the main androgen secreted by the testes is testosterone, in peripheral certain tissues, including the urogenital sinus, testosterone is converted to the more potent dihydrotestosterone by the action of 5 alpha-reductase. Testosterone mediates its cellular action by binding to the androgen receptor, which translocates to the nucleus where it regulates the transcription of a particular gene cassette. Mice lacking a functional androgen receptor fail to initiate branching morphogenesis, and in humans, both inactivating androgen receptor mutations and androgen insufficiency lead to prostate agenesis. Conversely, exposure of female urogenital sinuses to testosterone induces prostate branching, and female virilizing syndromes such as congenital adrenal hyperplasia result in increased accessory sex gland formation. In mice with mutations in 5 alpha-reductase that prevent the generation of dihydrotestosterone, prostate bud initiation still occurs, but duct development and branching morphogenesis are severely inhibited, indicating that testosterone is sufficient for gland initiation; conversion to the more potent DHT is necessary for full organogenesis. Interestingly the absolute requirement of branching morphogenesis for androgens is temporally restricted, as androgen ablation once the process is underway reduces the frequency of new branching but does not prevent further branching from occurring.

Immunohistochemical studies indicate that in the urogenital sinus, the androgen receptor is expressed in both the developing stroma and epithelium during branching morphogenesis, however with different temporal patterns. Whereas the androgen receptor is highly expressed in UGS mesenchyme before and during prostate morphogenesis, epithelial expression is discerned only after budding and branching have begun, suggesting independent roles in prostate gland development. Indeed, analysis of heterotypic recombinants of wild type and testicular feminization mice which harbor germline inactivating mutations in the androgen receptor indicates that stromal AR expression, but not epithelial AR expression, is necessary for prostate organogenesis. AR expression in the epithelium is however required for the expression of AR-dependent secretory proteins. These observations are supported by the reported phenotype of prostate epithelial AR knockout mice, where prostate glands

clearly form but with a smaller gland size associated with stunted cytodifferentiation of the prostate epithelium. Other steroids, such as estrogens and retinoids, although not necessary for prostate development, may modulate the expression of specific genes through imprinting to affect the growth potential of the fetal prostate as well as susceptibility to disease in later life.

The mechanism whereby testosterone acting upon the stromal compartment gives rise to branching morphogenesis and epithelial cell differentiation is essentially unknown, although two theories have been popularized; the andromedin and smooth muscle hypotheses, which are not necessarily mutually exclusive.

### The Andromedin Hypothesis

The andromedin hypothesis proposes that androgens act upon androgen receptor expressing cells in the stromal compartment to stimulate the production of growth factors or cell surface molecules that act upon prostate epithelial cells in a paracrine manner to regulate their growth and differentiation, although androgen repression of a growth inhibitor would be equally valid. Given that the activated androgen receptor acts as a transcription factor, in the most facile system, expression of the putative growth factor would be directly regulated by androgen binding. These characteristics therefore define a putative andromedin:

- Expression directly regulated by androgens
- Expressed by cells in the mesenchyme/stroma
- Present in the androgen target tissues
- Acts as a paracrine regulator of epithelia

Over the last decade, a number of different molecules have been identified that fulfill these criteria to a greater or lesser degree. For example, the small peptide growth factors FGF7 and FGF10 have been shown to promote prostate epithelial growth and induce branching morphogenesis in tissue culture [33, 34]. Both growth factors are synthesized by stromal cells and act by interacting with their cognate receptor FGFR2iiib, the expression of which is restricted to the epithelial compartment. Interestingly, prostate gland formation in FGF10 knockout mice is severely compromised, with only a reduced number of small prostate epithelial buds being formed. However, FGF10 expression is not regulated by androgens, whereas FGF7 knockout mice, expression of which is at least weakly stimulated by androgens, are not reported to demonstrate and deficit in prostate gland formation. These observations suggest FGF10 is important to the process of branching morphogenesis independent of androgens, whereas any putative andromedin activity of FGF7 is largely redundant. Similarly, other small peptide growth factors have been shown to promote or inhibit growth, branching, or ductal tips (TGF-beta, BMP4, BMP7), although these again fail to fulfill the assumptions of the hypothesis.

### The Smooth Muscle Hypothesis

An alternative mechanism to the andromedin hypothesis to explain the regulation of prostate epithelial growth by androgens through an effect on stromal cells has come from detailed histological analysis of tissue distribution in the developing rat prostate anlagen [34]. This theory proposes that the inductive capacity of the urogenital mesenchyme is regulated by the presence or absence of a smooth muscle layer that acts as a physical barrier between stromal cells and the developing epithelium. In early fetal life, a thin discontinuous smooth muscle layer is observed in both sexes; however, in female rat this develops into a broad continuous sheet that conceivably isolates the primitive epithelium from the inductive effects of the stroma. In male rats however, this layer remains incomplete, and epithelial buds are observed to grow out into the mesenchyme through these gaps where they undergo branching morphogenesis. Prostate epithelial buds form before the smooth muscle layer forms indicating that induction is independent of this event; however, its main effect may be in limiting subsequent ductal growth and branching. It has been shown that the extent and thickness of this smooth muscle layer are negatively regulated by androgens, and it is one possible mechanism for explaining the critical time window for the effect of androgens on prostate development. The smooth muscle hypothesis is not incompatible with the presence of andromedin(s), as it is easy to imagine that the smooth muscle layer may act as a barrier to the diffusion of paracrine growth signals or the interaction of cell surface molecules between compartments. In addition, it is conceivable that the formation of the smooth muscle layer is itself regulated by andromedins.

### Postnatal Development

The postnatal development of the prostate is dependent upon ambient circulating levels of sex hormones. At birth, the prostate gland is composed mainly of connective tissue with a relatively small proportion of smooth muscle [35]. The prostate gland is small, with a measured volume of approximately 1 cc. Glandular ducts end blindly near the periphery, with the precursors of adult gland alveoli represented only by terminal duct buds. The ducts themselves are lined by cuboidal or low columnar cells and in many areas appear as solid cords of cells. Squamous metaplasia is common, particularly in the terminal parts of the prostatic ducts usually in response to exposure to high levels of circulating estrogens toward the end of term. Over the long period from birth to prepuberty, the prostate changes little. With the fall in maternal estrogens, squamous metaplasia disappears. Extensive hyperplasia is noted in the ducts, with obliteration of the lumen in many areas, with pseudoacinar formation. The end buds themselves remain small in size but gradually increase in patency. The lining epithelium is mainly short columnar cells but are not mature secretory cells. Prostate volume

changes little over this time period, a little less than doubling up to 10 years of age. The onset of puberty, with its associated surge in testosterone production, is marked by a phase of rapid growth of the prostate gland with dynamic changes in the internal architecture. Gland volume increases up to 10 cc in as little as 6–12 months. As the hyperplastic epithelium of the terminal end buds thins out into a single layer of cells, the diameter of the acini increases. The height of the columnar epithelium lining the acini increases and the nuclei become more basally located, attaining the appearance of mature secretory epithelium.

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# Molecular Biology and Prostate Cancer

2

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## Introduction to Molecular Biology

Molecular biology is the study of the structure and activity of macromolecules essential to life such as nucleic acids and proteins. Over the past decade, progress in molecular biology has been rapid with advances in our understanding of the genome and cancer biology, computer power for bioinformatics, and development of novel techniques and equipment. This has changed molecular biology from being mainly limited to the study of particular candidate molecules to routine unbiased genome/expressome-wide analyses. Using this new technology, many novel candidate targets for prostate cancer (PCa) therapy have been identified. High-throughput screening allows rapid identification of candidate drugs, which have in vitro effects and which can go on to clinical testing.

For instance, the drug PLX4032 is the first to be specifically designed, based on the results of genome-wide association studies (GWAS). GWAS involves examination of the entire genome, and by comparing cases with control DNA, short sequences of bases, variation within which is associated with disease (short nucleotide polymorphisms or SNPs), can be identified. In melanoma, a subset of patients with a particular gene mutation (polymorphism) resulting in a single amino acid replacement in BRAF, a well-known cancer kinase target, was identified [1]. PLX4032 selectively inhibits the mutated form. Clinical testing showed that 80 % of patients with the V600E mutation had a response, which is remarkable for a patient group in whom treatment was largely futile [2]. Figure 2.1 illustrates the remarkable treatment response seen in a subset of patients.

In PCa, one focus has been to look for SNP variations predisposing to cancer. In a recent review of the current literature on SNPs associated with prostate cancer in Caucasians, 30 PCa risk-associated SNPs were identified. These SNPs have been shown to have moderate effects on risk of developing prostate cancer with odds ratios generally less than two. Surprisingly, most of the SNP variations associated with disease are found in the noncoding regions on the chromosome between genes (introns); it is speculated that these SNPs affect the tissue specific control of expression of coding genes [4].

## Pathways of Translational Research in Prostate Cancer Research

High-throughput drug testing means that with identification of a drug target, design of drugs to inhibit that particular target along with testing of panels of thousands of candidate inhibitor drugs can proceed rapidly. Preclinical work in PCa usually involves culture of the cell lines described in Table 2.1. Should cytotoxicity be demonstrated in cells, animal studies usually precede clinical studies. This approach has produced a large number of candidate drugs that are at various stages in clinical development, a selection of which are summarized in Table 2.2. The main delays and blocks in drug development are mostly related to delays in progress to studies in man.

The majority of PCa animal work is carried out with rodents, particularly mice. In dogs (the only other animal than humans to commonly develop spontaneous PCa), it takes too long before cancer develops to be practical. Previously, rat models such as Noble and Dunning models were used. Nowadays, most work is done using mouse models [5]. Transgenic mice models such as the TRAMP (transgenic adenocarcinoma mouse prostate) model utilize a promoter to overexpress the SV40 early oncogenes to induce

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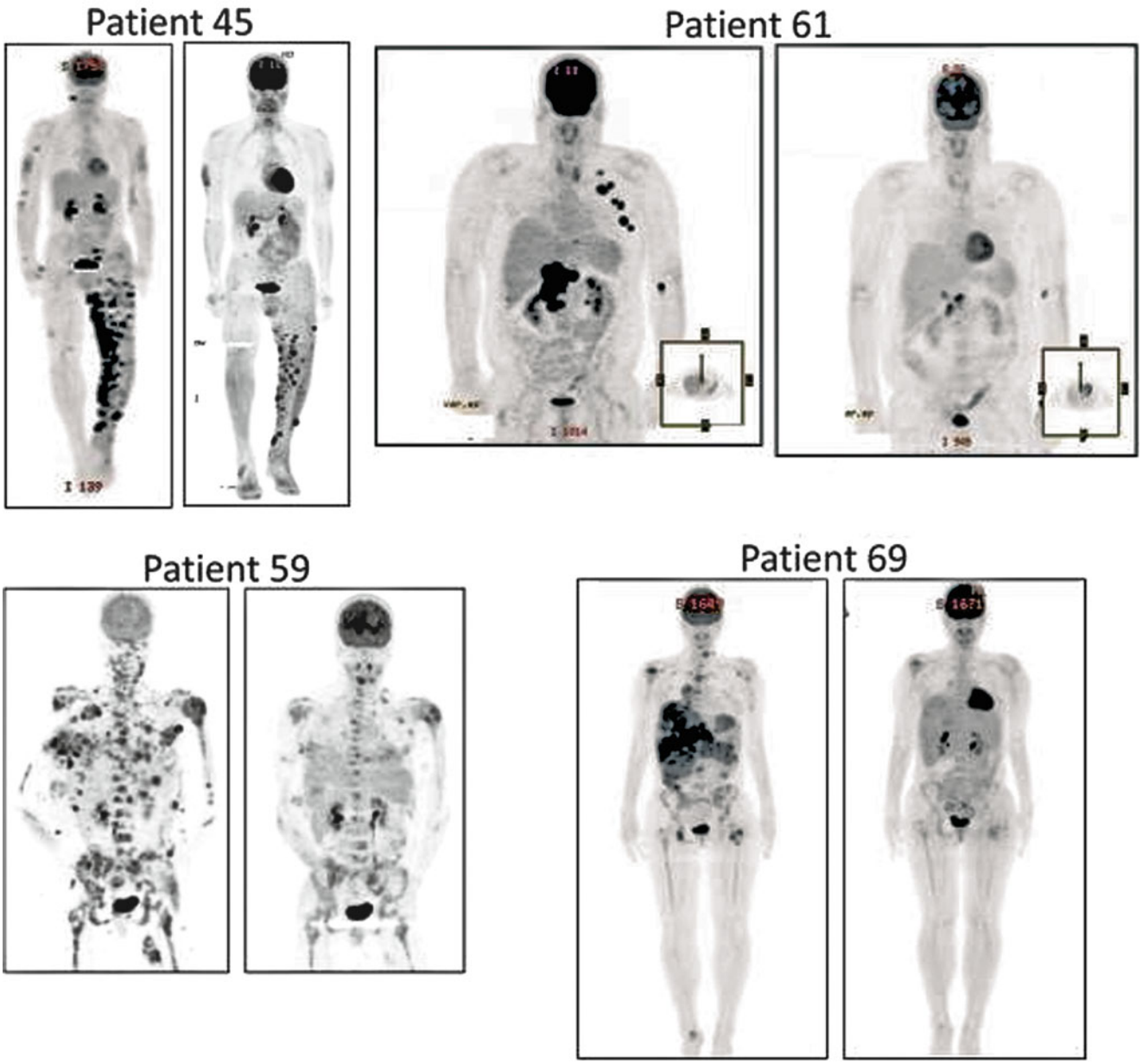


**Fig. 2.1** Representative PET scans for patients taken pre-dose and following 2 weeks of dosing with PLX4032. Each of these image pairs demonstrates significant reduction in FDG uptake following PLX4032 treatment. Note that tumor regressions were later documented for each of these patients: best responses were 70 % for patient 45, 70 % for patient 59, 68 % for patient 61, and 37 % for patient 69 (Reproduced with permission Nature Publishing Group. Bollag et al. [3])

progressive disease from epithelial hyperplasia or prostatic intraepithelial neoplasia (PIN) to adenocarcinoma and development of metastases. Knockout mice have specific genes deleted from the germ line. For example, knockout heterozygotes for *PTEN* (see below) develop PIN, while homozygotes develop invasive prostate adenocarcinoma [6]. Use of germ line knockout models is limited in that all cells in the animal have the deletion. It is not possible to attribute the phenotype solely to changes in the prostate epithelial cells. Conditional gene knockout, whereby gene function can be turned off using an inducible system such as Cre/Lox recombination, allows study of deletions that would be fatal in the germ line.

Xenograft models involve the transplantation of cell lines into immune-deficient animals. The cells used for these experiments are derived from established PCs meaning that study of transformation to cancer is limited in these models [7].

With the ability to analyze biochemical abnormalities present in the cancer of a particular patient and availability of novel agents targeting specific molecules/pathways, personalized

**Table 2.1** Derivation and basic characteristics of prostate cancer cell lines

| Tissue of origin | Cell line | PSA expression | Androgen receptor expression |
|---|---|---|---|
| Prostate | CWR22 | Y | Y |
| | WISH-PC2 | N | N |
| Lymph node metastases | LNCaP | Y | Y |
| | C42 | Y | Y |
| | C42b | Y | Y |
| | LuCaP 23.1 | Y | Y |
| | LuCaP 23.8 | Y | Y |
| | LuCaP 35 | Y | Y |
| | LuCaP 49 | Y | Y |
| | LAPC-4 | Y | Y |
| Bone metastases | PC-3 | N | N |
| | MDA PCa 2a | Y | Y |
| | MDA PCa 2b | Y | Y |
| | LAPC-9 | Y | Y |
| | VCaP | Y | Y |
| Brain metastases | DU145 | N | N |
| | DUCaP | Y | Y |
| Liver metastases | LuCaP 23.12 | Y | Y |

oncological treatment becomes feasible. For example, trastuzumab in addition to standard chemotherapy results in improved survival in the 30 % of patients with HER-2 positive breast cancer [8]. In one clinical trial in PCa, a biopsy of a metastatic lesion is taken and the level of androgen receptor activity quantified; those with high levels of AR activity are treated with the antiandrogen nilutamide, while those with low AR activity are treated with the anti-Src agent dasatinib (NCT00918385). Because of the heterogeneity of PCas and the ability of tumor cells to adapt to altered cellular conditions, combination therapy is of great interest in PCa, and synergistic drug effects are sought.

## Cellular Processes of Importance in PCa

### Survival/Apoptotic Regulators: PI3K/Akt/mTOR/PTEN

Key to mediating the effects of receptor signaling is the PI3K-Akt pathway. When activated by phosphorylation through tyrosine kinase activity at the receptor complex, PI3Ks promote the transfer of a phosphate group onto PIP2 (phosphatidylinositol-4,5 bisphosphate) to generate PIP3 (phosphatidylinositol-3,4,5 trisphosphate). In turn, PIP3 promotes activation of Akt by phosphorylation. Downstream targets of Akt, such as mTOR (mammalian target of Rapamycin), control critical processes such as growth, proliferation, apoptosis, nutrient response, glucose homeostasis, and DNA repair.

*PTEN* (phosphatase and tensin homolog) is a tumor suppressor gene (TSG) which codes for a lipid phosphatase that governs activity of the PI3K-Akt pathway by converting PIP3 to PIP2 [9]. *PTEN* knockout mice develop PIN and prostate adenocarcinoma [6]. *PTEN* deletion is also a marker of poor prognosis in humans and is frequently deleted in PCa and is expressed at low levels in 85 % of primary PCa [10].

There is accumulating evidence that the PI3K-Akt pathway contributes to CRPC by activating the androgen receptor and other androgen responsive genes [11]. PI3K/Akt/mTOR signaling is upregulated in 30–50 % of CaPs providing the rationale for targeting the PI3K/Akt pathway [12]. Inhibition of PI3K using agents such as wortmannin and LY294002 has been stifled by significant toxicity despite positive preclinical results [13]. This has led to the development of agents targeting mTOR, the downstream effector of this pathway. Rapamycin (also known as sirolimus) is the inhibitor of mTOR used in transplantation from which mTOR derives its name. In PCa, cell line and xenograft therapeutic potential has been shown when mTOR inhibitors are used in combination with Taxanes [13]. One small study using rapamycin in a small sample of patients demonstrated some antitumor activity [14]. Use of combined TKI and mTOR inhibition may negate unwanted activation of Akt in response to mTOR inhibition (Table 2.2).

Akt inhibitors such as perifosine are in development, and despite encouraging preclinical data, early clinical trial data suggest very limited activity in CRPC [15]. Celecoxib is a COX-2 inhibitor which also inhibits activation of Akt by phosphorylation in PCa cells and may be chemopreventative for PCa [16]. Further trials such as the MRC STAMPEDE trial will clarify the role of celecoxib in treating advanced PCa (Table 2.2).

**Table 2.2** Summary of the translational impact of molecular biology in prostate cancer in terms of recruitment into clinical trials based on preclinical results

| Target | | TKI/AB | Trial | Setting | Results |
|---|---|---|---|---|---|
| Histone deacetylase | | Vorinostat | NCT00330161 | CRPC monotherapy | Not yet available |
| | | | NCT00589472 | Presurgery with hormones | Not yet available |
| | | Panobinostat | NCT00667862 | CRPC monotherapy | Not yet available |
| | | | NCT00663832 | CRPC with prednisolone and docetaxel | Not yet available |
| | | | NCT00878436 | CRPC with bicalutamide | Not yet available |
| Clusterin | | OGX-011 | NCT00258388 | CRPC | Increased median overall survival vs docetaxel/prednisolone |
| mTOR | | RAD-001 | NCT00636090 | mCaP | Not yet available |
| | | Temsirolimus | NCT01020305 | CRPC | Not yet available |
| AKT | | Perifosine | NCT00060437 | mCRPC | Limited activity |
| | | | NCT00058214 | Recurrent PCa | Limited activity |
| | | Celecoxib | NCT00136487 | Biochemical recurrence | Slowed PSA velocity in 90, 25 % PSA response |
| Neuroendocrine differentiation | IL-6 | Octreotide | NCT00166725 | Advanced PCa | Not yet available |
| | | Sandostatin | NCT00510224 | Advanced PCa | Not yet available |
| | | CNTO 328 | NCT00433446 | mCaP | Not yet available |
| | | | NCT00401765 | | |
| Tyrosine kinase | EGFR | Gefitinib | NCT00241475 | CRPC | No activity |
| | | | NCT00265070 | Biochemical recurrence | |
| | | | NCT00025116 | | |
| | | | NCT00635856 | | |
| | HER-2,3,4 | Pertuzumab | NCT00058539 | Combination with docetaxel | >50 % PSA response |
| | VEGFR | Aflibercept Sunitinib, Bevacizumab | NCT00672594, NCT00329043 | Presurgery | Not yet available |
| | | | NCT00631527 | With radiotherapy | |
| | | | NCT00879619 | CRPC first line | |
| | | | NCT00137436 | | |
| | | | NCT00676650 | | |
| | | | NCT00550810 | CRPC second line | |
| | PDGFR | Imatinib | NCT00500110 | mCRPC with docetaxel | Several trials stopped early limited activity and toxicity |
| | | | NCT00861471 | | |
| | | | NCT00038194 | | |
| | | | NCT00251225 | | |
| | FGFR | TK1258 | NCT00831792 | CRPC | Not yet available |
| | IGF-1R | Figitumumab | NCT00313781 | Comb with prednisolone and docetaxel | Not yet available |
| | | *Cixutumumab* | NCT00683475 | 2nd line after docetaxel | Not yet available |
| | | | NCT00769795 | Presurgery, with hormones | Not yet available |
| | | | NCT00520481 | CRPC primary monotherapy | Not yet available |
| | | | NCT01026623 | mCaP with temsirolimus | Not yet available |
| Bone metastases | RANKL | Denosumab | NCT00321620 | mCaP | Not yet available |
| | Endothelin A | Atrasentan | NCT00036543 | CRPC monotherapy | Delayed disease progression |
| | | | NCT00134056 | CRPC combi with docetaxel and prednisolone | Not yet available |
| | | Zibotentan | NCT00626548 | Localized CRPC monotherapy | Not yet available |
| | | | NCT00554229 | Asymptomatic mCaP | Not yet available |
| | | | NCT00617669 | mCRPC with docetaxel | Not yet available |
| | SRC | Dasatinib | NCT00744497 | CRPC combi with docetaxel | Not yet available |
| | | Saracatinib | NCT00558272 | mCaP monotherapy versus zoledronic acid | Not yet available |

(continued)

**Table 2.2** (continued)

| Target | | TKI/AB | Trial | Setting | Results |
|---|---|---|---|---|---|
| Microtubules | | Ixabepilone | NCT00331344 | mCRPC with mitroxantrone | 31 % PSA response |
| DNA damage repair | PARP | ABT-888 | NCT01085422 | mCaP with temozolomide | Not yet available |
| | | Olaparib | NCT01078662 | Patients with BRCA mutation | Not yet available |

*mCaP* metastatic prostate cancer, *PSA* response = decrease in PSA to less than 50 % of baseline

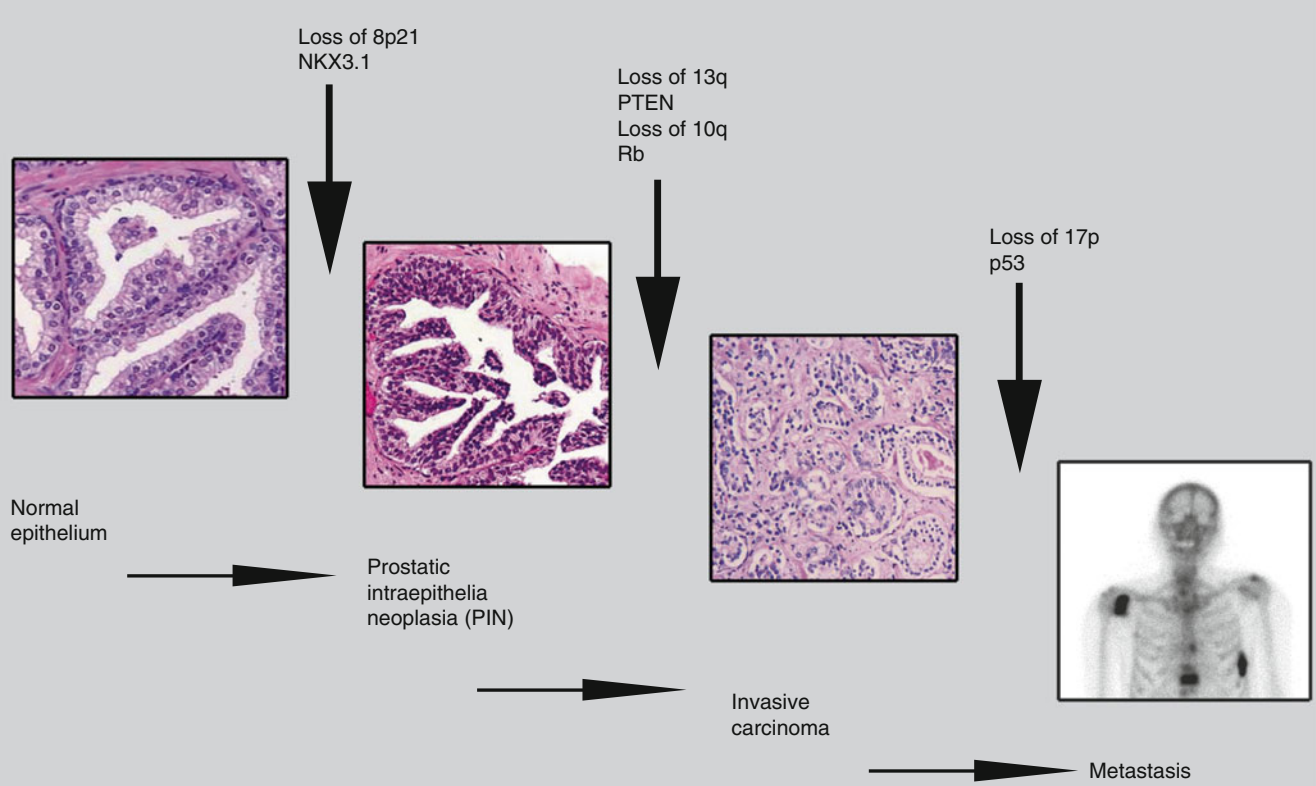


**Fig. 2.2** Pathway for progression in human prostate cancer. Loss of particular chromosomal regions with loss of function of candidate TSGs is associated with stepwise progression from normal epithelium to metastatic prostate cancer

## NKX3.1

The transcription factor NKX3.1 is a putative TSG in PCa. Loss of NKX3.1 protein expression is a common finding in human PCa and PIN. Expression of NKX3.1 precedes formation of the prostatic bud at the urogenital sinus by 2 days and is expressed in the areas where the buds appear suggesting a role in differentiation of the urogenital sinus to form the prostate gland during embryogenesis. Targeted gene disruption of NKX3.1 results in abnormal prostate duct morphology. NKX3.1 mutant mice develop PIN-like lesions that closely resemble human PIN, perhaps due to haploinsufficiency (where loss of a gene copy from one chromosome results in a decrease in the amount of gene product, enough to affect the organisms phenotype, rather than loss of both copies where the gene product is completely absent) [17].

PIN (which is thought to be a precursor to PCa) and early prostate cancer are associated with loss of specific regions of the short arm of chromosome 8 (8p) in up to 80 % of cases [18]. This leads to the hypothesis that this region might encode for a TSG, the loss of which promotes carcinogenesis. This region codes for NKX3.1 and no other known TSGs suggesting that NKX3.1 is an important TSG in early PCa [19].

Loss of chromosome 10q is also frequently seen in prostate cancer [20]. This loss is seen in early prostate cancer more commonly than PIN. *PTEN* maps to 10q23. It is thought that sequential loss of TSGs results in development of cancer that behaves in a progressively more aggressive fashion leading to invasion and metastasis when key TSGs are lost. Later mutations frequently seen in advanced PCa are loss of 13q (which contains the retinoblastoma TSG) and later 17p (which contains p53). Progression of the cancer toward increasingly aggressive behavior corresponds to loss of particular TSGs. This can be represented graphically in a so-called Vogelgram, after Vogelstein the geneticist who popularized the type of diagram shown in Fig. 2.2 [21].

## p53 and Cell-Cycle Regulation

Protein 53 (p53) is encoded by the *TP53* gene in humans and regulates the cell cycle and functions as a tumor suppressor. p53 suppresses carcinogenesis by activating DNA repair proteins when DNA has sustained damage, inducing growth arrest by holding the cell cycle at the G1/S regulation point, allowing DNA repair proteins to fix the damage. It can also initiate apoptosis, if DNA damage proves to be irreparable. p53 mutations are uncommon in early PCa, while in metastatic tumors, loss of p53 is frequently seen [22]. Preclinical work proceeds to attempt to discover compounds that exploit the p53 pathway by either seeking targets and compounds that cause cell death in cells with *TP53* mutations or by looking for activators of the p53 response which do not act by causing DNA damage [23].

MDM2 regulates p53 activity by promoting its degradation and limiting its transcriptional activity and is upregulated frequently in PCa [24]. This can lead to deregulated p53 activity in PCa. It may be possible to inhibit this interaction therapeutically. Small molecular MDM2 inhibitors, such as nutlin-3, have shown promise when used in LNCaP xenografts [25]. This drug also suppresses androgen receptor signaling [26]. Antisense MDM2 oligonucleotides have been shown to enhance the cytotoxic effect of androgen deprivation and radiation in PCa cell lines [27].

## Telomerase

Telomerase is an enzyme which adds repeated sequences of DNA (TTAGGG in humans) to the ends of chromosomes forming telomeres which play a critical role in the maintenance of genomic stability [28]. During replication, in which the end sequences of the chromosomes are most vulnerable to loss, only the telomeres capping the ends of the chromosomes are lost without adverse effect to the organism. Telomerase is composed of a ribonucleoprotein complex with RNA template and human telomerase reverse transcriptase (coded by the *hTERT* gene) components. In adults, telomerase expression is confined to germ line and regenerating tissues [29]. Activation of telomerase to maintain telomeres is required for self-renewal and proliferative expansion of a number of cell types, including stem cells, activated lymphocytes, and cancerous cells. Human telomerase is not usually active in benign mature tissues but is highly active in more than 85 % of primary cancers [29].

In cell lines and mouse xenografts, androgen deprivation leads to a decrease in *hTERT* expression, followed by a decrease in telomerase activity, which can be reversed by androgen administration demonstrating that the *hTERT* gene is regulated by androgens in human PCa cells [30]. The androgen-mediated repression of *hTERT* is abrogated in LNCaP cells which expresses a mutant AR (T877A), a mutation frequently occurring in PCa in vivo [31]. This suggests a possible mechanism of aberrant *hTERT* activity causing increased telomerase activity in PCa.

Telomerase inhibition in mouse xenograft models of PCa has been shown to lower PSA expression and increased fibrosis and apoptosis in telomerase inhibitor-treated cancers [18]. Using specific surface markers, cancer stem cells from several PCa cell lines with increased telomerase activity have been identified. Imetelstat sodium (GRN163L) is a new telomerase antagonist that is currently in phase II clinical trials for hematological and lung malignancies. When treated with GRN163L, PCa cell lines showed shortening of telomere length to a length comparable to non-stem cell cancer cells [32].

## Chaperones, Heat Shock Proteins, and Clusterin

Chaperones are proteins that assist the non-covalent folding or unfolding and the assembly or disassembly of other macromolecular structures and prevention of unwanted protein aggregation. Some of these chaperones are heat shock proteins (HSPs). HSPs are expressed when cells are exposed to elevated temperatures or other stress [33]. HSP60, HSP70, and HSP90 (the most widely studied HSPs) refer to families of heat shock proteins of 60, 70, and 90 kDa in size, respectively.

HSP 90 is vital in stabilizing the androgen receptor preventing its degradation. HSP 90 binding is ATP dependent. Small molecule inhibitors of histone deacetylase (HDAC) such as vorinostat and panobinostat can also result in the loss of HSP90 ATP-binding activity through acetylation resulting in degradation of the androgen receptor in PCa cell lines [34]. HDAC inhibitors block the AR-mediated transcriptional activation of many genes, including the *TMPRSS2* gene [35] (Table 2.2).

Gamitrinibs are a class of small molecules that inhibit the HSP 90 that is found within mitochondria (namely, TRAP-1). Systemic administration of Gamitrinibs to xenograft-bearing mice is well tolerated and inhibits tumor growth [36]. TRAP-1 is highly expressed in both high-grade human PCa lesions and mouse models of PCa but not in benign or normal prostate tissue. Treatment with Gamitrinibs results in PCa cell death but not death of benign prostate cells [37].

Clusterin (apolipoprotein J) is a 75–80 kDa, stress-induced chaperone protein associated with the clearance of cellular debris and apoptosis [38]. Clusterin overexpression is demonstrated in PCs at low levels in hormone-naïve tissue but significantly increased levels after castration [39]. Clusterin levels correlate to grade of PCa and may predict biochemical recurrence following radical prostatectomy [40] (Table 2.2).

## Autophagy (or Autophagocytosis)

Autophagy is a process whereby the cells' own components are broken down and the resulting elements are recycled. It has an important homeostatic function, maintaining protein and organelle quality control and preventing the accumulation of polyubiquitinated and aggregated proteins [41].

Various mechanisms of autophagy have been described, but all involve the degradation of intracellular components via the lysosome. The process of autophagy and its role in PCa are far from clear. Autophagy may halt the progression of some cancers [42]. The context in which autophagy occurs determines whether it enables cells to survive or enhances their death and depends upon the type of stimulus, nutrient availability, organism development, and apoptotic status.

Autophagy is the subject of much interest at present in the pathogenesis as well as the treatment of cancer [43]. Central to regulation of autophagy are the PI3K/Akt/mTOR pathway, members of the Bcl-2 family, p53, and death-associated protein kinases (DAPK) . Prostate cancer cells show impaired autophagy, due to either loss of the essential autophagy gene *beclin1* or activation of mTOR through the PI3K/Akt pathway [44].

## Cancer Cell Metabolism

Cancer cells metabolize glucose predominately by glycolysis rather than oxidative phosphorylation. This is known as the "Warburg effect" [45]. Cancer cells often have glycolytic rates that are up to 200 times higher than those of their normal tissues of origin even if oxygen is plentiful. Anaerobic glycolysis generates only 2 ATP molecules per molecule of glucose, whereas oxidative phosphorylation yields 36 ATP molecules. The cancer cells' environment is relatively hostile with limited blood supply, oxygen, and nutrient availability. This coupled with the cancer cells deranged autophagy, high metabolic demand, and inefficient glucose metabolism renders them frail, particularly where glucose metabolism is concerned. Inhibition of glycolysis through drugs such as 2-deoxyglucose (2DG) or oxamate exploits this fragility. Recently, 2DG has been shown to induce cytotoxicity in PCa-3 and LNCaP cells [46]. When 2DG is combined with metformin in LNCaP cells, synergistic induction of apoptosis results [47]. In a recent small clinical study 2DG, 5/6 patients had positron emission tomography (PET)-detectable decrease in tumor signal using the marker fludeoxyglucose (FDG) suggesting a need for further study [48]. Work using LNCaP xenografts has demonstrated an effect on survival resulting from no carbohydrate ketogenic diet which has an effect on IGF and insulin levels [49].

## Neuroendocrine Differentiation

Neuroendocrine (NE) cells are found in benign and malignant tissue. They are characterized by expression of the NE markers chromogranin A (ChrA) and neuron-specific enolase (NSE) and their particular neuron-like morphology which includes the presence of dendrites. They are found to varying degrees in PCa. Focal NE differentiation represents a common feature of PCa occurring in 30–100 % of the cases [50]. Pure NE cell PCa is very rare (<0.1 %) but exceptionally aggressive (35 % 2 year survival rate) [51].

NE cancer cells seem to be important in determining the rate of growth of prostate cancer cells. Work using mouse xenografts and transgenic mice has shown that tumor progression is more rapid when the number of cells with NE characteristics is increased [52]. Implantation of mouse NE prostate tumor in the flank of one side of castrated immunodeficient mice promotes growth of human PCa cell line tumor implanted in the opposite side. NE tumor cells also promote metastasis of LNCaP cell line xenografts [33]. This suggests that the NE component of the developing PCa produces factors able to stimulate growth. Factors produced by the NE cells which may be responsible for this effect include peptides, hormones, and growth factors. They also produce survivin, which inhibits apoptosis of cancer cells, and VEGF which stimulates the neighboring prostate cancer epithelial cells [53].

It is thought that blocking NE function and or NE differentiation might prolong the period of androgen sensitivity [34]. Somatostatin antagonists have been shown to inhibit tumor growth in preclinical models [35]. Interleukin 6 (IL-6) is a cytokine implicated in stimulating neuroendocrine differentiation. IL-6 inhibition has shown interesting results on tumor progression in preclinical models [54] (Table 2.2).

## Splice Variants of the Androgen Receptor

It is known that several alternative splice forms of the androgen receptor exist and that these variants have different structures and different levels of constitutional activity [55]. Overexpression of abnormal splice variants has been shown to be associated with more rapid disease recurrence after radical prostatectomy [56]. Abnormal splice variants are not expressed in normal prostate epithelium and rarely in primary PCa. It is thought that constitutively active splice variants of the androgen receptor play a role in the development of castrate-resistant growth in PCa [57].

## Microtubules and Chemotherapy

Microtubules are polymers of tubulin that form part of the cytoskeleton (see Fig. 2.3). They have a diameter of 25 nm

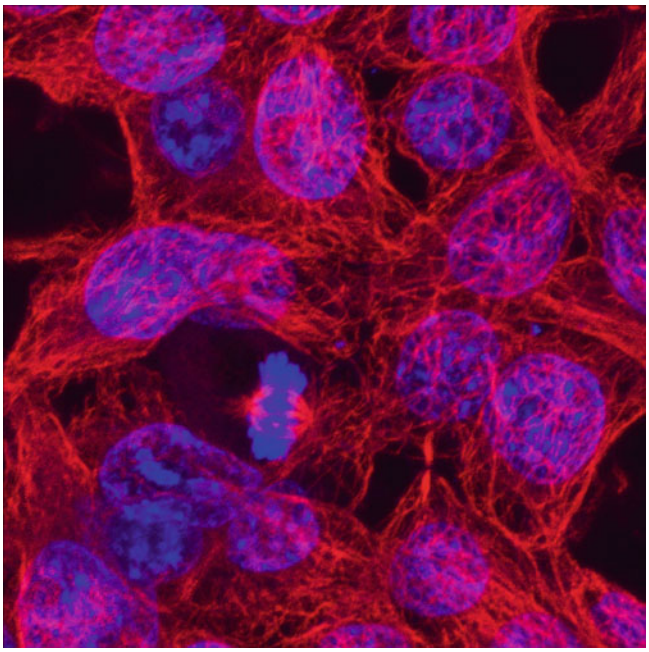

**Fig. 2.3** Human embryonic kidney HEK293 cells stained for alpha-tubulin (*red*) and DNA (*blue*). The mitotic cell to the lower left side of the center of the picture (with the condensed, "sausage-like" DNA) is easily seen. All other cells are in interphase (Reproduced with kind permission from Joana Borlido)

and length varying from 200 nm to 25 μm and are involved in many cellular processes including mitosis, cytokinesis, and vesicular transport [58].

Mitoxantrone is a type II topoisomerase inhibitor that disrupts DNA synthesis and repair. It was the first-line chemotherapeutic agent for CRPC until two clinical trials demonstrated a small but significant improvement in survival with the taxane Docetaxel [59, 60].The taxanes were initially isolated from plants of the genus Taxus (yews) and are now synthesized artificially. Taxanes include paclitaxel (Bristol-Myers Squibb), docetaxel (Sanofi-Aventis), and cabazitaxel (Sanofi-Aventis). Docetaxel is the standard of care in CRPC in men who have good performance status. The principal mechanism of the taxane class of drugs is disruption of microtubule function by binding to the β-tubulin subunit thereby inhibiting cell division.

Cabazitaxel is a novel taxane drug. It has been shown to double median progression-free survival from 1.4 to 2.8 months when compared with mitoxantrone therapy after failed docetaxel chemotherapy in a recent phase three trial [61].

Resistance to taxane chemotherapy is thought to occur due to the effects of ATP-binding cassette transporters (ABC-transporter) [62]. ABC-B1 (also known as P-glycoprotein or MDR-1) is responsible for the majority of systemic clearance of Docetaxel and is expressed in many normal tissues including liver, endothelial cells of the blood-brain barrier, and hematopoietic cells where it prevents toxicity by controlling distribution of the drug [63]. Hepatic ABC-B1 transports docetaxel into the biliary duct for clearance. Expression of ABC-B1 in CaPs is associated with high Gleason grade tumors which are chemoresistant and have a poor prognosis [64]. Polymorphism of the ABC-B1 gene rather than merely level of expression is linked with docetaxel-induced toxicity and overall survival [65].

A new class of microtubule stabilizers is the epothilones (Ixabepilone—Bristol-Myers Squibb, Sagopilone—Bayer, and Patupilone—Novartis). These drugs have a distinct mechanism of action to the taxanes and low susceptibility to drug resistance [66] (Table 2.2).

### DNA Damage Repair

DNA is damaged frequently during metabolic activity (producing reactive oxygen species) and through the effects of environmental factors such as radiation, chemical, and viruses. It is estimated that between 1,000 and 1,000,000 molecular lesions occur per cell per day [67]. While this only constitutes a small proportion of the genomes six billion bases (approx) it is important that this damage is repaired fully and rapidly in order to prevent carcinogenic mutation. A large number of enzymes with specific mechanisms to identify or repair DNA are described. When a cell's DNA is damaged beyond repair, the cell either undergoes apoptosis or enters a state of permanent dormancy called senescence. Occasionally, the DNA repair mechanism fails, and a mutation develops which renders the control of a cell's growth and proliferation uncontrolled. This mutation may provide the cell with a growth/survival advantage leading to development of cancer. A number of checkpoints in the cell cycle exist to ensure that cells with excessive damage to their DNA do not replicate.

Inherited mutations that effect DNA repair genes are associated with cancer, for example, the BRCA1 and BRCA2 mutations. Poly(ADP-ribose)polymerase-1 (PARP-1) is a protein that is important for repairing single-strand breaks. Several forms of cancer are more dependent on PARP than regular cells, making PARP an attractive target for chemotherapeutic cancer therapy (Table 2.2). In addition, radiotherapy causes DNA damage, and radiosensitization of tumors using PARP inhibitors holds some promise [68].

## Signaling Pathways of Importance in PCa

### Tyrosine Kinases

Kinase enzymes are a family of around 500 enzymes in the human that catalyze the transfer of a phosphoryl group from a nucleotide triphosphate donor (e.g., ATP) to an acceptor

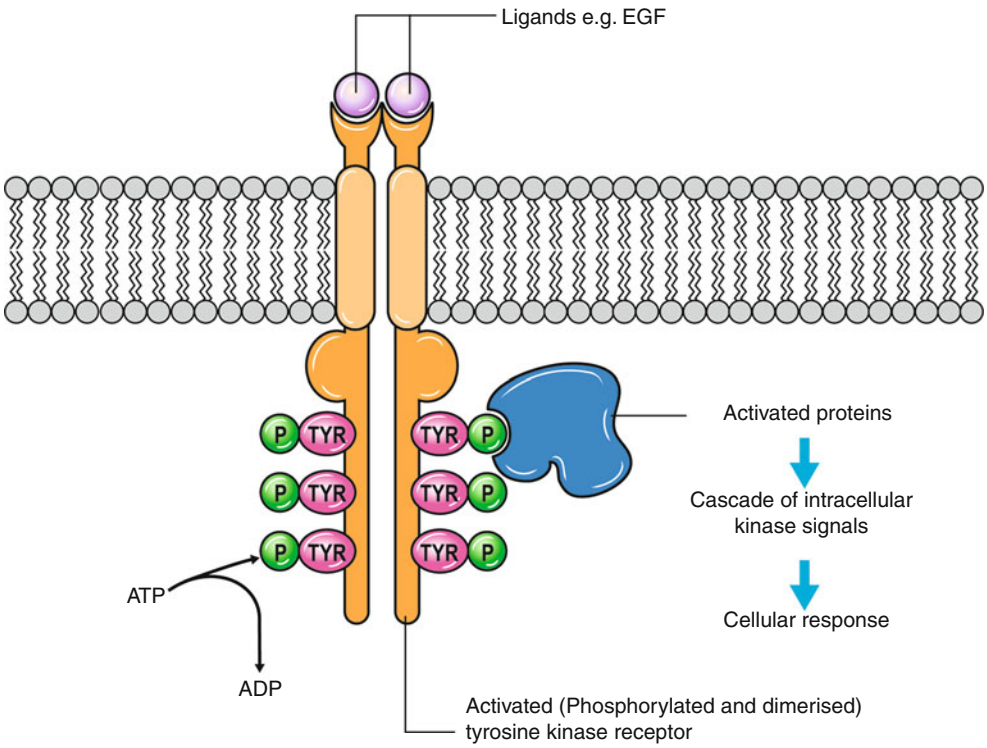


**Fig. 2.4** Cartoon depicting the mechanism by which receptor tyrosine kinases are activated. Ligand binding to the receptor causes dimerization. Phosphorylation of the tyrosine moieties is catalyzed by the receptor itself and results in activation of a cascade of kinase proteins which bring about the cellular response to ligand binding

molecule. More specifically, tyrosine kinases phosphorylate tyrosine moieties; other kinases phosphorylate serine/threonine residues and are named accordingly. Tyrosine kinases control mitogenic signals in human cells, while other kinases are involved with other intracellular signals. Phosphorylation of the target tyrosine moiety brings about a change in the structure and function of the target protein leading to signal transduction effecting a wide range of cellular activity including enzyme activity, subcellular localization, and interaction between molecules.

Receptor tyrosine kinases such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR) are membrane bound and function in transmembrane signaling. Binding of ligand to tyrosine kinase receptor usually results in *dimerization* of two monomeric receptor kinases. Other tyrosine receptor kinases (e.g., the PDGFR) can form heterodimers with other similar but not identical kinases of the same subfamily, allowing a highly varied response to the extracellular signal. The active tyrosine kinase phosphorylates specific target proteins, which are often enzymes themselves. Figure 2.4 demonstrates the mechanism by which tyrosine kinases are activated. Mechanisms by which receptor tyrosine kinases are implicated in oncogenesis include gene mutation, chromosome translocation, or overexpression, all of which result in increased kinase activity with uncontrolled, ligand independent stimulation of growth of the cancer cells [69]. Tyrosine kinase inhibition has not proven effective as monotherapy in prostate cancer, and current focus is on use in combination with other treatment modalities (Table 2.2).

### Vascular Endothelial Growth Factor Receptor (VEGFR)

As a tumor grows, it requires development of a blood supply brought about by a number of factors, which are known to be of importance in PCa. These include VEGF, which signals through VEGF receptors VEGFR1 and 2. In the TRAMP mouse model, overexpression of VEGFR, especially VEGFR 2, has been linked to tumor progression. It is also overexpressed in human PCa. In castrate-resistant PCa, increased plasma VEGF correlates with poor prognosis and disease progression [70]. Three drugs targeting VEGF signaling have shown promise in clinical trials. Aflibercept is a fusion of the extracellular portion of the VEGFR with an immunoglobulin. Sunitinib is a multitarget tyrosine kinase inhibitor (TKI) with activity at the VEGFR. Bevacizumab is a monoclonal antibody directed against VEGF-A (Table 2.2).

### Endothelial Growth Factor Receptor (EGFR) Family

The confusingly named ErbB family of receptor tyrosine kinases includes EGFR (ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). Both EGFR and ErbB2 have important roles in cell growth, differentiation, and motility mediated by downstream signaling pathways such as PI3K/Akt. In humans, overexpression of EGFR is an indicator of poor prognosis in PCa [71]. It is highly expressed in primary

PCa and metastases [72]. Overexpression is associated with progression from androgen dependent to independent disease [73].

Therapeutic agents with anti-EGFR activity include monoclonal antibodies and small-molecule tyrosine kinase inhibitors (TKIs). Erlotinib and gefitinib are TKIs which act primarily at EGFR. Gefitinib has been shown to suppress growth of PCa cell lines and in PCa cell line xenografts, where it also slows the rate of metastasis [74] (Table 2.2).

The role of HER-2 is far from clear in PCa. HER-2 overexpression is seen in 20 % of hormone-naive PCs and 67 % of hormone-treated tumors [75]. Despite this, trastuzumab, a monoclonal antibody against HER-2, has not thus far been proven to be of any benefit in CRPC [76]. Activation of HER-2 receptor by tyrosine phosphorylation (rather than HER-2 overexpression itself) has been implicated based on preclinical data, as a mechanism of castrate-resistant growth in PCa [77]. Lapatinib and PD168393 are TKIs, which have activity at EGFR and HER-2 receptors. PD168393 has been shown to potentiate the effect of taxane chemotherapy in castrate-resistant prostate cancer cell lines [78].

HER2 is an orphan receptor, and dimerization with HER3 has been shown to stimulate androgen-dependent signaling in the absence of androgen [79]. Pertuzumab is an antibody which inhibits dimerization of HER-2 with HER-3 or HER-4 is in clinical trials (Table 2.2). Agents to inhibit HER-3, which is necessary for EGFR and HER-2 signaling and is felt to have a role interacting with PI3K/Akt signaling, are in development.

### Platelet-Derived Growth Factor Receptor (PDGFR)

PDGFR is important in autocrine stimulation of tumor cells, regulation of stromal fibroblasts, as well as tumor angiogenesis [80]. Upon PDGF binding, the alpha and beta receptor subunits dimerize; these dimerized receptors have been shown to be expressed in the majority of metastatic (80 %) and even more primary (88 %) PCa tumors. The high level of PDGFR expression in both primary and metastatic PCa implies that it might be a suitable target for early treatment [81]. SU101 is a potent inhibitor of the PDGFR and has been trialed in a phase two study (Table 2.2).

Imatinib (Novartis) is an inhibitor of PDGFR as well as BCR-ABL tyrosine kinase. Clinical trials of imatinib for PCa showed limited efficacy with significant toxicity necessitating early closure of trials (Table 2.2). In mouse models of metastatic PCa, a synergistic effect between paclitaxel and imatinib has been demonstrated [82].

### FGFR (Fibroblast Growth Factor Receptor)

This receptor family consists of four receptors FGFR1, FGFR2, FGFR3, and FGFR4. Several of the 22 ligands for the FGFRs are overexpressed in PCa [83]. Stimulation of the FGFRs results in a wide variety of effects resulting in mitogenic, regulatory, morphological, and endocrine effects. They are "promiscuous" in that their actions exert multiple actions on multiple cell types [84]. One important function of FGF1 and FGF2 is the promotion of endothelial cell proliferation and the physical organization of endothelial cells into tube-like structures in angiogenesis. FGF1 and FGF2 are more potent angiogenic factors than VEGF or PDGF [85]. FGF signaling through activation of FGFR1-4 leads to downstream signaling of multiple pathways including MAPK and PI3K pathways. FGFR4 overexpression is strongly associated with high-grade disease and decreased survival [86]. Interference of FGF signaling in PCa cell lines using small interfering RNA molecules (siRNA) to target FGFR4 in PCa causes impairment of invasion and proliferation [87]. SU5402, a TKI which inhibits FGFR, has been used to decrease LNCaP xenograft tumor growth [88]. TK1258 (aka CHIR258) is the first TKI targeting FGFR activity to be studied in patients (Table 2.2).

### IGF-1R (Insulin-Like Growth Factor 1 Receptor)

The insulin-like growth factor pathway involves two growth factors IGF-1 and -2 and two transmembrane receptors (IGF-1R and IGF-2R). IGFs stimulate proliferation and differentiation and inhibit apoptosis. IGF-1 is the most potent natural activator of the Akt signaling pathway. Elevated levels of IGF-1 have been linked with PCa risk as well as aggressive cancer phenotype [89]. IGF-1R, IGF-1, and IGF-2 have been reported as being overexpressed in primary PCa, with increased levels in advanced disease [90]. Preclinical work on cell lines has implicated IGF-1 activity in castrate resistance and invasiveness [91, 92]. The human antibody IMC-A12 against IGF-1R has been shown to enhance the antitumor effects of castration and cytotoxic drugs in prostate xenograft models providing rationale for clinical trials targeting the IGF-R axis [93, 94]. Figitumumab and cixutumumab are humanized monoclonal antibodies against IGF-1R and are currently in clinical trials (Table 2.2).

## Biomarkers in PCa

### Alpha-Methylacyl-CoA Racemase (AMACR)

This biomarker was identified by comparison of cDNA from PCa and benign prostate tissue [95]. This resulted in the identification of P504S, which was selectively overexpressed in PCa with minimal expression in benign prostate tissue and non-prostate tissue. Immunohistochemical staining using rabbit monoclonal antibodies generated against P504S showed positive staining in PCa and negative staining in benign prostate tissue. The full-length 1,621 base pair sequence for P504S was cloned and found to encode human

AMACR (Genbank accession number 4204097), an enzyme with a key role in the metabolism of fatty acids and bile acid intermediates. Besides being produced in PCa tissue, the enzyme is encoded by a gene located in a region (5p13.3) that contains polymorphisms associated with PCa [96]. A meta-analysis of microarray data showed with high confidence that AMACR is upregulated in PCa [97]. The role of AMACR in PCa is unclear. Men who consume diets rich in dairy products and red meat are at increased risk for developing PCa, while these foods are the major dietary sources of the branched-chain fatty acid substrates of AMACR [98] suggesting that AMACR along with dietary factors might be important in PCa progression. Use of AMACR to identify aggressive tumors is limited. Recently, decreased AMACR expression has been shown to predict biochemical recurrence after radical prostatectomy and death due to PCa [99].

Currently, staining for AMACR is used to assist the histopathologist in distinguishing benign from malignant tissue on H&E staining of biopsies. It is particularly useful in diagnosing the small clusters of malignant cells that may either represent an under-sampled cancer or a very small focus of cancer. False positives do occur with HGPIN and occasionally benign prostate tissue. Four studies have evaluated the accuracy of immunohistochemistry using AMACR to identify PCa. Overall, they show sensitivities that range from 82 to 100 % and specificities ranging from 79 to 100 % [100].

Other applications of AMACR have been explored. Circulating concentrations of AMACR mRNA in serum and urine have been measured by reverse transcription-PCR analysis [101]. Increased concentrations of autoantibodies to AMACR were able to distinguish PCa patients from healthy individuals in the PSA interval of 4–10 g/L with a sensitivity of 62 % and a specificity of 72 % [102]. Studies to fully elucidate the potential uses of AMACR as a biomarker for PCa are in progress.

### Fusion Genes *TMPRSS2-ETS*

A fusion gene is a hybrid gene formed from two previously separate genes. It can occur as the result of a translocation, deletion, or chromosomal inversion. Often, fusion genes are oncogenic, where fusion produces a gene product with a new or different function from the two fusion partners or where fusion of a proto-oncogene to a promoter renders it oncogenic [103].

The *TMPRSS2* gene encodes the enzyme transmembrane protease, serine 2 which is a serine protease [104]. The biological function of this gene is unknown. Groundbreaking work by Tomlins et al. identified the recurrent fusion of the *TMPRSS2* to ETS (E twenty-six) family transcription factor genes. *TMPRSS2* is fused to *ERG* and *ETV1* in 55 and 27 % of PCa specimens, respectively[189]. *TMPRSS2* gene expression is governed by androgens in the prostate. ETS families are proto-oncogenes, and it has been postulated that fusion of *TMPRSS2* with an ETS proto-oncogene leads to increased expression of ETS in response to androgen.

The *TMPRSS2* and *ERG* oncogenes are situated on chromosome 21 and are very close. Fusion usually results from a deletion of the intervening short polynucleotide sequence. Figure 2.5 demonstrates the mechanism by which the fusion protein is formed and functions. There are approx 20 different variants of *TMPRSS-ERG* [61]. Study of *TMPRSS2*-ETS fusion products demonstrates the heterogeneity of PCs. Study of multifocal tumors revealed different fusion products in different tumors and different foci from the same tumor perhaps indicating that multifocal tumors develop from different origins [105, 106].

Attempts to utilize *TMPRSS2-ERG* detection to aid diagnosis using RT-PCR and southern blotting had a specificity of 93 % but was limited by a sensitivity of only 37 % [107]. *TMPRSS2* expression might also be of use as a prognostic marker having been found to correlate with PSA level, pathological stage, and Gleason score [108]. Cohort studies looking at PCa patients treated conservatively showed that *TMPRSS2*:*ERG* gene fusions were associated with a poor prognosis [109]. Recent work has linked *TMPRSS2*:*ERG* detection with recurrence after radical prostatectomy [110]. *TMPRSS2*:*ERG* status does not appear to predict response to hormone therapy despite apparent androgen-dependent *TMPRSS2* expression [111].

## Bone Homeostasis and the Molecular Biology of Metastatic PCa

Bone homeostasis is important in prostate cancer for a number of reasons. Firstly, metastasis to bone is the commonest site of progression of PCa, particularly the lumbosacral vertebrae. Bone metastases, despite appearing to be sclerotic on imaging, are characterized by increased bone turnover with increased osteoclastic activity [112]. Secondly, weakened bone at the site of metastasis may fracture, and either this or formation of bulky tumor with inherent inflammation in the vertebrae may lead to spinal cord compression which is severely disabling. Thirdly, castration (medical or surgical) for prostate cancer results in osteoporosis in a proportion of men for whom bisphosphonate therapy is indicated [113]. For these reasons, there is much interest in better elucidating the molecular mechanisms underpinning bone health in prostate cancer.

### RANKL (Receptor Activator for Nuclear Factor κ-B Ligand)

RANKL is important in bone metabolism. It binds to RANK to stimulate osteoclast proliferation and differentiation and

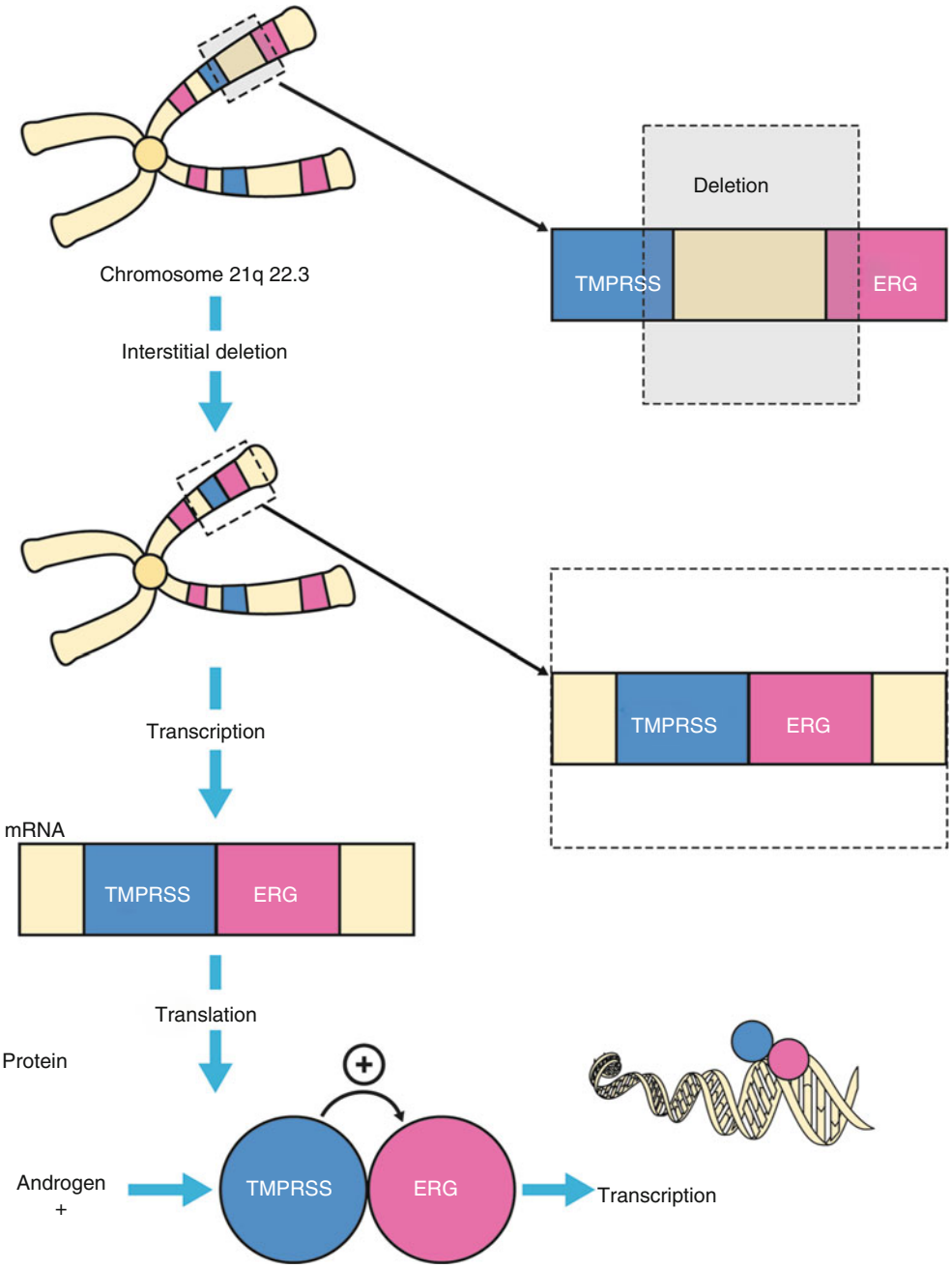


**Fig. 2.5** Mechanism of formation and consequences of *TMPRSS-ERG* gene fusion. An interstitial deletion at the short arm of chromosome 21 results in apposition of two genes *TMPRSS-2* and *ERG*. Transcription of the resultant DNA sequence into mRNA and translation of this into a sequence of amino acids generate a fusion protein composed of the *TMPRSS-2* and *ERG* gene products. The *TMPRSS-2* product is androgen responsive. The *ERG* product is a transcription factor. Activation of the *TMPRSS-2* moiety results in activation of the *ERG* transcription factor with consequent changes in target gene expression

inhibits apoptosis promoting bone resorption. Denosumab is a humanized monoclonal antibody against RANKL which limits bone resorption thereby and has been shown to reduce markers of bone turnover in patients with metastases from PCa [114] (Table 2.2).

## The Endothelins (ETs)

The ETs are a family of three peptides: ET-1, -2, and, -3. ET-1 mediates the osteoblastic response of bone to metastatic PCa leading to increased bone deposition in sclerotic bone lesions. ET-1 production is stimulated by osteoblasts, which are in turn stimulated by ET-1 in a cyclical fashion. ET-1 preferentially binds to the receptor ET-A, while ET-1 binding to ET-B has antagonistic effects. Thus, the differential expression and activation of ET-A and ET-B receptors in tissues determines the effect of the ET-1 [115]. ET-1 activates ET-A triggering several signaling pathways resulting in cellular growth and mitogenesis [116]. ET-1 also inhibits apoptosis via activation of PI3-K and Akt pathways. When ET-A receptor antagonist is applied to cells, the anti-apoptotic effects of ET-1 are reversed, implicating the ET-1/ET-A interaction as important in progression of PCa metastases in bone.

Atrasentan and zibotentan are highly selective inhibitors of the ET-A receptor currently being trialled (Table 2.2).

### Bisphosphonates (also called disphosphonates)

Bisphosphonates, such as zoledronic acid, palmidronate, and clodronate, inhibit resorption of bone by osteoclasts. They act by inhibiting activation of enzymes that utilize pyrophosphate (with which bisphosphonates are very similar structurally) [117]. Preclinical work suggests that bisphosphonates may play a role in immunomodulation and control of angiogenesis and have an antitumoral synergistic interaction with taxanes [118]. Bisphosphonates are increasingly used alongside specific anticancer treatments to prevent skeletal complications [119]. Zoledronic acid has been shown in a randomized trial to reduce skeletal-related events in PCa patients with metastases [120]. Zoledronic acid does not have a role in preventing metastasis [121].

### Src Family Kinases (SFKs)

Src was the first member of this family of tyrosine kinases to be identified. SFKs are proto-oncogenic and are not receptor bound. They interact with cytosolic, nuclear, and membrane proteins and modify these proteins by phosphorylating tyrosine residues to control migration, proliferation, adhesion, and differentiation. SFKs are involved in the downstream signal transduction of many receptors including EGFR, PDGFR, and VEGFR. SFKs are overexpressed in PCa cell lines and tissues, and inhibition of Src limits cell line proliferation [122]. Reduced cancer cell proliferation, invasion, and migration are seen following Src inhibition in mice models with increased survival [123]. Src/SFK inhibition therefore represents a potentially useful therapeutic strategy for patients with various stages of PCa.

Dasatinib is an agent with anti-Src activity. Trials in PCa using Dasatinib as a single agent failed to produce significant PSA responses; however, decreases in markers of bone turnover like alkaline phosphatase and urinary *N*-telopeptide were seen providing evidence of biological activity [122]. Other SRC inhibitors include saracatinib and bosutinib which both also have activity at another tyrosine kinase—Bcr-Abl. They have shown anti-PCa activity in preclinical studies and have been shown to block the RANKL stimulatory pathway in osteoclasts [124] (Table 2.2).

#### Conclusion

Significant investment in research into PCa is now yielding dividends in a better understanding of the molecular pathology of this disease. Early application of such research to human tissue samples is also making the findings more relevant to the disease itself. Human studies are a priority to confirm preclinical findings in terms of identifying new biomarkers and improving treatment of PCa. In order to take this forward, academic clinicians in urology, pathology, and medical oncology need to work together if we are to see the benefits that should come from this research over the next decade.

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# 3 Endocrine Mechanisms, Androgen Receptor and Carcinogenesis, and Hormone Escape

Kaustubh Datta and Donald J. Tindall

## Endocrine Mechanisms

Androgens are essential for prostatic development, growth, and function. They also regulate many physiological processes such as the development and maintenance of the immune and neural systems, determining gender-specific phenotypes associated with the male reproductive system and secondary male traits [1]. A connection between androgens and prostate cancer came with observations that eunuchs do not develop prostate cancer and that men who use androgens as anabolic agents or therapeutics develop prostate cancer at a higher rate [1, 2]. Although population-based case-control studies have failed to establish a clear association between prostate cancer risk and circulating sex hormones, a somewhat weak association between higher circulating testosterone and high-risk ethnic or racial groups has been observed [1]. Indeed, the best evidence for an androgen axis in prostate cancer is the significant clinical response that has been observed in patients with advanced-stage prostate cancer upon androgen ablation. This observation was first documented by Charles Huggins and Clarence Hodges in their landmark study in 1941 [3], which earned them the Nobel Prize in medicine in 1972.

The biosynthesis of androgen is a two-step process [4]. Testosterone, which is the main circulating form of androgen in men, is synthesized predominantly (95 %) by the leydig cells of the testes under the control of luteinizing hormone (LH), which is secreted by the anterior pituitary in a pulsatile manner. The secretion of LH is controlled by luteinizing hormone-releasing hormone (LHRH) or gonadotropin-releasing hormone (GnRH) of the hypothalamus. LH binds to its receptor on the membrane of Leydig cells and initiates a G-protein coupled signaling cascade and activation of adenylate cyclase. This event leads to increased intracellular formation of 3′5′-cyclic monophosphate (cAMP) and activation of protein kinase A. In the following, cholesterol is transferred to the inner mitochondrial membrane where P450scc/CYP11A1 converts cholesterol to pregnenolone. Pregnenolone is further converted to progesterone in the smooth endoplasmic reticulum by 3β-hydroxysteroid dehydrogenase (3β-HSD). In the next step, 17α-hydroxylase/C17-20 lyase (CYP17) converts progesterone to androstenedione, which is finally metabolized to testosterone by type 3 17β-hydroxysteroid dehydrogenase (17β-HSD3) [4]. High serum testosterone levels constitute a negative feedback mechanism by inhibiting LHRH release, thereby maintaining an optimum physiological concentration (Fig. 3.1).

A minor part of circulating testosterone (5–20 %) is synthesized by the adrenal glands along with androstenedione and dehydroepiandrosterone (DHEA), which also can be converted to testosterone in the prostate. All these androgens from the adrenal gland are secreted under the control of adrenocorticotropic hormone from the anterior pituitary, which is regulated by the corticotrophin-releasing factor from the hypothalamus [2, 4].

Serum testosterone exists as a complex with sex hormone-binding globulin (SHBG), albumin, and corticosteroid-binding globulin and, therefore, is not readily available as a free form. Only 2–3 % of total testosterone in circulation remains as free and available to target tissues [2].

Testosterone, which is taken up into prostate cells by passive diffusion, is converted into 5α-dihydrotestosterone (DHT) by 5-α-reductase enzymes. DHT (Fig. 3.2) has a higher affinity for the AR compared to testosterone and also dissociates more slowly from the AR [2]. It protects AR more efficiently than testosterone from proteolytic degradation and is, therefore, the primary androgen for AR-mediated growth and survival of normal, hyperplastic, and malignant prostate tissues. There are three isoforms of 5-α-reductases [1]. Isoform I expression increases in PCa relative to normal

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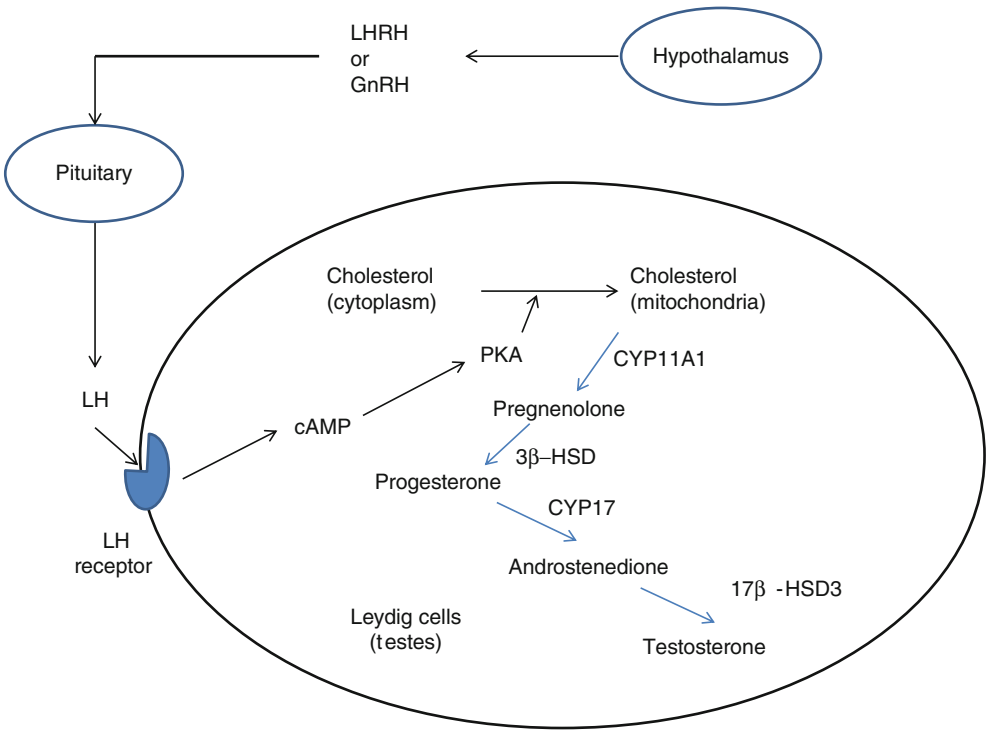


**Fig. 3.1** Biosynthesis of testosterone

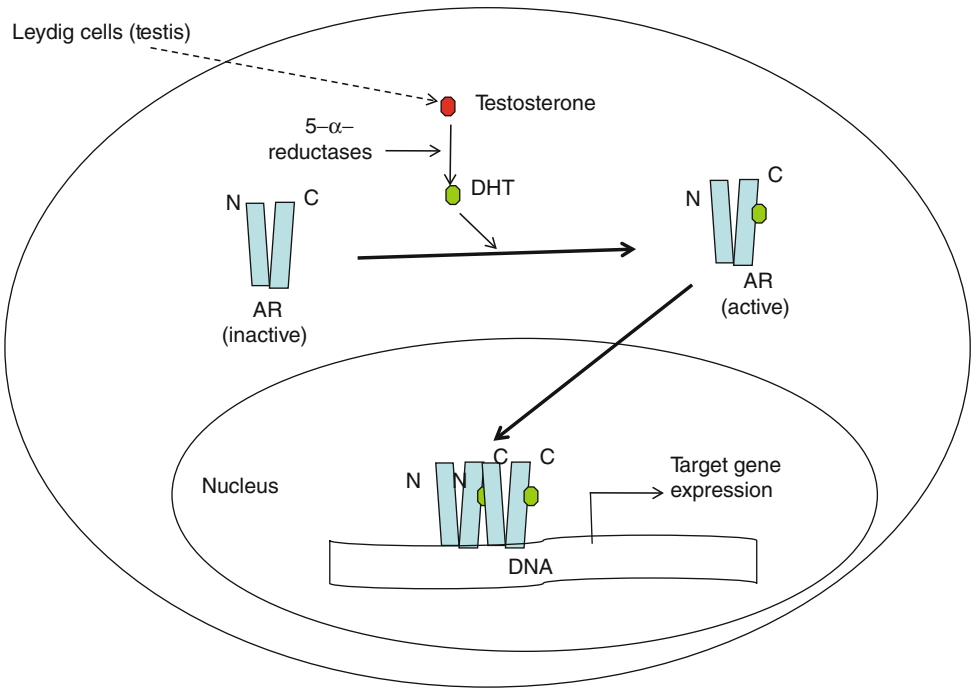


**Fig. 3.2** AR activation

prostate and BPH. Type II isoform is prevalent in prostate, seminal vesicles, and epididymis. It is also important for the growth of prostate cancer. Finasteride, which is a specific type II inhibitor, has been shown to significantly decrease the incidence of prostate cancer in the recent prostate cancer prevention trial (PCPT) [5]. Similar result was also observed in another recent trial known as reduction by dutasteride of prostate cancer events (REDUCE) where dutasteride, a 5-α-reductase inhibitor for both isoform I and II, was used [6–8]. Type III is detected mainly in castration-resistant

prostate cancer with insignificant expression in normal adult organs and, therefore, is suspected to play a role in the growth and progression of castration-resistant PCa. Epidemiologic evidence shows an elevated activity of 5-α-reductases among white and black men compared with men of Asian origin, suggesting a role in the increased incidence rates of PCa in these ethnic groups.

## Androgen Receptor and Prostate Carcinogenesis

### Androgen Receptor

Androgens act as intracellular ligands for the androgen receptor (AR) functioning as a transcription factor and transcribing a number of genes responsible for cell differentiation, proliferation, and survival. AR is expressed in all human organs apart from the spleen and bone marrow [9]. Loss or partial loss of AR function during male development leads to a condition termed androgen insensitivity syndrome (AIS) that is characterized by a female phenotype [10]. The androgen/AR axis regulates the expression of a number of prostatic enzymes that are secreted into the seminal fluid [9]. The best characterized among these include PSA, kallikrein 2, and prostatic acid phosphatase. There are also other androgen regulated genes involved in lipogenesis, cell cycle regulation, and cell survival [11]. The growth and survival of prostate luminal epithelial cells in the normal prostate are regulated by a paracrine effect of many growth factors secreted by the prostate stromal cells under the influence of the stromal androgen/AR signaling axis.

AR is a member of the steroid/thyroid receptor superfamily, in which all the members share basic structural and functional homology [9, 12–14]. AR in its unliganded state remains in the cytoplasm as a part of large heterocomplex. Several heat shock proteins, co-chaperones, and tetratricopeptide repeat proteins constitute this heterocomplex, which protect AR protein from irreversible aggregation and degradation [15]. These proteins also help keep the ligand-binding domain (LBD) of AR in a relatively stable, partially unfolded, and inactive state with a high affinity for androgen thereby prevents the premature activation of AR in the absence of androgen.

Androgen activates AR by binding to its C-terminal ligand-binding domain and inducing a conformational change in AR structure, which has several implications in its function. One such effect is the unmasking of the bipartite nuclear localization signal (NLS) sequences of AR, which facilitates entry of AR protein into the nucleus [16]. The NLS sequences of AR reside in the DNA-binding-domain (DBD) and hinge region (amino acids 625–671) and LBD (amino acid 722–805). Another remarkable AR conformation change upon ligand binding, which is crucial for AR function, takes place with intramolecular interactions between the AR N-terminal transactivation domain and the C-terminal LBD [17]. An FXXLF (F = phenylalanine, L = leucine, and X = any amino acid) motif in the AR N-terminal activation domain (NTD) facilitates this interaction as it specifically recognizes the activation function 2 (AF2) domain of the AR C-terminus. The N/C interaction prevents inappropriate coactivator interaction with AR before it binds to the AR responsive elements (AREs) of target genes.

Binding of the AR homodimer to a specific ARE of a gene involves cooperation between the AR DBD and LBD [9]. The DNA-binding domain of AR, like other nuclear receptor superfamily members, consists of two zinc fingers that provide the structural basis required for ARE recognition. The consensus ARE consists of a pair of 6 bp palindromic core sequence (5′-AGAACA-3′) separated by a spacer of three nucleotides. The second zinc finger loop enhances AR-DNA binding through interaction with the first loop. Sequences outside the DNA-binding domain also play a role in AR-DNA binding. In addition to canonical AREs, several noncanonical AR binding sites have been described [18]. AR binds with lower affinity to those noncanonical AR binding sites when compared to canonical AREs.

The AR NTD is highly disordered and possesses a molten-globular conformation [13, 19]. It contains activation function 1 (AF1), which promotes strong transcriptional activity [20]. Two major transactivation units present in AF1 are known as transactivation unit 1 (TAU1) (amino acids 142–485) and transactivation unit 5 (TAU5) (amino acids 351–528). TAU1 is considered the major transactivation domain that binds to basal transcription factors [19], transcriptional coactivators, and heat shock proteins [20]. The FxxLF motif also belongs to the AF1 domain and promotes the N/C interaction. The TAU5 region of AF1 is responsible for ligand-independent AR activity in castration-resistant prostate cancer cells. A WxxLF motif within TAU5 is sufficient to induce this ligand-independent activity [21].

Two polymorphic trinucleotide repeat segments within the AR NTD encode polyglutamine (amino acids ~58–78, nucleotide sequence CAG) and polyglycine tracts (amino acids ~449–472), which influence AR activity by regulating the N/C interaction [20]. Shortened trinucleotide repeat stretches result in increased AR activity and may be associated with prostate cancer predisposition [22].

A number of posttranslational modifications of AR can influence its function. One of the major posttranslational modifications of AR is phosphorylation. Most of the AR phosphorylation sites reside in the NTD [23]. AR phosphorylation has been related to growth and progression of prostate cancer under androgen-depleted conditions. Ubiquitination (both poly- and mono-), acetylation, and sumoylation are other important posttranslational modifications of AR and have been linked to the development and progression of prostate cancer [24–26].

Several coregulators interact with AR and enhance (coactivators) or reduce (co-repressors) AR transcriptional activity [27–31]. Coregulators modulate the chromatin structure surrounding the ARE, facilitating the DNA occupancy of the AR, and recruiting the basal transcriptional machinery such as RNA polymerase II. Coregulators can also promote AR posttranslational modifications, thereby modulating androgen/AR binding affinity, AR expression, AR stability, and AR nuclear translocation, thus making the AR competent for gene transcription [28]. Over 200 coregulators have been detected that exhibit a wide range of functions including histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases and demethylases, and protein scaffolds.

Co-repressor proteins usually possess a specific motif known as the co-repressor/nuclear receptor (CoRNR) box or LXXX IXXX I/L motif. This motif binds to the hydrophobic pocket of the ligand-binding domain and competes with co-activator binding to the AR [32]. Selective androgen receptor modulators (SARMs) function as antagonists by recruiting the N-CoR complex.

Recently, a mechanism for AR function independent of its transcriptional activity has been demonstrated. This non-genomic event is very rapid and activates signaling cascades such as the Src/Raf1/ERK, PI3K-AKT, and IL-6-STAT3 pathways located at the lipid rafts of the cell membrane [33, 34]. The functional significance of these non-genomic AR activities in prostate cancer remains unclear.

## AR Function in Androgen-Dependent Prostate Cancer

A majority of prostate tumors are dependent on androgen at initial diagnosis [14, 35, 36]. AR in prostate cancer cells promotes cellular proliferation. AR regulates the expression of cell cycle genes such as Skp2, cyclin D1, cycline A, p21, and p27 [11, 37, 38] and the activities of CDK2 and Rb, thereby facilitating cell cycle progression at the G1/S-phase [11]. Collaborating transcription factors such as GATA2 and Oct1 by binding to the AR are also important for androgen-induced cell proliferation [18]. Another proposed mechanism by which the AR regulates prostate cancer cell proliferation is through its role as a licensing factor for DNA replication [39, 40].

AR is also important for survival of prostate cancer cells. AR upregulates the cellular Fas/FasL-associated death domain protein-like inhibitory protein (FLIP), which inhibits the death receptor-mediated activation (FAS ligand and TRAIL) of procaspase-8 and procaspase-10 [41–43]. The androgen/AR axis also inhibits the p53 pathway in an indirect way, thereby influencing cell survival. Expression of the apoptotic regulator Caspase-2, which is a direct target of AR, is inhibited by androgen in prostate cancer cells.

In prostate cancer, AR controls angiogenic growth by regulating the synthesis of vascular endothelial growth factor-A (VEGF-A), the major angiogenic growth factor [44, 45].

A bioinformatics approach known as cancer outlier profile analysis (COPA) together with standard genomic techniques identified recurrent gene fusions of the 5′ untranslated region of the TMPRSS2 gene to ETS transcription factors (ERG or ETV1) in over half of all human prostate cancers [46]. Importantly, since the TMPRSS2 promoter contains an ARE, androgens can regulate the expression of the fused gene under the control of the AR. Moreover, the AR has been demonstrated to facilitate the fusion of these genes in an androgen-dependent manner. Cooperativity between the aberrant expression of ETS fusion genes and other signaling pathways, e.g., the PI3 kinase-AKT pathway, is evident in prostate cancer [47, 48].

## Hormone Escape

Due to the overwhelming effect of AR in the pathogenesis of prostate cancer, androgen ablation by pharmacotherapeutic or surgical means is the primary choice of therapy for advanced (locally extensive or metastatic) prostate cancer. Various pharmacological agents such as gonadotropin-releasing hormone (GnRH) agonists or antagonists, which block testosterone synthesis via the pituitary axis, are widely used in the clinic as a means of androgen ablation therapy [49, 50]. Also, 5-α-reductase inhibitors such as finasteride and dutasteride, as well as competitive inhibitors of androgen binding to AR (flutamide, nilutamide, and bicalutamide), are used extensively in the clinic.

Nonetheless, after a period of regression in response to these therapies, these tumors eventually recur as a highly aggressive and castration-resistant prostate cancer (CRPC) [14, 35, 49, 51–54]. The median survival time for men with CRPC is between 18 and 24 months. Interestingly, the AR still remains an essential transcription factor in CRPC, since inhibiting AR expression or function disrupts the growth of castration-resistant prostate cancer cells [55–57]. Mechanisms for AR reactivation in patients with prostate cancer after hormonal manipulation include AR gene amplification, AR mutations, increased AR mRNA and protein levels, increased nuclear localization of AR, altered expression of AR-associated coregulators, and cross talk between different signal transduction pathways [52, 53].

## AR Gene Amplification

AR copy number is amplified in metastatic and castration-resistant tumors [58]. The overall frequency of AR amplification occurs in a minority of patients (~20–30 %)

and, therefore, cannot be the sole mechanism of progression to castration-resistant disease.

### Increased AR Transcription and Protein Stability

Increased AR levels due to the increase rate of AR transcription or increased stability of AR protein plays a causal role in the transition from hormone-dependent to CRPC by sensitizing prostate cancer cells to low levels of androgen [59] or even anti-androgen.

### AR Mutations

Gain of function mutations of AR in both the NTD and LBD are linked to CRPC. However, AR mutations are rare. AR mutations in the ligand binding pocket create a more sensitive AR that can respond to low concentrations of androgens and make the AR more promiscuous to other steroid hormones such as estrogen, hydrocortisone, weak androgen precursors, and even therapeutic anti-androgens [60].

### Aberrant Expression of AR Coregulators

Altered expression of AR coactivators promote activation of AR by reducing its requirement for androgen in castration-resistant prostate cancer [61]. Coactivators such as p300, FHL2, TIF2, SRC1, TIP60, and BAG-1L are present at increased levels in the tissue specimens from castration-resistant prostate tumors [28, 29, 62, 63]. Interestingly, expression of several of these coregulators depends either directly or indirectly on AR activity, suggesting a feedforward loop for aberrant AR activity in castration-resistant prostate cancer. Increased expression of SRC-1 is associated with ligand-independent activation of AR by IL-6. Enhanced levels of p300 can activate the expression of AR target genes and AR-mediated cell proliferation in the absence of androgens or in the presence of anti-androgens [64]. In castration-resistant cells, p300-mediated AR activity depends on IL6/MAPK signaling axis. Coactivators such as CBP, ARA54, and ARA70 can potentiate AR activity in the presence of anti-androgens such as hydroxyflutamide and, thus, may contribute to anti-androgen withdrawal syndrome. Co-repressors such as N-CoR and SMRT are also decreased in the castration-resistant stage and, therefore, contribute to increased AR activity.

### AR Cross Talk with Growth Factor Pathways

The insulin-like growth factor-1 (IGF-1)/IGF-1 receptor (IGF-1R) axis is important in regulating cell proliferation, survival, and transformation [65]. Androgens induce the expression of both the IGF-1 and IGF-1R expression in prostate cancer cells [65, 66]. Interestingly, IGF-1R signaling also promotes AR activation through phosphorylation of the AR at serine 210 and 790, especially during hormone ablation [67]. Therefore, AR and IGF-1R pathways are engaged in a positive feedback loop in prostate cancer cells. Epidermal growth factor (EGF), keratinocyte growth factor (KGF), Interleukin-6 (IL-6), HER-2/ErbB2, oncostatin (OSM), and ligands also enhance the activity of the AR or its coactivators in castration-resistant prostate cancer cells via cAMP-dependent protein kinase A (PKA) [50, 68–70]. Growth factor pathways also activate PI3K-AKT, JAK/STAT, and NFκB pathways, which promote posttranslational modifications of the AR, thereby facilitating AR stability and DNA-binding [71–75].

### Intraprostatic Generation of Androgens

Recurrent prostate tumors may synthesize their own testicular androgens from adrenal androgens or cholesterol, thereby reactivating AR through a cell autonomous mechanism [76]. This is achieved due to the ability of castration-resistant prostate cells to express genes encoding many steroidogenic enzymes such as FASN, CYP17A1, HSD3B1, HSD17B3, CYP19A1, and UBT2B17 [77].

### Constitutively Active AR Splice Variants

The N-terminal transactivation domain (NTD) of AR plays a major role in AR-mediated gene expression in the castration-resistant state [78]. The WxxLF motif in the TAU5 domain is important for the transcription-activating function of the NTD of the AR [21]. One of the mechanisms by which CRPC cells circumvent androgen ablation is by synthesizing splice variants of AR, which lack the ligand-binding domain and retain the AR NTD [79]. In the absence of the LBD, the NTD drives constitutive transcriptional activity. Splice variants lacking the LBD are expressed in tissues isolated from patients with CRPC [80].

#### Conclusion

The AR signaling axis is distinct in prostate cancer and induces the expression of specific genes responsible of cancer cell proliferation, survival, and metastasis. Therefore, the AR axis is a target for therapeutic intervention during locally advanced prostate cancer. Several agents, which block the synthesis and activation of androgen, either by inhibiting the hypothalamus-pituitary axis or by inhibiting the conversion to DHT from testosterone, are currently used in clinics for treating prostate cancer. Anti-androgens, which compete with androgen for

binding to the ligand-binding domain of AR, are also therapeutic agents for treating prostate cancer. Androgen receptor is also important for the progression of prostate cancer to the castration-resistant state [49]. Several mechanisms have been postulated for the transactivation of AR in this stage of prostate cancer. Therefore, the AR remains a potential therapeutic target in castration-resistant prostate cancer, and new therapeutic approaches to inhibit AR are needed. Development of second-generation antiandrogens with higher AR binding ability or drugs that specifically inhibit the constitutively activated AR splice variants may lead to novel therapies for castration-resistant prostate cancer.

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# Molecular Mechanisms of Castrate Resistant Prostate Cancer

4

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## Introduction

Cancer has replaced heart disease as the leading cause of death in North America – nearly half will develop cancer, and one in four will die from the disease [1]. Prostate cancer (PCa) is the most common male cancer in North America and 2nd leading cause of cancer deaths, but even more importantly, its incidence and mortality will double by 2020 based on current incidence trends. PCa represents 1 % of all death and 13 % of death by cancer [2]. While many gains have been made in early detection and treatment of localized PCa, many men still die of recurrent or metastatic disease. Androgen ablation remains the most effective therapy for patients with advanced disease. While ~80 % of patients initially respond, most patients progress to castrate resistant prostate cancer (CRPC) metastatic disease after 18–36 months [3–15]. Androgen ablation precipitates apoptosis in subpopulations of PCa cells, but despite high initial response rates, remissions are temporary because surviving tumor cells usually recur with a castrate resistant phenotype [15, 16]. CRPC progression is a complex process by which cells acquire the ability to both survive and proliferate in the absence of androgens and involves variable combinations of clonal selection [17], the reactivation of the androgen receptor axis [18], as well as adaptive upregulation of anti-apoptotic genes [19–25], alternative growth factor pathways [26–32], and cytoprotective chaperone networks [22, 33]. Clinically, CRPC is defined as biochemical and/or radiographic progression despite castrate levels of serum testosterone (<50 ng/ml) [34]. Biochemical progression is defined as two consecutive increases in prostate-specific antigen (PSA) above a minimal value of 5 ng/ml. Usually, progression occurs following cessation of treatment with androgen blockers for 4–6 weeks.

Many strategies used to kill cancer cells, including androgen ablation or docetaxel chemotherapy, induce a treatment-resistant phenotype [35, 36]. Hence, PCa, like most cancers, progresses and recurs after hormone and chemotherapy to a lethally resistant stage. This development of therapeutic resistance is the underlying basis for most cancer deaths and results from multiple, stepwise changes in DNA structure and gene expression – a Darwinian interplay of genetic and epigenetic factors, arising in part from selective pressures of treatment. This highly dynamic process cannot be attributed to singular genetic events, involving instead cumulative changes in gene expression that facilitate escape from normal regulatory control of cell growth and survival. Improved understanding of the molecular basis underlying metastasis and resistance to ADT or chemotherapy will facilitate to design new therapeutic strategies to inhibit the emergence of this CRPC phenotype.

This chapter will describe molecular and cellular mechanisms involved in CRPC progression and metastases, focusing on pathways that are currently targeted for treatment including the AR axis, growth factors and their receptors in survival pathways (IGF, IL-6, EGF), anti-apoptotic proteins such as Bcl-2 or molecular chaperones, and, finally, the influence of the microenvironment and the bone metastasis.

## Androgen Receptor Pathway in CRPC

The androgen receptor (AR) plays a critical role in the development of male reproductive organs [37, 38]. In normal development, androgens are primarily required for differentiation and growth. By contrast, during the

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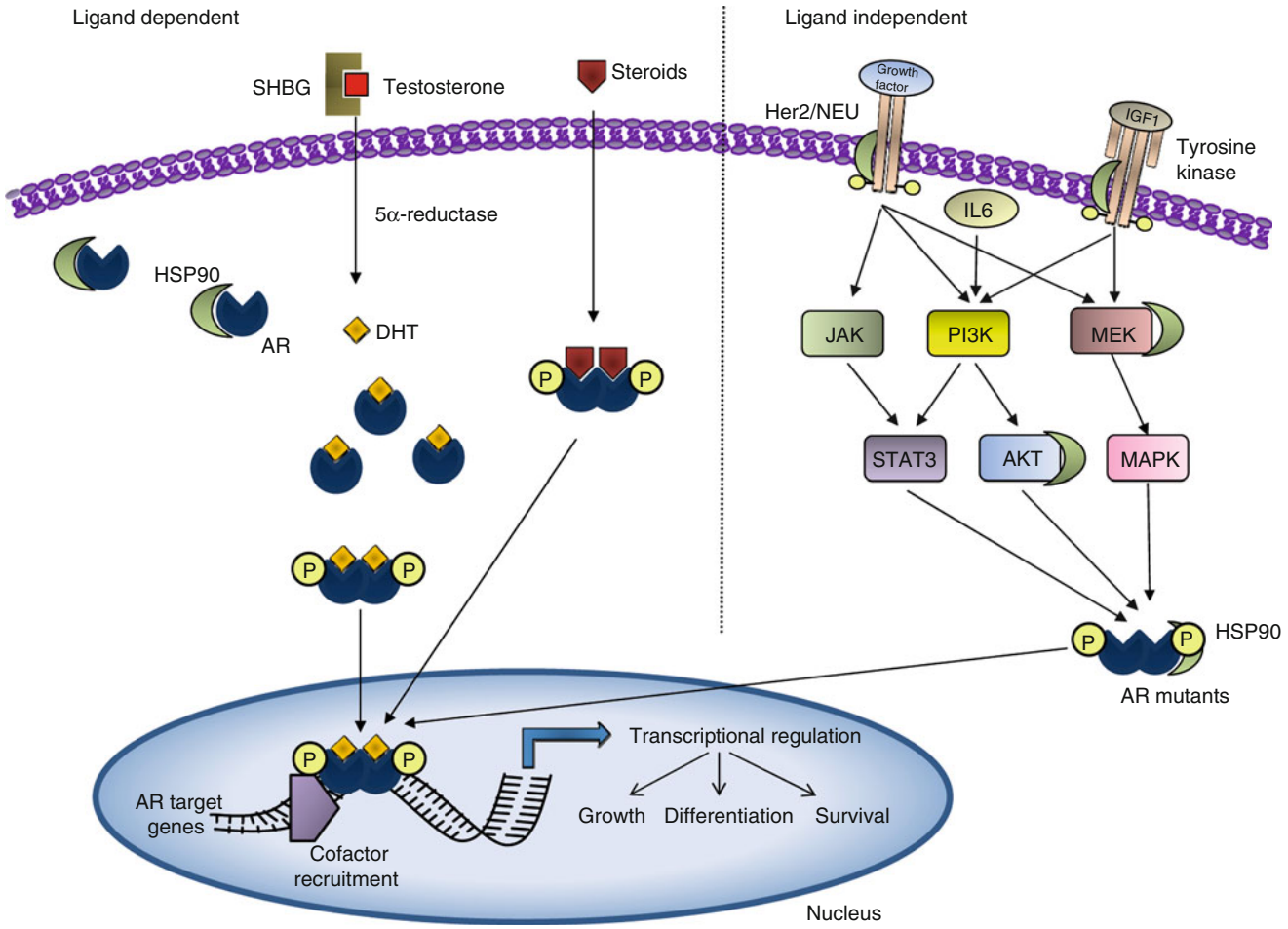


**Fig. 4.1** AR signaling in CRPC. Ligand-dependent pathway takes place through DHT or steroids stimulation of AR, while multiple signaling pathways, including PI3K and MAPK, stimulate and allow tumor cells to survive without androgens. These both ways (ligand dependent or ligand independent) induce cell proliferation, differentiation, migration, and survival. *AR* androgen receptor, *Hsp90* heat-shock protein 90, *IGF-1* insulin-like growth factor, *IL-6* interleukin 6, *SHBG* sex hormone-binding globulin, *DHT* dihydrostestosterone

development of PCa, androgen becomes a growth and survival factor for tumor cells.

Upon androgen binding, AR is phosphorylated and forms a dimer that translocates to the nucleus, where it binds to its specific DNA consensus site, termed androgen response element (ARE), on the promoter and enhancer regions of androgen-regulated genes, such as PSA, to initiate transcription. The transcriptional activity of AR is mediated by co-regulators (coactivators and corepressors) [39, 40] that, following androgen binding to AR, are assembled in a dynamic way at different ARE along the genome. The best recognized coactivators are the histone acetylases, such as p300 [41, 42] and the p160 SRC (steroid receptor coactivator) family [43–45]. These coactivators drive transcription by remodeling chromatin via histone acetylation and by recruiting RNA polymerase to the promoter.

As PCa initially progresses as an androgen-dependent, castrate sensitive tumor, androgen ablation therapy (i.e., surgical or medical castration) is highly effective in advanced stage of the disease. But this effect is short-lived, because castrate resistant subpopulations eventually emerge, resulting in treatment-resistant metastasis and mortality. Interestingly and despite ongoing growth post-castration, over 80 % of CRPC cases express AR and androgen-responsive genes, indicating that the AR axis remains activated, despite castration levels of testicular androgens. Three mechanisms have been postulated to account for aberrant AR activation in CRPC tumors: (1) activation of AR by nonsteroids such as growth factors and cytokines via multiple deregulated kinase signaling pathways; (2) amplification or overexpression of AR and its coactivators or chaperones, which sensitizes cells toward low levels of androgen; and (3) intratumoral steroidogenesis. These three mechanisms are not mutually exclusive and indeed likely work in concert to induce CRPC (Fig. 4.1).

## Nonsteroidal Activation of AR Via Kinase Signaling Pathways

The phosphorylation of the N-terminal domain (NTD) of the AR has been postulated as an underlying mechanism for a ligand-independent activation of AR by nonsteroidal agonists such as cyclic adenosine monophosphate (AMP)/protein kinase A (PKA), interleukin (IL)-6, and epidermal growth factor (EGF) [46–51]. Recently, splice variants of the AR that lack the ligand binding domain (LBD) have been reported in prostate cancer cell lines (LNCaP and 22Rv1) and also in CRPC patients [52–54]. These mutants are constitutively active and would not be inhibited by current therapies. Indeed, in vitro phosphorylation and activation of AR by serine/threonine kinases like the extracellular-signal regulated kinase (ERK) [28, 55], AKT [56], PKA [48, 57], and PKC [58] have been reported. IL-6 and EGF phosphorylate coactivators SRC-1 and SRC-2, respectively, which indirectly leads to activation of AR in CRPC [47, 50]. While serine/threonine kinases are direct modulators of AR and its transcriptional machinery, they are not the immediate effectors of growth factors or cytokines. Indeed, IL-6 and EGF both activate tyrosine kinases in PCa [59, 60] and induce AR phosphorylation on tyrosine (pTyr) via SRC and activated Cdc42-associated kinase (Ack) 1 [61–63].

Epidermal growth factor (EGF) has long been postulated to play a role in the regulation of AR transcriptional activity, especially under androgen-depleted conditions. However, the mechanisms by which growth factors modulate AR activity are not well understood. Though, several studies indicate it may be mediated by direct phosphorylation of AR or its cofactors through a kinase cascade involving tyrosine and serine/threonine kinases. Recently, Ack1 and SRC were demonstrated to phosphorylate AR, identifying the molecular basis for interplay between Ack1/AR and Src/AR signaling in PCa progression [61, 63]. Activated Ack1 phosphorylates AR on $Tyr^{267}$ [63] while SRC phosphorylates AR only on $Tyr^{534}$ [61, 62]. Recruitment of Ack1/AR complex at AREs results in androgen-induced gene expression in the absence of androgen with androgen-independent progression of prostate xenografts. EGF leads to AR phosphorylation on $Tyr^{267}$ via Ack1 and $Tyr^{534}$ via SRC [63]. Surprisingly, a small molecule inhibitor dasatinib targeting SRC and Ack1 activity abrogated EGF inducing AR phosphorylation on $Tyr^{534}$ but not EGF inducing AR phosphorylation on $Tyr^{267}$.

## Molecular Chaperones in Treatment Resistance and AR Stability

Molecular chaperones, including heat-shock proteins (Hsps) (described below), help cells cope with stress and act as genetic buffers stabilizing the phenotype of various cells at times of environmental stress. They enhance the Darwinian fitness of cells during transformation, progression, and treatment resistance [64]. Molecular chaperones are transcriptionally activated by heat-shock factor (HSF-1) and are involved in processes of folding, trafficking, and transcriptional activation of most steroid receptors, including AR. In the absence of ligand, AR is predominately cytoplasmic, maintained in an inactive but highly responsive state by a large dynamic heterocomplex composed of Hsp90 and Hsp70 and co-chaperones like FKBP52. Ligand binding leads to a conformational change in the AR and dissociation from the large Hsp90/Hsp70 complex. Subsequently, AR becomes associated with Hsp27, translocates to the nucleus, interacts with coactivators, and transcriptionally activates target genes [65, 66]. Dissociation of the AR-chaperone complex after ligand binding is viewed as a general regulatory mechanism of AR signaling [67]. Molecular chaperones remain important players in the events downstream of receptor activation and throughout the life cycle of the AR. For example, Hsp90 and Hsp27 inhibitors destabilize AR and increase its proteasomal degradation, thereby decreasing AR-regulated genes [66, 68]. Recent findings point out the importance of co-chaperones on AR activation. Hence, FKBP52, a co-chaperone, has shown to regulate AR transcriptional activity [69, 70], and FKBP52 knockout mice exhibited obvious defects in male reproductive tissue and prostate development [69, 70].

## Intratumoral Androgen Synthesis

Current androgen ablation strategies aim to inhibit gonadal androgen production. However, low circulating, and reasonably high intraprostatic, levels of androgens persist, in part due to peripheral conversion of adrenal steroids. Recent findings suggest that CRPC acquires the ability to synthesize androgen from cholesterol or adrenal precursors thereby creating an intracrine signaling system. Intratumoral steroidogenesis associated with overexpression of key enzymes including CYP17 can cause resistance to castration [71–73]. Cytochrome p450c17 (CYP17) catalyzes 2 essential reactions in androgen biosynthesis, including 17α-hydroxylation of $C_{21}$ steroids and cleavage of the $C_{17,20}$ bond of $C_{21}$ steroids [74]. These reactions are key in the biosynthesis of DHEA and androstenedione, precursors of testosterone and estradiol. Interestingly, Locke et al. demonstrated that cholesterol and its derivatives can be converted to androgens in prostate tumor cells through a series of well-characterized stepwise enzymatic events [72]. While androgen synthesis is often described in terms of the classical steroidogenic pathway through DHEA and testosterone, a recently described "backdoor pathway" can serve as an alternative synthesis pathway utilizing progesterone as the primary steroidal precursor of DHT, thereby bypassing T as an intermediate [74]. This evidence suggests that de novo androgen synthesis is one of the mechanisms leading to PCa progression following castration.

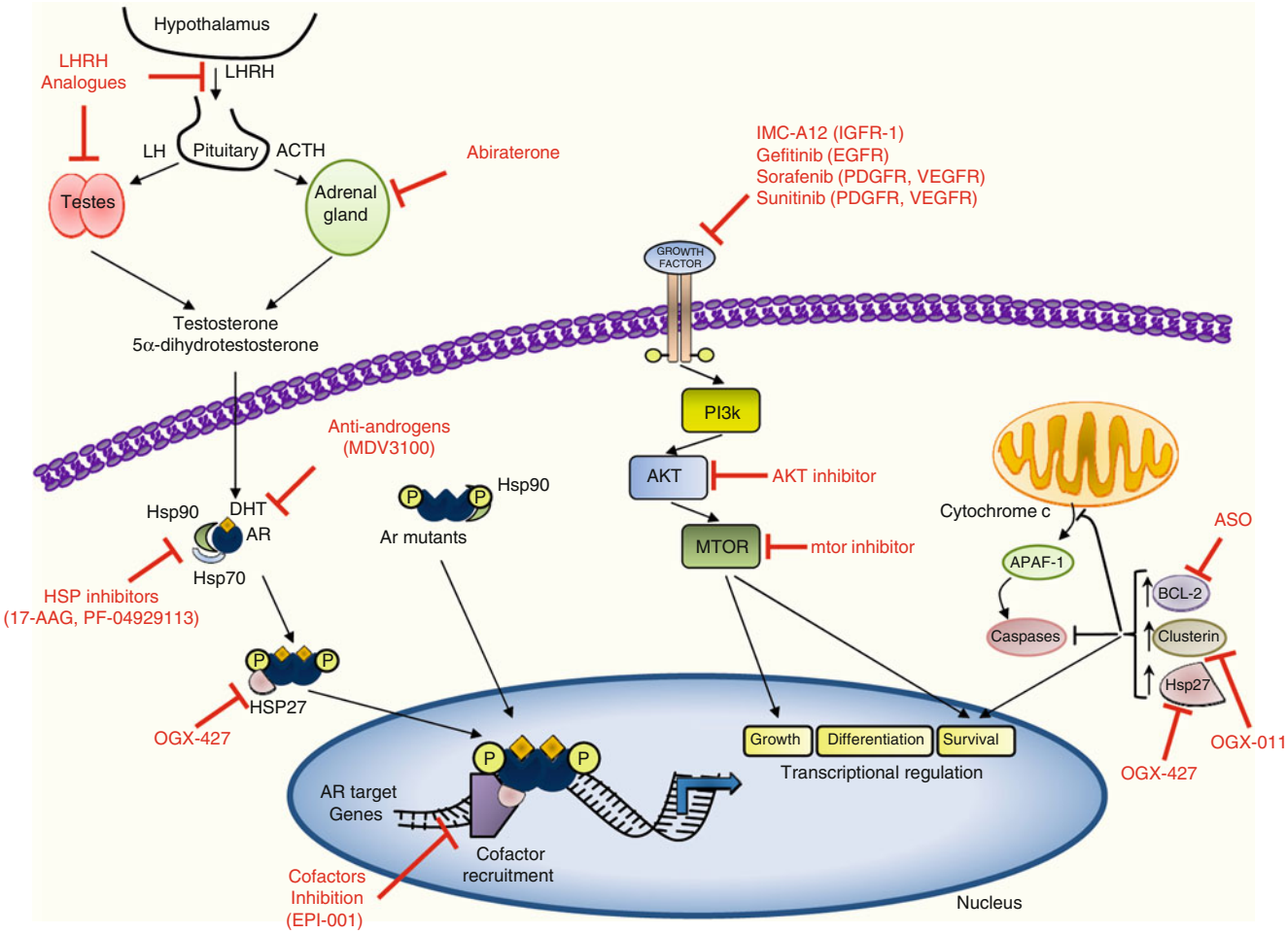


**Fig. 4.2** Molecular targets for the treatment of CRPC. *AR* androgen receptor, *BCl-2* B-cell lymphoma 2, *Hsp* heat-shock protein, *IGFR-1* insulin-like growth factor-1 receptor, *EGFR* epidermal growth factor receptor, *PDGFR* platelet-derived growth factor receptor, *VEGFR* vascular endothelial growth factor receptor, *mTOR* mammalian target of rapamycin, *LH* luteinizing hormone, *ACTH* adenocorticotropic hormone, *LHRH* luteinising hormone releasing hormone, *DHT* dihydrostestosterone, *ASO* antisense oligonucleotide

## Targeting Androgen Receptor Axis

Despite the failure of androgen blockage trials using nonsteroidal antiandrogens such as flutamide or bicalutamide, CRPC tumors are not uniformly hormone refractory and remain sensitive to therapies directed against the AR axis. Hence, several new classes of AR-targeting agents and molecules that destabilize AR are now in clinical development, including more potent AR antagonists (e.g., MDV3100), inhibitors of steroidogenesis (e.g., abiraterone, TAK700), and Hsp inhibitors (e.g., OGX-427, several Hsp90 inhibitors) (Fig. 4.2).

### Second-Generation Antiandrogens

MDV3100 is a second-generation, more potent nonsteroidal antiandrogen, rationally designed utilizing the AR crystal structure, modeling, and cell-based screening. Since bicalutamide has partial agonist activity in LNCaP cells that overexpress AR, candidate compounds were screened for pure antagonist activity in these cells. MDV3100 binds LBD of AR in cells with tenfold higher affinity than bicalutamide in competition studies and inhibits PSA secretion at tenfold lower concentrations. Preclinical studies showed that MDV3100 inhibits growth of castration-resistant xenografts [75]. Unlike bicalutamide, MDV3100 impairs AR nuclear translocation and blocks DNA binding [75]. Data from phase I/II trial suggest that MDV3100 treatment correlated with declining PSA, reduced circulating tumor cells, and radiographic disease stabilization [76]. Importantly, MDV3100 was active in both pre- and post-chemotherapy-treated patients [76], and it is currently in phase III trial in both pre- and post-chemotherapy-treated patients.

### CYP17 Inhibitors

Given its critical role in androgen biosynthesis, CYP17 has generated interest as a relevant biological target for CRPC. Several novel therapeutic entities that selectively inhibit

CYP17 are currently under clinical evaluation for CRPC. Abiraterone acetate is a highly potent, selective, irreversible inhibitor of CYP17.35, suppressing conversion of pregnenolone to DHEA and progesterone to androstenedione in the testes and adrenal glands. Abiraterone also appears to suppress de novo androgen production in prostate tumors, as evidenced by inhibition of CRPC growth in xenograft models devoid of testicular and adrenal androgens [73].

In phase I and II clinical studies of abiraterone acetate, 50–60 % of chemotherapy-naïve patients had a decline in PSA by 50 %, and the median time to PSA progression was about 230 days [77, 78]. Importantly, 20–30 % of patients had a 90 % PSA decline that was associated with a patient subgroup that had near complete radiological responses, normalization of CTC count, and PSA progression-free survival lasting longer than 1 year. Antitumor activity was reported at all doses from 250 to 2,000 mg daily, but 1,000 mg once daily was selected for phase II development due to a plateau in the feedback-driven increase of steroids upstream of CYP17 at 750, 1,000, and 2,000 mg daily [79]. Phase II studies reported significant antitumor activity in chemotherapy-treated patients, with a time to PSA progression of about 170 days, suggesting that docetaxel-treated CRPC remained hormone dependent [80, 81]. A phase III study comparing placebo to abiraterone in post-chemotherapy CRPC patients demonstrated a 4-month gain in overall survival from 12 to 16 months, supporting approval of abiraterone for this indication in 2011 [82].

### Chaperones Inhibitors

Inhibition of chaperones involved in AR stabilization is another promising approach to treat CRPC. Among these chaperones, targeting Hsp27 using antisense OGX-427 and Hsp90 using small molecule inhibitors have been used to disrupt AR axis and to delay CRPC, as described below (*3. survival regulation*; *c. cytoprotective molecular chaperones*).

## Growth Factors and Their Receptors

Development and progression of PCa involve a complex interplay of many growth factor-signaling pathways, including EGF, FGF, IGF, IL-6, and TGF, that collectively regulate cell differentiation, proliferation, migration, and survival [83, 84].

### EGF

Epidermal growth factor receptor (EGFR) and its ligands EGF, TGF-α, HB-EGF, and amphiregulin have been reported to correlate with high-grade PCa [83–88]. EGFR ligands are powerful mitogens for epithelial cells and fibroblasts that induce a sequence of events to increase the transcription activity of the pro-oncogene c-fos [89]. TGF-α, EGF, and EGFR are often overexpressed in PCa [90]. Several studies report high expression of EGFR associated with low expression of TGF-α in androgen-dependent tumors. However, in metastatic CRPC, co-expression of EGFR and TGF-α was found in the epithelial compartment [91]. These data suggest paracrine regulation of tumor growth during androgen-dependent stage, with autocrine regulation upon progression to androgen independence [91]. Tso et al. demonstrated that androgen suppression induces expression of EGFR in androgen-dependent LNCaP cells [92]. Furthermore, high expression of EGFR in androgen-independent PC-3 and DU145 cells correlates with autocrine activation [93]. The ability of tumor cells to auto-activate themselves could play a role in the androgen-independent tumor growth, because enabling tumor cells release critical growth factors for the cell proliferation and survival post-castration.

Activation of EGFR stimulates several mitotic cascades including MAPK, PI3K/Akt, nuclear factor kappa-β (NF-κB), phospholipase Cγ (PCγ), or Shc signaling pathways, all involved in cell proliferation, survival, motility, and invasion [84, 94, 95]. While this highlights EGFR as a therapeutic target in CRPC, unfortunately, EGFR inhibitors like gefitinib (250 mg or 500 mg) did not show any clinical activity in a randomized phase II study including 40 patients with CRPC [96].

### FGF

Fibroblast growth factors (FGF) are a family over 22 identified proteins secreted by the fibroblasts. The FGF family is involved in a many varied biological processes including embryogenesis, angiogenesis, and carcinogenesis [97–103] and is considered a key paracrine mediator of proliferation by stimulating mitosis of prostate stromal and epithelial cells [104–106]. The homeostatic balance of interactions between stromal and epithelial compartments is critical for prostate development and can lead to neoplastic transformation. In PCa, some members of the FGF family are involved in growth and survival of epithelial tumor cells by inducing Bcl-2 expression [107]. FGFR2IIIb is reported to be frequently lost or spliced to FGFR2IIIc isoform in epithelial cells during carcinogenesis [108, 109]. FGF8 can bind FGFR2IIIc, expressed in tumor cells suggesting an autocrine loop controlling the growth [110]. FGFR1 kinase is normally found in stromal cells and often expressed in prostate tumors [108, 111, 112]. The cooperation between the loss of FGFR2 and the ectopic expression of FGFR1 induces high-grade prostatic intraepithelial neoplasia (PIN) in mice [113]. Avecedo et al. reported that activation of FGFR1 induced the progression to adenocarcinoma involving the epithelial-mesenchymal transition [101]. This process is reversible after inactivation of FGFR1.

Additionally, FGF10 is reported to increase the expression of the epithelial AR leading to the formation of mutifocal PIN or adenocarcinoma [102]. All these data suggest that the FGF10/FGFR1 axis is a potential therapeutic target in the treatment of castrate sensitive or castrate refractory prostate cancer. Furthermore, FGF8 is reported to be frequently expressed in bone metastases of human prostate cancer and increases tumor progression in an in vivo intratibial PC-3 model of prostate cancer [114].

## IGF

The insulin-like growth factor (IGF) axis regulates cell growth, proliferation, survival, and metabolism through activation of the IGF-1 receptor (IGF-1R) tyrosine kinase and the mannose-6-phosphate receptor (IGF-IIR) [115–120]. Signaling proteins activated downstream of IGF-1R include extracellular signal-related kinase (ERK)/mitogen-activated protein kinase (MAPK), phosphate-inositol 3-kinase (PI3K), and Akt. IGF-1 signaling promotes tumorigenesis in a variety of human cancers [116]. Patients with PCa have higher serum IGF-1 levels, and the majority express high levels of IGF-1R [121–124]. IGF-1 is considered to be one of the most potent mitogens in PCa cells in vitro [121, 122]. Overexpression or activation of IGF-1R increases proliferation of transformed cells, activating many signaling pathways that converge to phosphorylate the pro-apoptotic protein BAD and block apoptosis. The transcription factor ELK is another endpoint of IGF-1 signaling, via that MAP kinase pathway. IGF-1 increases the expression of Hsp27 mRNA levels and induces Hsp27 protein phosphorylation. Many humanized antibodies or small molecules targeting IGF-1R are in early clinical development in CRPC such as CP-751,871, IMC-A12, or NVP-AEW541 [125–129]. However, cross-activity between IGF-1R and insulin receptor can induce toxicity and increased glucose.

In plasma or biological fluids, IGFs bind insulin-like growth factor binding proteins (IGFBPs) that are particularly involved in the tumor progression in PCa by modulating IGF/IGF-R biological activities [130–132]. IGFBPs are a family of six circulating proteins that bind IGF-1 and IGF-II and regulate IGF distribution, function, and activity [133, 134]. IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 are expressed in prostatic tissues and cell lines [135–139]. IGFBP-2 and IGFBP-5 are increased after castration in Shionogi and LNCaP models [140] and correlate with poor prognosis [135, 139]. Overexpression of IGFBP-5 in LNCaP cells increased cell proliferation in an IGF-1-dependent manner via PI3K and Akt/PKB activations and potentiates the anti-apoptotic effect of IGF-1 [29]. Knockdown of IGFBP-5 inhibited proliferation and tumor progression to CRPC [29, 141, 142]. IGFBP-2 levels also increase threefold in Shionogi and LNCaP models, as well as in human prostate tumors following androgen ablation [32, 140, 143]. Knockdown IGFBP-2 induces apoptosis and delays CRPC in LNCaP xenografts. All these data identify an important role for IGFBP-2 and IGFBP-5 in cell survival by potentiating the anti-apoptotic effect of IGF-1 and accelerating CRPC progression. Knockdown of IGFBP-2 and IGFBP-5 using the ASO OGX-225 promoted apoptosis and sensitized tumor to chemotherapy in preclinical models of human prostate, breast, bladder, and glioma cancers [144]. OGX-225 has completed preclinical pharmacology and is being evaluated for clinical trials.

## TGF-Beta

Under physiological conditions, TGF-beta inhibits prostate epithelial cell proliferation induced by EGF or FGF2 [145, 146]. In PCa, expression of TGF and their receptors are regulated by androgens. Consequently, androgen suppression increases expression of TGF-beta and betaglycans in human PCa cells to induce apoptosis [147]. The sensitivity of tumor cells to TGF-beta is correlated with the tumor aggressiveness [148]. In PCa, studies using human samples correlate loss of TGF-beta type II receptor (TBRII) with higher tumor grade [149–151]. TBRII transduces signals for TGF-beta in many pathways including growth inhibition, apoptosis, and differentiation [152–154]. Furthermore, TGF-beta I modulates cell adhesion, angiogenesis, and invasion in PCa [155]. High expression of TGF-beta I in bone can function as an autocrine-paracrine modulator of bone invasion in PCa [155] and has been implicated to play a paracrine role in CRPC progression [156].

## IL-6

Interleukin-6 is a pleiotropic cytokine that plays a central role in host defense mechanisms by regulating immune response and hematopoiesis and induces either differentiation or growth of a variety of cells. IL-6 modulates growth and differentiation of many cancers and is associated with poor prognosis in lymphoma, ovarian, and prostate cancer [157]. There is evidence that IL-6 is involved in development of CRPC [158–160]. Multiple studies demonstrate that IL-6 is elevated in sera of patients with metastatic PCa and IL-6 levels correlate with tumor burden, serum PSA levels, and metastatic burden [158, 159]. IL-6 functions as a paracrine growth factor in androgen-sensitive PCa cells (LNCaP) and as an autocrine growth factor in androgen-insensitive human PCa cells DU145 and PC-3 [161]. IL-6 induces neuroendocrine (NE) differentiation in LNCaP cells [60, 162, 163].

## Survival Regulation

### Bcl-2

Bcl-2 is an oncogene that contributes to neoplastic progression by enhancing tumor cell survival through inhibition of apoptosis [164]. In PCa, experimental and clinical observations strongly suggest that Bcl-2 plays a critical role in the progression to CRPC through inhibition of apoptotic cell death precipitated by androgen ablation [24, 165–170]. Moreover, Bcl-2 overexpression is also associated with survival in growth factor-deprived medium and resistance to heat-shock stress, several chemotherapies, and radiotherapy [23, 165, 168, 169, 171–175]. Intrinsic expression of Bcl-2 by PCa tissue may result in resistance to the effects of hormone manipulation because higher proportion of nonresponders or early relapsers to hormonal therapy occurred in patients strongly expressing Bcl-2 [176–178]. Tso et al. reported that an androgen-independent clone from androgen-dependent LNCaP cells was associated with decreased p53 and increased Bcl-2 expression [92]. Activation Bcl-2 inhibits p53-induced apoptosis without affecting cell proliferation [179]. Bcl-2 knockdown using ASOs synergistically enhanced the apoptotic triggers of androgen withdrawal or taxane chemotherapy in preclinical models [23, 24, 180–182]. These studies provided the preclinical proof of principle for the first phase I dose finding study of combined treatment with an Bcl-2 ASO (Genasense or oblimersen sodium) plus mitoxantrone in patients with metastatic CRPC [183] and a second phase I/II trial in combination with docetaxel [184]. Unfortunately, clinical studies in CRPC did not provide a clear signal of anticancer activity [185], putting future trials with this agent on hold. Issues persist about the dosing and regimen of this first-generation ASO and whether 6 days of 7 mg/kg/day treatment is enough to suppress target sufficiently.

### Cytoprotective Molecular Chaperones

Heat-shock proteins (HSPs) are a family of highly conserved proteins whose expression is induced by cell stressors such as hyperthermia, oxidative stress, and cytotoxic drugs [186–188]. HSPs have attracted attention as new therapeutic targets for cancer, especially since the discovery and characterization of geldanamycin as an inhibitor of Hsp90 [189, 190] and the targeting of *clusterin* [191], whose product has sHSP-like function.

#### Hsp27

Heat-shock protein 27 (Hsp27) is a 27-kDa molecular ATP-independent chaperone that forms oligomers during cell stress to inhibit protein precipitation and to regulate activity/degradation of certain client proteins [192]. The oligomerization status and chaperone activity of Hsp27 is regulated by stress-induced changes in phosphorylation involve three Ser residues catalyzed by p38 MAP kinase and other stress signaling pathways [193–196]. This phosphorylation is a reversible event modulating the oligomerization of Hsp27. Hsp27 sits as a "hub" at the center of many pathways regulating the response of a cell to stress and therapeutic stimuli. Similar to other chaperones, Hsp27 is a potent cell survival factor that contributes to thermotolerance [197]. Higher levels of Hsp27 are commonly detected in many cancers [188, 198, 199] including CaP [143, 200, 201], where it plays a role in cytoprotection, hormonal response, and molecular chaperoning. Hsp27 is highly overexpressed gene in castrate resistant LNCaP tumors in human CaP, and Hsp27 levels increase after hormone therapy to become highly expressed in CRPC [202].

Hsp27 interacts with many key apoptosis-associated proteins to regulate a cell's apoptotic rheostat through pathways involving both the intrinsic and extrinsic pathways. The intrinsic pathway functions primarily through intracellular death signals that trigger outer mitochondrial membrane permeabilization, leading to the release of cytochrome-c. Cytochrome-c interacts with Apaf-1 and caspase-9 to form the "apoptosome" which activates caspase-3, leading to an activation cascade of downstream caspases, the so-called "effectors" of cell death. The extrinsic pathway is activated through cell membrane associated proteins of the TNF receptor family (such as Fas, Trail-R1, Trail-R2, and others), which can trigger caspase-independent apoptosis or directly activate caspase-8, which leads to activation of the downstream effector caspases. Hsp27 prevents formation of the apoptosome, by either preventing release of mitochondrial cytochrome-c or directly sequestering cytochrome-c in the cytosol after mitochondrial release [203–205]. Also, Hsp27 may directly interact with and inhibit caspase-3 [206]. Hsp27 may also interfere with the extrinsic pathway by inhibiting Daxx, a mediator of Fas-induced caspase-independent apoptosis [207]. Hsp27 also inhibits apoptosis by decreasing reactive oxygen species within cells by increasing glutathione and reducing the toxic effect of oxidized proteins [208, 209]. In addition, Hsp27 can act early during a cell stress to stabilize and accelerate recovery of actin filaments, thus preventing disruption of the cytoskeleton [210, 211]. Hsp27 is also involved in regulation of the serine/threonine kinase AKT (protein kinase B), an important signaling molecule for cell survival and proliferation downstream of growth factor stimulation. Both MAPKAPK2 and Hsp27 are necessary for TGFβ-mediated increases in MMP-2 and cell invasion in human prostate cancer [210, 212, 213]. Finally, Hsp27 enhances NF-κB activity by facilitating proteasomal degradation of its main inhibitor I-κBα [214].

In addition to the above described generalized cancer mechanisms, Hsp27 also regulates ligand-activated AR and protein kinase D1 (PKD1) [66, 215]. Androgen-bound AR and PKD1 induce rapid Hsp27 phosphorylation on Ser(78) and Ser(82) residues that, in turn, enhance AR stability, shuttling, and transcriptional activity [66, 215]. Knockdown of Hsp27 using the Hsp27 inhibitor, OGX-427, decreases AR transcriptional activity, increases AR degradation via the proteasome, and induces apoptosis in AR-positive LNCaP cells [66]. In addition, Hsp27 expression and phosphorylation levels are correlated with IGF-1 signaling and CRPC progression [216]. IGF-1 induces Hsp27 phosphorylation via p90Rsk to promote CRPC progression. Hsp27 knockdown inhibits IGF-1-induced phosphorylation of p90Rsk and Akt destabilizing BAD/14.3.3 complexes, thereby inducing apoptosis [216].

This abbreviated summary illustrates that Hsp27 is associated with poor clinical prognosis and therapeutic resistance [22, 198, 217] highlighting that Hsp27 as a potential target for development of new therapies. Indeed, Hsp27 knockdown destabilizes BAD/14-3-3 complexes increasing apoptosis [216] and sensitizing cancer cells to hormone, chemo-, and radiotherapy [22, 202, 217]. Recently, inhibitors of Hsp-27 called triazol ribonucleosides (3-arylethynyltriazolyl ribonucleosides) were described to induce apoptosis in drug-resistant cancer cells [218]. Furthermore, others inhibitors such as biphenyl isoxazole KRIBB3 or p38 MAPK/MAPK-activated protein kinase 2 (MK2) inhibitors have been described to induce cell-cycle arrest and apoptosis [219] or to inhibit phosphorylation of Hsp27 at Ser78 and Ser82 by the MAPKAP kinase MK5 [220, 221]. Hsp27 knockdown with ASO (OGX-427) enhances apoptosis, sensitizes chemotherapy, and delays tumor progression in preclinical models [22]. OGX-427, a second-generation antisense inhibitor of Hsp27, has been tested in phase I/II clinical trials in many cancers, was well tolerated, and associated with decreased circulating tumor cells and reduced PSA levels in patients with CRPC [222]. OGX-427 is currently in phase II studies in CRPC.

## Hsp90

Hsp90 is a molecular chaperone that accounts for 1–2 % of all cellular proteins [223]. Hsp90 is a larger heat-shock ATPase-dependent chaperone [224] required for protein folding, maturation, and conformational stabilization of many "client" proteins, protecting them from degradation [225]. Its chaperone function involves a complex series of association with several co-chaperones including Hsp70, Hsp40, HOP, AHA1, and p23 [226]. Hsp90 interacts with more than 200 client proteins which some of them regulate proliferation and cell survival of tumor cells including growth factors receptors, cell-cycle regulators, and signaling kinases [64, 227, 228]. AR is a known client protein of Hsp90 [68, 229] that plays a key role in carcinogenesis and progression of CRPC. Thus, Hsp90 inhibitors like 17-AAG analogues are a rational approach to destabilize and disrupt nuclear localization of the AR in the treatment of CRPC [230]. For example, Lamoureux and al. demonstrated that Hsp90 inhibition using the novel inhibitor PF-04929113 inhibits LNCaP CRPC progression [229]. This activity is partially mediated by decreased AR levels, translocation, and activity. Her-2 is also one of the most important client proteins of Hsp90. Her-2 is often overexpressed in malignancies including PCa, inducing resistance to chemotherapy [231]. Several preclinical studies report a degradation of Her-2 after treatment with Hsp90 inhibitors (17-AAG, PF-04928473) [229, 232] supporting the therapeutic interest to target Hsp90 in PCa.

## Clusterin

Clusterin (CLU) is a stress-activated chaperone regulated by HSF1 that binds to a wide variety of biological ligands to potently inhibit stress-induced protein precipitation and stabilize protein conformations at times of cell stress [233–236]. While CLU is implicated in many physiological processes, its functional relationship to apoptosis has been studied most [237, 238]. In the prostate gland, CLU mRNA was originally cloned as "testosterone-repressed prostate message 2" (TRPM-2) from regressing rat prostate [239, 240], but CLU was reported as an apoptosis-associated gene protecting cells from apoptosis-inducing stressors, rather than as an androgen-repressed gene [33]. CLU expression increases following a diverse variety of stressors, including cytotoxic chemotherapy [21], radiation [241, 242], and androgen [33] or estrogen [243] withdrawal in hormone-dependent tumors.

CLU increases >threefold following androgen ablation and during CRPC progression. CLU is highly expressed in PCa specimens after neoadjuvant hormone therapy but low or absent in untreated low-grade tumors [33, 244]. Forced overexpression of CLU in LNCaP cells confers a hormone- and chemoresistant phenotype [21, 245]. Many reports document that CLU inhibits mitochondrial apoptosis, interacting with conformationally altered Bax to inhibit apoptosis in response to chemotherapeutic drugs [246]. In addition, CLU increases Akt phosphorylation levels and cell survival rates [247]. sCLU induces epithelial-mesenchymal transformation by increasing Smad2/3 stability and enhancing TGF-β-mediated Smad transcriptional activity [248]. CLU also promotes prostate cancer cell survival by increasing NF-kB nuclear transactivation, acting as a ubiquitin-binding protein that enhances COMMD1 and I-kB proteasomal degradation via interaction with E3 ligase family members. sCLU knockdown stabilized COMMD1 and I-kB, suppressing NF-kB translocation to the nucleus and suppressing NF-kB-regulated gene signatures [249].

This anti-apoptotic function for CLU results in broad-spectrum resistance to many anticancer therapies and

identifies it as a potential anticancer target. A CLU ASO inhibitor (OGX-011 or custirsen) has been developed that enhances cancer cell death after a variety of therapeutic stressors including hormone , radiation, and chemotherapy in preclinical models of prostate, lung, renal cell, urothelial, sarcoma, and breast cancers [21, 241, 244, 245, 250–258]. OGX-011 is a second-generation MOE gapmer ASO with prolonged tissue half-life of 7 days [250, 251]. Two Phase I trials evaluated OGX-011 given weekly by intravenous infusion as a single agent or in combination with docetaxel [259]. A novel presurgery study demonstrated that prostate tissue concentrations of OGX-011 increased with dose and tissue concentrations (>500 nM) associated with preclinical effect could be achieved. Moreover, >90 % dose-dependent decreases in prostate cancer cell CLU expression were also observed [191]. A randomized phase II trial of 82 chemotherapy-naïve patients compared docetaxel and prednisone with or without OGX-011. The OGX-011 group had a 6.9-month longer overall survival compared to docetaxel alone (16.9 months vs. 23.8 months), warranting further investigation with OGX-011 [260]. Phase III trials in CRPC began in 2010 (NCT01083615).

## Metastasis

Targeting the environment supporting metastatic growth is an expanding therapeutic strategy. Many biological processes promote site-specific osseous metastasis, such as extracellular matrix, angiogenesis, cell adhesions, and epithelial-mesenchymal transition (EMT). Underlying mechanisms and the therapeutic strategies targeting them will be discussed in this section (Fig. 4.3).

### Extracellular Matrix

Loss of cell adhesion is associated with degradation of extracellular matrix (ECM). Several proteolytic enzyme systems are involved in degradation of the ECM. Among them, urokinase plasminogen activator (uPA) and its receptors (uPAR) play an important role in tissue degradation, cell migration, angiogenesis, cancer invasion, and metastasis [261]. uPA is a member of the serine protease family and acts as a promoter of tumor progression in various human malignancies. Binding to uPAR, uPA converts the inactive zymogen, plasminogen, into the active serine protease, plasmin, which cleaves ECM components including laminin, fibronectin, vitronectin, fibrin, and collagen [262]. The uPA/uPAR system is associated with PCa metastasis. uPA and uPAR expression levels correlate with serum PSA levels and inversely correlate with overall survival in PCa [263]. Amplification of uPA gene is often found in CRPC metastatic lesions [264]. Moreover, uPA and uPAR are frequently overexpressed in tissues with high-grade primary tumors and lymph nodes metastasis and are related to PCa progression [265]. These results link uPA and uPAR to metastatic PCa and identify them as therapeutic targets to control metastasis and progression in CRPC.

### Angiogenesis

Angiogenesis is critically important for growth and metastatic development of tumors. Angiogenesis is regulated by a variety of factors, including growth factors, cytokines proteases, and adhesion molecules, released by tumor cells under stimuli such as hypoxia via the overexpression of hypoxia-inducible factor-1 (HIF1). Tumor cells also secrete factors involved in the activation of macrophages around the tumor, which are able to release other angiogenic factors and chemo-attractants to attract the endothelial cells [266]. Among the various angiogenic factors, vascular endothelial growth factor (VEGF) is the major angiogenic factor inducing migration and proliferation of endothelial cells by activating tyrosine kinase receptors VEGFR1 and VEGFR2. In PCa, the neo-angiogenesis density is correlated with the expression of VEGF and/or FGF [267].

Therapy targeting tumor neovasculature represents a promising area of research with more than 20 anti-angiogenic agents being evaluated in various phases of clinical trials [268]. Among the various angiogenic targets implicated in tumor angiogenesis, VEGF has evoked the most interest [269, 270]. While plasma VEGF levels are negative prognostic factors in CRPC [271], a phase III study of 1,020 patients using docetaxel/prednisone with and without the anti-VEGF monoclonal antibodies, bevacizumab, (CALGB 90401) reported no gain in overall survival.

Platelet-derived growth factor (PDGF) has also been linked to PCa bone metastasis and is expressed in 80 % of CRPC lesions [272]. Preclinical studies using imatinib mesylate (Gleevec®), a PDGF inhibitor, showed activity in prostate cancer cell lines, and a phase I trial of 21 patients with metastatic CRPC reported a 38 % PSA response rate [273]. However, a randomized phase II trial of imatinib and docetaxel in patients with CRPC showed increased toxicity without delaying progression. Sunitinib (Sutent®), vatalinib, and sorafenib (Nexavar®) are oral multi-targeted tyrosine kinase inhibitors that inhibit RAF kinase, VEGF receptor tyrosine kinase, and PDGF receptor, and are currently approved for treatment of metastatic renal cell carcinoma [274]. Unfortunately, phase II studies in CRPC [275–277] did not demonstrate consistent anticancer signals, and a phase III trial of sunitinib in docetaxel recurrent CRPC was closed early due to excessive toxicity and no survival benefit.

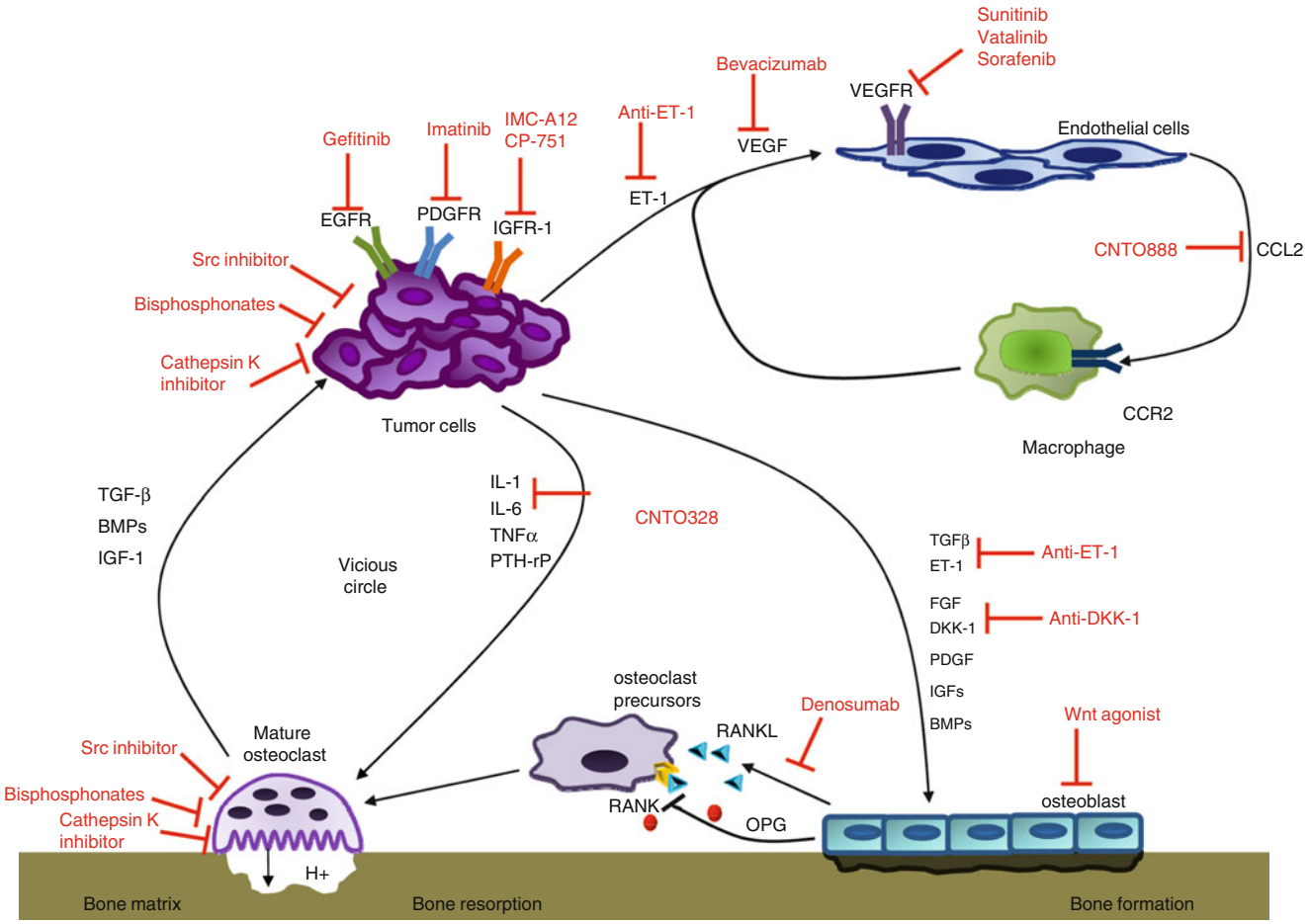


**Fig. 4.3** Therapeutic approaches in targeting bone metastasis in PCa. *IGF-1* insulin-like growth factor-1, *IGFR-1* IGF-1 receptor, *EGFR* epidermal growth factor receptor, *PDGFR* platelet-derived growth factor receptor, *VEGF* vascular endothelial growth factor, *VEGFR* VEGF receptor, *ET-1* endothelin 1, *TGF-β* transforming growth factor beta, *IL* interleukin, *TNFα* tumor necrosis factor alpha, *BMPs* bone morphogenetic proteins, *FGF* fibroblast growth factor, *DKK-1* Dickkopf-related protein 1, *OPG* osteoprotegerin, *RANK* receptor activator of NF-kB, *RANKL* RANK ligand, *PTH-rP* parathyroid hormone-related protein, *CCR2* chemokine (C-C motif) receptor 2, *CCL2* chemokine (C-C motif) ligand 2

Angiogenesis inhibitors have therefore been disappointing in CRPC to date.

## Cell Adhesion

Loss of cell adhesion increases migration, invasion, and, ultimately, vascular dissemination. In the prostate, the cadherin-catenin complex is a key regulator of cell-cell adhesion, whereas integrins mainly mediate cell-matrix adhesion. E-cadherin, β-catenin, and α-catenin are the best characterized in PCa to play important roles in cell-cell adhesion, in particular, post-androgen withdrawal. E-cadherin is attached intracellularly to the catin cytoskeleton via intracellular catenin. Beta-catenin, localized in the nucleus, induces cell proliferation and inhibits apoptosis, as well as the loss of E-cadherin expression, which is associated with EMT and resistance to hormone therapy.

Loss of E-cadherin leads to increased cell detachment and mobility [278, 279], whereas transfection of E-cadherin cDNA into invasive adenocarcinoma cells reverses this invasive phenotype [280, 281]. Indeed, E-cadherin is normally expressed in low-grade carcinomas, but its expression commonly decreases in high-grade cancers, bone metastasis, and poor prognosis [282–285]. However, McWilliam et al. found no correlation between E-cadherin expression and tumor progression or PCa death [286]. Interestingly, E-cadherin is re-expressed in metastatic CRPC [282], suggesting paracrine regulation from cells in the metastatic microenvironment. Rhodes et al. reported a correlation between low E-cadherin expression and PSA recurrence after radical prostatectomy, suggesting that the level of E-cadherin expression could be predictive of clinical outcome [287]. The results suggest that the loss of E-cadherin is important and can be considered as clinically relevant protein in the invasion-metastasis suppression, but it is not the only protein in the regulation of the metastatic cascade.

Beta-catenin is an adhesion molecule that binds E-cadherin via its intracytoplasmic domain to regulate signal transduction. Abnormal β-catenin expression is associated with poor prognosis in PCa [288] affecting the function of the cadherin-catenin complex. β-catenin can be mutated in PCa (<4 % of primary prostate tumors) [289], binding AR to enhance AR transcriptional activity and reduce effects of antiandrogen activity (i.e., bicalutamide) [289, 290].

Integrin expression, essential in the cell-matrix adhesion, varies between tumors, but overexpression of $\alpha_6$ and $\beta_3$ integrins was reported to increase invasion [291, 292] and plays an important role in the binding and migration processes at the metastatic site. Indeed, these integrins work together with matrix metalloproteinases (MMPs) to degrade the ECM and basement membrane [293] creating a breach in the membrane during invasion.

## Epithelial-Mesenchymal Transition

Malignant cells discard epithelial restraints and acquire invasive abilities that facilitate their dissemination to permissive microenvironments [294]. This epithelial-mesenchymal transition (EMT) is also a developmental program in which epithelial cells assume a mesenchymal phenotype during gastrulation and organogenesis, allowing single cell invasive movement away from the ectodermal layer [295]. Early carcinomas harboring oncogenic mutations (e.g., ras) are thought to undergo EMT as a result of contextual cell signaling responses to local tumor stromal signals in the inflammatory and hypoxic tumor microenviroment [296, 297]. EMT is activated by developmental transcriptional regulators, including Twist, Zeb1, and the Snail family transcription factors Snail and Slug [298]. These EMT transcription factors alter epithelial gene expression by repressing genes encoding epithelial junction complexes (e.g., E-cadherin) and cytokeratins and inducing expression of their mesenchymal counterparts, N-cadherin and vimentin. EMT is linked to metastatic progression and is associated with stem cell features and immunosuppression that collectively promote metastasis [299–301].

Several growth factors can induce EMT. IL-6 plays a central role in host defense mechanisms by regulating immune response and hematopoiesis and inducing differentiation or growth in a variety of cells. IL-6 induces neuroendocrine (NE) differentiation in LNCaP cells [60, 162, 163] and promotes EMT in breast cancer cells [302]. IL-6 overexpression in MCF-7 cells induces E-cadherin repression and increases vimentin, N-cadherin, Snail, and Twist [302]. IGF-1 induces EMT in epithelial PCa cells ($ARCaP_E$) [303, 304] and is associated with increased Zeb1, N-cadherin, and fibronectin expression [304]. Targeting Zeb1 by small interfering RNA (siRNA) in mesenchymal PCa cells $ARCaP_M$ [303, 304] abrogates IGF-1-induced cell migration and motility, induces upregulation of E-cadherin, and decreases N-cadherin and fibronectin. This suggests that IGF-1 induces EMT in $ARCaP_E$ cells via the IGF-1R-Erk-Zeb1 pathway [304].

TGF-β is a multifunctional cytokine that inhibits proliferation of normal prostate. Thus, targeting TGF-β signaling early in the tumorigenic process may mitigate its tumor suppressing activity and enable rapid tumor growth and metastasis in PCa [305]. CRPC and recurrent PCa frequently produce osteoblastic bone lesions stimulated by TGF-β released from the tumor microenvironment or bone matrix [306]. Interestingly, a strong correlation was found between elevated plasma TGF-β1 and PCa progression and metastasis in locally advanced disease patients [307]. Consequently, members of the TGF-β signaling family are being considered as predictive biomarkers and molecular targets for the prevention and treatment of metastatic PCa [308]. Indeed, elevated serum TGF-β is considered a poor prognosis marker [309, 310]. One mechanism by which TGF-β contributes to cancer progression is the induction of EMT. Upon TGF-β treatment, epithelial cells showed decreased expression of epithelial markers and enhanced expression of mesenchymal markers such as E-cadherin and vimentin, respectively [311]. TGF-β1 overexpression in the rat prostate carcinoma line resulted in enhanced primary tumor growth and both lung and lymph node metastasis after subcutaneous implantation. Targeting TGF-β1 with an antisense oligonucleotide inhibited primary tumor growth and metastasis [312]. Thus, TGF-β1 expression can enhance metastasis of rat prostate carcinoma cells. Mechanistically, TGF-β binds to cell surface receptors which in turn phosphorylate and activate Smad2 and/or Smad3. Smads then translocate to the nucleus and regulate gene transcription [313–315]. In advanced PCa, TGF-β enhances the metastatic ability of cells and provides a driving mechanism for high tumor vascularity [305]. TGF-β can also activate PI3K, MAPK, and p38 kinase signaling pathways in Smad-independent manner [316].

## Inflammation

Recently, inflammation has been functionally linked to metastasis [317]. Many inflammation-associated proteins, including tumor necrosis factor (TNF)-α interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-11 (IL-11), TGF-β, cyclooxygenase 2 (COX-2), NFκ, Stat3, stromal-derived factor-1 (SDF1), and hedgehog, facilitate PCa growth, tissue invasion, and, importantly, metastasis. Furthermore, inhibition of, for example, the COX-2 enzyme, which catalyzes the conversion of arachidonic acid to prostaglandins, has led to inhibition of tumor growth and suppression of metastasis in multiple cancers, including PCa [318]. Accordingly, inhibition of cancer-associated inflammation has emerged as a promising approach for treatment of metastatic PCa.

The nuclear transcription factor, NF-κB, is a key regulator of immune, inflammatory, and acute phase responses and has also been implicated in the control of cell proliferation and apoptosis [319]. It is overexpressed in many human cancers, including metastatic PCa [320, 321]. Stat3, which is both a cytoplasmic signaling molecule and a nuclear transcription factor, belongs to the seven-member Stat gene family of transcription factors. Recently, it has been reported that Stat3 is activated in PCa metastasis [322]. Hence, NF-κB and Stat3 may serve as potential targets for inhibition of metastatic progression of PCa. RTA 402, an NF-κB and Stat3 inhibitor, has demonstrated anticancer activity in preclinical studies and a recent clinical phase I pancreatic cancer trial [323]. This inhibitor is now moving into phase II trials. Moreover, several small molecule inhibitors for such targets are under preclinical development [324].

The chemokine stroma-derived factor, SDF-1/CXCL12, plays multiple roles in tumor pathogenesis, promoting PCa growth, enhancing angiogenesis, contributing to immune-suppressive networks within the tumor microenvironment, and facilitating tumor metastasis [325, 326]. The interaction of CXCL12 and its receptor CXCR4 leads to mitogen-activated protein kinase and phosphoinositide 3-kinase/Akt-mediated MMP-9 expression, migration, and invasion of PCa cells [327]. A wide variety of strategies, based on peptides (e.g., T22) [328], small molecules (e.g., AMD3100) [329], antibodies [330], and small interfering RNAs [331], have been used to target this pathway. Treatments in combination with current therapies seem to be especially promising in preclinical studies, and compounds are advancing into early stages of clinical development [332].

The hedgehog pathway has also been implicated in PCa development and metastasis [333]. The multi-transmembrane protein, patched (PTCH), is the receptor for various hedgehog ligands (Sonic, Indian, and Desert). In the absence of hedgehog, PTCH inhibits Smoothened (SMO), a G protein-coupled receptor protein encoded by the SMO gene of the hedgehog pathway [334]. When hedgehog binds to PTCH, SMO is disinhibited and initiates a signaling cascade that results in activation of GLI transcription factors and increased expression of target genes (including PTCH and GLI1). Inhibition of the hedgehog pathway induces apoptosis and decreases tumor invasiveness of PCa cells. For example, IPI-926 (Infinity Pharmaceuticals, Inc.), a small molecule inhibitor of the hedgehog-signaling pathway, has shown potent efficacy and specific inhibition of the hedgehog pathway in multiple preclinical animal cancer models. Currently, IPI-926 is in a clinical phase 1 trial for patients with advanced and/or metastatic solid tumors. GLI2 knockdown in preclinical models induces apoptosis, inhibits cancer growth, and chemosensitizes cells to chemotherapy in vitro and in vivo, providing preclinical proof of principle for CRPC [335]. The approach of regulating cancer-associated inflammation is a promising treatment strategy for a variety of tumors, including PCa.

## Site-Specific Bone Metastasis

Bone metastases represent 98 % of malignant bone tumors and are the most frequent metastases occurring in PCa. It estimated that 30–50 % of patients with PCa will develop bone metastases with the progression of the disease. Indeed, these bone lesions are often associated to pathological fractures, palpable mass, bone loss and/or formation, spinal cord compression, and severe bone pain [336].

The discovery by two different groups in 1997 of receptor activator of nuclear factor κB (NF-κB) (RANK) [337] and RANK ligand (RANKL) [338, 339] and decoy receptors osteoprotegerin (OPG) [340, 341] have allowed a better knowledge of the molecular mechanisms involved in the regulation of bone remodeling. In bone, OPG and RANKL are expressed by osteoblasts and bone marrow stromal cells whereas RANK is found at the surface of mature osteoclasts and osteoclast precursors. The binding of RANKL to RANK on pre-osteoclasts induces their differentiation, maturation, and activation leading to bone resorption. Therefore, RANKL is an essential mediator of osteoclast formation, function, and survival, whereas OPG, a decoy receptor for RANKL, operates as a real competitor of RANK/RANKL interaction and prevents this latter to interact with RANK. Consequently, OPG inhibits the osteoclastic differentiation and activation, leading to protection against bone loss.

Metastatic development within bone relies on a "vicious cycle" between bone resorption and tumor proliferation [342, 343]. Bone pathology from metastases is associated with altered expression of cytokines involved in the regulation of bone remodeling, including OPG, RANK, and RANKL (RANK Ligand), all members of the TNF (tumor necrosis factor)/TNF receptor superfamilies. Indeed, tumors in bone environment produce factors such as parathyroid hormone-related peptide (PTH-rP), which increases RANKL production by osteoblasts or by bone marrow stromal cells promoting differentiation, activation, and maturation of pre-osteoclasts into mature osteoclasts. Tumor cells also secrete various factors such as interleukin (IL)-6, IL-11, TNF-α, IL-1α, colony stimulating factor-1, or macrophage inflammatory protein-1α activating osteoclasts, which degrade the bone matrix. Bone matrix also store and release growth factors (e.g., IGF-1, TGF-beta) or chemo-attractants (e.g., SDF-1) to attract tumor cells and stimulate osteoblast proliferation [344–346]. Predominantly produced by stromal cells or osteoblasts, RANKL may be produced by tumor cells themselves increasing osteoclast activity and leading to excess bone loss [347–350].

The discovery in the past few years of this OPG/RANK/RANKL triad and its role in pathophysiology of skeletal metastasis has led to promising therapeutic targets [351–354]. For example, as OPG blocks the RANK/RANKL interaction, it represents a potent antiresorptive molecule to use in degradative bone pathologies by tumors [340, 343, 346, 355–357]. Furthermore, denosumab, a human monoclonal antibody that neutralizes RANKL in the tumor-bone microenvironment, inhibits osteoclastogenesis and bone degradation associated with prostate and other cancers. Randomized clinical studies of denosumab in metastatic PCa and elevated bone marker uNTX levels have shown promising results in normalizing uNTX more frequently than bisphosphonates [358]. Double-blind randomized phase 3 clinical trial is ongoing in CRPC patients with detected bone metastasis (e.g., ClinicalTrials. Gov Identifier: NCT00286091).

Endothelins (ETs), especially ET-1, and their receptors, ET-AR and ET-BR, are often overexpressed in tumor playing a role in tumor cell proliferation, angiogenesis [359], as well as osteoblasts proliferation increasing bone density in PCa bone metastasis [360, 361]. Several antagonists of ET-AR, including atrasentan and ZD4054, exhibited promising phase II results in CRPC [362]. Unfortunately, several phase III trials of atrasentan and ZD4054, either alone or in combination with docetaxel, were negative, and further targeting of this axis is unlikely.

Others important pathways in bone metastasis include Src, cathepsin K, RANKL, and WNT pathways. SRC expression is correlated with tumor progression and metastasis [363], and SRC inhibitors currently in clinical trials include saracatinib (AZD0530: phase II trial; NCT00558272) and dasatinib (phase III trial; NCT00744497). Cathepsin K is a key enzyme involved in osteoclastic bone resorption and bone matrix degradation [364]. Cathepsin K is often expressed in cancers with high tendency to metastasize to bone including PCa [365]. Several inhibitors of cathepsin K were developed including L006235 or odanacatib (MK-0822). Odanacatib is in clinical development [366] and showed reduced urinary NTx bone marker after 4 weeks in a randomized phase II study in metastatic breast cancer [367]. Wnt pathway is a major signaling pathway in osteoblasts and is regulated by soluble antagonists including DKK-1. DKK-1 increases RANKL/OPG ratio enhancing osteoclastogenesis. In a recent study, DKK-1-neutralizing antibodies increased the number of osteoblasts, reduced number of mature TRAP-positive osteoclast, reestablished the bone mineral density, and decreased the tumor volume in treated mice in myeloma model [368] indicating that targeting Wnt/DKK1 pathway is a rational therapeutic strategy for bone metastasis by regulating osteoblastogenesis and osteoclastogenesis.

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# Immunologic Aspects of Prostate Cancer

5

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## Prostate Cancer and the Immune System

The concept that cancer can be eliminated by the immune system has been put forward over 100 years ago [1]. At this time, it was already thought that immune effector cells can recognize cancer cells as non-self and can eliminate them in the same way as viral or microbial pathogens. Both the innate immune system and the adaptive immune system have a major role in the control of tumor cell growth. The innate immune system consists of nonantigen-specific cells including macrophages, dendritic cells, neutrophils, natural killer cells, gamma delta T cells, and complement. The adaptive immune system consists of cells such as antigen-specific cytotoxic and helper T cells and antibody-producing B cells which can obtain a memory phenotype against specific antigenic challenge. The result is the ability of the different immune cell types to recognize cancer cells as foreign [2]. Antigens produced by tumor cells are known to be recognized by T cells and B cells, and both tumor antigen-specific T cells and antibodies against tumor antigens can be detected in patients with cancers such as melanoma, ovarian cancer, colorectal carcinoma, and hepatocellular cell carcinoma [3, 4]. Tumor-related antigens fall into a number of types including unique patient or shared tumor-specific antigens, antigens which are in both tumors and normal tissues, and antigens derived from tumor-associated viruses. In prostate cancer, a number of antigens are expressed which can be used for prostate cancer diagnosis or monitoring and some viruses are also thought to be associated with prostate cancer pathogenesis (Table 5.1).

Tumor elimination is initiated by the initial recruitment of immune cells including either neutrophils, monocytes, and macrophages to the site of the tumor, normally through the presence of acute or chronic proinflammatory signals which are produced by normal or tumor cells reacting to the tumor microenvironment [13, 14]. These cells release cytokines and chemokines such as IL-8 and IL-6 which will attract T cells and NK cells to the sites of the tumor. Inflamed endothelium in these areas also expresses E-selectin, which will recruit cells such as T and B lymphocytes and neutrophils which express carbohydrate ligands such as Lewis x and sialyl Lewis X. Once T cells and NK cells enter tumor lesions, they will secrete other chemokines and cytokines such as interferon gamma and IL-2 and IL-12 for further recruitment of T cells, NK cells, B cells, and Dendritic cells – the latter cells are critical in taking up antigens for presentation to helper T cells in the lymph nodes for creation of antigen-specific T cells and for creation of an antibody response against the tumor antigens. B cells also take up antigen for processing either through T cells or independently and can process antigen for antibody production. During the last stages of the elimination phase, tumor-specific CD4 helper and CD8

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**Table 5.1** Tumor associated and viral antigens in Prostate Cancer

| Type of tumor-associated antigens | Example in prostate |
|---|---|
| Unique point mutation-specific tumor antigens | Spas-1 [5] |
| Tumor-specific antigens | Cancer–testis antigens, for example, NY-ESO1 [6] |
| Overexpressed antigens (greater expression in tumor vs. normal tissue) | GAD1 [7], CARM-1 [8], PSMA [9], PSA [10], Dickkopf-1 [11] |
| Viral antigens | Epstein bar virus and human papiloma virus 18 [12] |

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cytotoxic T lymphocytes from the lymph nodes and tumor-specific antibodies infiltrate the lesion to eliminate the tumor cells, with some antibodies acting through ADCC (antibody-dependent cellular cytotoxicity) via Fc receptors on NK cells.

## Immunoediting

The concept of tumor elimination by the immune system has been superseded by a new hypothesis, known as *immunoediting* [15] which is relevant in many cancers including prostate cancer. In this hypothesis, there is the initial phase described above where the immune system can recognize and actively react and eliminate tumor cells appearing within a normal tissue environment; however, there are two further phases known as equilibrium and escape.

In the equilibrium phase, there is a balance between the destruction of tumor cells by the immune system and the proliferation of new tumor cells in the lesion. The new cells formed are eliminated in due course, but the immune system cannot eliminate the lesion completely. In prostate cancer and breast cancer, this phase may last for many years with either a minimal residual tumor volume obtained after surgery or radiotherapy or with small tumors that are nonpalpable and therefore not detectable [16]. Although reasons for this equilibrium state are as yet unclear, the coexistence of tumor cells with immune cells has been observed in a number of animal models.

The third stage of the hypothesis is known as *escape*. In this phase, cells may be growing at a rapid or slow rate, but are now able to evade the immune system by one or more of a number of techniques. These include the production of factors to prevent attack or masking of the cell surface by a loss or alteration of surface antigens such as MHC molecules, or the ability to move away from the site of capture (metastasis). Such cells that are growing in the presence of an ongoing immune response have either grown to resist the immune system by selective pressure or have an inherent or induced genetic predisposition to evade recognition or to inhibit the effector cells that they encounter.

## Factors that Cause Immunosuppression in Prostate Cancer

There are a number of immunosuppressive factors that the tumor cells themselves or the cells or stroma of the tumor microenvironment are able to produce to enable to continue existence of a cancer population. The microenvironment of the cancerous prostate has been shown to be very immunosuppressive, and prostate cancer cells are frequently poorly immunogenic, that is, unable to give rise to an immune response.

### Suppressive Immune Cell Populations Within the Prostate Tumor Environment

Although the infiltration of functionally active lymphocytes into tumor lesions is a favorable state for elimination of the tumor cells, in high-grade prostate cancer, immune infiltrates of CD3+ T cells are significantly diminished [17]. Also, immune infiltrates have been shown to frequently consist of anergic or suppressive T cell populations such as CD4+CD25+FOXP3+ regulatory T cells (known as Tregs) and also a rarer CD8+CD25+FOXP3+ population [18]. Both these cell types suppress both T cell proliferation and activity and NK function. Other suppressor populations appearing in the infiltrate are myeloid suppressor cells – these are immature myeloid cells which are either resident in the tissue or migrate there through recruitment, but have a suppressor function against dendritic cells, T cells, and NK cells in the tissue. The phenotype of these cells is not well characterized, but is thought to consist of Cd33+CD11b positive cells. The suppressive cells are either recruited into the tumor lesion by chemokines secreted by the tumor itself, or they are formed from active nonsuppressive effector cell populations through the functions of cytokines secreted from the tumor or stromal tissue [19]. For example, prostate cancer cells and the cells of their surrounding environment such as fibroblasts can secrete TGF beta, IL-2, and IL-10 which can actively induce the production of Tregs and myeloid suppressor cells. Although Tregs can naturally occur in the immune system, they are of thymic origin, and therefore as the thymus is absent or atrophied in old age, the Tregs of prostate cancer patients (who are diagnosed later in life) are thought to be induced in the tumor environment itself. The molecule indoleamine 2,3-dioxygenase (IDO) secreted by myeloid suppressor cells and by fibroblasts and other stromal components also suppresses T cell and NK cell function.

### Suppressive Stroma-Associated Proteins in the Prostate Cancer Environment

A number of suppressive prostate-associated proteins have also been discovered, for example, fibroblast-associated protein (FAP-1) and ps20 [20, 21]. These proteins are secreted in the normal prostate microenvironment, but higher levels are associated with cancer progression with the proteins being expressed by the tumor cells in addition to the stromal cells. Their inhibitory functions have not been well

characterized, but they can inhibit proliferation and function of effector T cells and NK cells.

### Complement Regulatory Proteins

Complement attack of tumor cells can happen through direct antibody involvement or through ADCC mechanisms, as described previously. The inhibition of complement by tumor cells is an evasive mechanism, which attenuates the effects of antibodies toward tumor antigens and also may reduce the efficacy of antibody therapies such as Herceptin [22]. Membrane-bound complement regulatory proteins such as CD46, CD59, CD55, and CD97 (a receptor for CD55) are known to be expressed frequently on tumor cell populations [23, 24], and the receptors CD55 and CD97 are upregulated in prostate cancer biopsies from primary and metastatic disease and in patients with prostate intraepithelial neoplasia (PIN) compared to biopsies from normal prostate [25].

### Loss of Antigenic Proteins

MHC class I antigens are expressed on almost all human-nucleated cells and play a vital part in the antiviral and antitumor immune response by their ability to present intracellular protein-derived peptides to antigen-specific cytotoxic T lymphocytes (CTLs). In many cancers, including prostate cancer, there is a dramatic loss of MHC class I antigen with tumor progression, and 100 % of prostate metastases have no class I-expressing cells [26] Also, in one study, expression of class 1 protein, corresponding to an HLA-A genotype, has been shown to be partially or completely lost in approximately 90 % of the tumors examined: However, only 8 % of these patients also had a deletion of the HLA-A1 and HLA-A2 alleles – so that the loss of expression is mostly at the translational level [27]. Upregulation of expression of MHC class I protein on the cell surface is possible with some immunotherapeutic, chemotherapeutic, and radiotherapy regimens. For example, interferon gamma upregulates MHC class I expression on prostate cancer TRAMP-C1 MHC class I negative tumors [28]. Radiotherapy upregulates a number of cell surface molecules including MHC class I and FAS (CD95) that make tumor cells more susceptible to T cell-mediated immune attack [29]. Chemotherapeutic drugs such as 5-Aza-2′-deoxycitidine also increase expression of class I on a number of tumor cell lines including those of prostate cancer [30].

### Expression of Inhibitory Receptors

Tumor cells can also be eliminated by their lack of expression of MHC class I antigens which are monitored by NK cells through the missing self-hypothesis [31]. However, this hypothesis has also been modified on the discovery of families of inhibitory receptors on NK cells and their corresponding ligands on tumor cells [32, 33]. Such families of receptors including the KIR [32, 34] and LILR receptors [35–38] (which were originally discovered in myeloid cell populations such as monocytes and dendritic cells) and their ligands including nonclassical MHC molecules such as HLA-G [37, 39–41] and HLA-E [42] can promote potent immunosuppressive functions, and tumor cells commonly express these ligands in prostate cancer.

## Immunotherapy Strategies

Various ways to exploit the immune system to treat prostate cancer are being tried clinically. Either employing a whole tumor cell or part of its components is usually used to elicit a specific immune response. Below is a range of immunotherapy strategies.

### Cell-Based Immunotherapy

The concept of cell-based immunotherapy is to expose a whole tumor cell to the immune system to evoke a response to multiple antigens, thus acting as a vaccine. The allogeneic tumor cells are introduced into the patient where these cells can attract antigen-presenting cells (APCs) to the site of introduction. The introduced cells are destroyed and taken up by APCs, which present the antigen to T cells and activate T cell cytotoxic activity toward tumor cells in the patient. Dranoff et al. examined the immunogenicity of irradiated melanoma cells in mouse models [43]. Retroviral gene transfer of some cytokines into the tumor cells was used to enhance the immunogenicity of the tumor cells. Irradiated transduced vaccine tumor cells were injected. A high level of CD4+ and CD8+ T cell immune responses was observed. The GM-CSF attracts antigen-presenting cells to the injection site. Other cytokines did not show similar antitumor activity [43]. The treatment works by recruiting antigen-presenting cells (APC) such as dendritic cells to injection sites. The vaccine cells are lysed, and the debris are taken up by APC, resulting in TH1 and TH2 cell activation which activates cytotoxic cell tumor lysis.

The whole cell allogeneic immunotherapy treatment has been developed further and has used prostate cancer cell lines including the hormone-sensitive cell line LNCaP and hormone-resistant cell line PC3. In a phase II trial studying the effect of this type of treatment, dendritic cells and macrophages in addition to eosinophils were present at site of intradermal injection confirming the ability of the transduced cells to secrete GM-CSF in vivo [44]. Several patients mounted LNCaP and PC3 reactive antibodies. There is a

possible correlation between the antibody titre and time from vaccination. This treatment strategy exposes multiple tumor antigens to potentiate the antitumor immune response.

## Antigen-Based Immunotherapy

This strategy focuses on one antigen to evoke an antitumor immune response.

Various tumor-associated antigens (TAA) have been studied for this type of treatment. Three of them have been targeted. Prostatic-specific antigen (PSA) is a glycoprotein and a serine protease enzyme secreted by the epithelial cells of the prostate gland. Another antigen is prostate acid phosphatase (PAP), which is expressed in vast majority of prostate cancer cells. The third antigen is prostate-specific membrane antigen (PSMA). The selected antigen can be carried and introduced to its target using various mechanisms including a virus vector or DNA plasmid or using one of the host's own antigen-presenting cells as a vehicle. These methods are discussed in more detail below.

### Viruses as Antigen-Carrying Vector-Based Immunotherapy

A vaccine is used as a vehicle for the targeted antigen. The most commonly used vector is vaccinia virus as prime vaccine and fowlpox virus as booster vaccine (PROSTVAC VF). This vaccine has a DNA plasmid-encoding PSA, in addition to costimulatory molecules (lymphocyte function-associated antigen 3 LFA3, CD80, and intracellular adhesion molecule 1 (ICAM1)). All three molecules form the triad of costimulatory molecules (TRICOM) and are designed to synergistically enhance T cell proliferation [45]. The viral vector is injected intradermally infecting epithelial cells which eventually die with cell debris including the PSA as antigen which is taken up by antigen-presenting cells (APC) and present it to CD4+ and CD8+ which leads to immune responses against PSA-producing cancer cells. The immune response can be limited by antibody responses to the viral protein rather than the encoded antigen. This type of treatment is effective if cancer is caused by viruses (HBV, HPV) as the vaccine would be used as a preventive measure.

Virus-based vaccine strategy is limited to the small number of virus options that can be used; in addition, there is the need for a repeated booster dose. The immune response can be dual in effect, one against the viral vector which the undesirable but sometimes inevitable response and the other one against the target antigen carried in the vector virus which the desirable response. Plasmid DNA-based vaccines aim to avoid the disadvantages of having a carrier viral vector and use plasmid to carry the genetic code for the desired antigen to generate an antigen-specific T cell response. A plasmid vector is used to encode an antigen sequence, for example, PAP, and is injected intradermally with or without GM-CSF [46, 47] to elicit the desired immune response.

### Antigen-Presenting Cell-Laden-with-Antigen-Based Immunotherapy

In this type of approach, the antigen is loaded onto autologous APC. A recently Food and Drug Administration (FDA) approved treatment (Sipuleucel-T, Dendreon) is composed of autologous APCs which are loaded with PAP fused with GM-CSF [48]. This fusion protein is called PA2024 and is designed to help with antigen presentation by upregulating costimulatory molecules. The treatment starts by isolating the patient's dendritic cells (DC) by leukapheresis. Then, the cells are incubated with the fusion protein for 40 h. The cells take up the protein. The product is then injected intravenously into patient. GM-CSF mediates PAP presentation. The elicited immune response includes activation of CD4+ and CD8+.

## Antibody-Based Immunotherapy

The preferred antigen for this type of approach is PSMA, which is a transmembrane glycoprotein. It has an internalization motif which makes it ideal target for monoclonal antibodies [49]. An anti-PSMA antibody has been developed in the mouse and is deimmunized (J591). The antibody is labeled with a radioisotope $^{177}$lutetium. The antibody aims to bind the target prostate cancer cells where the radioisotope gamma emissions induce cell death [49, 50].

Another antibody used in immunotherapy is anti-CTLA-4. This is a monoclonal antibody also known as MDX-010 or Ipilimumab. This antibody targets the immune system rather than the tumor. CTLA-4 (Cutaneous lymphocyte antigen-4) is an immunoregulatory molecule on T cells which competes with CD28 on T cells to bind to B7.1 and B7.2 antigens and thus regulates T cell activation. The deficiency of CTLA-4 results in lymphoproliferative disorders [51], and the immune suppressive function of Tregs depends on CTLA-4 [52]. Inhibition of Treg activity by anti-CTLA4 can therefore potentiate anti-tumour immunity by activation of T cells [53, 54].

## Conventional Treatment and Immunology

Conventional prostate cancer treatment modalities such as hormone, radiotherapy, and chemotherapy alter the immune system.

Androgen ablation may boost the antitumor immune response. CD4+ number in the prostate gland increases after treatment with antiandrogen, expansion of naïve T cells, increase in effector T cell response, and production of prostate-associated antibodies. All indicate that androgen deprivation may facilitate a favorable antitumor environment [55]. Radiation treatment has similar effect on immune system. Hurwitz et al. found that in 13 prostate cancer patients treated with radiotherapy, there was increased number of CD8+ and NK cells in addition to higher level of heat shock protein

(HSP) 27 level. HSP27 acts as immunomodulator and has a role in activating cytotoxic T cells [56]. Another protein (HMGB1) is released by radiotherapy-treated dying cells; Apetoh et al. found that HMGB1 is the primary ligand for TLR4 which activates dendritic cells and provoke T cell response. The combination of these conventional treatment modalities with the new immunotherapeutic modalities is being explored in various trials [57].

## Clinical Trials in Prostate Cancer Immunotherapy

### Cell-Based Immunotherapy

#### GVAX

The GVAX platform involves injecting tumor cells to provoke immune response, thus presenting to the immune system a cocktail of antigens, which increases the likelihood of a tumor-specific immune response [43]. The tumor cells are genetically modified to secrete GM-CSF. Two cultured allogenic prostate cancer cell lines are used, PC3 and LNCaP. Cell lines are genetically modified to encode the GM-CSF gene and are irradiated to prevent proliferation.

The initial dose escalating study recruited 80 hormone refractory metastatic prostate cancer patients. Symptomatic patients were excluded from the study. Five dose levels were used. Patients divided into three different groups: low-dose, moderate-dose, and high-dose groups. Treatment ranges from once every 28, 14, and once, and it lasted for 6 months; doses started at $100 \times 10^6$ cells. The study was stopped prematurely due to disease progression in 90 % of patients in addition to adverse events in 2 %. However, it did record that the antibody response was proportional to dose and was highest for the high-dose group (89 %) and lowest for the low-dose group (43 %). The median survival was 35 months (high dose), 20 months (moderate dose), and 23 months (low dose) groups, respectively. PSA stabilized in 19 % of patients. The study couldn't determine a maximum tolerable dose [54].

In a phase III trial by the same group, GVAX was compared to docetaxel and prednisolone treatment for castrate resistant metastatic prostate cancer patients. Six hundred and twenty six patients were recruited from more than 100 centers in North America and Europe. GVAX was given in 13 doses every 2 weeks and then as maintenance doses for a total of 6 months. The study was prematurely terminated as it showed the futility of achieving the primary end point of increased overall survival. The survival analysis showed no superiority in survival of GVAX over the chemotherapy arm [58].

Another phase III trial comparing GVAX in combination with docetaxel was carried out with patients in the control arm receiving docetaxel and prednisolone. The study aimed at recruiting 600 castrate resistant prostate cancer patients; however, it was terminated following recruiting 408 patients due to high death rate in the treatment arm and survival advantage in the control arm [59].

### Antigen-Based Immunotherapy

#### PROSTVAC

Prostatic-specific antigen (PSA) is at target for immunotherapy as it is exclusively expressed in the prostatic epithelial cells. Vaccinia virus elicits humoral and cell-mediated responses, and a recombinant form of vaccinia virus encoding PSA (rV-PSA) is used to enhance the immunogenicity of PSA-producing cells and subsequently cell lysis. In a clinical trial of 33 men with prostate cancer recurrence after radical prostatectomy or radiotherapy, rV-PSA was given on three monthly dose basis. A PSA-specific T cell response was present in five patients in whom PSA blood level stabilized for up to 21 months posttreatment. IgG and IgM humoral response was observed in one patient only [60].

In a phase II randomized trial, rV-PSA was used as a prime vaccine with fowlpox virus encoding PSA as a boost vaccine (rF-PSA). Sixty-four patients were recruited with organ-confined prostate cancer with biochemical failure after local radical treatment of surgery or radiotherapy. An increase of absolute measure of PSA above 2 ng/ml after surgery or three consecutive increases after radiotherapy constituted biochemical failure. Neoadjuvant chemotherapy or hormonal treatment was given for 6 months prior to enrolling into the study. All participants had negative bone scans and no evidence of locally advanced disease. Patients were assigned to three treatment arms, one to receive 3rF-PSA vaccine alone, another to receive multiple doses of 3rF-PSA vaccine followed by one dose of rV-PSA, and a third arm to receive multiple doses of rV-PSA followed by single dose 3rF-PSA. The study did not have a control arm with conventional treatment. The results showed no objective biochemical response, with 45 % of patients showing no PSA progression and 78 % free of clinical progression at 19 months with no difference between the treatment arms. The immunologic response did not show increases in anti-PSA antibody, but there was an increase in PSA-induced T cell proliferation [61].

Another phase II trial evaluated the effectiveness of rV-PSA [62]; however, this group used a different T cell costimulatory molecule (B7.1) and IL-2. In addition, granulocyte-macrophage colony-stimulating factor (GM-CSF) was given to enhance dendritic cell recruitment. This treatment regime was compared to antiandrogen (nilutamide) treatment. A total of 42 hormone refractory metastatic-free prostate cancer patients were randomized to receive prime/boost strategy (rV-PSA, rF-PSA); however, the treatment continued rF-PSA boost on a monthly basis till disease recurrence contrary to the four doses regime in the previous trial. The antiandrogen treatment arm received nilutamide orally on

daily basis till disease recurrence. A crossover of 12 patients from the vaccine to the antiandrogen arm and 8 patients from the antiandrogen to the vaccine arm was observed. There was no difference in time to treatment failure for the vaccine arm (9.9 months) and nilutamide arm (7.6 months). Time to treatment failure for combined therapy was 13.9 months (vaccine then nilutamide) extending the overall treatment to 25.9 months and 5.2 months (nilutamide then vaccine) with total treatment of 15.9 months. PSA-specific T cell response was observed in varying degrees in the vaccine treatment arm. In the vaccine arm, 13 patients had decrease in their PSA velocity compared to 16 in the nilutamide arm. It is notable that sequential treatment with hormone following vaccine showed improved clinical outcome, but no conclusion can be drawn, as there is potential selection bias as patients receiving additional treatment had less aggressive disease.

The largest trial to assess PROSTVAC-VF randomized 125 patients from 43 centers in the United States (US) in 2:1 randomization ratio to achieve 80 % study power [63]. In the vaccine arm, the treatment regime included one priming dose of rV-PSA-TRICOM and six boosts of rF-PSA-TRICOM in addition to GM-CSF adjunct treatment. The control arm received empty vaccinia vector and empty fowlpox vector boosts in an identical regime as to the treatment arm. Patients who had minimally symptomatic castration-resistant metastatic prostate cancer (mCRPC) were eligible for the study. Progression-free survival were similar in both arms; however, at 3 years, the overall survival for the treatment group was better (30 %) compared to the control group (17 %), lengthening the survival by 8.5 months. The immunological studies did not detect humoral response to PSA vaccine. This well-designed study failed to find a correlation between treatment arm and progression. However, clinically, it did show the improvement in overall survival in the relatively small group of patients [63].

### DNA Vaccine

A dose escalating trial assessing the toxicity of pTVG-HP a plasmid DNA-encoding prostate acid phosphatase (PAP) has been conducted. Twenty-two patients were treated with escalating dose of intradermal injection of the vaccine with GM-CSF as adjuvant treatment for six times over 14 days interval. The trial confirmed treatment safety. Fourteen percent of patients developed PAP-specific IFNγ secreting CD8+ T cells. There was no significant clinical response; however, PSA doubling time was increased in some patients [64].

## Antibody-Based Immunotherapy

### Ipilimumab

A phase III double blind randomized controlled trial compared ipilimumab to placebo, in castrate resistant metastatic prostate cancer who are receiving radiotherapy. The study by Bristol Myers Squibb is ongoing and aims at recruiting 800 patients and is expected to conclude in 2012 (Trial number NCT00861614).

### Radioisotope Ab

A phase I study looked at anti-prostate-specific membrane antigen (PSMA) which was a murine deimmunized antibody (J591). It was attached to the radiometal $^{177}$Lu (lutetium-177). This study recruited 35 castrate resistant prostate cancer patients. All received the treatment up to 3 doses. The results showed that myelosuppression occurred with higher doses. There was no anti-J591 antibody development, and all sites of metastasis took up the radio-labeled antibody. PSA stabilization was observed in almost half of patients. This study confirmed excellent targeting ability of anti-PSMA [49].

A phase II randomized trial by Weil Cornell University is ongoing and is recruiting 140 patients into two arms. A monoclonal anti-PSMA (murine deimmunized J591) labeled with $^{177}$Lu is being used in the treatment arm, and $^{111}$In-J591 is being used in the control arm. $^{111}$In is a weak radioactive label that does not kill cancer cells. The study is recruiting patients who were previously treated with surgery or radiotherapy and have biochemical recurrence but not metastasis (NCT00859781).

Another trial by the same group is assessing the suitability of monoclonal antibody treatment of $^{177}$Lu-J591 and is recruiting patients with castrate resistant metastatic prostate cancer (NCT00195039).

A third trial is assessing the toxicity of radiolabeled monoclonal anti-PSMA treatment in adjunct with docetaxel. Castrate resistant metastatic prostate cancer patients are being recruited (NCT00916123).

## Antigen-Presenting Cell Loaded with Antigen-Based Immunotherapy

### Sipuleucel-T

This is a phase III trial that recruited 127 patients with 2:1 randomization ratio of treatment versus placebo. Eligible patients had metastatic prostate cancer with a prognosis of at least 3 months to live. The treatment arm patients were given APC8015 (Sipuleucel-T) in three doses 2 weeks apart for each dose. There was 48 h between the time of apheresis and infusion of treatment product. The placebo group received non-pulsed APCs. Results showed a significant median survival of 25.9 months for the treatment arm compared to 21.4 months for placebo, a total of 4.5 months improvement in survival. In addition, there was an eightfold increase in T cell stimulation in the treatment arm [65].

An updated study reported the survival results of randomized trial comparing three different doses of Sipuleucel-T to

placebo [66]. The same group recruited 512 castrate resistant metastatic prostate cancer patients in 2:1 treatment placebo ratio. The results confirmed the previous trial result of a survival benefit for the treatment arm of 25.8 months compared to 21.7 of placebo group. The treatment was generally well tolerated.

### Conclusion

The prostate may not be an ideal environment for a naturally effective antitumor immune response, but the new emerging evidence links chronic inflammation and cancer development. HGPIN is a precancerous lesion and chronic prostatitis may play a role in carcinogenesis, and more research into the immune homeostasis in these conditions may hold some keys to understanding of immune tolerance and cancer formation. The challenge for antitumor immune stimulation remains high, and to date the only approved treatment for prostate cancer is expensive and has survival advantage of 4.1 months [66]. It is huge step forward for immunotherapy in prostate cancer but hardly a paradigm shift. Most of the immunotherapy treatment modalities are aimed at end-stage prostate cancer or CRPC, and certainly there is "potential" for targeting early disease perhaps in precancerous conditions.

(Synopses of trials with NCT number are available on www.clinicaltrials.gov).

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# Stem Cells in Carcinogenesis of the Prostate

6

Shi-Ming Tu and Sue-Hwa Lin

## Introduction

A key to solving the beginning of cancer is to elucidate its *cell of origin*. Hence, an unspoken appeal of the *stem-cell theory of cancers* is its focus on the cellular aspects of cancer. Many biologic phenomena vital for cancer cells are shared by stem cells. Both stem-cell and cancer cell activities are tightly regulated by their respective microenvironments or niches. Therefore, it is not coincidental that epithelial-to-mesenchymal transition (EMT) and epithelial-stromal interactions, which are critical for organogenesis, also play an important role in carcinogenesis. We propose that the theory of a stem-cell origin of cancers that encompasses all aspects of cancer, including heterogeneity, metastasis, drug resistance, etc., may be our long-sought unified theory of cancer.

This chapter will illustrate the biologic ramifications and clinical implications of stem cells in carcinogenesis of the prostate. We would like to demonstrate that prostate cancer stem cells may be involved in the many facets of prostate cancer and that the theory of a stem-cell origin of cancers represents a major *paradigm shift*, which may completely overhaul our understanding and knowledge of prostate cancer.

## Prostate Stem Cells

Stem cells possess three unique properties, i.e., dormancy, self-renewal, and pluripotency. Stem cells have long been implicated in prostate glandular formation. The prostate undergoes regression after androgen deprivation and regeneration after testosterone replacement. This cycle of regression and regeneration can occur more than 30 times [1]. It is presumed that the cells responsible for this recycling are "immortal" stem cells. Furthermore, the putative prostate stem cells are capable of differentiation into at least three distinct cell types, namely, basal cells, neuroendocrine cells, and luminal cells.

The three prostate cell types can be distinguished by their location, cellular markers, and functions. *Basal cells* and *neuroendocrine (NE) cells* are found in the basal layer of the prostate gland. Basal cells are characterized by expression of high molecular weight cytokeratins (CK) 5 and 14, CD44, integrin $\alpha6\beta1$, and p63. P63 is involved in stem-cell maintenance and differentiation in the normal prostate. Basal cells also express bcl-2 and c-met, which mediate cell survival and invasive growth, respectively. Some NE cells express basal cell CK while others co-express prostate-specific antigen (PSA) and chromogranin A, suggesting that these cells may arise from local stem cells [2]. It is unclear whether NE cells are a subset of the basal cell lineage, belong to a unique epithelial lineage, or represent a lineage derived from a separate stem-cell population [3]. The third are *luminal cells,* terminal differentiated cells located in the luminal layer of the prostate. The luminal phenotype is characterized by expression of low molecular weight CK 8 and 18, androgen receptor (AR), and PSA.

Central to the idea of prostate stem cells is the existence of *intermediate cells*. Intermediate cells that express CK5/14/18 or CK5/18 may be cells in transit between basal and luminal cells [4]. A subset of $K19^+$ intermediate cells could be seen within both the basal and luminal layers, representing basal cells in the process of differentiating into luminal cells [5]. Another rare murine intermediate cell type co-expresses luminal CK8 and AR as well as NE markers [6]. Prostate stem cell antigen is also considered to be a marker of late intermediate prostate epithelial cell [7].

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**Table 6.1** Stem-cell markers and animal/human models of the prostate and prostate cancer

| Stem-cell markers | Cell lines/models | Reference |
|---|---|---|
| *Mice* | | |
| Bcl-2$^+$ | | Salm et al. [19] |
| Sca1$^+$/α6$^+$/Bcl-2$^+$ | Prostate-specific p53 and RB gene deletion mice | Burger et al. [12] |
| | | Zhou et al. [30] |
| Lin$^-$/Sca1$^+$/CD133$^+$/CD44$^+$/CD117$^+$ | | Leong et al. [45] |
| Sca-1$^+$/Clu$^+$/Tacstd2$^+$ | PSA-Cre; Pten-loxP/loxP mice | Korsten et al. [50] |
| Lin$^-$/Sca-1$^+$/CD49f$^{hi}$ | Pb-Cre; Pten null mice | Mulholland et al. [48] |
| | CARN: Nkx3.1-specific Pten deletion | Wang et al. [62] |
| Wnt, Shh | Fetal and adult prostate stem cells | Blum 2010 [29] |
| Lin$^-$/Sca-1$^+$/CD49f$^{hi}$ | | Lawson 2010 [49] |
| Lin$^-$/Sca-1$^+$/CD49f$^{hi}$ | cPten$^{-/-}$ | Liao 2010 [17] |
| *Human* | | |
| CD44$^+$/α2β1$^{hi}$/CD133$^+$ | Primary tumors | Collins et al. [35] |
| CD44$^+$/α2β1$^+$ | DU145, LAPC4, LAPC9 | Patrawala et al. [36] |
| CD133$^{hi}$/CD44$^{hi}$/OCT4$^{hi}$ | NHPrE1 | Jiang et al. [61] |
| Nanog/Sox2/Oct4/Lin28B | PC3PDGF-D | Kong et al. [47] |
| CD49f$^{hi}$/Trop2$^{hi}$ | Primary tissue | Goldstein et al. [23] |

## Stem Cell Markers and Assays

Study of prostate stem cells is still work in progress. A unique prostate-specific stem-cell marker has not yet been found. However, certain stemness markers that are generally present in various normal and cancer stem cells are also found in prostate stem cells. Among these stemness markers are β1 integrins, CD133, Sca-1, CD44, and the ABCG2-associated drug resistance proteins.

Collins et al. [8] showed that integrin α2β1$^+$ cells possessed stemness properties by displaying clonogenic growth and initiating *prostate acinus-like growth in xenografts*. Of interest, β1 integrin was crucial for sustaining a functional stem-cell population and establishing asymmetric division in the mammary system [9]. β1 integrin was also required for stem-cell maintenance and positioning of the stem-cell niche in the Drosophila [10].

*CD133* (prominin-1) is expressed in hematopoietic stem and progenitor cells as well as in non-hematopoietic (epithelial and endothelial) stem cells. *Fluorescence-activated cell sorting (FACS)* based on CD133$^+$ expression is commonly used to isolate and characterize putative stem/progenitor cells. CD133$^+$ prostate cells displayed stemness characteristics by virtue of their ability to form *prostaspheres* and develop prostatic-like acini in immunocompromised male mice [11]. Subclones of CD133$^+$ cells also expressed CK14 or TERT and engendered more numerous and larger branching ducts consisting of basal and luminal cells compared with their CD133$^-$ counterparts.

Stem-cell antigen-1 (*Sca-1*) is expressed by stem/progenitor cells in various tissues including hematopoietic, cardiac, mammary, integumentary, muscular, and testicular. Sca-1$^+$ cells are located in the proximal region of the developing prostate [12]. A majority of Sca-1$^+$ cells also expressed α2 integrin, CD49f, and bcl-2. Isolated Sca-1$^+$ cells were able to regenerate prostatic tubules [13]. Because the regenerated ducts are clonal and contain both basal and luminal cells, these Sca-1$^+$ cells are believed to possess stemness features and the capacity for multilineage differentiation.

*CD44* is a cell-surface receptor involved in cell-cell interactions, cell adhesion, and migration. A specialized sialofucosylated glycoform of CD44 functions as a "bone homing receptor" directing migration of hematopoietic stem cells and mesenchymal stem cells to the bone marrow. Subpopulation of CD44$^+$ prostate cells preferentially formed prostaspheres [14].

Flow cytometry-separated *side population* is another technique used to identify cells with stem-cell properties. The ATP-binding cassette membrane transporter *ABCG2* is associated with multidrug resistance and stem-cell phenotype. It enables efflux of the Hoechst 33342 dye and isolation of enriched stem cells from the prostate [15]. These side population cells developed spheroids and branching structures in 3-D Matrigel culture.

One should point out that the above-mentioned markers are definitely not exclusive, or even specific, for stem cells. Distinct prostate stem/progenitor cells are likely to be present in different species, i.e., CD44$^+$α2β1$^{high}$ in humans and Lin$^-$/Sca-1$^+$/CD49f$^{high}$ in mice (Table 6.1). A recent report refuted CD133 as a potential human or mouse stem-cell marker [16]. Another study indicated that expression of CD44, CD133, or Sca-1 did not correlate with the ability to form spheroids or generate prostate glandular structures [17]. There are bound to be additional, unique stem-cell markers awaiting discovery.

## Location of Prostate Stem Cells

Where do stem cells reside in the prostate? Regenerative studies suggest that prostate stem cells may be found in the proximal duct and in the basal layer of the prostate. Indeed, studies using stem-cell markers in mice have localized prostate stem cells to these sites.

### Proximal Duct

In the mouse prostate, the regenerative capacity occurs in the proximal ducts close to the urethra [18–20]. This is the region characterized by the presence of abundant smooth muscle cells that secrete high levels of TGF-β, which is known to be a prostate stem-cell niche factor [19]. This is also the region within the prostate that contains high proportion of castrate-resistant $CK5^+$, $Bcl\text{-}2^+$, $Sca\text{-}1^+$, and $\alpha6^+$ putative stem cells [12, 13, 20]. Further support for stem cells being located at the proximal ducts of the prostate comes from experiments showing that $Sca\text{-}1^+$ cells isolated from this region reconstitute prostate tissue more effectively than $Sca\text{-}1^-$ cells from the same region or $Sca\text{-}1^+$ cells from other regions [12].

### Basal Layer

Since there is preferential survival of basal cells after androgen ablation, the basal layer of the prostate gland is believed to harbor prostate stem cells [1]. The fact that mice devoid of the basal cell marker p63 are born without a prostate also supports a basal origin of prostate stem cells [21]. Further, luminal secretory cells of the prostate arise from $p63^+$ basal cells [22]. Recently, Goldstein et al. demonstrated that basal cell is a potential cell of origin for prostate cancer [23]. Importantly, they showed that cellular origins of cancer do not necessarily correlate with its histological features.

But not all basal cells are stem cells, because fetal urogenital sinus tissue from p63 null mice can form and regenerate prostate tissue in the absence of basal cells after implantation in immunodeficient mice [24]. Therefore, prostate stem cells are likely to be found in the basal layer of the proximal duct in the prostate. Stromal cells that constitute the stem-cell niche at this site can support and sustain prostate stem cells even in the absence of basal cells.

## Stem-Cell Niche

The stem-cell niche is a specialized microenvironment that houses stem cells. It is known that the stem-cell niche affects stem-cell development. When a stem-cell niche is aberrant, it becomes an onco-niche. Therefore, the niche plays a critical role in the final manifestations of a stem cell—and a cancer cell.

Stevens was the first to demonstrate that a normal stem cell derived from the genital ridge formed a malignant teratoma when implanted in the vicinity of the testes [25]. Conversely, Mintz and Illmensee showed that malignant cells obtained from an embryonal carcinoma behaved like normal cells when inserted into the body of a blastocyst [26]. Also, Rous sarcoma virus did not induce sarcomas in chicken embryos [27], and B16 murine melanoma cells failed to form tumors after exposure to embryonic niche factors [28].

These findings suggest that normal stem cells in an aberrant niche are sufficient for the formation of cancer. Whether an aberrant stem cell becomes a cancer cell or not could also be determined by its niche. Results of these experiments confirm the importance of a cellular origin and the niche effect during carcinogenesis.

## Prostate Onco-Niche

In many respects, the relationship between stem cell and its niche is also observed in prostate cancer. The prostate provides a unique opportunity to study interactions between stem cell and its adjacent stroma, because the urogenital sinus mesenchyme that comprises the embryonic stem-cell niche can be easily separated from the epithelial stem cells. Using this approach, Blum et al. showed that the embryonic prostate stem-cell niche might be representative of the mammalian stem-cell niche in general [29]. Furthermore, disruption of the stromal-epithelial signaling pathways contributed to oncogenesis.

Zhou et al. showed that inactivation of p53 and RB in the stem/ progenitor cells of the proximal prostatic ducts led to the formation of malignant tumors [30]. However, the *same genetic defects* affecting lineage-committed transit-amplifying and/ or differentiated prostate cells in the distal prostatic ducts did not form malignant tumors. Furthermore, prostatic intraepithelial neoplasia (PIN) that developed in the proximal prostate progressed to carcinoma. In contrast, PIN in the distal prostate *never* progressed to carcinoma by the time the mice expired. Interestingly, when Zhou et al. performed the same experiments in a different cellular context (i.e., ectopic transplantation assay), mutant cells derived from either the proximal or distal prostatic ducts developed neoplasms within 3 months [30]. Since p53 and RB genes are absent in both proximal and distal ducts of this mouse model, the biologic manifestation of carcinoma must be a consequence of its locations, which contain different stromal cells.

These observations are consistent with a recent report that demonstrated cancer-associated fibroblasts (CAF) played an important role in the spheroid and glandular formation of prostate cancer stem cells [17]. Another study showed that

human prostate cancer samples expressing high levels of the mesenchymal stem-cell marker CD90 were more likely to contain CAF with tumor-promoting potential compared with those expressing low levels of CD90 [31].

Results from these experiments confirm that stromal cells are an integral component of the onco-niche, which plays a critical role in the development of prostate cancer. In other words, both the right genetic defects and the proper onco-niche contribute to the formation prostate cancer.

## Prostate Cancer

Many characteristics of prostate cancer indicate that it originates from stem cells. For example, *androgen independence* could allude to its stem-cell roots, and the androgen-sensitive cells ($AR^+$) represent the bulk of differentiated prostate cancer cells. In addition, the androgen-regulated gene fusion, *TMPRSS2-ERG*, could be used to clarify the cells of origin as well as the evolution of prostate cancer cells.

### Androgen Independence

A hallmark of prostate cancer is its intrinsic androgen independence. Several studies suggest that androgen independence is an inherited rather than acquired trait of prostate cancer [32, 33]. Furthermore, androgen-independent prostate cancer (AIPCa) expresses stem-cell genes within the basal cell layer [34].

Normal prostate stem cells are $AR^-$. It is possible that prostate stem cells are the source of AIPCa, which is also $AR^-$. Collins et al. showed that primary human prostate cancer cell population with the highest proliferative potential was $AR^-$: It had a stem-cell profile ($CD44^+\alpha2\beta1^{high}$ $CD133^+$) and a basal cell phenotype [35]. The $CD44^+$ tumor-initiating cells from prostate xenograft models were $AR^-$ and expressed stemness genes, such as *OCT3/4*, *BMI1*, *beta-catenin*, and *SMOOTHENED* [36]. Likewise, tumor-initiating cells from a clonally derived hTERT-expressing human prostate cancer cell line were $AR^-$, $p63^-$, and expressed stemness genes, such as *OCT4, Nanog, Sox2, nestin*, CD44, CD133, and *c-Kit* [37]. The regenerated tumor contained basal, luminal, and neuroendocrine-like cells, suggesting that the original clone that engendered the tumor had multilineage differentiation capacity of a stem cell.

AR expression promotes differentiation of prostate epithelial cells. Indeed, overexpression of AR alone does not induce pathological growth but reduces the tubule-forming capacity (i.e., stemness) of normal prostate stem cells [38]. It is important to point out that AR function in mesenchymal cells is sufficient for the development of the nascent prostate [39]. Mesenchymal cells ($AR^+$) produce growth factors and cytokines, which act on epithelial progenitor cells ($AR^-$) and affect the latter cells' AR expression and differentiation. Similarly, bone stromal cells such as osteoblasts are $AR^+$ and may produce growth factors and cytokines that affect metastatic prostate cancer stem cells ($AR^-$) in the bone [40]. These findings indicate that mesenchymal cells influence prostate epithelial cells and that the cellular origin of AIPCa may indeed be inherently $AR^-$.

### TMPRSS2-ERG

Whether TMPRSS2-ERG (fusion of the prostate-specific gene, TMPRSS2, with the transcription factor, ERG) could be a useful biomarker to trace the evolution of prostate cancer-initiating cells during carcinogenesis remains to be determined. Yu et al. found that ERG disrupts AR signaling by binding to and inhibiting AR expression at certain gene-specific loci [41]. Furthermore, ERG directly activates H3K27 methyltransferase EZH2, a polycomb group protein, which prevents the affected cell from differentiation (and from AR signaling) and maintains it in a stem-cell-like epigenetic state. Hence, depending on the affected cell of origin, the TMPRSS2-ERG fusion proteins may cause maturation arrest in an early prostate stem cell or endow stemness properties to a late prostate progenitor/differentiated cell, thereby predisposing and propelling it into a path of carcinogenesis. Although both cell types may express the same TMPRSS2-ERG fusion proteins, we postulate that they will pursue distinct clinical courses, because of their different cells of origin.

## Prostate Cancer Stem Cells

If cancer stem cells are derived from normal stem cells, one may be able to purify cancer stem cells using stem-cell markers because the two cell types share certain stem-cell markers. Bonnet and Dick were the first to isolate so-called cancer stem cells (CSC) from human acute myeloid leukemic cells with the stem-cell marker $CD34^+$ and propagate these cells in immunodeficient mice [42]. Subsequently, subpopulations of CSC with stem-cell phenotypes have also been demonstrated in breast [43], brain [44], and other cancers.

In prostate cancer, Collins et al. identified putative prostate CSC from primary human prostate tumors using the same stem-cell markers ($CD44^+/\alpha2\beta1^{high}/$ $CD133^+$) as those used to designate prostate epithelial stem cells [35]. Interestingly, the $CD44^+/\alpha2\beta1^{high}/$ $CD133^+$ prostate CSC displayed high capacity for self-renewal and for differentiation into $AR^+$ cells. Importantly, Leong et al. showed that a single $Lin^-/Sca\text{-}1^+/CD133^+/CD44^+/$ $CD117^+$ cell was able to produce wild-type prostatic acini in the mouse [45].

Patrawala et al. showed that CD44⁺ prostate cancer cells were intrinsically more tumorigenic and metastatic than their CD44⁻ counterparts [36]. A fraction of CD44⁺ prostate cancer cells undergo asymmetric division, which is a hallmark of slow-cycling stem cells. In addition, Hurt et al. showed that CD44⁺ LNCaP cells exhibited stem-cell features, including formation of prostaspheres in cell culture, colonies in soft agar, and tumors in NOD/SCID mice [46].

Recently, Kong et al. demonstrated that prostate cancer cells exhibiting CSC features also expressed an EMT phenotype [47]. Not only did the PC3 PDGF-D cells showed increased clonogenic and prostasphere-forming capacity, which were used to define CSC characteristics, they also lost epithelial markers and gained mesenchymal markers. Moreover, these cells overexpressed numerous stem-cell genes, such as Nanog, Oct4, Sox2, Lin28B, and activated polycomb repressor complex 2.

## Origin of Prostate Cancer

We know very little about the origin of prostate cancer-initiating cells. For the longest time, we have focused on the nature of oncogenic change. But it is equally important for us to identify the cells of origin within which the oncogenic change occurs. Knowing the cells of origin will help us validate the actual role of oncogenic change during oncogenesis.

### Hierarchy of Stem-Cells Versus Cancers

Results from several lines of experiment support a hierarchical order of stem/progenitor/differentiated cells within which a particular genetic change (or epigenetic aberrations) could elicit different and disparate biologic as well as clinical phenotypes.

Patrawala et al. discovered a hierarchical order in the tumorigenic potential of human prostate xenograft tumors [36]. In particular, a subpopulation of prostate stem cells ($CD44^+/\alpha2\beta1^+$) was enriched in tumor-initiating cells. Hence, the tumorigenic potential of 3 human xenograft tumors (DU145, LAPC4, and LAPC9) was dependent on their cellular origins in a hierarchical order of $CD44^+/\alpha2\beta1^{+/hi} = CD44^+/\alpha2\beta1^{-/lo} > CD44^-/\alpha2\beta1^{+/hi} >> CD44^-/\alpha2\beta1^{-/lo}$.

Mulholland et al. isolated LSC ($Lin^-/Sca\text{-}1^+/CD49f^{high}$) stem/ progenitor cells using FACS in the Pten null prostate cancer model [48]. Using cells derived from in vitro sphere culture or isolated from primary tumors, they performed in vivo regeneration assays and showed that the LSC subpopulation (as opposed to the more differentiated luminal subpopulation) are basal-like cells that recapitulated the pathology of primary Pten prostate tumors and elicited a preponderance of tumor-initiating activity.

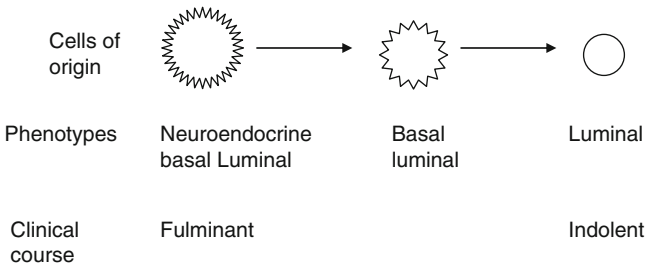


**Fig. 6.1** The stem-cell theory of cancer predicts that tumors arising from earlier stem cells in a stem-cell hierarchy tend to express a more diverse phenotype and pursue a more fulminant clinical course than later progenitor stem cells, which are more inclined to display a more restricted phenotype and follow a more indolent clinical course

Lawson et al. isolated distinct subpopulations of prostate basal/stem cells, luminal cells, and stromal cells using FACS [49]. By introducing various oncogenic stimulations (i.e., FGF activation, ERG1 expression, PI3K signaling) into these cells, they demonstrated that prostate basal/stem cells possessed a greater capacity (i.e., efficiency) for cancer initiation compared with luminal cells and could produce luminal-like disease.

Prostate tumors arising from luminal cells were consistently found to be less aggressive than those originating from basal/stem cells. PSA-driven *Pten* deletion in prostatic luminal cells resulted in hyperplasia [50]. In contrast, Probasin-Cre-induced *Pten* inactivation involving prostatic basal/stem cell led to neoplasia [51]. Similarly, overexpression of AKT1 in Sca-1⁺ cells led to the formation of ductal structures containing PIN while its expression in Sca-1⁻ cells led to predominantly normal ducts [13].

### Cellular Origins of TMPRSS2-ERG

The stem-cell theory of cancers predicts that the same oncogenic stimuli cause differential effects in different cells of origin [52, 53]. Earlier stem cells give rise to tumors that are potentially more heterogeneous and metastatic than the later progenitor cells do (Fig. 6.1).

The TMPRSS2-ERG fusion gene alludes to the relevance of a particular oncogenic gene rearrangement versus the cell types within which it occurs during prostate carcinogenesis. A prospective multicenter study showed that the prevalence of TMPRSS2-ERG was almost 50 % in prostate cancers diagnosed among men who underwent prostate biopsies [54]. But TMPRSS2-ERG transcripts were also discovered in benign prostatic hyperplasia or nonmalignant tissues, not just primary or metastatic prostate cancers [55–57]. These disparate observations could be attributed to the phenomenon of field effect. An alternative explanation is that the cell of origin within which a particular oncogenic gene rearrangement occurs is also important for the expression of a malignant phenotype.

We propose that when the cell of origin has more stemness features, the resultant malignancy is potentially more deadly; when it is more differentiated, the tumor formed tends to be more indolent. This hypothesis could account for the discordant prognostic significance of TMPRSS2-ERG in prostate cancer when the *same* genetic aberration develops in *different* cells of origin. It would explain the discrepancy of TMPRSS2-ERG being associated with a poor clinical outcome in some studies [58, 59], but an improved prognosis in others [60].

## Future Directions

We need stem cells to test the hypothesis that distinct tumor phenotypes arise from unique stem cells in a stem-cell hierarchy. The spontaneously immortalized prostate progenitor (NHPrE1) and intermediate (BHPrE1) cells could be used for this purpose [61]. Of note, NHPrE1 cells expressed higher levels of stem-cell markers (CD133, CD44, OCT4) than BHPrE1 cells. Although it is unavoidable that both of these human cell lines contain mixed populations, they do not produce colony formation in vitro and tumorigenicity in vivo. Furthermore, there is no extrinsic DNA or viral modification being introduced into these cells. These cell lines are as "normal" as they possibly can be for the purpose of such experiments.

A preview of such experiments is already ongoing with the use of homeobox promoter genes in prostate cancer research. Homeobox genes regulate lineage differentiation during development. Different homeobox genes impart different progenitor cells with different stemness packages that confer different stem-cell or malignant phenotypes in a hierarchical manner. Hence, prostate basal stem cells (a relatively early progenitor stem cell) may contain a certain homeobox gene and become a more heterogeneous or form mixed tumor that metastasizes more widely with Pten loss [48]. On the other hand, prostate CARN cells (a relatively late progenitor stem cell containing Nkx3-1) are likely to express a more restricted phenotype and become the more conventional prostate acinar adenocarcinoma with the same Pten loss [62].

### Conclusions

Until recently, the notion of cancers arising from specific mutations that occur and accumulate over time has been the groundwork for cancer research and therapy. The idea that distinct types of cancer are due to abnormalities that occur within unique cells, if proven correct, will be a major *paradigm shift* in prostate and other cancers. The *stem-cell theory of cancers* provides us with a novel frame of reference for better understanding the intricacies of cancer. Importantly, it enables us to discover alternative ways to elucidate the mechanisms of cancer. Ultimately, the stem-cell theory of cancers will affect how we practice clinical oncology: our diagnosis, management, and therapy of prostate and other cancers.

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# Murine Models of Prostate Cancer

7

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## Introduction

Preclinical investigation of prostate cancer (CaP) has been greatly assisted by the availability of animal models which enable experimentation in physiologic tissue microenvironments that cannot be recapitulated by current *in vitro* platforms. Such modeling is necessary to study carcinogenesis steps requiring interaction between the cancer cell and microenvironment, such as local invasion, circulatory transit/dissemination, lodging and survival of tumor cells at secondary tissue sites, and tumorigenesis itself. Animal models thus provide invaluable preclinical tools for elucidating molecular mechanisms of CaP carcinogenesis and testing novel CaP therapies.

The development of animal models that accurately recapitulate human disease has been a considerable challenge. The only large animal known to develop spontaneous CaP is the dog; indeed, Charles Huggins first noted the hormone dependence of CaP in aged ferrell dogs. Unfortunately the study of canine CaP has been hindered by infrequency of cases, high cost of maintaining colonies, long gestation and life span, difficult genetic manipulation, and relatively complex regulatory issues.

A variety of rodent models have been developed that recapitulate different biologic states of human CaP, are readily available to biomedical researchers, and have considerable practical utility. Certain rat strains, for example, develop frequent spontaneous prostate tumors, and this tumorigenesis can be accelerated using specific chemical carcinogens or tumor transplant approaches. Unlike rat prostates, mouse prostates do not develop spontaneous tumors and are resistant to carcinogens. However, mouse prostate tumors may be induced by experimental approaches, including recombinant DNA genomic (i.e., transgenic) alteration or *in vivo* reconstitution of genetically transformed urogenital sinus tissue. In addition, immunocompromised mouse strains provide effective hosts for human CaP xenografts.

Murine models are practical for CaP research due to a relatively short life span and gestation period. Furthermore, they are relatively inexpensive to maintain and easy to handle and manipulate. Numerous preclinical discoveries in murine models of CaP have translated well clinically, from the earliest demonstration of androgen-independent subpopulations as a mechanism of androgen-independent clinical progression to the more recent discovery of metastasis suppressor genes. This chapter reviews different approaches to murine modeling of CaP and summarizes various models with respect to their histology, androgen sensitivity, invasiveness, metastatic potential, molecular profiles and important preclinical findings.

## Murine Prostate Anatomy

The murine prostate, similar to the human prostate, is composed of glandular epithelium within a sea of stromal cells and loose collagenous extracellular matrix [1]. The stroma is comprised of smooth muscle, mesenchymal cells including fibroblasts and myofibroblasts, nerve endings, lymphatics, leukocytes, endothelial cells, and their supporting pericytes. The epithelium-stroma ratio is high (5:1) in the murine prostate, a largely parenchymal organ, while in the human gland, the stroma is more equally represented (1:1–2:1). In contrast to the human prostate, which contains zones without clear lobar delineations, the murine prostate has distinct anatomic

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lobes: dorsal, lateral, ventral, and anterior/coagulated. Each lobe has a characteristic ductal branching pattern [2]. As with the human gland, murine prostatic ducts are lined by cuboidal-to-columnar epithelium and proximal urothelium, including scattered basal cells lacking a luminal surface [1]. In spontaneous or carcinogen-induced rat CaP, lesions tend to develop in one of two specific regions: (1) the ventral lobe, often microscopic and indolent, or (2) the dorsal and lateral lobes, often macroscopic and invasive, with frequent seminal vesicle involvement. While the dorsal lobe is considered anatomically most similar to the human peripheral zone, which is the site of clinical CaP, it has not been shown that cancers from any one prostate lobe are more representative of human disease.

## Overview of Murine Models of Prostate Cancer

### Murine Model Goals

The foremost goal of CaP murine models is to replicate clinical histopathology and simulate the clinical course of disease, while reliably predicting patient response to various treatments. Secondary goals relate to practicality of study, including accessibility, abundance, ease of handling, and costs. Thus, the ideal murine model would begin with prostatic intraepithelial neoplasia (PIN) and progress to androgen-dependent multifocal adenocarcinoma with stable or increased expression of the androgen receptor (AR) and prostate-specific markers (PSA/PAP/PSMA), followed by preferential metastatic colonization of lymph nodes and bone, with androgen-independent outgrowth following hormonal therapy. On the other hand, common clinical features such as a slow cancer growth rate and a late age of onset may be preferable to avoid in these models to allow more expeditious investigation. Additional desirable features include the availability of large number of rodents, high tumor penetrance/incidence, and technical simplicity for generalized usage. Currently, no murine model recapitulates all aspects of clinical prostate carcinogenesis, and the utility of any one model is often best assessed by its "track record" of predicting clinical CaP biology and outcomes.

### Murine Model Types

Many different murine models are available to the CaP investigator. These models differ in their species of tumor origin (human, rat, or mouse) and species of rodent host (rat or mouse). Murine models are additionally distinguished by whether prostate tumors are **autochthonous**, originating de novo within the host rodent, or whether they are introduced by **tumor transplantation or grafting** (Fig. 7.1). A transplant is referred to as **syngeneic** when the species and strain of tumor is identical to that of the host, in contrast to a **xenograft** (heterotransplant/xenotransplant) in which the species of host and tumor differ. Xenografts require an **immunocompromised** host rodent, while all other types of murine models use an **immunocompetent** host, preserving potential cancer cell-immune cell interactions.

The site of tumor development is another key distinction. Transplanted prostate tumors may be implanted **orthotopically** (intraprostatically) but are most often studied **ectopically** within the subcutaneous tissue (typically in the flank), under the renal capsule or in/over the bone. Autochthonous rodent prostate tumors may similarly be orthotopic or ectopic (Fig. 7.1). Ectopic autochthonous tumors are studied exclusively using the *mouse prostate reconstitution model*, which implants urogenital sinus tissue under the renal capsule to induce prostate organogenesis along with carcinogenesis. Orthotopic autochthonous prostate tumors can develop either *spontaneously* (certain rat strains only), after *induction by carcinogens* (rats only), or using *transgenic DNA recombination* (mice or rats) (Fig. 7.1).

A final key distinction is whether initial transformation steps of prostate carcinogenesis are represented or bypassed in the model. For example, in transplant models, prostate cells are already transformed at the time of inoculation into rodents, thereby *bypassing the initiation and early progression of carcinogenesis*. Accordingly, these models are less useful for studying early tumorigenesis or chemoprevention but enable expeditious investigation of advanced disease. In contrast, autochthonous models recapitulate the entirety of tumorigenesis and are more appropriate for chemoprevention study.

## Spontaneous Prostate Cancer Models

The overall incidence of spontaneous prostate tumors in rodents is very low. Yet for reasons unclear, two rat strains, **Lobund-Wistar** and **August-Copenhagen**, develop frequent spontaneous CaP and are the only animals known to do so besides dogs and humans (Table 7.1). These models are advantageous in that they allow study of "natural" multistep tumorigenesis including precancerous events in an immunocompetent host without added carcinogens or genetic manipulation. Because spontaneous rat CaP models include the earliest steps of neoplastic transformation, they are useful for **chemopreventation studies**. Disadvantages of these models are the long tumor latency (2–3 years) relative to other murine models and lack of bone metastases.

### Lobund-Wistar Model

The identification of spontaneous rat prostate tumors in a Wistar rat strain was reported in 1973 by Pollard, who

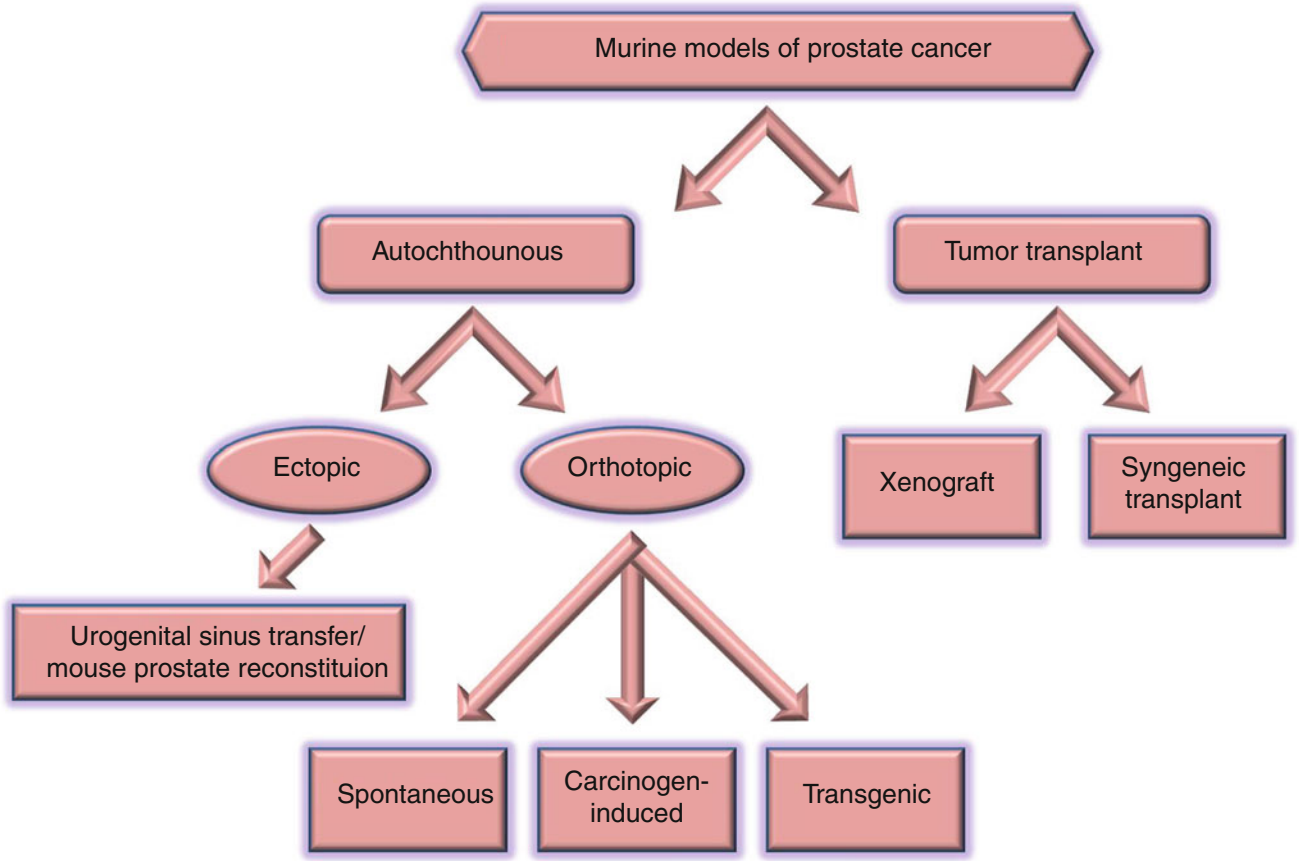


**Fig. 7.1** Murine models of prostate cancer

**Table 7.1** Spontaneous and carcinogen-induced rat models of prostate cancer

| Rat strain | Carcinogen | Incidence | Tumor location | Invasion phenotype | Metastatic |
|---|---|---|---|---|---|
| Lobund-Wistar | (None) | ~30 % by 2–3 years | Dorsolateral and anterior prostate lobes, seminal vesicles | Macroscopic | Yes |
| | MNU + testosterone | ~60–90 % by an average of 11 months | Dorsolateral and anterior prostate lobes, seminal vesicles | Macroscopic | Yes |
| ACI | (None) | ~35–80 % by <3 years | Ventral prostate lobe | Microscopic >>> Macroscopic | No |
| | DMAB (± estrogen) | ~10–50 % by 12–14 months | Ventral prostate lobe | Microscopic | No |
| Wistar, Wistar-Unilever | MNU + testosterone | ~30–75 % by 15–18 months | Dorsolateral and anterior prostate lobes, seminal vesicles | Microscopic > Macroscopic | Yes |
| Fischer 344 | DMAB | <50 % by 14 months | Ventral prostate lobe | Microscopic | No |
| | DMAB + testosterone | ~85 % by 13 months | Dorsolateral and anterior prostate lobes, seminal vesicles | Macroscopic | Yes |
| Noble | Testosterone + estrogen | ~90 % by >18 months | Dorsolateral and anterior prostate lobes, seminal vesicles | Microscopic > Macroscopic | Yes |

Adapted/updated from [3]

observed large pelvic tumors with synchronous lung metastases in two aged rats [4]. The tumors appeared to originate from the prostate and were determined to have adenocarcinoma histology. The rat subline was conventionalized by Pollard to establish the current Lobund-Wistar (L-W) strain, of which **nearly 30 % of rats develop spontaneous tumors by approximately 2 years of age, with slightly higher rates by 3 years** [5]. The etiology of frequent CaP in these rats is unclear, given the parental Wistar line had no known incidence. While Pollard attributed the phenomenon to genetic drift, the cause is generally believed to relate to the naturally high levels of circulating testosterone in L-W rats.

L-W spontaneous prostate tumors grow to palpable size with **aggressive local invasion**, often displacing the entire pelvic cavity, and are **highly metastatic** to the lungs, lymph nodes, and peritoneum. They are believed to originate in the **dorsolateral and anterior lobes** and typically involve the **seminal vesicles**. Whether L-W seminal vesicle tumors develop independently of prostate tumors or as a result of direct extension remains controversial. Necropsies in younger L-W rats reveal occasional (6 %) microscopic involvement in the dorsolateral prostate alone, without seminal vesicle involvement, supporting a prostatic origin [6]. Further support comes from demonstration of PSA expression in cancer cells derived from a L-W spontaneous prostate tumor [7].

The L-W spontaneous CaP model shares several features with clinical CaP. **L-W prostate tumors increase with age**, occurring in 10 % of young adults and 30 % of elderly rats [5, 8]. At the earliest stage of detection, these tumors appear as premalignant intraluminal hyperplasia or carcinoma in situ, similar to clinical PIN [5, 6, 8]. L-W spontaneous prostate tumors **express both AR and PSA**, although with reduced levels relative to benign epithelium [6, 7, 9]. They are initially **androgen dependent** based on suppression with chemical castration [10, 11]. Subsequent outgrowth of androgen-independent disease is suggested based on studies with *carcinogen-induced* L-W CaP tumors (described later in this chapter); however, the genetic etiology of these tumors may be different [8]. Compared to clinical CaP, L-W spontaneous prostate tumors are more locally aggressive, with more common SV involvement, but do not metastasize to bone.

*Preclinical findings*. The L-W model provided the **first demonstration of a role for dietary modifications in CaP prevention**, showing that moderate caloric restriction or fat reduction significantly reduced L-W prostate tumor incidence [5, 12]. More recently, the L-W rat model has supported the chemopreventative use of specific soy protein isolates based on a tenfold (30 % vs. 3 %) reduction in CaP incidence in supplemented rats [8]. The L-W spontaneous rat CaP model has had limited study due to long tumor latency and limited incidence of tumorigenesis, and many investigators have opted instead for more expeditious variants of the L-W model using carcinogen induction or tumor transplant approaches.

## August-Copenhagen (ACI) Model

Spontaneous rat CaP is also observed in the strain, ACI, established in 1926 by Curtis and Bullock by crossing an inbred Copenhagen and August (ACI = A × C with an "Irish" marker; a.k.a. ACI/seg or ACI/segHapBR) [13]. In 1975, Shain and colleagues first described spontaneous prostate tumors in 7/41 (17 %) 3-year-aged ACI rats [14]. Subsequently, a larger investigation by Ward and colleagues demonstrated a 35–40 % incidence of histologic CaP by 33 months, and **rates up to 60–80 % in aged rats** are more recently reported [13, 15, 16]. These cancers are most often **microscopic**, in contrast to L-W spontaneous prostate tumors. ACI rats also develop **PIN-like atypical hyperplasia with virtually 100 % incidence by 2 years of age** [13, 16]. As with L-W rats, spontaneous CaP in ACI rats may be due to high levels of circulating testosterone, and a role for testosterone to estrogen ratio has also been proposed [13].

Histologically, spontaneous CaP in ACI rats is **multifocal** and occurs solely in the **ventral lobe**, in contrast to the dorsolateral/anterior lobe in L-W rats [13, 14]. ACI CaP lesions have a **cribriform** appearance, as observed clinically with high-grade and ductal adenocarcinomas [16, 17]. Varma and colleagues have concluded close ultrastructural similarity with human prostate cancer cells by electron microscopy [17].

In contrast to L-W prostate tumors, ACI tumors are indolent and typically **lack gross invasion or metastasis**, despite high-grade histology. Several heterogeneous and clonal cell lines have been established from spontaneous ACI tumors after serial syngeneic transplantation (C, D, and T families) [18, 19], and much of the known biology of the spontaneous ACI CaP model has been extrapolated from studies in these cell lines or their transplant tumors, including the presence of **both androgen-sensitive and androgen-insensitive cell populations** [18–20]. In serial transplants, **AR and PAP are both expressed** at higher levels than the ventral prostatic epithelium [19]. Levels of AR are variable in isolated cell populations and do not correlate with androgen sensitivity [20].

*Preclinical findings*. The high incidence of microscopic disease in ACI rats, approaching 100 % with advanced age, and the lower incidence of macroscopic invasive disease is considered to mimic the epidemiology of human prostate cancer. Thus, the ACI spontaneous cancer model may be useful for investigation of early CaP tumorigenesis and preventative medicine. As with the L-W model, several groups have employed ACI rats to investigate **dietary modifications**. Kondo and colleagues demonstrated suppression of histologic CaP in ACI rats fed only a low-fat diet [21], and similar outcomes were observed in ACI rats fed a cholesterol-free diet [22]. The ACI spontaneous CaP model also provided among the earliest *in vivo* demonstrations of **chemopreventative activity of a 5-alpha reductase inhibitor in CaP** [15]. More recently, this model has contributed to linkage and microarray analyses for identification of candidate prostate susceptibility genes [23].

### Other Rat Strains

Spontaneous CaP is infrequent to nonexistent in other rat strains. A spontaneous rat prostate tumor discovered in a **Copenhagen** rat was used to establish what is the now the most extensively studied syngeneic transplant tumor model of CaP (see later in chapter, *Dunning model*) [24]. The precise incidence of Copenhagen spontaneous CaP is unclear, but rates of microscopic disease as high as 10 % are suggested [13]. The incidence of CaP in **Noble** rats is <1 % [25]. In **Fischer 344** (**F344**) rats, Reznik and colleagues observed spontaneous prostatic CaP/adenomas in 4 % of animals, which were ventral, cribriform and nonmetastatic, similar to ACI rat CaP [26]. Spontaneous CaP has not been described in other common rat strains, including Wistar, Sprague-Dawley, and Lewis.

## Carcinogen-Induced Models

A classic mechanism used to study tumor initiation and progression is the exposure of animals to chemical carcinogens. The most thoroughly characterized carcinogens in CaP murine models are **DNA-modifying agents**, ***3,2′-dimethyl-4-aminobiphenyl*** (**DMAB**) **or** ***N-methyl-N-nitrosourea*** (**MNU**), **in combination with testosterone supplementation** (Table 7.1). Carcinogen induction enables more expeditious investigation of rat prostate tumorigenesis, with tumor latency periods of months rather than years, and CaP incidence approaching 100 %. Similar to spontaneous models, carcinogen-induced models are useful for investigating chemoprevention because they recapitulate the earliest steps of carcinogenesis, including precancerous changes. The main disadvantage of carcinogen models is the lack of an established role for chemical carcinogens in clinical prostate tumorigenesis, and the resulting rat cancers may not be biologically representative of clinical disease.

### Testosterone/Estrogen

A carcinogenic role for testosterone in CaP is suggested by the high incidence of spontaneous CaP in rat strains with high circulating levels of this hormone; additionally, testosterone supplementation enhances susceptibility to chemical carcinogens, MNU and DMAB, as described below. However, the carcinogenic effect of testosterone alone in fact appears to be minimal in most rat strains. Pollard et al. observed only one case of CaP after chronic testosterone supplementation in 25 Sprague-Dawley rats (4 %) [27]. Among other strains (ACI, Noble, L-W, and Wistar-Unilever) treated with testosterone only, the reported incidence of CaP is similarly just 0–14 % [13, 28–30]. Testosterone supplementation alone thus appears to be insufficient for rat prostate tumorigenesis.

On the other hand, **long-term supplementation with combined testosterone *plus estrogen* leads to frequent CaP** (**microscopic >80 %**, **gross 10–15 %**) **specifically in the Noble rat strain** [31]. Noble testosterone/estrogen-induced tumors originate in the **dorsolateral and anterior prostate lobes**, and intermediate treatment duration (16 weeks) generates dysplasia without adenocarcinoma [32]. The effect of testosterone itself may be due to its aromatization into estrogen [32]. Drago and colleagues, as well as others, have thoroughly described the Noble testosterone/estrogen-induced CaP model, including evaluation of several chemotherapeutic agents [33–36].

### N-Methyl-N-Nitrosourea + Testosterone (MNU + T)

MNU is a **DNA alkylating agent** and the most commonly studied chemical carcinogen in rat CaP models. It is **conveniently administered as a one-time dose** and is most effective in combination with testosterone (MNU + T). Testosterone, in contrast, is more effective in this model when administered continuously and long term. The mechanism behind synergy between MNU and testosterone is unknown. The efficacy of MNU + T is rat strain dependent, with **Wistar-related and Sprague-Dawley** strains having highest susceptibility.

*Wistar-related rat strains*. The carcinogenic effect of MNU + T has been most extensively characterized in L-W rats, which develop **precocious CaP** (**<1 year**) **with up to 90 % incidence** [28, 37]. In comparison, MNU alone generates CaP in just 10 % of these rats by 14 months, similar to testosterone alone [28]. Tumors in other L-W rat tissues are not observed [28]. MNU + T-induced L-W prostate tumors have similar biology as L-W spontaneous prostate tumors. Both originate in the **dorsolateral and anterior prostate lobes with frequent seminal vesicle involvement and express AR**, **with initial androgen dependency** [12, 38]. While it has not been definitively shown in the spontaneous model, androgen-independent outgrowth is described in the carcinogen-induced model [8]. MNU + T treatment also induces dorsolateral CaP with occasional anterior/seminal vesicle involvement and metastasis in the L-W parental strain, Wistar, but the incidence is only 10–30 % (depending on timing of treatment initiation) by 1.5 years [39, 40]. These rats also develop infrequent prostate carcinoma in situ, atypical hyperplasia, and sarcomas, in addition to ear duct/Zymbal

gland tumors. Using another Wistar-related strain referred to as Wistar-Unilever (W-U), McCormick and colleagues recently described CaP (mostly microscopic) in 50–75 % of rats in response to MNU + T treatment compared to 3 % with MNU or testosterone alone [29, 41]. Similar to other Wistar strains, MNU + T cancers in W-U rats form in the dorsolateral/anterior prostate lobes, frequently involve the seminal vesicles and express AR, with lower levels in advanced grade disease [29, 42]. Other neoplasms occur with lower frequency (10–20 %) in this model, including leukemias/lymphomas, kidney tumors, and Zymbal gland tumors [29].

*Sprague-Dawley rat strain*. In contrast to Wistar-related strains, Sprague–Dawley rats treated with MNU + T develop predominantly **precancerous prostatic lesions**. Specifically, 60, 50, and 30 % of rats form prostatic hyperplasia, dysplasia, and PIN, respectively, with only occasional progression to adenocarcinoma [43, 44]. These changes occur in the **ventral prostate lobe** in contrast to the dorsolateral/anterior lesions in Wistar-related strains and may be detectable by as early as 5 months of age. The Sprague-Dawley model may thus provide a useful model for studying early prostate tumorigenesis.

*Preclinical findings*. In MNU + T-induced Wistar rat tumors, Sukumar and colleagues identified a 70 % rate of **mutated Ki-ras gene**, which encodes a GTPase signaling protein mutated in up to 13 % of clinical prostate cancers [47]. Other investigators have shown an important role for **increased Akt activation** in association with decreased AR levels during progression of MNU + T-induced CaP in W-U rats [42]. Preclinical efficacy of numerous **chemopreventative agents** have been demonstrated using MNU + T rat CaP models, including isoflavone [8, 48], vitamin D [8], linomide [8], garlic isolate [49], myoinositol [50], limonene [50], retinoids [29], cocoa powder [51], and COX-2 inhibitors [52].

## 3,2′-Dimethyl-4-Aminobiphenyl + Testosterone and/or Estrogen (DMAB + T/E)

DMAB is an **aromatic amine** similar to benzidine, historically used to manufacture azo dyes which have been linked to clinical bladder cancers. In rats, DMAB forms **DNA adducts** that lead to tumors of the prostate, bladder, colon, mammary glands, preputial glands, and subcutaneous skin. Common DMAB regimens include weekly or biweekly dosing over 20 weeks, in contrast to the one-time dosing of MNU. Low doses over a longer interval are more effective [53].

CaP induced by DMAB alone occurs solely in the **ventral lobe** [54]. These cancers are **microscopic with cribriform histology**, **express AR**, **and lack gross invasion or metastasis** [54, 55]. CaP formation with DMAB occurs at a lower incidence than in MNU + T models. As with MNU + T, there is differential susceptibility to DMAB among different rat strains. **F344 and ACI are most susceptible**, with variable CaP incidence (10–50 %) by approximately 1 year of age and PIN/atypia formation in 70–80 % of rats by 60–74 weeks [54, 56, 57]. Lewis and CD rat strains demonstrate lower susceptibility, while Wistar and Sprague-Dawley rats are resistant [54].

*Testosterone effect*. Long-term testosterone supplementation generates a dramatic shift in DMAB-induced cancer phenotype, **suppressing ventral prostate microscopic lesions while promoting macroscopic CaP in the dorsolateral/anterior lobes and seminal vesicles of >80 % of mice** [58, 59]. These macroscopic lesions demonstrate **noncribriform** glandular differentiation of variable grade, abundant reactive stroma, prominent polynuclear leukocyte infiltration, and frequent perineural invasion. They are **locally invasive and frequently metastatic to the lungs and peritoneum**, with incidence and invasiveness increasing with duration and dose of testosterone supplementation [55, 60]. Histologically and phenotypically, these lesions are similar to those arising spontaneously in Wistar-related rat strains treated with MNU + T. In contrast to these models and tumors induced by DMAB alone, tumors induced by DMAB + T are mostly **AR negative** [55].

*Estrogen enhancement*. While estrogen has no effect on CaP induced by DMAB alone [57, 61], estrogen supplementation does enhance DMAB + T-induced CaP [59, 60]. The effect of estrogen is tissue-specific, however, **increasing CaP in all prostatic lobes but causing reversion of seminal vesicle cancers**. A carcinogenic role of estrogen could explain reports of increased CaP in DMAB-treated rats receiving either AR antagonists or 5-alpha reductase inhibitors, both of which may elevate estrogen levels [62].

*Androgen sensitivity*. In F344 rats treated with DMAB or DMAB + T, androgen sensitivity and AR expression each vary with CaP location. AR-positive microscopic cancers of the ventral lobe are androgen dependent while macroscopic cancers of the dorsolateral/anterior prostate and seminal vesicles lack AR and are androgen independent [55, 63]. Three cell lines have been established from dorsolateral tumors in this model which accordingly lack AR expression, forming metastatic castration resistant tumors when xenografted into nude mice [64]. Castration resistance may occur by a different mechanism than in clinical CaP, given the discrepancy in AR expression.

*Preclinical findings*. TGF-betaRII is a key mediator of TGF-beta signaling and is frequently downregulated in human, rat, and mouse prostate cancers [65]. Yamashita and colleagues recently used microarray analysis of three DMAB cancer lines to demonstrate aberrant methylation of the TGF-betaRII gene, and confirmed this finding in clinical CaP [65]. Masui and colleagues used DMAB-treated rats to identify Ki-ras mutations in CaP lesions [66]. As with other autoch-

thonous rat CaP models, the DMAB model has been used to study the efficacy of chemopreventative agents such as flavonoid antioxidants, and dietary modifications including reduced beef fat intake [67–69]. Conflicting results are reported regarding therapeutic efficacy of AR antagonists and 5-alpha reductase inhibitors in this model [56, 62, 70].

### Other Chemical Carcinogens

Other chemical carcinogens inducing CaP in rats include N-nitrosobis (2-oxopropyl) amine (**BOP**) and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (**PhIP**) [3, 71]. Both agents are DNA alkylating agents that form CaP in the ventral prostate lobe, similar to DMAB, although with increased tumorigenesis from testosterone supplementation. These carcinogen models have undergone only limited characterization and are not routinely studied.

## Syngeneic Transplants

A common approach enabling long-term study of a specific CaP tumor is to serially transplant the tissue in rodents, with or without interval *in vitro* culturing. **Syngeneic models** transplant tumors into the same (i.e., isogenic) strain as which they originated. Most syngeneic transplant models utilize **rat tumors in rat hosts** and originate from either spontaneous or carcinogen-induced rat CaP. The typical site of transplantation is the subcutaneous flank but may also be intraosseous to model bone metastasis.

Advantages of syngeneic transplant models are characteristic of transplant models in general: by **bypassing precancerous steps and initial transformation**, transplant models enable more expeditious investigation compared to other murine models, with relatively **short tumor latency periods**. These models have been embraced by researchers for practical reasons, although there is growing recognition that "faster may not be better" when studying CaP development. Because early carcinogenesis steps are circumvented, transplant models are less useful for chemopreventative study and more appropriately **employed to investigate CaP progression and treatment of advanced disease**. Transplant models are technically simple and allow continuous monitoring of tumor size when grown subcutaneously. Unlike xenograft transplants, syngeneic transplants have the advantage of being performed in an **immunocompetent host**, allowing assessment of immune system effects on carcinogenesis. A disadvantage of syngeneic transplants is the lack of autochthonous tumor development. Also, syngeneic transplants fail to generate spontaneous bone metastases unless using specialized transplantation techniques with a specific rat CaP line described below.

### Dunning (R3327) Model (Table 7.2)

The Dunning rat CaP model was first described by W. F. Dunning in 1963 as a spontaneous tumor developing in the prostate of an aged Copenhagen rat, grossly involving the dorsolateral lobe and a large portion of the lower abdomen, with no identified metastases [24]. The original tumor, designated **R3327**, was transplanted back into the parental Copenhagen strain and passaged serially *in vivo*. The resulting tumors were slow growing, hormonally sensitive, and expressed AR and endogenous 5-alpha reductase activity [73, 74].

During serial *in vivo* passaging of the R3327 tumor, several sublines have been established, including **R3327-A**, **R3327-G**, **R3327-H**, **and R3327-S** [75] (Table 7.2). While these R3327 sublines retain androgen sensitivity, Isaacs and colleagues postulated in 1978 that an androgen-insensitive population comprised 8–29 % of cells in R3327-H tumors based on limited growth in castrate rats [76]. Prolonged hormonal selection in these rats led to the establishment of the hormonally insensitive **HI sublines**, each defined by a specific growth rate, including **HI-S** (**slow**), **HI-M** (**medium**), **and HI-F** (**fast**) [76]. HI tumors differ in histology and molecular biology from H tumors. Histologically, the latter shows abundant large glands with high secretions and appears almost identical by both light and electron microscopy to well-differentiated human CaP [74]. In contrast, HI tumors form small glands with few secretions and a more cuboidal epithelium [76]. HI tumors are AR positive but have lower levels (30–80 %) than hormonally sensitive H tumors, in contrast to stable or upregulated levels often observed with clinical castration resistance [73, 75]. Five-alpha reductase activity is also decreased in HI tumors relative to H tumors, while levels of PAP are unchanged [75].

While hormonally insensitive HI lines retain moderate to high glandular differentiation, clinical castration-resistant CaP is often more dedifferentiated. **R3327-H-G8A1** is a hormonally insensitive Dunning subline originating from a single cell clone of R3327-H which generates undifferentiated CaP *in vivo* [77]. It is unclear whether H-G8A1 derives from a hormonally insensitive clone or mutated from an androgen-sensitive clone. As with HI tumors, H-G8A1 remains AR positive despite androgen insensitivity and also expresses 5-alpha reductase activity. **Together, the H, HI, and H-G8A1 Dunning tumor lines provide a useful system for study of AR-positive CaP progression to hormonal insensitivity** (Table 7.2).

On occasion, genetic instability of serially passaged R3327-H tumors has given rise to anaplastic tumor sublines, designated **AT** [75, 76] (Table 7.2). AT lines are **hormonally insensitive and do not express AR**, in contrast to clinical castration-resistant disease and the HI and H-G8A1 Dunning lines [75]. AT lines also have no estrogen

**Table 7.2** Characteristics of Dunning R3327 rat prostate tumor lines

| Tumor line | Histologic differentiation | Mean tumor doubling time (days) | Androgen sensitive? | Metastatic potential |
|---|---|---|---|---|
| G | Low | 4.0 | Yes | Low |
| A-sublines: | | | | |
| PAP | High | 10.5 | Yes | Low |
| PIF-1 | Moderate | 3.7 | No | Low |
| PAT | Anaplastic | 2.8 | No | Low |
| H-sublines: | | | | |
| H | High | 22 | Yes | Low |
| HI-S | High | 24 | No | Low |
| HI-F | Moderate | 4.8 | No | Low |
| AT1 | Anaplastic | 2.5 | No | Low |
| MAT-Lu | Anaplastic | 2.5 | No | High |
| MAT-LyLu | Anaplastic | 1.5 | No | High |
| AT2 | Anaplastic | 2.5 | No | Low |
| AT3 | Anaplastic | 1.8 | No | High |
| AT6.1 | Anaplastic | 3.0 | No | High |

Adapted/updated from [72]

receptor despite expression in parental H tumors; however, **PAP and 5-alpha reductase expression** is retained [75, 78, 79]. Several AT lines have high metastatic potential and have become among the best characterized lines of the Dunning model, including **AT3**, **AT6.1**, **AT6.3**, **MAT-Lu**, and **MAT-LyLu**, the last two being sublines of AT1 [75]. While **spontaneous lung metastases** are common to each of these lines, MAT-LyLu additionally form frequent **spontaneous lymph node metastases** similar to human CaP. Furthermore, **bone metastases** of mixed osteoblastic/osteoclastic character can be induced with high frequency using MAT-LyLu and alternative implantation techniques, including intracardiac injection, tail vein injection with inferior vena cava (IVC) clamping, and direct intraosseous injection. **The MAT-LyLu Dunning model variant provides a unique investigational tool as a rat CaP model that can generate high-frequency skeletal metastases**. Other Dunning sublines such as those derived from RR3327-A provide a spectrum of CaP differentiation, including high (**PAP**), moderate (**PIF-2**), and low/anaplastic (**PAT-2**), the latter two of which are also androgen insensitive [80].

The Dunning model has been studied by a number of different approaches. Numerous cell lines established from these tumors are described. Isaacs and colleagues characterized seven of these cell lines with comparison to the original primary tumors. In all but one cell line, tumorigenicity in rats was retained with 100 % preservation of various genetic, biochemical, and histologic features [75]. Dunning tumors can also be successfully transplanted into ACI rats because of this strain's genetic similarity to its parental Copenhagen strain. Dunning tumors are also frequently studied as xenografts in immunodeficient mice.

*Preclinical findings*. Collectively, the Dunning tumor lines recapitulate the heterogeneity of growth rates, differentiation, androgen sensitivity, and metastatic potential seen in human prostate carcinogenesis and have generated numerous findings with successful clinical translation. Oltean and colleagues recently demonstrated enrichment of clinical metastatic gene expression patterns in the metastatic Dunning AT3 line relative to its nonmetastatic parental line [81]. Pfundt and colleagues compared the expression of 5,000 genes between hormonally sensitive (H) and insensitive (HI) Dunning tumors, revealing dozens of differentially expressed genes with important roles in carcinogenesis [82]. In addition, **the Dunning model was central for the discovery of metastasis suppressor genes**, genes which inhibit cancer metastasis without affecting primary tumor growth [80, 83]. Carcinogenic roles for survivin, motility factors, anomalous heat-shock protein regulation, nuclear matrix protein alterations, and epithelial-to-mesenchymal transition (EMT) have been demonstrated in this model [80, 84, 85]. Ki-Ras point mutations are also present in the more aggressive Dunning lines, as frequently observed in clinical CaP [86].

The Dunning model also provided **among the first demonstrations of outgrowth of androgen-independent cell populations as a mechanism of androgen-independent relapse** [87], as well as the therapeutic efficacy of LHRH antagonists [88]. More recent hormonal therapy research in this model provides support for (1) combined use with chemotherapy or targeted tyrosine kinase inhibitors [89–91], (2) neoadjuvant administration prior to radiotherapy [92], (3) the additive benefit of 5-alpha reductase inhibition to castrate testosterone levels [93], and (4) the importance of the prostatic stromal microenvironment in hormonal treatment efficacy [94].

With regard to other therapies, the *in vivo* efficacy of suramin, a synthetic multitarget growth factor receptor inhibitor, was demonstrated in the Dunning model leading to phase II and III trials in castration-resistant CaP patients [95–98]. Dietary agents implicated in clinical CaP prevention have been shown to have efficacy in this model, including vitamin D, selenium, vitamin E, lycopene, and certain vegetables [99–102]. The role of the immune system including tumor-specific leukocytes and cytokines has also been extensively characterized in the Dunning model [103–105], and efficacy is described for various immunologic treatments including adoptive immunotherapy, cytokine administration, vaccines, IL2-based gene therapy, and targeting of tumor-associated macrophages [105–110]. A variety of local tumor therapies have been thoroughly investigated in this model, including radiotherapy [92, 111, 112], cryosurgery [113], high-frequency ultrasound [114–117], photodynamic therapy [118, 119], and hyperthermia [120, 121].

## Other Syngeneic Rat Prostate Tumor Models

*Syngeneic grafts from spontaneous L-W rat CaP*. Four syngeneically transplantable cell lines (**PA I–IV**) have been established from spontaneous L-W prostate tumors and are collectively referred to as the **Pollard model** [9, 122–124]. These lines retain the **high metastatic potential** of the original L-W prostate tumors when transplanted subcutaneously in the flank of syngeneic rats, with distant spread to the lymph nodes, lungs, and liver. Additionally, the **PA-III cell line forms osteoblastic/osteolytic bone lesions** when injected over the calvarium and scapula after disruption of the periosteum with the inoculating needle, providing a rare murine mode of CaP bone colonization. The PA-I and PA-IV cell lines, but not PA-II cell line, form less frequent bone tumors with this approach [123]. The PA-III bone colonization model has implicated insulin growth factors (IGF), urokinase plasminogen activator (uPA), and transforming growth factor beta (TGF-beta) in the formation of osteoblastic lesions [9, 125]. There are conflicting reports regarding AR status in PA-III cancers [9, 124].

*Syngeneic grafts from spontaneous ACI rat CaP*. Shain and colleagues have characterized serially transplantable grafts established from spontaneous ACI rat prostate ventral lobe cancers, including morphologic features and C-19 steroid metabolism [126]. Three initial cell lines (C, D, and T) were established, and subsequently eight sublines were derived and characterized [18, 19]. All lines retain tumorigenic potential in ACI rats with prostatic differentiation, cribriform morphology, and AR/PAP/5-alpha-reductase expression. T-family sublines are androgen sensitive, while C- and D-family sublines are androgen insensitive. Extensive investigation of these cell lines has been focused *in vitro*, largely on the role of fibroblast growth factors in prostate carcinogenesis.

*Syngeneic grafts from DMAB-induced F344 rat CaP*. Several studies have employed DMAB carcinogen-induced F344 prostate tumors grafted back into their parental rat strain. Zhao and colleagues characterized the kinetics and timing of spontaneous lung metastasis in this model [127]. Kawai et al. used this model to demonstrate therapeutic efficacy of hyperthermia-activated magnetic cationic liposomes (MCL) [128]. The host rat immune system was shown to play a key role in MCL activity, underscoring the value of an immunocompetent model. DMAB-induced F344 prostate tumors can also be injected directly into the bone of F344 hosts, and the resulting bone lesions are mixed osteoblastic/osteoclastic [129]. Microarray analysis of these lesions by Lynch and colleagues has revealed specific genes upregulated at the tumor-bone interface, such as *MMP-7*, *cathepsin-K*, and *apolipoprotein D* [129].

*Syngeneic grafts from Noble rat testosterone/estrogen-induced CaP*. The Noble rat CaP model induced by combined testosterone and estrogen was described earlier in this chapter. Several tumor lines from this model have been characterized after grafting in syngeneic hosts [33, 35]. These transplants are androgen sensitive with androgen-independent growth potential and are metastatic to both lungs and liver. Numerous chemotherapies agents have been evaluated by Drago and colleagues using this syngeneic transplant model [35, 130, 131].

## Xenograft Transplants

Unlike syngeneic transplants, **xenografts** grow in a different species from which the tumor originates and therefore require an **immunodeficient host**. Immunocompromised strains of mice are most often used (although immunodeficient rats are commercially available) and include ***severe combined immunodeficiency*** (***SCID***) ***mice*** and ***nude mice***. SCID mice have a mutated DNA repair enzyme gene that results in depletion of functional B and T cell lymphocytes and an inability to mount any cell-mediated or humoral immune response. In nude mice, mutations in the *FOXN1* gene prevent thymus development and associated T cell lymphocyte maturation. However, T cell lymphocyte depletion is generally not absolute.

Xenografts can be categorized into two groups: (1) cancers passaged in rodents without *in vitro* culture (**serial *in vivo* heterotransplants**) and (2) cancers cultured *in vitro* prior to

grafting into mice (**cell line xenografts**) (Table 7.3). The site of tumor transplantation is typically the subcutaneous flank, orthotopic, or renal subcapsular [138]. Xenografts share advantages with syngeneic transplant models, including technical simplicity and familiarity. **The primary advantage of xenograft models is the ability to study *human* CaP**. Disadvantages include nonautochthonous tumor formation and an inability to form bone lesions without intricate implantation approaches. As with syngeneic transplants, xenografts are not appropriate for investigating chemoprevention due to circumvention of initial transformation steps. Findings must also be interpreted with caution given the likely importance of the immune system in prostate carcinogenesis, which cannot be assessed in its entirety in these models.

## Serial In Vivo Heterotransplants

Human and rat prostate CaP may be directly transplanted into immunodeficient mice using either minced tumor tissue or cell suspensions after tumor dissociation. When passaged durably in mice, these cancers are referred to as **serial *in vivo* heterotransplants** (**SIVH**). Inefficient murine uptake of engrafted patient CaP tissue has provided a historic challenge for researchers, with early studies in nude mice achieving 0–20 % success rates [139–141]. Several studies suggest compromised xenograft uptake following **cryopreservation**, indicating that tissue quality plays a role [142–144]. Graft uptake may benefit from **androgen supplementation** [139, 144, 145]. Schroeder and colleagues noted 28 and 5 % rates of human prostate tumorigenicity in nude mice with and without androgen supplementation, respectively [139]. However, improved graft uptake with androgen supplementation is not consistently observed [140, 145, 146]. According to Jones and colleagues, **tumor grade** may be more important. These investigators observed no graft uptake for well-differentiated human prostate tumors mice despite hormonal supplementation, compared to occasional (28 %) uptake without growth of moderately differentiated tumors and common (60 %) uptake with growth of poorly differentiated tumors in the absence of androgen supplementation [140].

While features inherent to the primary tumor are important, the most critical factor for successful xenograft uptake appears to be the **host microenvironment**. The role of the **immune system** was demonstrated in 1981 by Reid and colleagues, who showed that treatment with anti-mouse interferon serum or anti-mouse lymphocyte serum increased the efficiency of tumor uptake in nude mice from 0 to 100 % [141]. Subsequently, a 10-fold increase in graft efficiency was described using nude mice with reduced natural killer cells [146]. With the more recent use of immunodepleted SCID mice, high uptake efficiency (60–75 %) has been achieved regardless of testosterone supplementation [138, 144, 147, 148].

**Matrigel** (Becton-Dickinson, Franklin Lakes, NJ, USA) is a mouse sarcoma-derived extracellular matrix gel composed of type IV procollagen, laminin, and heparin sulfate proteoglycan [149]. The microenvironment formed by this matrix is conducive to grafting many types of human cancers into mice, including CaP [150–152]. Co-inoculation of human CaP with Matrigel lowers the critical cell mass for tumorigenesis by 25,000-fold [153]. Matrigel may not be necessary during the second heterotransplant passage for repeat uptake [154]. The **anatomic site of transplant** is also important for uptake; however, studies disagree regarding whether subcutaneous, renal subcapsular or orthotopic sites provide the best "soil." [138, 140]

Many SIVH lines have been generated with human CaP over the past three decades, each representing a unique patient tumor (Table 7.3a). **SIVH tumors typically retain biologic features of the original primary tumors**, such as histologic differentiation, androgen sensitivity, and AR/PSA/PAP expression (Table 7.3a). The first reported SIVH CaP line, PC82, showed durable maintenance of each of these biologic features even after 2.5 years of continuous *in vivo* passaging [155]. In a study characterizing seven different SIVH CaP lines, van Weerden and colleagues noted that the histology and AR/PSA/PAP levels generally reflected the original patient tumors after 5–23 *in vivo* passages [146].

Tumor latency is around 1–3 months in SIVH models, although periods approaching 1 year are reported [146, 147]. The histology of most SIVH model tumors is **moderately or** (**more often**) **poorly differentiated**, consistent with higher-grade tumors grafting more efficiently [140]. These lesions may retain a small stromal constituent [132, 156, 157]. Maintenance of original tumor histology is reported after >30 *in vivo* passages [146, 154, 158–160] and may be retained regardless of cryopreservation, anatomic site of transplantation, or type of host immunodeficiency type [138, 143].

As summarized in Table 7.3a, **the large majority of SIVH models retain expression of AR and PSA and show initial androgen dependence** [146, 154, 156–158, 160–165]. However, only few SIVH lines, including **PC82**, **PC-EW**, **KUCaP**, **and BM-18**, **remain androgen sensitive** even with prolonged androgen deprivation [154, 157, 165]. More commonly, outgrowth of androgen-independent populations occurs during prolonged *in vivo* hormonal selection. These SIVH lines include **LuCap 23.1**, **LuCap 23.12**, **LuCaP-35**, **LuCaP-58**, **LuCaP-73**, **LAPC-4**, **PAC-120**, **and CWR22** and may be useful for **recapitulating progression to androgen independence** [132, 147, 164, 166, 167]. Several of these lines were established from

**Table 7.3** Patient xenograft models of prostate cancer

| Xenograft line | Patient tissue origin | Androgen sensitivity | Androgen receptor expression | PSA expression |
|---|---|---|---|---|
| (a) *Serial* in vivo *heterotransplants* (*SIVH*) | | | | |
| PC-82 | Prostate | Yes | Yes | Yes |
| Honda | Testis | Yes | Yes | No |
| 9479 | Bone | No | No | No |
| PC-EW | Lymph node | Yes | Yes | Yes |
| PC-EG | Prostate | Yes | – | Yes |
| PC-133 | Bone | No | No | No |
| PC-135 | Prostate | No | No | No |
| PC-295 | Lymph node | Yes | Yes | Yes |
| PC-310 | Prostate | Yes | Yes | Yes |
| PC324 | Prostate | No | No | No |
| PC-339 | Prostate | No | No | No |
| PC-346 | Prostate | Yes | Yes | Yes |
| PC-346B | Prostate | Yes | Yes | Yes |
| PC-374 | Prostate | No | No | No |
| TEN/12 | Prostate | Yes | Yes | Yes |
| DU5683 | Lymph node | Yes | – | Yes |
| LuCaP 23.1 | Lymph node | Yes | Yes | Yes |
| LuCaP 23.8 | Lymph node | Yes | Yes | Yes |
| LuCaP 23.12 | Liver | Yes | Yes | Yes |
| LuCaP 35 | Lymph node | Yes | Yes | Yes |
| LuCaP 41 | Prostate | Yes | Yes | Yes |
| LuCaP 58 | Lymph node | Yes | Yes | Yes |
| LuCaP 69 | Bowel | – | Yes | Yes |
| LuCaP 70 | Liver | – | Yes | Yes |
| LuCaP 73 | Pelvis | Yes | Yes | Yes |
| LAPC-3 | Prostate | No | Yes | Yes |
| LAPC-4 | Lymph node | Yes | Yes | Yes |
| LAPC-9 | Bone | Yes | Yes | Yes |
| MDA PCa-31 | Liver | – | Yes | Yes |
| MDA PCa-40 | Liver | – | No | No |
| MDA PCa-43 | Adrenal | – | Yes | Yes |
| MDA PCa-44 | Skin | – | No | No |
| CWR22 | Prostate | Yes | Yes | Yes |
| CWR22R | Prostate (derived from CWR22) | No | Yes | Yes |
| CWR91 | Prostate | No | – | Yes |
| PAC120 | Prostate | Yes | Yes | Yes |
| BM18 | Bone | Yes | Yes | Yes |
| KUCaP | Liver | Yes | Yes | Yes |
| (b) *Cell line xenografts* | | | | |
| DU-145 | Brain | No | No | No |
| PC-3 | Vertebrae | No | No | No |
| LNCaP | Lymph node | Yes | Yes | Yes |
| C4-2 | Lymph node (derived from LNCaP) | No | Yes | Yes |
| JCA-1 | Prostate | No | No | No |
| DUPRO | Lymph node | No | No | No |
| ND-1 | Prostate | No | No | Trace |
| PacMetUT1 | Lymph node | Yes | Yes | No |
| CA-HPV-10 | Prostate | No | No | Low |
| WPE1 lines | Prostate | Yes | Yes | Yes |

Adapted/updated from [132, 133]; see also [134–137]

patients who later received androgen deprivation and progressed to castration resistance [132, 147, 161, 165]. Some SIVH lines, including **CWR22 and KUCaP**, have **AR missense mutations** that account for androgen independence. The CWR22 mutation confers AR hypersensitivity to estradiol [168]. Outgrowth of KUCaP tumors occurs with bicalutamide treatment, consistent with the original patient's clinical progression on this therapy [165]. Although the SIVH line, **PC346**, expresses wild-type AR, prolonged *in vitro* androgen deprivation has generated **sublines with AR anomalies**, including tenfold upregulation of AR (*PC346-Flu1*) and the T877A point mutation (*PC346-Flu2*), both frequent findings in clinical disease [166].

Other SIVH lines demonstrate **pure androgen insensitivity**, including **PC324**, **P339**, **PC374**, **and LAPC-3** [146, 147]. The former two are anaplastic with loss of AR expressed in their original patient tumors. In contrast, **PC374 and LAPC-3** retain AR/PSA/PAP expression and may therefore be useful for the study of AR + castration-resistant prostate cancer, as observed clinically.

## Cell Line Xenografts

Xenografts can also be generated by transplantation of cancer cells cultured *in vitro*. Due to the technical and logistic ease, this approach represents **the most common approach to murine modeling of CaP**. Numerous cell line xenografts using human CaP cells have been described, several of which are listed in Table 7.3b. Cell line xenografts tend to be **poorly differentiated** probably due to preferential *in vitro* immortalization of poorly differentiated cancers and artificial selection pressures with *in vitro* culturing over time. Cell line xenografts therefore commonly have **disparate histology and molecular biology relative to their original patient tumors** [139, 169]. In contrast to most SIVH xenografts, cell line xenografts usually lack androgen sensitivity and expression of AR/PSA/PAP. (Table 7.3) Furthermore, stromal cells are removed by *in vitro* selection, precluding study of stromal-epithelial interactions.

**A significant proportion of murine model research has focused on cell line xenografts from three patient tumors** [170–172]. These cell lines, **LNCaP**, **PC3**, **and DU145**, which contribute to over 7,000 peer-reviewed publications based on abstract citations alone, are each **derived from metastatic lesions** (lymph node, bone, and brain, respectively) and display numerous chromosomal alterations. Both PC3 and DU145 are androgen insensitive but lack AR expression, in contrast to clinical castration-resistant prostate cancer. LNCaP tumors are androgen sensitive and express the first identified mutated AR. However, LNCaP is not reliably tumorigenic, limiting its use in xenograft modeling. Numerous findings beyond the scope of summary in this chapter are reported for these three cell lines, with frequent but inconsistent clinical translation.

## Other Xenograft Models

*Small cell prostate cancer xenografts*. Small cell cancer is a rare and highly aggressive clinical variant of prostate cancer characterized by neuroendocrine differentiation. The **UCRU-PR-2** xenograft model developed by Van Haaften-Day and colleagues has histology, ultrastructural features, and a protein expression profile similar to the original patient primary small cell prostate tumor, including expression of the neuron marker, enolase [173]. UCRU-PR-2 tumors lack AR but express low levels of PAP. Despite frequent metastasis of clinical small cell prostate cancer, UCRU-PR-2 tumors are nonmetastatic, and invasive potential varies with site of transplantation [174]. Other small cell prostate cancer xenograft models include **WISH-PC2** and **LuCaP-49**, which lack AR and PSA expression [175, 176]. While spontaneous metastases have not been demonstrated in these models, WISH-PC2 colonizes both bone and liver with direct organ injection. Bone lesions are osteolytic with foci of osteoblastic activity [175].

*Dunning rat CaP xenograft*. Similar to human tumors, rat prostate tumors and cancer cell lines may also be xenografted into immunodeficient mice [177]. The most frequent example of this approach uses the Dunning rat prostate tumor sublines described above. Research in SCID mice using the highly metastatic AT sublines of the Dunning model was central to the initial discovery of metastasis suppressor genes [79, 83].

# Mouse Prostate Reconstitution Model

In the 1970s, the laboratory of Dr. Gerald Cuhna provided a series of investigations describing the ability of urogenital mesenchyme to induce prostate glandular development from urogenital epithelium. It was therein demonstrated that urogenital sinus tissue enzymatically dissociated *in vitro* into its mesenchymal and epithelial components could be reconstituted as a mouse renal subcapsular graft with subsequent *in vivo* prostate organogenesis [1, 178]. In the late 1980s and early 1990s, Thompson and colleagues added retroviral vectors to this model allowing introduction of select genes to generate renal subcapsular prostate tumorigenesis [179, 180]. This *in vivo* reconstitution of genetically modified uro-

genital sinus tissues has been referred to as the **mouse prostate reconstitution** (**MPR**) **model**. This model was among the first to study the effect of selectively modified genes on *in vivo* prostate carcinogenesis and metastasis.

The MPR model offers several advantages as a murine model. Tissues at no point require *in vitro* culturing, thus avoiding associated artificial selection pressures. In addition, unlike transgenic models in which all cells in the mouse prostate contain the transgene, only a small portion (e.g., 0.1 %) of prostate cells are initially affected [180]. This may more accurately reflect tissue patterns of clinical CaP both in terms of multifocality and in terms of limited initial disease with preservation of a largely benign prostate gland [181]. Furthermore, each infected cell will contain a unique retroviral insertion site, allowing tracking of outgrowth and metastasis patterns for different clonal CaP foci. Finally, because urogenital tissue is acquired from the same mouse strain of reconstitution, a fully immunocompetent host can be studied.

The MPR model characterized by Thompson and colleagues employed urogenital sinus tissue with adenoviral vector-mediated overexpression of *ras* and *myc* oncogenes [179–181]. While infection with either gene alone yields only prostatic dysplasia or hyperplasia, respectively, combined ras/myc overexpression in urogenital sinus tissue results in poorly differentiated nonmetastatic CaP with variable incidence based on the mouse strain, including >90 % in C57BL/6 mice [179]. Additional modification of the ras/myc-overexpressing urogenital sinus tissue by mutant p53 introduction increases the penetrance of CaP to 100 % and additionally generates **metastases to bone**, **lymph nodes**, **lungs**, **and liver** [182]. This MPR modification is **among the only murine models of CaP that give rise to frequent spontaneous bone metastases**. Cell lines established from both primary tumors and metastases in this model retain tumorigenic and metastatic potential when grafted orthotopically or subcutaneously in mice [183, 184]. Primary tumor cell lines express AR and appear androgen sensitive initially but progress to AR-positive androgen independence with prolonged passaging *in vitro*.

*Preclinical findings* of significance with this model include among the first demonstrations of high levels of TGFbeta1 and apoptotic bodies in CaP, both of which have been corroborated clinically [181]. MPR studies have also revealed a role for caveolin-1 in progression to metastasis as subsequently implicated in the clinical setting as well [185, 186]. The MPR model has also supported a chemopreventative benefit of retinoids and efficacy of viral-based gene therapy using "suicide genes" or cytokines [181]. However, use of the MPR model is limited by its considerable technical challenge.

## Transgenic Murine Models

Transgenic models are the most recently developed murine models of prostate cancer. Using site-specific recombinant DNA methodology, specific genes of interest (e.g., candidate oncogenes) may be inserted into the mouse genome, and the resulting mouse phenotype examined. Alternatively, specific genes (e.g., tumor suppressor gene candidates) may be "knocked out" of the mouse genome using the **Cre-Lox system** of DNA recombination, which employs a Cre (cyclic recombinase) enzyme derived from bacteriophage P1 to catalyze DNA removal between two 34 base-pair sequences referred to as Lox-P sites. Because gene knockouts are often lethal during embryonic mouse development, investigators frequently choose to knock out only one of two alleles (*heterozygous knockouts*). Alternatively, a nonlethal *conditional* homozygous knockout may be generated employing either prostate-restricted expression or time-restricted expression, inducible following animal development with various pharmacologic or dietary triggers.

*Transgenic models provide the advantage of knowing the precise genetic change*(*s*) *responsible for tumorigenesis*, *and contributions of specific proteins or signaling pathways to carcinogenesis can thus be individually examined*. Tumors form orthotopically and in an immunocompetent host. Transgenic models may recapitulate the entirety of prostate carcinogenesis from precancerous transformation to metastasis, although most of the current models simulate only initial dysplastic changes.

*Promoters*. Expression of transgenes can be limited to the rodent prostate gland by employing a *prostate tissue-specific promoter*. The prototypical example is the promoter for **probasin** (**PB**), a "house-keeping" protein with androgen-driven and prostate-specific expression in rodents and humans. Variants of PB, including **long PB** (**LPB**) and **ARR$_2$PB**, have additional androgen response regions yielding higher levels of transgene expression. Less commonly used prostate-specific gene promoters include the **PSA** promoter and the promoter for the PSA analogue, **PSP94** (prostate secretory protein of 94 amino acids), which is among the most abundant prostate secreted proteins. Other promoters which have been used in transgenic models have lower prostate tissue activity and specificity, leading to tumors of other organs, including the promoter for the mouse mammary tumor virus (**MMTV**) and the androgen responsive gene for the **C3**(**1**) steroid binding protein. Different promoter activities can lead to dramatic changes in prostate phenotype for the same transgene [187, 188].

*Transgenes*. Transgenic model phenotypes using different transgenes are summarized in Fig. 7.2. The first transgenic

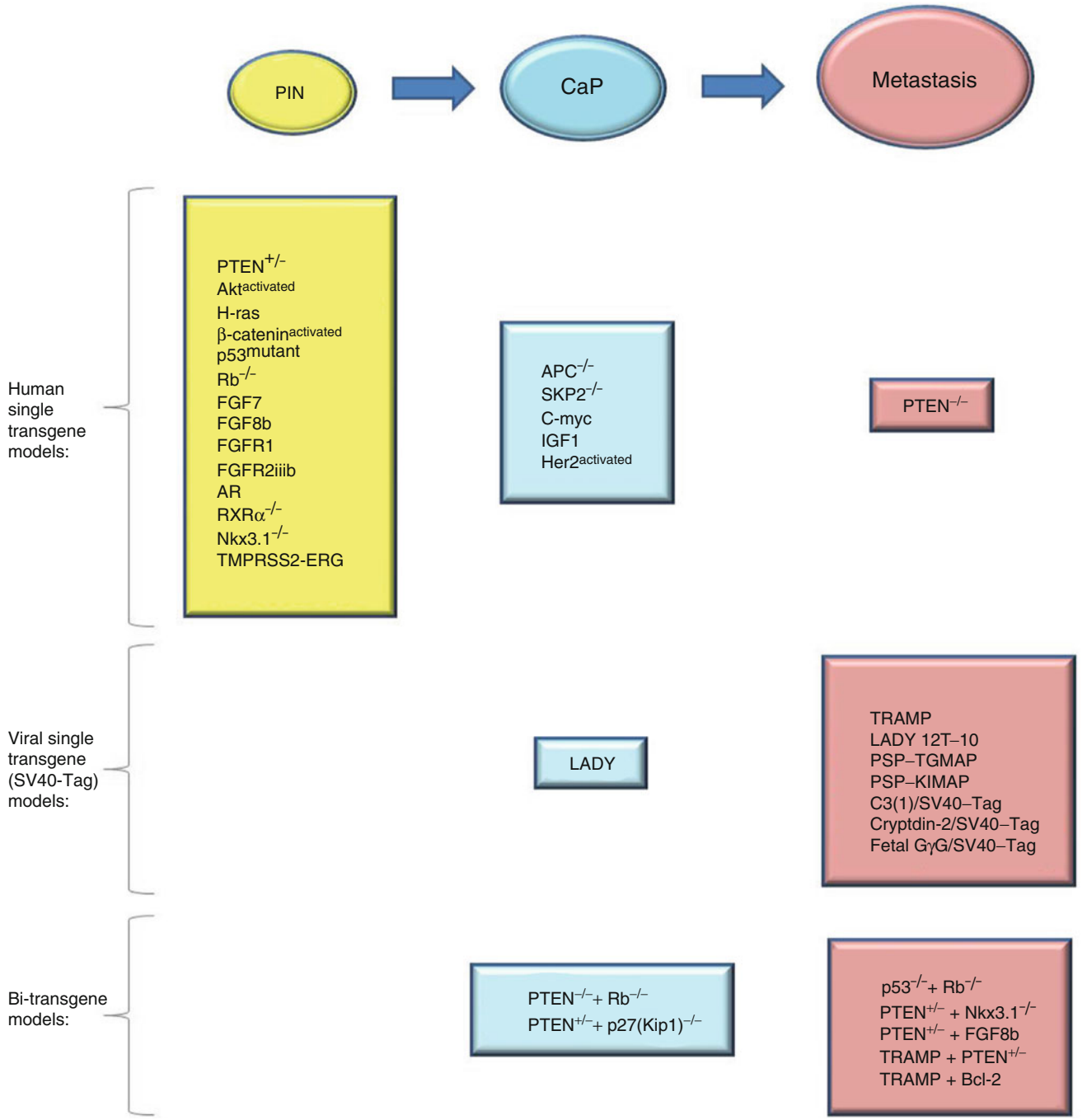


**Fig. 7.2** Transgenic murine models of prostate cancer

murine models of CaP employed ***viral*** **oncogenes** as transgenes, namely, SV40-Tag oncogene derived from simian virus 40 (SV40), which encodes both "large T" and "small t" oncoprotein antigens. SV40-Tag models generate aggressive CaP with high penetrance and short latency (Table 7.4). However, use of these models has been limited due to (1) a lack of a role for the SV40-Tag oncogene in clinical CaP and (2) a predominant neuroendocrine differentiation which is rare in clinical CaP. Other transgenic models employ as trangenes ***human*** **oncogenes/tumor suppressor genes** which are already implicated in clinical CaP. This approach has gained recent popularity with increasing identification of genes and signaling pathways contributing to prostate carcinogenesis. Human transgene models are generally more

**Table 7.4** Metastatic transgenic murine models of prostate cancer using the SV40-Tag oncogene

| Transgenic model name | Promoter | Oncogenes within transgene | Frequency of metastasis (months) | Site of metastasis |
|---|---|---|---|---|
| TRAMP | PB | Large T antigen, small t antigen | 100 % at 6 months | LN, lung, bone, kidney, adrenals |
| LADY 12T-10 | LPB | Large T antigen | 66 % at 6 months<br>88 % at 9 months | LN, liver, lung |
| PSP-TGMAP | PSP94 | Large T antigen, small t antigen | 100 % at 4 months (line A) | LN, kidney |
| PSP-KIMAP | PSP94 | Large T antigen, small t antigen | 85 % at 14 months (LN)<br>25–50 % at16 months (distant) | LN, lung, liver |
| C3(1)/SV40-Tag | C3(1) | Large T antigen | <5 % at 8 months | Lung |
| Cryptidin-2/SV40-Tag | Cryptdin-2 | Large T antigen, small t antigen | 40 % at 6 months | Lung, liver, LN, bone |
| Fetal Gγ-globin/SV40-Tag | Fetal Gγ-globin | Large T antigen, small t antigen | 75 % at 5 months | Kidney, lung, bone, adrenals |

Adapted/updated from [189]
*PB* probasin, *LPB* long probasin, *LN* lymph nodes

indolent than viral transgene models, with infrequent progression beyond PIN (Fig. 7.2). The following section summarizes specific transgenic murine CaP models using viral or human transgenes.

## Viral (SV40-Tag) Oncogene Transgenic Models

*C3(1)/SV40-Tag*. The first described transgenic prostate cancer model overexpressed the SV40-Tag transgene in prostate tissue by fusing it to a 4.5-kb promoter sequence of the androgen responsive (but not prostate-specific) gene, C3(1) [190–192]. In addition to dysplastic changes in various other organs, male mice develop frequent LGPIN and HGPIN in the ventral and dorsolateral lobes by 3 months, with histologic and genetic changes similar to those seen in humans. Progression to CaP occurs in the ventral lobe after 8 months of age and the dorsolateral lobe after 11 months of age. Ha-Ras, Ki-ras, and p53 mutations are observed in these cancers [191]. However, the C3(1)/SV40-Tag model has received limited study due to relatively low tumor penetrance (40 %) and only rare metastasis (<4 %) limited to the lungs.

*TRAMP model (Pb/SV40-Tag)*. The TRAMP (transgenic adenocarcinoma of the mouse prostate) model is the most extensively characterized transgenic mouse model of CaP. This model was the first to use a prostate-specific promoter to restrict transgene expression to the mouse prostate, fusing SV40-Tag to a rat Pb promoter. Male TRAMP mice develop **highly metastatic tumors in the dorsolateral and ventral prostate lobes with 100 % penetrance**, beginning with PIN by 8 weeks that progresses to poorly differentiated neuroendocrine carcinoma with distant metastasis by 16–32 weeks [193–195]. Tumors are AR positive and initially androgen dependent; however, outgrowth of a metastatic castration-resistant population eventually occurs [196]. While the most common sites of metastasis are the lymph nodes and lungs, **occasional spontaneous metastasis to bone is observed** [197]. The specific mouse strain may alter CaP phenotype with respect to tumor size, distribution, and potential for bone metastasis [198]. Cancer cell lines established from a TRAMP tumor (TRAMP-C1, TRAMP-C2) have been characterized which retain AR expression and tumorigenicity in syngeneic mice [199].

*LADY model* (*LPB/SV40-Tag*). In the LADY model, the SV40-Tag transgene (encoding the large T antigen only) is fused to the long variant of the probasin promoter (LPB/SV40-Tag). LADY tumors begin as PIN-like multifocal lesions in 100 % of mice by 10 weeks, followed by microinvasive carcinomas with neuroendocrine differentiation by 20 weeks [200]. Because the small t antigen is absent, the cancer phenotype is **less aggressive and penetrant than the TRAMP model**, yielding only rare metastases, although initial androgen dependence with progression to androgen independence is similarly observed. Seven LADY model lines have been generated, of which only the *12 T-10* line is metastatic [201]. **LADY 12 T-10 mice develop prostate tumors that spontaneous metastasize to bone**, albeit with lower frequency than observed in TRAMP mice [197, 201].

*Other SV40-Tag models*. Other mouse models similarly use the SV40-Tag transgene (with or without the small t antigen) fused to alternative promoters (Table 7.4). As with TRAMP, these models yield aggressive cancers that progress to metastasis with predominant neuroendocrine differentiation. They are also frequently androgen independent at or near the onset of carcinogenesis. In general, these variant SV40-Tag models have undergone only limited characterization. In rats, a transgenic model using the PB/SV40-Tag transgene referred to as the TRAP (transgenic rat adenocarcinoma of the prostate) model generates strictly androgen-dependent CaP in 100 % of animals by <4 months of age, with complete involution in response to castration at 5 months of age [202].

*Preclinical findings*. Most investigations of SV40-Tag models have been in TRAMP mice. Haram and colleagues performed RNA microarray expressional analysis and

identified 66 genes with concordant alterations in TRAMP and human prostate cancers relative to normal prostate, including the *SOX4* transcription factor gene implicated in many malignancies [203]. Other studies have shown that TRAMP mice have alterations in levels or activation of proteins observed in clinical prostate carcinogenesis, including PI3K/Akt and growth factor receptors for IGF, FGF, and EGF [204–206]. The TRAMP model has also been used to demonstrate efficacy of numerous chemopreventative agents, including genistein, alpha-difluoromethylornithine, COX-2 inhibitors, toremifene, flurbiprofen, green tea polyphenols, catechins, selenium, lycopene, and grape seed extract [207–211]. Chemoprevention studies in the LADY 12 T-10 model support a protective role for reduced dietary fat and various antioxidants, including selenium, vitamin E, and lycopene [212, 213].

## Human Transgene Models

Most human transgene models employ one or more transgenes with functions related to *cell signal transduction*, *regulation of* the *cell cycle/apoptosis*, or *growth factor signaling*. In contrast to viral oncogene models, human transgene models typically generate indolent neoplasms and most often lack progression beyond PIN.

The Wnt/FRZ/beta-catenin signaling pathway regulates cell adhesion and growth, and its dysregulation is implicated in clinical prostate carcinogenesis. **APC** is a negative regulator of Wnt/FRZ/beta-catenin signaling, the loss of which leads to hereditary colon uterine and urothelial cancers, and is frequently observed in spontaneous CaP. Transgenic mice with prostate-specific knockout of APC develop high levels of beta-catenin and PIN-like lesions by 2 months of age that progress to **invasive CaP by 4–7 months of age** [214]. These tumors are androgen dependent based on regression following early castration, with castration-resistant outgrowth observed after an additional 2 months. While upregulation of the oncoprotein, **beta-catenin**,may be responsible for CaP in these mice, only PIN (without CaP) is observed in transgenic mice with prostate-specific beta-catenin constitutive activation [215].

The phosphatidylinositol 3-kinase (PI3K)/Akt pathway mediates a variety of extracellular signals for survival, growth, and migration, and its dysregulation has been increasingly implicated in prostate carcinogenesis. **PTEN** (phosphatase and tensin homolog deleted on chromosome 10) is a key negative regulator of PI3K/Akt signaling and the most commonly mutated gene in clinical CaP. While homozygous PTEN transgenic knockouts cause embryonic lethality, single allele heterozygous knockouts develop LGPIN by 8–10 months, suggesting PTEN haploinsufficiency to be adequate for transformation [216, 217]. In PTEN homozygous knockouts restricted to the prostate (Pb-Cre4/PTEN$^{-/-}$), **100 % of mice develop PIN with rapid progression to CaP by 3 months**, **and 45 % of mice develop metastasis to lungs and lymph nodes by 7 months** without neuroendocrine differentiation [218]. Pb-Cre4/PTEN$^{-/-}$tumors regress in response to castration, although residual cancer cells are observed with a 17-fold higher proliferation rate [218]. PTEN-null prostate tumors have increased Akt kinase activation and demonstrate expression profile signatures similar to clinical metastatic CaP [218]. Bone metastases are not observed in this model. Transgenic mice with a constitutively activated **Akt kinase** transgene develop PIN but not CaP, suggesting carcinogenesis in PTEN-null mice may be in part Akt independent [219]. The GTPase oncoprotein, **H-ras**, activates cell growth through many downstream signaling pathways, including PI3K/Akt and is implicated in several malignancies. Transgenic models with prostate-specific H-ras overexpression form PIN-like lesions but do not progress to invasive CaP, suggesting additional changes are required for carcinogenesis [220].

Loss of cell-cycle and apoptosis regulation is believed to be an important step in the development of many types of malignancies. **p53** and Rb are the most extensively studied cell-cycle/apoptosis regulators, and the former is the most commonly mutated gene in human malignancy. *p53* mutation is common in advanced CaP, and functional loss may occur in up to half of patients with early stage disease as well [221]. While the *Rb* gene is rarely mutated in CaP, loss of a single allele is observed in 17–60 % of early stage tumors. Despite these clinical observations, Evalish et al. observed HGPIN but no CaP in mice with prostate-specific p53 knockout, while Hill et al. observed similar findings in Rb homozygous knockout mice [222, 223]. Similarly, in transgenic models resulting from prostate-restricted overexpression or knockout of the **bcl-2**, **p27$^{Kip1}$** or **c-fos** cell-cycle/apoptosis regulators, no neoplastic phenotype is observed [224–226]. In contrast, invasive CaP is occasionally observed in transgenic mice with prostate-specific overexpression of the **S-phase kinase-associated protein 2** (**SKP2**) proto-oncogene, a ubiquitin ligase which targets p27 and other cell-cycle inhibitors for degradation [227]. However, despite PIN formation in most mice by 4–7 months of age, the incidence of CaP in this model is only 4 %.

*Thus*, *alteration of individual cell cycle/apoptosis regulators is generally insufficient for malignant transformation*. The main exception is highly penetrant invasive CaP observed with ARR$_2$PB-driven prostate-specific overexpression of **c-myc**, a transcriptional activator of cell cycle progression commonly amplified in clinical HGPIN and CaP [187]. Of these mice, **100 % develop HGPIN and invasive CaP** within 3–6 months or 10–12 months depending on whether c-myc levels are high (“Hi-Myc” founder line) or low (“Lo-Myc” founder line), respectively, possibly due to dose dependence. Complete tumor regression occurs with early castration (4

months), but androgen-independent outgrowth occurs with delayed castration (8 months), suggesting a therapeutic benefit for earlier androgen deprivation. RNA microarray comparison between mouse and patient prostate tumors revealed concordant expression patterns for a number of CaP-related genes, including *TMPRSS2, Nkx3.1, and PIM1*. On the other hand, only HGPIN is observed in mice expressing a c-myc transgene driven by the C(3)-1 androgen responsive promoter [188]. This phenotypic discrepancy may reflect lower prostate-specific activity of the C(3)-1 promoter relative to $ARR_2PB$, further supporting dose-dependent transformation.

Increased signaling from cell surface growth factor receptors is a common feature of many malignancies including CaP. **Insulin growth factor 1** (IGF-1) is a potent activator of the PI3K/Akt pathway through its receptor IGF-1R and shows increased levels in CaP patient serum. DiGiovanni and colleagues found that transgenic expression of *IGF-1* in the mouse prostatic basal epithelium using the bovine keratin 5 (BK5) promoter results in **PIN and CaP with rates of 100 and 50 %, respectively**, after >6 months [228]. Li and colleagues observed similar findings in transgenic mice with prostate-specific expression of constitutively activated **HER-2** (Neu/ERBB2/EGFR2), a member of the epidermal growth factor receptor (EGFR) family and PI3K/Akt activator commonly upregulated in advanced clinical CaP [229]. Pb/HER-2 mice develop **LGPIN**, **HGPIN**, **and invasive CaP in a median of 12**, **16**, **and 18 months**, which is notably slower than in PTEN, IGF-1, or c-myc transgenic models. Cancers do not extend beyond the prostatic capsule and are poorly differentiated but negative for neuroendocrine markers. Pb/HER-2 tumors express phosphorylated AR; however, androgen sensitivity has not been evaluated. Other transgenic models overexpress various members of the **fibroblast growth factor** (**FGF**) **family**, whose expression is commonly altered in clinical prostate cancers, including FGF8b, FGFR1, FGF7, and FGFR2iiib. However, these models form only benign changes or PIN-like lesions, and dysregulated FGF signaling alone appears insufficient to induce invasive CaP [230–232].

Steroid hormone receptors are key intracellular regulators of cell growth and apoptosis believed to contribute to many malignancies. Signaling through **AR** has long been implicated in clinical prostate carcinogenesis based on clinical responsiveness of this cancer to androgen deprivation. Stanbrough and colleagues have characterized transgenic mice with high levels of prostatic AR protein using an AR transgene driven by a rat PB promoter (Pb/AR) [233]. These mice have hyperproliferative but otherwise histologically normal prostates up until 1 year of age, after which they develop lesions consistent with HGPIN but without progression to invasive CaP. Other studies have characterized the prostate phenotype in transgenic models of dysregulated **estrogen receptor** (ER) signaling. Knockouts of ER-alpha or ER-beta yield normal prostate morphology or benign prostatic hyperplasia, respectively, without progression to invasive CaP [234, 235]. **Retinoic acid receptors** (RAR/RXR) are steroid hormone receptors of retinoids, regulators of differentiation and apoptosis implicated in the suppression of clinical CaP. Prostate-specific knockout models of different RAR/RXR receptors develop normal prostates, squamous metaplasia, or PIN-like changes [236, 237]. *Overall*, *dysregulated steroid hormone receptor signaling appears to be insufficient for prostate carcinogenesis in transgenic models*.

The **NKX3.1** and **TMPRSS2-ERG** genes are heavily implicated in prostate tumorigenesis and progression. NKX3.1 is an androgen-regulated, prostate-specific homeobox (required for organogenesis) transcription factor with tumor suppressive function that is downregulated in clinical CaP and PIN. This gene maps to a region on human chromosome 8p21 with allelic loss in most CaP tumors and PIN lesions, suggesting haploinsufficiency as a possible early tumorigenic event. Independent studies show that whole-body or prostate-specific NKX3.1 homozygous knockout results in only PIN-like lesions, without progression to CaP [238, 239]. Loss of a single NKX3.1 allele is sufficient to generate low-grade PIN, supporting a role for haploinsufficiency [238]. The TMPRSS2-ERG gene fusion consists of the androgen-driven serine protease TMPRSS2 fused to the ERG member of the ETS transcription factor family and is commonly detected in CaP patients. Transgenic models using a TMPRSS2-ERG transgene yield PIN by 3–4 months but without progression to invasive CaP [240]. *Thus*, *the NKX3.1 and TMPRSS2-ERG genes may contribute to transformation of the prostate but by themselves appear to be insufficient for CaP formation*.

## Multi-Transgenic Models: The Future of CaP Murine Models

With few exceptions (*SV40-Tag*, *PTEN*, *APC*, *c-myc*, *SKP2*, *HER-2*, *and IGF-1*), a single transgene is generally insufficient for progression beyond benign prostatic hyperplasia or PIN-like lesions, suggesting the requirement of multiple genetic mutations for invasive CaP and metastasis (Fig. 7.2). Mouse models with a combination of two or more transgenes have recently been generated and yield invasive CaP with high penetrance and frequent metastasis (Fig. 7.2). For example, while Rb or p53 homozygous knockout mice each fail to develop CaP, combined **$Rb^{-/-}$/$p53^{-/-}$**prostate-specific knockout mice develop **highly metastatic CaP by 6–12 months with 100 % penetrance** [241]. Sites of metastasis include lymph nodes, liver, lungs, and infrequently the adrenal gland. Prostate tumors in this model have neuroendocrine differentiation and AR-positive androgen-independent growth regardless of castration timing. Not surprisingly, this phenotype is similar to transgenic models

of SV40-Tag, which functionally inactivate both p53 and Rb. Several multi-transgenic models have also been generated by crossing PIN-forming **PTEN$^{+/-}$** heterozygous knockouts with various single-transgene mice that alone similarly fail to form invasive CaP, including **p27$^{-/-}$**, **NKX3.1$^{-/-}$**, **or FGF8b$^{+/+}$** [242–244]. The resulting bi-transgene models form **rapidly growing CaP**, **with the latter two metastasizing to lymph nodes**.

In single transgene models that already form CaP, the addition of a second transgene enhances CaP incidence and aggression. For example, **p53$^{-/-}$/PTEN$^{-/-}$**dual homozygous knockout results in **CaP with high local aggression lethal within 7 months** [245]. As technologic advances allow whole genetic profiles of clinical CaP to be readily determined, multi-transgenic mouse modeling will provide a useful tool for investigating mutation-specific directed treatments.

## Murine Modeling of Prostate Cancer Bone Metastasis

Bone metastasis is the underlying cause of significant morbidity and mortality for the vast majority of CaP patients. The development of more effective therapies has been hindered by a scarcity of preclinical models to study this process, as murine models of CaP generally fail to demonstrate the affinity for bone marrow colonization observed clinically. Nevertheless, few murine models have provided useful tools for CaP bone metastasis research. The main examples are described below.

### Transgenic SV40-Tag Models

Several transgenic mouse models using the SV40-Tag oncogene form bone metastases, although generally with only low frequency. In the initial characterization of TRAMP metastases, Gingrich et al. observed only a single skeletal metastasis [194]. The lesion was well differentiated with a cribriform pattern and occurred in the lumbar vertebrae of a young (23 week) mouse. Gupta et al. have since reported a **25 % incidence of TRAMP model bone metastasis by 32 weeks**, as well as complete suppression achieved by chemopreventative green tea phenol [197]. In the **LADY model line 12T-10**, Masumori et al. observed **bone lesions in 9 % of mice >6 months of age**, some without other metastatic sites [201]. Low frequency of bone metastasis is also reported in SV40-Tag models using the cryptdin-2 or fetal gamma globin promoters, although these models are not well characterized [246, 247]. Overall, use of SV40-Tag models for investigation of bone metastasis therapies has been limited by the low incidence of events and predominant neuroendocrine differentiation of metastatic lesions.

The addition of a second transgene to SV40-Tag models may provide an effective approach for increasing bone metastasis, as observed with the **LPB-SV40-Tag/PB-hepsin$^{-/-}$model**. Hepsin is a serine-threonine transmembrane protease involved in maintaining basement membrane organization and is overexpressed by up to 34-fold in clinical CaP. Although PB-hepsin$^{-/-}$mice are nontumorigenic, crosses with the 12T-7 nonmetastatic LADY line have generated offspring that form **bone metastases with a nearly 40 % incidence** [248]. As with other SV40 models, LPB/SV40-Tag// PB-hepsin$^{-/-}$metastases have predominant neuroendocrine differentiation, limiting the model's clinical generalizability. *In transgenic models without SV40-Tag*, *bone metastases are yet to be observed*.

### MPR Models

The **MPR model** recreates prostate tumorigenesis by ectopic implantation of urogenital sinus under the renal capsule of syngeneic immunocompetent mice, as described earlier in this chapter. Using urogenital sinus tissue genetically manipulated to have loss of p53 and overexpression of ras and myc, investigators have achieved bone metastasis in **almost 100 % of mice with high affinity for the sternum and lumbar vertebrae**, common clinical sites of CaP metastasis [182, 249]. **Metastasis formation is rapid**, **requiring less than 2 months**. Shaker and colleagues have used this model to demonstrate a suppressive effect of a synthetic retinoid on bone metastasis [249]. Histopathologic description of bone metastases is needed, and the technical complexity of the MPR model has limited its use.

### Tumor Transplant Models

Two types of assays in tumor transplant models have traditionally been used in mice to study metastasis: *spontaneous* metastasis assays, which generate primary tumors (subcutaneous, renal subcapsular, or orthotopic) that disseminate to form distant metastases, and *experimental* metastasis assays, which bypass primary tumor formation by injection of cancer cells directly into the venous circulation (typically via the tail vein) to induce metastatic colonization. For some cell lines, including CWR22R, LAPC-4, and PC-3 cell lines (and their sublines), micrometastases in bone have been demonstrated using various molecular techniques; however, overt lesions are generally not observed [147, 250–252]. An exception is the **C4-2 clonal tumor line derived from LNCaP xenografts**. Unlike its parental line, the C4-2 xenograft is androgen independent and **metastatic to the lymph nodes**, **long bones**, **and spinal column**, more so in castrated mice. C4-2 bone lesions are mixed osteoblastic/osteolytic and occur

grossly **in approximately 50 and 20 % of castrate mice using subcutaneous and orthotopic transplantation, respectively**, and at higher frequency with specific modifications such as supplementation with parathyroid hormone [253, 254].

Alternative implantation approaches have been described that reliably generate bone metastases when performed with select CaP cell lines, particularly **PC3 and the MAT-LyLu rat CaP cell line**. Specific techniques include (1) intracardiac (left ventricle) injection, (2) tail vein injection with inferior vena cava (IVC) clamping, and (3) direct in intraosseous injection. **Intracardiac injection of the PC3 cell line, or its subline PC3-M, leads to bone metastases involving the femur, thorax, and mandible with variable (20–100 %) incidence** [255–257]. Lesions are osteolytic only, in contrast to clinical bone metastases. While spinal metastases are rare with PC3, **intracardiac injection of MAT-LyLu cells yields lumbar spinal metastases with 100 % incidence** in parental Copenhagen rats which present with hind limb paresis by 2–3 weeks [258, 259]. Mat-LyLu bone lesions are mixed osteoblastic/osteolytic as in clinical disease. MAT-LyLu overexpression of urokinase increases spinal metastasis and involvement of other skeletal sites as well [260].

Similarly, **tail vein injection with transient IVC clamping using Mat-LyLu cells (Geldof model) reliably generates symptomatic lumbar spinal metastases** within a short time frame of two weeks [261]. The incidence of PC3 bone metastases is lower with this approach (20 %), although higher rates are possible with specific PC3 sublines [262].

**Direct intraosseous injection** may also enable study of cancer cell colonization of rodent bone while avoiding metastasis of other organs. Common implantation sites include the calvarium, tibia, and femur. Successful implantation requires prior mechanical disruption of periosteum, often using the inoculation needle [123]. Corey and colleagues used this approach to establish **osteolytic lesions with PC3 and LuCaP35 cell lines, osteoblastic lesions with LuCaP23 cells, and mixed osteolytic/osteoblastic lesions with LNCaP, with success rates of 50–100 %** [263]. Rat prostate cancers studied with intraosseous injection include the **Dunning MAT-LyLu cell line, the Pollard PA-III cell line, and DMAB carcinogen-induced F344 rat CaP** [124, 129, 264, 265]. Each of these cancers generates **mixed osteoblastic/osteoclastic lesions with direct injection in the calvaria, scapula, or femurs of their parental rat strains with near 100 % efficacy**. Preclinical findings using the PA-III line support an important role for insulin growth factor signaling in osteoblastic metastases to bone [125]. Intraosseous injection studies also support a critical role for urokinase plasminogen activator (uPA) and TGF-beta1 activation in osteoblastic reactions, in addition to metallomatrix proteases and RANKL (receptor activation of nuclear kappa-B ligand) signaling in osteoclast reactions [125]. Caveats of this approach include that it disrupts bone architecture and that it may turn out to be more representative of primary tumor bone colonization than metastasis.

## SCID-Human Model of CaP Bone Metastasis

The scarcity of human CaP cell lines which are able to colonize rodent bone may reflect the absence of a growth-promoting microenvironment in mouse bone that is present in human bone. The **SCID-Human (SCID-Hu) model** of CaP bone metastasis described by Nemeth and colleagues uses human bone fragments implanted subcutaneously in SCID mice as targets for metastatic colonization by human CaP cell line xenografts. Supporting the importance of the bone microenvironment in CaP metastasis development, **human CaP cell lines (PC3, LNCAP, DU145, LAPC-4) injected via the tail vein or directly into subcutaneous human bone transplants preferentially colonize the human bone rather than mouse bone or subcutaneous human lung and intestine transplants** [266–268]. Rates of colonization of human adult bone are 35 and 65 % for intravenously injected LNCaP and PC3, respectively [268]. Direct injection using fetal bone approaches 100 % for each cell line [266]. PC3, DU145, and LAPC-4 cell lines generate osteoclastic bone lesions, whereas LNCAP uniquely makes mixed osteoblastic/osteoclastic lesions, and colonization is preferentially in the bone marrow cavity [267]. Bone-tumor interaction sites express high levels of PTHrP, TNF alpha, and IL-6, consistent with osteoclast recruitment and activity [267]. Preclinical findings with the SCID-Hu model support *in vivo* efficacy of an endothelin-1 receptor antagonist in combination with docetaxel and indicate the ability of TIMP to suppress CaP osteolysis [269, 270].

### Conclusion

Murine models are critical to preclinical CaP investigation, as they enable hypothesis-driven experimentation in a diverse tissue/multicellular microenvironment that cannot be recapitulated by available *in vitro* platforms. Numerous of such models for CaP have been characterized and vary widely in both practicality and ability to simulate key aspects of clinical disease. Currently, no murine model mimics all the attributes of clinical prostate carcinogenesis, and the value of any one model may be best assessed by its "track record" for predicting treatment response in the clinical setting. Future challenges of murine modeling of CaP include the development of improved bone metastasis models, avoiding elaborate technical modifications currently required. Ultimately, the generation of multi-transgenic mouse models may provide the most useful tools for evaluating "personalized" treatment of patient tumors with defined mutational profiles.

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# Prostate Cancer and the Metabolic Syndrome

8

Stephen E.M. Langley and Jenny P. Nobes

## Introduction

Men with prostate cancer have higher rates of noncancer mortality than men in the general population, with some of this excess attributed to the adverse effects of treatment [1], and there is evidence for an increased prevalence of metabolic syndrome with the therapeutic use of androgen deprivation therapy (ADT) in prostate cancer [2]. The metabolic syndrome is characterized by a cluster of metabolic risk factors for cardiovascular disease (CVD). Because of the generally favorable prognosis for early prostate cancer, decisions about which treatment is likely to offer the most benefit in the long term are particularly important.

ADT may be used to treat men with local and locoregional disease and is the mainstay of treatment for metastatic prostate cancer [3]. ADT may be achieved either through surgical castration (bilateral orchidectomy) or chemical castration with a gonadotropin-releasing hormone (GnRH) agonist, the most common approach in modern clinical practice [4].

Traditionally, the use of ADT was reserved for advanced prostate cancer [5]. There has, however, been a trend toward increasing use of ADT in prostate cancer patients [5–9], both as neoadjuvant and primary therapy, since the advent of PSA testing. A population-based cohort study concluded that widespread detection and aggressive treatment of prostate cancer in the USA has been associated with more, rather than less, use of ADT over time [5].

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## The Metabolic Syndrome

The metabolic syndrome (also known as syndrome X, Reaven syndrome [10], insulin resistance syndrome) is defined by a cluster of lipid and non-lipid metabolic risk factors for CVD, with insulin resistance (IR) as the central characteristic.

In IR, there is an exaggerated insulin response to ingested carbohydrates, especially those with a high glycemic index (GI). Insulin acts on fat cells resulting in hydrolysis of stored triglycerides, which elevates plasma levels of free fatty acids. These free fatty acids are absorbed by the liver, resulting in an increased production of triglycerides and very low-density lipoprotein (VLDL) cholesterol and a decreased production of high-density lipoprotein (HDL) cholesterol. Insulin acts on muscle to reduce glucose uptake, whereas in liver it reduces glucose storage, with both effects serving to elevate blood glucose. High levels of insulin cause increased renal sodium absorption, arterial vasospasm, and consequently hypertension. Endothelial effects of elevated insulin levels are also seen, mediated by nitrous oxide. In addition, impairment of cellular repair is apparent, with increased levels of pro-inflammatory cytokines. Concentrations of bound and free serum testosterone, sex hormone-binding globulin (SHBG), and androgen receptor are reduced [11].

The prevalence of metabolic syndrome has increased markedly over the last two decades, coincident with the global epidemics of obesity [12] and type II diabetes [13]. Studies using data from the Third National Health and Nutrition Examination Survey (NHANES III) have indicated that the age-adjusted prevalence of the metabolic syndrome increased from 29.2 % in 1988–1994 to 32.3 % in 1999–2000 [14, 15]. Prevalence varies by race and sex and increases with age [16–18].

## Definitions of the Metabolic Syndrome

Three of the most commonly recognized definitions of the metabolic syndrome are outlined in Table 8.1. Most studies

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**Table 8.1** Comparison of three commonly used definitions of the metabolic syndrome (criteria listed may differ for women)

| NCEP adult treatment panel III (ATP III) definition [19] | WHO definition [22] | IDF definition [21] |
|---|---|---|
| Three or more of the following: | Impaired glucose tolerance or diabetes and/or insulin resistance and two or more of the following: | Central obesity (or BMI >30 kg/m$^2$) and two or more of the following: |
| Fasting glucose ≥6.1 mmol/l | Impaired glucose tolerance or diabetes | Fasting glucose ≥5.6 mmol/l or previously diagnosed type 2 diabetes |
| Triglycerides ≥1.7 mmol/l | Triglycerides ≥1.7 mmol/l and/or HDL <0.9 mmol/l | Triglycerides >1.7 mmol/l (or treatment) |
| HDL <1.0 mmol/l | | HDL <1.03 mmol/l (or treatment) |
| Blood pressure ≥130/85 mmHg | Blood pressure ≥140/90 mmHg | Blood pressure ≥130/85 mmHg or treatment |
| Central obesity: waist circumference >102 cm | Central obesity: waist to hip ratio >0.9 and/or BMI >30 kg/m$^2$<br>Insulin resistance (under hyperinsulinemic, euglycemic conditions, glucose uptake below lowest quartile for background population)<br>Microalbuminuria | Central obesity: waist circumference >94 cm (Europid[a] men); >90 cm (South Asian men) |

*NCEP* National Cholesterol Education Program, *WHO* World Health Organization, *IDF* International Diabetes Federation, *HDL* high-density lipoprotein, *BMI* body mass index
[a]In the USA, NCEP ATP III definition of central obesity (waist circumference >102 cm) recommended

published to date on the metabolic syndrome, prostate cancer, and ADT have used the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) definition – the presence of three or more of the following: central obesity, elevated triglycerides, low HDL cholesterol, raised blood pressure, or raised fasting plasma glucose [19, 20]. The panel advised that central obesity is more highly correlated with metabolic risk factors than body mass index (BMI) and measurement of the waist circumference is, therefore, recommended to confirm the diagnosis.

Other definitions have been published by The International Diabetes Federation (IDF) [21] and the World Health Organization [22] (Table 8.1). The NCEP ATP III and IDF definitions are very similar, although the IDF definition excludes any person without central obesity and defines central obesity according to geography-specific thresholds.

## The Metabolic Consequences of Androgen Suppression

The importance of treatment-related morbidity and mortality in prostate cancer patients is well-recognized [23]. ADT-induced hypogonadism has been associated with increased BMI and fat mass, reduced lean body mass and muscle strength, osteoporosis (see section "Androgen Deprivation Therapy and Bone Health"), sexual dysfunction, and poor quality of life [2, 24–26], probably as a direct consequence of hypogonadism as prevalence was significantly higher in men prescribed ADT compared with men who had surgery and/or radiotherapy alone or controls [24]. GnRH agonists have also been shown to decrease insulin sensitivity [2, 27] and increase fasting insulin levels [28, 29]. Changes in serum lipoproteins [2, 26, 29] and arterial stiffness [28, 29], as well as possible QT interval prolongation [30, 31], have also been reported.

Male hypogonadism is an independent risk factor for the development of metabolic syndrome. Epidemiological studies have shown that low serum testosterone levels are associated with dyslipidemia, particularly elevated total cholesterol, LDL cholesterol, and triglycerides [32] and that testosterone replacement can improve lipid profiles in hypogonadal men [33]. A cross-sectional survey of 400 men aged between 40 and 80 years revealed that higher testosterone and SHBG levels were independently associated with higher insulin sensitivity and a reduced risk of metabolic syndrome, independent of insulin levels and body composition [11]. Other studies have found that low total testosterone and SHBG levels independently predict the development of metabolic syndrome in middle-aged men [34, 35].

Metabolic syndrome, according to NCEP ATP III criteria, was present in 55 % of men undergoing long-term (12+ months) ADT for prostate cancer, a prevalence significantly higher than in age-matched hormone-naïve patients with prostate cancer (22 %; $p<0.01$) and age-matched controls without prostate cancer (20 %; $p=0.03$) [20]. Men on ADT had significantly higher abdominal obesity and hyperglycemia compared with the other groups and significantly elevated triglycerides compared with controls.

Short-term prospective studies of ADT in men with prostate cancer have shown the development of adverse body compositional changes and increased serum insulin levels after only 3 months' treatment, indicative of reduced insulin sensitivity [28]; and in long-term ADT (12+ months), there are higher levels of fasting insulin and glucose compared with disease and age-matched controls not on ADT, with

evidence of IR in men on ADT, according to the homeostatic model assessment for IR ($HOMA_{IR}$) [36].

Two studies published in 2007 examined the association between ADT and the development of diabetes or worsening glycemic control [37, 38]. Lage et al. [37] concluded that, after controlling for other factors, the relative risk (RR) of incident diabetes was 1.36 ($p=0.01$) in men who received ADT, while Derweesh et al. [38] observed an increase of ≥10 % in serum HbA1c or fasting glucose levels in 19.5 and 28.6 %, respectively, of men with preexisting diabetes. More recently, Keating et al. [39] reported that the use of ADT was associated with a significantly increased risk of incident diabetes (HR 1.28 [95 % CI 1.19,1.38]).

The characteristics of the metabolic syndrome occurring in androgen-suppressed prostate cancer patients may differ from the classic metabolic syndrome [40]. In a prospective study, 26 patients with recurrent or locally advanced prostate cancer were treated with leuprolide for 12 months before analysis. At follow-up, GnRH agonists increased subcutaneous fat mass, HDL cholesterol, and adiponectin but did not alter the waist to hip ratio, blood pressure, or C-reactive protein level.

## Androgen Deprivation Therapy and Bone Health

Another important side effect of ADT with a GnRH agonist is a reduction in bone mineral density (BMD) as a consequence of the decline in sex steroid levels. The loss of BMD affects multiple skeletal locations, is most rapid during the first few months of ADT, and continues with further use [41–44]. Bone loss at the lumbar spine has been estimated at 2–8 % and 1.8–6.5 % at the femoral neck during the first 12 months of continuous ADT [25, 43–46]. Ultimately, osteopenia may lead to osteoporosis, thereby increasing the risk of fracture, as confirmed by epidemiological studies. Shahinian et al. [47] studied the records of 50,613 men with prostate cancer using the Surveillance, Epidemiology and End Results (SEER) database and found that for men surviving at least 5 years after diagnosis, 19.4 % of ADT-treated had a fracture compared with 12.6 % of men who were not treated with ADT ($p<0.001$). Adjusted Cox proportional hazards analysis indicated a statistically significant relationship between the number of doses of GnRH agonist received during the 12 months after diagnosis and the subsequent risk of fracture. While the Shahinian et al. [47] study population included men with metastatic disease, Smith et al. [48] conducted an analysis in a sample of Medicare beneficiaries with non-metastatic prostate cancer and confirmed that GnRH agonists significantly increased the risk of any clinical fracture, hip fracture, and vertebral fracture. The rate of any fracture was 7.88/100 person-years in men receiving a GnRH agonist ($n=3,887$) compared with 6.51/100 person-years in matched controls ($n=7,774$) (relative risk 1.21 (95 % CI 1.14,1.29); $p<0.001$). GnRH agonist treatment independently predicted fracture risk in multivariate analyses, and a longer duration of treatment conferred greater fracture risk.

Randomized-controlled trials have demonstrated that bisphosphonates can help to prevent loss of BMD during ADT [49–54]. Diamond et al. [49] demonstrated the beneficial effects of a single injection of pamidronate (90 mg) while Smith et al. [50] reported the advantages of 4 mg zolendronic acid every 3 months for a year on BMD at multiple sites. Michaelson et al. [51] investigated the effect of a single treatment with zoledronic acid (4 mg) compared with placebo and reported that mean BMD at the posteroanterior lumbar spine decreased by 3.1 % in men assigned to placebo and increased by 4.0 % in men assigned to zoledronic acid ($p<0.001$). BMD of the total hip decreased by 1.9 % in men assigned to placebo and increased by 0.7 % in men assigned to zoledronic acid ($p=0.004$). Satoh [52] also demonstrated that a single infusion of zoledronic acid (4 mg) reduces bone mineral loss and maintains BMD at 12 months during ADT. Among 112 men with non-metastatic prostate cancer receiving ADT, alendronate (70 mg once weekly) was associated with an increased BMD over 1 year of 3.7 % at the spine and 1.6 % at the femoral neck, compared with losses of 1.4 % at the spine and 0.7 % at the femoral neck in men who did not received alendronate [53]. Alendronate has also been shown to reduce fracture risk. Treatment with once-weekly 70 mg alendronate significantly improved the BMD at the lumbar spine and femoral neck in patients with prostate cancer on ADT who had severe osteopenia or osteoporosis and significantly decreased the risk of femoral neck fracture [54].

Smith et al. [55] have reported beneficial effects on BMD and fracture risk with denosumab, a monoclonal antibody, in a double-blind multicenter study in men receiving ADT for non-metastatic prostate cancer. Patients were randomly assigned to receive placebo or denosumab (60 mg) every 6 months. After 24 months, the BMD of the lumbar spine had increased by 5.6 % in the denosumab group compared with a loss of 1.0 % in the placebo group ($p<0.001$). Significant differences between the two groups apparent after only 1 month were sustained at 36 months. Denosumab therapy was also associated with significant and sustained increases in BMD at the hip, femoral neck, and distal third of the radius. Compared with patients who received placebo, patients who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5 % vs. 3.9 %; relative risk 0.38 (95 % CI 0.19,0.78); $p=0.006$).

In other studies by Smith et al. [56–58], the effects of selective estrogen receptor modulators on BMD have been observed. In a 12-month open label study of raloxifene (60 mg/day), BMD at the hip was significantly increased and

there was a (nonsignificant) increase in BMD of the spine [56]. In a double-blind, placebo-controlled phase III study, Smith et al. [57, 58] reported fracture incidence in men receiving ADT for prostate cancer during a 2-year period. Six hundred and forty-six men were assigned to toremifene (80 mg daily) and 638 were assigned to placebo. The 2-year incidence of new vertebral fractures was 4.9 % in the placebo group compared with 2.5 % in the toremifene group, a significant relative risk reduction of 50 % (95 % CI −1.5,75.0, $p<0.05$). Compared with placebo, toremifene significantly increased BMD at the lumbar spine, hip, and femoral neck ($p<0.0001$ for all comparisons) and there was a concomitant decrease in markers of bone turnover. Toremifene also significantly improved lipid profiles (see below). It should be noted, however, that venous thromboembolic events (none fatal) occurred more frequently with toremifene than with placebo (7 patients [1.1 %] in the placebo group and 17 [2.6 %] in the toremifene group).

Bicalutamide increases serum concentrations of testosterone and estradiol and may, therefore, have a less deleterious effect on bone health than GnRH agonists [59]. Wadhwa [60] found that among 618 men with prostate cancer who were about to commence ADT, 41 % were osteoporotic, 39 % were osteopenic, and 20 % had normal BMD. Patients with osteoporosis were commenced on bicalutamide while patients with osteopenia or normal BMD were commenced on a GnRH agonist. Both groups received calcium and vitamin D supplements. Men treated with a GnRH agonist had significant decreases in BMD (1.2 % at 1 year, 12.7 % at 6 years) while the osteoporotic group treated with bicalutamide maintained BMD over 6 years.

Results of retrospective studies of ADT-treated patients who did not receive antiresorptive therapy have demonstrated a 21–37 % increase in fracture risk [44], reinforcing the conclusion that an assessment of bone health in men starting ADT is recommended. General measures to prevent bone loss should be encouraged, including regular physical activity and maintaining calcium and vitamin D sufficiency. The use of a pharmacological agent to reduce loss of BMD during ADT may be indicated.

## Androgen Deprivation Therapy and Cardiovascular Disease

From the early 1940s, estrogen was used to treat men with prostate cancer [61]. Reports of a discrepancy between disease-specific survival and overall survival emerged in the late 1960s/early1970s [62–64], however. Although estrogen therapy achieved clinical responses in up to 80 % of patients and delayed disease progression, there was little evidence of improved overall survival; estrogen use was associated with cardiovascular toxicity in up to 35 % of patients [64]. Because of this, GnRH agonists, which were thought to have negligible cardiovascular toxicity, replaced estrogens as standard treatment [65].

It has been reported that men with prostate cancer have higher cardiovascular mortality [66, 67] and death from CVD has become the most common cause of non-prostate cancer-related deaths in these men [68, 69]. Now, several studies have raised awareness of the adverse cardiovascular consequences of androgen suppression in prostate cancer patients.

Keating et al. [70] analyzed outcomes of 73,196 patients treated for locoregional prostate cancer, diagnosed between 1992 and 1999, using the SEER–Medicare database. The mean age of study participants was 74.2 years and follow-up was for a median of 4.5 years. Overall, 36.3 % of men received a GnRH agonist and 6.9 % underwent a bilateral orchidectomy during follow-up. Compared with untreated men, the risk of a cardiovascular event was significantly higher in men treated with ADT (hazard ratios [HRs]: coronary heart disease [CHD] 1.16, $p=0.001$; myocardial infarction [MI] 1.11, $p=0.03$; sudden cardiac death 1.16, $p=0.004$). The risks of cardiovascular events among men who had an orchidectomy were not similarly increased, although this may have been due to small numbers.

Another observational study from Keating et al. [39] used data from the Veterans Healthcare Administration for 37,443 men diagnosed with prostate cancer between 2001 and 2004. After adjusting for age, ethnicity, and other relevant variables, the use of ADT was associated with a significantly increased risk of incident CHD (HR 1.19 [95 % CI 1.10,1.28]), MI (HR 1.28 [1.08,1.52]), sudden cardiac death (HR 1.35 [1.18,1.54]), and stroke (HR 1.21 [1.05,1.40]).

Tsai et al. [67] conducted a retrospective analysis of data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry to assess whether the use of ADT was associated with shorter time to cardiovascular death, after controlling for age and CVD risk factors at baseline. Data were included for 3,262 men with localized prostate cancer who had undergone radical prostatectomy and 1,630 patients who had received EBRT, brachytherapy, or cryotherapy. The median follow-up was 3.8 years. In total, 1,015 patients had received ADT (26.2 % of those were treated by radical prostatectomy), with a median duration of 4.1 months. In the prostatectomy group, 8.2 % of patients had received ADT, compared with 46 % in the group treated by EBRT, brachytherapy, or cryotherapy. Using competing risks regression analysis, the investigators found that ADT use (HR 2.6 [95 % CI 1.4,4.7]; $p=0.002$) and age (HR 1.07 [1.02,1.1]; $p=0.003$) were associated with a significantly increased risk of cardiovascular death in patients treated with radical prostatectomy and that the 5-year cumulative incidence of cardiovascular death among those patients aged 65+ who received ADT was 5.5 % (1.2, 9.8 %) and 2.0 % (1.1, 3.0 %) for those who did not.

Saigal et al. [71] used the SEER-Medicare database to identify patients diagnosed with prostate cancer between 1992 and 1996. Patients were followed for 5 years, and any who experienced a cardiovascular event during the first year of follow-up were not eligible for inclusion. The analysis was based on 22,816 individuals; ADT had been prescribed to 4,810 (21 %). On multivariate analysis, ADT was associated with a significantly increased risk of cardiovascular morbidity (HR 1.2 [95 % CI 1.15,1.26]).

D'Amico's group [72] retrospectively analyzed data for 1,372 men who were pooled from three randomized-controlled trials between1995 and 2001 to investigate whether the use of ADT affected the frequency and timing of MI. The analysis found a shorter time (by 2 years) to fatal MI in men aged over 65 years treated with 6 months of ADT, compared with men of the same age who were hormone naïve ($p=0.017$). Patients aged 65+ who had received ADT for 3 months had an incidence of fatal MI that was similar to that observed in men who had used ADT for 6 months ($p=0.97$), supporting the observation that a 3-month treatment period is enough to cause deleterious cardiovascular effects [28]. In addition, the incidence of fatal MI in ADT-treated patients had an earlier onset than in hormone-naïve patients.

## Metabolic Syndrome as a Risk Factor for Cancer

It is possible that the metabolic syndrome may contribute to tumorigenesis and that the individual components of metabolic syndrome work synergistically to increase cancer risk beyond that of the individual components [73]. At present, however, conflicting evidence exists as to any causal relationship between metabolic syndrome and prostate cancer.

Tande et al. [74] analyzed data for over 1,800 men with metabolic syndrome. After adjusting for other risk factors, men with metabolic syndrome (NCEP ATP III criteria) were significantly *less* likely to develop prostate cancer (RR = 0.77 [95 % CI 0.60,0.98]). Similarly, prevalent diabetes has been associated with a decreased incidence of prostate cancer [75]. Another study by Laukkanen et al. [76], however, assessed the association between IR and the development of prostate cancer in 1,880 men, 19 % of whom had IR. After a mean follow-up of 13 years and after adjusting for age, lifestyle, and diet, the RR of prostate cancer was two (95 % CI 1.07,3.53; $p=0.03$). In patients with IR who were also obese, the RR was three (95 % CI 1.22,7.34; $p=0.02$).

Although the relationship between prevalent diabetes and prostate cancer risk is unclear, diabetes is commonly associated with obesity and obesity has been associated with an increased risk of disease recurrence [77] and greater prostate cancer mortality [78]. Smith et al. [79] analyzed data from the Radiation Therapy Oncology Group (RTOG) 92–02 cohort of men with locally advanced prostate cancer receiving radiation therapy and ADT, where 765 deaths occurred after a median follow-up of 8.1 years. After controlling for age, race, tumor stage, Gleason score, prostate-specific antigen, weight, and treatment, overweight (>89.5 kg) was associated with greater prostate cancer mortality (HR 1.77 [95 % CI 1.22,2.55]; $p=0.002$), whereas overt diabetes was not (HR 0.80 [95 % CI 0.51,1.25] $p=0.34$). The increased insulin and IGF-1 levels apparent in obese patients may be responsible for this association [80], rather than the metabolic consequences of diabetes.

There is some evidence, too, that metabolic factors may accelerate tumor growth. Central obesity and high levels of fasting insulin have been associated with a poorer prognosis in patients with breast cancer [81, 82]. Although the exact mechanism for this association is unclear, increased fat stores are thought to be associated with higher concentrations of bioavailable estrogen, insulin, and insulin-like growth factors (IGFs), which may in turn promote tumor growth [83]. Increased concentrations of IGF-1 and IGF-binding protein-3 have been associated with an increased risk of prostate cancer in epidemiological studies [84].

Mistry et al. [85] suggested that obesity and adipokines could have a role in promoting the progression of established prostate cancer, based on their study of leptin and adiponectin, two adipokines that at high circulating levels are, respectively, stimulatory and inhibitory to prostate cancer development. In addition, there is evidence from in vitro studies suggesting that the unsaturated fats are particularly influential on prostate cancer migrational signaling [86]. Prostate cancer cells take up lipid directly as an energy source in early in vitro bone marrow metastatic development [87], and because prostate cancer cells commonly migrate to adipocytes in bone marrow rather than in subcutaneous fat indicates that adipocytes in different locations may exert different effects [88]. Furthermore, the use of statins has been reported to reduce prostate cancer mortality by 50 % [89].

## Prevention of the Metabolic Syndrome

The metabolic syndrome is characterized by several potentially modifiable lifestyle factors. In the diabetes prevention program, an analysis was undertaken to determine the prevalence of metabolic syndrome, as defined by NCEP ATP III criteria, at baseline, and the effect of intensive lifestyle intervention (diet and exercise) and metformin[1] therapy on the syndrome's incidence and resolution [91]. Study participants ($n=3,234$) were recruited between June 1996 and May 1999;

[1] Metformin is an oral biguanide which acts via a hepatic pathway ultimately to increase muscle uptake of glucose. Although its method of action is not completely understood, metformin remains a mainstream therapy for type 2 diabetes [70, 90].

all had impaired glucose tolerance and no history of CHD or diabetes. Patients were followed-up for a mean of 3.2 years after being randomly assigned to intensive lifestyle intervention, metformin (850 mg bd), or placebo. In a proportional hazards model using data for individuals without the syndrome at baseline ($n=1,523$) compared with the placebo group, the incidence of metabolic syndrome was 41 % lower in the lifestyle group ($p<0.001$) and 17 % lower in the metformin group ($p=0.03$). The cumulative incidence of metabolic syndrome overall (per 100 person-years) was 61 % for the placebo group, 50 % for the metformin group, and 38 % for the lifestyle group.

A pilot study was completed recently at the Royal Surrey County Hospital in the UK in which 40 men with prostate cancer scheduled for ADT received either ADT alone (control group; $n=20$) or metformin, a moderate exercise program and dietary advice (low GI diet) in addition to ADT (intervention group; $n=20$) [92]. After 6 months, there were significantly fewer men with metabolic syndrome (NCEP ATP III criteria) in the intervention arm ($p=0.04$), with significant improvements in abdominal girth, weight, BMI, and systolic blood pressure. The potential benefits of metformin and lifestyle changes in ADT-treated men need to be explored further as it is evident that overall survival may be improved.

Finally, the selective estrogen receptor modifier toremifene has been shown to significantly decrease total cholesterol, LDL cholesterol, and triglycerides and increase HDL cholesterol after 24 months in men being treated with ADT for prostate cancer [5, 8, 93]. The primary end point of this study among men aged 50+ years who had an increased fracture risk (aged 70+ or osteopenia) was new vertebral fracture, and the beneficial effects of toremifene on BMD and fracture risk have been summarized above.

## Conclusion

A complex relationship exists between prostate cancer, ADT, metabolic syndrome, and CVD. Alongside the expanding indications for ADT in prostate cancer, there is emerging (but not conclusive) evidence that ADT increases the risk of cardiovascular morbidity and mortality. The detrimental metabolic effects of ADT have been recognized in a science advisory from the American Heart Association, American Cancer Society, and American Urological Association and endorsed by the American Society for Radiation Oncology, who recommended careful evaluation of patients both before and during therapy [23]. Thus, for men requiring even short-course androgen suppression, efforts to reduce cardiac risk through lifestyle modification and the use of lipid-lowering agents may mitigate some of the risks of ADT, particularly those with early organ-confined disease, who would be expected to have the best long-term prognosis after curative therapy.

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# Inflammation and Cancer of the Prostate

9

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In response to cell injury elicited by trauma or infection, the inflammatory response creates a complex network of molecular and cellular interactions leading to the facilitation of tissue repair and to return to a physiological homeostatic condition. In case the healthy tissue is not restored, or in response to a stable low-grade irritation, inflammation becomes a chronic condition that incessantly damages the surrounding tissue and whereby immune response, tissue injury, and healing processes occur simultaneously [1].

The inflammatory process is not "per se" a negative phenomenon. Inflammation is a teleonomic response built up by the natural selection to protect human beings until the reproductive age. Humans were set to live about 40 or 50 years, but, nowadays, the immune system has seemingly learned to be active for much longer as compared with the past centuries. This prolonged period of activity may eventually lead to chronic inflammation that inexorably damages most tissues/organs and is phenotypically reflected in both aging and chronic disease(s), including cancer [2].

Chronic inflammation appears in fact to be involved in the pathogenesis of all age-related diseases, including Alzheimer, atherosclerosis, diabetes, sarcopenia, and cancer. The genes involved in the inflammation process are numerous, as well as the genomic variations within most of those genes. Several genes involved in the inflammatory network are important candidates influencing the degree and phenotype of individual response to damage [3]. Furthermore, as recently indicated, the microenvironment surrounding the tumor highly resembles an inflammation site, being featured by interactions between inflammatory cells and neoplastic cells that might facilitate tumor progression [4]. Cytokines, chemokines, lymphocytes, and macrophages might all contribute to neovascularization, increased blood supply, vessel permeabilization, immunosuppression, and metastasis [5]. On the other hand, the inflammatory microenvironment has high levels of growth factors and cytokines, which may in turn stimulate proliferation of initiated cell leading to the promotion and/or progression of a clonal tumor cell population. Specific examples are TNF-α, IL-1β, and IL-6, which have been associated with tumor invasiveness and protease production, inflammatory response, angiogenesis, and metastasis. Cytokines derived from neoplastic cells, activated resident stromal cells, or infiltrating immune cells can regulate tumor growth by affecting angiogenesis and cell survival, death, or differentiation [6].

Production of acute-phase protein, which is evident in systemic inflammation, has also been associated with an increased tumor stage/grade, cachexia, hypercalcemia, anemia, and reduced survival in various malignancies [7]. Interestingly, Toll-like receptor (TLR) is highly expressed in various types of human carcinomas compared with adjacent normal tissue, suggesting a potential role in tumor development [8]. Accordingly, TLR genes may be implicated in cancer development also as a consequence of their role in innate

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immunity and in the regulation of inflammatory reactions and activation of the instructive immune response [9]. In this framework, activation of innate immunity and inflammation may eventually lead to the production of cytokines that can either stimulate or inhibit tumor growth and progression. As previously stated, by and large, most proinflammatory cytokines produced by either host immune cells or tumor cells themselves promote tumor development [1, 10]. On the other hand, anti-inflammatory (IL-10 and TGF-β) cytokines usually interfere with tumor development. Chronic inflammation caused by persistent infection with a parasite, bacterium, or virus, the release of inflammatory mediators, and the resulting inflammatory environment may be a driving force in development of several human tumors, including prostate cancer [11].

## Prostate Cancer

Prostate cancer represents a common cause of morbidity and mortality in men in Western countries, being the most common non-skin tumor and the second leading cause of cancer death in men in the United States, with 217,730 new cases and 32,050 deaths from this disease expected in the year 2010 (*American Cancer Society*, *2010*) [12]. African American men have the highest incidence and mortality rates [12]. In Europe, prostate cancer has exhibited a steady increase in incidence during years, while mortality rates have started to decline since the late 1990s. Incidence rates of prostate cancer vary considerably also across Northern and Southern Europe, respectively being 80.1/100,000 and 44.7/100,000 in 2000 (*IARC databases*). In particular, Sweden has the highest incidence rates (139.3/100,000), while Greece has the lowest (43.4/100,000), with a cumulative risk that ranges from 0.5 up to 2.2 across European countries. Both genetic and environmental factors may contribute to explain this large geographic variation. Previous studies on populations migrating from countries with low incidence/mortality rates (e.g., China or Japan) to countries with higher rates of prostate cancer (United States) have revealed a significant increase in prostate cancer incidence/mortality as compared with their peers in the countries of origin [13–16]. In addition, prostate cancer incidence is rising rapidly in Asian countries, including Japan, as Asians gradually adopt a westernized diet and lifestyle [17, 18]. This evidence suggests that environmental and, especially, lifestyle factors play a dominant role in prostate cancer development. For example, sedentary lifestyle and high-fat diet have been associated with an increase in prostate cancer risk [19] and as an example the involvement of the α-methylacyl-CoA racemase (*AMACR*), the enzyme that plays a key role in the peroxidation of fatty acid. The AMACR gene is overexpressed in prostate cancer but not in the healthy prostate. Upregulation of α-methylacyl-coenzyme A-racemase *AMACR* might explain some of the association between dairy products and prostate cancer [20].

Despite the most recent advances in both basic and translational research, the molecular basis of human prostate cancer remains mostly obscure. Endogenous sex steroids, along with genetic factors, environmental factors (including diet), and host immune and inflammatory responses, are likely to concur in the pathogenesis of this disease.

## Inflammation and Prostate Cancer

It is widely accepted today that inflammation has a role in many human cancers. In particular, clinical and epidemiological studies have suggested a strong association between chronic infection, inflammation, and cancer [21, 22] An inflammatory microenvironment is in fact reputed to promote carcinogenesis through cell and DNA damage, increase of cell proliferation, and angiogenesis [1]. This microenvironment is primarily featured by the presence of infiltrating stromal leukocytes and by hypoxic conditions [23, 24]. Tumor-associated macrophages represent a key player in the inflammatory process, as they produce a multitude of growth factors for epithelial and endothelial cells, along with inflammatory cytokines and chemokines [21] (Table 9.1).

As far as human prostate gland is concerned, there is accumulating evidence that the regenerative epithelium produced in consequence of inflammatory and/or infectious conditions may eventually lead to cellular insults and may precede the development of prostatic intraepithelial neoplasia (PIN) and early carcinoma. Several meta-analyses have indicated a small increase in the relative risk of prostate cancer in men with a history of clinical or symptomatic prostatitis [11].

Pathologists have proposed that a prostatic lesion referred to as proliferative inflammatory atrophy (PIA) is a precursor of PIN and prostate cancer. The PIA lesion is thought to be a consequence of the regenerative proliferation of prostate epithelial cells in response to an inflammatory insult. Epithelial cells in PIA show several genetic alterations, including somatic mutations, gene deletions or amplifications, chromosomal rearrangements, and changes in DNA methylation, along with molecular signs of stress, such as elevated glutathione S-transferase p1 (GSTP1), GSTA1, and cyclooxygenase 2 (COX-2) [34, 35]. The GSTP1 gene, which is expressed in both PIA lesions and over 90 % of prostate cancer cases, does not seem to act as a tumor suppressor gene but as a caretaker gene to prevent genome damage induced by environmental and/or endogenous carcinogens, such as oxidant compounds produced by inflammatory cells [34, 35].

In a recent paper, Harris and colleagues [36] have reported that a 4-week administration of estradiol to Wistar rats, in the presence of dihydrotestosterone propionate, results in the

**Table 9.1** Association between inflammatory genes and prostate cancer

| Genes | Age-associated cancer | References | Association with cancer |
|---|---|---|---|
| IL-6 | Prostate cancer | Culig [25] | Yes |
| IL-10 | | | |
| | Gastric adenocarcinoma | El-Omar et al. [26] | Yes |
| | Hepatocellular cancer | Shin et al. [27] | Yes |
| | Prostate cancer | Howell and Rose-Zerilli [28] | Yes |
| TNF-α | | | |
| | Gastric adenocarcinoma | El-Omar et al. [26] | Yes |
| | Prostate cancer | Howell and Rose-Zerilli [28] | Yes |
| TLR1-6-10 | Prostate cancer | Sun [29] | Yes |
| TLR1-6-10 | Prostate cancer | Chen et al. [30] and Sun et al. [31] | No |
| TLR4 | Prostate cancer | Zheng et al. [32] | Yes |
| Cox-2 | Prostate cancer | Ghosh et al. [33] | Yes |

production of proinflammatory cytokines, chemokines, and inducible nitric oxide synthase (iNOS) in the prostate. The mechanism(s) by which estrogen induces inflammation is still unknown. It is likely that estrogens act in combination with immunoregulatory factors produced locally within the prostate. Regardless, it is clear that elevated estrogens may eventually lead to a prostate-specific inflammatory response in the presence of testosterone. Since combined treatment of testosterone and estradiol induces prostate inflammation as early as 4 weeks and prostate carcinomas occur only after 50 weeks, it is plausible that estrogen-driven early inflammatory events serve as a prerequisite for the development of prostate cancer.

As there is accumulating evidence that the human prostate is a primary target of estrogen action, it would be important to assess aromatase expression and activity locally and to identify any change that may be associated with prostatic disease, including cancer. In human breast cancer, recent experimental evidence has indicated a direct association of cyclooxygenase (COX)-1 and -2 with aromatase expression [37]. In particular, it has been reported that prostaglandin E2 (PGE2), produced through the COX-2 pathway, induces, along with proinflammatory cytokines, both expression and activity of aromatase [38, 39]. On the other hand, there is consistent evidence that estrogen induces the synthesis of various prostaglandins through the upregulation of either COX-1 or COX-2 or both. This would generate a self-maintaining vicious cycle where estrogen and prostaglandin(s) increase each other's production through the induction of the respective synthesizing enzymes.

Studies that propose a key role of inflammation in triggering prostate cancer development have shown a positive correlation with local accumulation [40, 41] of eicosanoids, including prostaglandins (PGs) and leukotrienes (LTs). These compounds have been implicated in the pathogenesis of a variety of human diseases, including cancer, and are now believed to play a role in tumor promotion, progression, and metastatic disease. The enzymes involved in the conversion of arachidonic acid to PGs and LTs are COXs and lipoxygenases (LOX) [40, 41].

The two isoforms of COX, COX-1 and COX-2, are almost identical in structure but have important differences in substrate and inhibitor selectivity and in their intracellular location. The constitutive COX-1 is present in many tissues, and the PGs synthesized are involved in maintaining tissue homeostasis. The inducible COX-2 is responsible for PGs produced in sites of inflammation and is upregulated by oncogenes, cytokines, growth factors, hypoxia, UV, and tumor necrosis factor alpha [42, 43].

Upregulation of COX-2 has been reported in a variety of human tumors, including prostate cancer, PIN, and the premalignant lesion PIA. This may eventually lead to an increase of PG synthesis that is in turn responsible for inhibition of apoptosis, stimulation of angiogenesis, immunosuppression, and promotion of metastasis [44]. Some studies have indicated that a prolonged treatment with aspirin reduces the incidence of prostate cancer, suggesting that this effect might be, at least in part, a consequence of COX-2 inhibition [45]. Lastly, COX-2 promoter can be modulated through transcriptional and posttranscriptional mechanisms implicating oncogene products, growth factors, cytokines, chemotherapeutics via protein kinase C, *ras* signaling, interleukin (IL)-6, and NF-kB transcription factor [46, 47]. Recently, it has been shown that histone acetyltransferase activity of the CREB-binding protein/p300 coactivator complex is important for AP1-mediated induction of COX-2. Interestingly, a new compound that reduces both expression and activity of CREB may restore the sensitivity of prostate cancer cells to apoptotic stimuli through downregulation of COX-2 [46].

As regards LOX mediators, there is evidence to support an important role for LO-catalyzed products, LTs, and hydroxyeicosatetraenoic acids (HETEs) on development and progression of human cancers. A significant increase of LOX metabolites has been observed in patients with lung, breast, colon, and skin carcinoma, while increased 12-LOX mRNA and 12(S)-HETE levels have been positively correlated with

**Table 9.2** Inflammatory mediators and cancer

| | |
|---|---|
| CCL5 | A chemotactic for T cells, eosinophils, and basophils that plays an active role in recruiting leukocytes into inflammatory sites |
| CCR5 | A *beta*-chemokine receptor involved in the migration of monocytes, NK cells, and some T cells to the inflammation site |
| COXs | Enzymes involved in the conversion of arachidonic acid to inflammatory mediators, prostaglandins. The isoform COX-2 is upregulated in a variety of malignancies, including prostate cancer, throughout the tumorigenic process |
| LO | Enzymes involved in the conversion of arachidonic acid to inflammatory mediators |
| IL-1 | IL-1, IL-1*alfa*, and IL-1*beta* might be considered the prototypic proinflammatory cytokines of the IL-1 family. IL-1Ra competes for receptor binding with IL-1*alfa* and IL-1*beta*, blocking their role in immune activation |
| IL-4 | Member of the Th2 cytokines and is a potent anti-inflammatory cytokine as it reduces the production of proinflammatory cytokines |
| IL-6 | Mediator of experimental cachexia and is a well-documented mediator of inflammation |
| IL-13 | Exerts anti-inflammatory and antitumoral effects through the activation of the IL-13 receptor complex |
| IL-8 | Regulates angiogenesis and tumor growth |
| IL-10 | Anti-inflammatory function, with pleiotropic effects in immunoregulation and inflammation. It downregulates the expression of type 1 cytokines, MHC class II antigens, and costimulatory molecules on macrophages |
| IL-18 | Produced by macrophages and other cells, belongs to the IL-1 superfamily. It is a multifunctional cytokine that induces interferon-gamma secretion and plays an important role in antitumor immunity mediated by type 1 positive regulation loop |
| TGF-*beta*1 | Polypeptide member of the transforming growth factor beta superfamily of cytokines. It is a multifunctional modulator of cellular proliferation, differentiation, and production and degradation of extracellular matrix |
| TLRs | Receptors able to detect microbial conserved components and trigger protective host responses |
| TNF-alpha | Associated with tumor invasiveness and protease production, inflammatory response, angiogenesis, and metastasis |

the metastatic potential of colon and prostate carcinoma [48, 49]. Increased levels of 5-HETE have been reported to stimulate tumor cell growth, while 5-HETE depletion results in massive apoptosis in lung and prostate cancer [50]. Furthermore, it has been observed that LOX-5 is overexpressed in prostate tumors, suggesting that selective LOX-5 inhibitors may be helpful in either prevention or treatment of this malignancy [51].

Accordingly, Caruso and colleagues have reported a significantly increased frequency of COX-2 -765 G/C and of LOX-5 -1708 G/A proinflammatory SNPs in prostate cancer patients, as compared with age-related controls and centenarians (taken as a typical human model of disease-free subjects) in the Sicilian population [52]. This evidence incidentally confirms previous studies suggesting that proinflammatory alleles have an opposite role in longevity and age-related diseases, including cancer [53, 54].

Toll-like receptors (TLRs) represent critical players in both innate and instructive immune response, recognizing ligands for pathogens-associated molecular patterns. In prostate cancer, TLRs seem to represent a potential link between infections, chronic inflammation, and tumor development. In particular, it has been proposed that activation of the innate immune response is brought about through a TLR-mediated recognition of infectious agents or endogenous molecules, such as those produced by cell and/or DNA damage [55, 56]. In addition, most of TLR-activated signaling molecules are also implicated in tumorigenesis and malignant cell proliferation, reinforcing the idea that TLRs may affect tumor development and growth [57, 58].

Importantly, dysregulated or inappropriate TLR activation may result in an excessive production of proinflammatory factors. Upon TLR4 activation, tumor cells produce in fact mediators of inflammation, including nitric oxide, IL-6, and IL-12, mimicking some characteristics of inflammatory cells. In this respect, an interesting TLR4 polymorphism, the ASP299GLY, is known to regulate the inflammatory response, and it has been associated with an increased risk of prostate cancer [58, 59] (Table 9.2).

## Cytokines

Several studies have shown an increased level of proinflammatory cytokines, in both prostatic tissue and fluids in prostatitis [60, 61]. Furthermore, recent reports indicate that the assessment of both pro- and anti-inflammatory cytokine levels in prostatic fluid may be useful not only to diagnose prostatic inflammation but also for early cancer detection and prognosis [60]. Most adult prostate tissues contain an increased proportion of inflammatory cells, also depending on the extent and type of inflammation. This results in a larger pool of cytokines and growth factors, including IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-18, transforming growth factor-β (TGF-β), and IFN-γ in the prostate tissue. It is of particular interest that cytokines, such as IL-4, IL-10, and IL-13, significantly affect the biological behavior of monocytes/macrophages and result in a microenvironment that may favor tumor growth [61, 62].

Polymorphisms of cytokine genes may have an impact on inflammation and immune response, and some have been reported to be associated with susceptibility to prostate cancer in a large number of case–control studies, twin studies, and segregation analyses [1].

TGF-β1 is a powerful and multifunctional regulator of cellular proliferation, differentiation, and production and turnover of extracellular matrix. TGF-β1 signaling pathways are regulated through several mechanisms by a variety of oncogenic and anti-oncogenic proteins. Since TGF-β1 behaves as a potent inhibitor of growth for most epithelial cells, alterations of TGF-β1 signaling are thought to favor progression of various tumors. Conversely, TGF-β1 has been shown to act as an oncogenic growth factor through the induction of extracellular matrices, angiogenesis, and immune suppression. Therefore, its ultimate effect on tumor progression may essentially depend upon preservation or impairment of TGF-β1 receptor and/or post-receptor mechanisms and, consequently, be divergent in early or advanced tumors [63].

TGF-β1 is synthesized as a larger precursor (pre-pro-TGF-β1) and secreted in a latent complex that needs to be activated to release the mature form of the peptide. The latter, in turn, binds to specific membrane receptor(s) and triggers relevant signal transduction pathways. Hence, the occurrence of modified sequences in the signal peptide could be responsible for the alteration of TGF-β1 signaling, an event that is common to cancer cells in advanced stages of tumor progression. In particular, a leucine-to-proline substitution in codon 10 drastically affects the three-dimensional conformation of the protein leading to the inability of the active form of TGF-β1 to localize into a cell. This would hinder the efficient transduction of the anti-proliferative and pro-apoptotic signals of the TGF-β1, favoring the clonal expansion of refractory tumor cells.

The Leu10Pro genotype confers a 1.8-times greater risk of prostate cancer with respect to general population [64].

Interleukin (IL)-1α and IL-1β might be considered the prototypic proinflammatory cytokines of the IL-1 family. IL-1α is produced by prostate epithelial cells and induces fibroblast growth factor 7 (FGF-7) expression in prostatic stromal cells. The FGF-7, in turn, induces epithelial cell growth and a further increase of IL-1α expression, ultimately leading to an expansion of the prostatic transition zone, which is critical in the pathogenesis of benign prostatic hyperplasia (BPH) [65]. Senescent prostatic epithelial cells are reported as a source of IL-1α. Hence, secreted IL-1α might be one of the major factors responsible for age-related growth of prostatic epithelial cells observed in BPH. Surprisingly, IL-1α receptor is expressed in both BPH and prostate cancer, though its expression is inversely related to tumor grade [66].

Interleukin 4 (IL-4), a member of the Th2 cytokines, is a potent anti-inflammatory cytokine as it reduces the production of proinflammatory cytokines. IL-4 has diverse activities, including the stimulation of fibroblasts' proliferation and the inhibition of smooth muscle cell outgrowth from prostatic stromal clones. Several studies have reported that hyperplastic prostatic tissues and BPH-derived T cells express high levels of IL-4 [67].

Interleukin 6 (IL-6) has many physiologic roles and has been implicated in a number of pathophysiologic processes. A variety of tumor types are stimulated by IL-6, including melanoma, renal cell carcinoma, Kaposi's sarcoma, ovarian carcinoma, lymphoma and leukemia, multiple myeloma, and prostate carcinoma [68].

There is accumulating evidence that IL-6 may contribute to the progression of human prostate cancer. IL-6 has been shown to act as a mediator of experimental cachexia and is a well-documented mediator of inflammation. Elevated levels of this cytokine is associated with signs of morbidity, such as anorexia, anemia, cachexia, asthenia, acute-phase proteins, hypoalbuminemia, edema, anergy (lack of body immunological reaction), and diffuse bone pain, in a number of chronic diseases, including prostate cancer [69]. A cross talk between IL-6 and androgen receptor activation has also been demonstrated [70] Interleukin 10 (IL-10) and 8 are the most studied cytokines in prostate cancer. IL-10 is an anti-inflammatory cytokine that suppresses Th1 response and regulates differentiation of B-lymphocytes, natural killers, and cytotoxic and helper T cells. In prostate cancer, low expression of IL-10 seems to be not associated with PCa susceptibility maybe due to the relatively minor effect that a single SNPs may have on the disease [71]. However, it is more probable that a combination of SNPs in haplotypes or an SNP–SNP interaction may modify the risk for developing a malignancy. In Caruso and collaborators' meta-analysis, it was shown that in the interactions of nine functionally characterized SNPs of three cytokine genes (IL1-$\beta$,-511 CT; IL-1 $\beta$,-31 TC; IL- 1 $\beta$ +3954 CT; IL-10 -1082 AG; IL-10 -819 CT; IL-10 -592 CA; TNF-$\alpha$,-857 CT; TNF-$\alpha$, -308 GA; and TNF-$\alpha$, -238 GA), a single SNP did not modify, unless marginally when adjusted for age, family, smoking, and BPH, the risk of developing PCa, but it was noted that the risk was greatly modified by SNP–SNP interaction [52]. Furthermore, Richardsen and colleagues in their studies did not find differences in IL-10 expression between primary prostatic tumors neither in tumors and corresponding metastases although other studies appear having better association with IL-10 [72]. The apparently conflicting data may reflect the biological function of IL-10 as an anti-inflammatory (potentially cancer promoting) and antiangiogenic (potentially cancer inhibiting) cytokine in relation to the biological patterns of prostate cancer development and progression [72].

IL-8, also known as CXCL8, is a proinflammatory CXC chemokine having documented activity in the regulation of angiogenesis and tumor cell growth. A recent report has indicated that neutralizing antibodies directed against IL-8 inhibit angiogenesis in a human prostate cancer cell line/murine model and reduced tumorigenicity in vivo [73]. Recent studies have measured the production of the

CC-chemokine CCL5 (RANTES), a potent chemotactic factor for inflammatory cells, and its receptor (CCR5) in different human prostate cancer cell lines. It has been demonstrated that chemokine CCL5 may function as an autocrine factor that binds to its CCR5 receptor, expressed on the cell surface, and activates cellular responses favoring tumor progression [74].

Interleukin (IL)-13 exerts anti-inflammatory and antitumoral effects through the activation of the IL-13 receptor complex, a heterodimer consisting of the interleukin-13 receptor α1 (IL13Ralpha1) and the interleukin-4 receptor A (IL4RA) subunits. IL-13 appears to have opposite effects on different cancer cells, being able to inhibit growth of breast cancer and renal carcinoma cells or to promote proliferation in some other cancer cell types. In a recent paper, abnormal expression of IL-13Ralpha 2 has been consistently revealed in prostate cancer tissues [75].

Interleukin 18 (IL-18) is a multifunctional cytokine that induces IFN-gamma secretion and plays an important role in antitumor immunity mediated by type 1 positive regulation loop. A reduced expression of IL-18 in consequence of promoter abnormalities seems to be associated with a reduced stimulation of type 1 response and might be involved in susceptibility to prostate cancer [52].

Apart from the inflammatory molecules mentioned herein, additional studies have suggested that macrophage scavenger receptor 1, a protein with critical functions in host response to infections, and macrophage inhibitory cytokine-1 (MIC-1) may be implicated in the etiology of human prostate cancer [76–78]. The MIC-1 is a secretory protein, and elevated serum levels of MIC-1 are present in a number of diseased conditions. As far as prostate cancer is concerned, elevated levels of circulating MIC-1 are associated with the metastatic progression of the disease. Furthermore, MIC-1 has been associated with inflammatory-related pathways, representing a potential biomarker of p53 pathway activation, a key response to inflammatory stress [79].

**Take Home Message**

- Chronic inflammation and the release of inflammatory mediators and the resulting inflammatory environment may be a driving force in development of several human tumors, including prostate cancer.
- Inflammation can strongly influence prostate growth either in terms of hyperplastic (BPH) or neoplastic changes.
- Cytokines and chemokines play an important role in prostate cancer development.

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# HIV and Prostate Cancer

10

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## Background

Prostate cancer is the most common noncutaneous malignancy and the second most common cause of cancer-specific death in men from the United States. There were 240,890 estimated new cases and 33,720 deaths in 2011[1]. While prostate screening has identified an increasing number of cases, the increased surveillance has facilitated earlier diagnosis in asymptomatic men and led to subsequent stage migration towards localized disease [2, 3].

Recent data from the World Health Organization and UNAIDS indicate that the worldwide HIV prevalence has plateaued and that new infections have fallen; however, 33.2 million people in 2007 were estimated to be living with HIV, 2.5 million people became infected, and 2.1 million people died from AIDS. Among these patients, 1.2 million individuals, including 870,000 males, carried the diagnosis of HIV/AIDS in the United States [4]. More than 50 % of all newly diagnosed HIV patients are African American, and greater than 25 % are older than 45 years. Prostate cancer incidence increases with age, African American descent, and in some reports with immunocompromised conditions such as HIV/AIDS [5].

Prior to 1995 (the beginning of the highly active antiretroviral therapy (HAART) era), individual case reports described patients with AIDS and prostate cancer exhibiting rapid progression of prostate cancer likely secondary to severely depressed immune system and poor response to androgen deprivation therapy [6–8]. Possible explanations for prostate cancer development in the HIV-positive population include suppressed cell-mediated immunity, dysfunctional immune surveillance, decreased apoptosis, and increased angiogenesis. Since 1995, the utilization of multiple synergistic medications to prevent viral replication has altered the natural spectrum of HIV disease. The progression of HIV to AIDS as well as AIDS-specific mortality has been decreased by HAART. Additionally, there has also been reduced incidence of AIDS-related malignancies including non-Hodgkin's lymphoma, Kaposi sarcoma, and cervical cancer. Although multiple studies identify increased incidence of certain non-AIDS-defining malignancies (melanoma, Hodgkin's lymphoma, anal cancer, and prostate cancer) [9–19], other studies report decreased incidence of other non-AIDS-defining malignancies (breast, uterine, and prostate cancer) [17, 20–29].

During the HAART era, HIV-positive patients with PCa appear to respond to treatment in a similar manner to patients without HIV/AIDS. Despite the increased prevalence of HIV/AIDS and prostate cancer, there is no universally accepted consensus regarding treatment. In this chapter, we summarize the literature regarding this topic and describe the most recent diagnosis and treatment recommendations to guide physicians in the optimal management of HIV/AIDS patients with prostate cancer. A PubMed search was completed utilizing the terms "HIV and prostate cancer," "AIDS and prostate cancer," "prostate cancer and non-AIDS-defining malignancy" "HIV and prostate cancer and diagnosis," "HIV and prostate cancer and treatment." All results were reviewed and cross-referenced for all available English-language articles and review articles between 1975 and 2011.

## Incidence

The precise incidence of prostate cancer (PCa) in HIV-infected patients is unknown. The relative lack of literature on this topic may result from limited association between the conditions, or more likely due to decreased screening of

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**Table 10.1** Published rates of HIV-associated prostate carcinoma

| Reference | Country | Study period | Total population (*n*) | Standard Incidence Rates (95 % CI) |
|---|---|---|---|---|
| Engels et al. [13] | USA | 1985–2002 | 375,933 | 0.50 (0.35–0.69) |
| Frisch et al. [24] | USA | 1978–1990 | 302,834 | 0.7 (0.59–0.82) |
| Shiels et al. [43] | USA | 1980–1991 | 287,247 | 1.00 (0.58–1.60) |
| | | 1992–2007 | | 0.5 (044–0.57) |
| Gallagher et al. [28] | USA (NY state) | 1981–1994 | 122,993 | 0.6 (0.45–0.88) |
| Patel et al. [17] | USA | 1992–1995 | 54,780 | 0.3 (0.1–0.3) |
| | | 1996–1999 | | 0.7 (0.4–1.3) |
| | | 2000–2003 | | 0.7 (0.4–1.0) |
| Newnham et al. [29] | UK | 1985–2001 | 33,190 | 0.9 (0.29–2.08) |
| Van Leeuwen et al. [26] | Australia | 1982–1995 | 20,232 | 1.19 (0.57–2.18) |
| | | 1996–1999 | | 0.63 (0.23–1.38) |
| | | 2000–2004 | | 0.27 (0.11–0.52) |
| Hessol et al. [15] | USA | 1990–2000 | 14,210 | 1.4 (1.0–2.0) |
| Grulich et al. [51] | Australia | 1985–1999 | 13,067 | 1.06 (0.53–1.89) |
| Dal Maso et al. [11] | Italy | 1985–1998 | 12,104 | 1.16 (0.14–4.20) |
| Clifford et al. [9] | Switzerland | 1985–2002 | 7,304 | 1.43 (0.29–4.17) |

Adapted from Pantanowitz et al. [15], Grulich et al. [51]

HIV-infected men [30]. The Silberstein review from August 2008 identified 12 studies describing 60 unique HIV-positive men with prostate cancer [16, 18, 31–40]. We describe an additional 19 patients from our cohort (not previously published), but no additional case reports have been published. Before 2008, population-based studies described 322 patients with HIV and prostate cancer [15, 23, 24, 28]. Since 2008, there have been several additional population-based studies describing 769 HIV-infected patients with prostate cancer [17, 26, 41, 42]. Overall, there is available clinical and demographic data for 87 patients (described in case reports) and 1,091 patients (described in population-based studies). Standardized incidence rates (SIR) of prostate cancer in HIV-positive populations from published literature are described in Table 10.1. Multiple large linkage-based population studies report a lower than expected PCa risk both overall and in the post-AIDS onset period [17, 23–26, 28, 29, 43], but other smaller studies describe contrasting findings of similar or elevated rates of prostate cancer in comparison to the general population [9, 11, 15, 37, 41, 44].

Many recent large population-based studies report decreased prostate cancer incidence in HIV infected men which is similar to the trend in breast cancer incidence in HIV-positive patients and immunosuppressed transplant recipients [20–22, 45, 46]; such findings may reflect a protective role of immunodeficiency [45, 47], the capability of HIV to infect, replicate in, and impair cancer cell proliferation [48, 49], or may be due to HAART-associated changes [50]. Importantly, PSA screening in the detection of prostate cancer may explain the mechanism for decreased incidence found in HIV-infected patients because they receive less rigorous screening than the general population. In an analysis of the US HIV/AIDS Cancer Match study, a linkage of population-based HIV/AIDS and cancer registries in 15 US areas, Shiels et al. examined the epidemiology of prostate cancer among 287,247 HIV-infected men compared with the general population [43]. PSA testing rates were calculated from the Johns Hopkins HIV Clinical Cohort in men ≥40 years of age during 2000–2008. This study identified that prostate cancer rates were higher in the general population than among men with AIDS. Men with AIDS had equivalent prostate cancer risk as the general population in the pre-PSA era before 1992 (before 1992, SIR = 1.00, 17 observed cases), but had a significant reduction during the PSA era (after 1992, SIR = 0.5, 230 observed cases with incidence rate of 28.3/100,000) after accounting for baseline characteristics. The decreased risk was identified in patients with local and regional stage prostate cancer (SIR 0.49 and SIR 0.14), but the difference in risk was not demonstrated in patients with metastatic disease (SIR = 0.85). The authors hypothesize that if a biologic mechanism accounted for decreased risk of prostate cancer in HIV-infected men, then there would have been consistent decreased risk across all stages of prostate cancer. Decreased PSA screening among HIV-infected men may lead to decreased detection of prostate cancer in HIV-infected men in early stage cancers during the PSA era. In men with AIDS, localized/regional prostate cancer was not associated with increased risk of death compared with the general population, similar to trends in the general population. The fivefold increased risk of mortality following distant stage prostate cancer in men with AIDS was similar to the general population. The conclusions regarding differential PSA testing in this study may be confirmed in the future with additional diverse HIV-infected cohorts.

Patel et al., in one of the large analyses of United States cancer incidence trends in HIV-infected patients, compared cancer incidence rates in two multicenter prospective

observational cohorts among 54,780 HIV-infected patients, the Adult and Adolescent Spectrum of HIV Disease (ASD) Project, and the HIV Outpatient Study (HOPS), with noninfected individual data derived from the Surveillance, Epidemiology, and End Results (SEER) program [17]. The authors identified 3,550 cancer cases of which 20 % were non-AIDS-defining cancers. Incidence rates for HIV-infected individuals decreased significantly from 1992 to 2003 for non-Hodgkin's lymphoma and Kaposi's sarcoma and increased significantly for anal, colorectal, and prostate cancer (14.7 in 1992 to 37.5 in 2003 per 100,000 person-years, $p < .01$). The increase in prostate cancer incidence in HIV patients may be secondary to PSA screening which is also reflected by a similar rise in the general population incidence during this time (47.4–60.9 per 100,000 person-years, $p < .001$). Overall, there was decreased incidence of prostate cancer in HIV-infected patients compared to the general population. Antiretroviral therapy was not independently associated with decreased risk for prostate cancer. However, this study may not be generalizable since the SEER database does not record HIV status and thus populations may overlap between the HIV group and the "general population group." Further, the ASD and HOPS databases do not reflect all HIV patients, and the SEER database does not represent the entire United States population.

A study by van Leeuwen et al. from Australia confirmed the results of Patel et al. with identification of 24 HIV-infected patients with diagnosed prostate cancer (cohort of 20,232) between 1982 and 2004 from the Australian National HIV/AIDS Registries [26]. A significant decline in prostate cancer incidence was noted throughout the study period in multivariate analysis ($p = .026$). From 2000–2004, the incidence was decreased compared with the general population. An additional large meta-analysis including 444,172 men with HIV/AIDS identified a decreased risk for prostate cancer in HIV-infected men [51]. Shiels et al. also noted a decreased incidence of prostate cancer in HIV-infected patients compared to the general population [43].

Bedimo et al. completed a retrospective analysis of non-AIDS-defining malignancies in HIV-infected versus matched noninfected patients between 1997 and 2004 using the Veterans Affairs registry which revealed that prostate cancer was diagnosed with equivalent frequency among HIV-infected and HIV-uninfected subjects (441 of 33,420 HIV-infected patients during 5.1 year follow-up vs. 1,041 of 66,840 HIV-negative patients) [41]. Prostate cancer was the only malignancy associated with a higher CD4 count (311 vs. 266; $p < .001$) in HIV-infected individuals when compared with matched non-cancer patients [41]. In a retrospective study (1988–2003) of 4,144 HIV-infected men, the rate of prostate cancer exceeded national rates even after age adjustment [44].

Hessol et al. identified greater than 14,000 adults with AIDS between 1990 and 2001 and noted 482 non-AIDS-defining cancers during the 60 months prior to or following AIDS diagnosis. This included 32 cases of PCa, which resulted in a significantly increased standardized incidence ratio of PCa when compared to general population (Table 10.1) [15]. Another retrospective analysis of 857 consecutive patients with prostate cancer confirmed by prostate biopsy performed in HIV-positive and HIV-negative patients during a 5.5-year period revealed that the likelihood of positive biopsy was significantly higher among 18 HIV-positive patients compared to 839 patients with negative HIV tests (adjusted OR = 3.9; 95 % CI: 1.3–11.5) [42]. In this study conducted at a Veterans Affairs medical center, analyses restricted to prostate cancer patients revealed that HIV-positive patients were not different from the remaining group with respect to their prostate cancer stage, PSA level, PSA velocity, PSA density, or Gleason grade [42].

Epidemiologic analysis of PCa in HIV-infected patients relies on PSA and DRE screening detection. Reports of decreased incidence may be the consequence of decreased screening of these patients [38], although many men with HIV are followed with more intense medical supervision than noninfected men. In addition, men with HIV frequently have decreased androgen levels, which may reduce their likelihood of prostate cancer detection since normal testosterone levels are required for accurate PSA level. It is also feasible that HIV reduces the risk of specific cancers based on viral protein R (Vpr) or gp120-IIIB of HIV-1, for example, which have been shown to enhance host/target cell apoptosis, suggesting possible antineoplastic activity for these proteins [52–54]. Prospective screening studies include analysis of 269 HIV-positive men age 35 years or older during 18 months of follow-up [37]. No patients had abnormal DRE, and 80 % had PSA testing which revealed elevated PSA in seven patients [37]. Of these patients, six had normal PSA on repeat testing, and one patient had prostate biopsy revealing HGPIN. They identified that age, African American ethnicity and duration of HIV infection may be associated with prostate cancer development.

## Case Reports

In the Silberstein review, 60 patients described from case reports between 1996 and 2008 had mean age 57.8 years (40–79), mean PSA 172.7 ng/ml, PSA range 3–5,638, and had average Gleason score of 5–8 with clinical stage T1c (27 %), T2 (19 %), T3 (3 %), and T4 (4 %) [31]. Race data was not available for the majority. Patients had HIV for mean of 8.8 years (0.5–20), with average viral load of 10,006 copies/ml, and average CD4 count of 425.2 cells/mm$^3$ (24–1,070).

In the authors' institutional cohort of 29 patients, the average patient had an age of 56.5 years at diagnosis (range

42–69), had been HIV positive for 9.5 years, had a CD4 count of 517 cells/mm$^3$ (range 75–1,475; 3 patients had CD4 count <200 at diagnosis of prostate cancer), a viral load of 4,713 copies/ml (range 25–106,000; disregarding one outlier, mean viral load was 110 copies/ml), a PSA level of 8.8 ng/ml (range 2.72–33.0) at PCa diagnosis, and a Gleason score of 6.38. Twenty-four (82.7 %) patients had received HAART. Seventeen patients were of African American descent, five were Caucasian, and seven were Hispanic. Family history was identified to be positive for prostate cancer in four patients. Patient treatment and outcomes are described later in this chapter in the treatment section. In addition to the above cohorts, Silberstein et al. describe eight additional HIV-infected patients undergoing robot-assisted laparospic prostatectomy with mean age 54 years (45–66), diagnosis of PCa 14.4 years following HIV diagnosis, with 100 % of patients receiving HAART [55]. Mean PSA of patients was 6.4, mean biopsy Gleason score was 6.6, with 38 % cT1c, 50 % cT2a, 12 % cT2b, mean CD4 count 634 cells/mm$^3$ (506–980), mean viral load <50 with short follow-up of 2.6 months. Outcomes are described in the treatment section.

## Risk Factors in Prostate Cancer

While the specific etiology of prostate cancer remains unclear, it is probable that multiple factors including genetics, infection, inflammation, and environment influence the evolution of the disease [27, 56–60]. Established risk factors include family history, race, and diet (obesity, polyunsaturated fat intake) [5, 58, 61–64]. Increased BMI (body mass index), which can be a consequence of HAART [65], has been consistently associated with increased biochemical progression risk, metastasis, and prostate cancer-related mortality [66, 67]. Relative risk increases according to the number of affected family members, the degree of relation, and the age at time of diagnosis [5, 58, 61]. African American age-adjusted prostate cancer mortality is double when compared to Caucasian men. While studies of similar or reduced incidence of prostate cancer in HIV-positive patients indicate a potential protective role from HIV-induced apoptosis of cancer cells, or a masking effect by HIV or HAART-related hypogonadism, there are suggestions that HIV-positive status may increase the risk of prostate cancer [10, 68, 69]. This may result from delayed diagnosis secondary to hypogonadal state with artificially low PSA levels. Alternatively, immunocompromised patients may be less capable of preventing genetic damage or changes that lead to prostate cancer. The purported mechanism includes impaired cell-mediated immunity, decreased immune surveillance, increased angiogenesis, reduced apoptosis, and chronic inflammation [70].

During the pre-HAART era, there were multiple descriptions of HIV being associated with aggressive prostate cancer, especially in those patients who were hypogonadal at the time of their prostate cancer diagnosis [6–8, 10, 38]. Hypogonadotropic hypogonadism is common in HIV-positive male patients [71–73]. Androgen deficiency in HIV-positive men has been associated with reduced CD4 cell counts, advanced stage of disease, and weight loss or wasting syndrome [74–76]. Hypogonadism is 20 % more common in HIV-positive patients when compared to age-matched healthy cohorts [77]. The etiology may be related to HIV (the testis may provide a sanctuary for the virus to replicate) or to malnutrition. A study of men with weight loss revealed that hypogonadism occurred frequently despite elevated CD4 counts and HAART use [76]. HAART may have a beneficial effect, however, on free testosterone levels (42.6 vs. 69.2 pmol/l in 9 naive compared to 50 HAART treated HIV-positive men, $p = .04$) [78]. The increased frequency of testosterone supplementation and replacement therapy in HIV-positive men may account for an increased risk of prostate cancer detection due to rises in PSA levels.

The effect of HAART on decreasing cancer risk may result from CD4+ T cell counts. Other potential factors include decreased immune activation and cytokine levels, improved immune responses unmeasured by CD4 cell count, and HAART-related suppression of oncogenic viruses. The effects of antiretroviral therapy on the hypothalamic-pituitary-gonadal axis remains unclear [79]. Combination antiretroviral therapy can induce insulin resistance which may cause decreased sensitivity of the hypothalamic-pituitary-gonadal axis and decreased testosterone production by Leydig cells [80] and possibly reduced DHEA levels [81, 82]. With consequently lower PSA levels, these HIV-positive men undergoing HAART are less likely to receive prostate biopsy and therefore have a lower incidence of prostate cancer than the general population.

In the general population, prostate biopsy is frequently completed before testosterone replacement therapy, regardless of DRE or PSA. Since the association between HIV and PCa is currently ambiguous, patients should undergo complete evaluation prior to start of testosterone replacement. In the HIV population, similar to the general population, testosterone therapy is suggested for symptomatic men, with decreased testosterone levels, to improve sexual function, muscle mass, and bone mineral density. Contraindications to starting testosterone therapy include patients with prostate cancer, a palpable prostate nodule or PSA >3 ng/ml without further urological evaluation, erythrocytosis (hematocrit >50 %), untreated obstructive sleep apnea, severe lower urinary tract symptoms (International Prostate Symptom Score (IPSS) greater than 19), or class III or IV heart failure [83].

Some hypothesize that human papillomavirus (HPV) may be related to prostate cancer [84–86]. Since HPV and HIV have been intensely investigated and HIV infection is recognized to elevate the risk of persistent HPV infection, then the role of circumcision and or vaccination against HPV will likely be investigated in additional studies in the future [87]. More recently, xenotropic murine leukemia virus-related virus (XMRV), a gammaretrovirus, has been isolated in human prostate cancers (23 % of 334 specimens had evidence of protein expression), most often in aggressive tumors [88]. Additionally, among ten licensed anti-HIV-1 compounds, zidovudine (AZT) has been shown to block XMRV infection and replication through inhibition of viral reverse transcription [89]. Given this possible viral influence on prostate cancer, the use of HAART therapy, which incorporates AZT, may explain study outcomes of decreased incidence of prostate cancer in HIV-1 patients during the HAART era.

## Diagnosis

Prostate cancer screening includes digital rectal exam and annual serum PSA level measurement. The role of population-wide prostate cancer screening remains controversial following the PLCO and ERSPC studies published in 2009 [90, 91]. Screening of HIV patients for non-AIDS-defining malignancies, such as prostate cancer, remains equally debatable [92]. Screening practices during the PSA era have resulted in stage migration, with enhanced detection of cancer with lower stage and lower volume. The American Urological Association (AUA) current guidelines recommend screening of all men aged 40 years or older with life expectancy of more than 10 years [93]. Baseline PSA is established at this time which determines future screening intervals. Men with increased malignancy risk and life expectancy greater than 10 years (it is common for most HIV patients to now have life expectancy greater than 10 years) should begin screening earlier, although no official recommendations are available from the AUA [94]. According to AUA best-practice guidelines, PSA testing in patients with a serum PSA level greater than 4.0 ng/ml has a sensitivity of approximately 20 % in contemporary series with associated PSA testing specificity of 60–70 % at this cutoff. For men in their 40s and 50s, baseline PSA level above the median value for age is a stronger predictor of future prostate cancer risk than family history or race. Serum testosterone level should also be quantified to ensure that measurement of PSA levels is accurate. Those without prostate cancer may be candidates for chemoprevention, similar to the general population, based on the PCPT and REDUCE trials [95, 96].

Transrectal ultrasound-guided prostate biopsy is indicated in patients with an elevated PSA level or abnormal DRE findings. There are no reports in the literature suggesting increased complications from biopsy in HIV-infected patients when compared to noninfected patients [97]. Patients should refrain from receptive anal intercourse and ejaculation for at least 48 h before a PSA test, as either activity could lead to transient abnormal PSA elevation [98].

## Treatment of Prostate Cancer in HIV/AIDS Patients

The patient's life expectancy and medical comorbidities are of key significance in determining management strategy for prostate cancer and in choosing optimal treatment. Figure 10.1 summarizes management guidelines of prostate cancer in HIV-positive patients. Figures 10.2 and 10.3 summarize special considerations for treating prostate cancer in HIV-positive homosexual men. With the dramatic decline in life expectancy of AIDS patients in the pre-HAART stage, physicians usually offered radiation as treatment for localized disease rather than radical prostatectomy as primary treatment for localized disease since life expectancy for these patients was usually shorter than 10 years. With widespread HAART use and subsequent prolonged life expectancy, the natural history of prostate cancer in the HIV setting is similar to that in the general population in terms of PSA kinetics and cancer stage. Similarly, immunosuppressed renal transplant recipients with prostate cancer (21 patients of 3,150 transplant recipients) can be treated according to standard guidelines for general population with encouraging oncologic results with minimal morbidity [99]. Short-term outcome analyses appear similar, but long-term outcome results are not yet published [97]. Table 10.2 illustrates published reports of patient characteristics by treatment type.

It must be considered whether the HIV-positive patient will exhibit a different response to PCa therapy than HIV-negative patients. Of the 29 patients in our cohort, 6 patients with recent diagnosis of CaP (<6 months) have not had follow-up beyond initial treatment. Of the remaining 23 patients, most recent mean PSA was 3.56 (undetectable in 8: 6 underwent RRP, 1 EBRT, 1 brachytherapy), from baseline PSA 8.8 at diagnosis of prostate cancer. Median follow-up for those followed for <1 year was 6.7 months (1–11) and mean follow-up was 5.5 months. Median follow-up for those patients followed for greater than 1 year was 52.2 months (14–108 months) and mean follow-up was 60.3 months. Mean Gleason biopsy score at diagnosis was 6.38 (5–7). Treatment for this group included prostatectomy ($n=9$), EBRT ($n=4$), brachytherapy ($n=3$), cryotherapy ($n=1$), ADT ($n=5$), and active surveillance ($n=1$). The most recent PSA values indicate that PCa was controlled or stable in all patients regardless of treatment type. No patient has had clinical recurrence at this time (three patients were lost to follow-up with elevated PSA). More specific details of our

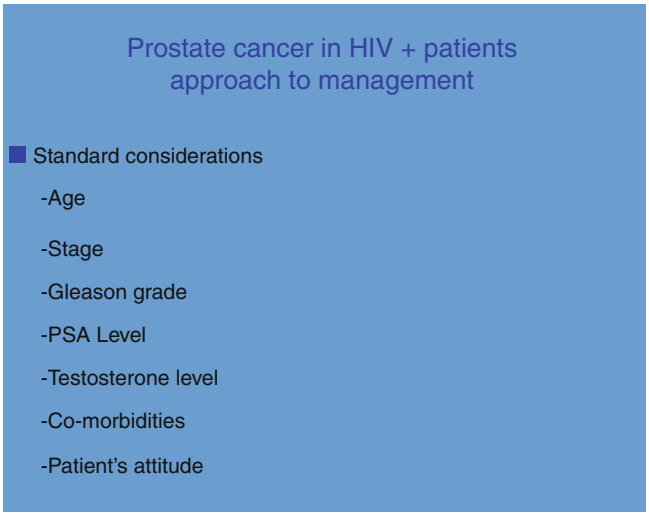


**Fig. 10.1** Prostate cancer in HIV+ patients: approach to management, standard considerations

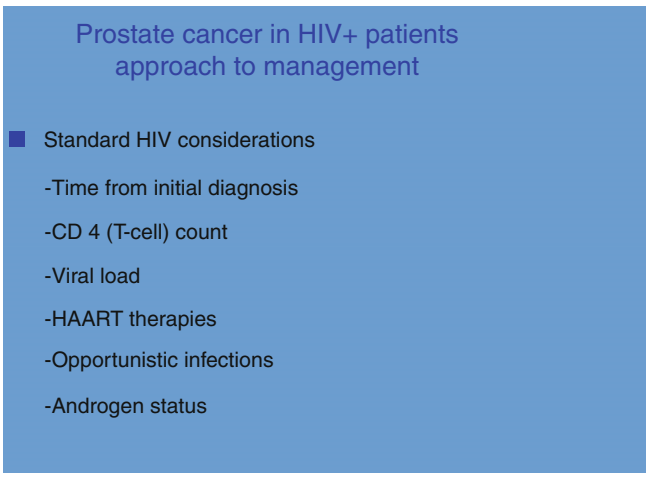


**Fig. 10.2** Prostate cancer in HIV+ patients: approach to management, standard HIV considerations

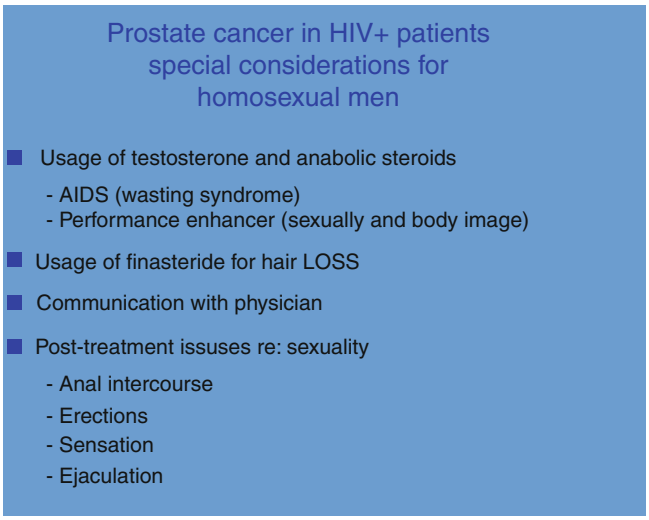


**Fig. 10.3** Prostate cancer in HIV+ patients: special considerations for homosexual men (Santillo and Lowe [98])

cohort according to treatment modality are described throughout this section.

Radiation therapy was shown to be effective with minimal short-term morbidity. One study describes three patients with HIV and clinically-localized PCa that received external-beam radiation therapy with short-term tolerance similar to the general population with 60 % having ≤ grade 1 toxicity and declining PSA measured at 1 month [36]. One patient also underwent concurrent hormone therapy. Patient mean age was 55 years (range 50–58), PSA 5.1 (range 3–9.1), $n=1$ with Gleason score 6, $n=1$ Gleason score 7, and $n=1$ Gleason score 8. Two of three patients were of African American descent, all underwent HAART treatment, and had HIV infection for mean 19.4 months (range 5 months–14 years), and CD4 count of 331 cells/mm$^3$ (range 281–425). The authors hypothesize that RT tolerance may be associated with CD4 count according to a study of HIV-infected patients with anal cancer being treated with chemotherapy and radiation which found CD4 ≥200 cells/mm$^3$ to have reduced morbidity compared to those with lower CD4 count [100]. Overall, there was immediate tolerance, much improved compared with radiation for rectal cancer. Quatan et al. describe two patients with HIV and PCa ages 58 and 64 receiving neoadjuvant hormonal therapy and RT (with subsequent decrease in PSA at last follow-up) and hormonal treatment for metastasis (with good initial response and palliative RT for bone pain), respectively [18]. In our cohort of 29 patients, 4 patients (13.8 %) underwent external-beam radiotherapy with mean age at diagnosis 60 (51–65) years, clinical stage cT1c ($n=3$) and cT2a ($n=1$), and pretreatment PSA 8.15 (4.5–14.5). Mean HIV duration at prostate cancer diagnosis was 18.6 years (14–22), mean CD4 count at diagnosis of prostate cancer was 630 cells/mm$^3$ (76–1,208), and mean viral load was 204 copies/ml (25–501). Mean posttreatment PSA was 0.45 (1.47 <1 year post-XRT, others 0.24, 0.07, and 0.024 respectively) at median follow-up 3.5 years (mean 5.3 years) without major complications.

Brachytherapy has been shown to be safe as a short-term intervention in a retrospective study of 14 HIV-infected patients with PCa, of which 2 received external-beam radiotherapy, 4 received brachytherapy, and 8 completed a combination of brachytherapy and external-beam radiotherapy [33]. All patients were assessed for urinary, bowel, and sexual symptoms after treatment, and the patients fared well when compared with other series. Their conclusion was that radiation therapy and brachytherapy of the prostate were not contraindicated in HIV-positive patients. Brachytherapy has also been reported by Staiman et al. who describe an HIV patient with prostate cancer who underwent brachytherapy

**Table 10.2** Treatment of Prostate Cancer in HIV/AIDS Patients: Published studies including patient characteristics and outcomes

| Treatment | Patients | Study | Mean age | Mean HIV duration | HAART | Mean PSA | Mean biopsy Gleason sum | Clinical stage |
|---|---|---|---|---|---|---|---|---|
| RRP | 5 | Huang et al. [35] | 52 (45–59) | 8.75 years (2–14) | 60 % | 11.3 (4.1–30.8) | 6.8 (6–7) | T1c (60 %); T2a (40 %) |
| | 8 | Silberstein et al. [55] | 54 (45–66) | 14.4 years (10–22) | 100 % | 6.4 (3–10) | 6.6 (6–8) | T1c (38 %); T2a (50 %); T2b (12 %) |
| | 9 | Lowe et al. (2011) | 55 (50–62) | 6.5 years (2–17) | 50 % | 6.0 (4.1–9.5) | 6.4 (6–7) | T1c (100 %) |
| External beam radiation | 3[a] | O'Connor et al. [36] | 55 (50–58) | 19.4 months (5 months–14 years) | 100 % | 5.1 (3–9.1) | 7 (6–8) | T1c (33 %); T2a (67 %) |
| | 4 | Lowe et al. (2011) | 60 (51–65) | 18.6 years (14–22) | 100 % | 8.15 (4.5–14.5) | 6 (6) | T1c (75 %); T2a (25 %) |
| | 2 | Quatan et al. [18] | 61 (58–64) | 13 years (8–18) | 100 % | 2823.8 (9.5–5,638) | 5 and metastatic (N/A) | T1c (50 %); M1 (50 %) |
| Brachytherapy | 3 | Lowe et al. (2011) | 47 (44–48) | 4.7 years (2 months–13 years) | 100 % | 6.7 (4.8–8.5) | 5.75 (5–6) | T1c (100 %) |
| Brachytherapy/ XRT/ or combo | 14 | Ng et al. [33] | 61 (49–71) | N/A | 79 % | 14.3 | 6.5 (6–8) | T1c (43 %); T2b (36 %); T2c (21 %) |
| Androgen deprivation therapy | 5 | Lowe et al. (2011) | 57 (44–67) | 9.25 years (1months–20 years) | 80 % | 17.3 (6.9–33) | 6.5 (5–8) | T1c (20 %); T2b (80 %) |
| Cryotherapy | 1 | Lowe et al. (2011) | 60 (60) | 19 (19) | 100 % | 6.4 | 7 | T1c (100 %) |
| Active surveillance | 1 | Lowe et al. (2011) | 60 (60) | 4 (4) | 100 % | 12.2 | 6 | T2a (100 %) |

| Treatment | Patients | Study | Mean CD4 count | Mean viral load | Follow-up (median) | Outcome | Recurrences |
|---|---|---|---|---|---|---|---|
| RRP | 5 | Huang et al. [35] | 617 (269–870) | 4,475 (und-18,700) | 26 months | All undetectable PSA | None |
| | 8 | Silberstein et al. [55] | 634 (506–980) | <50 (<48-<50) | 2.6 months | All undetectable PSA | None |
| | 9 | Lowe et al. (2011) | 616 (377–837) | 102 (<50–386) | 10 months | 6 undetectable | None |
| External Beam Radiation | 3[a] | O'Connor et al. [36] | 331 (281–425) | 18,700 (400–37,000)[b] | 8 months | All declining PSA (0.3, 0.8,1.3) | None |
| | 4 | Lowe et al. (2010) | 630 (76–1,208) | 204 (25–501) | 64 months | PSA stable; 1 undetectable; mean post-treatment PSA 0.45 (.02–1.47) | None |
| | 2 | Quatan et al. [18] | 421 (356–485) | 621 (und-1,242) | 24 months (12–36) | PSA stable 1.1; Rising PSA (>100) | 1/2 |
| Brachytherapy | 3 | Lowe et al. (2011) | 505 (415–620) | 37 (25–61) | 91 months | PSA 1 undetectable, PSA N/A in 2 | None |
| Brachytherapy/ XRT/ or combo | 14 | Ng et al. [33] | 523 (200–946) | N/A (und-27,000) | 26 months (8–73) | 13/14 patients post-treatment PSA <1.1; one patient metastatic likely 10.1-->18.9 | 1/14 |
| Androgen deprivation therapy | 5 | Lowe et al. (2011) | 387 (75–620) | <50 (und-50) | 25.2 months | PSA 0.38–23.9; all PSA stable following treatment | |
| Cryotherapy | 1 | Lowe et al. (2011) | 132 (132) | 106,000 (106,000) | 48 months | PSA 1.05 stable | None |
| Active surveillance | 1 | Lowe et al. (2011) | 379 (379) | 348 (348) | 90 months | PSA 4.74 | None |

[a]1 patient had concurrent hormonal therapy started 5 months prior to EBRT
[b]1 patient N/A

and developed a prostatic abscess requiring drainage [40]. In our study cohort, 3 of 29 patients (10 %) underwent brachytherapy with mean age 46.5 (44–48) years, clinical stage cT1c with neoadjuvant leuprolide acetate/bicalutamide, mean pretreatment PSA 6.7 (4.8–8.5), mean HIV duration at time of prostate cancer diagnosis 4.7 years (2 months–13 years), mean CD4 count 505 cells/mm$^3$ (415–620), and mean viral load 37 copies/ml (25–61). Mean biopsy Gleason score 5.7 (5–6). Mean posttreatment PSA <0.1 in one patient at follow-up of 7.6 years; the other two patients were lost to follow-up without known PSA recurrence. A major consideration in the treatment determination for homosexual men is the potential consequences of either XRT or brachytherapy upon the rectum, especially if the patient participates in anal receptive intercourse [101].

Preoperative assessment of HIV-positive patients that are candidates for radical prostatectomy should include the standard variables used in HIV-negative patients (age, stage, and grade of disease, PSA level and comorbid conditions) as well as CD4$^+$ T cell counts, viral load, and serum albumin level (Figs. 10.1 and 10.2). Radical prostatectomy and perioperative complications were described by Huang et al. in a population of five HIV-infected male patients from Memorial-Sloan Kettering Cancer Center [35]. Age range was 45–59 years, PSA 4.1–30.8 ng/ml, and biopsy Gleason sum 6 or 7. CD4 counts prior to surgery ranged from 269 to 870 cells/mm$^3$ and viral load ranged from <50 to 18,700 copies/ml. Three patients were treated with HAART at time of surgery and median follow-up was 26 months. After RP, two of five had wound infections, one requiring hospitalization for IV antibiotics. No patients progressed to AIDS during the study period, and none had biochemical recurrence during follow-up. The authors describe that the patient with the deep wound infection necessitating intravenous antibiotic therapy also had the lowest CD4 count (300 cells/mm$^3$) [102]. An additional recent study of eight HIV-positive men undergoing robot-assisted laparoscopic prostatectomy for prostate cancer demonstrated increased prevalence of perioperative transfusions ($p = .03$) and ileus ($p = .02$) when compared to HIV-negative men with similar preoperative characteristics [55]. There were no significant differences identified between groups in terms of short-term oncologic outcomes or complications.

In our cohort, there was no increased risk of wound infection. Nine (31 %) patients (four open retropubic; five laparoscopic/robotic) who had radical prostatectomy were mean age 54.5 years (50–62) at diagnosis with clinical stage T1c and preoperative mean PSA 6.0 (range 4.1–9.5). Biopsy Gleason score was Gleason 6(3 + 3) ($n = 5$), Gleason 7(3 + 4) ($n = 1$), Gleason 7(4 + 3) ($n = 2$), and 1 unknown. Mean HIV duration at prostate cancer diagnosis was 6.5 years (2–17) and mean CD4 616 (377–837) cells/mm$^3$ and mean viral load 102 (<50–386) copies/ml. Post-prostatectomy Gleason score was Gleason 6(3 + 3) ($n = 1$), Gleason 7(3 + 4) ($n = 4$), Gleason 7(4 + 3) ($n = 1$), Gleason 8(3 + 5) ($n = 1$), Gleason 8 (4 + 4) ($n = 1$). One patient did not have post-prostatectomy pathology available from outside hospital. Prostatectomy specimens revealed biopsy undergrading (by 1 unit of Gleason score) in five patients undergoing surgery with biopsy overgrading (by 1 unit of Gleason score) in one patient. Mean posttreatment follow-up PSA <0.1 ($n = 6$, 2 with follow-up PSA pending as surgery done in 9/2010, 1 patient with recent diagnosis <2 months prior without additional follow-up) without evidence of recurrence at median follow-up of 10 months. Preoperative assessment should include variables used in seronegative patients, along with CD4+ count, viral load, and albumin level. Overall, for patients with CD4 counts above 500 cells/mm$^3$ and asymptomatic HIV infection, prostatectomy is well tolerated and advised [98].

Our study cohort additionally included five patients receiving potency-preserving androgen deprivation (one patient had neoadjuvant ADT and EBRT), one patient receiving cryosurgery, and one patient on active surveillance. For patients receiving ADT, mean age was 56.6 (44–67), median follow-up was 2.1 years (mean 3.6 years), mean duration of HIV diagnosis was 9.25 years (1 month–20 years), mean CD4 count was 387 cells/mm$^3$, (range 75–620), mean viral load <50 copies/ml in all patients, and mean pretreatment PSA level was 17.3 (6.9–33), and mean posttreatment PSA was 11 (0.38–23.9). Mean biopsy Gleason score was 6.5 (5–8). The patient undergoing cryotherapy had pretreatment PSA of 6.4, Gleason biopsy score of 7 (3 + 4) posttreatment PSA 1.05 at 4 years follow-up. The patient on active surveillance protocol had stable PSA level (diagnosis PSA 12.2, most recent PSA 4.74) with initial Gleason biopsy score of 6 (3 + 3) without disease progression at 7.5 years follow-up. This patient did require greenlight laser PVP for LUTS. Active surveillance should be initiated according to the same criteria for the general population following the criteria of Carter et al., which includes Gleason sum ≤6, <3 biopsy cores with cancer, and <50 % involvement of any core with prostate cancer, free/total serum PSA ratio of ≥0.15 [103, 104]. Repeat biopsy within 6 months of diagnosis is the most important predictor of progression for patients on active surveillance [105].

Similar to our cohort receiving various treatments, another cohort study described 17 patients with HIV (mean duration of disease 8.5 years) and PCa [16]. One patient had distant metastasis and one had regional lymph nodes metastasis. Three patients underwent radical prostatectomy, three received brachytherapy, seven received androgen suppression and radiation, and two received androgen suppression alone. The authors noted that all patients with initial localized disease undergoing treatment had a complete response with undetectable PSA level and without

tumor recurrence. No serious treatment-related side effects were noted, and the authors concluded clinical presentation, PSA, and outcomes were not appreciably different in HIV-positive men on HAART. From these relatively small cohorts, response to therapy in HIV-positive patients with prostate cancer seems similar to that of the general population. The reader must recognize, however, that all investigated groups are small, heterogeneous, and not matched to non-HIV positive men so there may be multiple confounding factors limiting definitive conclusions.

## Adverse Effects of Prostate Cancer Treatment in HIV Patients

All therapies for the treatment of prostate cancer can negatively impact quality of life, sexual function, urinary and bowel function as well as psychological state. For patients undergoing surgery, radiation, or androgen deprivation, urologists must evaluate baseline sexual dysfunction. A study of 189 HIV-infected men with mean age 36.8 years described sexual dysfunction in 19.5 % which was postulated to be affected significantly by antiretroviral treatment, particularly protease inhibitors [106]. HIV-induced hypogonadism was not the cause of sexual dysfunction. Patients must be counseled regarding risks of erectile dysfunction following treatment which may be exacerbated by HAART.

For those undergoing surgical procedures, CD4+ counts are important because it has been shown in HIV-positive women having gynecological surgery that those with CD4+ counts <200 have up to four times greater complication risk than HIV-negative age and procedure matched controls [102]. Furthermore, serum albumin, a marker for nutritional status, has been correlated with morbidity and mortality outcomes for those undergoing surgery with end-stage renal disease, cardiovascular disease, numerous types of cancer, and HIV infection [107–110]. Serum albumin is described to have possible prognostic significance for the morbidity and mortality of HIV-infected patients, but our cohort did not include routine examination of preoperative albumin levels [107]. Again, homosexual men who engage in anal receptive intercourse should be advised about radiation effects upon the anus and rectum secondary to both brachytherapy and external beam radiation therapy.

When treating HIV-positive patients with prostate cancer, the physician must consider the tolerability of the treatment regimen. Although studies of patients with prostate cancer are limited, comparison to anal cancer studies is helpful to determine effects of radiation on HIV patients. From published data, the use of combined chemoradiotherapy is reported to be "tolerable" or to result in increased morbidity in immunodeficient patients compared with immunocompetent patients. The oncologic outcome of anal SCC in immunodeficient versus immunocompetent patients is characterized by similar or reduced disease control. Some data indicate increased morbidity and decreased time to cancer-related death in patients with HIV and anal cancer treated with chemoradiation [111]. Direct comparison of prostate cancer and anal cancer treatment is hindered by the use of chemotherapy for anal cancer treatment. A study of 17 HIV-positive patients with anal cancer treated during the pre-HAART era with concurrent chemotherapy (5FU and/or mitomycin C, and/or cisplatin) and radiation (median dose 5,180 cGy) revealed that patients with CD4 ≥ 200 had excellent disease control with acceptable morbidity while patients with CD4 < 200 had markedly increased morbidity (skin, hematologic, gastrointestinal), although disease was controlled in 7 out of 8 of these patients [100]. In the HAART era, Seo et al. studied 19 immunocompetent and 17 immunocompromised patients with anal cancer (14 HIV and 3 post-solid organ transplant patients) who received concurrent chemoradiotherapy [112]. There were no differences in overall or disease-specific survival or toxicity between the two groups.

In the setting of HIV and androgen-independent prostate cancer, there is evidence of possible benefit from protease inhibitors used concomitantly with docetaxel. In addition to protease activity, protease inhibitors have been identified to inhibit growth of DU145 and PC-3 androgen-independent prostate cancer cells using the clonal proliferation assay [113]. Ritonavir blocked docetaxel-induced expression of CYP3A4 at the mRNA level in DU145 cells and enhanced the antitumor effect of docetaxel in vitro and in BNX nude mice bearing DU145 tumors [114]. The group hypothesized that using an active chemotherapeutic drug and a PI (ritonavir) could reverse drug resistance.

### Conclusion

With the prolonged survival of HIV-positive patients receiving highly active antiretroviral therapy, the screening, diagnosis, and treatment of non-AIDS-defining malignancies, such as prostate cancer, now need to be addressed. Although the largest studies of cancer incidence trends among HIV-infected patients have identified significantly higher rates of prostate cancer in the HAART era, the incidence rates appear to be decreased compared with the general population. It is probable that the increasing incidence of prostate cancer amongst HIV-positive patients is related to their longevity and that they are more often now being screened for prostate cancer with PSA testing. Similar to the general population, stage migration secondary to increased PSA screening has identified more prostate cancer at an earlier stage. It is

unclear why the incidence is lower than the general population except for possible differences in racial demographics, less PSA screening in the HIV-infected cohort, HIV-induced apoptosis of cancer cells, or hypogonadism secondary to HIV or HAART. In the HAART era, PSA kinetics and prostate cancer behavior has not been demonstrated to be different between HIV-positive and HIV-negative patients. Prostate cancer screening for HIV-positive patients should be initiated beginning at age 40 following recommendations for the general population along with continued close surveillance of CD4 count, viral load, and serum testosterone level. The extended life expectancy of the typical HIV patient on HAART requires consideration of the full spectrum of treatment modalities including active surveillance, prostatectomy, radiation, cryosurgery, and androgen deprivation in accordance with the AUA guidelines for the general population. Early results indicate that responses to prostate cancer therapies in HIV-positive patients are comparable to those in the general population. The physician must recognize numerous special issues to optimally manage the HIV patient with prostate cancer. With extended follow-up data from population-based and prospective randomized studies, long-term outcomes will further refine treatment algorithms.

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# Prostate Cancer Genetics

# 11

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## Introduction

Prostate cancer (PCa) is one of the commonest cancers in men and a major cause of cancer-related mortality. Family history is the strongest known risk factor for developing PCa. This is illustrated by the observation that a man with one close relative (such as a father or a brother) with PCa has approximately twice the risk of developing PCa when compared to a man with no family history. A man with two close male relatives affected has a fivefold increase in lifetime risk. This degree of relative risk and the increase in its magnitude indicate a strong genetic component to disease development. However, unlike other cancers such as breast, ovarian, and colonic cancers, the search for mutations in candidate genes is proving to be more elusive. Uncovering the genes that predispose to PCa among families where disease is clustered has been the objective of many research groups over the past 15 years. Epidemiological and twin studies support a role for the genetic predisposition to PCa. Familial cancer loci have been identified, but discovery of the genes that cause familial prostate cancer (FPC) remains largely elusive. Unraveling the genetics of PCa is challenging and is likely to involve the analysis of numerous predisposing factors, which may be manifestations of multiple mutagenic pathways. Increased familial risk of prostate cancer could be due to the inheritance of multiple moderate-risk genetic variants. Although the study of hereditary prostate cancer (HPC) has increased our understanding of its genetic etiology, many issues remain largely unresolved. This difficulty with identification of PCa predisposition genes may be due to a number of reasons. PCa, in terms of total prevalence, is a very common condition, and it may not be far wide of the mark to say that the majority of prostates in the Western world will eventually harbor some cancer cells. The disease varies significantly in the spectrum of aggressiveness. We do not know, with absolute conviction, which patients who have been diagnosed with PCa require treatment. It is against this quandary that genetics could play its influence. PCa is diagnosed in the later years of life; therefore, obtaining DNA samples from living affected men for more than one generation is often not possible, and linkage in large pedigrees may be unfeasible. The presence within high-risk pedigrees of phenocopies (individuals with PCa but without the genetic alteration) weakens the linkage results. The genetic heterogeneity of this complex disease (the fact that different pedigrees may be due to different genetic mutations) and the uncertainty regarding the optimal genetic model could render linkage results inaccurate, making gene identification difficult.

Significant linkage in FPC was first published by a group from Johns Hopkins University, USA [1]. They reported linkage at a locus on chromosome 1q24-25, which they named hereditary prostate cancer 1 (*HPC1*). Since then, several large linkage studies have taken place, and the results of many different groups have uncovered new loci and challenged others [2–5]. To this date, research on PCa linkage has reported genotyping data in over 1,600 families. There are numerous contradictory studies reporting or refuting linkage within a multitude of areas in the genome, and this challenges our understanding of the genetic basis of this disease. This is in contrast from the search for a familial breast cancer predisposition gene in which analysis of linkage in select regions revealed a site where the *BRCA1* gene was situated [6]. This demonstrates that the genetic predisposition to PCa is highly

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complex, probably involving numerous predisposition genes and that a high proportion of high-risk families may not be attributable to a single high-risk gene. Conventional linkage may not be the best method of predisposition gene identification in this disease because of genetic heterogeneity whereby various familial clusters are due to different genes. This chapter addresses the current evidence that supports a genetic component to the etiology of PCa and attempts to put into context the diverse findings that have been implicated with the development of HPC. It explores why understanding the genetics of PCa has been so difficult. Lastly, management strategies of men with HPC are discussed.

## Evidence for Genetic Etiology

Current evidence for the genetic etiology of PCa can be grouped into epidemiological evidence, case–control studies, cohort studies, and twin studies.

### Epidemiological Evidence

In the 1950s–1960s, it was noted that the risk of PCa development in relatives of sufferers was higher than the population average [7, 8]. Large families have been observed, in which prostate cancers seemed to cluster. Early observations were made in large families studied in Utah [9, 10]. To further explore the evidence for a familial component to PCa development, case control, cohort, and twin studies have been reported.

### Case–Control Studies

Case–control studies can be divided into two broad strategies. One strategy compares prostate cancer incidence in first-degree relatives of PCa patients (cases) with the incidence in relatives of cancer-free individuals (controls). The second strategy compares the percentage of PCa cases vs. controls with a family history of the disease [7–9, 11–26]. These studies indicated that the relative risks (RR) among first-degree relatives of affected individuals range from 0.64 to 11.00-fold [27–29]. With the exception of the RR of 0.64 [11], in a study, which was carried out on a small sample set of 39 families, 15 of these 16 studies reported an RR of 1.76 or more. This RR increases further when more than one relative is affected. Steinberg et al. [15] demonstrated that the RR with an affected first-degree relative was 2.0, with a second-degree relative was 1.7, but with both first- and second-degree relatives combined, RR rose markedly to 8.8. Additionally, the RR increased as the number of family members increased, with RRs of 2.2, 4.9, and 10.9 observed for 1, 2, and 3 additional affected relatives besides the proband, respectively [15]. This is robust evidence for the involvement of a genetic component in familial disease as these increases in RR are too large to be dismissed solely as an environmental effect. Further evidence of a genetic influence is demonstrated by the observation that the RR to relatives increases as the age of the proband decreases [9, 30]. A brother of a proband with PCa at the age of 50 has a 1.9-fold higher risk of developing prostate cancer compared with a brother of a man diagnosed with the disease at the age of 70 [30].

### Cohort Studies

Cohort studies attempt to avoid potential bias through probing an unselected population. Goldgar et al. [31] showed an FPC RR of 2.21 in first-degree relatives of 6,350 probands from an unselected population from the Utah Population Database. Likewise, Gronberg et al. [32] found an RR of 1.70 from their study involving 5,496 sons of Swedish men from Cancer Registry data.

### Twin Studies

These have demonstrated an increased RR in mono compared with dizygotic twins of just over 3- to 6-fold [33]. Page et al. [34] studied 15,924 male twin pairs and found pairwise concordance (twin pairs where both men were affected) rates among monozygotic twins was 15.7 %, while for dizygotic twins the frequency was 3.7 % ($p = <0.001$). Probandwise concordance (number of concordant affected twins divided by total number of affected twins) was 27.1 % for monozygotic twins and 7.1 % for dizygotic twins, which gives a risk ratio of 3.8. Similar results were noted in a Finnish study [35]. A further study concluded that up to 42 % of PCa risk could be attributable to heritable factors [36]. The absolute risk of prostate cancer for twins diagnosed up to the age of 75 was found to be sixfold higher for mono- vs. dizygotic twins (18 % vs. 3 %). It also demonstrated a statistically significant reduction in time interval between the age at diagnosis for monozygotic twins compared with dizygotic twins (5.7 years vs. 8.8 years; $p = 0.04$).

## Segregation Analyses

"Segregation analyses" is a method that studies the structure of familial clusters and describes the likely mode of inheritance, age-specific cumulative risk (penetrance), and allele frequency of genetic predisposition to a disease. Carter et al. [30], using such analyses, suggested that early-onset PCa (<55 years) may be due to a rare autosomal dominant highly penetrant allele, which could account for up to 43 % of disease in this age group and up to 9 % of PCa in men aged

up to 85 years. Alleles for such a rare autosomal dominant gene were predicted to exist at a frequency of 0.003 and to cause a cumulative risk of disease of 88 % by 85 years of age compared with 5 % for noncarriers. Other researchers have arrived at similar conclusions but have suggested a commoner allele frequency and a lower penetrance of about 67 % (Gronberg et al. [32], allele frequency 0.0167; Schaid et al. [37], allele frequency 0.006). A recessive or X-linked model is suggested by some studies, which noted higher risks to brothers of PCa cases compared with fathers [38, 39]. Ewis et al. [40] report an odds ratio of 2.04 ($p=0.02$) for allele C of dYs19 in Japanese prostate cancer patients, while other alleles of this region were protective against the disease (allele D, OR 0.26 $p=0.002$). The Y chromosome (father-to-son transmission) is therefore also implicated. It is possible that a mixture of several models coexist, giving rise to age-related risks [41]. Dominantly inherited risk allele(s) may predispose to early-onset disease, and a recessive or X-linked model could account for its later onset [42].

## Molecular Analysis Evidence: Linkage Studies (Genome-Wide Scans)

Linkage analysis is a gene-localizing technique that looks for co-segregation of a disease in sizeable, high-risk families, with disease-causing genetic mutations. Linkage analysis has been used to successfully map many familial cancer loci, e.g., colorectal cancer, breast/ovarian cancer, and melanoma [43]. Initially, linkage analysis helps to pinpoint the region within which a disease-causing locus may lie by analyzing co-inheritance of polymorphic stretches of DNA, e.g., microsatellite markers. The sequencing of the human genome will facilitate the use of single nucleotide polymorphisms (SNPs). As these are more common than polymorphic runs of DNA sequence, a denser linkage maps can be determined. Once a region of linkage is identified, then candidate gene mutation analysis within the region can be undertaken to identify the disease-causing mutation.

## Candidate Gene Analysis Evidence

The search for genetic markers of disease susceptibility often utilizes the candidate gene approach. Here, a gene is targeted based on the properties and metabolic pathways of its protein product. PCa cases were noted to be clustered among breast cancer families as far back as the 1990s [44, 45]. The relative risk (RR) of PCa development in male carriers of mutations in the breast cancer predisposition genes *BRCA1* and *BRCA2* is increased. The RR with respect to *BRCA1* was found to be 3.33 [46] and 1.82 in a further analysis by the BCLC [47]. That of *BRCA2* was found to be 4.65. The RR is higher in men with PCa diagnosed before 65 years (RR 7.33), with an estimated cumulative incidence by the age of 70 of 7.5–33.0 %. A founder mutation 999del5 in *BRCA2* has been identified in study carried out in Iceland. This mutation is reported to confer a cumulative PCa risk to carriers of 7.6 % by the age of 70 [48]. Sixty seven percent of men who had the mutation all developed advanced PCa associated with a high mortality rate [49], implying that *BRCA2* predisposes to more aggressive disease. A report in a Swedish family carrying the *BRCA2* mutation 6051delA [50] adds weight to the evidence that such mutations are pathogenic. A mutation screen of *BRCA1* and *BRCA2* genes was conducted by Gayther et al. [51]. Two germline deleterious *BRCA2* mutations were discovered. A study conducted by Edwards et al. [52] on 263 men aged <55 at diagnosis discovered six pathogenic mutations located outside the ovarian cancer cluster region in the gene, implying a genotype/phenotype correlation that accounted for 2 % of PCa at this young age. This equated to an RR of 23 by the age of 60 and conferred an absolute risk of PCa of 1.3 and 10 % by the age 55 and 65, respectively. This supports the notion that *BRCA2* is a high-risk PCa gene. Two recent studies have reported an increased risk of prostate cancer associated with the Ashkenazi founder mutations in the *BRCA* genes, lending further evidence to these data [53, 54]. Subsequently, germline mutations have been found in the *NBS* gene in the Slavic population at a higher frequency in PCa cases than controls [55] and in the *CHEK2* gene [56]. This implies that PCa predisposition may in some instances be due to mutations in genes in the DNA repair pathway, that in the homozygous form give rise to a severe phenotype (in the case of *BRCA2* this would be Fanconi's anemia D2 and in the case of *NBS* would be Nijmegen Breakage Syndrome), but in the heterozygous form, would increase the risk of PCa development.

## Genome Searches

The running of a large number of microsatellites, typically in the region of 400, has many terms: genome-wide search, genome-wide scan, or genome-wide screen – and can conveniently be abbreviated to GWS. Numerous linkage analysis experiments have been conducted across the genome to identify prostate cancer susceptibility loci. The ACTANE (Anglo-Canadian-Texan-Australian-Norwegian-EU Biomed) group has focused on the collection of early-onset clinically detected disease. This is because the disease manifests 10 years later on average than PSA-detected disease, and therefore these men would have had a raised PSA level at even earlier age and may therefore be highly predisposed genetically [28]. Thus far, several GWS have been published for PCa [1, 3, 5, 57–72]. The significant results are as follows.

## 1q23-24: HPC1 and the RNASEL Data

The first GWS identified a locus named *HPC1* (hereditary prostate cancer 1) at 1q24-25. A group from Johns Hopkins University, Baltimore, carried out the study in 91 North American and Swedish families, and their report suggested that up to 34 % of families could be linked to this locus [1]. Several other groups have since either confirmed [73–76] or refuted [57, 58, 60, 64, 77, 78] the original report. Goode et al. [64] and Goddard et al. [79] found evidence of genetic linkage in families with more aggressive PCa. A meta-analysis conducted by Xu et al. [80] representing many groups within the International Consortium for Prostate Cancer Genetics (ICPCG) reported data obtained on 772 families and reported that a lower estimate of 6 % of all families was linked to 1q24-25. A more extensive analysis concluded that *HPC1* might have a role in a subset of families with numerous young-onset cases, particularly among Afro-Caribbean men. Carpten et al. [81] subsequently found mutations in the cell proliferation and apoptosis-regulating gene *RNASEL* which was in this region. Of 8 families that were linked to the 1q region, two had germline mutations; one was a stop Glu265Ter (E265X) termination codon, but the other was a missense mutation. Neither segregated with the disease. Some, but not all, further reports have shown *RNASEL* mutations to be associated with PCa risk but with a much lower relative risk than would have been predicted by the linkage evidence. Rokman et al. [82] showed that the Glu265X in *RNASEL* was present 4.5-fold more often in affected family members compared with controls. Other groups have found that *RNASEL* may confer much smaller PCa risks or have found no mutations at all in PCa cases; therefore, it is likely to be low-penetrance PCa cancer gene that is at odds with the linkage evidence [83, 84]. This suggests that either the linkage results are misleading or that a highly penetrant *HPC1* exists but is still to be discovered.

## Other Loci and Candidates from GWS

Other loci have unfortunately had a similar history to that described above, namely, loci are identified that have significant logarithm of the odds (LOD) scores, and candidate genes have mutations described therein which are subsequently refuted or whose risks fall on further detailed analysis [85, 86].

## Other Significant Loci

*PCaP* (1q42.2-43; Berthon et al. [57]) – this was a locus that was identified in the German/French population but not corroborated by other researchers. *CAPB* (1p36; Gibbs et al. [59]) – a locus which is associated with primary brain tumor and PCa which on further analysis seemed more associated with young-onset PCa than brain tumor [87]. A locus has been described on chromosome 16q in sibling pairs by Suarez et al. [58] and one on 20q (*HPC20*) by Berry et al. [63], but these are yet to be independently confirmed. Another locus has been described on the long arm of chromosome X (*HPCX*; Xq27-28) by Xu et al. [88]). This has been corroborated by some other researchers, but the gene has yet to be identified. There are also loci that are implicated in the development of more aggressive disease, e.g., 7q, 19q [89–91]. Eight GWS have been published recently in one issue of the Prostate (ACTANE Consortium [72]; Lange et al. [65]; Schleutker et al. [66]; Cunningham et al. [67]; Xu et al. [68]; Wiklund et al. [69]; Janer et al. [70]; Witte et al. [71], Dec 2003). A summary of these was published in a review by Easton et al. [5]. The conclusion of these GWS to date is that there are numerous loci suggested by the GWS from various groups which are not consistently replicated by independent groups on study of further PCa families. This implies that there is considerable genetic heterogeneity in PCa. The possibility that PCa is due to a combination of low penetrance means that more common genetic variants may be entertained when large families are rare and it is difficult to locate predisposition genes by linkage. Candidate studies of polymorphisms are presently under way in PCa. There is currently no uniform pattern of polymorphisms that confers markedly increased risk from the data. The most consistent polymorphisms to date that confer a moderately increased risk are in the *SRD5A2*, *GSTP1*, and the *AR* genes [92–102].

## Recent Findings of the UK GWAS and Potential Clinical Role

Eeles et al. previously conducted a genome-wide association study in which 541,129 SNPs were genotyped in 1,854 PCa cases with clinically detected disease and in 1,894 controls. They then extended the study to evaluate potential correlations in a second stage in which they genotyped 43,671 SNPs in 3,650 PCa cases and 3,940 controls and in a further stage involving an additional 16,229 cases and 14,821 controls from 21 studies. They identified seven new PCa susceptibility loci on chromosomes 2, 4, 8, 11, and 22 (with $P = 1.6 \times 10(-8)$ to $P = 2.7 \times 10(-33)$) [103]. It is possible that the seven novel genetic loci found could contain several potential candidate genes, which could contribute to PCa development and progression. A key association was found on chromosome 10, just 2 bp away from the transcription start site of the microseminoprotein B (*MSMB*) gene. *MSMB* encodes PSP94, a member of the immunoglobulin-binding factor family made by

epithelial cells of the prostate and secreted into seminal plasma. Loss of expression of PSP94 is linked with recurrence after radical prostatectomy. This seems to suggest that this SNP may be causally related to disease risk [104]. Therefore, PSP94 could be a future screening target especially as it can be found in blood. There is a region on chromosome 7 that the gene *LMTK2* (also known as *BREK*) which codes for a signaling protein [105] and could act as a novel target for drug therapy. The chromosome 19 hit contains kallikrein genes *KLK2* and *KLK3* which code for the proteins hK2 and PSA, respectively. There is evidence that hK2 may be useful for PCa screening and prognosis [106]. Twenty-four SNPs in the *KLK3* (PSA) gene have subsequently been evaluated in men from five studies, and no association was reported with PCa risk [107]. Eeles et al. looked at the variation in KLK genes, PSA, and risk of PCa. In the first stage of a study, they used controls selected for low PSA levels. Stage 2 controls were not selected for a low PSA. However, they still found an association. Following this a study involving 13 groups worldwide where the controls were not selected for a low PSA level, still showed an association of the chromosome 19 SNP (between *KLK2* and *KLK3*) with PCa risk [108]. The chromosome 6 association is in intron 5 of *SLC22A3*, one of the organic cation transporter (OCT) genes. These have been shown to be critical for elimination of some drugs and toxins [109]. Many genes are near the SNP of interest on the X chromosome. The *NUDT10* and *NUDT11* genes encode enzymes that determine the rate of phosphorylation in DNA repair, stress responses, and apoptosis [110].

### Other PCa GWAS

Two other groups of researchers, CGEMS (USA) [111] and deCODE Group (Iceland) [112], published their PCa GWAS at the same time as the UK GWS. Both confirmed previously reported associations at chromosomes 8q and 17q. CGEMS found similar hits to UK GWS on chromosomes 10 and 11. They additionally found novel tagSNP associations on chromosomes 7 and 10. The deCODE team found a novel region on chromosome 2p15 in their population. Duggan et al. in another GWAS investigated aggressive PCas that were defined by having at least one of the following: stage T3/T4, N+, M+, Grade III, Gleason score ≥8, or preoperative serum PSA of at least 50 ng $mL^{-1}$. This group reported a different association on chromosome 9 located within the *DAB2IP* gene, which encodes a novel Ras GTPase-activating protein [113]. More recently, Sun et al. from the same group identified a second independent risk locus in chromosome 17q12 within the *HNF1B* gene [114].

## Prostate Cancer Predisposition Gene Discovery

There are many uncertainties in the area of genetic predisposition that are currently taxing researchers in this area. These include (a) what is the optimal genetic model for PCa? (b) are there different predisposition genes in different populations? and (c) how much concordance is there between various groups for the putative loci? The results of future large-scale multicenter studies will ultimately answer these questions. It is entirely possible that the studies undertaken thus far are underpowered and pooling of data may improve the chances of finding genuine underlying linkage. This is the aim of the creation of groups such as the International Consortium of Prostate Cancer Genetics (ICPCG). Groups undertaking linkage analyses worldwide collaborate within the umbrella of this consortium. In 2000, via a meta-analysis, the ICPCG found that the 1q24 locus may contribute to about 6 % of PCa families and was more commonly found in larger prostate cancer clusters whose average age of onset was <65 years [80]. Current data indicates that progression to clinical disease is more likely following a raised PSA and occurs a median time of 10 years after the PSA has risen [115]. In theory, patients in families that are diagnosed with clinically detected disease may have different set of predisposing genes to those involved in PSA screen detected patients. At present, whether this is true, this is unknown. On the issue of genetic heterogeneity for linkage, i.e., presence of more than one PCa predisposition genes, it has been shown that two percent of early-onset cases have deleterious mutations in the *BRCA2* gene and that a further small percentage is due to *NBS* and *CHEK2* mutations. Yet models suggest that up to 43 % of such cases may harbor a predisposition gene [30]. This indicates that there are further PCa susceptibility genes that are yet to be discovered. In an age when the majority of monogenic human disease genes have been identified, a particular challenge for human geneticists will be resolving complex polygenic and multifactorial diseases. It is likely that the majority of genetic predisposition to PCa will follow this model where there exist many rather than one PCa predisposition gene per family.

## Clinical Management Concepts for HPC

The question of whether a genetic change influencing PCa causation is associated with factors altering treatment is an important consideration. Recent reports are contradictory. Carefully documented multicentered, prospective family history data collection and outcome analysis are crucial to improving our understanding of this condition. The current management issues surrounding HPC involve several considerations: (i) the degree of biological aggressiveness of HPC, (ii) whether HPC per se is an independent predictor of

treatment outcome, (iii) whether there is a difference in the survival curves between sporadic and HPC, and (iv) the outcome patterns in those patients treated various radical treatments, i.e., prostatectomy vs. radiotherapy by family history.

### Determining the Degree of Biological Aggressiveness

Walsh initially observed that there was no significant difference between phenotypes of sporadic, familial, and HPC undergoing radical prostatectomy with respect to clinical stage, pre-op PSA, PSA density, prostate weight, Gleason score, pathologic stage, or tumor histology [115]. This was challenged by subsequent observation that patients with localized PCa who reported a positive family history tended to have a worse outcome at 3 and 5 years following treatment, be it radiation therapy or surgery, than those with sporadic cancers [116]. This was then again refuted by three subsequent studies that found no difference in the aggressiveness of HPC compared to sporadic disease [117–119]. This area therefore remains unresolved.

### Is HPC an Independent Predictor of Treatment Outcome?

Kupelian et al. [120] first indicated that a positive family history for PCa correlates with treatment outcome, in a sizeable unselected series of patients, suggesting that familial PCa may have a more aggressive course than nonfamilial PCa.

### Is There a Survival Differences Between Sporadic and HPC?

No significant differences in either overall or cause-specific survival were found between sporadic, familial, and HPC patients [121]. Present treatment guidelines do not differ based on presence or absence of FPC.

### Should Men with a Family History of Prostate Cancer Avoid Conservative Treatment?

Based on current evidence, there is a rationale for genetic screening of men at risk once the genes responsible for prostate cancer are identified. The American Urological Association (AUA) recommends that men who are at high risk for developing PCa such as men with a family history of disease or men of African-American descent commence routine PCa screening at the age of 40 [122], whereas The American Cancer Society recommends that men receive PSA or digital rectal examination testing annually at the age of 50 or earlier if they have a family history of the disease or are of African-American descent [123]. In outcomes in HPC men treated with radiotherapy vs. radical prostatectomy, Hanlon et al. [124] found no significant difference in biochemical failure rates between carefully matched men with and without a family history of PCa. This backs other studies that failed to show an elevated risk of failure after definitive therapy for clinically localized PCa in men with either combined hereditary and familial and patients with the sporadic form of the disease.

## Chemoprevention Trials

PCa chemoprevention is the judicious administration of agents that impair one or more steps in prostatic carcinogenesis. The principle aspects of chemoprevention include agents, their molecular targets, strategic endpoint biomarkers, their critical pathways, and cohorts identified by genetic and acquired risk factors [125]. The identification of genetic susceptibility loci would enable a cohort of men at high risk of developing PCa to be identified to serve as subjects for chemoprevention trials. If such trials yield favorable outcomes, they could potentially lead to a recommendation for preventative therapy in genetic mutation carriers. Several putative chemopreventive agents are currently being trailed. Results of a large population-based, randomized phase III trial demonstrated that finasteride might prevent PCa. However, the paper indicated that only low-grade tumors were prevented and in fact the number of high-grade tumors was significantly higher in the finasteride arm. Clarke et al. [126] studied the possible effect of supplemental dietary selenium on the change in the incidence of PCa. They found that although selenium confers no protective benefit on the primary study endpoint of squamous and basal cell carcinomas of the skin, the selenium-treated group in their series had substantially lower incidence of PCa as a secondary endpoint. Further investigations are clearly warranted. Initial data seem to suggest at least some benefit with the use of other agents may potential confer preventative effect. These include vitamin E, vitamin D, other 5-alpha-reductase inhibitors, cyclooxygenase-2 inhibitors, lycopene, and green tea. Some of which are being tested in new large-scale phase III clinical trials [127]. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is an intergroup phase III clinical trial that aims to test the efficacy of selenium and vitamin E alone and in combination in the prevention of prostate cancer [128]. The emergence of new powerful techniques such as proteomic analysis of tissue-based and secreted proteins [129] and gene chip cDNA microarrays for multiplex gene expression profiling is likely to facilitate the identification of new molecular targets, cohorts at risk, and the design of appropriate combination trials.

## Targeted Screening

Several controversies surround the management of the relatives of PCa patients. Targeted screening involves monitoring serum PSA levels in relatives of young- or early-onset PCa or families with multiple cases. The optimal age at which screening should be initiated is yet to be determined. The sub-30- and sub-40-year-old groups would not be screened by the majority of clinicians, and many would commence screening either at age 5 years younger than youngest age at diagnosis of a relative or 40 years but not normally younger than this. Targeted screening studies have demonstrated a higher proportion of raised PSA levels in relatives of cases in families compared with sporadic cases. In a screening study of PCa, among high-risk families [130], it was shown that previously unsuspected and clinically relevant cancers were found in 24 % of a total of 34 first-degree relatives compared to the approximately 1 (3 %) expected ($p < 0.01$). The study emphasized the paramount importance of thorough screening in first-degree relatives of prostate cancer patients. The first targeted screening study based on *BRCA1/2* genotype started in 2003 (the IMPACT study; Tischkowitz and Eeles, 2003) [131]. In 2011, the team published the findings of one wing of their study involving 300 men (205 mutation carriers; 89 BRCA1, 116 BRCA2, and 95 controls) over 33 months. At the baseline screen (year 1), 7.0 % (21/300) underwent a prostate biopsy. PCa was diagnosed in ten individuals, a prevalence of 3.3 %. The positive predictive value of PSA screening in this cohort was 47·6 % (10/21). One PCa was diagnosed at year 2. Of the 11 PCas diagnosed, 9 were in mutation carriers, 2 in controls, and 8 were found to be clinically significant. Thus, suggesting that the positive predictive value of PSA screening in BRCA mutation carriers is high. Furthermore, it showed that screening seems to detect clinically significant PCa. The findings of this study support the rationale for continued screening in such "high-risk" men [132].

## Future Perspectives

With the recent exponential increase in the development and improvement of techniques involving proteomics, there has been increased optimism in the prospect of finding clinically relevant candidate genes, gene clusters, and signaling pathways. This would potentially lead to better diagnostic and/or more specific targeted therapeutic plans in the management of sufferers of PCa [133].

The current ability to tally and compare genome-wide expression profiles in tissue samples could potentially shed light on the molecular pathology toward PCa detection and monitoring of disease progression and/or recurrence. Early gene expression signature studies were hindered by the inherent limitations of bioinformatic tools. It is anticipated that the validity of molecular signatures of PCa will ultimately be proven by cross-validation on novel datasets and direct coupling of these to prospective and translational studies [134]. Sun et al., in an attempt to predict PCa recurrence based on molecular signatures, conducted a computational analysis of gene expression profile data obtained from 79 cases. Of these, 39 were classified as having disease recurrence. At the 90 % sensitivity level, a novel-derived prognostic genetic signature achieved 85 % specificity. The results were compared to a clinically validated postoperative nomogram. The study was purported to be the first reported genetic signature to outperform a clinically used postoperative nomogram. They demonstrated the feasibility of utilizing gene expression information for potential PCa prognosis [135].

PCa inheritance following a simple Mendelian pattern may be identified in the families of probands with early-onset cases. Currently, the only clinically applicable measure to try to reduce PCa mortality in families with hereditary disease is screening, which aims to diagnose the disease when it is still at a curable stage. The precise mechanism of how gene mutations contribute to an increased susceptibility for PCa remains elusive, but the finding of germline mutations in the *BRCA2*, *CHEK2*, and *NBS1* genes suggest that a proportion may occur due to mutations in the DNA repair pathway. This has ramifications on treatment of such individuals with DNA-damaging agents. It is most likely that the cause of the majority of PCa cases will be multifactorial and will involve environmental and genetic factors. The recent exponential advances in understanding the clinical genetics of PCa offer great optimism toward optimizing the management of PCa. From a clinical genetics point of view, this could usher with it a new paradigm in the way we manage PCa.

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# Gene Expression Profiling and Somatic Genome Changes

12

Michael Ittmann

## Introduction

Prostate cancer is the most common visceral malignancy in US men and the second leading cause of cancer deaths. It is estimated that in 2010 more than 215,000 men will be diagnosed with prostate cancer and almost 32,000 will die of this disease. Prostate cancer is extremely heterogeneous in its clinical behavior, ranging from indolent disease to aggressive metastatic cancer with rapid mortality. Over the last 20 years, there have been intensive efforts to elucidate the underlying genetic and epigenetic alterations and associated gene expression changes that lead to prostate cancer. The goal of these studies has been to understand the pathogenesis of prostate cancer, identify therapeutic targets, and to better guide treatment of this disease. Over this timeframe, there have been tremendous advances in our understanding of the molecular basis of prostate cancer, facilitated by continuous improvements in technology and bioinformatics. This chapter will focus on somatic genomic changes and high-throughput gene expression analysis, and, as will be shown below, these topics are intimately related.

## Copy Number Alterations in Prostate Cancer

The study of copy number alterations has played an important role in understanding the pathogenesis of prostate cancer. The initial impetus for such studies was the paradigm that tumor suppressor genes may be inactivated by somatic genomic changes in two ways. In some cases there may be homozygous deletion of both alleles or alternatively, loss of one allele with mutation of the remaining allele. While this has proven to be true in some cases, there is often loss of a single allele without homozygous deletion or mutation of the retained allele, and this has led to the realization that at times loss of even a single allele may be sufficient to promote tumor initiation and/or progression by decreasing expression of the tumor suppressor, which is known as haploinsufficiency [1]. In contrast oncogenes may be overexpressed by amplification. As will be described below, while there are amplifications within the genome of prostate cancers, they are less common than genomic losses, but they are associated with aggressive disease.

Initial studies of copy number alterations were initiated in the early 1990s restriction fragment length polymorphisms and microsatellite polymorphisms. While these techniques have relatively low resolution compared to current technologies, they were quite successful in identifying a number of recurrent copy number alterations in prostate cancer, for example, loss of 8p21 and 13q14 [2]. Comparison of copy number alterations in primary tumors versus metastatic or recurrent tumors in these early studies revealed that copy number alterations are much more frequent in the latter [3].

Compared to these relatively low-resolution techniques, high-density mapping of genetic losses and gains can reveal additional tumor suppressor or oncogene loci. Therefore, high-throughput methods such as comparative genomic hybridization (CGH) arrays and single-nucleotide polymorphism (SNP) arrays have been the method of choice for analysis of copy number alterations in prostate cancer as they have become available due to their high resolution and high throughput. A large number of prostate cancers have been analyzed using CGH, and these studies have identified consistent areas of chromosomal loss and gain [4–10]. SNPs occur at more than two million sites in the genome, allowing high-resolution whole genome allelotyping with accurate copy number measurements. Several studies of allelic gain and loss in prostate cancer using SNP arrays have been reported, which have shown multiple areas of gain and loss, that are broadly similar to many of the common areas detected with array CGH, although unique areas were also identified

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**Table 12.1** Regions of high-frequency genomic loss and gain in prostate cancer

| Genomic region | Putative target |
|---|---|
| *Loss* | |
| 2q21–22 | |
| 5q13–15 | |
| 6q14–21 | |
| 8p21–23 | NKX3.1 |
| 10q23–25 | PTEN |
| 12p13 | CDKN1B (p27) |
| 13q14–22 | RB1 and BRCA2 loci |
| 16q13–24 | |
| 17p31.1 | p53 |
| 18q12–23 | |
| 21q21 | TMPRSS2/ERG fusion |
| *Gains* | |
| 3q23–26 | |
| 5p13 | RICTOR |
| 7 | EZH2 |
| 8q13 | TIF2 |
| 8q21–24 | MYC |
| 17q24–25 | |
| Xq11–21 | Androgen receptor |

in these studies as well, perhaps reflecting the higher resolution of later-generation SNP arrays [11–15]. Table 12.1 summarizes regions of high-frequency loss or gain in prostate cancer based on CGH and SNP array studies.

As seen on Table 12.1, putative targets of the losses and gains have been identified in many cases, and many have been validated as being biologically important in prostate cancer. For example, the site of PTEN locus was identified as being lost in prostate cancer prior to the identification of this gene [16]. The PTEN tumor suppressor gene, which encodes a lipid phosphatase that negatively regulates the PI3-kinase/AKT pathway, was subsequently identified in this region, and at least one copy of PTEN is lost in approximately 30 % of prostate cancers [17–22]. Homozygous loss of PTEN has been demonstrated in a subset of prostate cancers [20] as well as mutation and loss of the second allele in PTEN. Knockout mice with homozygous prostate-specific deletion of PTEN develop early onset PCa with metastases [23, 24]. However, in human prostate cancers, in the majority of cases, only a single allele is lost without mutation. Subsequent studies have shown in mouse models with other oncogenic events that loss of PTEN is haploinsufficient to promote cancer initiation and/or progression [1]. PI3- kinase is activated by growth factor receptors causing production of second messenger phospholipids that bind AKT to the plasma membrane and facilitate its phosphorylation by PDK1(Thr308) and mTORC2 (S473), leading to activation of AKT kinase [25]. AKT phosphorylates numerous intracellular proteins that can promote cancer initiation and progression by enhancing cell survival, cell growth and proliferation, angiogenesis, invasion, and metastasis [17]. High levels of phosphorylated AKT (Ser 473) are present in prostate cancer, and this is an independent predictor of biochemical recurrence following radical prostatectomy [26, 27]. It is now widely accepted that activation of the PI3-K/AKT pathway via a number of processes [28] plays a central role in the pathogenesis of prostate cancer [17], and numerous therapies targeting this pathway are currently under preclinical and clinical development for treating prostate cancer. These studies over the last 15 years are strong validation of the concept that studies of copy number alterations can provide critical insights into the pathogenesis of prostate cancer.

It should be noted however that in many cases the target of specific losses has not been clearly identified although candidate genes have been proposed. Even for strong candidate genes, such as c-MYC on 8q24, there is some controversy as to whether this is the only target for this common amplification [29]. It is likely that in some cases multiple genes are affected by loss and amplification, and though one gene may be a dominant driver, other genes may contribute to the phenotype.

One approach to better understanding the genomic alterations in prostate cancer is to carry out cluster analysis to understand whether there are specific patterns of loss and gain that are associated with each other and/or clinical outcome. Lapointe et al. [7] carried out CGH analysis of 55 primary tumors and 9 metastatic lesions and performed cluster analysis on the resulting genomic profiles. This highlighted several distinct groups including a set of cancers with minimal genomic alterations, a group with loss of 6q15, a group with loss of 8p21 and 13q14, as well as a group with 8q24 amplification. Analysis of lymph node metastases revealed much more widespread copy number alterations (consistent with prior results) with more frequent amplifications, particularly on 8q and chromosome 7 as well as other loci and frequent losses including the PTEN and p53 loci. Our group has analyzed primary tumors from 20 African American men using SNP arrays [15]. We carried out hierarchical clustering of our cohort and the entire cohort analyzed by LaPointe et al. (including two African Americans). Interestingly, the majority of African American cancers clustered in two major subgroups. One subgroup consisted aggressive cancers and was characterized by loss of 8p and gain of 8q. The more aggressive Caucasian cancers clustered with this group including a number of the metastatic lesions. The second major subgroup of African American cancers was enriched with less aggressive cancers. Notable features of cancers in this subgroup are loss of 6q and infrequent loss of 13q. These findings indicate that African Americans have specific patterns of copy number alterations that differ from Caucasian patients. Of note, on average, the African American patients had copy number alterations in primary tumors that more closely resembled metastatic lesions in

Caucasian patients when compared to primary tumors of Caucasian patients at an equivalent clinical stage, which may in part account for the higher mortality from prostate cancer in African Americans. Rose et al. [10] compared prostate cancers from African Americans and Caucasians by CGH and also found widespread differences in patterns of loss and gain between these two racial groups. Recent studies of prostate cancers of men in China reveal distinct patterns gain and loss that differ from both African American and Caucasian men [30]. Taylor et al. [8] have recently reported results of the largest current integrated genomic analysis of prostate cancer including 157 primary tumors and 37 metastases analyzed by CGH. They identified a total of six clusters based on cluster analysis of their CGH data. One cluster had minimal copy number alterations as described above and was associated with extremely good outcome. Three other clusters were defined by loss on 6q, 13q, and 8p, respectively. Two clusters were identified which contained the majority of metastatic lesions as well as some primary cancers. These clusters were characterized by either widespread genomic losses and gains or amplification of 8q24 or chromosome 7. Of note, the primary tumors in different clusters had significant differences in the probability of biochemical recurrence following radical prostatectomy. Overall the patterns in these studies are fairly consistent and indicate that patterns of chromosomal alterations have promise in identifying subgroups of cancers with different clinical aggressiveness and differ in prostate cancers from different racial groups. Given the relative stability of DNA even in paraffin-embedded tissues, this finding holds promise for development of new biomarkers of outcome based on DNA copy number analysis.

## Clonal Point Mutations

Most studies to date have shown only infrequent clonal point mutations in clinically localized prostate cancer which usually involve tumor suppressor genes (reviewed in [31] ). The most commonly clonally mutated gene, the transcription factor ATBF1, is mutated in approximately 25 % of localized PCas [32], and other tumor suppressors are mutated at significantly lower rates. For example, work from our group and many others have shown that point mutations in the tumor suppressor PTEN are rare in clinically localized PCa [20] but are present in approximately 30 % patients with of metastatic prostate cancer lesions at autopsy [22]. Similarly, clonal p53 mutations are rare in clinically localized PCa [33] but more common in advanced disease [31]. In most cases mutations have been analyzed using sequencing of isolated tumor RNAs or DNAs. Using such techniques, the mutation must be present in at least 50 % of tumor cells to be reliably detected even in highly enriched tumor samples. Clonal androgen receptor mutations are fairly common in castrate-resistant prostate cancer and appear to be selected for as a mechanism by which PCa cells can survive in low androgen environment [31]. Interestingly, it has been shown that androgen receptor mutations are rare in primary prostate cancer but were present in almost 30 % of pelvic lymph node metastases from men not treated with hormone ablation therapies [34]. This chapter also discusses a number of methodological pitfalls that can lead to overestimation of mutation frequency. Activating clonal mutations in oncogenes, such as RAS, are unusual in prostate cancer in US men but are present in approximately 25 % of Japanese prostate cancers [31]. Taylor et al. [8] have recently reported high-throughput sequencing of the exons of 138 selected genes from 75 primary and 5 metastatic lesions and found that clonal mutations were relatively rare with the androgen receptor in metastatic lesions being the most commonly mutated gene. This is in contrast to the more frequent mutation observed in other common human cancers such as colon and lung cancer. Thus, available data indicate that clonal point mutations are rare in clinically localized prostate cancer, and, while more common in advanced cancer, they are not common in comparison to other epithelial malignancies.

## Expression Array Analysis of Prostate Cancer

A major technical advance in our ability to understand the molecular changes underlying the pathogenesis of cancer is the development of high-throughput technologies such as expression microarray analysis. In expression microarray analysis, thousands of cDNAs or oligonucleotides corresponding to individual genes are spotted on slides. RNAs from two different sources are then labeled with nucleotides-bearing molecules that are fluorescent at different wavelengths, and both labeled RNAs are then hybridized to the array slide. The relative gene expression is then determined by the ratios of the intensity of fluorescence at the two wavelengths in each individual array element. Thus, changes in gene expression associated with two different conditions, that is, normal versus cancer, can be rapidly assessed in thousands of genes simultaneously.

This new technology has been applied to prostate cancer by many groups over the last 10 years. Many of these studies have compared gene expression in prostate cancer tissues to benign prostatic tissues [35–40]. A large number of changes in gene expression in prostate cancer have been identified using this approach, and markers of potential diagnostic utility as well as genes that may be involved in the etiology of prostate cancer have been identified. A recent statistical meta-analysis of these studies has concluded that the results of these studies were significantly similar in the genes identified as up- and down-regulated in prostate cancer despite differences in methodology employed [41], indicating the robustness of this technique.

## Discovery of Genes Involved in the Pathogenesis of Prostate Cancer

Expression array analysis has played an important role in identifying novel genes that play a role in prostate cancer pathogenesis. In 2005, the Chinnaiyan group, using a bioinformatics analysis of expression microarray data, discovered the existence of recurrent gene fusions of ETS transcription factors in prostate cancer [42]. In most cases these fusions involved the androgen-regulated TMPRSS2 gene. The discovery of recurrent fusion of the androgen-regulated TMPRSS2 gene to the ETS transcription factors, most commonly the ERG gene, was a paradigm-shifting discovery since it indicated that a single common pathway is altered in most human prostate cancers. The TMPRSS2/ERG (T/E) fusion gene occurs in approximately 50 % of prostate cancers [43–49]. The T/E gene fusion arises by fusion of the promoter and 5′ exons of the TMPRSS2 gene on chromosome 21q22.3 with the coding sequences of the ERG gene at 21q22.2 [50, 51]. Experiments in prostate cancer cells containing the T/E fusion indicate that the TMPRSS2 promoter can lead to the overexpression of ERG in PCa cells in response to androgens [42]. The almost universal presence of androgen receptor in prostate cancer cells results in the constitutive high-level expression of ERG fusion transcripts in the cancers containing this fusion gene. The extremely high prevalence of the T/E gene fusion implies that ERG plays a critical role in the pathogenesis of many prostate cancers. Other ETS transcription factors are fusion targets at a lower rate but collectively are probably altered in 5–10 % of prostate cancers. On the other hand, analysis of expression microarray data has identified SPINK1 as a gene that is overexpressed in about 10 % of prostate cancers and is an independent predictor of recurrence [52]. Expression of this gene is almost never found in fusion gene expressing cancer and represents a distinct type of prostate cancer.

Several groups, including our own, have examined the biological effects of the T/E fusion gene in vitro in immortalized prostate epithelial cells, VCaP prostate cancer cells, the only prostate cancer cell line that expresses the T/E fusion gene, and in orthotopic and transgenic mouse models. These studies have consistently shown that the T/E fusion gene can promote prostate cancer invasion and to a lesser extent proliferation and decrease differentiation via increased expression of urokinase plasminogen activator (uPA), matrix metalloproteinases (MMP3 and MMP9), and c-MYC [53–55]. More recent studies have also identified activation of the Wnt [56] and NF-κB pathway [57] by the fusion gene. It should be noted that the T/E fusion gene protein has significant biological effects on prostatic epithelial cells but is not able to fully transform them. Importantly, studies by our group have shown that knockdown of expression of the T/E fusion gene decreases primary tumor growth in a VCaP orthotropic mouse model, in which VCaP cells are injected directly into the prostate of immunodeficient mice [53]. Such studies provide the rationale for developing novel therapeutic approach targeting T/E fusion proteins in prostate cancer. Several groups have generated transgenic mice with expression of ERG in the prostate using the androgen-driven ARR2-Pb promoter. Both Tomlins et al. [54] and Klezovitch et al. [58] reported the development of mouse prostatic intraepithelial neoplasia (mPIN) in these mice. Both King et al. [59] and Carver et al. [60] reported that loss of PTEN in conjunction with expression of ERG accelerated development of mPIN, and Carver et al. found fully developed prostate cancer in this context. Activated AKT could also accelerate the development of mPIN in transgenic mice expressing the fusion gene [59]. Using a prostate regeneration system in which genetically engineered prostate stem cells are grown in immunodeficient mice with urogenital sinus mesenchyme under the kidney capsule the Witte group has shown that when ERG was co-expressed with activated AKT or with an shRNA-targeting PTEN, carcinoma develops [61]. These observations support the concept that AKT activation can synergize with fusion gene expression in promoting prostate cancer progression. Expression of ERG rapidly declines in response to removal of androgen in vitro and castration in vivo, and T/E fusion expression was fully restored in castrate-resistant prostate cancer, which indicates that reactivation of T/E fusion expression may contribute to androgen-independent tumor progression [62].

Another major discovery made using expression microarray analysis was the identification of EZH2, a polycomb protein, as an important player in the etiology of aggressive prostate cancer [63]. Recent studies have shown that the T/E fusion gene, the androgen receptor, and EZH2 may form an interacting network that plays an important role in the pathogenesis of prostate cancers with the fusion gene [64].

## Discovery of Diagnostic Biomarkers

In the clinical arena one major success of expression microarray analysis was the identification of alpha-methylacyl-CoA racemase as a gene that is significantly upregulated in prostate cancer [40]. Immunohistochemistry for this marker, usually in conjunction with basal cell specific markers such as high molecular weight cytokeratins and/or p63, is now a part of routine clinical practice. While there are limitations to this marker, including its expression in high-grade prostatic intraepithelial neoplasia and some benign mimics of prostate cancer, it can be extremely useful in the diagnosis of limited PCa in needle biopsies [65].

## Discovery of Novel Prognostic Biomarkers for Analysis by Immunohistochemistry

A number of studies have been performed to identify potential prognostic biomarkers in prostate cancer using expression microarrays. Dhanasekaran et al. [35] compared gene expression in 11 clinically localized and 7 metastatic prostate cancers to normal prostate tissues. These investigators found by cluster analysis that there were significant differences in gene expression between localized and metastatic prostate cancers, as well as many similarities, and both were significantly different than normal prostate. Two genes identified as upregulated in prostate cancer (Hepsin and Pim-1) at the RNA level were correlated with PSA recurrence in localized prostate cancer by using immunohistochemistry of tissue microarrays. As described above, this group also confirmed that tissue expression, as assessed by immunohistochemistry of tissue microarrays, of another gene identified in this analysis (*EZH2*) was correlated with PSA recurrence in localized prostate cancer [63]. Other immunohistochemical prognostic markers discovered by microarray analysis include MUC1 and AZGP1 [66]. In addition, SPINK1 (described above) is associated with aggressive disease [52]. The Rubin group has used a combined expression microarray and proteomic approach to define 12 proteins that as a panel can help predict recurrence following radical prostatectomy [67] and prostate cancer-specific death in a watchful waiting cohort [68]. Thus, expression microarray analysis can identify differentially regulated genes that can be used as prognostic markers on immunohistochemistry.

## Gene Signatures to Predict Prognosis in Prostate Cancer

There have been a number of studies addressing gene expression signatures to predict prostate cancer recurrence, which have employed a wide variety of statistical and laboratory methods. Singh et al. [69] studied expression of 12,600 genes in 21 prostate cancers for which recurrence data was available (8 recurrent, 13 nonrecurrent). Based on this limited set of samples, they were able to define a set of five genes whose expression levels were able to predict recurrence with 90 % accuracy in their samples. These samples included many cases with Gleason scores of 8–10, and such samples were overrepresented in the recurrent group, so it is unclear if their model would work robustly in patients with intermediate Gleason scores. Glinsky et al. [70] reanalyzed this same data set and, by correlation with expression analysis in prostate cancer xenografts, developed three alternative five gene prognosis signatures that could correctly classify the arrays into the appropriate recurrence categories for up to 95 % of cases. However, these studies did not specifically distinguish between early and late recurrence, which is an important distinction clinically since men with early PSA recurrence are significantly more likely to develop metastatic disease. Yu and colleagues [71] developed a 70-gene model by comparing expression profiles between 29 aggressive tumors (defined as cancer invasion into adjacent organs or seminal vesicles, metastases, or recurrence) versus 37 nonaggressive tumors lacking such features. Thus, this study did not look at recurrence specifically. Their 70-gene model was able to classify the original data set into the appropriate category in 86 % of the cases. Lapointe et al. [66] identified a set of 23 genes whose expression levels were either positively or negatively associated with early recurrence in a set of seven prostate cancers with early recurrence and 22 nonrecurrent tumors, although their false discovery rate (FDR) was quite high (16 %), perhaps due to limited clinical follow-up.

A major issue with such gene expression signature approaches is the difficulty in translating them into clinical practice. While RNA extraction from formalin-fixed paraffin-embedded tissues is feasible, it may be difficult in routine clinical practice given limited amounts of cancer in many needle biopsies, variable post-procedure time to fixation in radical prostatectomies as well variable fixation times and other postfixation variables. Despite these difficulties, a 17-gene expression signature predictive of systemic progression and prostate cancer-specific death after PSA recurrence post-prostatectomy has been developed by Jenkins and his colleagues using paraffin-embedded tissues [72]. Kosari et al. [73] examined laser-captured cancer cells from paraffin-embedded tissues to identify genes associated with systemic progression. Whether these signatures and/or gene sets can be applied in other institutions with different clinical practice patterns will need to be determined.

Unfortunately, the gene expression signatures identified in these studies do not show significant overlap. These models are derived from a variety of sample sets, using different platforms (Affymetrix vs. spotted arrays) with a wide variation in the number and identity of genes analyzed, different clinical endpoints (recurrence, early recurrence, systemic progression, etc.), and different statistical approaches. In addition, some studies used laser-captured cells and others enriched tumors. It is clear that prostate cancer stroma contributes to the gene signatures in RNAs extracted from prostate cancer tissues [74, 75] so that different amounts of stroma in tissues and variability within stroma can also contribute to variable in gene signatures, and only a few studies have used laser-captured cancer cells. Thus, it is not surprising that there is little agreement among these gene sets. However, it is highly likely that the genes identified have some importance in determining recurrence following radical prostatectomy.

## Expression Microarrays and Prostate Cancer Classification

One approach that has been successfully applied to breast cancer [76] and non-Hodgkin's lymphoma [77] is to use cluster analysis of large-scale microarray data to classify tumors into categories that are biologically and prognostically relevant. Using this approach, Lapointe et al. [66] were able to identify three subtypes of prostate cancer based on an analysis of 61 primary and 9 metastatic prostate cancers. Subgroup 1 displayed a gene expression profile that was similar to normal prostate, and such tumors were less aggressive, while subgroups II and III were more likely to be higher stage and grade and to recur early. The same group later correlated gene expression patterns with patterns of specific copy number alterations using comparative genomic hybridization as described above. Subgroup 1 was characterized by loss of 5q21 and 6q15. Subgroup 2 was characterized by loss of 8p21 and the presence of the T/E fusion gene. Subgroup 3 showed more diffuse losses and gains at loci similar to Subgroups 1 and 2 but without the distinct features seen in these two groups. To date, there is not a widely accepted molecular classification based on either gene profiling or copy number alterations (see above), but current data indicates that such approaches may be fruitful if combined with other markers such as the presence of the TMPRSS2/ERG fusion gene.

## Alternative Spicing in Prostate Cancer

It is well known that the majority of human genes undergo alternative splicing and that such alternative splicing may have significant impact on cellular biology. Numerous examples of individual genes that are differentially alternatively spliced in prostate cancer have been reported that affect the biology of tumor cells. For example, our group has reported extensive alternative splicing of the T/E fusion gene that is associated with differences in clinical outcome, cellular proliferation and invasion, and signal transduction pathway activation [44, 53, 57]. Little is known about more global changes in alternative splicing in prostate cancer. Recent studies by Thorsen et al. [78] examined relatively small numbers of prostate, bladder, and colon cancers and matched normal tissues using Exon arrays that can detect differences in expression of individual exons, reflecting primarily changes in alternative splicing, although alternative promoter utilization and other posttranscriptional events could also impact results. These authors found more than 2,000 alternative splicing events that were differentially present in cancer and normal tissues. Such preferentially expressed alternatively spliced isoforms are potential diagnostic and prognostic biomarkers. Clearly, more work is needed to define the repertoire of prostate cancer-specific alternative splicing events and whether they will prove to be clinically useful.

## Integrated Analysis of Genomic and Expression Array Data

In order to integrate the large amount of data generated by high-throughput analysis as described above, it has proven useful to focus on alterations in specific signaling pathways in a global manner. This approach was first used analysis of the glioblastoma [79] and has been applied to prostate cancer by Taylor et al. [8]. Using this approach, they examined alterations in gene expression (up and down) and mutations in specific pathway proteins in both primary and metastatic tumors. For example, multiple genes in the PI3-kinase pathway are altered including PTEN (as discussed) above, INPP4 [28], PI3K regulatory subunits, PI3-kinase itself, and the PHLPP phosphatase. By examining all of these components in each tumor, it was determined that at least one component of this pathway was altered in 100 % of metastatic prostate cancers, providing a strong rationale for targeting this pathway in all such cancers. Other key pathways such as the retinoblastoma signaling pathway and the RAS/RAF/MAPK pathway were also altered at high frequency in prostate cancer. This roadmap of cancer signaling alterations will prove extremely useful in designing targeted therapies.

## High-Throughput Sequencing: The Future of Prostate Cancer Genomics

Next-generation sequencing is rapidly evolving with the cost of sequencing dropping precipitously. This technology when linked to appropriate informatics will revolutionize our ability to comprehensively analyze the prostate cancer genome. By sequencing highly enriched cancer DNA and matched normal DNA with high coverage (i.e., with large numbers of sequence reads per DNA region), one can detect both copy number alterations and mutations by comparing the number of reads and their sequence in cancer and normal DNA across the entire genome. Similarly, massive sequencing of RNAs (as cDNAs) can allow quantitative analysis of expression levels (based on numbers of reads) as well as alternative splicing. Expression analysis by sequencing with sufficient reads has an extremely broad dynamic range and is both more sensitive and linear than expression microarrays. In addition, microRNAs can also be sequenced, adding an additional dimension to genomic and expression analysis.

## Limitations to Genomic and Expression Microarray Analysis

As described above, prostate cancer genomics and expression array analysis have been extremely useful in defining many of the key alterations in prostate cancer. We have not discussed epigenomics, that is, modifications of DNA and its associated proteins. Epigenetic changes such as DNA methylation are widespread in prostate cancer and presumably act primarily via changing gene expression, so they should be reflected in expression microarrays. Similarly changes in microRNA expression are widespread in prostate cancer [80], but again such changes seem to primarily impact mRNA levels via alterations in RNA degradation. However, changes in translational efficiency, protein degradation, and posttranslational protein modifications are not reflected in genomic or expression microarray analysis. It is clear that such posttranscriptional and/or posttranslational changes can play an important role in cancer. While there are numerous examples cited above where expression microarrays have identified overexpressed proteins, it is clear that there is far less than 100 % correlation between protein and mRNA levels. Thus, a truly comprehensive understanding of the biology of prostate cancer awaits a high-throughput, accurate, and inexpensive proteomic analysis.

## Summary

Prostate cancer is the most common visceral malignancy in US men and the second leading cause of cancer deaths. Over the last 20 years, there have been intensive efforts to elucidate the underlying genetic and epigenetic alterations and associated gene expression changes that lead to prostate cancer. The goal of these studies has been to understand the pathogenesis of prostate cancer, identify therapeutic targets, and to better guide treatment of this disease. Over this timeframe, there have been tremendous advances in our understanding of the molecular basis of prostate cancer, facilitated by continuous improvements in technology and bioinformatics. Genomic studies of prostate cancer have identified multiple regions of chromosomal loss and gain and have played a key role in identifying and validating specific genes and pathways involved in prostate cancer pathogenesis. Recent high-throughput studies are beginning to identify specific patterns of chromosomal loss and gain that define different types of prostate cancer which differ in pathogenesis and clinical outcome. High-throughput gene expression microarray studies have also been critical in defining key genes in prostate cancer pathogenesis such as the TMPRSS2/ERG fusion gene and EZH2. In addition, these studies have identified a clinically useful diagnostic marker alpha-methylacyl-CoA racemase. Expression microarray studies have also been used to attempt to define specific subtypes of prostate cancer based on patterns of gene expression. Finally, there have been intensive efforts to use expression microarrays to develop better prognostic markers in prostate cancer by identifying single genes or panels of genes whose proteins can be analyzed by immunohistochemistry to aid in assessment of prognosis or by defining specific gene signatures associated with clinical outcome. As next-generation sequencing drops in price, it holds great promise as a means of rapidly and comprehensively defining genomic and gene expression changes in individual patients to help predict clinical outcome and define optimal therapy.

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# The Proteomic Approach to Prostate Cancer

13

Sashi S. Kommu and Emanuel Petricoin

## Introduction

Prostate adenocarcinoma (PCa) is currently the second most common cause of cancer death in men and is recognized as one of the most important medical problems facing the male population [1].

Despite major advances in the diagnosis and treatment of PCa, the clinical course of the disease is largely unpredictable. Hence, there is a major thrust, among many groups, toward the early detection of PCa and an optimal and tailored approach to the aggressive forms of the disease. This is complicated by the evolving need to distinguish the aggressive forms from the slower growing indolent tumors. Several studies correlate PCa's etiology to hereditary [2], dietary factors [3], exposure to toxic agents [4], and/or specific medications and inflammatory conditions [5–7]; however, one of the best-established risk factors is increasing age. Previous studies seem to indicate that prostate stem cells that give rise to secretory luminal and neuroendocrine cells could potentially be affected by age-related events such as genetic mutations and alterations in individual stromal-epithelial interactions or in the basement membrane/ECM composition. This in turn could lead to transformation of normal prostate progenitor/stem cells into cancer stem cells [8].

Whereas the incidence of PCa in men of age <50 rises significantly, the clinical course of the disease is poorly understood and hence difficult to predict. PCa can be a localized indolent disease with no impact on quality of life or life span or could significantly affect quality of life and/or lead to death despite treatment. There is hence an imminent and critical need for the early detection and stratification into aggressive and nonaggressive forms. The FDA, in the mid-1980s, approved prostate-specific antigen (PSA) testing for the detection of recurrent PCa and then for early detection. The preliminary diagnostic tests that are still practiced include PSA in conjunction with a digital rectal examination [9]. The combined use of PSA testing with digital rectal examination resulted in an observed decrease in the mortality rates from PCa and a significant increase in the reported incidence of PCa in the United States [10]. However, the continued and widespread use of this approach for screening and diagnosis is controversial [11]. The European Randomized Study of Screening for Prostate Cancer initiated in the early 1990s and ended in 2006 concluded that PSA-based screening reduced overall death rate from PCa by 20 % but is associated with a high risk of overdiagnosis [12]. PSA is a serine protease produced and secreted by prostatic epithelium and from the epithelium of periurethral glands, secreted from benign as well as cancerous cells of the prostate. It has been demonstrated to be largely a marker of prostate volume than of malignant conditions. It is established that serum PSA values correlate closely with both benign prostatic hyperplasia (BPH) and PCa [13, 14]. As observed during the Prostate Cancer Prevention Trial, 80 % of the biopsies taken in patients with PSA levels between 4 and 10 ng/ml were negative for malignancy [15]. Furthermore, Thompson et al. in their study, found that up to 15 % of patients with levels of PSA lower than 4 ng/ml had PCa and of these 14.9 % had a Gleason score of 7 or higher [16]. Candidate biomarkers for PCa under evaluation are itemized in the Early Detection Research Network (EDRN) report. The EDRN is a collaborative initiative of the National Cancer Institute (NCI), geared at coordinating the effort of multiple institutions and laboratories in cancer biomarker research. The prime aim is to accelerate the translation of evolving information about biomarkers into clinical applications.

Current tissue- and blood-based biomarkers under active investigation include the ETS-TMPRSS2 gene fusion product

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[17], the noncoding prostate-specific mRNA PCA3 overexpression in tumor cells, and the GSTP1 promoter methylation observed in PCa and high-grade prostatic intraepithelial neoplasia (HGPIN).

The level of expression of CD90 in prostate tissue and urine of PCa patients, loss of expression of CD10 [18], and autoantibodies against the metabolic enzyme N-methylacyl-coenzyme A racemase (AMACR) [19] are also evolving as potential markers. AMACR autoantibodies can be used for the detection of PCa with 72 % specificity and 62 % sensitivity. The early prostate cancer antigen (EPCA) has been recently found to detect patients with PCa with 94 % sensitivity and 92 % specificity [20]. The identification of optimal treatment stratification of patients with PCa remains a daunting challenge. Whereas some groups seem to suggest PSA screening could potentially save lives, PSA screening does not provide a definitive answer to the principal clinical questions as to whether the patient has a cancerous or benign disease. Furthermore, even following biopsy-proven PCa, tumor progression remains ill understood. Established treatment options of PCa currently used include radical prostatectomy, external beam radiotherapy, brachytherapy, and androgen deprivation therapy. Despite published long-term survival rates with each strata of treatment, there is still disease progression in a significant number of men following "definitive" treatment. Following radical prostatectomy, up to 35 % of patients could have biochemical recurrence. The identification of those men at high risk of recurrence could aid the uro-oncologist to design a targeted and signatured treatment plan for adjuvant therapy such as androgen depletion or chemotherapy [21]. Androgen deprivation therapy has been studied since 1940s [22], based on the observation of the dependence of PCa cells for growth and development on androgens, and is currently the therapy of choice for advanced and metastatic disease. Nevertheless, many side effects are associated with androgen deprivation therapy that should be taken into consideration when applied in those clinical settings in which no efficacy on overall survival has been demonstrated [23]. It is thought that clonal selection of androgen-independent PCa cells leads to a more aggressive disease [24]. A personalized diagnosis including the evaluation of risk and benefit for each possible therapy could improve treatment efficiency [25]. In a study of 695 men with T1-T2-b PCa who underwent either watchful waiting or radical prostatectomy, it was observed that while the risk of developing metastasis and death for PCa was lower in men undergoing radical prostatectomy, the overall survival and quality of life does not change significantly [26, 27].

The proteome is the entire set of proteins expressed by a genome, cell, tissue, or organism. More specifically, it is the set of expressed proteins in a given type of cell or an organism at a given time under defined conditions. Proteomics is the study of an organism's complete complement of proteins. Whereas tumors could potentially arise from single or multiple genetic defect(s), proteins are the structural and functional elements of cells. It is postulated that any gene mutation that confers a survival advantage to cells must be conferred to the cell at the level of the proteome. Many investigators are of the impression that the proteome may contain the most highly informative biomarkers for detection of aggressive PCa and patient-tailored therapy once the disease is positively detected. The current status of high-throughput proteomic technologies is that of a promising and evolving platform [28–36]. Proteomic analysis platforms now have the potential to elucidate, in a single experimental step, the abundance, expression, and activation state of hundreds of proteins in tissues and biological fluids. This potentially could offer an insight into the complex events, which underpin tumor development and progression. Herein, we discuss the current proteomic platforms being utilized for the molecular characterization and recently identified candidate biomarkers for detection, prognosis, and tailored therapy of PCa.

## Proteomic Technology in Prostate Cancer Biomarker Discovery

Novel evolving proteomic technologies (Fig. 13.1) now permit a high-throughput approach to the fields of biomarker discovery. To date, the most established proteomic approach is two-dimensional polyacrylamide gel electrophoresis (2D-PAGE), which was described by O'Farrell in 1974 [37]. This allows for the separation of complex mixtures of proteins in two dimensions according to an isoelectric point and molecular weight. During the 1990s, when mass spectrometry (MS) technology was incorporated into the realm of proteomics, 2D-PAGE was successfully coupled to downstream MS analysis for individual protein detection. It then became the tool of choice for the resolution of complex protein mixtures. This permitted the detection of differences in the proteome of clinical samples such that they could be stratified into "normal" and "diseased" tissue. Kuruma et al. analyzed PCa proteomes using two-dimensional gel electrophoresis coupled with mass spectrometry and demonstrated the potential to detect changes in PCa high molecular mass proteomes [38]. While 2D-PAGE methodology brought significant advances in the field of proteomics, it had several technological limitations largely due to the inability to selectively detect the most abundant soluble proteins. Many low and high molecular weight proteins, as well as extremely acidic or basic proteins, cannot be accurately focused. This severely limits the detection of cell surface receptor membrane proteins that are present and differentially expressed within normal, BPH, and PCa tissues [38].

Serum and urine are the preferred sources of biological material to identify stage-specific prostate biomarkers [39–43]. These fluids can be acquired by less invasive means and with little additional cost to accrue thus adding to the

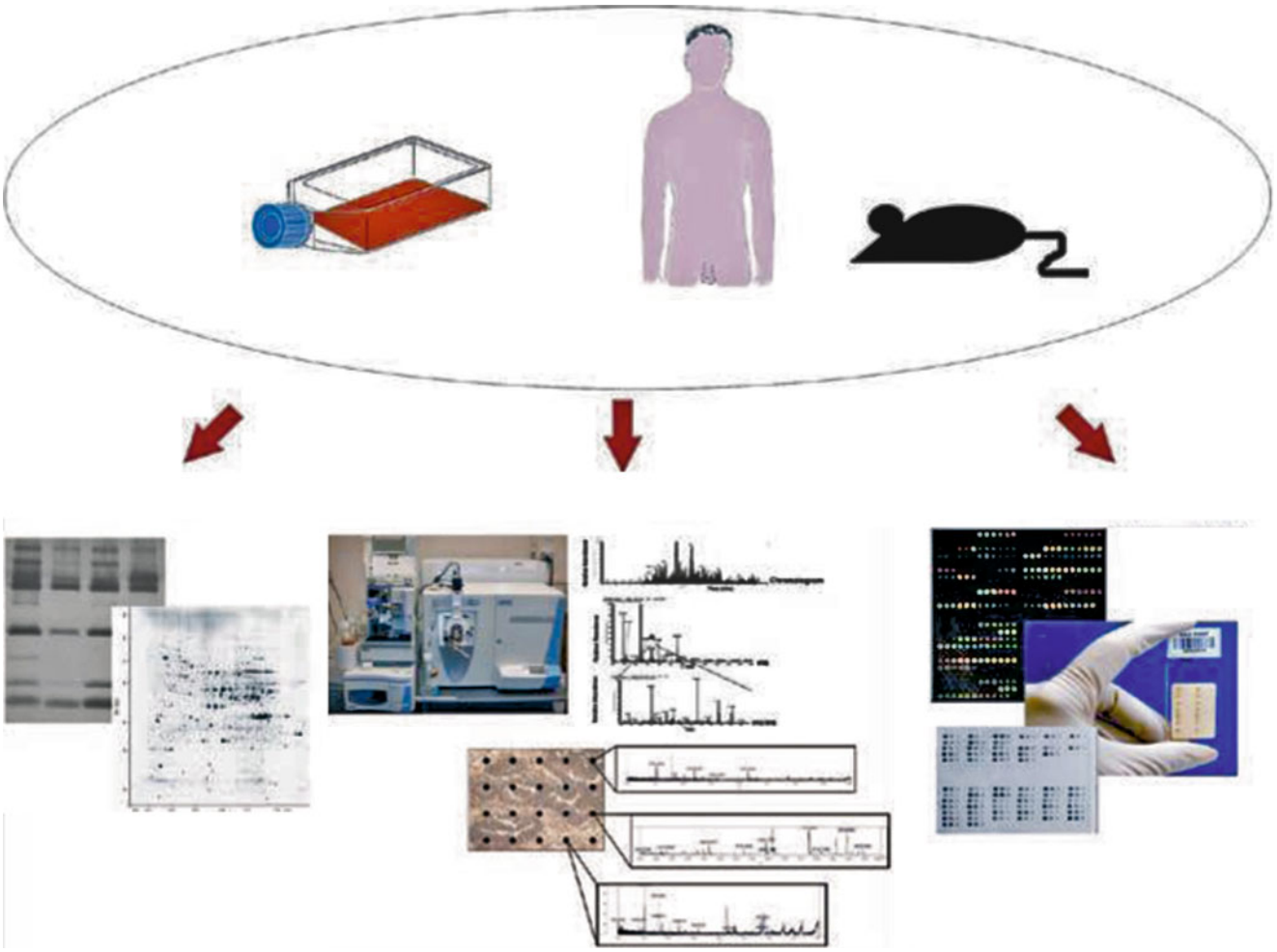

**Fig. 13.1** Proteomic evaluation of prostate cancer. Proteomic analysis can be done to explore the "proteome" of cell lines of prostatic origin, biological fluid, and/or tissue from human or animal models. The tools used include monodimensional gel electrophoresis or two-dimensional gel electrophoresis for protein separation and traditional mass spectrometry. More recently, techniques developed include mass spectrometry imaging (MSI) and reverse and forward protein arrays

potential ease of diagnosing and monitoring diseases such as PCa. Serum, in particular, acts as a large source of biological information. Blood perfuses organs and tissues collecting a "proteomic" record of physiopathological conditions. Intracellular enzymes and pathway components which are shed from various cell types, chemokines, growth factors, and other molecules involved in the cell-cell and cell-stroma interactions diffuse into the circulatory system [44]. The endothelial basement membrane aids proteomics by acting as a filter so that only small proteins, fragments, or parental molecules subjected to proteolytic cascades in the tissue microenvironment enter the bloodstream. Based on this theory, ideal biomarkers could be discovered in the potentially informative low molecular and low-abundant fractions of the blood proteome. A panel of such biomarkers, which could achieve high diagnostic sensitivity and specificity, could potentially be identified.

In 1998, SELDI, a new class of matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) was introduced. Serum SELDI-TOF profiling is based on on-chip retentate chromatography separation of proteins in microliter volumes, using various affinity surfaces to reduce complex protein mixtures to a set of proteins with common properties. Serum is deposited on commercially available array platforms. These are subjected to MALDI-TOF mass spectrometry to produce spectral protein mass profiles. SELDI-TOF technology initially generated a significant amount of optimism due to the seeming ability to simultaneously identify multiple protein changes with a high degree of sensitivity in a rapid high-throughput process. In fact, this technology was used to analyze complex protein mixtures from PCa in 1999 by Wright et al. [45]. PSA, prostate-specific peptide, prostate acid phosphatase, and prostate-specific membrane antigen were identified in cell lysates

and serum and seminal plasma. In 2002, Petricoin investigated the relationship between benign and malignant prostate disease diagnosed histopathologically and by serum proteome profiling [46]. The ability of a SELDI profile to discriminate PCa from benign prostate conditions in men with normal or elevated PSA levels was investigated. Parts of the genetic algorithms described by Holland and elements of cluster analysis methods by Kohonen were used to create initial bioinformatic algorithms. A signature was identified from a pilot sample collected from patients with benign prostatic conditions and PCa. The pattern of ions identified was applied to a blinded sample set of 266 sera. The algorithm was able to correctly predict the presence of PCa in 36 of 38 case subjects. Among men previously diagnosed by histopathologic analysis to have benign disease, 70 of 75 who were asymptomatic and had PSA levels less than 4 ng/ml were correctly classified as having benign disease. Furthermore, 10 of 16 men with high PSA levels (>10 ng/ml) and negative biopsy were found to have been classified correctly as having benign conditions. Although these results seemed promising, a more formal evaluation of SELDI-TOF was performed when Semmes, McLarren, and colleagues undertook a collaborative multicenter study coordinated by the National Cancer Institute/Early Detection Research Network. Their main aim was to validate the utility of serum SELDI profiling for the early detection of PCa [47–49]. They initially attempted to develop and validate a standard platform for processing serum in order to minimize potential error from human and mechanical factors. They then set out to decipher whether, following the process of instrument calibration and output standardization, the separate sites could achieve comparable correct classification rates when challenged with a set of previously characterized PCa and control samples. They concluded, in their study, that "between-laboratory" reproducibility of SELDI-TOF-MS serum profiling approaches that of "within-laboratory" reproducibility as determined by measuring discrete m/z peaks over time and across laboratories [49].

These findings were later followed by two further studies by McLerran regarding attempts to validate the specific SELDI-based biomarker ion fingerprint and development of potential algorithms for the diagnosis of PCa diagnosis. They concluded, based on the findings of the later studies, that the results from their preliminary studies were not generalizable and that SELDI-TOF MS-based protein expression profiling approach did not perform well enough to advance further [47–49]. The failure was attributed to earlier study samples bias that, upon removal, resulted in the technique's inability to discriminate cancer from noncancer samples. Additionally, differences in study design and limitations of proteins detected by SELDI applied to unfractionated serum were attributed to the inability of the validation study to identify men with PCa. It was suggested that the specific failure was not a failure of the "SELDI platform" but of the specific selected pattern. It soon became clear that major challenges existed including identification of a diagnostic ion fingerprint profile that is strictly dependent on a particular MS technology, specific capture chemistry, and precise sample handling and processing techniques. Thus, approaches that exploit patterns of unidentified ions were at inherent risk of being platform-dependent. Therefore, it was critical that the sequencing and identification of the peptides or proteins underpinning the diagnostic ions were identified [50]. It was postulated that the identified proteins could then be validated by any immunoassay platform. If, however, the antibody was not available, MS technology such as multiple reaction monitoring, immuno-MS, and high resolution MS profiling, which may not require a well-performing antibody, could be used.

It is an immense challenge to detect clinically significant biomarkers represented at a concentration less than 1 ng/ml in serum which also contains highly abundant proteins at a concentration of 30–50 mg/ml. Factoring in the fact that for SELDI-TOF analysis the starting volume of serum is 1–10 ul, only few pg of a biomarker of interest at a concentration of 1 ng/ml will be present in the sample. Assuming that the biomarker is fully retained on the chromatographic surface and ionized into the mass spectrometer MS or MS/MS detection, 320 amol of the biomarker would be available for the detection [51]. The detection of this amount of protein may be possible if directly injected into the mass spectrometer in its pure form. However, detection among other protein peak masses in a complex spectrum such as that obtained from a serum sample would be challenging even with the most sensitive mass spectrometers. The adoption of methods that could fractionate and remove high-abundance proteins from the serum prior to the "affinity chromatography step" is expected to increase the likelihood of detecting low-abundance biomarkers in serum by MS methods. Several preprocessing steps have been proposed [52–55] with depletion of high-abundant proteins being the major processing step utilized. The limitation in this case, however, is that low molecular weight proteins exist in solution bound to carrier proteins such as albumin. Thus, albumin depletion will eliminate many of the most important analytes from subsequent analysis [56]. In some studies, investigators have analyzed the serum free media of prostate cell lines as a source for biomarker discovery [57]. Medium from LNCaP (lymph node metastasis) cell was analyzed by SELDI-TOF in order to determine a profile of regulated proteins. Several ion peaks were differentially regulated depending upon the stimulation conditions. A significant androgen-regulated peak of 11.8 kDa that was specifically stimulated by androgen but not by estrogen or IL-6 was identified as beta-2 microglobulin (B2M). The expression of B2M was evaluated in multiple cell lines derived from

patients with PCa and in prostate acinar cells. Human BM2 was found in serum of mice bearing human PCa xenografts and significantly elevated in serum of patients with advanced PCa and in human expressed prostatic secretions [42] suggesting that B2M could be a potential marker of PCa progression. Sardana et al. aimed to investigate the "secretome" of prostate cell lines of different origin. They characterized the conditioned media from three different PCa human cell lines to identified secreted proteins that could serve as novel PCa biomarkers PC3 (bone metastasis), LNCaP, and 22Rv1 (localized to prostate). They worked on the premise that shed and secreted proteins will most likely be produced by the tumor in a measurable amount to be detected via a blood test and focused on this approach. Two-dimensional chromatography and tandem mass spectrometry were applied, and four candidates follistatin, chemokine 16, pentraxin 3, and spondin 2 were validated in serum from patients with or without PCa [58].

A novel approach to proteomic-based biomarker discovery for circulating markers, especially for PCa, is to use the immune systems' "signature" of information. Investigators are currently looking for circulating autoantibodies that are preprogrammed to target tumoral antigens, as a natural "amplification" tool for the detection of low-abundance tumor biomarkers. The concept of creating overexpression or posttranductional modification of specific proteins in tumor cells to induce antibody generation toward tumor related antigens has been explored [59]. Taylor et al. exploited the humoral response of patients with benign prostatic hyperplasia versus clinical localized PCa to identify the profiles of candidate biomarkers. They utilized two-dimensional protein fractionation of localized and metastatic PCa tissue lysates and screened patient autoantibody response by protein microarray [60]. Approximately two thousand fractions were used to generate protein microarrays, probed with 34 sera, 18 from PCa patients and 16 from individuals with BPH. To help with identification of low-abundance proteins, serum samples from patients with PCa and those with BPH were fractionated using anion displacement liquid chromatofocusing chromatography. This separates proteins by a pH gradient and a positively charged column. Results showed improved resolution of proteins within a given preselected pH gradient when compared to the unfractionated samples. Several proteins that were differentially expressed in serum from patients with PCa were identified in the fractionated serum. Of note, from the proteins identified, squamous cell carcinoma antigen 1 (SCCA1), calgranulin B, and haptoglobin-related protein were present in the serum at levels below 1 mg/ml. This study demonstrated that the use of anion displacement liquid chromatofocusing chromatography might reduce the complexity of the serum proteome by separating proteins into distinct pH ranges and aid with the identification of low-abundance proteins [61].

## Hydrogel Nanoparticle Technology: A Novel Platform for Biomarker Discovery

The postulate that there could be information that is still untapped within the low molecular weight proteomic fraction of blood recently led to exploration of nanoparticle technology. The physiological malleability and high surface areas of nanoparticles render them good candidates for developing biomarker-harvesting platforms. It would be useful to tailor nanoparticle surfaces to selectively bind a subset of biomarkers thus collecting them for further evaluation using high-sensitivity proteomic tests. Nanoparticle technology has thus far mostly focused on imaging systems and drug delivery. Biomarker harvesting is an evolving nanoparticle technology [62]. Hydrogel nanoparticles have gained considerable attention in recent years due to their unique potential by combining the characteristics of a hydrogel system (e.g., hydrophilicity and extremely high water content) with a nanoparticle with favorable stability, uniformity, and chemical versatility [63, 64]. In 2008, Luchini et al. demonstrated that NIPAm (N-isopropylacrylamide) hydrogel nanoparticles could be used as a tool to collect low molecular weight candidate biomarkers in serum (Fig. 13.2). Using this technique, low-abundance molecular analytes such as serum proteins, peptides, and metabolites were captured, concentrated, and protected from enzymatic degradations thus preventing erroneous results, which are known to occur when the serum is processed at room temperature [65]. When the nanoparticle is in solution, the three-dimensional NIPAm network acts as a sieve, which traps small proteins and peptides, while the high molecular weight proteins such as carrier proteins and endogenous and exogenous proteases are excluded. The same group demonstrated that by introducing a charged "chemical bait" incorporated into the NIPAm, the affinity of the particles for the target analytes increased significantly. In a study using platelet-derived growth factor (PDGF) as a model of very low-abundant and highly labile clinical biomarker, PDGF was inserted into a solution of diluted serum at an undetectable concentration and mixed with NIPAm/AAc particles. The concentration of the PDGF eluted from the particles was noted to increase to within the levels needed for detection by ELISA and mass spectrometry. A number of rare and low molecular weight proteins were identified within the proteins captured by particles in the diluted serum thus illustrating the role of hydrogel nanoparticle technology [66]. Hydrogel nanoparticles can be produced in large quantity at low cost, are reproducible and uniform in size, and can be coupled with different chemical bait ligands with tailored affinity for a wide range of proteins. Urine is a potential source of diagnostic biomarkers for detection of diseases. However, proteomic evaluation of urine is challenging due to the very low concentration of diagnostic biomarkers (usually below the sensitivity of common immunoassays). Another challenge is the rapid degradation of

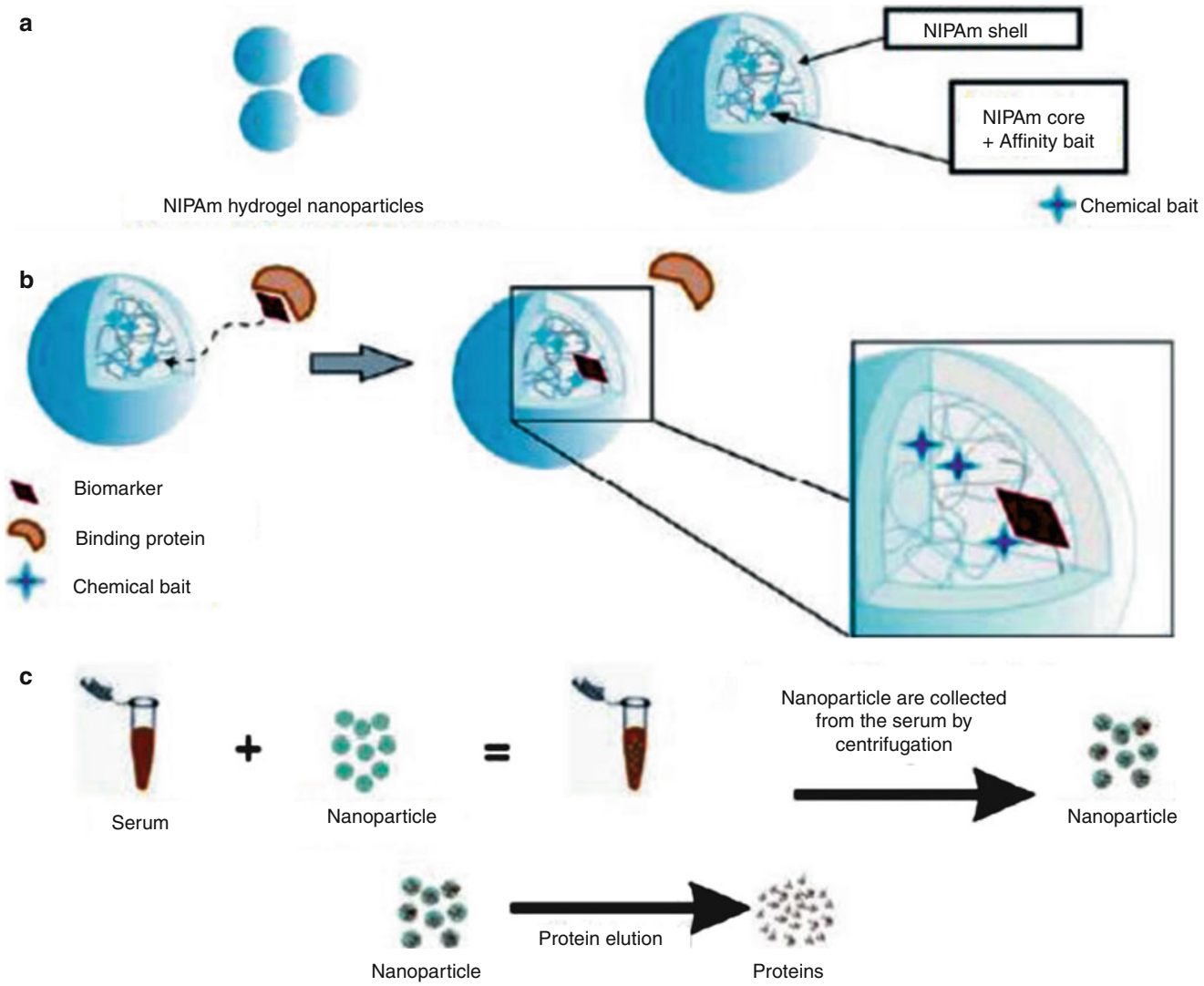


**Fig. 13.2** NIPAm hydrogel nanoparticles—a tool for the collection of low molecular weight potential biomarkers in serum. (**a**) Hydrogel nanoparticles composed of a NIPAm core and coupled to a chemical bait that has affinities for a wide range of proteins together with a shell. (**b**) Low molecular weight proteins in circulation bind to carrier protein attracted from the bait in the particle while the carrier-binding protein is excluded. (**c**) To capture the low-molecular fraction of the serum proteome, serum is incubated with nanoparticles and collected following centrifuge. The proteins are eluted from the particles and can be analyzed

urinary contents. Hydrogel nanoparticles functionalized with Cibacron Blue F3GA (CB) have been applied to address some of the challenges for urine biomarker measurement. Fredolini et al. demonstrated that use of Cibacron Blue F3GA-loaded hydrogel particles allowed detection of human growth hormone (hGH) (one of the most difficult to detect low-abundance hormones) in urine [67]. This was again ratified by studies by Sutkeviciute et al. [68]. Because of the capacity of these nanoparticles to concentrate the target protein to levels not attained by other methods coupled with the ability to exclude high-abundance nonspecific proteins, the sensitivity of the current biomarker measurement and discovery has improved significantly. Several groups are currently working on platforms using hydrogel particles in PCa biomarker discovery.

## Proteomic-Based Molecular Analysis of Prostate Cancer: Tumor Classification

It is known that PCa is primarily an androgen-dependent tumor [22, 69, 70] in which tumor regression occurs in patients in whom serum androgen concentrations are reduced by physical or chemical means. Androgen deprivation therapy and antiandrogens are the commonly utilized adjuncts in the management of advanced PCa. However, following an initial response to these modes of treatment, many cancers develop "androgen-independence" or "resistance." It is thought that this is due to clonal selection of resistant and more aggressive PCa cells. Novel therapeutic and molecularly directed agents are currently under evaluation to target

"androgen-independence" or "resistance." A better understanding of androgen receptor function and proteins that are involved in the pathways that regulate androgen-dependent/independent growth and metastasis is needed in order to help identify novel therapeutic targets. Some mechanisms identified thus far include overexpression of the androgen receptor, mutations in the receptors that permit activation by antiandrogens or other endogenous steroids, ligand-independent activation by growth-factor signaling pathways or loss of phosphatase and tensin homolog, changes in levels of androgen-receptor transcriptional cofactors (e.g., steroid receptor coactivator (SRC) 1, SRC2, CREB-binding protein, and filamin A), and upregulation of the enzymes involved in androgen biosynthesis. These have recently been shown to produce higher concentrations of androgen in tumors relative to blood [71]. Johansson et al. conducted proteomic analysis of the androgen-sensitive PCa cell line LNCaP-FGC and androgen-resistant line LNCaP. Proteins were separated by 2D-PAGE, and differentially expressed proteins were subsequently identified of which HSP60 (60 KDa heat shock protein) was found more abundant in LNCaP-r. This showed a correlation with the resistant phenotype [72]. To date, immunohistochemistry studies on prostate tissues showed a moderate to strong HSP60 staining of prostate epithelial cells without any noticeable correlation between Gleason grade and staining intensity. Furthermore, prostate tissues from androgen-ablated patients showed no obvious predictable staining patterns; i.e., some tumor cells were stained for HSP60 whereas others were largely unstained. The role of this protein in PCa progression and its value as biomarker remains unclear [73, 74]. Alaiya et al. showed alterations in the pattern of polypeptide expression in PCa that are similar to those observed in other carcinomas. Cells were collected from benign prostatic hyperplasia and PCa specimens and subjected to two-dimensional gel electrophoresis (2-DE). The resulting polypeptide patterns were analyzed with computer software (the PDQUEST). Malignant tumors were found to show significant increases in the level of expression of proliferating cell nuclear antigen (PCNA), calreticulin, HSP 90 and pHSP 60, oncoprotein 18(v), elongation factor 2, glutathione-S-transferase pi (GST-pi), superoxide dismutase, and triose phosphate isomerase. Furthermore, decreases in the levels of tropomyosin-1 and 2 and cytokeratin 18 were observed in PCa compared to prostate hyperplasias. The EST-database for prostate tumors [available from NCI (CGAP)] interrogated for the expression of the mRNAs corresponding to proteins identified in the study gels. Large differences in the relative expression of mRNAs and proteins were observed [75]. Rowland et al. worked on the theory that proteins that are responsive to androgen and antiandrogens could be involved in the development and progression of PCa, and the resultant failure of androgen-ablation therapy and that proteins represent potential diagnostic and therapeutic targets for improved management of PCa. They investigated the effect of androgen (R1881) and antiandrogen (bicalutamide) on the androgen-responsive prostate cancer LNCaP cell line using 2D-DIGE and found many proteins within metabolic processes, stress response, oxidative stress, and ER stress to be significantly changed. Moreover, proteins implicated in PI3K /Akt, p38 MAPK, JAK/STAT, and JNK/SAPK pathways were found to be altered. These could act as potential candidates for development as diagnostic/prognostic markers and drug targets [76].

Protein expression is largely influenced by the cellular microenvironment. Hence, the implementation of cellular enrichment and purification techniques is essential for proteomic-based molecular analysis and biomarker discovery. One such technique utilizes laser capture microdissection (LCM), which could potentially aid in collecting pure cell populations under direct microscopic visualization of the tissue [77, 78]. The problem with LCM is that it can be time-consuming process. However, it could be coupled with techniques that require small numbers of cells for molecular analysis such as some MS and protein microarray techniques. A protein microarray platform that is particularly well suited for clinical specimen analysis and multiplexed analyte profiling is the reverse-phase protein microarray (RPMA) [79–81] (Fig. 13.3). RPMA technology has been developed to minimize the analytical challenges of the sandwich and forward phase protein arrays (e.g., mismatch of sandwich antibody affinity, imprecision within and between analytes, and poor sensitivity). The platform has been designed to permit an objective, quantitative, and multiplexed analysis of specific forms of cellular proteins (e.g., phosphorylated, unphosphorylated, and cleaved) from a limited amount of starting sample, such as with a fine needle aspirate or laser capture microdissected (LCM) cellular material to secure populations of the specific target cells. The main advantage of RPMA is the ability to quantitatively measure hundreds of signaling proteins concomitantly from relatively few cells, thus providing a critical means of broad-scale cell signaling analysis directly from tissue samples, cell culture models, and animal tissues from preclinical studies. The RPMA platform (Fig. 13.3) immobilizes or creates a "frozen snapshot" of an individual test sample in each array spot. A given protein array may comprise up to hundreds of patient samples or cellular lysates. Each array is basically incubated with a single primary antibody, and a single analyte end point is tallied. With the RPMA technology, serial dilutions are printed of each sample and control or standard to maintain sample concentration. Each spot contains a "bait" zone measuring only a few hundred microns in diameter. A detection probe can be tagged and signal amplified independently from the immobilized analyte protein. Coupling the detection antibody with highly sensitive amplification systems can yield detection sensitivities to fewer than 1,000–5,000 molecules

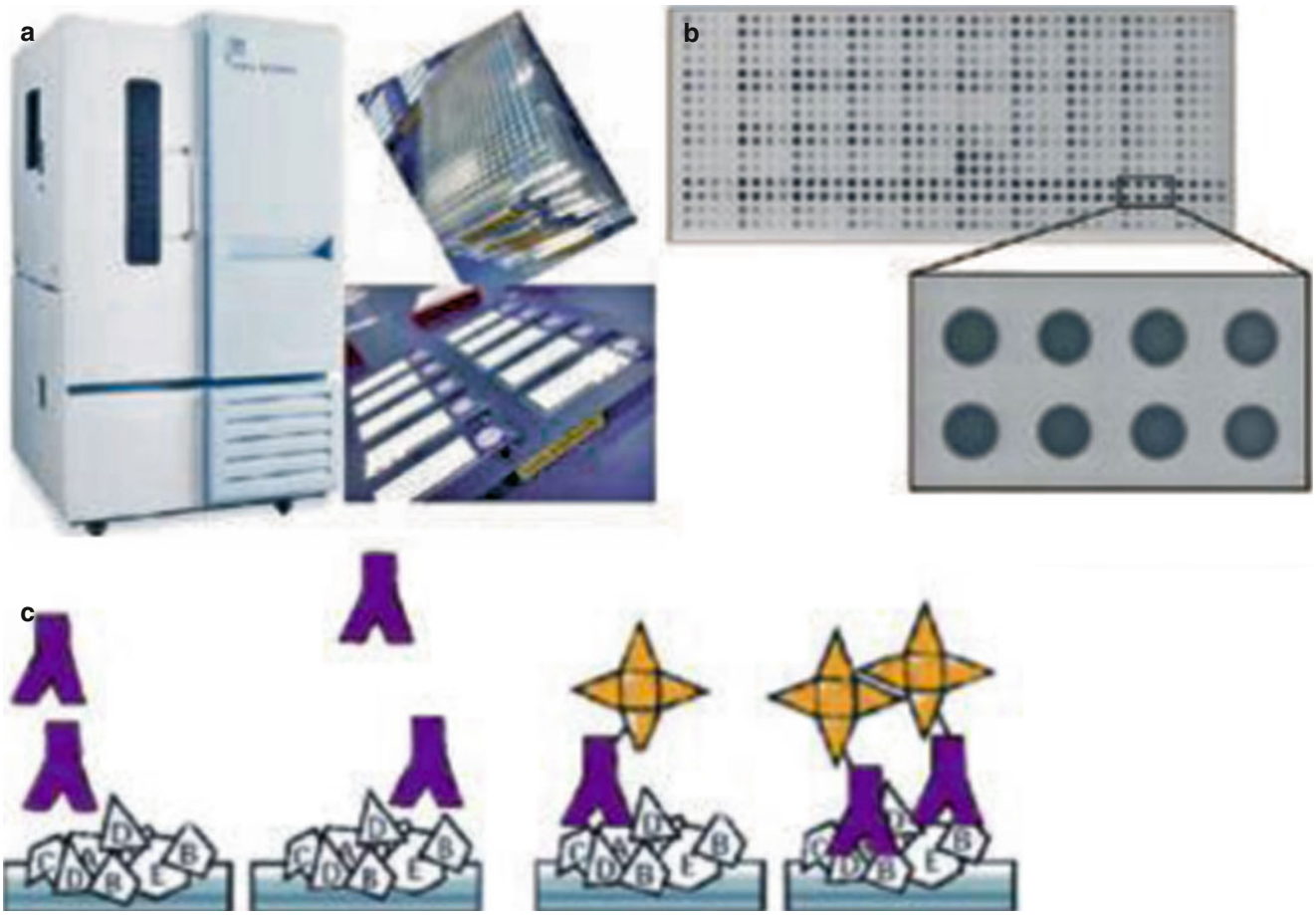


**Fig. 13.3** Reverse-phase protein microarray (RPPM). (**a**) Protein samples obtained from lysates of cells or body fluids are deposited in a nitrocellulose-coated slide by means of an arrayer. (**b**) Multiplicity of samples can be spotted in duplicate or triplicate on the same slide. (**c**) Each slide can be probed with an antibody that specifically binds to a target protein. A signal-amplification system increases the sensitivity. Signal-detection systems include fluorescent, chemiluminescent, or colorimetric methods

per spot [82]. This technology has been applied to evaluate the state of activation of proteins involved in prosurvival, mitogenic, and apoptotic signal pathways within prostate tissue samples. In a recent study, radical prostatectomy specimens were obtained from men with clinically localized PCa with Gleason Score ranging from [2+3=5] to [5+4=9] [80, 81]. For each patient, normal, cancerous, and stromal cells were microdissected, and the cell lysates analyzed by RPMA. An increase on AKT activation was observed in the transition from normal to tumor phenotype, while ERK kinase activation decreased. There was also an activation of GSK3 beta, a known substrate of AKT, indicating pathway network activation was taking place [80]. More recently, Grubb et al. used the same approach to evaluate variations in signaling pathways related to PCa progression [81]. Tissues from androgen-stimulated localized PCa, patients undergoing androgen deprivation therapy for recurrent local disease, and patients with metastatic cancer were profiled by RPMA of LCM procured cells and the activation state, and expression of 38 proteins was evaluated. Unsupervised clustering of the data revealed noticeable differences between stromal and benign epithelial cells compared to the malignant epithelial cells. The proteins Smac/Diablo and Bax, proteins implicated in apoptosis regulation, were more activated in stromal than in malignant cells while proteins involved in EGFR pathway (EGFR, cERBb2, MEK, ERK, and STAT3) were more activated in tumor cells than in stroma. Metastatic prostate epithelial cells from bone, liver, lung, and soft tissues sites were compared to malignant prostatic epithelium from the primary site. Phosphorylation of p38 and SAPK and JNK, all MAPK family members, along with STAT3 was found to be more highly phosphorylated in the malignant epithelial tissues with high Gleason scores. STAT3 is well known for its involvement in malignant transformation [81].

Most recently, there has been an exponential increase in the interest toward mass spectral imaging (MSI) directly from tissue due to the inherent potential for rapid profiling technology to provide clinically important information. Identification and visualization of protein signals directly on thin sections cut from fresh frozen tissue specimens could

combine the advantage of MS to discover protein expression changes to the spatial localization of protein(s) of specific interest in the tissue. Schwamborn et al. in 2007, described the application of MSI on tissue obtained from radical prostatectomy with a bid to identify MS peak patterns that can distinguish cancerous from noncancerous regions. They were able to do this with a sensitivity and specificity of 85 and 91 %, respectively [83]. Other peaks from this study were no different from other proteomic studies in which tissue lysate from normal or cancerous prostate was analyzed by SELDI. IMS analysis has potential clinical importance as it may support and/or enable computer-assisted clinical evaluation of tissue specimens. There are, however, a number of technical challenges. One of the challenges is in obtaining optimal sensitivity (only the top 1 % most abundant proteins are detectable). These limit MALDI-MSI from becoming a routine clinical laboratory technology at present [84, 85].

### Conclusions

The current shortcomings in the ability to distinguish indolent from aggressive forms of PCa and subsequent limitations in tailoring of optimal targeted treatment make clinical management difficult. The paradigm of "personalized or signatured" medicine, which includes proteomic technologies that could facilitate the discovery of new blood- and tissue-based biomarkers, would be particularly helpful in PCa. This is because current-evolving analyses in the proteome could allow the identification of the most aggressive and clinically "significant" cancers thus aiding in individualized and specialized treatment planning. In the past two decades, many types of proteomic technologies have been applied for potential discovery of putative biomarkers for PCa with the added aim of identifying prognostic biomarkers. In particular, MS methods and protein microarrays, which can characterize tissue and blood by high-throughput means, have great potential in translating research findings to clinical practice. It is envisioned, in the near future, that patients with the aggressive forms of PCa could be identified, through proteomic evaluation, at the earliest stages such that and these patients could be effectively treated with targeted chemoprevention techniques to stop the tumorigenic progression before full cellular transformation and invasion starts.

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# Epigenetic Changes in Prostate Cancer

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During the pathogenesis of prostate cancer, prostate cells acquire both genetic and epigenetic alterations [1]. Genetic defects have long been considered hallmarks of cancer, but because such changes tend to accumulate during cancer pathogenesis, i.e., they are essentially *irreversible*, only a fraction are likely to act as drivers of the malignant phenotype at any given time [2]. In contrast, epigenetic changes, which affect gene function rather than gene sequence, are potentially *reversible* and thus tend to be maintained only when contributing to cancer growth and progression. During prostatic carcinogenesis, epigenetic alterations can be detected in the earliest of cancer precursor lesions, in localized cancer lesions, and at lethal disease progression [3]. Furthermore, new technologies for genome-wide characterization of chromatin structure and function in normal and neoplastic prostate cells have revealed broad corruption of the regulation of gene function [4, 5]. How the myriad somatic epigenetic alterations collaborate with genetic accidents to create prostate cancer has not yet been fully elucidated. Nonetheless, improved understanding of the nature, extent, and functional consequences of epigenetic defects in prostate cancer appears poised not only to provide new insights into the causes of the disease, but also to yield new diagnostic tests for disease detection and risk stratification and new treatment approaches for disease control.

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## DNA, Chromatin, Regulatory RNA, and the Cancer Cell Epigenome

Normal cells with different specialized functions comprising different organs and tissues can be distinguished by patterns of gene expression. These gene function differences are a consequence of differences in chromatin organization, referred to as the *epigenome*. Epigenome states tend to be established during embryonic development and can be propagated through cell replication and division by virtue of distinct DNA and chromatin protein "marks." The key DNA mark is the 5-methyl modification of cytosine bases in self-complementary CpG sequences. More than 70 % of the CpG sequences in the human genome contain 5-methyl-cytosine [6]. The unmethylated CpGs typically cluster at or near the transcriptional regulatory regions of genes, producing chromatin permissive for transcription. When such CpG clusters, termed CpG islands, carry 5-methyl-cytosine, the resultant chromatin structure constitutes a barrier to loading of RNA polymerase, rendering the gene transcriptionally silenced. The 5-methyl-cytosine modification is created and maintained through mitosis by DNA methyltransferases (DNMTs) enzymes, which catalyze the transfer of a methyl group from *S*-adenosyl-methionine (SAM) to cytosine bases [7]. Studies of mice carrying disrupted genes encoding the various DNMTs have both underscored the vital function of the enzymes in the creation of somatic epigenome states during embryonic development and hinted that dysregulation of enzyme activity, resulting in either under- or overmethylation of the genome, might lead to cancer development [8, 9].

Histone proteins, which are present at near stoichiometric equivalence with DNA in the cell nucleus, bear most of the chromatin protein epigenome marks, present as posttranslational modifications which constitute a histone "code" [10]. Histones assemble genomic DNA into nucleosomes, the first order of DNA organization in eukaryotic cells. One of the most studied of the histone marks, the methylation of lysine-27 in histone H3 by polycomb complex enzymes, provides an instructive example [11]. Polycomb complexes act

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during development to ensure selective gene expression in differentiated cells, placing H3-K27 methylation marks at sites targeted for gene repression. In metastatic prostate cancers, a polycomb complex component, enhancer of zeste homolog 2 (EZH2), which possesses H3-K27 methyltransferase activity is overexpressed [12]. An analysis of the distribution of acquired abnormal H3K27 methylation marks in prostate cancer cells provides evidence for an epigenome state, which undermines androgen-regulated terminal differentiation in favor of activating embryonic stem cell pathways of gene expression [13]. Elucidating the interplay between enzymes which place and maintain DNA marks and histone marks may ultimately divulge the mystery of how the epigenome is corrupted during cancer development. Regions of the genome, which carry polycomb-associated chromatin marks seem to be disproportionately targeted for de novo DNA methylation, especially in the setting of chronic inflammatory states prone to spawn most solid organ cancers [14, 15]. Often, genes repressed by polycomb complexes can be maintained in a transcriptionally silenced state by DNA methylation changes at the gene promoter, even when the H3-K27 histone mark is lost [16].

The DNA methylation marks attract complexes of proteins containing 5-methyl-CpG-binding domain (MBD) proteins [17]. MBD proteins contain both amino acid motifs that mediate binding to DNA carrying 5-methyl-cytosine and transcriptional repression domains (TRDs) that allow recruitment of enzymes capable of remodeling chromatin structure and placing histone marks, leading to heterochromatin formation [18]. One of the MBD family proteins, MBD2, plays a significant role in somatic epigenome silencing in cancer cells, as siRNA knockdown of *MBD2* mRNA expression unleashes transcription from hypermethylated gene promoters in cancer cells in vitro, and disruption of *Mbd2* genes prevents intestinal tumorigenesis in $Apc^{Min/+}$ mice in vivo [19, 20]. The heterochromatin formed during somatic epigenetic gene silencing segregates apart from more active chromatin regions in the cancer cell nucleus. New insights into the organization and function of DNA in mammalian cell nuclei have been afforded by chromatic conformational capture technologies, capable of revealing high-order chromatin architecture at a DNA sequence level of resolution [21]. Two higher order structures merit consideration: *chromatin globules*, reflecting looping interactions between genes and regulatory elements along the length of chromosomes and *transcription hubs* (also called *transcription factories*), created by movement of activated genes to fixed sites for high-intensity transcription [22]. Steroid hormone receptor-induction of selective gene transcription is one pathway known to trigger both new looping interactions and migration of target genes to transcription hubs [23, 24]. The corruption of this higher order structure in cancer cells may underlie the oft-noted chromatin defects seen by cancer pathologists using routine cytopathology and histopathology stains.

In addition to chromatin regulation of gene transcription, microRNAs (miRs) provide additional epigenetic control of gene product expression. miRs are 20–24 nucleotide stem-loop RNAs that can bind to 7 nucleotide regions of mRNAs to promote degradation and/or prevent translation [25–27]. Synthesized from as many as 300–1,000 miR genes in the human genome by RNA polymerase II, primary miR transcripts are processed in the cell nucleus into 70 nucleotide stem-loop pre-miR precursors by a complex containing the RNase III endonuclease Drosha and its partner Pasha, exported into the cell cytoplasm by exportin 5 and Ran-GTP, and then further processed into miRs by a complex containing the RNase III endonuclease Dicer and its partner Loqacious. The processed miRs are then loaded into the RNA-induced silencing complex (RISC), composed of Dicer, a double-stranded RNA-binding protein (TRBP), and another nuclease named Argonaute2 (Ago2) [28]. By base pairing with a 7 nucleotide sequence in miRs, the miRs direct the RISC effector functions to specific mRNA targets. Computational analyses and transcriptome profiling studies have hinted that each miR may have as many as 200 target mRNAs and that the efficiency of mRNA degradation/repression may depend on the number of 7-nucleotide miR-binding sequences in the target mRNA, the level of miR expression, and/or the level of target mRNA expression. Altered expression of miR has been found to contribute to the pathogenesis of several different cancers, with both increased and decreased expression of specific miRs regulating the neoplastic phenotype. In one example, the *let-7* miR, which targets the mRNA products of the *RAS* oncogenes, exhibits decreased expression in lung cancers, leading to increased RAS protein levels [29]. In another example, *R-15a* and *R-16-1* miRs, which target the mRNA product of the anti-apoptotic *BCL2* gene, have been reported to be downregulated in chronic lymphocytic leukemia (CLL) cells which express high levels of BCL2 protein [30]. The mechanism(s) by which miRs are expressed at higher or lower levels in cancer cells have not been fully elucidated, though somatic genome and epigenome alterations, including deletions, mutations, DNA methylation changes, etc., have been suspected and/or reported [31–33].

MiRs are not the only RNA species that may play a regulatory role in gene function. Poliseno et al. have reported that pseudogenes, and other noncoding transcripts, might compete for miRs by acting as "sponges," thwarting the fine tuning of translation needed for the ordered behavior of somatic cells [34]. An example of this phenomenon is the noncoding pseudogene *PTENP1*, which when expressed physiologically upregulates *PTEN* mRNA and its translation by functioning as a decoy for miRs binding 3′-untranslated sequences in *PTEN*. Loss of *PTENP1* sequences commonly occurs in human cancers, leading to downregulation of *PTEN*; i.e., *PTENP1* can be considered a tumor suppressor which acts

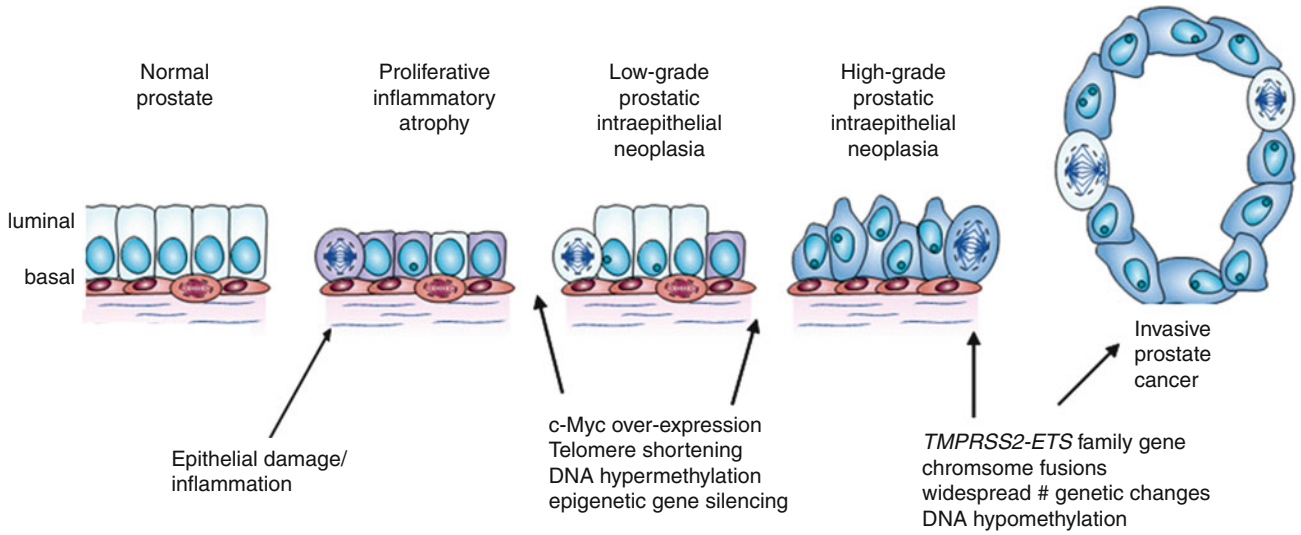


**Fig. 14.1** Epigenetic and genetic defects accumulate during prostatic carcinogenesis (Adapted from De Marzo et al. [42]. With permission)

via an epigenetic mechanism [34]. Long noncoding RNAs, which often contain antisense sequences to coding RNAs, can affect gene function, providing another epigenetic layer to gene and chromatin regulation [35–38]. These antisense RNA species attenuate gene transcription by interacting with RNA sequences polymerized from the sense strand of the gene promoter [39]. Other noncoding RNAs, such as *PCA3*, differentially expressed in prostate cancer cells versus normal cells, do not yet have a known function [40]. In a cancer cell containing a collection of genome and epigenome alterations, somatic corruption of the expression and function of the various regulatory RNAs will further undermine normal patterns of gene expression, permitting the disordered growth and defective differentiation that leads to malignant cancer progression.

## The Molecular Pathogenesis of Prostate Cancer

Like most solid organ cancers, prostate cancers arise in a milieu characterized by chronic or recurrent inflammation, likely in response to some sort of damage to the prostate epithelium [1, 41]. The source of the epithelial injury has not been established, though dietary carcinogens, infections, estrogens, ischemia, and urinary reflux have all been plausibly implicated as candidate carcinogens [42]. What is more clear is that epithelial damage and regeneration in the context of inflammation tends to give rise to distinct lesions termed proliferative inflammatory atrophy (PIA), which constitute the earliest precursors to prostate cancers [42, 43] (see Fig. 14.1). PIA lesions, on rare occasions, can progress to prostatic intraepithelial neoplasia (PIN) lesions and to invasive adenocarcinomas. The first consistent molecular events evident in PIA lesions giving rise to PIN tend to be overexpression of C-MYC, shortening of telomere sequences and epigenetic gene silencing [44–46]. The induction of *C-MYC*, which occurs by a mechanism not yet elucidated, directly modulates the chromatin structure in nuclei of the epithelial cells such that an increased number of enlarged nucleoli become readily apparent by routine histopathology evaluation [47]. C-MYC accomplishes this transformation of nuclear structure by activating the transcription of *FBL*, a gene encoding the nucleolar component fibrillarin and other target genes [47]. Telomere shortening, a common phenomenon seen in chronic tissue injury and/or accompanying cancer development in many organ sites, either reflects a history of cell proliferation in the absence of adequate telomere maintenance or some sort of direct damage to telomere sequences. Whether short telomeres directly affect cell phenotype, or merely present a risk for critical shortening, triggering genome damage responses and genetic instability has not been fully resolved. Like telomere shortening, the appearance of epigenetically silenced genes has been consistent finding in cancer precursor lesions and in inflamed tissues at many different organ sites at risk for cancer development [48]. Unlike telomere shortening, epigenetic gene silencing directly alters cell phenotype. Nonetheless, mechanism by inflammatory stress to epigenetic gene silencing has remained elusive, though in inflamed bowel tissues, at least 70 % of genes carrying new DNA methylation marks appeared to be targets of polycomb complex enzymes [49].

In normal prostate epithelial cells, the androgenic hormones testosterone and dihydrotestosterone, acting via the androgen receptor, promote terminal differentiation to a columnar cell that contributes secretions to the ejaculate. Prostate cancer cells co-opt this androgen signaling pathway to drive cell proliferation and survival. The cells appear to do so by virtue of chromosome deletions and translocations that

produce fusion transcripts between androgen-regulated genes, such as *TMPRSS2*, *KLK2*, *CANT1*, *SLC45A3*, *AX747630*, and putative oncogenes, including *ERG1* and other members of the ETS family of transcription factors [50]. As a consequence, antagonism of androgen signaling, through therapeutic reduction in androgen levels and/or the administration of antiandrogens, can attenuate prostate cancer progression [51]. The acquisition of the targeted gene deletions and translocations may itself be a consequence of dynamic chromatin organization and function. The androgen receptor is a ligand-dependent transcription factor capable of coordinating prostate cell differentiation by activating transcription of hundreds of genes or more. To do so, the receptor binds to regulatory regions of genes distributed throughout the prostate cell nucleus, dramatically changing its chromatin structure. For access to high intensity transcription, many such genes are moved by actin-myosin motors to transcription hubs [24]. In PIN lesions, the movement of these genes appears error-prone in that the recruitment of the DNA untangling enzyme topoisomerase IIβ (TOP2B) leads to DNA double strand breaks and illegitimate recombination via nonhomologous end-joining, producing *TMPRSS2-ERG1* and other translocations [23]. These genetic alterations, driven by changes in chromatin structure, may be what demarcate prostate cancers from PIN lesions. Nonetheless, why the initiation of transcription should generate more TOP2B-mediated double strand breaks in PIN cells than in normal prostate cells has not been determined. Perhaps, since c-MYC activation, telomere shortening, and epigenetic gene silencing precede the development of androgen-target gene translocations and fusions, one or more of these events may increase the vulnerability of the chromatin in PIN cells to dysfunction upon activating the androgen receptor-associated transcription program.

## Epigenome Changes in Prostate Cancer

Changes in DNA comprise the earliest somatic epigenome defects in human prostate cancer, resulting in gene silencing. Hypermethylation at the transcriptional regulatory region of *GSTP1*, encoding the π-class glutathione S-tranferase (GST), an enzyme responsible for detoxifying carcinogens and reactive oxygen species, has been the most intensively studied [3, 52]. As described above, the pathogenesis of prostate cancer may begin with the appearance of the precursor lesion PIA. *GSTP1* methylation changes, present in >90 % of prostate cancers, may define this initiation step, with *GSTP1* methylation evident in 5–10 % of PIA lesions [46, 53]. Progression of rare PIA lesions to PIN and prostate cancer may involve the acquisition of somatic genetic defects, such as *TMPRSS2*-ETS family translocations, which are thought to arise in PIN lesions or prostate cancers [23]. At the earliest stages of prostatic carcinogenesis, activation of *C-MYC* appears coincident with *GSTP1* silencing in rare PIA cells. This may reflect a tumor suppressor function of *GSTP1* in c-MYC-expressing cells: loss of π-class GST function renders prostate cells vulnerable to accelerated tumorigenesis in mice with forced *c-Myc* expression in the prostate. Also, loss of GSTP1 enzyme activity may render PIA, PIN, and prostate cancer cells sensitive to heterocyclic amine carcinogens, such as those found in overcooked meats, providing an explanation for the contribution of diet to prostate cancer development in epidemiology studies [54].

The mechanism by which *GSTP1* acquires de novo methylation changes at the gene promoter has not been established, though detection of *GSTP1* hypermethylation in PIA lesions implicates chronic or recurrent inflammation in a causative role for epigenetic gene silencing. Curiously, epithelial cells in all but a few PIA lesions tend to express very high levels of GSTP1 and other GSTs, likely exhibiting stress induction of GST gene transcription [43, 55, 56]. Whether an open chromatin state accompanying *GSTP1* activation might constitute a configuration that is particularly vulnerable to overmethylation of DNA at the gene promoter is not known. Nonetheless, inflammation has been associated with epigenetic gene silencing in gastritis, hepatitis, and inflammatory bowel disease [48]. The mechanism for this association has been proposed to involve: (1) dysfunction of DNMTs, (2) recruitment of DNMTs to selected regions of the genome carrying defined chromatin protein marks, or (3) modulation of chromatin protein marks at specific genes by stress or inflammatory signal transduction pathways (Nelson review). In support of these possibilities, nitric oxide formed at sites of inflammation might augment DNMT activity, interleukin 1β, and other inflammatory cytokines have been found to cause epigenetic silencing of key genes, and the intestinal epithelial cells of mice genetically prone to intestinal inflammation and carcinogenesis show new DNA methylation marks in some 250 genes, with 70 % of the genes representing targets of polycomb complex-mediated repression [39, 57].

Of course, the epigenetic catastrophe that leads to *GSTP1* hypermethylation at the initiation of prostatic carcinogenesis in PIA cells affects hundreds of sites in the genome, both near genes and in regions without known genes [5, 58]. Also, because the epigenetic changes are potentially reversible, corruption of the epigenome may well be ongoing throughout the pathogenesis of prostate cancer through progression to lethal metastatic disease. The propensity for epigenome defects to be maintained only if providing a selective growth or survival advantage renders the detection of epigenetically silenced genes potentially useful for discriminating indolent from aggressive disease states. Yegnasubramanian et al. reported that while hypermethylation at *GSTP1* was present in early localized cancers and maintained throughout

metastatic dissemination, hypermethylation at *ERα*, *hMLH1*, and *p14/INK4a* were only found in metastatic prostate cancers at autopsy [59]. The appearance of these changes appeared to represent clonal evolution of a lethal prostate cancer cell phenotype [59].

A reduction in total 5-methyl-cytosine content evolves progressively during prostate cancer progression, with physiologic or higher total 5-methyl-cytosine levels characteristic of prostate cancer precursor lesions, and variably low levels found in metastatic prostate cancer deposits [6, 60]. This undermethylation of the genome is likely attributable to poor fidelity of 5-methyl-cytosine maintenance during genome replication and cell division. Repeat sequences distributed throughout the genome, which usually carry methylated CpG dinucleotides, illustrate this phenomenon. In one case series, diminished *LINE-1* repeat methylation was detected in up to 53 % of prostate cancer cases, with decreased methylation of LINE-1 repeats in 67 % of cases with, and 8 % of cases without, lymph node metastases [61]. Reduced repeat sequence methylation may provide a mechanistic connection between epigenetic and genetic alterations in cancer cells. Mice carrying disrupted *Dnmt* genes exhibiting low 5-methyl-cytosine levels are prone to genetic instability via a tendency toward illegitimate recombination, and when crossed to mice with *p53* gene defects, show increased tumorigenesis [8, 62]. Life-threatening prostate cancers show large numbers of gene copy number gains and losses, of gene deletions, and of gene amplifications [63]. Whether the epigenetic defect of inadequate DNA repeat sequence methylation contributes to these genetic defects has not been rigorously established but the available evidence supports this hypothesis: there is a clear correlation between reduced DNA methylation and copy number alterations involving chromosome 8 in prostate cancer cases, and lethal prostate cancers at autopsy show both low 5-methyl-cytosine levels and high numbers of copy number changes throughout the genome [38, 64].

Reductions in DNA methylation, when affecting the transcriptional regulatory regions of genes physiologically maintained in a silent state in normal prostate cells, can result in gene activation (Yegnasubramanian). Such genes, which include *CTAG1B*, *CTAG2*, *GAGE2*, *GAGE3*, *GAGE4*, *GAGE6*, *GAGE7*, *GAGE7B*, *MAGEA1*, *MAGEA3*, *MAGEA6*, *MAGEA12*, *PAGE1*, and *TSPY1*, tend to be expressed at some critical stage of development but become epigenetically repressed in adult tissues [38]. For this reason, many of the protein products encoded by these genes have attracted interest and "neo-antigens" for prostate cancer vaccine immunotherapy [65]. Of interest, while the somatic hypermethylation changes at *GSTP1* and other genes seen in prostate cancers tend to be maintained throughout the natural history of the disease, the hypomethylation changes, which occur *within the same cells* as the disease progresses appear quite variable case-to-case, lesion-to-lesion within a case, and cell-to-cell within a lesion [38]. By causing both genetic and epigenetic instability in such a variable manner during prostate cancer progression, DNA hypomethylation may be the major driver of tumor cell heterogeneity during prostate cancer progression.

The expression and function of miRs is also extensively corrupted in prostate cancers [66]. In a systematic review of dysregulated miRs (from more than 100 published papers) in prostate cancer, 10 upregulated and 16 downregulated miRs were identified, with predicted functions in critical neoplastic phenotypes, including androgen signaling, apoptosis avoidance, cell proliferation, cell migration, and cell metabolism [66]. The mechanisms by which the various miRs are over- or underproduced in cancers can include genetic alterations, including deletions and amplifications, and epigenetic changes, with as many as 40 % of miR-coding sequences located in proximity with CpG islands [66]. Somatic loss of *mIR-101*, which targets *EZH2* mRNA encoding a component of the epigenetic regulator polycomb complex, is evident in as many as 38 % of localized prostate cancers and 67 % of metastatic prostate cases [67]. As a consequence, an acquired genetic defect affects the epigenome, with resultant increases in EZH2 disrupting polycomb complex action. In addition to the somatic cis-regulatory defects leading to alterations in miR expression, the trans-regulatory consequences of other genetic and epigenetic alterations can also contribute to miR dysfunction in prostate cancers. C-MYC, a master trans-regulator of genome function that is consistently overexpressed in prostate cancers, triggers significant perturbations in miR levels and actions which can dramatically alter cell phenotype. As an example, C-MYC-mediated transcriptional repression of *miR-23/b* in PC-3 prostate cancer cells results in increased production of mitochondrial glutaminase, which converts glutamine to glutamate, promoting a metabolic shift to glutamine consumption as a source of energy production [68]. Finally, marked changes in mIR expression have been reported to accompany prostate cancer progression from androgen-dependence to castration-resistance. In a comprehensive assessment, 41 miRs were found to be upregulated and 42 downregulated in castration-resistant LNCaP prostate cancer cells, most targeting genes encoding signal transduction pathway participants [69]. *MiR-221* and *miR-222*, which target mRNA for p27/Kip1 and other key proteins, have been implicated in maintenance of a castration-resistance phenotype in prostate cancer cell lines [70].

The accumulating body of knowledge of the epigenome of prostate cancer has revealed that epigenetic changes precede genetic alterations and continue to accrue during disease progression from PIA to PIN to invasive cancer to metastatic dissemination to castration resistance. As a result, there is no prostate cancer phenotype unaffected by epigenome defects. Furthermore, many interactions between processes corrupting the genetic and epigenetic regulation of

genome function have been recognized, leading to a complex and dynamically evolving prostate cancer cell genome, endowing many progressive prostate cancers with the propensity to ultimately resist all attempts at therapeutic intervention.

## Epigenome Biomarkers for Prostate Cancer Screening, Detection, and Diagnosis

The screening and early detection of prostate cancer, though responsible for improvements in prostate cancer mortality, leave much to be desired [71]. Neither serum prostate-specific antigen (PSA) values nor the texture of prostate tissue felt by digital rectal examination direction reliably discriminates prostate cancer from other prostate disorders. In an early study, a serum PSA between 4.0 and 9.9 ng/mL was associated with a 22 % chance of finding prostate cancer by prostate biopsy; in a later study (the placebo arm of the Prostate Cancer Prevention Trial), 24.4 % of men with a serum PSA less than 3.0 ng/mL were found to have prostate cancer [72–74]. The diagnostic approach to localized prostate cancer is also inadequate. Because no imaging strategy can distinguish prostate cancer lesions from other anatomic disruptions of the glandular architecture in the prostate peripheral zone, such as inflammation and atrophy, the preferred approach to prostate biopsy is transrectal ultrasound (TRUS)-guided sampling of ~0.3 % or so of prostate tissue. Of course, TRUS-guided prostate biopsies can miss significant cancer lesions, under- or overestimate the extent of cancer, and sample low grade but not high-grade cancer lesions when both are present. Despite all of these difficulties, at least 48 million serum PSA tests are done each year, prompting more than a million prostate biopsy procedures to diagnose 250,000 prostate cancers. If an epigenome biomarker can improve prostate cancer screening, detection, and diagnosis, a significant unmet medical need could be addressed.

Ideal attributes of any new biomarker for prostate cancer screening include a high enough test sensitivity and specificity that when applied to a population of men at risk for disease, the biomarker would exhibit better positive and negative predictive values than serum PSA tests and digital rectal examination. In this way, men most likely to have prostate cancer could be navigated toward prostate biopsy, while men not likely to have the disease could be steered away from biopsy procedures. Several epigenetic biomarkers might have such attributes. Two such markers, hypermethylation of the *GSTP1* CpG island and overexpression of the noncoding RNA *PCA3*, are under development for this purpose, though establishing the clinical utility of the markers has been difficult. One challenge has been the need for better assays. For example, *GSTP1* hypermethylation, though present in nearly all prostate cancers, could be detected only in 90 % or so of prostate cancer cases using first generation DNA methylation assays, performed using bisulfite modification and polymerase chain reaction (PCR) amplification [58]. This challenge may have been overcome as second generation assays for *GSTP1* hypermethylation, featuring capture of 5-methyl-cytosine-containing DNA using MBD protein fragments followed by PCR, and have shown 99.2 % sensitivity and 100 % specificity for prostate cancer versus normal prostate tissue [75]. A second difficulty has been determining which biospecimen to target for epigenetic prostate cancer tests: would such biomarkers best be tested in blood, expressed prostate secretions, or urine? Prostate cancer DNA showing *GSTP1* hypermethylation has been detected in each of these types of specimens, while prostate cancer RNA with *PCA3* has mostly been found in the urine [76–82]. The third and most daunting challenge has been that for each biomarker, a positive test (the presence of the biomarker) has been well correlated with the presence of cancer in the prostate, while a negative test (the absence of the biomarker) has not had a high enough of a predictive value to preclude the need for a biopsy. The problem may be that prostate cancer DNA and RNA may only be intermittently present, or present at too low an amount, in blood, prostate secretions, or urine to be reliably sampled. In this way, many biospecimens giving "negative" tests might be more accurately labeled "uninformative." To minimize the mischaracterization of "uniformative" as "negative" for *PCA3* tests, a ratio of *PCA3* RNA to *PSA* mRNA is typically provided, ensuring that prostate epithelial cells, which could be normal or neoplastic, were in the biospecimen assessed [81]. To further increase the negative predictive value of epigenetic prostate cancer tests for prostate cancer screening, the frequency of "uninformative" tests need to be minimized, perhaps by combining *GSTP1* hypermethylation and *PCA3* RNA tests, introducing assays for additional DNA methylation changes and/or RNA targets, or repeatedly sampling the biospecimens [83]. Of interest in this regard, the negative predictive value of fecal occult blood testing for colorectal neoplasia screening reaches an adequate level only after three successive tests.

Because of the limitations of TRUS-guided prostate biopsies for prostate cancer, many men with negative biopsies are subjected to additional biopsy procedures before a prostate cancer diagnosis is established. The clinical quandary confronted by urologists is whether and when to perform additional biopsies for men suspected to harbor prostate cancer despite a negative biopsy. To address this unmet medical need, both *GSTP1* hypermethylation and *PCA3* RNA tests of biopsy tissues, of plasma, and especially of urine, which tend to outperform serum PSA testing in predicting prostate biopsy results, have been introduced into this clinical setting [81, 84]. In a recent study of the placebo arm of the REDUCE trial, which tested the propensity for dutasteride to lower the risk of

prostate cancer in men with negative prostate biopsies, *PCA3* urine tests were performed before planned prostate biopsy procedures at years 2 and 4 [85]. The findings were that an elevated *PCA3* was predictive of prostate cancer before each biopsy; furthermore, an elevated *PCA3* at year 2 predicted a positive biopsy at year 4 even if the biopsy at year 2 was negative. The sensitivity and specificity of the current prostate cancer epigenome assays may be good enough now to permit informed decision-making regarding the timing of repeat prostate biopsies for men suspected to have prostate cancer. Of course, as the assay strategies continue to improve, the clinical utility of epigenome urine tests for prostate cancer will improve as well, hopefully complementing advances in prostate imaging that might allow better targeting of prostate biopsies.

## Epigenome Biomarkers for Prostate Cancer Risk Stratification and Treatment Monitoring

The propensity for prostate cancers to arise in more than half of men in the USA and the developed world aging beyond 50 years but to threaten life far less often has triggered a backlash against prostate cancer screening and early detection [71, 86]. The worry is that as prostate cancer screening tests become progressively more sensitive, the overdiagnosis of nonthreatening prostate cancer will tend to increase. A current estimate suggests that for prostate cancers detected by screening, nearly 50 men need to be subjected to aggressive local therapy to save one life [71, 87]. In response to this evolving challenge, many men with prostate cancer found by screening pursue conservative treatment approaches, termed watchful waiting or active surveillance, in which aggressive local therapy is used only for disease progression to a more risky state. The key tool used for treatment decisions in such approaches tends to be Gleason grading of cancer deposits seen in prostate biopsy specimens; as an example, an increase in Gleason score from 3 + 3 = 6 seen on initial biopsy to 4 + 4 = 8 on a subsequent biopsy would likely steer a man with prostate cancer on active surveillance toward prostate surgery or radiation therapy. When applied by an expert prostate pathologist, Gleason grading provides a fairly accurate prognostic tool: a study of more than 2,500 men with Gleason 6 or less prostate cancer treated with radical prostatectomy revealed that none had died of the disease [88]. The unmet needs that could be addressed by epigenome biomarkers arise out of three major limitations with Gleason scoring. The first is that many of the pathologists reading prostate biopsies, especially those who are not expert prostate pathologists, have difficulty assigning Gleason grades. A biomarker tool that might aid in the accuracy of Gleason grading could improve Gleason scoring throughout the USA and elsewhere. Another difficulty is the reduced utility of Gleason scoring for prostate cancer seen in biopsies versus in radical prostatectomy specimens, as the biopsy sampling can miss higher Gleason grade cancers, leading to apparent "upgrading" at surgery. This problem, which bedevils active surveillance approaches, could be solved using epigenome biomarkers that can be assayed in biospecimens that sample the entire prostate gland, such as blood or urine. Finally, the possible presence of rare aggressive prostate cancer cells in some Gleason pattern 3 lesions may be a harbinger of poor prostate cancer outcome despite favorable histopathological appearance. If an epigenome biomarker can be detected with high sensitivity, such as through amplification of nucleic acid sequences, this possibility could be addressed, leading to an improvement in prognostic accuracy beyond that which can be achieved by Gleason scoring.

Epigenome biomarkers that define the prostate cancer phenotypes captured by Gleason grading, or add additional prognostic information, will likely be applied to biopsy tissues, blood, and urine, in hopes of refining prostate cancer prognosis. Already, 5-methyl-cytosine marks at *EDNRB*, *RAR*β, *RASSF1a*, *ER*β, and *TIG1* in prostate cancer DNA have been reported to correlate with tumor stage and/or Gleason grade [59, 89–92]. Another epigenome biomarker, methylation at *PTGS2*, better predicted recurrence of localized prostate cancer after radical prostatectomy than did tumor stage or Gleason grade [59]. Increased serum miR-141 levels may also portend a poor prognosis [93], while serum miR-21 levels appear to be associated with docetaxel resistance [94]. With new genome-wide platforms available for discovery of DNA methylation biomarkers, miR biomarkers, and other species, a plethora of candidate epigenome biomarkers of prostate cancer prognosis are forthcoming. The challenge will be to pursue critical approaches to sifting through such candidate to identify biomarkers that accurately direct clinical decision-making to improve prostate cancer outcomes.

## Epigenome Defects as Rational Therapeutic Targets for Prostate Cancer

Epigenome defects in cancer cells are attractive therapeutic targets because the DNA-coding sequences remain intact. Epigenetic treatments that have advanced to human use thus far act to reverse epigenetic gene silencing enforced by DNA methylation and by the removal of histone acetylation modifications. Four drugs are currently on the market: azacitidine (Vidaza®) and decitabine (Dacogen®) are DNMT inhibitors approved for the treatment of myelodysplasia, while vorinostat (Zolinza®) and romidepsin (Istodax®) are inhibitors of histone deacetylases (HDACs) approved for the treatment of cutaneous T cell lymphomas [95–102]. In addition, several epigenetic drug targets, particularly enzymes that catalyze histone modifications, are being evaluated and credentialed for new drug discovery and development

throughout the biotechnology and pharmaceutical industry. Nonetheless, clinical trials of epigenetic drugs for prostate cancer have been limited. In one small phase 2 clinical trial ($n = 14$ men), decitabine was administered intravenously every 8 h at a dose of 75 mg/m$^2$ for x doses every 5–8 weeks to men with androgen-independent metastatic prostate cancer [103]. Only 2 of the 12 men who could be evaluated for response to treatment showed any hint of benefit, with disease stabilization for as long as 10 weeks or so [103]. This experience is reminiscent of the activity of the nucleoside DNMT inhibitors for other solid organ cancers, where use as a single agent has been disappointing. Newer preclinical data, which have emphasized the epigenetic properties of the drugs over the cytotoxic properties per se, have suggested that different dose and/or dosing schedules of DNMT inhibitors, or DNMT inhibitors given in combinations with other drugs, might be more effective for prostate cancer and other solid organ tumors [59, 104–114]. One attractive therapeutic avenue may be the use of epigenetic drugs to activate expression of key drug targets, rendering cancer cells sensitive to growth inhibition or cytotoxicity mediated by existing drugs that hit the targets. The paradigm for such a target is the silenced *ER* gene in estrogen-independent breast cancer cells, where induction of receptor expression in tamoxifen-resistant breast cancer cells by DMNT and HDAC inhibitors promotes sensitivity to growth suppression by tamoxifen [115]. A candidate therapeutic target for epigenetic reactivation in prostate cancer cells, as well as in other cancer cells, is retinoic acid signaling: each of the available epigenetic drugs seems to be able to restore the signaling pathway in cancer cells, sensitizing the cells to growth suppression by isotretinoin [106, 108–110].

## Conclusions

Somatic alterations of the epigenome constitute the earliest, most extensive, and most reversible drivers of prostatic carcinogenesis, collaborating with genetic defects to promote malignant prostate cancer progression. New genome-wide discovery platforms promise to provide new epigenetic biomarkers that can serve to improve prostate cancer screening, detection, diagnosis, and disease stratification. Already, several such markers are under development as clinical tests, including assays for *GSTP1* hypermethylation and for *PCA3* RNA species; more candidates will be introduced in the future. Epigenetic treatments have had only limited use in clinical trials for advanced prostate cancers, and the results have been underwhelming. New epigenetic drugs and drug combinations will be needed to realize more significant benefits.

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# Biomarkers of Potential Therapeutic Value

15

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## Introduction

Prostate cancer is the most frequently diagnosed malignancy and the second leading cause of cancer-specific deaths in men in Western-industrialized countries; that is, prostate cancer currently constitutes up to 25 % of all male cancer diagnoses and accounts for 10 % of cancer deaths among men in these countries [1]. In recent years, the majority of patients with prostate cancer have been diagnosed at an early stage without any symptoms [2]; therefore, the conventional approaches for prognostic prediction, such as the Partin tables and the Kattan nomograms [3, 4], are no longer variable as in the past. Accordingly, the focus has now moved from early detection to characterizing the clinical features of this disease diagnosed at an early stage.

To date, intensive efforts have been made in the field of prostate cancer research, and thus the molecular mechanism mediating the progression of prostate cancer has been gradually clarified [5, 6]. However, there have not been any biomarkers introduced into the clinical practice, except for prostate-specific antigen (PSA). Although PSA is demonstrated to be useful for the detection as well as the monitoring of prostate cancer, several limitations of PSA as a cancer-specific biomarker have been pointed out [7, 8]. In fact, no concentration of PSA exists below which the risk of prostate cancer does not exist, and high PSA values sometimes reflect a large prostate volume rather than a high risk of the presence of prostate cancer. Considering these findings, it would be necessary to identify novel and useful biomarkers that can assist in clinical decision-making during the prostate cancer diagnosis and treatment.

With progress in the research targeting molecular biology of prostate cancer, upcoming biomarker candidates mainly involved in the acquisition of aggressive phenotype have been identified [9, 10]. In the following, therefore, we have attempted to summarize recent progress in the development of biomarkers that show promise for the management of patients with prostate cancer.

## Limitations of PSA as a Prognostic Indicator

PSA, a serine protease secreted by the epithelial cells of the prostate, is considered to be the most useful tumor marker currently in use [11]. The common use of PSA testing has resulted in an increased detection of prostate cancer at an earlier stage. PSA is also shown to be useful as a marker related to the extent of prostate cancer and the prognosis in some categories of men with this disease.

However, there are serious limitations of the PSA test mainly due to the absence of cancer specificity [12]. For example, elevations of PSA are observed in men with benign enlargement of the prostate gland, such as benign prostatic hyperplasia (BPH) and those with inflammatory disease in the prostate [13]. Similarly, PSA levels do not have a direct association with increase in grade and stage of prostate cancer, particularly in patients with comparatively low PSA values [14]. This lack of specificity to the PSA test led to both overdiagnosis and overtreatment of clinically insignificant disease [15]. Furthermore, it is usually difficult to precisely predict the prognosis of patients with prostate cancer based on the PSA test even after combined assessment with other clinical parameters, since the prognosis of patients after prostate cancer diagnosis is extremely variable [16]. Collectively, these findings suggest that there is pressing need for new prognostic biomarkers that can distinguish between indolent and aggressive prostate cancers.

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## Novel Prognostic Biomarkers

### PSA-Derived Biomarkers

One attractive approach for overcoming limitations of the PSA test is to measure PSA derivatives, including PSA velocity, PSA density, and age-specific PSA intervals, but the significant utilities of these derivatives over the PSA test have not been clearly demonstrated [17].

PSA is present in serum in various molecular forms that can be divided into the two major categories of free and complex forms [18]. Of these, the significance of percent free PSA (%fPSA) as a prognostic indicator is intensively investigated; however, these findings remain controversial [19, 20]. For example, Southwick et al. found %fPSA to be a better predictor of postoperative pathological outcome than Gleason score [19], whereas Graefen et al. reported that %fPSA has no significant impact on the prediction of disease progression following radical prostatectomy [20].

### Biomarkers Specifically Produced by the Prostate

The usefulness of several genes, that are specifically expressed in the prostate gland like PSA, as possible biomarkers for prostate cancer have been investigated, and promising findings have been demonstrated in studies assessing the significance of some of these candidate genes, such as human kallikrein-related peptidase-2 (KLK2), prostate cancer antigen-3 (PCA3), prostate-specific membrane antigen (PSMA), and prostate stem cell antigen (PSCA) [21].

For example, KLK2, a member of the kallikrein gene family of secreted serine proteases same as PSA, shows greatest abundance in the prostate gland. It has been well documented that measurement of serum KLK2 levels could contribute to enhance the diagnostic accuracy of prostate cancer [22]. KLK2 has also shown to provide precise prognostic information in men undergoing radical prostatectomy compared with PSA [23]. Furthermore, PCA3, also known as differential display code 3, is a noncoding RNA produced exclusively in the prostate gland, particularly in the prostate cancer cells. Several previous studies have demonstrated the utility of the PCA3 test by the measurement of PCA3 mRNA in urine sediment for improving the diagnostic specificity of PSA [24]. In recent studies, PCA3 urinary assay has been shown to be useful for predicting pathological features in prostate cancer patients [25]; however, it remains unknown whether this test could be used as a prognostic prediction.

### Apoptosis-Related Biomarkers

A number of studies have demonstrated the involvement of apoptosis-related molecules in the progression of prostate cancer [26]. Of these, the Bcl-2 protein family, including anti-apoptotic (such as Bcl-2 and Bcl-xL) and proapoptotic (such as Bax and Bak) genes that have opposite role in the process of apoptotic cell death, is one of the most intensively investigated molecules as biomarkers of prostate cancer [27]. In consistent with preclinical studies demonstrating powerful activity of Bcl-2 resistant to a wide variety of therapeutic stimuli [28], several studies have reported the significant impact of Bcl-2 expression on the prognosis of patients with prostate cancer. Overexpression of Bcl-2 was shown to be closely correlated to the subsequent development of biochemical recurrence in patients with prostate cancer following radical prostatectomy [29, 30]. In addition, Pollack et al. reported the increased biochemical failure in patients with Bcl-2 overexpression in biopsy specimens who underwent radiotherapy [30]. In the study by Pollak et al. altered Bax expression, defined as under- or overexpression compared with staining intensity of nonneoplastic cells, also appeared to be an independent predictor of biochemical recurrence [30].

Recently, changes in expression profiles of numerous genes at various time-points after castration have precisely characterized using animal model systems mimicking the diverse behavior of human prostate cancer and highlighted genes showing dramatic changes during progression to castration resistance. Based on these outcomes, special attention has been paid to several genes that become upregulated after castration, most of which are associated with antiapototic activities and functions like a molecular chaperone [31, 32]. To date, these genes, such as clusterin and heat shock protein 27 (HSP27), have been mainly investigated as molecular targets for the treatment of prostate cancer [33], while it is currently under active assessment whether these genes could be used as biomarkers for predicting the prognosis of prostate cancer [34–40].

Clusterin, also known as testosterone-repressed prostate message-2, apolipoprotein J, or sulfated glycoprotein-2, is associated with a wide variety of pathophysiological processes, including tissue remodeling, lipid transport, reproduction, complement regulation, and apoptosis [41]. In prostate cancer, experimental and clinical studies have demonstrated that clusterin expression is associated with the development of castration-resistant progression and plays a protective role against a wide variety of apoptotic signals; therefore, clusterin is regarded as a cytoprotective gene upregulated by apoptotic triggers and conferring resistance to conventional therapeutic modalities used in a clinical setting [42]. Recently, several studies have addressed the significance of clusterin as a biomarker for prostate cancer [34, 35]. Miyake et al. also previously showed that the expression of clusterin is significantly increased in radical prostatectomy specimens after neoadjuvant hormonal therapy compared with that in biopsy specimens and that the expression level of clusterin in prostate cancer tissue after neoadjuvant hormonal therapy could be a useful parameter predicting biochemical

recurrence [36], whereas the expression level of clusterin protein failed to show a significant correlation with biochemical recurrence in patients undergoing radical prostatectomy without neoadjuvant hormonal therapy [37]. In consistent with these studies, we measured serum levels of clusterin in prostate cancer patients and showed that serum clusterin level and its density in men with prostate cancer are shown to be closely correlated to disease extension and that postoperative biochemical recurrence-free survival in patients with elevated clusterin density was significantly lower than that in those with normal density [38].

HSP27, an ATP-independent molecular chaperone, is one of the most potent cytoprotective proteins, is highly induced as a stress response, and forms oligomers to increase affinity for client proteins, preventing their precipitation and aggregation [43]. Like clusterin, HSP27 expression is highly upregulated by proapoptotic stimuli and inhibits therapy-induced apoptosis in prostate cancer models [44]. In clinical specimens, overexpression of HSP27 is observed in various kinds of malignant tumors, including prostate cancer [39]. In addition, we previously reported that despite the lack of independent significance, the expression level of HSP27 in prostate cancer tissue after neoadjuvant hormonal therapy, which may inversely reflect the therapeutic effect of neoadjuvant hormonal therapy, could be a useful parameter predicting biochemical recurrence in patients undergoing radical prostatectomy [40].

## Cell-Cycle-Related Biomarkers

Abnormalities in the regulation of cell cycle are present in the majority of malignant tumors [45]. In prostate cancer as well, a number of studies have shown the association between the outcomes of prostate cancer treatment and the expression of cell-cycle-related markers, including p16, p21, p27, Aurora-A, and Ki-67 [46–51]. Of these markers, p27, an endogenous inhibitor of cyclin-dependent kinase, is one of the most widely characterized proteins as a biomarker of prostate cancer [47, 48]. For example, Freedland et al. showed that low expression of p27 in biopsy specimen could be used as an independent predictor of biochemical recurrence in patients with prostate cancer following radical prostatectomy [48].

We also previously analyzed the prognostic significance of a potential cell-cycle regulator, Aurora-A, a serine/threonine protein kinase belonging to the Drosophila aurora and Saccharomyces cerevisiae Ip11 kinase family, that has been shown to play a crucial role in chromosome segregation and centrosome functions [52], in patients with prostate cancer [50]. In this study, we demonstrated that the expression of Aurora-A was significantly decreased in radical prostatectomy specimens compared with that in biopsy specimens prior to neoadjuvant hormonal therapy; however, persistent overexpression of Aurora-A was detected in approximately 40 % of radical prostatectomy specimens after neoadjuvant hormonal therapy and that the expression level of Aurora-A in prostate cancer tissue after neoadjuvant hormonal therapy could be a useful parameter predicting biochemical recurrence in patients undergoing radical prostatectomy [50]. We subsequently assessed the predictive value of twelve kinds of molecular markers as well as conventional prognostic parameters for biochemical recurrence in patients undergoing radical prostatectomy alone. Of these markers, Ki-67, p53, androgen receptor (AR), matrix metalloproteinase-2 (MMP-2), MMP-9, and HSP27 expression were shown to be significantly associated with biochemical recurrence; however, only Ki-67, reflecting a tumor proliferation index, in addition to seminal vesicle invasion and surgical margin status appeared to be independently related to biochemical recurrence on multivariate analysis [51].

## Signal Transduction-Related Biomarkers

Aberrations in signal transduction pathways are demonstrated to play crucial roles in the progression of a wide variety of malignant tumors [53]. In prostate cancer, the molecules that are able to drive signal transduction through the phosphoinositol 3′-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and the RAS/mitogen-activated protein kinase pathways are shown to stimulate cell-cycle progression and proliferation of prostate cancer cells, resulting in the conferment of aggressive phenotypes [54]; thus, these molecules and downstream pathways could be promising biomarkers for predicting therapeutic outcomes in patients with prostate cancer.

McCall et al. reported the interesting findings using clinical specimens that upregulation of the PI3K/Akt pathway is associated with phosphorylation of the AR during development of castration-resistant prostate cancer [55]. Similarly, Dai et al. also showed the activation of at least one component of the mTOR signaling pathway in most patients with prostate cancer, which was significantly proportional to clinicopathological variables, including serum PSA level, Gleason score, and pathological T stage [56]. Furthermore, caveolins, which act as regulators of signal transduction, have also been assessed for their prognostic values in prostate cancer, and overexpression of caveolin-1 was demonstrated to be related to an increase in biochemical recurrence in patients undergoing radical prostatectomy [57].

## Other Biomarkers

In addition to possible biomarkers described above, there have been a number of molecules showing close association with prognosis in prostate cancer patients, such as cellular

adhesion-related markers, angiogenesis-related markers, epithelial-mesenchymal transition (EMT)-related markers, cytokines, and epigenetic markers [58–62]. For example, Gravdal et al. reported that cadherin switching characterized by low E-cadherin and high N-cadherin expression indicated a strong relation to biochemical recurrence in patients after radical prostatectomy [58], while microvessel density (MVD) in prostate cancer specimens has been shown to be an prognostic predictor in patients undergoing radical prostatectomy; that is, biochemical recurrence was likely to develop in patients with high MVD disease [59]. Inflammatory cytokines are currently regarded as promising biomarkers in several types of malignant tumors [63]. Of these, interleukin-6 (IL-6), a pleiotropic cytokine involved in various pathophysiological processes, has also been shown to be a potential factor having strong protumorigenic activity through the modulation of growth, angiogenesis, invasion, metastasis, and apoptosis in various types of malignant tumors, including prostate cancer [64]. In addition, circulating levels of the IL-6 and its receptor have been found to be elevated proportional to features of aggressive prostate cancer, such as that with higher Gleason score, advanced stage, and decreased survival [60].

## Novel Approaches for Identifying Useful Biomarkers

### Discovery of Biomarkers Using Microarray

In recent years, microarray technology has been widely used for evaluating the complex molecular aberrations involved in cancer development at a genome-wide scale [65]. In the field of prostate cancer research, microarray expression profiling studies have been performed and identified a number of genes with differential expression, including α-methylacyl-CoA racemase (AMACR), enhancer of zeste homolog 2 (EZH2), TMPRSS2-ERG, miR-221, and miR-141, in several settings, such as nonmalignant versus malignant prostate tissues, localized versus metastatic prostate cancer tissues, and hormone-naive versus castration-resistant prostate cancer tissues [66–70]. Although variation among outcomes from different studies should be overcome, data on such genes could be a valuable source for identification of novel useful biomarkers.

AMACR, an enzyme involved in oxidative metabolism and synthesis of branched chain fatty acids, is one of the first genes that were identified as consistently overexpressed in prostate cancer tissue compared with benign prostate tissue by microarray expression profiling [68]. In addition, Rubin et al. reported that low AMACR expression in localized prostate cancer correlated with biochemical recurrence and cancer-specific death [69]. Another major discovery achieved by microarray technology is the detection of gene fusions between the androgen-regulated transmembrane serine protease, TMPRSS2, and the Ets family transcription factor genes, ERG and ETV1. It has been shown that approximately 60 % of prostate cancers harbor Ets gene fusions, and of these fusion genes, TMPRSS2: ERG has been found to have a close association with high Gleason score, metastasis, and poor survival [70].

### Development of Urine Biomarkers

In recent years, intensive efforts have been made to discover biomarkers using urine samples from patients with prostate cancer, since noninvasive urine-based tests might be particularly attractive for carrying out large-scale screening. To date, there have been some promising urine biomarkers in prostate cancer, such as glutathione-S-transferase P (GSTP1), PCA3, AMACR, annexin-3, metalloproteinase, sarcosine, and telomerase activity [71–73]. As described above section, of these urine candidates, the PCA3 urine test is one of the best tests to supplement serum PSA, and it has proven clinical relevance, providing diagnostic accuracy superior to traditional serum biomarkers [24]; however, the prognostic significance of the PCA3 urine test remains unknown.

The loss of GSTP1 expression due to promoter hypermethylation is one of the most common molecular abnormalities in prostate cancer [74]. To assess the prognostic value of this gene as a urine biomarker, Woodson et al. analyzed aberrant methylation of GSTP1 in urine sediment DNA and observed a high frequency of GSTP1 methylation in the urine specimens from men with advanced-stage cancer [75]. It would be an interesting approach to identify urine biomarkers using proteomic or metabolomic profiling, which enables analyses of alterations in their posttranslational modifications and total protein expression levels [71]. Of several markers identified this strategy, sarcosine, an N-methyl derivative of the amino acid glycine, is one of the most promising biomarkers predicting the prognosis of patients with prostate cancer [76].

### Introduction of Biomarkers into Conventional Nomograms

Nomograms are multivariable tools that combine clinical as well as pathological data to provide physicians with various risks for individual patients. Although several nomograms have been introduced into the field of prostate cancer [3, 4], considering unique biological features of prostate cancer characterized by the heterogenous genetic backgrounds, it would be difficult to exactly predict clinical outcomes in patients with prostate cancer using limited conventional

**Table 15.1** Lists of major biomarkers as candidates for predicting therapeutic outcomes in patients with prostate cancer

| Biomarker | Classification | References | Biomarker | Classification | References |
|---|---|---|---|---|---|
| PSA | PSA-derived | [11–16] | AR | Signal transduction-related | [51, 55] |
| PSA density | PSA-derived | [17] | mTOR | Signal transduction-related | [56] |
| PSA velocity | PSA-derived | [17] | Caveolin-1 | Signal transduction-related | [57] |
| Percent free PSA | PSA-derived | [18–20] | HER-2 | Signal transduction-related | [26] |
| PSMA | Prostate-specific | [21] | EZH2 | Signal transduction-related | [54] |
| PSCA | Prostate-specific | [21] | E-cadherin | Angiogenesis-related | [58] |
| KLK2 | Prostate-specific | [21–23] | N-cadherin | Angiogenesis-related | [58] |
| PCA3 | Prostate-specific | [24, 25] | MVD | Angiogenesis-related | [59] |
| Bcl-2 | Apoptosis-related | [29, 30] | GSTP1 | Epigenetic | [74, 75] |
| Bax | Apoptosis-related | [30] | TMRPSS2:ERG | Epigenetic | [70] |
| Bcl-xL | Apoptosis-related | [30] | TMRPSS2:ETV1 | Epigenetic | [70] |
| p53 | Apoptosis-related | [26, 51] | IL-6 | Cytokine | [60, 64, 77] |
| MDM2 | Apoptosis-related | [26] | TGF-β1 | Cytokine | [77] |
| Clusterin | Apoptosis-related | [34–38] | miR-221 | MicroRNA | [66] |
| HSP27 | Apoptosis-related | [39, 40, 51] | miR-141 | MicroRNA | [66] |
| p16 | Cell-cycle-related | [46] | MMP2 | Cell invasion | [51, 61] |
| p21 | Cell-cycle-related | [49] | MMP9 | Cell invasion | [51] |
| p27 | Cell-cycle-related | [47, 48] | AMACR | Oxidative stress | [68, 69] |
| Aurora-A | Cell-cycle-related | [50] | Annexin-3 | Immune response | [71] |
| Ki-67 | Cell-cycle-related | [51] | Telomerase activity | Cell immortality | [71] |

parameters alone. Therefore, it has recently been investigated whether a significant improvement in predictive accuracy could be achieved by adding biomarkers to established parameters in the nomogram [77–79].

In this context, Kattan et al. added preoperative plasma IL-6 soluble receptor and transforming growth factor-β1 (TGF-β1) levels to the standard nomogram for predicting risk of biochemical recurrence following radical prostatectomy using pretreatment PSA values, clinical stage, and biopsy Gleason score [77]. They reported an improved prognostic ability of the nomogram with these additional biomarkers; that is, the novel nomogram resulted in the increase in predictive accuracy of biochemical recurrence from 75 to 83 %. Similarly, Stephenson et al. analyzed gene expression profiling using microarray technology in prostate cancer specimens from patients undergoing radical prostatectomy [79]. In this study, models combining conventional parameters and gene expression profile could accurately classify 89 % of patients in terms of the development of postoperative biochemical recurrence with a predictive accuracy superior to the standard nomogram.

## Conclusions

Prostate cancer is shown to have a biologically heterogeneous nature, and the prognosis of patients after a diagnosis of this disease is extremely variable. Accordingly, despite the widespread use of the PSA test, it would be absolutely necessary to identify molecular biomarkers for exactly predicting the clinical course of this disease in an individual patient. As summarized in Table 15.1, based on recent intensive studies for the identification of novel biomarkers for prostate cancer using newly developed attractive approaches, a number of candidate biological markers have been discovered. Then, the relevance of these candidate markers has been validated in clinical setting, and some of them showed promising outcomes. Furthermore, the integration of selected biomarkers with conventional clinicopathological variables has been reported to produce predictive models showing outcomes superior to standard predictive system, like a nomogram. Collectively, these findings suggest that despite several limitations to be overcome prior to the introduction of these biomarkers into clinical practice of prostate cancer, once strictly evaluated, such biomarkers may help provide variable information on clinical decision-making during treatment of patients with prostate cancer.

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# Prostate Tissue Banking

16

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As the most common non-dermatologic malignancy affecting males in the Western world, and the second leading cause of male cancer-related deaths, the importance of prostate cancer research needs little justification [1]. Epidemiologic reports have described the significant heritability of such malignancies, with one twin-study attributing 42 % (CI 29–50 %) of prostate cancer cases to heritable factors [2]. Genome-wide linkage analyses of germline single nucleotide polymorphisms (SNPs) continue to uncover many low-risk genetic associations with prostate cancer [3]. These findings are being supplemented with expression arrays in an effort to identify individual somatic mutations such as TMPRSS2-ERG gene fusions [4] as well as more global gene expression profiles.

Despite these advances, the low predictive function of such screening tests (with ROCs of 0.61–0.63 for current SNP-based models) [3, 5] suggests that the real clinical value may be found in identifying markers which distinguish aggressive from latent disease in men already found to have prostate cancer. Indeed, gene mutations are beginning to emerge which correlate with disease aggressiveness [6] and, in combination with unique molecular signatures, may yield invaluable prognosticators to help guide clinical decisions.

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This sophisticated genetic research places a great reliance upon the accumulation of large amounts of high-quality prostatic tissue and has led to the development and refinement of *biobanking* protocols which seek to provide pathologic samples without compromising the patient's histopathologic evaluation. At the heart of a well-developed prostate biobank is the proficiency and regularity with which the protocol can be implemented, and this is in no small part a function of the expertise of the urology and pathology services which underlie it. We have benefited from a high throughput of patients undergoing radical prostatectomy at our institution and are able to describe a validated biobanking protocol, which has been used to collect over 2,000 prostate specimens.

## Patient Consent and Ethical Approval

Before a biobank can be established, the appropriate ethics approval must be sought, in keeping with local and national governance. In the USA, Institutional Review Board (IRB) approval is obtained in order to support specific research endeavors; in the case of the *Weill Cornell Medical College* (*WCMC*) *radical prostatectomy biobanking protocol*, this was obtained in order "to collect prostate samples after robotic prostatectomy for the treatment of clinically localized prostate cancer."

Each patient must receive adequate explanation of tissue biobanking and the details of the consent form, allowing ample time for an appropriately qualified member of the biobanking team to answer any questions which the patient may have.

## Specimen Procurement

A fundamental requirement of a successful tissue biobank rests with the method of tissue collection, its reliability, consistency, and impact on specimen quality. The WCMC protocol relies upon prostate specimens derived entirely from a single institution and

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led by a single surgeon (AKT). An Advanced Robotic Technique™ is employed to complete the radical prostatectomy, centered on delicate handling of prostatic and periprostatic tissues in order to preserve the trizonal neural architecture while ensuring maximal cancer clearance [7]. Once the prostate is devascularized, the vesicourethral anastomosis is completed before extirpating the prostate within an EndoCatch bag (Covidien, North Haven, CT). Suspicious nodules and nerve-sparing details are recorded before rapidly transporting the sample to the pathology department to be received by a technician for immediate preparation.

## Specimen Preparation

Once received, the prostate is weighed and correctly orientated using permanent black and green ink to highlight the left and right sides, respectively. The apex and base are shaved and sectioned perpendicularly to the distal and proximal inked margins. The prostate is then cut in 5 mm serial sections perpendicular to the urethra and sequentially labeled A to D–H (depending on prostate size), starting from apex to base. Further preparatory steps require the additional division of each section into four (or six) equal parts (depending on the size of the sections) in order to place the samples into individual cassettes. Alternate sections (i.e., A, C, E, and G) and samples from the surgical margins are formalin-fixed for histopathologic evaluation, allowing the remaining alternate prostate samples (i.e., B, D, F, and H) to be coated in optimal cutting temperature (OCT) media (Sakura Finetek, Torrance, CA) prior to snap freezing in liquid nitrogen. Typically, two to three sections of the biobanked specimens are retained, equating to approximately 40 % of the total prostate body per specimen. This ensures enough tissue remains for diagnostic evaluation without compromising gross tissue architecture [8] and the ability to select specific cell populations for microarray studies.

The biobanked cassettes are labeled with unique identifiers in order to sufficiently de-identify samples and are then stored in a plastic bag at −80 °C in a specifically designated secure tissue laboratory. The storage of adjacent biobanked sections permits the retrieval of stored samples from the tissue laboratory in the unlikely event that an area of suspicion is only identified at the border of a sample section.

This process of specimen collection is summarized in Fig. 16.1.

## Pathological Characterization

The utility of biobanked specimens can be further enhanced by preparing hematoxylin- and eosin-stained microscopic slides for each biobanked tissue sample. Each slide is evaluated for cancer grade, stage, and margin status. Furthermore, the demarcation of malignant and benign as well as epithelial and stromal compartments permits accurate notation of tissue histology of the biobanked samples. This is vital for utilization of those samples for future molecular biologic research.

## Robotic Prostatectomy Biobank Database

In addition to the pathologic data on the series of samples for each prostate specimen, detailed pre-, intra-, and postoperative data are also collected and stored in an encrypted biobank database (Microsoft Access, Redmond, WA). Variables stored include patient age, body mass index, preoperative prostate-specific antigen, console time, total operative time, estimated blood loss, grade of nerve sparing, prostate volume, the presence of any positive surgical margin, Gleason score, pathologic stage, and storage time.

## Quality Assessment

The ability of any biobank to provide useful tissue for prostate cancer genetic studies is determined by the quality of the nucleic acid material within each sample. In order to validate our tissue biobanking process, we have performed a quality assessment of samples procured by the above protocol, using advanced electrophoretic techniques. We obtained the RNA integrity numbers (RIN) for 142 biobanked specimens and obtained a mean RIN of 7.25 (standard deviation 1.64), with 73 % of sample demonstrating a RIN ≥7, and hence of sufficient quality for genetic studies [9].

A general belief of RNA quality diminishing with ischemic time hypothetically raised doubts as to the appropriateness of robotic platforms for the collection of high-quality prostate specimens, given the extended periods of ischemia in which samples are subjected to between devascularization and extirpation. However, our validation study not only confirmed the attainment of high-quality specimens using such a technique but, using multivariate regression analysis, established the lack of a relationship between warm ischemia time (averaging 120 min, standard deviation 30 min) and RIN (unstandardized coefficient −0.010, $p=0.147$) [8]. Quality assurances are fundamental to assessing the suitability of collected tissue for studies which require different standards of cellular and genetic material.

### Conclusions

A successful biobank requires the concerted efforts of both urologic and pathologic services in order to produce a consistent and reliable process of tissue procurement, processing, and storage. The specimens collected by the

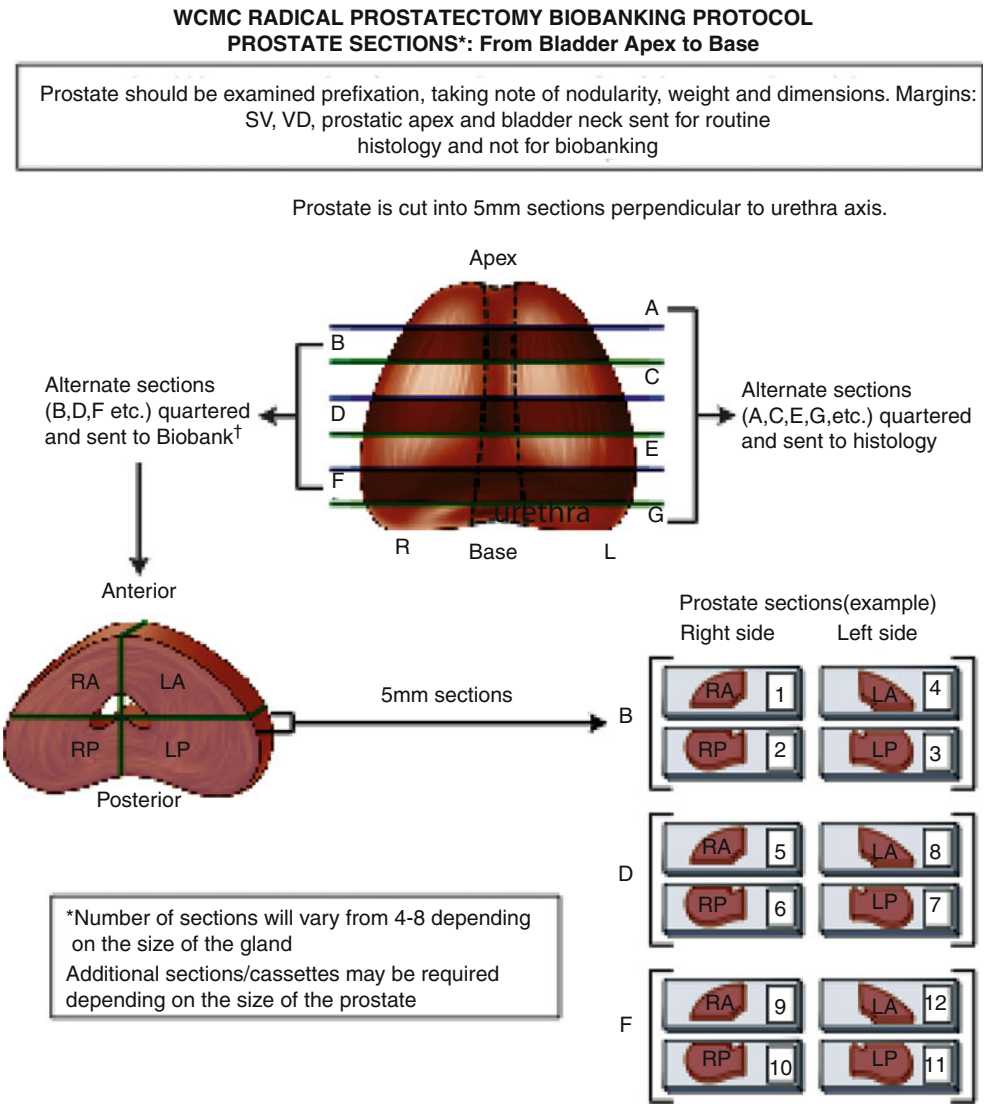


**Fig. 16.1** WCMC radical prostatectomy biobanking protocol. Prostate sections: from bladder apex to base

protocol should be validated in order to verify the quality of the tissue and its appropriateness for the studies which it is being used for. We are able to demonstrate the suitability of the robotic radical prostatectomy procedure for procuring specimens which are suitable for high-quality genetic research.

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# Molecular Imaging in Diagnostics

17

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## Introduction

Prostate cancer is the most common malignancy and the second most common cause of cancer-related mortality in men. Despite the downstaging we have observed over the last 20 years with the widespread use of PSA screening, we continue to observe conflicting data regarding its effect on prostate cancer survival [1, 2]. While treatment for localized prostate cancer is highly successful, about 30–50 % of men will experience a biochemical failure within 10 years from the primary treatment, suggesting that prostate cancer can metastasize relatively early in the course of disease [3–6]. This is supported by the discovery of circulating prostate cancer cell in bone marrow biopsy of patients with apparently localized disease [7]. A portion of men with biochemical failure will develop locally recurrent disease, and as many as two-thirds will have evidence of osseous metastatic involvement [8–11]. In the study by Pound et al. after primary surgical treatment, 15 % of patients developed biochemical recurrence. The median actuarial time to metastases was 8 years from the time of PSA relapse. Once men developed metastatic disease, the median survival time to death was 5 years [12]. If men develop castrate resistant metastatic disease, the 1-year survival is about 24 % with a median survival of only 8-18 months [13]. The hormone-refractory state is believed to occur via bypassing or sensitizing the androgen receptor (AR) signaling pathway. Patients with biochemical recurrence and metastatic disease are left with imaging modalities that neither provide enough information to change management nor are able to predict patient's prognosis or evaluate patient's treatment progress. The reason is that traditional imaging techniques are focused on evaluating the anatomy rather than the function of prostate cancer. Unlike traditional structural imaging, molecular imaging takes advantage of the functionality of tumor. These imaging techniques can theoretically provide functional information regarding prostate cancer. In this chapter, we review the current literature on the potential and emerging role of molecular imaging in prostate cancer.

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## Molecular Mechanism of Various Markers

### FDG

Several hallmarks of cancer include self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and launch of metastasis envoys, evasion of tumors from the immune system, and increased glucose metabolism [14]. The ability of FDG–PET to detect cancer is based on the latter hallmark (Warburg effect). The relationship between tumor growth and the inefficient energy production from glucose metabolism is not well understood but may be explained in terms of adaptation to hypoxia through upregulation of glucose transporters and increased enzymatic activity of hexokinase [15].

Glucose transporter (GLUTx, currently approved gene symbol is SLC2Ax) is the first rate-limiting step for glucose metabolism that allows energy-independent glucose transport across the cell membrane down the concentration gradient, while hexokinase-II phosphorylates glucose to glucose-6-phosphate. Similarly, FDG is phosphorylated to

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FDG-6-phosphate but, contrary to glucose-6-phosphate, it cannot be metabolized further in the glycolytic pathway and becomes trapped in the cell because of its negative charge and the very low activity of the reverse enzyme, glucose-6-phophatase, in most cancers.

GLUT1 mRNA expression has been assessed in the androgen-independent cell lines DU145 and PC-3 and the androgen-sensitive cell line LNCaP [16]. The poorly differentiated androgen-independent cell lines showed higher mRNA expression than the well-differentiated androgen-sensitive cell line, suggesting that GLUT1 expression may be directly related to the malignancy grade [17]. Another study evaluated the expression of several hypoxia-associated genes within benign prostatic hyperplasia (BPH) and human prostate cancer tissue (Gleason score, 5–10). GLUT1 gene expression was not only significantly higher in the tumor than in BPH but also correlated directly with Gleason score ($R=0.274$; $P=0.026$), corroborating the direct relationship between GLUT1 expression and tumor grade [18]. Castration has been shown to decrease glucose metabolism in prostate tumors [19–21]. This results in accumulation of higher levels of FDG in castrate resistant tumors than in castrate sensitive tumors as demonstrated by Jadvar et al. [19]. Because of this unique quality, it is believed that FDG–PET imaging can be used to monitor androgen deprivation therapy and to potentially predict an impending hormone-refractory state in patients with castrate responsive disease.

## Choline ([18F] or [11C])

Increased choline uptake in prostate cancer cells may be explained by increased cell proliferation in tumors and by upregulation of choline kinase in cancer cells. Hallmark of cancer growth is uncontrolled cell proliferation. Choline is believed to participate in cancer growth through two mechanisms, the malignancy-induced upregulation of choline kinase that leads to the incorporation and trapping of choline in the form of phosphorycholine and the collection of large amounts of phospholipids, in the form of phophatidylcholine, which may induce signaling processes within cells for cell proliferation and differentiation [22, 23]. Choline uptake in prostate tumor appears to be uncorrelated to cellular proliferation but may be affected by hypoxia [24]. It has been demonstrated that under aerobic conditions, both androgen-sensitive and androgen-independent prostate tumors show higher choline uptake than that with radiolabeled acetate or with FDG. However, during hypoxia, the tumor uptake with FDG and acetate is higher than that with choline [25]. 11C-choline has a shorter half-life (20 min) that requires an onsite cyclotron facility and generally displays no or little bladder urine activity [26].

## Acetate ([18F] or [11C])

The biological basis for radiolabeled acetate uptake in tumors is likely related to increased fatty acid synthesis. 11C-acetate is actively transported across cell membranes through monocarboxylate transporters. After conversion to acetyl-CoA in mitochondria, acetyl-CoA enters the TCA cycle in tissues with high rates of oxidative metabolism, resulting in carbon dioxide production. Acetate participates in cytoplasmic lipid synthesis, which is believed to be overexpressed in prostate cancer [27]. The cellular retention of radiolabeled acetate in prostate cancer cell lines is primarily due to incorporation of the radiocarbon into phosphatidylcholine and neutral lipids of the cells [28]. It has been suggested that fatty acid metabolism rather than glycolysis may be dominant in prostate cancer in view of alteration in several enzymes involved in the metabolism of fatty acids and enhanced beta-oxidation pathway [29] Recent in vitro and animal model in vivo studies by the group at Washington University in St. Louis confirmed the extensive involvement of the fatty acid synthesis pathway in 11C-acetate uptake in prostate tumors as an imaging marker for fatty acid synthase expression [30]. Fatty acid synthase is the major enzyme required for converting carbohydrates to fatty acids, and its upregulation plays a role in prostate tumor progression in the transgenic mouse prostate model [31]. A suitable 3-compartment, 3-parameter model for 11C-acetate uptake kinetics in prostate cancer and the radiation dosimetry in humans has been reported [32, 33].

## In-111-Capromab Pendetide (Prostascint)

Originally known as murine monoclonal antibody CYT-356, capromab recognizes prostate-specific membrane antigen (PSMA). PSMA is a non-secreted protein anchored to the plasma membrane of prostate cancer cells. Even though it is expressed in certain non-prostate cells, such as small intestine, proximal renal tubules, and salivary glands [34], it is expressed at 100–1,000× lower level than in prostate tissue [35]. Not only is it expressed at significant elevated concentration by prostate cancer cells, its expression is correlated with tumor grade [36, 37]. Despite various advantages offered by capromab, it suffers from a major weakness; the antibody is targeted against the intracellular portion of the PSMA motif. As a result, capromab has no binding site on the extracellular and is only able to bind to cells that have disrupted cell membrane, such as necrotic cells. For this reason, capromab could not be used to help identify patients with early bony metastasis. Unlike soft tissue lesions where cells more commonly outgrow their blood supply resulting in cell death, micrometastases in marrow are well perfused with intact cells that do not allow for capromab binding to

the intracellular portion of the PSMA moiety. Currently, capromab scan is FDA approved to detect small volume soft tissue disease, such as in the lymph nodes.

## Localized Disease

### FDG-PET

Currently, the role of FDG-PET in patients with localized disease is limited. The major barrier to its use is the strong activity in the urine found in the adjacent urinary bladder [38]. The authors found only 4 % sensitivity for detecting primary prostate cancer with FDG-PET. Attempts have been made to ameliorate FDG activity from urine by performing continuous bladder irrigation during the scan, but the results were not encouraging [39]. Even if we are able to overcome urinary activity, a comparative study showed that there is no difference in FDG uptake between primary prostate cancer, benign prostatic hyperplasia, recurrent prostate cancer, local scar tissue, or post-radiation inflammation [40]. These findings were confirmed by other authors [41–43].

### Choline

There is conflicting data on choline's ability to differentiate between normal prostate tissue, BPH, and prostate cancer. Sutinen et al. observed that there is no difference in 11C-choline uptake in prostate cancer and benign prostate tissue [26]. The authors also did not find any association between uptake of 11C-choline and prostate cancer aggressiveness based on histological grade, Gleason score, volume of the prostate, or PSA. On the other hand, Li et al. analyzed choline PET data from 49 patients with prostate lesions visually and semiquantitatively by measuring maximum standardized uptake value (SUV) of the prostate lesions and the muscles and calculating their P/M ratios. The authors found that 11C-choline PET-CT is able to differentiate between BPH and prostate cancer. It had a sensitivity of 90.5 % and a specificity of 85.7 % and a negative predictive value of 92.3 % for differentiating BPH tissue from prostate cancer [44]. When comparing 11C-choline PET to MRI, Testa et al. found that the sensitivity and specificity for detecting prostate cancer were 55 and 86 % for PET-CT, 54 and 75 % for MRI, and 81 and 67 % for spectroscopic MR, respectively [45]. The authors concluded that 11C-choline PET-CT demonstrated a lower sensitivity relative to spectroscopic MR alone or combined with MRI. The conflicting results may be due to differing methodology in data collection or analysis and in patient population. Currently, there is ongoing study to provide enhanced image fusion software to accurately register anatomic MRI, diffusion MRI, 11C-choline PET, and histologic section of prostate gland [46].

In terms of staging, a group of 57 intermediate or high-risk prostate cancer patients underwent 11C-choline PET/CT prior to radical prostatectomy with extended pelvic lymphadenectomy [47]. The authors found on patient analysis, the sensitivity, specificity, PPV, and, NPV were 60.0, 97.6, 90.0, and 87.2 %, respectively; while on node analysis, these values were 41.4, 99.8, 94.4, and 97.2 %, respectively. There was a significant difference in the mean diameter of metastatic deposit of true-positive and false-negative lymph nodes (9.2 cm vs. 4.2 cm, $p=0.0001$). Compared to the Briganti et al. [48] and the Kattan [49] nomogram, PET/CT showed higher specificity and accuracy than the nomograms; however, the areas under the curve were not statistically different. These promising results suggest that an improved 11C-choline PET/CT may one day be incorporated into the preoperative workup for high-risks patients.

18F-fluorocholine offers no significant improvements over 11C-choline for primary diagnosis of prostate cancer. Schmid et al. reported no significant difference in 18F-fluorocholine uptake between malignant and benign lesions [50]. Disease was missed in up to 75 % of patients with elevated PSA [51]. Semiquantitative analysis performed with maximum SUV was not helpful in the discrimination of malignancy with significant overlap with benign prostate tissue and normal prostate tissue. In the same study, the use of dual-phase protocol offered no clear improvements in discriminating between benign and malignant tissue. This finding contradicts an earlier study by Kwee et al. on 26 patients (15 with newly diagnosed prostate cancer, 2 with recurrent prostate cancer, 6 with no evidence of prostate cancer recurrence after treatment, and 3 with no history of prostate cancer). It suggested that dual-phase protocol used in conjunction with 18F-fluorocholine may be helpful in distinguishing malignancy from benign tissue in view of the observation that malignant tissue displays stable or increasing tracer accumulation, whereas benign tissue shows decreasing uptake [52].

In terms of staging, Beheshti et al. prospectively evaluated 132 patients with intermediate-risk prostate cancer and found that 18F-fluorocholine PET/CT demonstrated sensitivity, specificity, and positive and negative predictive values of 45, 96, 82, and 83 %, respectively, for detecting malignant lymph nodes [53]. Husarik et al. evaluated 115 lymph node samples from 25 patients [54]. Only one of these lymph nodes showed pathologic 18F-fluorocholine uptake and was proven to be a metastasis of greater than 1 cm. Four lymph nodes that did not show accumulation turned out to contain metastatic cell with the overall tumor load measuring less than 0.5 cm. Because of the inability to detect micrometastasis to the lymph nodes, the authors concluded that the results were discouraging for 18F-fluorocholine PET/CT to evaluate nodal status in the preoperative setting. However, it must be noted that detection of micrometastases is challenging for any imaging modality, and its impact on long-term outcome remains unsettled.

## Acetate

The literature on acetate PET for the purpose of primary prostate cancer detection is very limited. Because of the lack of accumulation of 11C-acetate in urine, it offers significant advantages over FDG. Various studies have been performed comparing 11C-acetate and FDG-PET. In a study by Oyama [55], 18 patients with prostate cancer underwent both 11C-acetate and 18F-FDG PET scans. Adenocarcinoma of the prostate showed variable uptake of 11C-acetate, with SUVs ranging from 3.27 to 9.87. In contrast, SUVs for 18F-FDG ranged from 1.97 to 6.34. By visual inspection, 11C-acetate uptake in primary prostate tumors was positive in all patients, whereas 18F-FDG accumulation was positive in 15 of 18 patients. The authors concluded that 11C-acetate PET was more sensitive in detection of prostate cancer than 18F-FDG PET. However, 11C-acetate was not able to differentiate benign prostate tissue from prostate carcinoma. In 36 patients (6 with prostate cancer, 21 with no prostate pathology, and 9 with benign prostate hyperplasia), Kato et al. showed that the prostate was clearly visualized and distinguished from adjacent organs in PET images in most of the cases [56]. The SUV of the prostate ($2.6 \pm 0.8$) was significantly higher than that of the rectum ($1.7 \pm 0.4$) or bone marrow ($1.3 \pm 0.3$) ($P < 0.0001$ in each case); the difference in the SUV between subjects aged ≥50 with normal prostate or with BPH and the patients with prostate cancer ($1.9 \pm 0.6$) was not statistically significant. The authors concluded that 11C-acetate uptake is not specific for prostate cancer and not well suited as a screening tool. From a clinical planning standpoint, early results from Seppala et al. revealed that 11C-acetate PET can be used to define the intraprostatic lesions in prostate cancer and in combination with a simultaneous integrated IMRT; the defined areas can theoretically be treated to ultra-high doses without increasing the treatment toxicity [57].

## Capromab

There is currently no indication to use capromab scan to diagnose prostate cancer. One study from Duke showed that it did not localize prostate cancer to a particular quadrant based on comparison with radical prostatectomy specimens [58]. Mouraviev et al. performed a prospective comparison between 111In-capromab pendetide scans and final pathology in 25 hormone-naïve men with clinical localized prostate cancer. The authors found that the capromab scan provided a sensitivity of 37–87 % for four quadrants with 0–50 % specificity. But in the preoperative staging setting, several studies have evaluated capromab's ability to detect disease in lymph nodes. In a small series, 22 preoperative patients with heterogenous risk categories of prostate cancer (PSA range 3.9–33 ng/mL and Gleason range 6-9) underwent capromab scan to evaluate obturator and iliac lymph node involvement. The scan yielded a sensitivity of 17 %, specificity of 90 %, negative predictive value of 94 %, and a positive predictive value of 11 % [59]. In a larger series looking specifically at intermediate and high-risk patients, Manyak et al. performed capromab scans on 152 patients prior to pelvic lymph node dissection. The authors found that the sensitivity and specificity for lymph node detection was 62 and 72 %, respectively. In comparison, the sensitivity of CT and MRI was 4 and 15 %, respectively. Unfortunately, given the positive predictive value of 62 % and a negative predictive value of 72 %, nearly a third of lesions were missed by capromab scans. For the purpose of predicting biochemical failure in the pre-radiation treatment setting, Ellis et al. evaluated the use of capromab pendetide scan with computerized tomography to detect occult metastatic disease in patients about to undergo radiotherapy [60]. The authors found that extra-periprostatic metastatic disease on SPECT/CT significantly predicted a 4.2-fold great risk and a 4.5-fold great risk of failure than organ confined disease adjusting for treatment and risk group. The intermediate risk group appears to benefit most from the scans. While the study provides some intriguing data, it must be confirmed with a larger cohort of patients with longer follow-ups.

## Biochemical Failure

About 30–50 % of patients can experience biochemical failure after definitive treatment for prostate cancer. Radical retropubic prostatectomy is associated with overall 5- and 10-year actuarial biochemical progression-free survival rates ranging from 59 to 84 % and from 47 to 75 %, respectively [3–6]. Clinical and pathologic stage, pretreatment PSA, and pathologic Gleason score are all predictors of progression after surgery [61]. Accurate delineation of local versus metastatic disease is critical for selection of appropriate therapy, to irradiate the prostatic fossa in those patients with presumed local recurrence or to provide systemic therapy for those with disease outside the fossa.

## FDG

Multiple studies have suggested that FDG-PET may have a role in the evaluation of patients with biochemical failure (Fig. 17.1). In one of the very first studies, Sanz et al. evaluated ten patients with biochemical recurrence after radical prostatectomy, radiotherapy, or orchiectomy [62]. The authors reported that FDG-PET was able to show recurrence of prostate cancer more clearly than did CT in two patients; both patients had recurrence in soft tissue. These findings were further reinforced by Chang et al. who performed FDG-PET on 24 patients with biochemical failure after either radical prostatectomy or radiation therapy for localized prostate

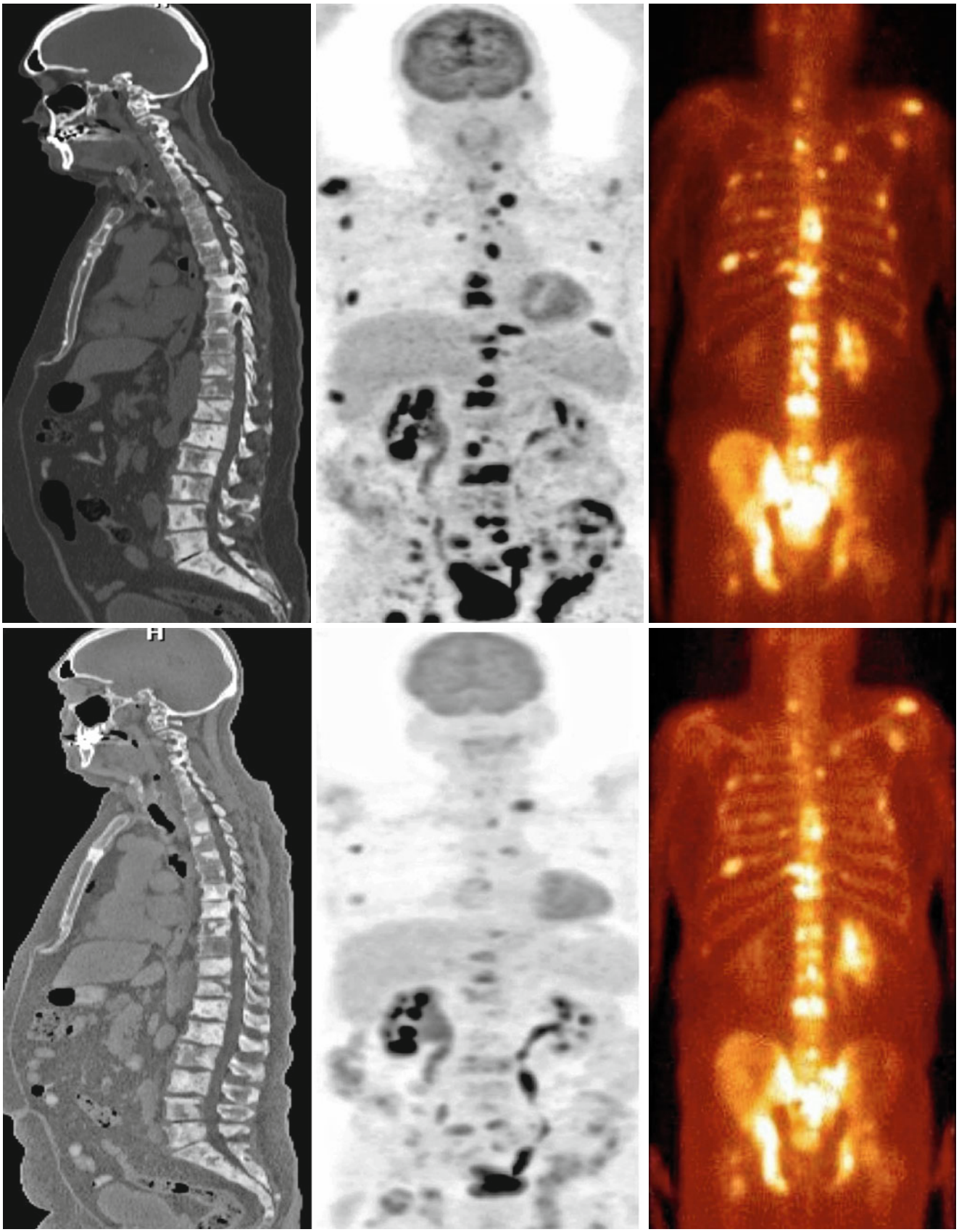

**Fig. 17.1** Midsagittal CT scan at bone window level (*left*), 18F-FDG PET scan (*middle*), and 99mTc-methylene diphosphonate bone scan (*right*) images of a 63-year-old man with castrate-resistant metastatic prostate cancer before (*top row*) and after chemotherapy (*bottom row*). Note that 18F-FDG PET best demonstrates the favorable response to treatment concordant with decline in serum PSA level (from 223 to 52 ng/mL). Also note that the sclerosis of osseous lesions on CT increase as the corresponding metabolic activities on 18F-FDG PET decline with treatment

cancer prior to pelvic lymph node dissection [63]. All patients had normal CT and whole-body bone scans. Histology revealed that 16 of the 24 patients had lymph node metastases, and increased FDG uptake was found in 12/16 patients. The sensitivity, specificity, accuracy, and positive and negative predictive values of FDG-PET in detecting metastatic pelvic lymph nodes were 75, 100, 83.3, 100, and 67.7 %, respectively. Among patients with bony metastases, Oyama et al. found that there was a tendency for higher FDG uptake accumulation in prostate cancer [39].

In a series looking more specifically at biochemical failure after radical prostatectomy, researchers from Memorial Sloan-Kettering Cancer Center retrospectively evaluated 91 patients who underwent FDG-PET [64]. Local or systemic disease was found in 31 % of patients. Imaging revealed lesions in the prostate bed ($n=5$, all true positives), bones ($n=22$, 20 true positives), lymph node ($n=7$, 6 true positives), and one liver metastasis. Receiver operating characteristic analysis showed that a PSA of 2.4 ng/mL and PSA velocity of 1.3 ng/mL/year resulted in the optimal sensitivity (80 % for FDG-PET positive and 71 % for FDG-PET-negative patients) and specificity (73 % for FDG-PET-positive and 77 % for FDG-PET-negative patients). When compared to capromab scans, one study seems to suggest that FDG-PET may be superior. Seltzer et al. evaluated 45 patients with PSA relapse after treatment for localized prostate cancer and found that FDG-PET had a detection rate of 50 % in all patients with elevated PSA or elevated PSA velocity, greater than 4 ng/mL or greater than 0.2 ng/mL/month, respectively [65]. In the subset of patients who also underwent fine needle aspiration, monoclonal antibody scan was true positive in only 1 of 6 patients, while FDG-PET was true positive in 6 in 9 patients.

## Choline

Similar to FDG-PET, the use of choline PET for evaluation of patients with biochemical failure has been well studied. In one of the first studies, de Jong et al. evaluated 36 patients with localized prostate cancer treated by either radical prostatectomy or by external beam radiation [66]. Choline PET was able to detect the site of recurrence accurately in 78 % of patients after external beam radiation compared to 38 % of patients after radical prostatectomy. It is important to note that no positive PET scans were observed in patients with a serum PSA of less than 5 ng/mL. When comparing choline PET to FDG-PET for patients with biochemical failure, Picchio et al. found that out of 100 patients (77 post-prostatectomy and 23 post-radiation), all except one of 14 choline-PET-positive findings were concordant with conventional imaging and all except 1 choline-PET-negative cases had negative conventional imaging after 1 year [67].

More recent studies sought to determine if choline PET could be utilized for patients with PSA less than 4-5 mg/dL. Krause et al. found that out of 63 patients with biochemical recurrence after primary therapy for prostate cancer, 56 % of them showed a pathological 11C-choline uptake [68]. More importantly, the authors demonstrated a relationship between the detection rate of choline PET/CT and the serum PSA level. The detection rate was 36 % for a PSA-value <1 ng/mL, 43 % for a PSA-value 1 to <2 ng/mL, 62 % for a PSA-value 2 to <3 ng/mL, and 73 % for a PSA-value ≥3 ng/mL. The use of antiandrogen therapy did not affect the detection rate. These findings were confirmed in a study by Giovacchini et al. [69]. After evaluating 358 patients who experienced biochemical failure after prostatectomy for prostate cancer, the authors found that choline PET was positive for recurrence in 161 (45 %) patients. The most common sites of recurrence were in the pelvic lymph nodes (66 %), prostatectomy bed (34 %), and skeleton (29 %). These findings were validated by either histological criteria or follow-up clinical and imaging criteria. The overall sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were 85, 93, 91, 87, and 89 %, respectively. The authors also correlated positive PET scan results with PSA levels. The percentage of positive scans was 19 % in those with a PSA level between 0.2 and 1 ng/mL, 46 % in those with a PSA level between 1 and 3 ng/mL, and 82 % in those with a PSA level higher than 3 ng/mL. ROC analysis showed that PET/CT-positive and PET/CT-negative patients could be best distinguished using a PSA cut-off value of 1.4 ng/mL. To evaluate the diagnostic value of choline PET/CT in patients with suspected lymph node involvement before salvage lymphadenectomy, Rinnab et al. evaluated 15 patients with rising PSA following primary treatment for prostate cancer [70]. Eight of the 15 patients were found to have positive histology. Despite being a small study, the authors believed that choline PET/CT may be a useful technique in detection of lymph node metastases in patients with biochemical failure. Reske et al. further evaluated the accuracy of choline PET/CT for localizing occult relapse of prostate cancer by comparing 36 patients with and 13 patients without biochemical failure after prostatectomy [71]. In the test group, PET/CT showed true-positive focal lesions with increased choline uptake in 70 % of the patients with histological verification of local recurrence. The sensitivity and specificity of choline PET/CT were 0.73 and 0.88, respectively.

## Acetate

In one of the earliest trials, Kotzerke et al. evaluated 31 patients with biochemical failure after prostatectomy [72]. Transrectal ultrasound biopsies were also obtained. TRUS biopsy revealed recurrence in 18 patients and acetate PET demonstrated local recurrence in 15 out of the 18 patients. No focal acetate uptake was seen in the prostate bed in patients with negative biopsy. In the subgroup of patients with PSA <2.0 ng/dL, five had positive PET findings with four of them verified by biopsy.

Similar to choline PET, it appeared that there is a correlation between PSA level and detection of prostate cancer recurrence with acetate PET. Fricke et al. demonstrated that acetate PET and FDG-PET were able to detect lesions in 83 and 75 % of patients, respectively [73]. A positive correlation was observed between serum PSA level and both acetate and FDG uptake. This data conflicted with the findings from Oyama et al. [74]. After evaluating 46 patients with biochemical recurrence (30 post prostatectomy, 16 post radiation), the authors found that while 59 % of patients with serum PSA >3 ng/dL had positive finding on acetate PET, only 4 % of patients with serum PSA levels <3 ng/dL had positive findings. Furthermore, acetate PET had higher sensitivity for detecting metastatic lesions with positive finding in 59 % of patients compared to only 17 % using FDG-PET.

In an attempt to increase the accuracy of detection, Wachter et al. performed fused acetate-PET images with either CT or MRI in patients with biochemical failure [75]. Fusion images were able to precisely define the anatomic location of abnormal uptake in 73 % of sites. It also changed characterization of equivocal images as normal in 10 % of 51 suspicious sites and abnormal in 18 % of the 51 sites. More importantly, findings from acetate PET/CT influenced patient management in 28 % of patients. Using acetate PET/CT, Sandblom et al. analyzed 20 patients with biochemical failure after undergoing radical prostatectomy [76]. Pathologic uptake was seen in 75 % of the patients; eight patients had solitary lesion and seven had multiple lesions. The false-positive rate was 15 %, but additional investigations in these men revealed pathologic findings other than prostate cancer (primary lung cancer, esophagitis, and lymphadenitis). Because acetate is not cancer-specific, any disease mechanisms that increase lipid metabolism can result in false positivity. Looking specifically at the use of PET-CT in patients with low PSA levels, Vees et al. evaluated patients with PSA <1 ng/mL by comparing the use of choline and acetate PET/CT with endorectal MRI [77] (Fig. 17.2). The authors found that while both choline and acetate PET/CT were able to detect local residual or recurrent disease in half the patients, endorectal MRI was a more sensitive study, detecting local disease in 15 of 18 patients. Acetate PET is able to detect recurrent disease in patients with biochemical recurrence. The use of fusion images with either CT or MRI can enhance the quality of these studies. However, tumor detection was limited by patients with low PSA. In that cohort of patients, endorectal MRI appeared to be the optimal imaging modality.

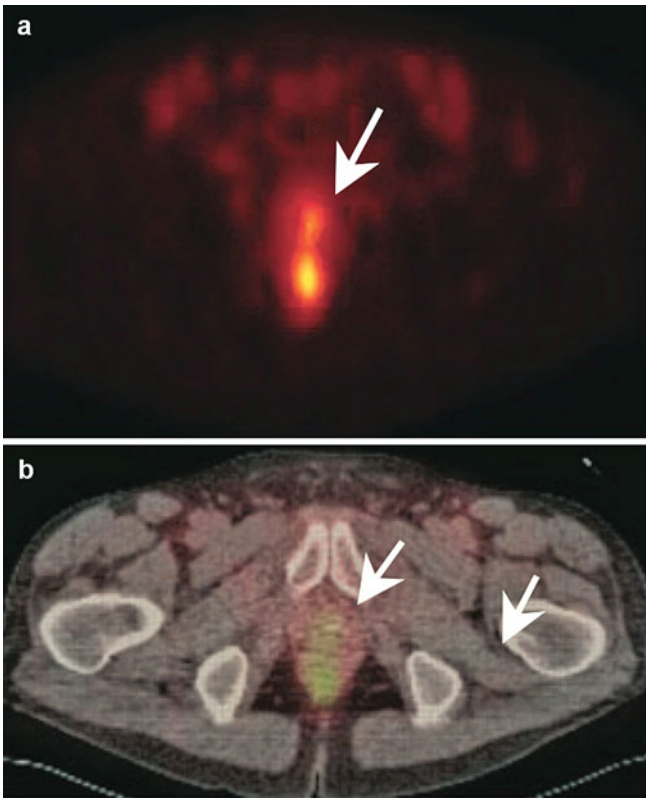


**Fig. 17.2** Example of the use of 11C-acetate PET to detect recurrence. Focal hyperactivity is seen in the prostate bed (**a**) and the fused imaging with the corresponding CT (**b**). The small, focal hyperactivity (*arrow*) reached a SUV of 2.5 (Used with permission from publisher. Vees et al. [77])

## Capromab

Capromab pendetide imaging can localize early PSA recurrence. In one of the largest series, Raj et al. for the Prostascint study group, looked at 255 hormone-naïve men with biochemical failure after radical prostatectomy [78]. Capromab pendetide uptake was seen in 72 % of 255 men with PSA ranging from 0.1 to 4.0 ng/mL, with 31 % of them having local recurrences only. Among those who underwent additional imaging studies, only 12 and 16 % showed evidence of recurrent disease by bone scintigraphy and computed tomography, respectively. Given such promising results, various researchers sought to evaluate if the use of capromab pendetide scan could improve outcomes in patients with localized recurrent disease. One of the first studies to evaluate capromab pendetide's role in evaluating patients with biochemical failure after prostatectomy came from Khan et al. [79]. The author evaluated 32 patients who had biochemical failure after radical prostatectomy. The predicted probability that a durable complete response would be obtained with a normal scan was 0.88; for men with a positive scan limited to the prostatic fossa, it was 0.62; and for men with a positive scan outside the pelvis, it was 0.27. While the median pre-radiation PSA in the nonresponders was higher, multivariable analysis showed that a negative capromab scan was the only significant predictor for durable complete response. These findings were confirmed by Levesque et al. [80]. In 48 patients with biochemical failure following prostatectomy, 13 of the 48 patients underwent adjuvant radiation. Among the six patients who had activity beyond the field of radiation, four patients did not attain durable disease control; on the other

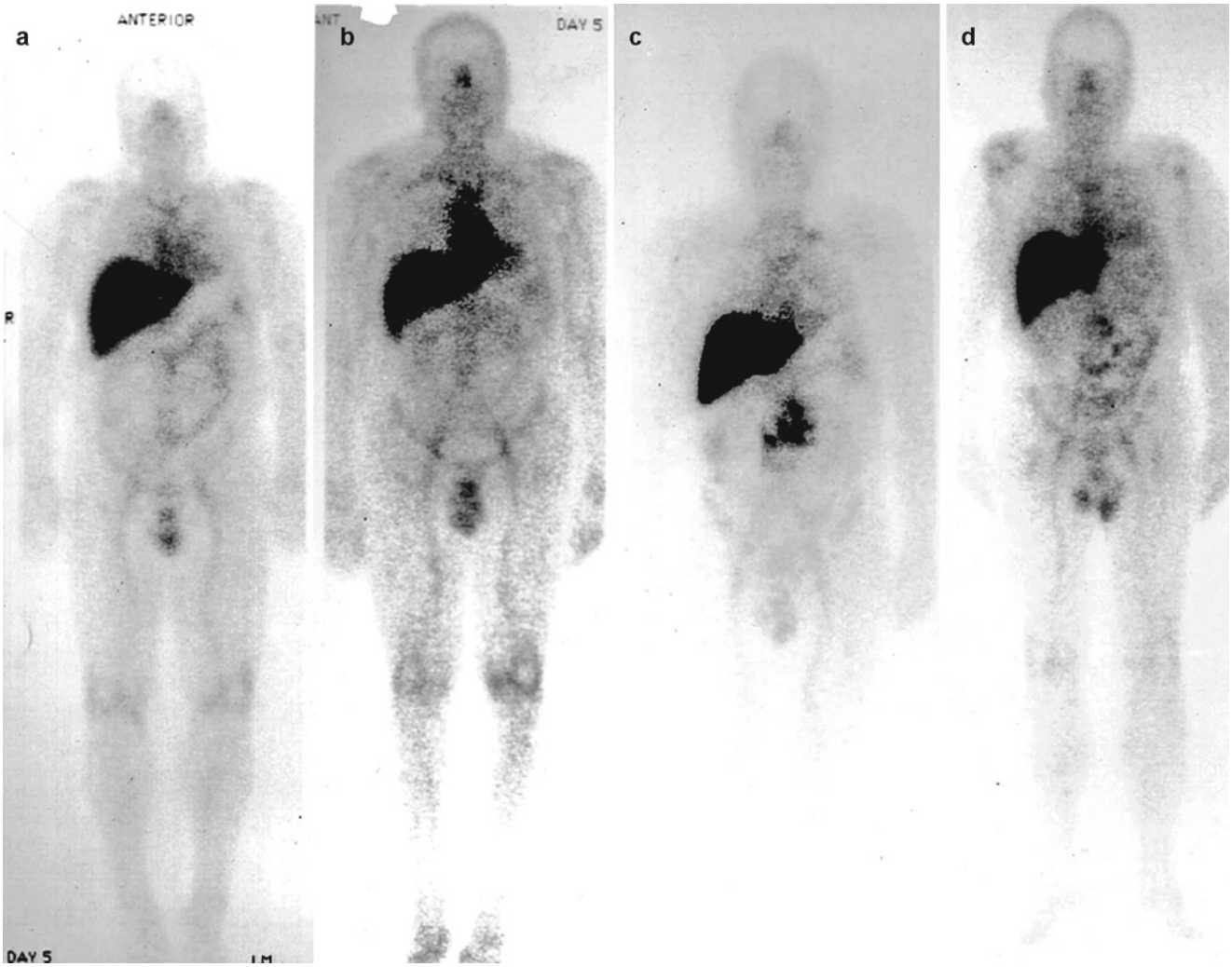


**Fig. 17.3** Coronal images of indium-111-labeled capromab pendetide scans in four patients. (**a**) Negative scan outside the pelvis; prostate-specific antigen (PSA) was uncontrolled by salvage radiation (RT). (**b**) Negative scan outside the pelvis; PSA controlled following RT. (**c**) Positive mesenteric and para-aortic lymph nodes; PSA uncontrolled following RT. (**d**) Positive mesenteric and para-aortic lymph nodes; PSA controlled following RT (Used with permission from publisher. Thomas et al. [81])

hand, of the seven patients who had no activity beyond the field of radiation therapy, only two patients failed treatment.

However, these findings were refuted by data from Thomas [81] and Wilkinson and Chodak [82]. Thomas et al. retrospectively reviewed 30 men with biochemical failure after prostatectomy who underwent salvage radiation therapy. The cumulative 2-year PSA control after salvage radiation therapy was 0.38 compared to 0.31 for men with a positive scan and a normal antibody scan in and outside the prostate fossa, respectively (Fig. 17.3). The hazard ratio for 2-year probability of PSA control after salvage radiotherapy for men with positive scan results outside the prostate bed was 0.81, with the 95 % confidence interval of 0.17–3.78. Meanwhile, Wilkinson and Chodak similarly evaluated 16 patients who underwent salvage radiation therapy for biochemical failure. Of the 15 patients who had isolated uptake in the prostatic fossa based on capromab scans, only 7 (46.7 %) showed a durable response to salvage radiation therapy. Both studies found that capromab scan findings outside the prostate fossa were not predictive of biochemical control.

## Metastatic Disease

### FDG

In terms of metastatic staging, FDG-PET was found to be less sensitive than bone scintigraphy at identifying bony metastases. Shreve et al. evaluated 34 patients with biopsy-proven prostate cancer with known or suspected metastatic disease [83]. Blinded interpretation of the PET images was compared with bone scan, CT, and clinical follow-up findings. The authors found that FDG-PET can help identify metabolically active osseous and soft tissue metastases. Furthermore, in patients undergoing treatment for metastatic prostatic cancer, utility of FDG-PET is fairly limited. Sung

et al. sought to determine the value of FDG PET-CT in evaluating patients with advanced prostate cancer [84]. The authors compared FDG PET-CT scans with bone scintigraphy in 30 patients with advanced prostate cancer (13 with locally extensive prostate cancer and 17 with metastatic disease). They found that staging of advanced prostate cancer may be enhanced by FDG-PET imaging in patients who are untreated, who have had an incomplete response to therapy, or who have a rising PSA despite treatment. Twenty of the 30 patients were positive for radioisotope uptake in the prostate or extraprostatically. The patients with PET-detected prostate cancer were untreated ($n=7$), treated hormonally while they had rising PSA levels ($n=8$), or treated hormonally with a detectable but stable PSA ($n=5$). The remaining ten patients with negative scans were receiving hormone therapy and had undetectable PSA levels.

FDG-PET has been investigated for its use in the assessment of response to treatment of prostate cancer. In one report, FDG accumulation in the primary prostate cancer and metastatic sites decreased over a period of 1–5 months after initiation of androgen-deprivation therapy, which was consistent with results from animal xenograft studies [19, 85, 86]. However, an earlier study of prostate cancer in rats showed that the global FDG SUV was unchanged after treatment with gemcitabine [87]. Preliminary results show that tumor FDG uptake decreases with successful treatment (using androgen-deprivation or various chemotherapy regimens), in concordance with other measures of response, such as decline in serum PSA level [88] (Fig. 17.1).

## Choline

Even though bone scintigraphy is the current gold standard for evaluation of osseous metastatic disease, one of its weaknesses is the lack of differentiation between metastatic and benign inflammatory bone disease. Beheshti et al. evaluated 72 men with prostate cancer with fluorocholine (FCH)-PET/CT for metastatic disease [89]. A total of 262 lesions demonstrated FCH-PET uptake, of which 210 of them were osseous metastases. Fifty-six sclerotic lesions that were considered highly suspicious for metastatic disease on CT or bone scintigraphy demonstrated no FCH uptake. The overall sensitivity, specificity, and accuracy of FCH-PET/CT in detecting bone metastases from prostate cancer were 79, 97, and 84 %, respectively. In a larger cohort of patients, FCH-PET was performed on 111 patients prior to radical prostatectomy with extended pelvic lymph node dissection [53]. The authors found that on a per-patient analysis, the sensitivity, specificity, and positive and negative predictive values of FCH-PET/CT in the detection of malignant lymph nodes were 45, 96, 82, and 83 %, respectively. If the analysis were limited to lymph nodes greater than or equal to 5 mm in diameter, the sensitivity, specificity, and positive and negative predictive values were 66, 96, 82, and 92 %, respectively. FCH-PET/CT led to a change in therapy in 15 % of all patients and 20 % of high-risk patients. Results from these two studies appear to suggest that FCH-PET/CT could be useful to preoperatively exclude high-risk patients with possible metastatic disease (Fig. 17.4). When compared to MR, a small study performed

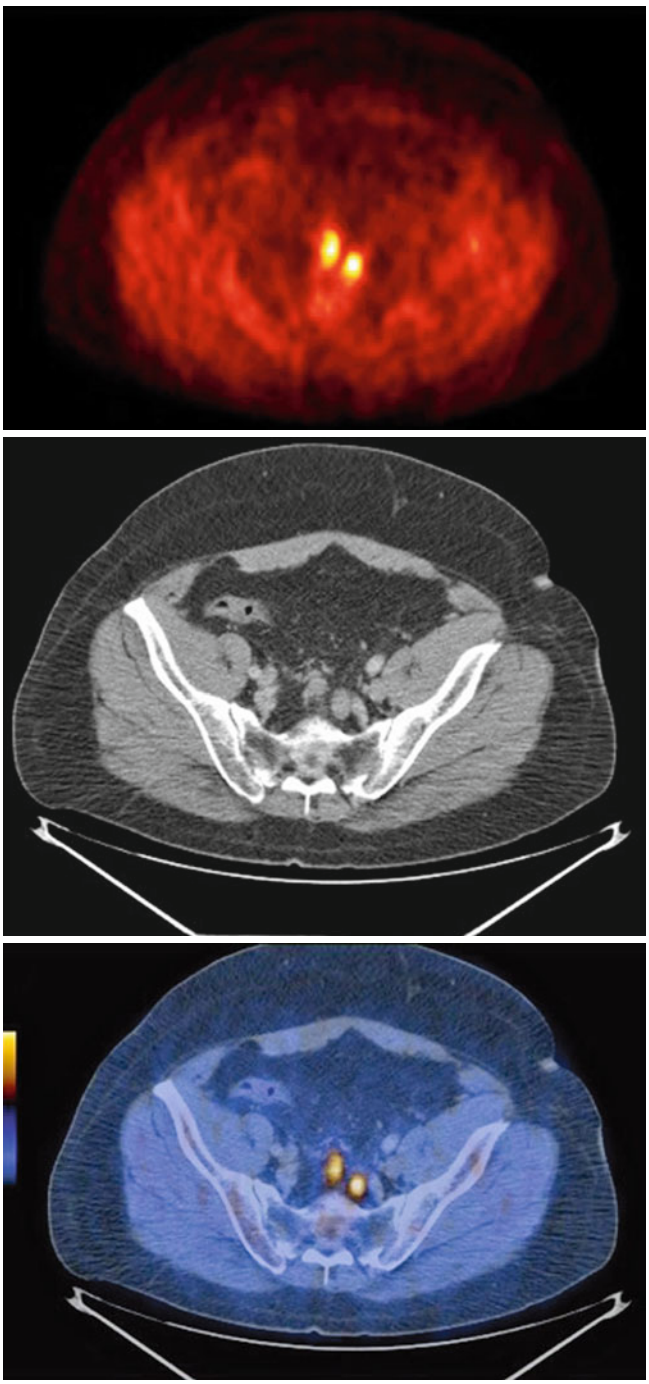

**Fig. 17.4** 18F-fluorocholine PET-CT in metastatic prostate cancer. From *top* to *bottom*: 18F-fluorocholine PET, pelvis CT, and fused PET/CT images demonstrating abnormal accumulation of radiotracer in pelvic lymph node (Courtesy of Mohsen Beheshti, St. Vincent's Hospital, Linz, Austria)

by Luboldt, et al. found that 11C-choline PET/CT was equally effective in detection of bone metastases as diffusion-weighted MRI [90]. But not all choline-based tracers are created equal. Steuber et al. evaluated the use of 18F fluroethylcholine in 20 patients with localized prostate cancer and greater than 20 % risk of lymph node metastases based on published nomogram [91]. Forty-five percent (45 %) of the patients had positive lymph nodes, but fluroethylcholine PET/CT did not detect one single positive lymph node. In terms of evaluation of hormonal therapy status, there is a case report of the use of choline PET/CT that demonstrated decline in tracer localization in lymph nodes of a patient with metastatic prostate cancer [92]. This finding would be of great interest, but a formal series in a much larger cohort of patients would be required.

### Fluoride

Currently, bone scintigraphy scan is the standard method for detecting bone metastases in prostate cancer. More recently, SPECT/CT has been evaluated due to higher sensitivity [93]. 18F-fluoride PET/CT has been shown to be superior to Tc-99m-based bone scintigraphy. In a recent study [94],18F-Fluoride PET/ CT was statistically more sensitive and more specific than planar or SPECT bone scintigraphy ($p=0.05$). The sensitivity, specificity, positive predictive value, and negative predictive value of planar bone scintigraphy were 70, 57, 64, and 55 %, respectively; of multi-FOV SPECT were 92, 82, 86, and 90 %; and of 18F-Fluoride PET/CT were 100 % for all parameters. Furthermore, study by Beheshti et al. prospectively compared 18F-fluorocholine and 18F-fluoride PET-CT for the detection of bone metastases for 38 prostate cancer patients [95]. The sensitivity, specificity, and accuracy of PET–CT in the detection of bone metastases in prostate cancer was 81, 93, and 86 for 18F fluoride, and 74, 99, and 85 % for 18F fluorocholine, respectively. Fluoride PET/CT appears to be an extremely promising tool to detect bone metastases in men with prostate cancer.

## Other Promising PET Radiotracers in Prostate Cancer

Although beyond the scope of this chapter, it is of note that several other promising radiotracers have been investigated in the imaging evaluation of prostate cancer including 16b-18F-fluoro-5a-dihydrotestosterone (FDHT), targeted to the androgen receptor; anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid (anti-FACBC), which is a synthetic L-leucine analog, 1-(2′-deoxy-2′-fluoro-beta-D-arabinofuranosyl)thymine (FMAU), which is a cellular proliferation biomarker; and prostate-specific membrane antigen (PSMA)-based PET radiotracers (96-101) [96–100]. However, the exact diagnostic roles of these radiotracers remain undefined and will require additional studies. It is, however, quite plausible that different PET radiotracers, singly or in combination, may be best suited for accurate imaging evaluation of the various clinical phases of such heterogenous disease as prostate cancer [101, 102].

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# Molecular Risk Profiling

18

Neil E. Martin

## Introduction

Despite a stage migration toward lower-risk disease at diagnosis in the setting of prostate-specific antigen (PSA) screening [1], prostate cancer remains a heterogeneous disease with the prognosis, treatment approach, and outcomes largely dependent on the biology of the tumor. Prostate cancer is the second most common cause of cancer death in males in the United States, but the rate of prostate cancer mortality is relatively low with 8-year cause-specific survival of more than 95 % [2]. Currently, in populations with PSA screening, over 90 % of prostate cancers are clinically localized at time of diagnosis [1], and in this setting, traditional methods of stratifying patients into groups with similar outcomes following local therapy based on clinical and pathologic features [3] lose much of their discriminatory power. Additionally, evidence from randomized trials of PSA screening [4–6] demonstrate that a significant fraction of newly diagnosed men are being treated for insignificant disease. With an expanding set of tools capable of broadly profiling the biology underlying prostate cancer, novel therapeutic agents coming to the market, and a need to better categorize those men with low-risk disease who should be treated, there has been an increasing interest in the molecular prognostic factors in prostate cancer.

## Risk Profiling

The most consistent clinical and pathologic predictors of outcome in prostate cancer are the Gleason score [7, 8], T-category [9], and PSA value at diagnosis [10, 11] which, when combined, form the basis for a widely used risk stratification system [3]. Alone though, these markers lose their power to capture the heterogeneous clinical course for men with low- and intermediate-risk disease. To improve upon these factors, researchers have investigated both genomic and molecular markers of prognosis in prostate cancer. In this chapter, we will focus on molecular prognostic factors believed to be driving many of the features of cancer.

## Tumor Factors

Selective markers from each general characteristic of malignant cells are outlined in Table 18.1. Broadly, most markers have been tested predominantly in radical prostatectomy (RP) samples given the tissue availability and so inform disease recurrence following surgery and not necessarily at the time of diagnosis. There is very limited data about markers of prognosis in active surveillance or watchful waiting cohorts despite the clear clinical need. For structure, markers are categorized according to the six broad hallmarks of cancer [45].

### Self-Sufficiency in Growth Signals

In contrast to normal cells, tumor cells develop the ability to promote growth in the absence of normally regulated signaling systems. There are numerous pro-growth signaling pathways implicated in prostate cancer progression including androgen signaling, phosphoinositol 3-kinase (PI3K), epidermal growth factor receptor (EGFR), RAS, and metabolic dysregulation. Selected studies for each of several pathways of interest are presented in Table 18.1 as they relate to prognosis.

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**Table 18.1** Selected tumor-specific molecular markers associated with prognosis in prostate cancer

| Marker | Action | Notes |
|---|---|---|
| *Self-sufficiency in growth signals* | | |
| Androgen receptor | Acts as a transcription factor mediating cell growth | Heterogeneous data based on IHC but large RP series appear to support its prognostic value [12] Mutations are common in the castration-resistant setting and are associated with response [13] |
| Ki67 | Nuclear antigen used as a marker of cellular proliferation | Ki67 has been found to be prognostic in radiation-treated patients [14] as well as those undergoing RP [15] |
| TMPRSS2:ERG | Gene fusion between androgen-responsive element and a family of transcription factors | Present in approximately 50 % of localized prostate cancers, this gene fusion has been associated with lethal disease in watchful waiting cohorts [16, 17] but in contrast was not associated with outcomes in other RP series [18] |
| AKT/PTEN | Components of the phosphoinositol 3-kinase oncogenic pathway | Loss of the tumor suppressor gene *PTEN* is related to clinical outcomes in RP specimens [19, 20]. Similarly, the presence of the activated form of AKT [21] and the unaltered protein itself [22] have prognostic value following RP |
| Epidermal growth factor receptor (EGFR) | Transmembrane receptor mediating extracellular pro-growth signals to numerous downstream pathways | Increased EGFR staining and copy number is associated with an increased risk of recurrence following RP [23]. Only 18 % of tumors overexpressed EGFR, and there was heterogeneous amplification in most tumors |
| RAS | Oncogene related to numerous pro-growth pathways | Despite extensive research, mutations in *RAS* are infrequent and apparently unrelated to clinical course [24] |
| Fatty acid synthase | Metabolic enzyme critical in long chain fatty acids | The *FASN* gene is implicated as an oncogene in prostate cancer [25] and has independent prognostic value following RP [26] |
| EZH2 | Gene silencing protein | High expression of *EZH2* is associated with a poor prognosis in localized disease and is present in metastatic disease [27] |
| *Insensitivity to antigrowth signals* | | |
| p16/INK4A | Tumor suppressor gene related to cell cycle control | Overexpression of p16/INK4A is independently related to recurrence of disease [28] |
| p21/WAF1/CIP1 | Regulates $G_1$ of the cell cycle | Increased p21/WAF1/CIP1 staining is independently prognostic for recurrent disease following RP [29] |
| p27/KIP1 | Cell cycle inhibitor | Decreased expression of the protein is independently associated with poor outcomes [30]. The protein SKP2 targets p27/KIP1 for degradation, and higher levels also correlate with worsened outcome [31] |
| C-MYC | Oncogenic transcription factor | Fluorescence in situ hybridization (FISH) copy number for the gene significantly predicts progression and survival [32] though with IHC, expression of C-MYC is not independently related to clinical outcome [33]. Single-nucleotide polymorphisms in the region of 8q24, the region of the *MYC* gene are associated with an increased risk of prostate cancer [34] |
| *Limitless replicative potential* | | |
| Telomeres | Nucleoprotein complexes capping chromosome ends | Though there is limited looking at telomeres in prostate cancer, decreased telomere length is associated with a poor prognosis [35] |
| *Evasion of apoptosis* | | |
| p53 | Tumor suppressor gene associated with DNA repair | In the post-RP setting, nuclear p53 expression is independently associated with disease progression [36] |
| BCL2 | Apoptosis regulator | Increased nuclear expression of BCL2 is independent prognostic for recurrence following RP [37, 38]. Similar results were found on biopsy specimens from patients receiving radiation [39] |
| BAX | Proapoptotic member of the BCL2 family | The ratio of BCL2:BAX was predictive of worsened outcome following radiation [40] |
| *Sustained angiogenesis* | | |
| Vascular endothelial growth factor | Driver of neovascularization | Among patients receiving radiation [41] and surgery [42], VEGF staining predicted shored time to biochemical recurrence |
| *Tissue invasion and metastasis* | | |

**Table 18.1** (continued)

| Marker | Action | Notes |
|---|---|---|
| E-cadherin | Cell adhesion molecule | Low expression of E-cadherin is independently associated with death in men treated with TURP [43] |
| Transforming growth factor-β (beta) | Pro-growth cytokine | TGF-β (beta) is implicated as a key factor in the tumor microenvironment of prostate cancers, and increased tumor expression is associated with metastases and poor prognosis [44] |

### Insensitivity to Antigrowth Signals

Progression through the cell cycle in normal cells is a well-regulated process involving the interplay of numerous signaling factors. Loss of these control mechanisms provides tumor cells the opportunity to grow unchecked. In prostate cancer, disruption of several of these molecular features provides prognostic information following RP including p16/INK4A, p21/WAF1/CIP1, and p27/KIP1 (Table 18.1). An additional marker thought to be central to antigrowth regulation is the oncogenic transcription factor C-MYC. High gene copy number for *MYC* is prognostic for worsened outcome in prostate cancer.

### Limitless Replicative Potential

Normal cells have a finite capacity to replicate as determined by telomeres. These base-pair repeats at the ends of chromosomes shorten with each cell division ultimately leading to cell death when they are no longer capable of protecting the chromosome ends. Shortened telomere length in tumor cells has been associated with a poor prognosis though there are relatively few studies investigating this marker in prostate cancer.

### Evasion of Apoptosis

Tumor development is characterized not only by increased pro-growth and decreased control signaling but also decreased cell attrition through apoptosis. This well-regulated process of cell death is mediated by a variety of factors; some of which have been explored as prognostic factors in prostate cancer. A central signaling molecule for DNA damage and regulator of apoptosis is p53. The *TP53* gene is commonly mutated in other solid tumors but less frequently in prostate cancer [46]. Localization to the nucleus of the p53 molecule in prostate tumors has been independently associated with poor prognosis though as have other markers of disrupted apoptosis signaling (Table 18.1).

### Sustained Angiogenesis

In light of the limited diffusion capacity of oxygen and essential nutrients, tumors require the development of new blood vessels as they increase in size. This typically highly regulated process becomes disorganized in tumors and in prostate cancer, and both vessel density [37] and morphology [47] have been shown to have prognostic implications. Additionally, vascular endothelial growth factor (VEGF) expression has been associated with poor prognosis in those receiving both surgery and radiation as primary treatment (Table 18.1).

### Tissue Invasion and Metastasis

Lethal prostate cancer inevitably metastasizes to distant sites in the body. The processes controlling this capacity to invade and ultimately metastasize are not fully understood, but the tumor microenvironment is thought to play a crucial role. As seen in Table 18.1, markers of cell adhesion such as E-cadherin and cytokines such as transforming growth factor beta (TGF-β) have prognostic significance following surgery in prostate cancer.

## Circulating Biomarkers

While tumor markers are appealing because they are thought to reflect true biologic changes within the cells of interest, investigators have also looked to other sources for prognostic markers in prostate cancer. Blood or urine markers are appealing not only for their ease of access but also because they may ameliorate concerns of the sampling errors and heterogeneity from the tumor itself.

### Circulating and Disseminated Tumor Cells

The development of overt metastases has been typically considered a late event in the malignant progression, but there is evolving evidence suggesting that dissemination of primary cancer cells to distant sites might occur earlier in tumorigenesis [48].

Several assays for the detection of disseminated tumor cells (DTCs) in bone marrow and circulating tumor cells (CTCs) in the peripheral blood have been developed to better understand this process and its clinical implications. Broadly, the two techniques employed are based on an immunological

identification of cell-surface markers and a PCR-based approach of identifying prostate-specific RNA in cells [49]. Although antibody-dependent, the immunological method has the advantage of being easy to perform and enables the evaluation of cell size and morphology. The PCR-based assays have the advantage of being extremely sensitive and able to detect aberrations at a single-cell level, though may not be more sensitive for detecting circulating tumor cells. Transcripts specific to prostate such as PSA, prostate stem cell antigen (PSCA), and prostate-specific membrane antigen (PSMA) are typically utilized as single or multiplexed surrogate markers in blood CTCs using PCR. The major limitation of the molecular approach is poor specificity due to illegitimate transcripts and heterogeneous expression of target markers. A cell-enrichment step during the CTC isolation process and identification of reliable cutoff values for analysis may overcome these problems [50].

The bone represents the most common location of metastatic disease in prostate cancer, and therefore most clinical reports on DTC focus on the bone marrow. There are significant correlations between the presence of DTC and clinical-pathological parameters such as high Gleason score or metastatic disease [51, 52]. The presence of DTC in the bone marrow at the time of diagnosis is also an independent negative prognostic parameter in patients with localized prostate cancer [53].

Because bone marrow aspiration is invasive and potentially uncomfortable for the patients, more recent efforts have focused on the detection of CTCs in the peripheral blood. Using PCR, CTCs can now be detected in the blood at the time of diagnosis as well as over the course of therapy. Their increased number has been positively associated with higher Gleason score and stage [54]. Using PCR, the detection of PSA mRNA is significantly correlated to time to progression and overall survival [55].

Immunologic approaches to detecting CTCs were developed in the face of technical limitations of the PCR technique and the need for more standardized methods in the peripheral blood. The Food and Drug Administration has now approved a technology (Cell Search, Veridex) that can be used for the monitoring of metastatic breast, colon, and prostate cancer. With recently collected peripheral blood, this device is able to isolate single CTCs by immunomagnetic enrichment followed by fluorimetric count.

Data generated using this system shows that CTCs are detectible in 55–62 % of patients with castration-resistant prostate cancer [56, 57]. A baseline CTC count ≥5 cells/7.5 mL of blood before therapy was found to represent a powerful predictor of poor overall survival [58]. The change in detectable number of CTCs following therapy is also predictive of clinical outcomes [55]. In one study, patients with a CTC count that dropped from ≥5 cells at baseline to <5 cells after treatment had a better overall survival compared with those showing an increase during therapy [59]. Though potentially valuable in the metastatic setting, in patients with organ-confined prostate cancer, few CTCs are detectible using currently available technologies and do not appear to correlate with known prognostic factors, though further studies are needed [60].

In addition to their potential prognostic value, there is clearly potential utility in characterizing CTC or DTC in cancer patients to provide additional information on cancer biology and treatment selection. Both high- and low-resolution techniques such as FISH or CGH can be performed on isolated cancer cells to obtain a genomic profile of CTCs/DTCs that could be related to prognosis and response to therapy [61–63]. In non-small cell lung cancer, a proof of concept study showed that CTCs could identify tumors with specific *EGFR* mutations sensitive to anti-EGFR small molecules demonstrating the value of these "liquid biopsies." [64].

## Urine Markers

Given the proximity of the urethra and bladder to the prostate, urine is also considered a potential source of clinically useful biomarkers in men with prostate cancer. The prostate cancer antigen 3 (PCA3) gene is differentially expressed in prostate cancer samples compared to normal prostate tissue [65]. The protein product can be identified in urine, particularly in the first void after a digital rectal exam when tumor cells are known to be present [66, 67]. To date, much of the work with PCA3 has been limited to the diagnosis of men with prostate cancer. In this setting, it has been shown that PCA3 can improve upon the specificity of PSA [68]. One study also showed that PCA3 was independently correlated with extracapsular extension identified on radical prostatectomy [69]. The *TMPRSS2:ERG* fusion has also been investigated in the urine [70, 71]. Using FISH or PCR, it can be detected in post-DRE urine, and its presence may eventually be used in combination with other biomarkers to improve the specificity of screening for prostate cancer [72, 73]. The kinetics of these markers with treatment and disease progression has not been fully investigated, and they may eventually be used to help follow response to treatment.

## Serum Markers

Multiple serum markers have been investigated for their potential role in providing prognostic information in prostate cancer. Members of the human kallikrein gene family which include PSA and bone turnover markers have been investigated for their utility in prognostication in prostate cancer with mixed results [74, 75]. Given its proven role in the tumor microenvironment, TGF-β (beta) has also been

explored in the serum as a prognostic factor [76]. Another marker believed to come from the tumor microenvironment is interleukin-6, and levels of its soluble receptor in the blood have been shown to be prognostic following RP [77].

**Conclusions**

As outlined in this chapter, molecular markers of prognosis in prostate cancer are plentiful in the literature. Despite this, they remain, to a large extent, unused clinically. This is likely the result of numerous factors including relatively modest effect size for any given marker and poor standardization of the tools of detection and analysis: from antibody selection to interpretation to selecting cut points for "positive" and "negative," there is significant room for variability. This variability leads frequently to poor reproducibility between studies and difficulty interpreting negative results. To improve the interpretability of these molecular markers, there are now standardized reporting criteria which are used by some journals for biomarker studies [78]. The widespread adoption of these recommendations will help overcome some of these methodological issues. Technologic advances in biomarker assessment such as multispectral imaging [79] may also prove useful as multiple markers may be needed simultaneously to best predict the clinical course. Despite continued advances in our understanding of the molecular underpinnings of prostate cancer, and some markers which show promise, there remains a strong clinical need for reliable molecular prognostic factors in prostate cancer.

## Updates

Advances in our understanding of the underlying genetics and genomics of prostate cancer have recently led to new molecular signatures of poor outcome in prostate cancer. As with any prognostic marker, a molecular signature should be predictive of outcome independent of Gleason score and other clinical markers. Four potentially useful signatures are outlined below:

*Copy number alterations.* Taylor performed an integrative genomic analysis of 218 prostate cancer tumors from patients followed for a median of 5 years for biochemical recurrence [80]. Whole genome mRNA, miRNA, and copy number aberrations were assessed. No mRNA signatures could be identified relating to poor outcome following surgery. They were able to identify a signature within the copy number data that predicted differences in time to biochemical relapse, independent of Gleason grade.

*Cell-cycle progression signature.* Cuzick used a pathway-based approach to identify a prognostic signature, focusing on genes involved in cell cycle progression [81]. They measured mRNA levels of a set of 31 genes to robustly capture cellular proliferation. Among 366 prostate cancer patients who underwent prostatectomy, mRNA expression of genes in the cell-cycle progression signature significantly predicted biochemical recurrence, independent of Gleason and other clinical factors. Additionally, in a cohort of 337 men with prostate cancer diagnosed on transurethral resection of prostate, the same signature predicted prostate cancer mortality, independent of Gleason grade and Ki67 expression.

*4-marker signature of lethal prostate cancer.* Ding and colleagues performed comparative oncogenomics to derive a signature of prostate cancer prognosis [82]. After identifying *SMAD4, PTEN, SPP1, and CCND1* as drivers of invasive and metastatic prostate cancer in a mouse model, they explored the protein expression of these same markers in a human cohort. At the mRNA level, the signature was significantly associated with biochemical recurrence and lethal prostate cancer in two small cohorts. Among 367 prostate cancers from men in the Physicians' Health Study who had undergone radical prostatectomy, the 4-marker signature was a significantly better predictor of lethal prostate cancer than Gleason score alone.

*Signature of Gleason score*. In light of the importance of the Gleason score in prediction clinical course, Penney and colleagues developed a 157-gene mRNA expression signature of Gleason grade [83]. To develop the signature, tumors comprised of Gleason 3 + 3, and Gleason ≥8 was compared. When applied to Gleason 7 tumors, an increased probability of high-grade disease was associated with a significant increased risk of lethal prostate cancer. For every 33 % increase in the prediction of the higher-grade tumor, there was an odds ratio of 1.47 (95 % CI 1.11–1.94) for lethal outcome in a multivariate model.

These four signatures illustrate the promise of molecular and genetic signatures in the prognostication of outcome for men diagnosed with prostate cancer. As with all biomarkers, clinical validation in additional cohorts with lethal prostate cancer as the endpoint will be crucial before they can be used widely in the clinic.

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# Premalignant Lesions of the Prostate

19

Daniel M. Berney and Anne Y. Warren

## Introduction

A premalignant condition is a disease, syndrome, or constellation of features that, if left untreated, may lead to invasive cancer. When discovered, it demonstrates a significantly increased risk of cancer for that individual when compared to the general population. In pathological terms, premalignancy equates to morphologically altered tissue in which cancer is more likely to occur than its apparently normal counterpart.

In many organs, premalignancy has been described and defined for centuries. In 1851, Sir James Paget was the first to specifically suggest an association between a benign oral mucosal lesion and the subsequent development of oral malignancy [1]. A century later, Slaughter found premalignant lesions adjacent to tumor in squamous cell carcinomas of the head and neck leading to hypotheses of "field change" secondary to carcinogens in tobacco and alcohol [2]. Since this time, nearly every epithelial tissue has been shown to be associated with a premalignant morphological stage. In the vast majority of these, the threshold between premalignancy and malignancy has been invasion of the basement membrane, though this is not universal.

The premalignant lesions associated with prostate cancer have proved a more recent development and harder to elucidate and define. This is for a number of reasons. Firstly, the extremely high rate of malignancy in developed countries on full inspection of the prostate means that associated premalignancies cannot be identified in comparison with control populations.

Secondly, difficulty in examination of the whole gland in control cases makes contemporary comparisons difficult. Thirdly, as we have limited knowledge of the etiological causes of prostate cancer, the reasons for its unusual geographical distribution, and have minimal knowledge of its molecular biology, linking premalignancies with known epidemiological factors is virtually impossible. This chapter will consider the development, morphology, and significance of each of the putative premalignant conditions associated with prostate carcinoma, as well as morphological changes, which are not premalignant in themselves, but their identification is significantly associated with the later diagnosis of prostate cancer.

## Prostatic Intraepithelial Neoplasia (PIN)

Prostatic intraepithelial neoplasia (PIN) is defined as a neoplastic proliferation of the prostatic acinar cells, which is confined by the basement membrane and is therefore intraepithelial and unlike prostatic adenocarcinoma does not display invasion of the stroma. It demonstrates specific morphological features, which separate it from other potential premalignant conditions, which will be discussed later. A morphological constellation of features termed high-grade prostatic intraepithelial neoplasia (HGPIN) is the most likely precursor of prostatic adenocarcinoma according to virtually all available evidence; however, the development of this entity is tortuous and a historical resume of its evolution is necessary.

### The History of PIN

Morphologically identified atypical lesions, which do not display stromal invasion, have been identified for many

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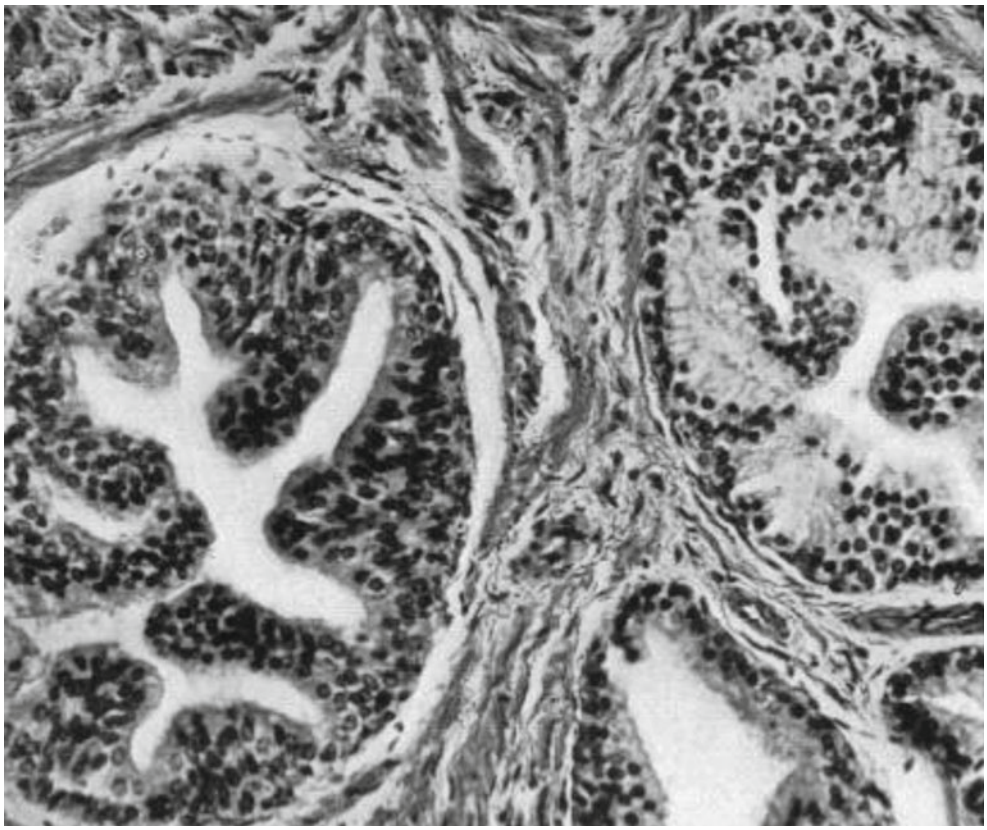


**Fig. 19.1** Andrews' paper showing on the left, a gland showing nuclear hyperchromasia and papillary infoldings, probably representing PIN, though the grade cannot be determined as the quality is insufficient to see nucleoli (With permission from *J Clin Path*)

years. In 1949, with remarkably astute observational work, Andrews from Bristol, UK, identified a "latent carcinoma of the prostate" in which he discussed lesions which could be identified in cases of prostatic carcinoma where the basal cell appeared absent, but the relationship with the stroma was that of a benign gland [3]. Illustrations from this article could serve as exemplary articles of PIN today (Fig. 19.1).

A large number of diagnostic labels have been applied to PIN. Atypical hyperplasia was a term used by Gleason among others [4]. Two different potential preneoplastic entities were described by McNeal which he termed intraductal dysplasia (what we now term PIN) and adenomatous hyperplasia (which we now call adenosis or atypical adenomatous hyperplasia) [5]. Morphological characteristics of the grades of dysplasia were provided by McNeal and Bostwick in 1986 [6] and shortly after this, it was advocated that the preneoplastic lesion should be termed PIN, which was accepted at a consensus conference in 1989 [7], as well as adoption of a high-grade and low-grade stratification rather than a three level stratification. This is the system in use today.

PIN is characterized by cellular proliferations within preexisting ducts and acini, with nuclear and nucleolar enlargement similar to that seen in prostate cancer, although unlike cancer, HGPIN retains a basal cell layer. The recognition of HGPIN is clinically important because of the strong association between this disease and prostatic carcinoma. The predictive value for cancer of an initial diagnosis of HGPIN on needle biopsy has substantially declined, with values falling from 36 to 21 %. A major factor contributing to this decline is related to increased use of needle biopsy core sampling, which has provided the means for many cancers associated with HGPIN to be detected on initial biopsy; repeat biopsy, even with good sampling, does not detect many additional cancers. Other possible findings in the prostate might indicate premalignant disease (low-grade prostatic intraepithelial neoplasia, atrophy, malignancy-associated changes, and atypical adenomatous hyperplasia or adenosis), but the data for these premalignant diseases are much less convincing than those for HGPIN.

## The Morphology of Low-Grade PIN

Low-grade PIN is a challenging descriptor that is placed on non-invasive epithelial lesions, where the amount of atypia falls short of a diagnosis of HGPIN. In low-grade PIN, there is nuclear enlargement compared with normal secretory cells and increased nuclear pleomorphism and hyperchromatism (more intense staining with hematoxylin secondary to increased DNA content of the nucleus). Crucially, there are small or inconspicuous nucleoli [6]. Mitotic figures are difficult to identify and lower than HGPIN but higher than in normal prostate tissue [8]. The poor interobserver reproducibility of low-grade PIN even between expert

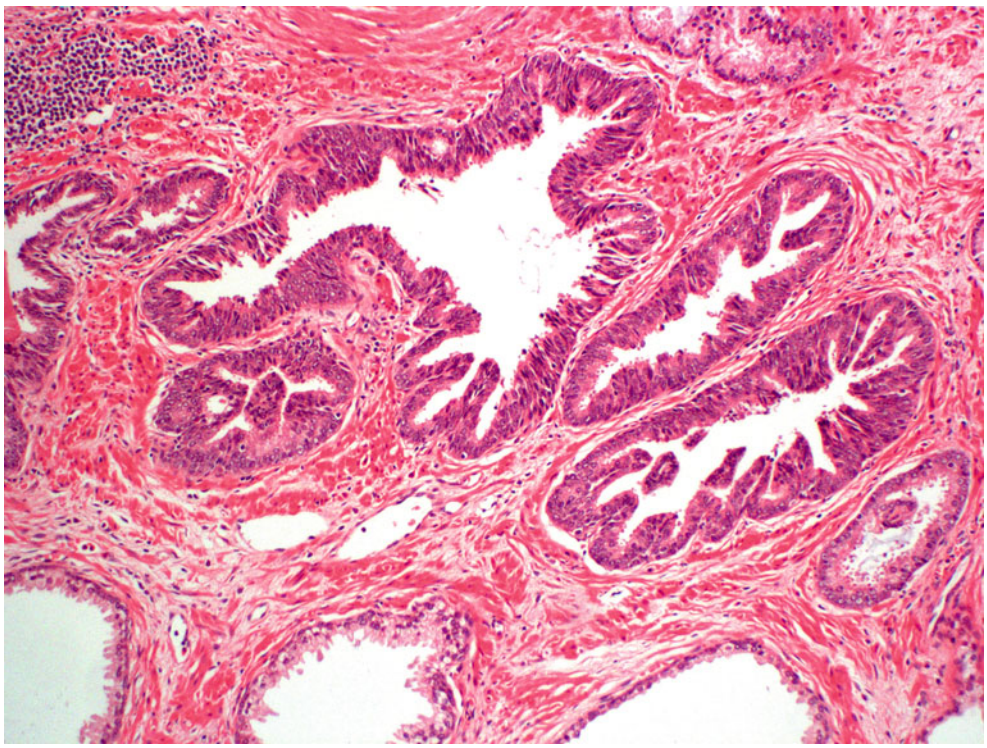


**Fig. 19.2** High-grade PIN. Low-magnification image showing glands with high-grade PIN (*center*) more deeply staining than surrounding benign glands

pathologists [9], and its unproven relationship to invasive carcinoma, means that it is not a useful entity to report in routine diagnostic work.

Low-grade PIN alone, therefore, is regarded as part of the spectrum of changes seen in benign prostatic tissue in histology reports and does not represent a well-defined pathological entity. For these reasons, we have chosen not to illustrate low-grade PIN as it remains unhelpful in the diagnosis and treatment in prostate cancer. Should it become better defined and interobserver error-improved, it may prove of interest in the future both for epidemiological and pathogenetic reasons, and it has been reported in studies linking morphology with genetic changes [10]; however, at present, it remains unproven as a robust diagnosis.

## The Morphology of HGPIN

In all cases of HGPIN, it is a requirement, by definition, that the lesion is not invasive. Together with this requirement are nuclear features, which resemble those of invasive prostatic adenocarcinoma. These include many of the features seen in low-grade PIN but usually to a greater extent: nuclear enlargement, hyperchromatism, and increased clumped chromatin. High-grade PIN is usually recognizable at low-power magnification in normal-sized or enlarged ducts due to its complex architectural features (discussed below) and darker appearance imparted by its deeply stained "amphophilic" cytoplasm and atypical nuclear features, when compared with adjacent normal ducts (Fig. 19.2). Characteristic partial duct involvement by the atypical epithelium may also aid recognition. The principle morphological features are summarized in Table 19.1 (Fig. 19.3). Most authors would not diagnose HGPIN without the presence of macronucleoli (greater than 3 μm). However, unsurprisingly, there is a spectrum of morphological features between HGPIN and low-grade PIN, and number, clarity, and size of nucleoli can all affect diagnosis. There appears to be no minimum requirement of the number of macronucleoli seen in HGPIN. Additional features, such as perinuclear haloes, a sharp luminal border, and a variety of luminal contents similar to those in invasive carcinoma, may also be helpful in diagnosis. Distinction from benign mimics of HGPIN that may also have prominent nucleoli, such as basal cell hyperplasia [11], inflammatory atypia, or atypia in glands adjacent to an infarct, can be difficult and results in over diagnosis of PIN or malignancy [12]. Other well-known benign pitfalls are radiation atypia, normal central zone glands [13], cribriform hyperplasia, seminal vesicle or ejaculatory

**Table 19.1** Morphological features of high-grade PIN

| |
|---|
| Nuclear crowding and stratification |
| Nuclear enlargement |
| Nuclear hyperchromasia |
| Irregular chromatin |
| Prominent nucleoli |
| Amphophilic cytoplasm |
| Cytoplasmic apical blebs |

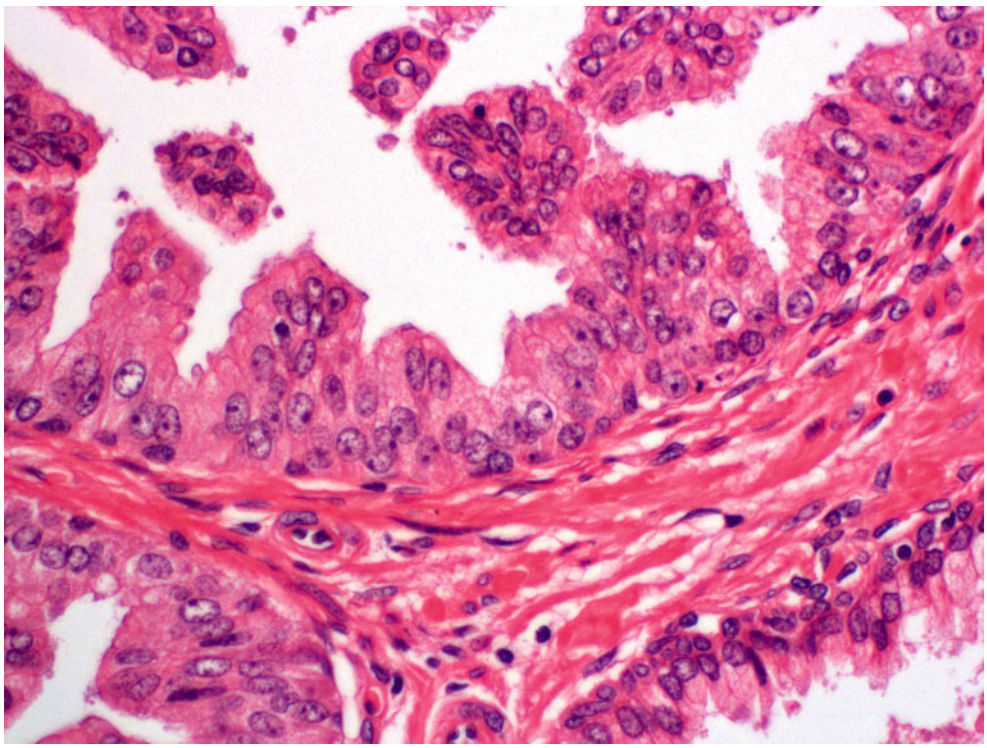


**Fig. 19.3** High-grade PIN nuclear atypia. The nuclear abnormalities contrast with the smaller nuclei of the adjacent benign gland (*bottom right*)

duct epithelium, and transitional and squamous metaplasia [14]. The correct diagnosis requires careful assessment of the architectural and cytological appearances and an appreciation of other associated features that aid distinction.

High-grade PIN can be defined according to its architectural variations and also occasionally by variations in the differentiation patterns of the cells.

There are four main architectural patterns: tufting, micropapillary, cribriform, and flat [15]. Tufting and micropapillary are the commonest, although multiple patterns are often present, with the tufting pattern present in 97 % of cases. In the tufting pattern, the luminal cells have an undulating arrangement of the thickened epithelium due to the cellular crowding and stratification. The micropapillary pattern has fine papillary structures, usually lacking in fibrovascular cores that protrude into the duct lumen. The cribriform pattern is characterized by a more florid and solid cellular proliferation, with intercellular spaces that impart a sieve-like appearance. The uncommon flat pattern may be overlooked due to the lack of an obvious architectural abnormality at low power, as the atypical epithelium often consists of only a single layer of cells (Fig. 19.4a–d).

## Differentiation Patterns in HGPIN

Several variants of HGPIN have been described in terms of the cytoplasmic differentiation of the cells rather than overall architectural patterns: signet ring cell [16], small-cell neuroendocrine, mucinous [16], foamy [17], and inverted [18], solid and squamous differentiation. They are inevitably associated with corresponding differentiation patterns in the invasive component, but are rare, and probably have no clinical significance. However, the presence in HGPIN of these various histological features provides additional support for a close relationship between HGPIN and the variants of invasive prostate carcinoma.

## Immunochemistry of HGPIN

The majority of cases of HGPIN show immunochemical positively for α-methylacyl-CoA racemase (AMACR), which, similar to carcinoma cells, decorate the cytoplasm with a coarse apical pattern though there is a lower frequency of expression than is seen in invasive adenocarcinomas [19–21] (Fig. 19.5a–d). By definition, the basal cell layer is intact in PIN, but while circumferential basal cells are usual in low-grade PIN, there may be a high degree of loss of basal cells in HGPIN where they are interrupted, less frequent, and occasionally lost altogether [22]. Immunohistochemistry for basal cell markers such as nuclear p63 [23, 24] or a cytoplasmic high-molecular-weight cytokeratin such as 34βE12 [25] therefore reveals patchy staining but no widespread complete loss. Correlation of basal cell patterns of loss with the hematoxylin and eosin slide is necessary to fully interpret the nature of difficult foci. Rare cases of carcinoma that express 34βE12 may also prove diagnostically problematic [26].

## Incidence of HGPIN

The incidence of HGPIN is extremely variable in reported series. This is due partly to differences in specimen type but also due to differences in population (age or ethnicity), biopsy procedure, and also on the thresholds for diagnosis of the reporting pathologist.

Prostate glands may be removed in total for invasive carcinoma and also may be removed when no carcinoma is suspected, such as for a radical cystectomy and also at postmortem. When carcinoma is present, the incidence of HGPIN that has been reported varies from 31 to 99 % [27, 28], though the vast majority report rates of 60 % or higher [6, 29, 30]. When carcinoma is not present, the rate is lower,

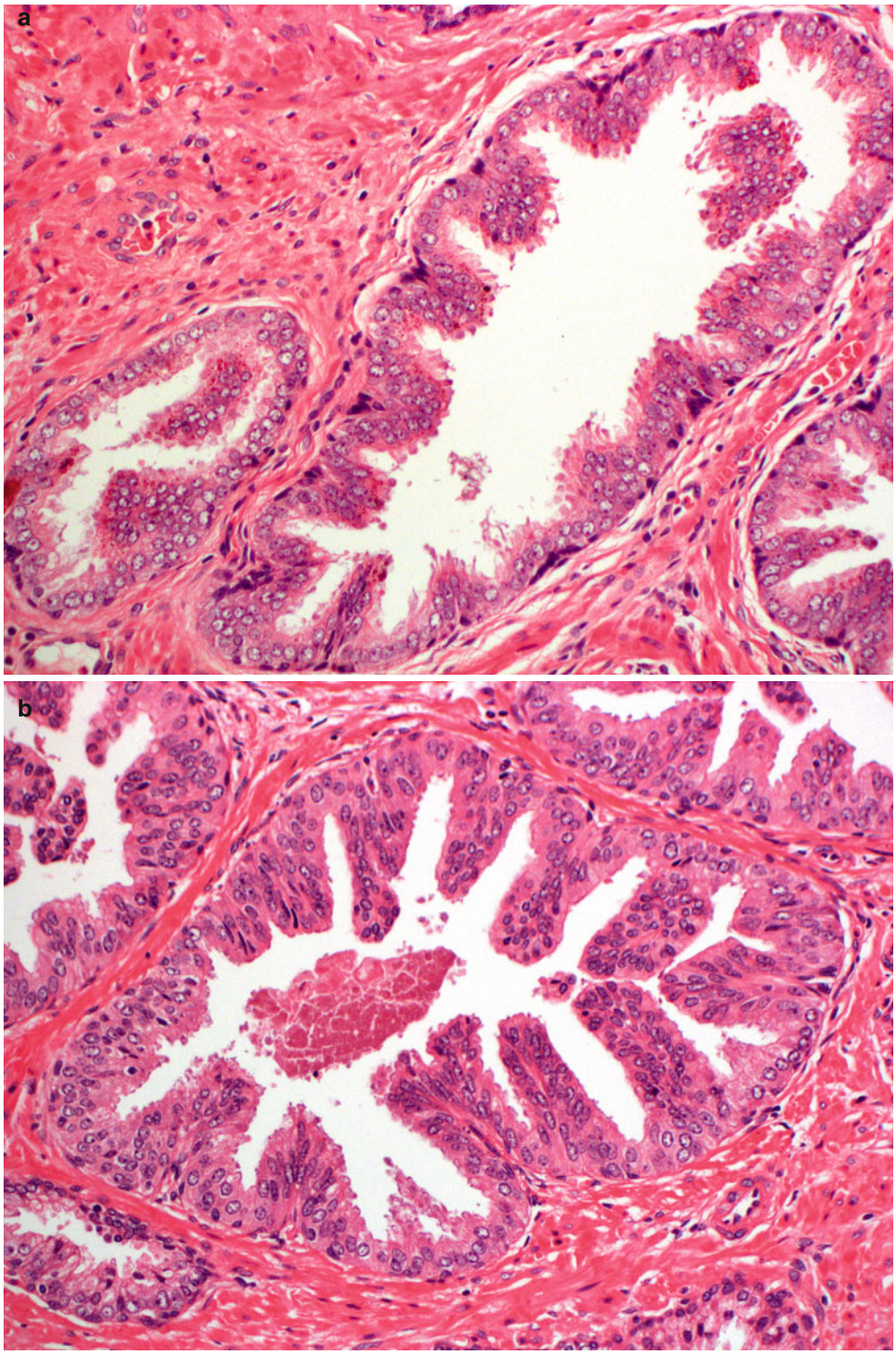
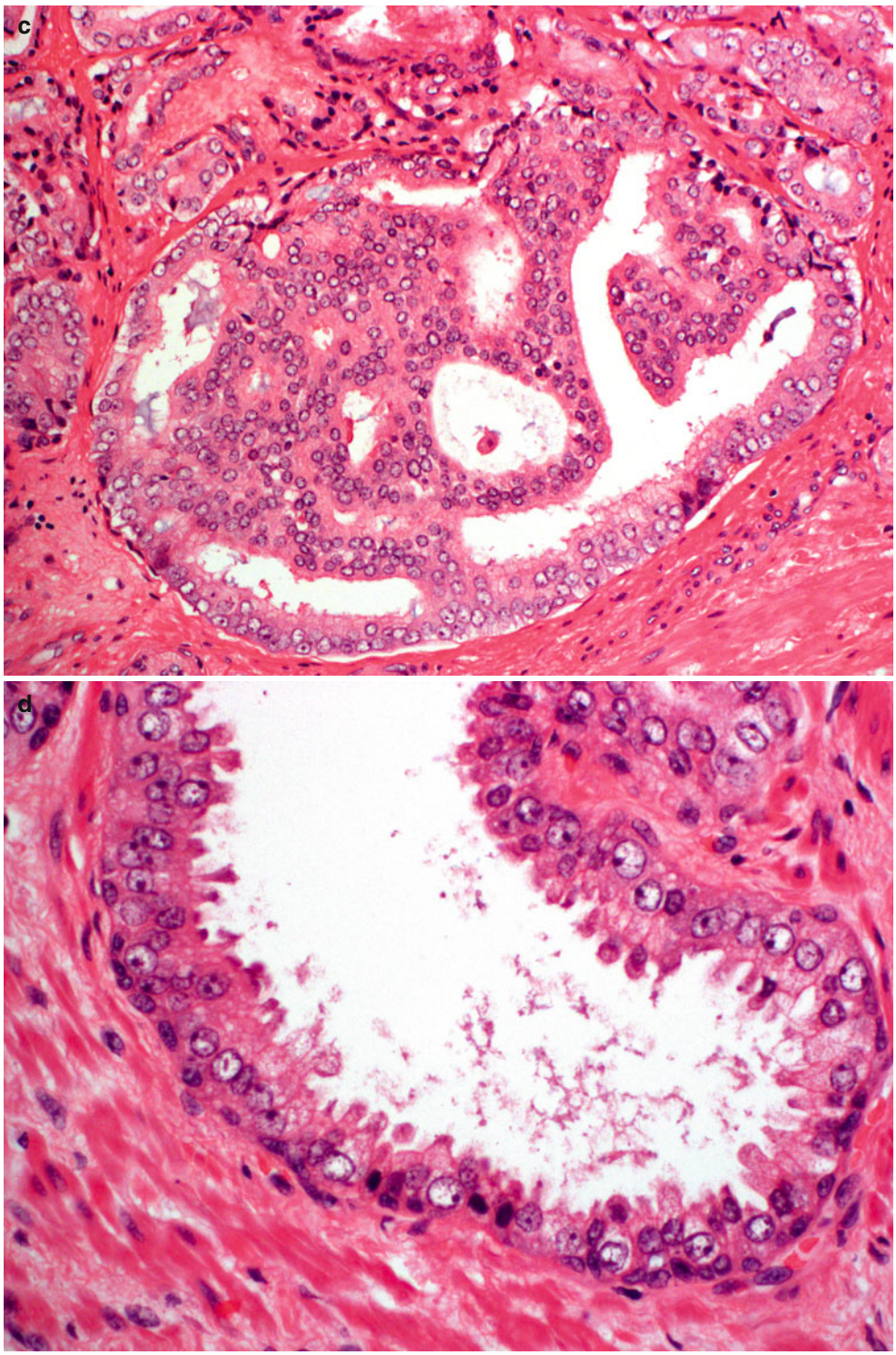



**Fig. 19.4** Patterns of high-grade PIN. Tufting (**a**), micropapillary (**b**), cribriform (**c**), and flat (**d**). The small atypical acini in (**c**) are invasive cancer adjacent to the high-grade PIN (*center*)

**Fig. 19.4** (continued)




ranging from 3 to 60 % [6, 27] and is related greatly to age. The incidence appears to reach 5–10 % in the age range 30–40 but is greater than 40 % after age 50.

In transurethral resection specimens (TURP), the incidence of HGPIN is far lower, ranging from 2 to 15 % in specimens without cancer and 3–58 % in specimens with cancer [31–34]. This is probably because the vast majority of prostate cancers arise in the peripheral zone: usually poorly sampled on TURP and therefore HGPIN, a largely peripheral zone lesion, is rarely seen.

Although all the above studies are of great academic interest, the incidence of PIN and its association with cancer in needle core biopsy specimens is of far more interest. The incidence of HGPIN in studies, which are largely

retrospective, varies from 0.7 to 25 % [35, 36] though most are intermediate falling into the 5–10 % range [37–42]. However, in some of these studies, the distinction between high- and low-grade PIN is not made. Unsurprisingly, HGPIN is also seen in biopsies which also contain invasive carcinoma, ranging from 10 to 40 % in incidence [33, 43–45].

The multifactorial reasons for such widely discrepant results are worthy of consideration. Different patient populations may account partly for this variability, including ethnicity and also method of detection: screening, symptomatic, or serendipitous. While prostate biopsy strategies involved taking two to four cores in the 1980s and early 1990s, the increase in the number of biopsies taken, to sextant, decant,

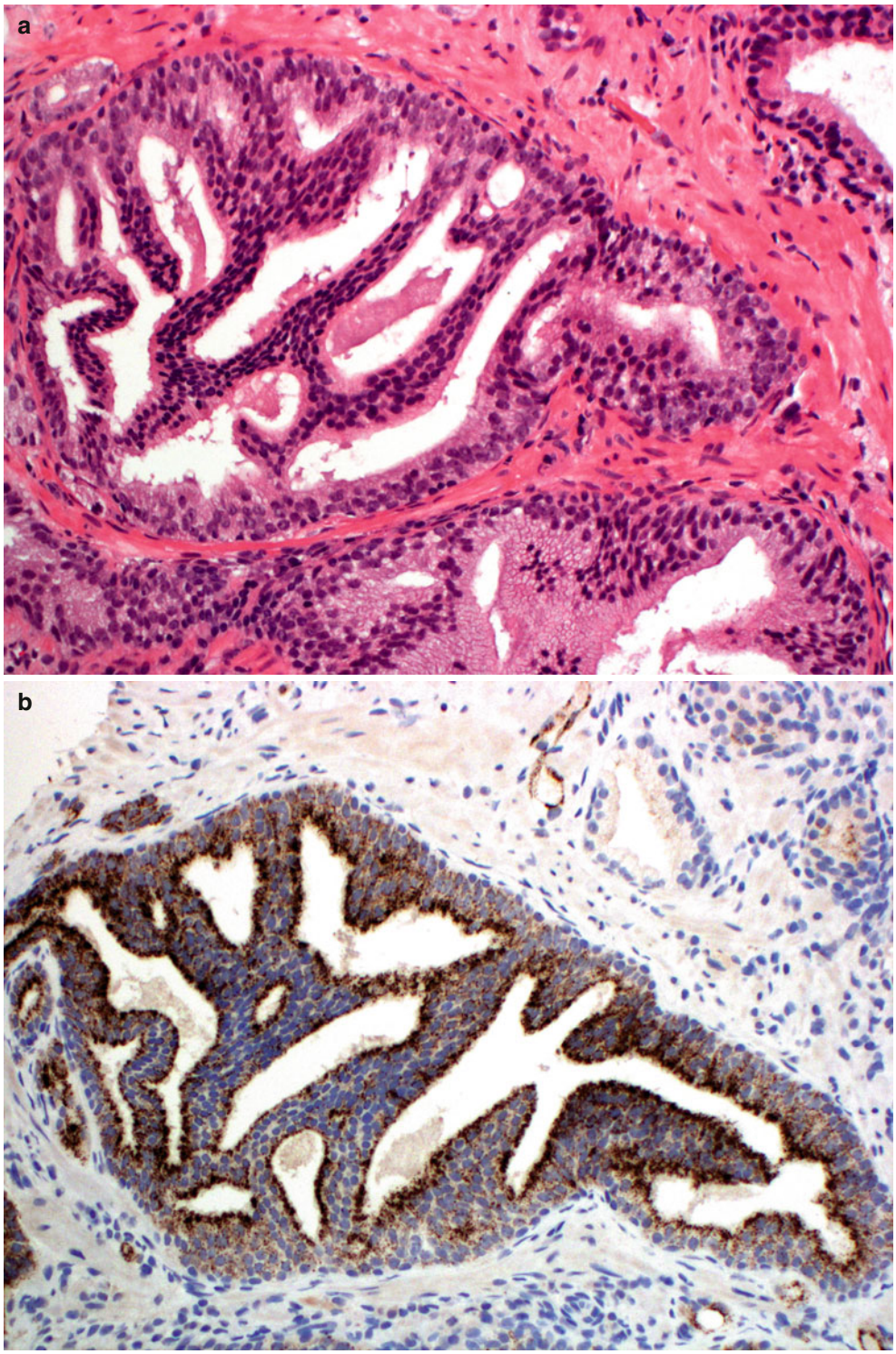
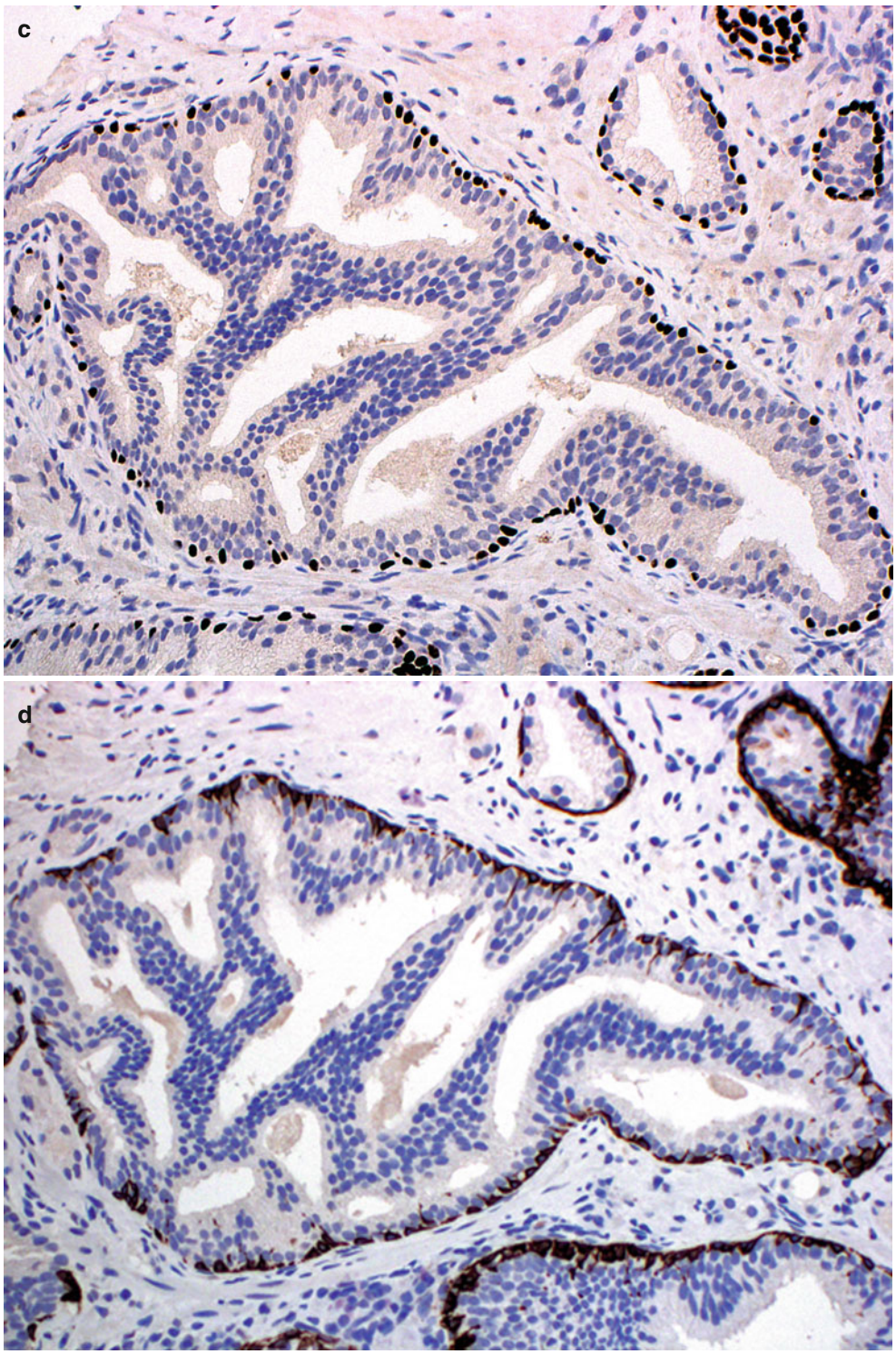



**Fig. 19.5** (**a**–**d**) High-grade PIN immunohistochemistry. Hematoxylin and eosin (**a**) of a gland showing high-grade PIN (*center*), with positive staining for AMACR (**b**) and basal cells demonstrated with p63 (**c**) and 34βE12 (**d**)

**Fig. 19.5** (continued)




and later saturation biopsies, will affect incidence, as small foci of HGPIN will be more likely to be detected. There will also be an effect on the balance of HGPIN detected in isolation and that detected with cancer, as more intensive biopsy strategies will also detect smaller prostate cancers with increased frequency [46].

Unfortunately, methods of pathological processing may also affect the incidence of HGPIN diagnosis. Bouin's fixative gives better nuclear detail than formalin fixation, and therefore nucleoli are easier to see and HGPIN more readily diagnosed [47]. Section thickness and quality of hematoxylin and eosin staining may also affect the diagnosis.

Interobserver variation is also, inevitably, an important factor [48].

## Review of Evidence Linking HGPIN and Malignancy

The evidence that HGPIN is the precursor lesion for at least some adenocarcinomas of the prostate comes from a variety of sources including epidemiology, histopathological morphology, immunochemistry, and increasingly shared genetic changes. As suggested by the incidence of HGPIN above, it may be identified in prostates at a younger age than carcinoma, preceding it by about 10 years. With increasing age, there is an increase also in the amount of HGPIN seen, and multifocal cancers are associated with increasing HGPIN [27, 49, 50].

HGPIN has been shown by a number of studies to be more common in the peripheral zone, mirroring the location of invasive adenocarcinoma [51, 52]. The cytological features of HGPIN mirror those of invasive carcinoma (by definition), but there is also, as suggested earlier, an association between the differentiation patterns seen in HGPIN and the associated malignancy [16]. HGPIN is sometimes associated with small "outpouchings" of invasive cancer (covered in more detail later) [53].

While benign glands with no HGPIN almost always have a complete basal cell layer and invasive malignancy shows a lack of basal cells, HGPIN often shows a disrupted and incomplete basal cell layer [22].

Immunohistochemical positivity for AMACR in HGPIN is frequently seen, though probably lower than that in invasive carcinoma [19–21], and this mirrors the literature in most of the identified immunochemically investigated oncogenes and tumor suppressor genes such as BCL-2 [54], RER [55], hK2 [56], and EGFR [57].

HGPIN tends to be aneuploid but less so than invasive carcinomas [58]. The TMPRSS2-ERG fusion gene which has been described as a common change in prostate cancer [59] has also been described in a significant but lower percentage of HGPIN lesions [60, 61] and also in whole-mount prostatectomy specimens where there is a definite, though complex, relationship between the fusion gene in HGPIN and adjacent cancers[10]. Among other chromosomal changes, loss of chromosome 8p and gain of 8q have been both described in prostate cancer and HGPIN. Gain of chromosomes 7,8,10, and 12 has also been described [62]. Telomere shortening is seen in both HGPIN and invasive carcinomas [63].

Unlike many other organs, such as the cervix, where the preneoplastic lesions can be monitored and rebiopsied, it is not possible at present to identify HGPIN with the certain knowledge that there is no invasive malignancy present or to prove that the invasive focus arises from a known premalignant focus. For these reasons, the evidence linking HGPIN to prostate cancer remains circumstantial but extremely convincing.

However, there is circumstantial evidence that some cancers may not arise from HGPIN. Many prostate cancers identified in the transition zone by TURP are low grade and show no HGPIN. Even in radical prostatectomy specimens, which have been completely embedded, many early cancers lack associated HGPIN, and there is frequently a lack of spatial relationship between the HGPIN and the invasive focus [27, 64]. Possible preneoplastic lesions other than HGPIN will be described later.

## HGPIN and Diagnosis of Adenocarcinoma on Repeat Biopsy

The only clinical import of a diagnosis of HGPIN, at present, is when it is diagnosed without associated malignancy in biopsy specimens. Probably uniquely among all cancers, prostatic adenocarcinoma is now largely diagnosed by a nonspecific test (PSA) and using an essentially "blind" biopsy method where lesions are not targeted. Therefore, a negative biopsy does not completely exclude malignancy, though recent increases in the number of biopsies taken and use of saturation techniques have reduced this false negative rate. If patients with HGPIN in isolation on prostatic biopsies are to be followed up in a different manner than a negative biopsy, then it must be clearly proven that they are at increased risk of harboring or developing a significant invasive malignancy.

Unfortunately, the evidence for this is clouded by a number of different factors. As mentioned above, when discussing the incidence of HGPIN, multiple pathological factors lead to variation in the diagnosis of HGPIN as well as clinical factors such as the number of cores taken and patient population. In addition to this, follow-up strategies have varied over the past 20 years and from center to center, which means that results are not easily comparable. Table 19.2 summarizes some selected series over the past 20 years. It can be seen that the incidence of cancer detection on rebiopsy varies wildly from 2 to 100 % [65, 66] with virtually every percentage in between [67–93]. However, this crude analysis fails to appreciate fully the differences in techniques used and changes in biopsy practice, which may allow a refinement of clinical practice in the future.

Due to the insensitivity of prostate biopsies to detect invasive cancer, there remains a false negative rate of cancer diagnosis with first biopsy even after a biopsy with normal histological appearances, varying in the literature between 2 and 32 % [83, 94] with a reported aggregate mean in one analysis of all studies as 19 %[95]. As can be seen from

**Table 19.2** Publications on HGPIN rates

| Author | Year | Carcinoma on rebiopsy/total no of HGPIN cases | Percentage (%) | No. of cores taken |
|---|---|---|---|---|
| Brawer et al. [66] | 1991 | 10/10 | 100 | 6 or less |
| Weinstein et al. [67] | 1993 | 10/33 | 30 | ? |
| Keetch et al. [68] | 1995 | 19/37 | 51 | 4–6 |
| Davidson et al. [69] | 1995 | 35/100 | 35 | Mean 3.7 |
| Aboseif et al. [70] | 1995 | 19/24 | 79 | ? |
| Ellis et al. [71] | 1995 | 5/5 | 100 | 6 |
| Raviv et al. [72] | 1996 | 23/48 | 48 | 6 |
| Langer et al. [73] | 1996 | 13/48 | 27 | 6 |
| Perachino et al. [74] | 1997 | 15/21 | 71 | 6 |
| Fleshner et al. [93] | 1997 | 9/16 | 56 | 8 |
| Kamoi et al. [75] | 2000 | 10/45 | 22 | Variable |
| O, Dowd et al. [76] | 2000 | 295/1,306 | 22.6 | Variable |
| Alsikafi et al. [77] | 2001 | 3/21 | 14 | ? |
| Vis et al. [78] | 2001 | 3/30 | 10 | ? |
| Kronz et al. [79] | 2001 | 79/245 | 32.2 | ? |
| Borboroglu et al. [80] | 2001 | 20/45 | 44 | Variable |
| Park et al. [81] | 2001 | 21/43 | 49 | Variable |
| Maatman et al. [82] | 2001 | 14/86 | 16 | 6 |
| Lefkowitz et al. [65] | 2001 | 1/43 | 2 | 12 |
| San Francisco et al. [83] | 2003 | 5/21 | 24 | 10–12 |
| Goeman et al. [84] | 2003 | 14/63 | 22 | 6 |
| Roscigno et al. [85] | 2004 | 21/47 | 45 | 10–12 |
| Postma et al. [86] | 2004 | 6/41 | 13 | 6 |
| Abdel-Khalek et al. [87] | 2004 | 30/83 | 36 | 6 |
| Herawi et al. [88] | 2006 | 69/323 | 13.3 | 8–10 |
| Gokden et al. [89] | 2005 | 25/190 | 13.2 | 6 |
| Netto et al. [90] | 2006 | 16/41 | 39 | 10–12 |
| Akhavan et al. [91] | 2007 | 15/48 | 31 | 12 |
| Merrimen et al. [92] | 2010 | 25/120 | 21 | 10–12 |
| *Aggregate* | | *830/3,183* | *26.1* | |

Table 19.2, between 1991 and 2010, there has been an increase in the number of biopsies taken at initial consultation, which will have reduced this false negative rate (as smaller cancers are detected). Saturation biopsies, which are now more common, and also transperineal biopsies, which sample the anterior portions of the prostate, will further distort the figures in the literature.

Unfortunately, very few studies have shown this in a systematic fashion, with only two studies showing a significant difference between cancer rates after HGPIN compared to a benign diagnosis [69, 83] while many others show no difference [76, 86, 89, 96, 97].

More recent studies have attempted to refine the risk factors for invasive cancer by examining the amount of HGPIN seen on biopsy. While some studies have shown there is no association between the amount of cancer seen on rebiopsy by looking at the number or percentage of cores involved [79, 80, 83], other studies have suggested that two or more cores involved with HGPIN are significant risk factors, whereas those cases where only a single focus of HGPIN can be seen are less significant and can probably be followed up in a similar manner as a negative core [85, 87]. Two very recent studies from the same group [92, 98] involving 12,304 prostate biopsies and studying only extended set biopsies in one paper [98] confirmed the association between cancer risk and the number of involved cores with HGPIN.

## Intraductal Carcinoma

Intraductal carcinoma (IDC) is a controversial entity, which has come under increasing attention in the past 20 years. It was first characterized in 1985, when prostatic ducts "invaded" by tumor cells were associated with Gleason grade and tumor extent [99].

McNeal et al. showed that cribriform carcinomas were often intraductal and concluded that these intraductal cancers actually arose within the affected ducts and were of more aggressive appearance and stage than noncribriform cancers [100]. In 1996, McNeal and Yemoto suggested the term "intraductal carcinoma" to describe intraductal proliferations that were associated with poor prognostic factors [101].

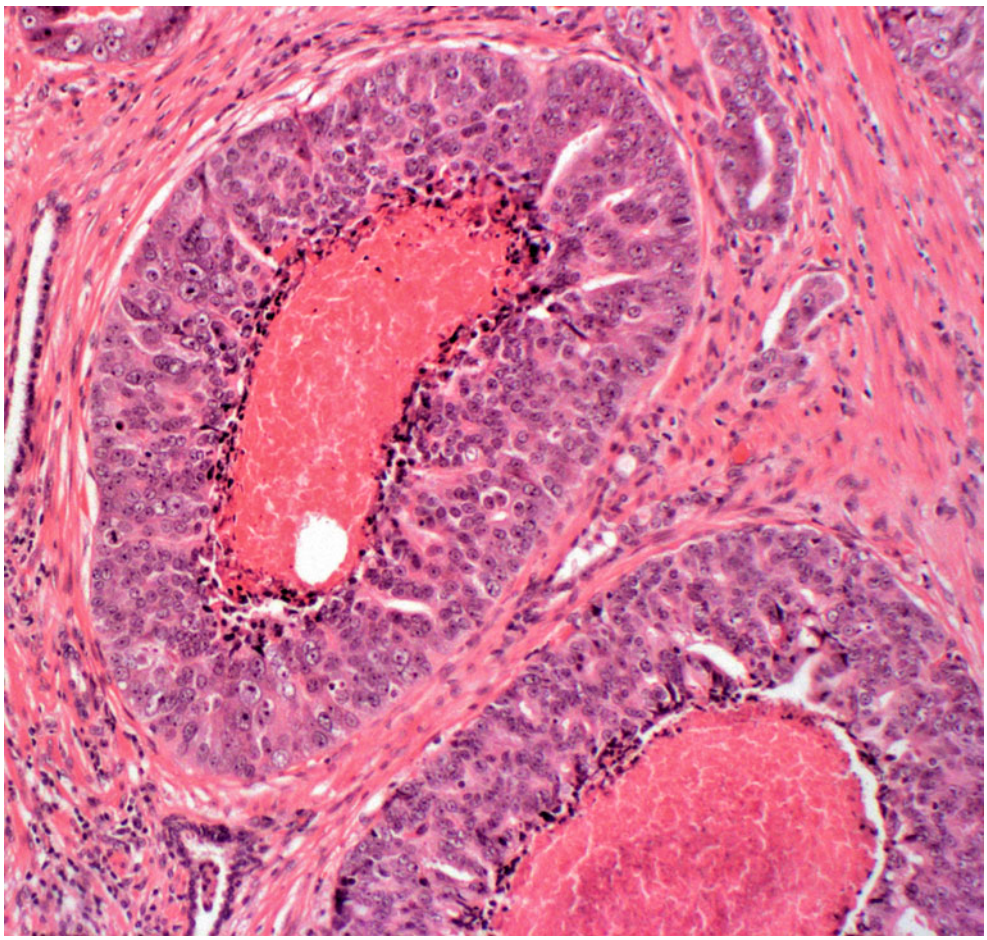


**Fig. 19.6** Intraductal carcinoma in two large ducts. The central "comedo" type of necrosis precludes this from being high-grade PIN. There are intervening small atrophic benign glands (*left*) and invasive malignant glands (*right*)

**Table 19.3** Comparison of morphology of intraductal carcinoma with HGPIN

| | HGPIN | IDC |
|---|---|---|
| Duct/gland size | Normal | Increased (2×) |
| Lumen spanning cells | Absent | Present |
| Patterns | Flat | Micropapillary/trabecular |
| | Tufted | Cribriform |
| | Micropapillary | Solid/comedo |
| | Cribriform | |
| Nuclear size | Slightly increased (×2–3) | Markedly increased (6×) |
| Nuclear atypia | Mild atypia only | Marked pleomorphism |
| Mitoses | Absent | Present |
| Comedo necrosis | Absent | May be present |
| Immunohistochemistry | AMACR+ve | AMACR+ |
| | PSA+ve | Central compartment: PSA+ |
| | | Peripheral compartment: AR+ |

This aimed at distinguishing these lesions from HGPIN, low-grade PIN, and invasive cribriform tumors. They postulated that this lesion represents intraductal spread of adenocarcinoma [101] (Fig. 19.6). An alternative would be an "end-stage" of PIN before invasion. There are overlapping morphological features between HGPIN and IDC, hence the controversy with the diagnosis, although comedo necrosis and more extreme atypia are indicative of the latter (Table 19.3). In support of the association with malignancy, a number of groups have shown that IDC has a very high risk of carcinoma elsewhere in the prostate [102, 103] showing that these cancers tended to be of high stage and grade. More recently, it has been advocated that if IDC is diagnosed on needle biopsy, the outcome for the patients is so adverse

that radical therapy can be contemplated without the need for identification of invasive tumor [103].

A recent study examined 83 men with IDC in isolation without associated cancer [104]. Twenty-one of these cases went on to radical prostatectomy, and although 19 of the cases had invasive tumors which tended to be high stage and grade, 2 patients (10 %) had IDC only with no invasive malignancy. Although the authors recommend that all cases of IDC should be treated radically, their results suggest there may be dangers in this approach.

## Glandular Atypia as a Premalignant Lesion: "ASAPs"

Occasionally, a pathologist will encounter an area of glands that fulfill some, but not all, of the cytological and architectural features of a carcinoma. There is, however, little consistency between pathologists in the diagnosis of essentially subjective criteria [105]. The question of the number of atypical glands that are required for a diagnosis of malignancy is unanswerable. These glandular foci therefore include a chimeric assembly of different entities including undersampled carcinomas, reactive changes in benign glands, PIN, or inflammatory atypia (Fig. 19.7a, b).

Assigning a name to this constellation of uncertain entities has proven difficult: mostly because any name assigned immediately invites an acronym and therefore by default, it becomes an entity in its own right. Therefore, the synonyms focal glandular atypia (FGA) and atypical small acinar proliferation (ASAP) have been used, as well as terms such as "borderline for malignancy" and "suspicious for carcinoma"[106–108]. For practical reasons, we will refer to ASAPs, without in any way agreeing that this term implies an entity, merely an uncertain diagnosis for carcinoma.

However, the diagnosis of ASAP in a clinical setting is important because, as will be discussed, of its association with a higher risk of prostatic malignancy than HGPIN.

### Incidence of ASAPs

The challenge of diagnosis of ASAP is largely confined to needle biopsies where it has clinical significance. Larger prostate specimens such as TURPs or radical prostatectomies are occasionally "dignified" with the diagnosis of ASAP; however, where there is the possibility of more complete assessment of the lesion, with multiple immunohistochemistry assessments, logic dictates that this assignation should be avoided where possible. There is variability in the diagnosis of ASAP in TURP specimens [109], and the clinical significance of such a finding is doubly dubious. We suggest that the diagnosis of ASAP should be rendered for prostate biopsies alone where it has clinical significance.

The incidence in needle biopsies varies from 1 to 9 % [39, 110] in contemporary series, with most studies falling between 2 and 5 % [78, 80, 107].

### The Diagnosis of ASAP

ASAP is, by definition, limited in extent, though there may be multiple foci of ASAP in one case [107]. Reasons for making the diagnosis include a focally infiltrating pattern, nuclear features in limited glands, or features which are often contributory to the diagnosis of malignancy, but which in isolation are of limited value. These include the presence of blue mucin or crystalloids.

The uncertain nature of the lesion means that some lesions that are benign are "interpreted" as ASAPS and includes lesions such as adenosis, atrophy, basal cell hyperplasia, or changes induced by hormones or radiation.

Additional further studies may be performed to differentiate ASAPs into definitive benign and malignant categories. These include further levels as well as immunochemistry for basal cell markers [111] or AMACR [112]. Importantly, the presence of basal cells in these atypical foci may help definitively render a benign diagnosis. However, absence of basal cells in a few glands may not be enough to diagnose malignancy as foci of adenosis may show occasional glands lacking basal cells. AMACR can also be used in this setting but should be used cautiously as occasionally benign glands can show positivity. In our experience, pathologists use AMACR cautiously in foci that they are "almost certain" are cancer in order to provide the final proof before sign out, and in those cases this seems a reasonable activity. There are, of course, degrees of pathological uncertainty, between benign and malignancy, and the term ASAP may cover a broad spectrum of lesions. Stratification of risk in atypical lesions has been attempted in the past [106, 113] but has not proven helpful in determining later risk for cancer. Unsurprisingly, interobserver error has recently shown to be high for the diagnosis of ASAPs, especially when the gland number falls below 6 [105]. Expert uropathologists are more likely to render a definitive diagnosis than general pathologists [48].

### ASAP and Diagnosis of Adenocarcinoma on Repeat Biopsy

Many studies have shown that the diagnosis of ASAP places the patient in a higher risk group for the later diagnosis of malignancy. However, the level of risk varies between different studies due to variations, not only in pathological diagnosis but also in number of biopsies taken (a higher number of biopsies will detect a higher percentage of low-volume cancers and lower the rate of ASAP diagnosis), operator, and whether spares are kept for immunochemistry later, which

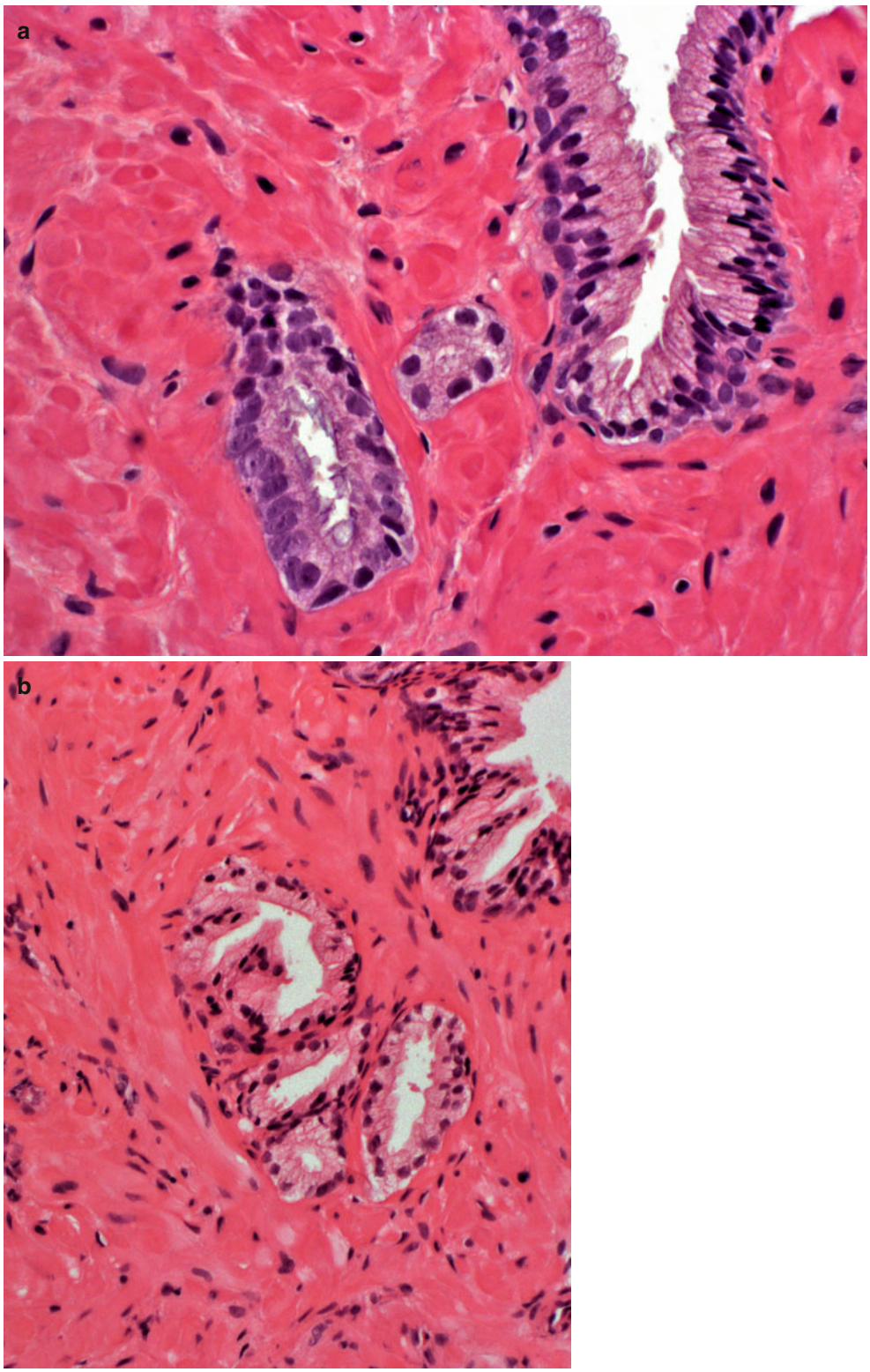



**Fig. 19.7** ASAP. Atypical small acini that lacked basal cells. Those in (**a**) are more suspicious of malignancy than those in (**b**). A benign large gland is on the right in (**a**) and (**b**)

may lower the rate of ASAP diagnosis as more definitive diagnoses can be made at first biopsy.

Virtually all studies suggest, however, that the risk of prostate cancer on repeat biopsy is substantially higher following a single ASAP focus than for PIN with the risk varying between 29 and 60 % [71, 107] with an average of 45 % [35, 76, 78, 80, 86, 106, 108, 110, 113–117] (Table 19.4). There is no significant trend in positivity rate over the past 20 years. This high rate of later diagnosis of cancer means that, in contrast to PIN, diagnosis of ASAP always warrants early repeat biopsy.

**Table 19.4** Publications on ASAP rates

| Author | Year | Carcinoma on rebiopsy/total no. of ASAPs | Percentage |
|---|---|---|---|
| Ellis et al. [71] | 1995 | 5/17 | 29 |
| Cheville et al. [99] | 1997 | 15/25 | 60 |
| Iczkowski et al. [100] | 1997 | 15/33 | 45 |
| Renshaw et al. [101] | 1998 | 22/59 | 37 |
| Allen et al. [102] | 1998 | 56/124 | 45 |
| Iczkowski et al. [103] | 1998 | 125/295 | 42 |
| Chan et al. [104] | 1999 | 45/92 | 49 |
| Hoedemaeker et al. [35] | 1999 | 15/39 | 38 |
| O'Dowd et al. [76] | 2000 | 629/1,321 | 40 |
| Borboroglu et al. [80] | 2001 | 23/48 | 48 |
| Vis et al. [78] | 2001 | 36/93 | 39 |
| Postma et al. [86] | 2004 | 35/96 | 36 |
| Amin et al. [105] | 2007 | 13/22 | 59 |
| Lopez et al. [106] | 2007 | 12/45 | 27 |
| *Aggregate* | | *1,046/2,309* | *45 %* |

## High-Grade PIN associated with ASAP

Occasionally, prostate biopsies show both HGPIN and ASAPs. These can be of two types. The ASAP focus and the HGPIN may be unrelated spatially: either because they are in different biopsies or because they are in different parts of the same biopsy.

A second and more studied entity is when the ASAP is in association with the HGPIN. This has been given a variety of names including PIN with "outpouchings," PINATYP, or PIN/ASAP (Fig. 19.8).

The challenge of these foci is that the association of the atypical glands with the HGPIN creates a problem. HGPIN may show an interrupted basal cell layer and may be slightly irregular in appearance due to tangential cutting of the sectioning or "budding." There are few studies on the significance of PINATYP, but they confirm the high risk of later diagnosis of malignant disease, which is equivalent or possibly even higher than that of either HGPIN or ASAPs alone with studies by Alsifaki and Kronz showing rates of 46 and 75 %, respectively [77, 118]. Therefore, similar to ASAPs, these cases warrant early rebiopsy.

## Other Potential Preneoplastic Entities

Despite a wealth of epidemiological data, the causes of prostate cancer are still unclear. While inherited genetic risk factors have been identified [119, 120], there is a widespread belief that the differences in prostate cancer incidence in different ethnic groups may be due to environmental influences, which are yet to be fully identified. It has been suggested that chronic inflammation may be a key etiological factor in the development of prostate cancer [121].

In support of this, an entity has been described where glandular atrophy is associated with glandular proliferation and chronic inflammatory cells. This has been termed proliferative inflammatory atrophy (PIA) [122].

The finding that atrophic changes in the prostate could show a high proliferation rate was shown serendipitously initially [123] and the potential significance not recognized. However, more recent studies provided indirect evidence that these lesions may be an intermediate stage between PIN and normal prostate, which has a low proliferation rate [124–126].

Other evidence linking PIA to cancer include studies which show shared genetic and immunohistochemical changes with PIN and invasive malignancy [124, 127–129]. Morphological papers show contradictory findings with some studies showing transitions between PIN and PIA [130–132], while others show no morphological association [133–135].

An animal model has shown that in rats fed a carcinogen present in charred meat it leads to significant prostatic inflammation and atrophy followed by HGPIN [136]. However attractive this hypothesis, it remains unproven. PIA is common throughout the prostate and is present in young adults [137], whereas HGPIN and cancer develop predominantly in the peripheral zones in older age groups. PIA is likely to remain as an addendum to any discussion of premalignant lesions until considerable further evidence is forthcoming.

### Conclusions

The Red Queen Hypothesis [138] is a term used primarily for evolutionary theory taken from the Red Queen's race in Lewis Carroll's *Through the Looking-Glass*. The Red Queen says to Alice, "It takes all the running you can do, to keep in the same place." Such problems also occur in

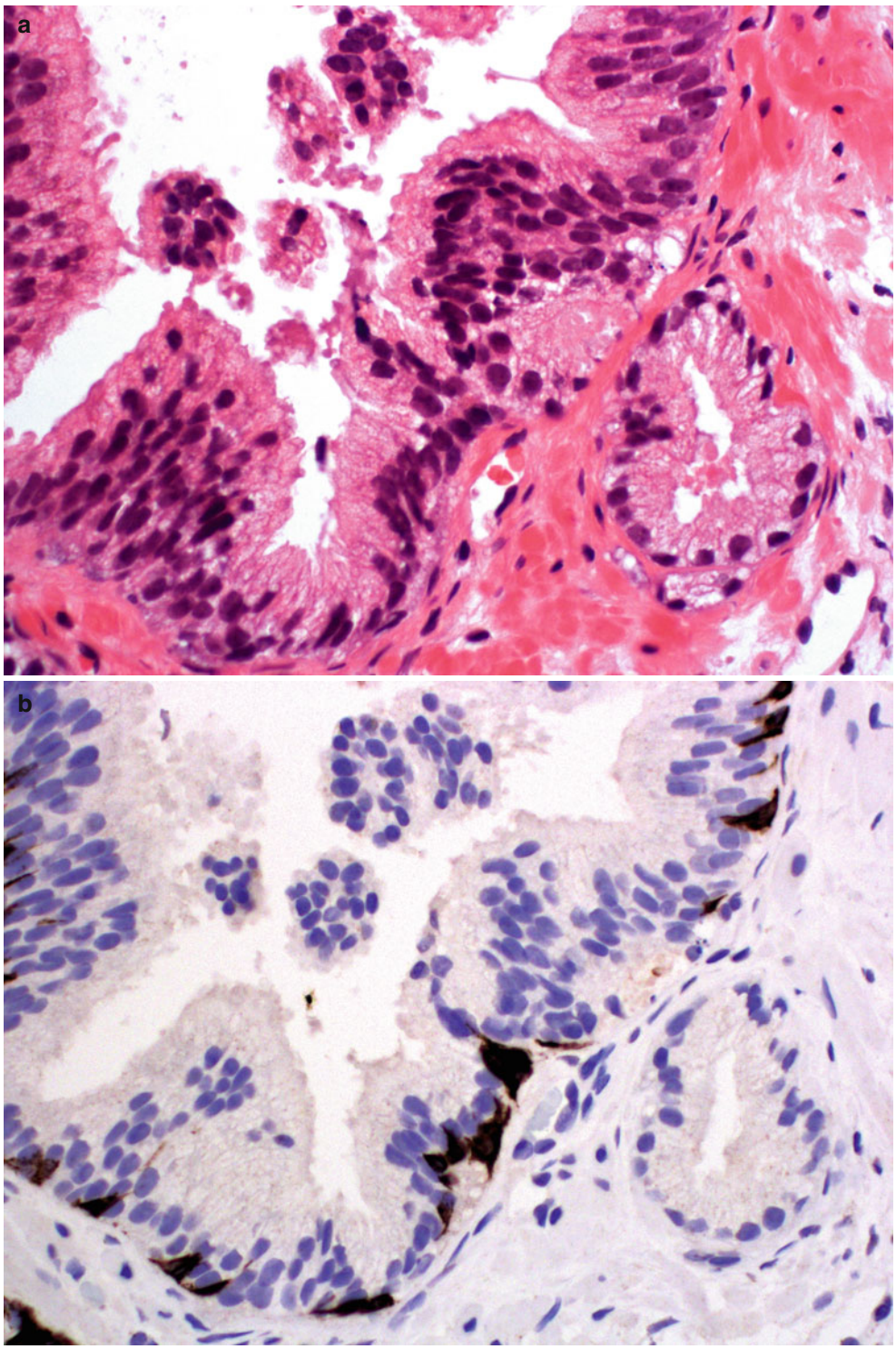



**Fig. 19.8** High-grade PIN with a closely adjacent atypical acinus that could represent an "outpouching" from the PIN or invasive carcinoma (**a**). This acinus lacks basal cells on the 34BetaE12 immunohistochemistry (**b**)

rapidly evolving medical problems where every study is immediately outdated by the time it is published as practice has changed.

The revolutions that have occurred in the treatment and diagnosis of prostate cancer over the past 20 years have enhanced our understanding of the disease in many respects but left other problems unsolved and confusing for clinicians, pathologists, and basic researchers. On the positive side, we now understand the pathogenesis of probably the majority of prostate cancers, with a clear association with HGPIN. However, other entities such as "ASAP" and low-grade PIN are often used with little understanding of their role or otherwise in the pathogenesis of prostate cancer or their risk for the development of malignancy.

Also, most importantly, changes in practice have led to immense variability in the predictive value for cancer when these lesions are diagnosed, and many papers where sextant biopsy data has been utilized are no longer relevant, rightly or wrongly, to modern practice. Progress in these areas is undoubtedly necessary if we are to optimize the treatment of patients with a diagnosis of HGPIN or ASAP. Only close collaboration between urologists, pathologists, other members of the multidisciplinary team, and basic researchers in multiple institutions will help to solve the many conundrums of premalignancy in the prostate.

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# The Pathology of Prostatic Carcinoma

20

Maria M. Shevchuk and Brian D. Robinson

## Adenocarcinoma

### Diagnosis

*Adenocarcinoma* of the prostate comprises 95 % of the malignant neoplasms of the prostate, and most of these are of the "conventional" acinar type. The histopathologic diagnosis of adenocarcinoma (also referred to as prostatic carcinoma) is made on the basis of a combination of several histologic features. No one feature is sufficient on its merits, except for perineural invasion and possibly mucinous fibroplasia and glomeruloid bodies (glomerulations). The diagnostic features are grouped into primary and secondary criteria. Tertiary criteria are helpful and supportive of the diagnosis.

*Primary criteria* refer to the *architecture* or *pattern* of the glands. Benign prostatic glands are medium-sized and arranged in lobules. Carcinomatous glands are (1) frequently small (microacini), (2) crowded, (3) haphazardly arranged, not in lobules, (4) fused, (5) have an infiltrative pattern, and (6) invade between benign glands or cut-across muscle fibers, splitting them (Table 20.1) (Fig. 20.1). *Perineural invasion*—the presence of malignant glands in a perineural space—is an architectural feature that most pathologists consider to be diagnostic of prostatic carcinoma on its own merits (Fig. 20.2). There are two other relatively uncommon architectural features some consider to be diagnostic on their own merits. *Mucinous fibroplasia* consists of scar-like fibrous replacement of extravasated glandular mucin. *Glomerulations*, which are intraglandular cribriform and papillary proliferations attached to the malignant gland at one pole that resemble fetal glomeruli, are the third rare diagnostic feature (Fig. 20.3).

*Secondary criteria* are *cytologic* (Table 20.1). They include (1) *the absence of the basal cell layer* and (2) the presence of *large*, *hyperchromatic nuclei* with *prominent nucleoli*.

Since prostatic adenocarcinoma derives from the inner secretory cell layer, malignant acini *lack a basal cell layer* and are lined by a single layer of cells (Fig. 20.4). Immunohistochemistry can be used to confirm the absence of a basal cell layer, and pathologists typically employ both the cytoplasmic stain for high molecular weight cytokeratin (*HMWCK*, also known as CK903 and 34BE12) as well as the nuclear stain for *p63*. These two stains are frequently combined with an immunohistochemical stain for *AMACR* (alpha-methylacyl-CoA-*racemase*), which is positive in the cytoplasm of approximately 85 % of prostatic adenocarcinomas, and generally negative or only faintly positive in benign glands (Fig. 20.5). The triple immunohistochemical stains are used only for confirmation of diagnostically challenging or minute tumor foci and should never be used as the sole or main criterion for the diagnosis of prostatic carcinoma.

The other main cytologic criterion is the presence of *large*, *occasionally red*, *nucleoli* in large hyperchromatic nuclei (Fig. 20.4). These nuclear features are important for the diagnosis of carcinoma, but they may occasionally be obscured by suboptimal fixation and by other artifactual changes.

*Tertiary criteria* are supportive of the diagnosis of malignancy and often help to distinguish malignant glands from the adjacent benign counterparts. These tertiary criteria include (1) *luminal blue mucin*, (2) *luminal pink amorphous secretions*, (3) *crystalloids*, (4) *sharp luminal borders*, *and* (5) *amphophilic or foamy cytoplasm* (Fig. 20.6) [1].

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**Table 20.1** Criteria for the diagnosis of prostatic carcinoma

| |
|---|
| Primary criteria |
| *Architectural—diagnostic* |
| 1. Small glands (microacini) |
| 2. Crowded glands |
| 3. Haphazardly arranged glands, not in lobules |
| 4. Fused glands |
| 5. Infiltrative pattern |
| 6. Small glands around/between benign glands |
| 7. Perineural invasion |
| 8. Mucinous fibroplasia |
| 9. Glomerulations |
| Secondary criteria |
| *Cytologic—diagnostic* |
| 1. Absence of basal cells |
| 2. Large nucleoli |
| 3. Large hyperchromatic nuclei, with an increased nucleus-cytoplasm ratio |
| Tertiary criteria |
| *Cytoplasmic/luminal—supportive* |
| 1. Luminal blue mucin |
| 2. Luminal pink amorphous secretions |
| 3. Crystalloids |
| 4. Sharp/rigid luminal borders |
| 5. Amphophilic or foamy cytoplasm |

## Clinicopathologic Summary

*Diagnosis of prostatic adenocarcinoma*:

1. The *diagnosis* of prostatic *adenocarcinoma* is made on the basis of a combination of *primary* (*architectural*) and *secondary* (*cytological*) criteria.
2. Features, which are diagnostic on their own merit (although uncommon), are
   (a) *Perineural invasion*
   (b) *Mucinous fibroplasia*
   (c) *Glomerulations*
3. *Tertiary—cytoplasmic/luminal* criteria are supportive of the diagnosis of carcinoma.
4. The diagnosis of adenocarcinoma might require confirmation from immunohistochemistry to show the *absence of HMWCK and p63* staining for basal cells and the *presence of AMACR*.

## Gleason Grading

Grading of tumors gives important information about the malignant potential of the neoplasms and is usually based on their degree of deviation from normal histology. For prostatic carcinoma, the Gleason grading system is the internationally accepted standard, with extensive clinical validation. It was developed in the 1960s by Donald Gleason and his colleagues [2, 3] and has recently been updated to accommodate current diagnostic practices [4]. The Gleason grading system is based on the premise that the prognosis of prostatic carcinoma is related to the degree of differentiation of the two most common patterns/grades and is not solely determined by the least differentiated foci, as is commonly done for most other tumors. The *Gleason grading system* is based entirely on the primary criteria of *architecture*, evaluated at low to intermediate magnification (using the 4× and 10× objective lenses). The grade of the most common (*primary*) pattern *is added* to the grade of the second most common (*secondary*) pattern. Patterns range from 1 to 5, with pattern 1 being the most differentiated (Fig. 20.7). The sum of the primary and secondary patterns is called the *Gleason score* and ranges from 2 to 10. An example is a Gleason score 7 (4+3) (primary pattern 4+ secondary pattern 3). Should only one pattern be present in the prostatic carcinoma that pattern is doubled to give the Gleason score. An example is Gleason score 6 (3+3). Reporting of the Gleason score, along with the primary and secondary patterns, is recommended because this gives valuable information to the treating physician.

The *2005 ISUP consensus* update also stipulates that should there be a *tertiary pattern 5* on needle biopsy, it should replace the secondary pattern in computing the Gleason score. For example, a positive core with Gleason patterns 4+3 and tertiary pattern 5 should be diagnosed as Gleason score 9 (4+5) to reflect the significant impact that a Gleason pattern 5 carcinoma has on prognosis and the uncertainty about possible sampling error of a tumor that contains a Gleason pattern 5. However, in prostatectomy specimens, the consensus is to grade such a tumor as Gleason score 7 (4+3; primary pattern+secondary pattern) with tertiary pattern 5 because the entire carcinoma is available for evaluation.

*Gleason pattern 1* consists of a completely circumscribed nodule of tightly packed microacini. The international consensus is that in almost all cases, this pattern represents *atypical adenomatous hyperplasia* (*AAH*) (Fig. 20.8), and therefore Gleason pattern 1 should not be used in grading prostatic carcinoma.

*Gleason pattern 2* consists of a circumscribed nodule of small acini, with some variation in size, which are less tightly packed than in pattern 1 and may show minimal peripheral invasion into stroma but never into benign lobules (Fig. 20.9). This pattern is rarely diagnosed in needle biopsies because the entire nodule cannot be visualized on the thin needle biopsy core, and, therefore, the nodule's circumscription cannot be ascertained. Furthermore, this pattern is most common in the transition zone, which is usually not biopsied.

*Gleason pattern 3* consists of glands infiltrating benign lobules and stroma. These glands are discreet microacinar and occasionally macroacinar structures, frequently with irregular contours. Infiltrating glands in needle biopsies belong to this pattern (Fig. 20.10).

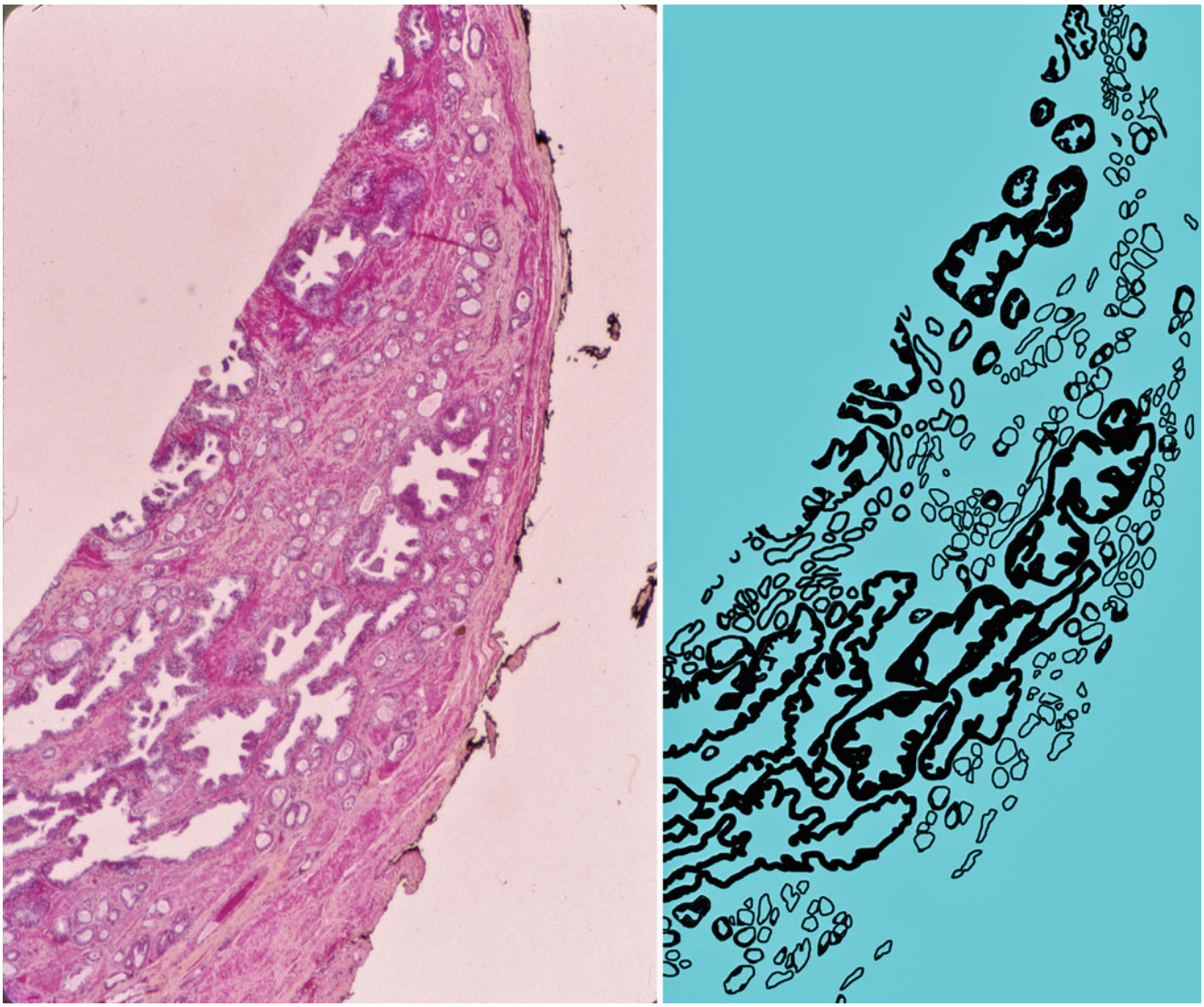

**Fig. 20.1** Malignant microacini infiltrating between two benign lobules. The *right panel* emphasizes the lobular pattern of the benign larger glands, in contrast to the haphazardly infiltrating abnormal small glands of the carcinoma

*Gleason pattern 4* is considered a high-grade pattern, with important clinical implications. It consists of fused glands either forming "chains" or cribriform sheets. The 2005 ISUP consensus also added "ill-formed" glands to this category. Several studies found a worse prognosis for tumors in which pattern 4 was primary, as compared with those in which pattern 4 was secondary: Gleason score 7 (4+3) versus Gleason score 7 (3+4) [5]. Therefore, the primary and secondary Gleason patterns should always be indicated in these cases in addition to the Gleason score sum (Fig. 20.11).

*Gleason pattern 5* is the highest grade, constituting an essentially undifferentiated adenocarcinoma. Glandular architecture is completely lost, and the tumor cells grow in single file, nests, and sheets. The comedo pattern—glandular tumor with central necrosis—also belongs to pattern 5. As mentioned in the discussion about tertiary patterns, the presence of pattern 5 is so clinically significant that it should be part of the biopsy Gleason score, irrespective of its quantity (Fig. 20.12).

In cases with *multiple positive cores with different Gleason scores/primary and secondary patterns*, the most common practice is to assign the highest Gleason score to the case and use it in nomograms and tables [6]. The highest Gleason score on biopsies correlates reasonably well with the subsequent prostatectomy Gleason score. The global Gleason score, which is the sum of the primary and secondary patterns of the tumor foci on all the positive cores taken together, predicts the prostatectomy Gleason score slightly better than the highest Gleason score (though not statistically significant) and gives additional information to the clinician. It also presents an opportunity to indicate whether a Gleason pattern 5 is likely to be the secondary or the tertiary pattern in the prostatectomy [7].

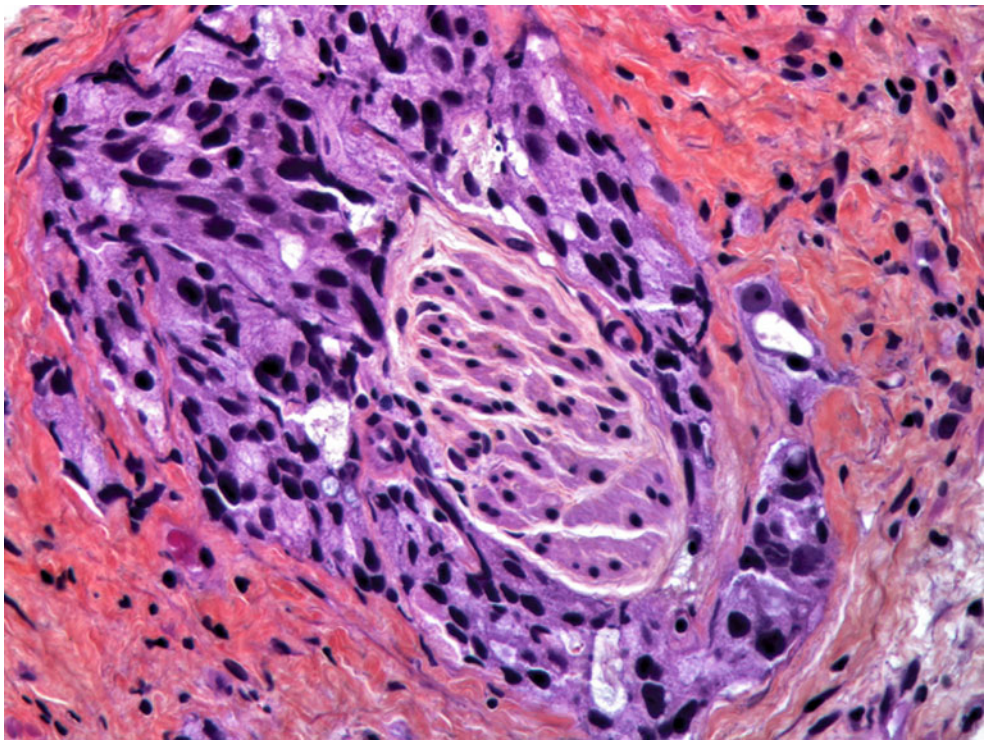

**Fig. 20.2** Perineural invasion. Cribriform malignant glands occupy the perineural space and completely surround the nerve

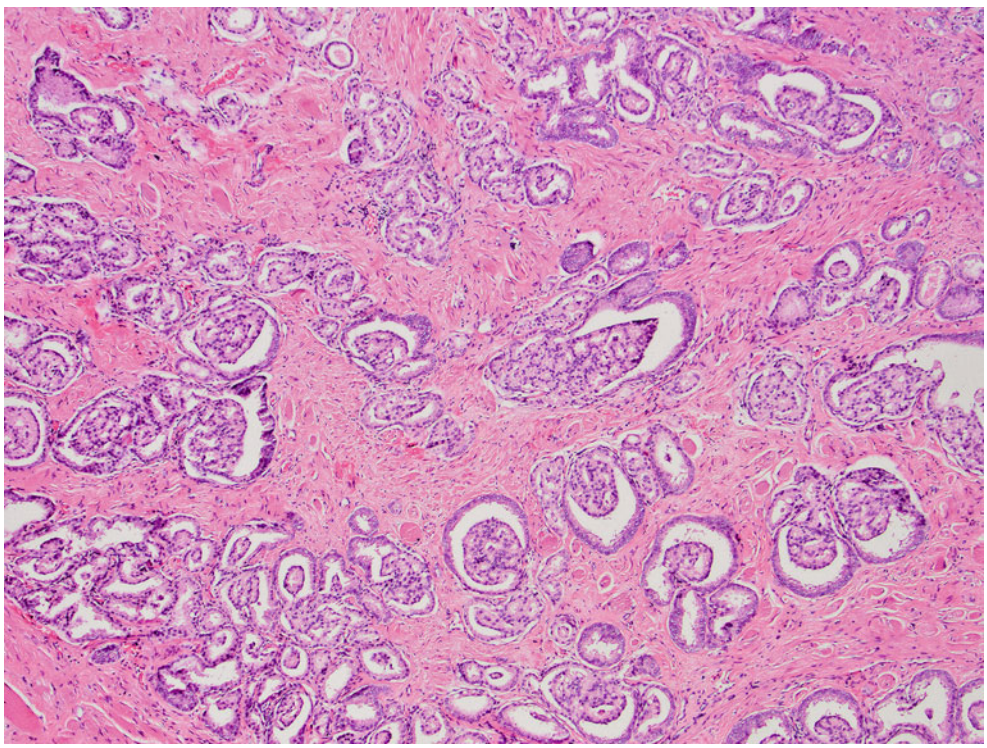

**Fig. 20.3** Glomerulations. Intraglandular cribriform and papillary growth with a unipolar attachment within the malignant glands. These bear some resemblance to fetal glomeruli, accounting for their name. These structures are considered to be part of Gleason pattern 4

## Reproducibility of Gleason Grading

Since the Gleason grade plays such an important role in treatment choice and prognosis of prostatic carcinoma, urologists and other treating clinicians need to factor in issues of reproducibility and reliability of the Gleason grading rendered on biopsy. Gleason himself addressed this question in a study in which he graded the same series of prostatic carcinomas twice, 1 year apart. He assigned the same score on both reviews in 50 % of cases and a score of ±1 in 85 % of

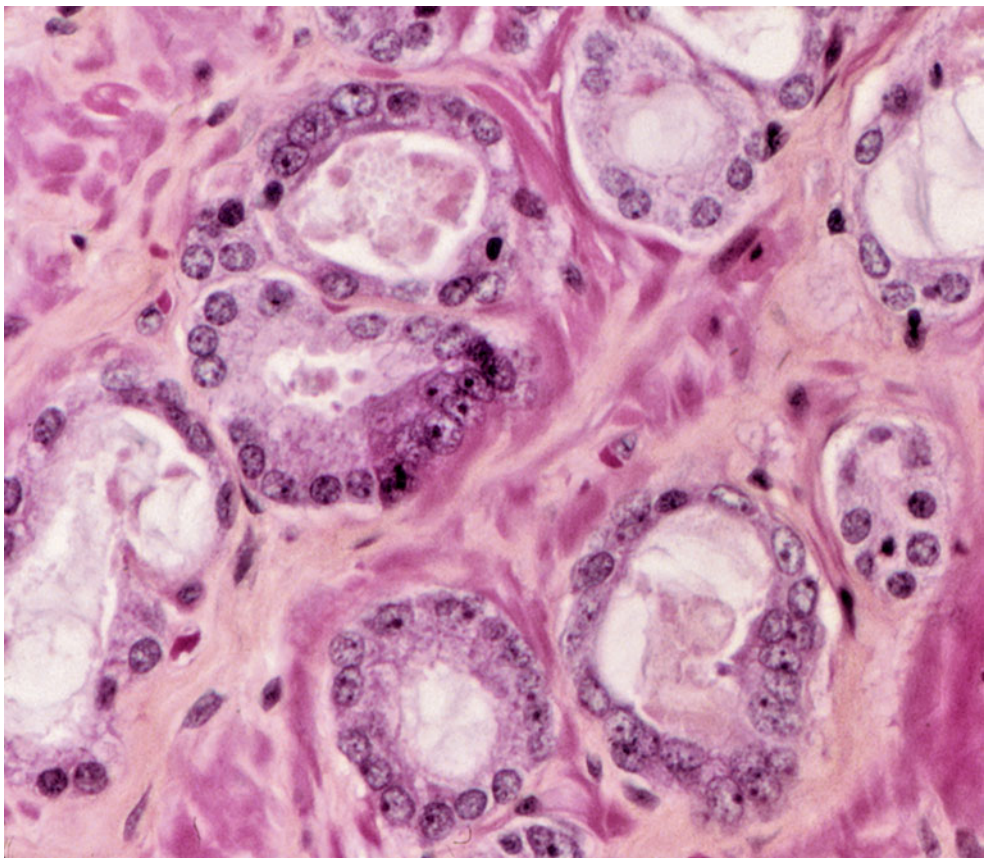

**Fig. 20.4** Cytologic features of malignancy. The malignant glands have a single cell layer, and the nuclei are enlarged and hyperchromatic with prominent nucleoli. The cytoplasm is amphophilic

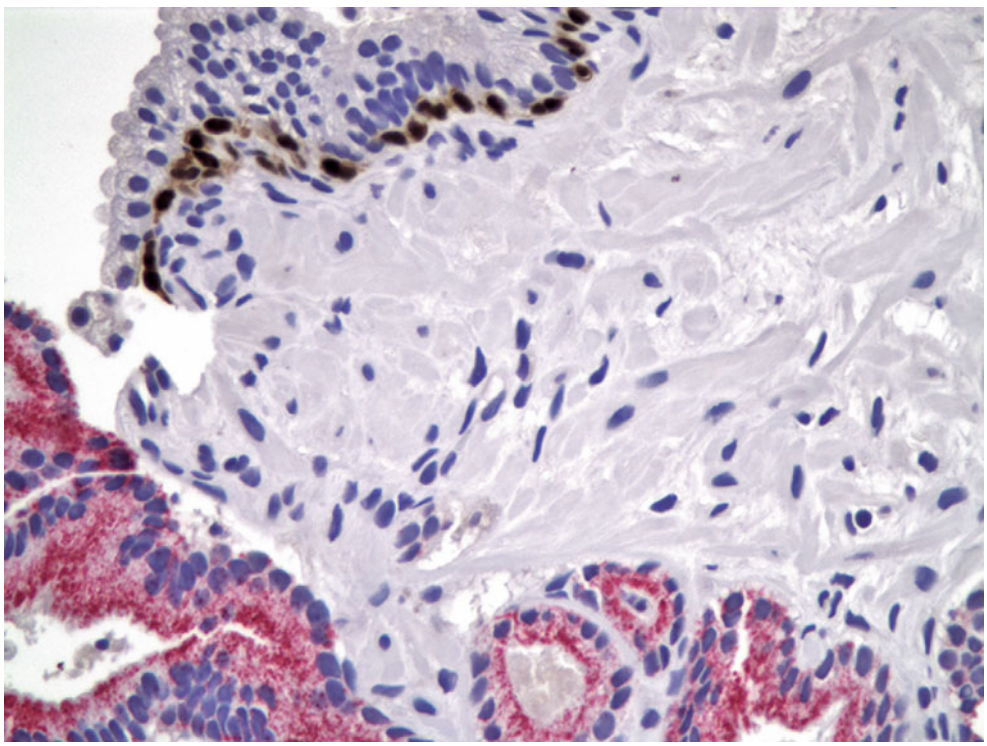

**Fig. 20.5** Triple immunohistochemical stains. The benign gland in the left upper corner is outlined by basal cells, whose cytoplasm is positive (*brown stain*) for HMWCK and whose nuclei are positive (*brown stain*) for p63. The malignant glands at the bottom of the image lack the brown basal cell stains but are strongly positive for the red-staining AMACR

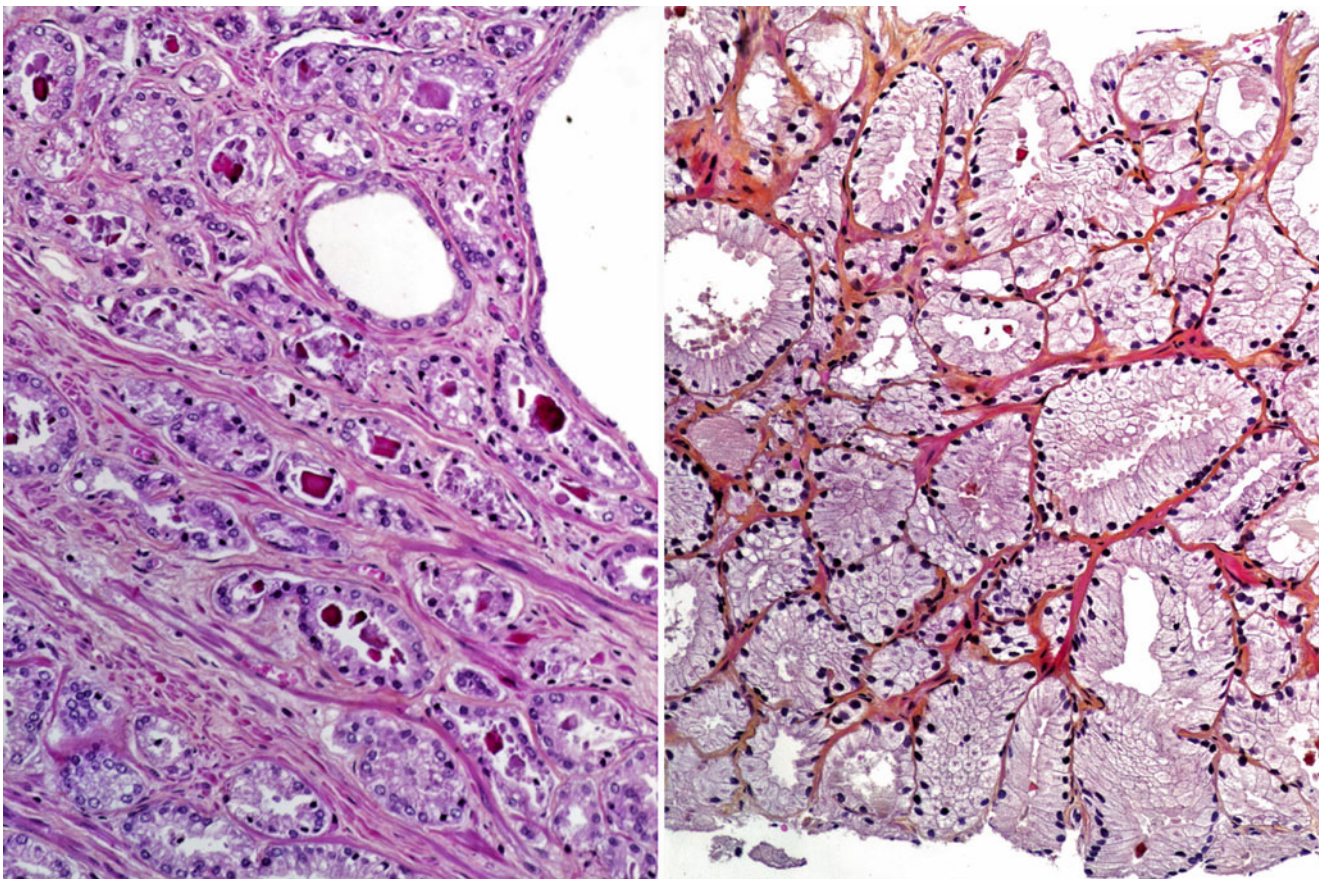

**Fig. 20.6** Examples of tertiary criteria. The malignant glands in the *left panel* show an amphophilic cytoplasm, and the lumina contain prominent crystalloids. The malignant glands in the *right panel* show a foamy cytoplasm

cases [8]. Subsequently, good reproducibility of Gleason grade has been documented among expert uropathologists [9], but not among general pathologists [10].

## Biopsy Versus Prostatectomy Gleason Score

The predictive value of the biopsy Gleason score versus the subsequent prostatectomy score has been addressed by many studies. In one study, the exact Gleason score was recorded in 40 % of prostatectomies and a ±1 Gleason score in 87 % of the cases when compared to the needle biopsies if diagnosed by an uropathologist [11]. However, a review of the Gleason score that had been rendered on these same cases by multiple general pathologists "in real-life practice" revealed the exact Gleason score in only 20 % of cases. Other studies by expert uropathologists reported the exact Gleason score on biopsy versus prostatectomy in the range of 60–81 % of cases [1]. This is a fair-good correlation, and Gleason grading of biopsies does provide valuable information.

In discrepant cases, there is usually an *upgrade* of the Gleason score in the prostatectomies. This is particularly true of cases diagnosed as Gleason score 4 (2+2) and Gleason score 5 (2+3; 3+2), in which an upgrade should be expected in virtually all cases.

However, Gleason score *downgrading* is also seen. Donahue et al. [12] reported significant downgrading in cases with biopsy Gleason scores of 8–10.

## Reason for Discrepancy Between Biopsy and Prostatectomy Gleason Scores

In the experience of uropathologists, there are two main reasons for Gleason score discrepancy between biopsy and prostatectomy:

1. There is a continuum of changes between the Gleason patterns (Fig. 20.7), such that tumor foci may have borderline features, and there can be *interobserver* (and even intraobserver) *variability* in assigning Gleason patterns (Fig. 20.13).
2. The second reason for a discrepant Gleason score is a *sampling* problem. Needle biopsies represent a minute fraction of the prostate and may not have sampled the entire histologic spectrum of the tumor present in the prostate (Fig. 20.13).

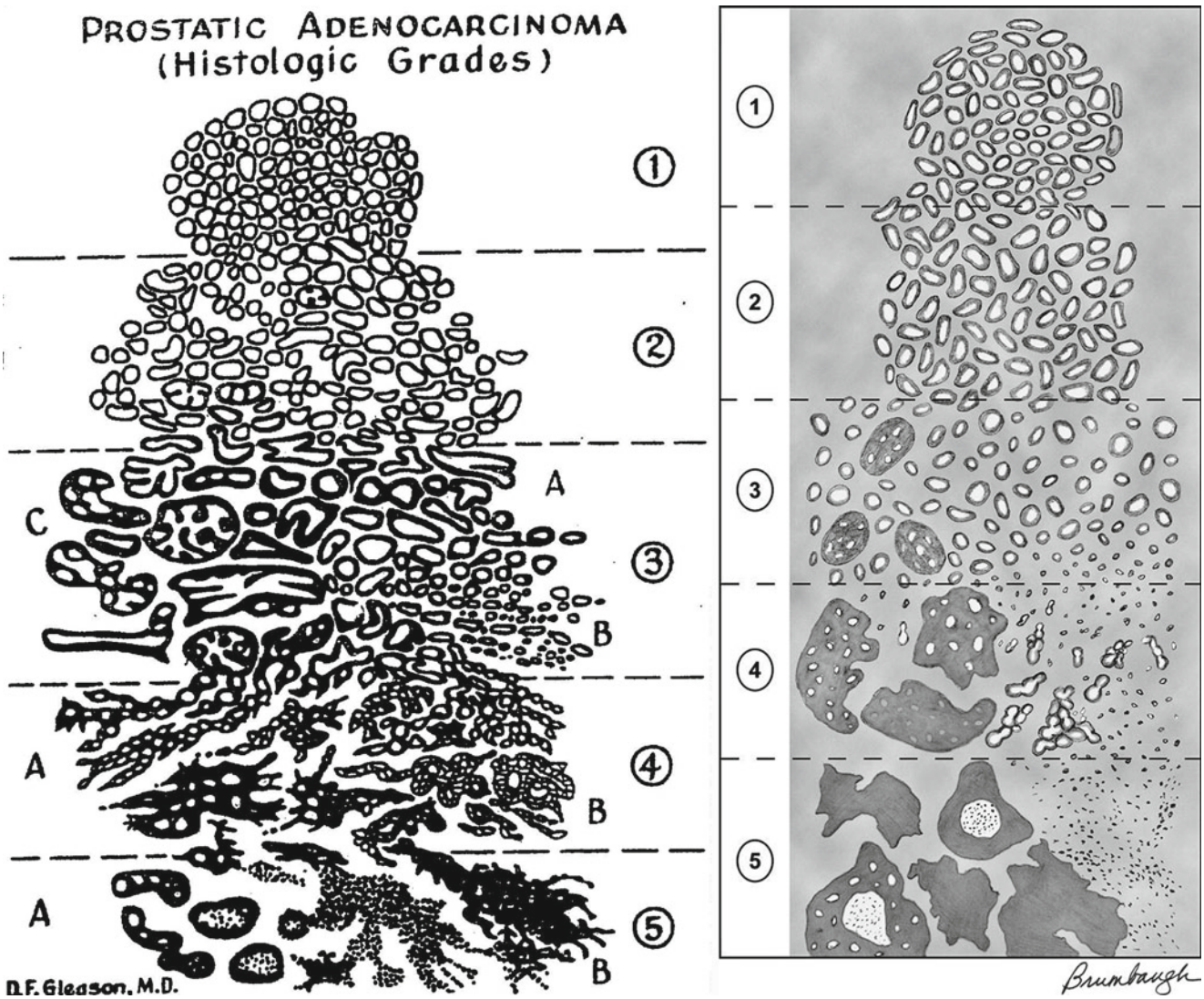


**Fig. 20.7** Gleason's patterns for his grading system. In the *left panel* is Gleason's original drawing of the various patterns. In the *right panel* are the patterns as modified by the 2005 ISUP Consensus Conference

## Changes in Gleason Grading after the 2005 ISUP Consensus Conference and "Gleason Score Inflation"

The 2005 ISUP Gleason Grading Consensus Conference resulted in the following main clarifications and modifications of the Gleason grading system:

1. Gleason pattern 1 is almost always atypical adenomatous hyperplasia (AAH), which has now been confirmed in most cases by basal cell stains. The stains were unavailable to Gleason when he developed his grading system. Therefore, Gleason pattern 1 and Gleason scores 2 and 3 are incorrect and should not be used.
2. Gleason pattern 2 requires circumscription of the tumor focus, which cannot be ascertained on needle biopsy. Therefore, Gleason pattern 2 and the corresponding Gleason score 4 should generally not be diagnosed on needle biopsies.
3. Infiltrating microacini, seen on needle biopsies, are Gleason pattern 3.
4. Most cribriform tumor foci and "ill-formed glands" are Gleason pattern 4.

As a consequence of the 2005 ISUP Consensus Conference, urologists have noted "Gleason grade inflation." Most of the "inflation" is due to the correction of the erroneous assignment of Gleason patterns 1 and 2 and scores 2–4. An additional reason for the "inflation" is the assigning of cribriform foci and "ill-formed" glands into pattern 4, rather than pattern 3. A recent study found an overall increase in Gleason scores following the 2005 Consensus Conference but also noted that the new Gleason scores corresponded to the patients' prostatectomy results and outcomes even better

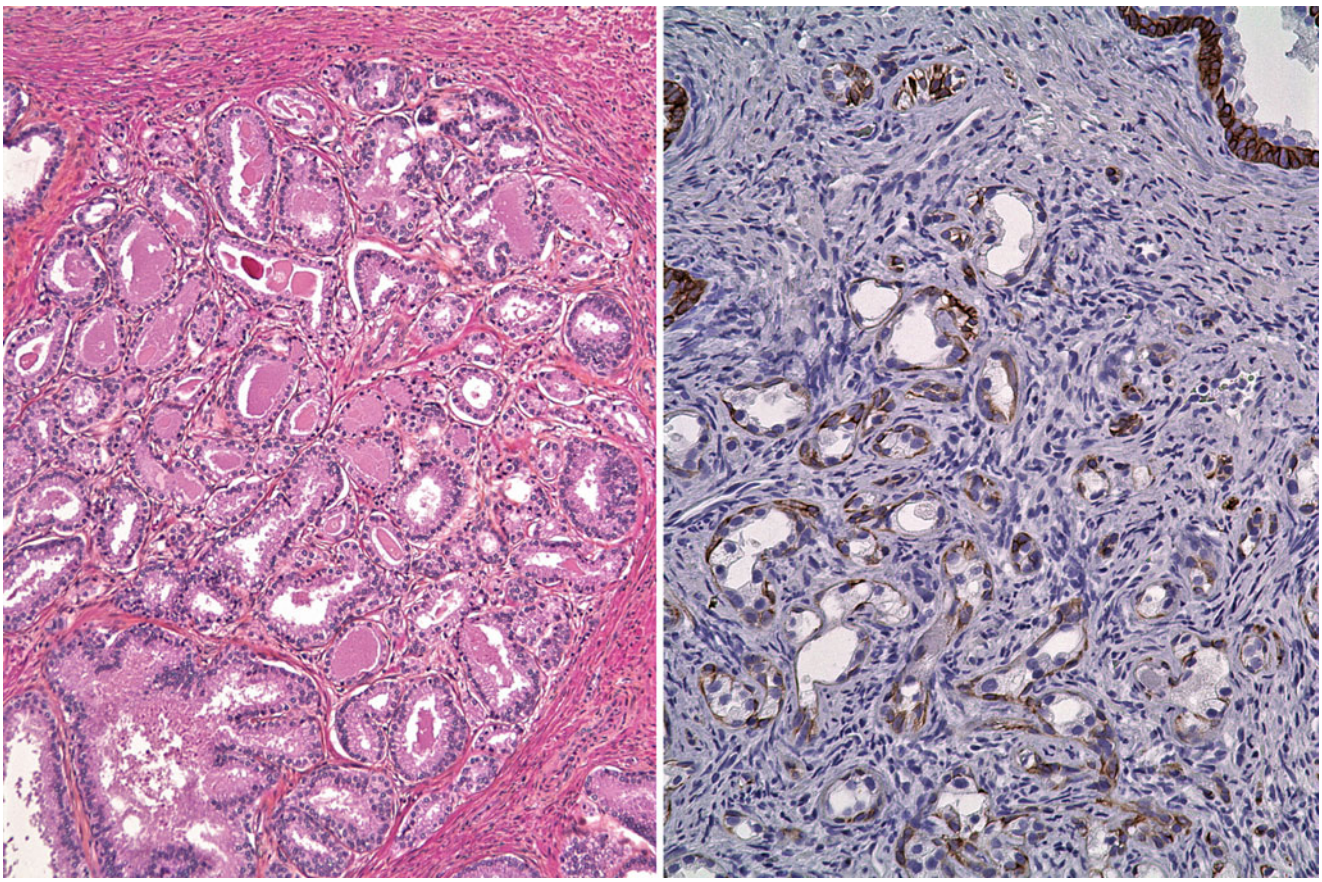

**Fig. 20.8** Gleason pattern 1, consisting of a nodule of tightly packed microacini. This pattern is now considered to represent AAH, as demonstrated by the presence of the brown-staining discontinuous basal cell layer in the *right panel* (Stain is for HMWCK)

than the Gleason scores assigned prior to the 2005 Consensus Conference [13].

## Clinicopathologic Summary

*Gleason grading of prostatic carcinoma*:

1. Each biopsy core or separately submitted specimen (set of cores) should be Gleason graded, including the Gleason score and the component primary and secondary patterns.
2. *Gleason scores 2–5*. The diagnosis of adenocarcinoma Gleason score 2–3 should never be rendered, and the diagnosis of adenocarcinoma Gleason score 4 is almost always incorrect, except in rare prostatectomy cases. A Gleason score 5 adenocarcinoma on needle biopsy is almost always upgraded in the prostatectomy. An expert second opinion might be indicated in some of these cases [4].
3. *Gleason scores 8–10*. A Gleason score of 8–10 on biopsy indicates that there is a clinically significant high-grade component, although a number of these cases will be downgraded on prostatectomy. Catalona's group has shown that if the Gleason score 8–10 carcinoma is present in only 1 core or in less than 15 % of the biopsy material, 2/3 of these patients will have organ-confined disease and can benefit from radical prostatectomy [14].
4. *Tertiary pattern 5*. Because of its clinical prognostic significance, tertiary pattern 5 should replace the secondary pattern in needle biopsy diagnoses but remain as tertiary pattern 5 if it is a minor component of prostatectomy specimens.
5. *Gleason score on biopsy as predictor of prostatectomy Gleason score*. The prostatectomy Gleason score is expected to be ±1 of the biopsy Gleason score in 85–90 % of cases, especially when diagnosed by uropathologists. Extended sampling of the prostate has been reported to increase the likelihood of better tumor sampling and therefore to improve the reliability of Gleason grading in biopsy specimens [15, 16].
6. *Multiple positive cores with different Gleason scores*. The global Gleason score is the best predictor of prostatectomy Gleason score, but the highest Gleason score is a good predictor and most widely used.

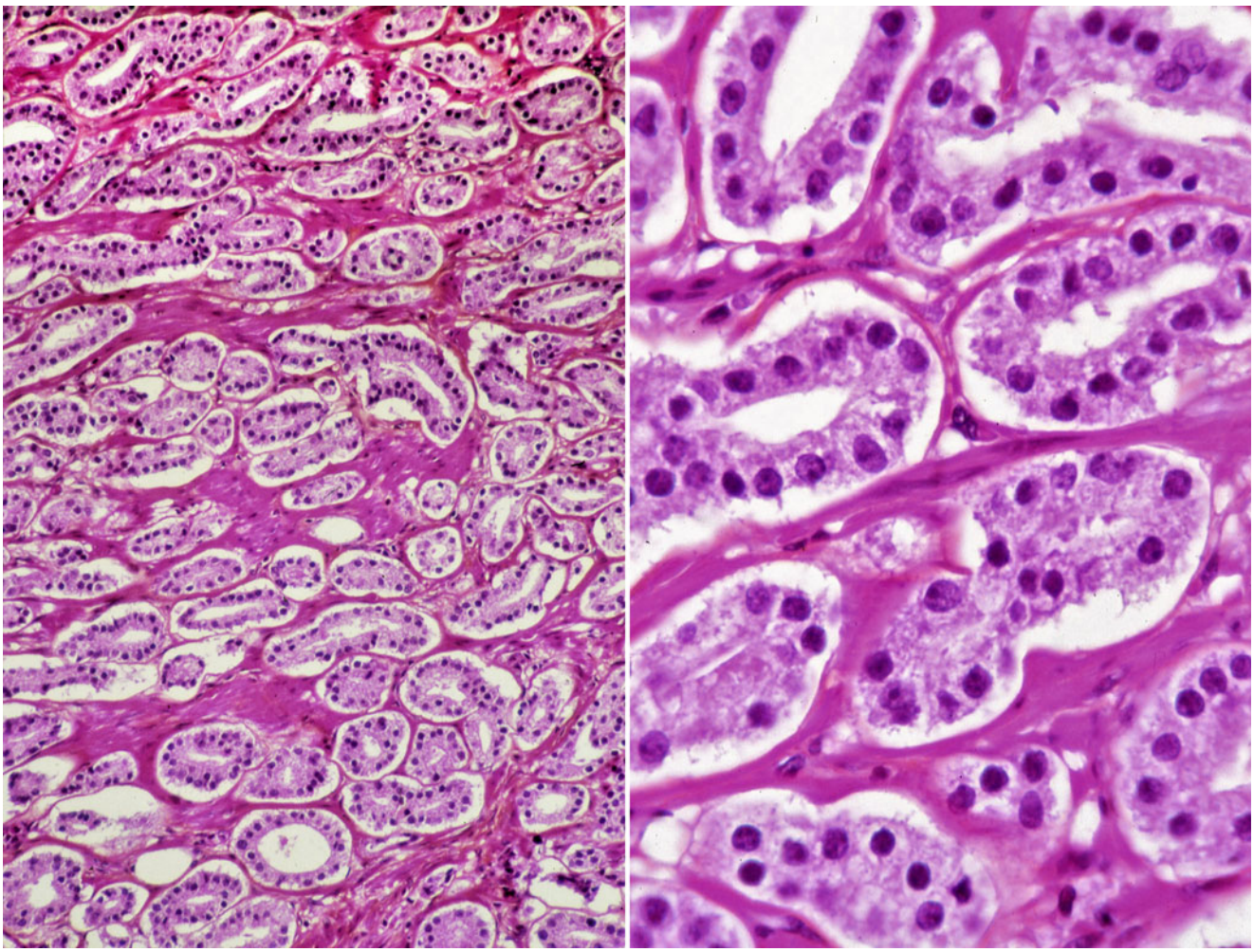

**Fig. 20.9** Gleason pattern 2. This is the center of a well-circumscribed nodule of well-formed, crowded microacini, characteristic of Gleason pattern 2. In the *right panel* is a higher magnification of this tumor

## Mimickers of Prostatic Carcinoma

The main mimickers of prostatic carcinoma are considered here since these entities can cause diagnostic difficulties and are frequently mentioned as differential diagnoses for prostatic carcinoma (Table 20.2).

*Clear cell cribriform hyperplasia* is a mimicker of prostatic carcinoma because of its intraglandular cribriform proliferation. However, this growth occurs in preexistent normal ducts, with small nuclei without nucleoli, and is surrounded by a basal cell layer. This lesion is completely benign (Fig. 20.14).

*Atrophy* can mimic adenocarcinoma because it consists of small glands (microacini), which can be tightly packed and have dark nuclei. However, atrophic glands are usually arranged in a lobular pattern around a central duct and have scant cytoplasm. The benign diagnosis occasionally requires confirmation with basal cell stains, which usually show a discontinuous basal cell layer. AMACR can be faintly positive.

An even more problematic mimicker of prostatic carcinoma is *partial atrophy*. Although part of the lobule may show the changes described above for atrophy, other microacinar units contain moderate cytoplasm, enlarged nuclei, and a few nucleoli. The presence of basal cells, although sometimes very sparse, helps to confirm the benign nature of these lesions (Fig. 20.15).

*Basal cell hyperplasia* is frequently associated with atrophy and consists of the proliferation of basal cells with hyperchromatic nuclei and occasional nucleoli. HMWCK and p63 stains are intensely positive in basal cell hyperplasia, and therefore the benign nature of these proliferations can be easily confirmed (Fig. 20.16).

*Atypical adenomatous hyperplasia* (*AAH*) *and adenosis*, which most expert uropathologists now consider the same entity, are reported by Epstein with a prevalence rate of 1.6 % in TURP specimens and in 0.8 % of needle biopsies [17]. The consensus is that AAH is not a premalignant lesion,

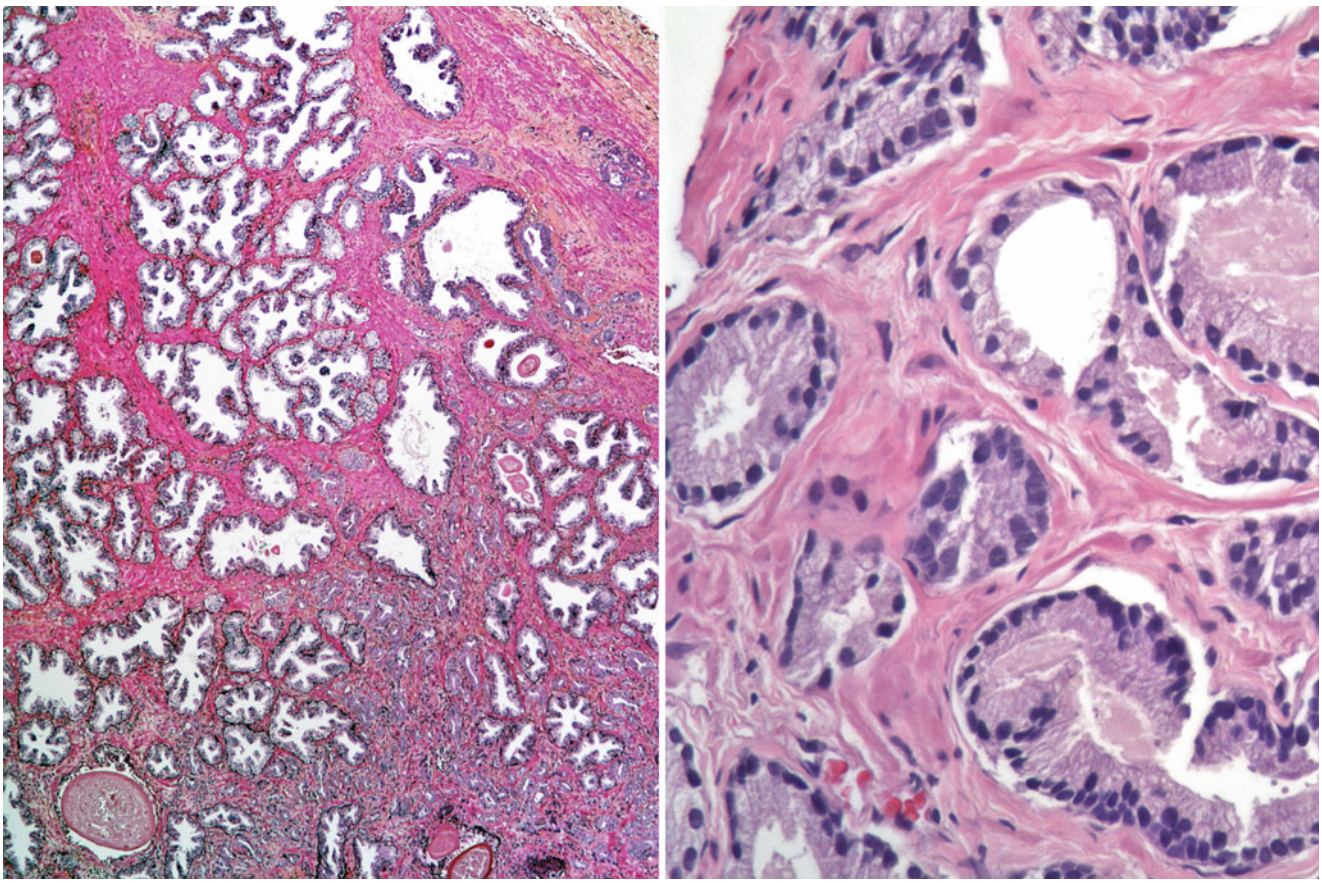

**Fig. 20.10** Gleason pattern 3. The *left panel* shows the characteristic infiltrative pattern of a Gleason pattern 3 carcinoma. The carcinoma invades the stroma of a benign lobule and surrounds the benign glands. The *right panel* is a higher magnification, highlighting the greater irregularity of these infiltrating malignant microacini

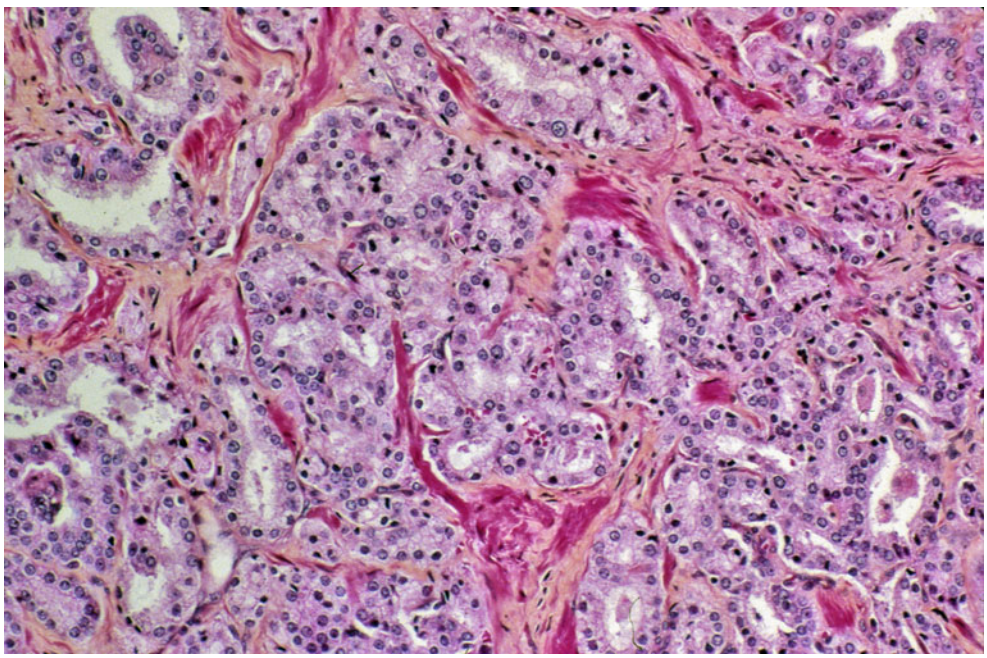

**Fig. 20.11** Gleason pattern 4. The malignant glands are no longer discrete and separate. They are fused into chains and cribriform sheets

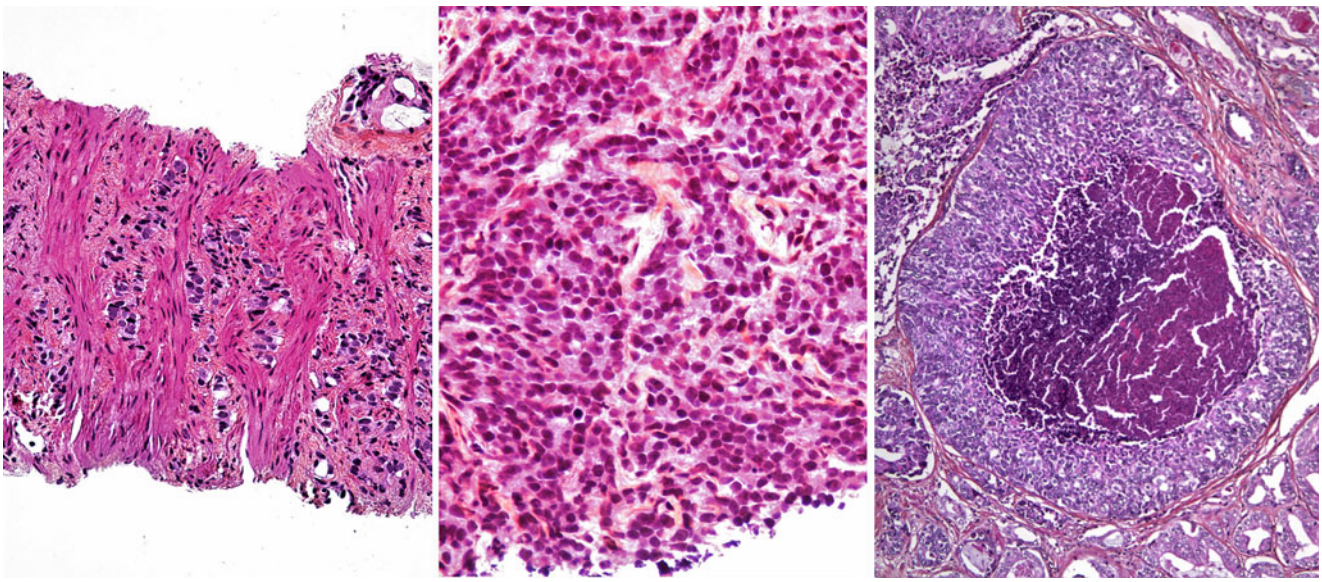

**Fig. 20.12** Gleason pattern 5. No glandular architecture remains. This is an undifferentiated carcinoma, growing in single file and sheets. The *middle panel* is a higher magnification of the Gleason pattern 5 carcinoma, which highlights the total lack of glandular structures. The *right panel* shows comedonecrosis in carcinoma, which is part of pattern 5

although several investigators suggest that it might be a precursor lesion for some of the low-grade tumors seen in the transition zone [18].

Adenosis consists of a circumscribed nodule of tightly packed microacini. Atypical adenomatous hyperplasia (AAH) has the same architecture but also includes enlarged nuclei with nucleoli. These lesions, therefore, demonstrate some primary (architectural) and secondary (cytologic) criteria of malignancy. As mentioned above, most uropathologists consider Gleason pattern 1 to be AAH. A definitive diagnosis of these foci requires immunohistochemical staining to identify the rare basal cells. Faint AMACR staining is also usually present (Fig. 20.17).

*Seminal vesicles and ejaculatory ducts* can be mistaken for prostatic carcinoma in small thin needle biopsy specimens. They consist of tightly packed small glands around the central lumen and contain pleomorphic, hyperchromatic nuclei with large nucleoli. However, recognition of the relationship of these clustered atypical glands to a central duct and the characteristic of cytoplasmic golden-brown lipofuscin pigment is usually sufficient for proper diagnosis [19]. Rarely basal cell stains, positive in seminal vesicles and ejaculatory ducts, need to be performed for confirmation.

## Clinicopathologic Summary

*Mimickers of prostatic carcinoma*:

The main benign mimickers of prostatic carcinoma, *clear cell cribriform hyperplasia*, *atrophy*, *partial atrophy*, *basal cell hyperplasia*, *adenosis*, *atypical adenomatous hyperplasia*, *seminal vesicles*, *and ejaculatory ducts* (Table 20.2), are recognized by their characteristic architecture and cytology. Occasionally immunohistochemical stains are required for confirmation.

## Special Issues Relating to Needle Core Biopsies of the Prostate

In the current PSA screening and extended core biopsy era, a diagnosis of carcinoma is rendered in approximately 25–30 % of biopsied patients. In the study by Berger et al., the mean was 27.7 % and the range was 25.1–30.1 % for positive cancer diagnoses in their series of cases [20].

The small size and thinness of the biopsy core specimens has implications for the pathologists' ability to diagnose and grade prostatic carcinoma. The inability to definitely diagnose Gleason pattern 2 has already been mentioned. In addition, foci suspicious for carcinoma may be very small, at a tissue edge, or crushed. Immunohistochemical stains, particularly the triple stains, are frequently utilized and can help to resolve diagnostic difficulties. In other cases, the diagnosis of atypia or ASAP (atypical small acinar proliferation) is used to indicate that the focus may represent carcinoma, but it cannot be definitively diagnosed.

The presence of *perineural invasion* should always be reported if identified in needle biopsies because it indicates an increased *risk of extraprostatic extension* of carcinoma [17, 25]. The number and percent of positive cores, as well as the length of tumor in involved cores, are all reported to be predictors of extraprostatic extension as well [21]. Occasionally

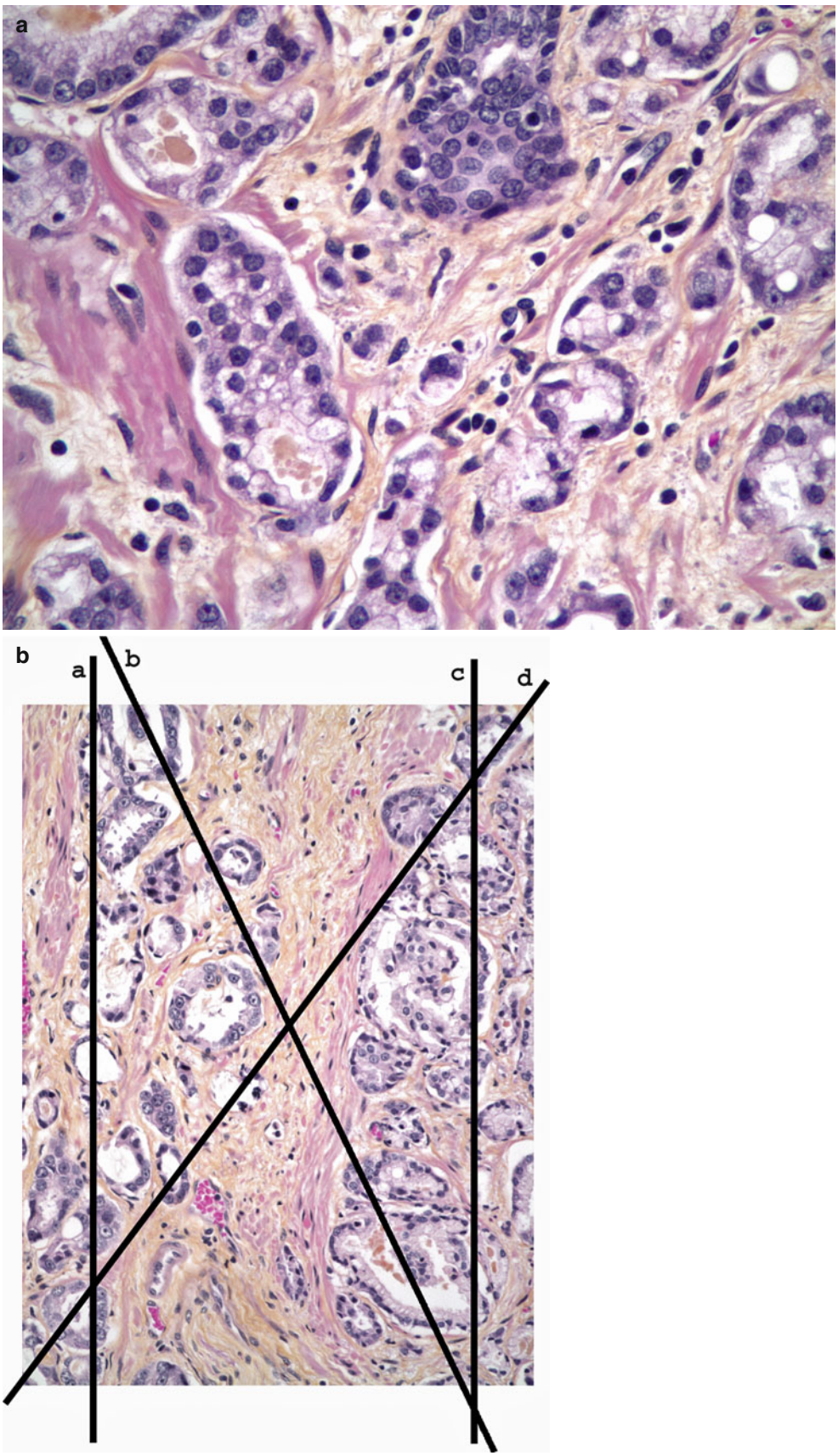


**Fig. 20.13** (**a**) This is an example of histology, which is borderline between patterns 3 and 4. Some observers would consider the entire focus to fit into pattern 3 (Gleason score 6 (3+3)); whereas others would consider the glands on the right to be "ill-formed" and beginning to fuse and would assign a Gleason pattern 4 to this focus (Gleason score 7 (3+4)). (**b**) This section from a prostatectomy specimen is used to demonstrate sampling issues related to needle biopsies of the prostate. In this section, if the needle tract were represented by *line a*, the diagnosis would be carcinoma, Gleason score 6 (3+3). If the needle were to follow *line b*, the diagnosis would be carcinoma, Gleason score 7 (3+4). If the needle were to follow *line c*, the diagnosis would be carcinoma, Gleason score 8 (4+4). If the needle were to follow *line d*, the diagnosis would be carcinoma, Gleason score 7 (4+3)

adipose tissue or seminal vesicle tissue, present in the biopsy core, contains invasive adenocarcinoma. In such cases the prostatic carcinoma can be *pathologically staged as pT3* disease.

Favorable parameters on needle biopsy, such as a *small tumor focus/small tumor volume and a low Gleason score*, do not necessarily predict a favorable outcome or an insignificant tumor on prostatectomy [17, 22–24].

## Special Issues Relating to TURP Specimens

Incidental adenocarcinoma is less frequent in TURP (transurethral resections of prostate) currently than it was prior to PSA screening. However, all TURP specimens are examined carefully. Epstein advocates submitting eight cassettes initially (or nine cassettes, if an additional cassette would sample the entire specimen) [1]. The standard in other institutions is to initially submit 12 cassettes.

**Table 20.2** Benign mimickers of prostatic carcinoma

| |
|---|
| 1. Clear cell cribriform hyperplasia |
| 2. Atrophy |
| 3. Partial atrophy |
| 4. Basal cell hyperplasia |
| 5. Adenosis |
| 6. Atypical adenomatous hyperplasia (AAH) |
| 7. Seminal vesicle and ejaculatory duct |

Should a carcinoma be found in the initial set of sections, many uropathologists would then submit the entire TURP specimen in order to properly Gleason grade the tumor and to stage it: *stage pT1a if there is <5 % tumor or pT1b if there is >5 % tumor*. Other authors suggest taking more sections only if there is <5 % tumor on the initial set of sections [1].

## Special Issues Relating to Radical Prostatectomy

### Characteristics of Prostatic Carcinoma at Prostatectomy in the Current PSA Screening Era

Prostatic adenocarcinomas are generally smaller and at a lower stage currently than those reported before PSA screening was instituted [20, 25]. Eighty-five percent of stage pT1c and pT2 tumors are in the *peripheral* zone [17]. Single, grossly visible dominant tumor masses are less common. Eighty-five percent of prostatic adenocarcinomas are now *multifocal*, and 70 % are *bilateral*. Taking this information into account is essential if one is contemplating focal or localized treatment of prostatic adenocarcinoma.

### Grossing Prostatectomy Specimens

Upon receipt in the pathology laboratory, the prostatectomy specimen is weighed and measured with notation of any specific

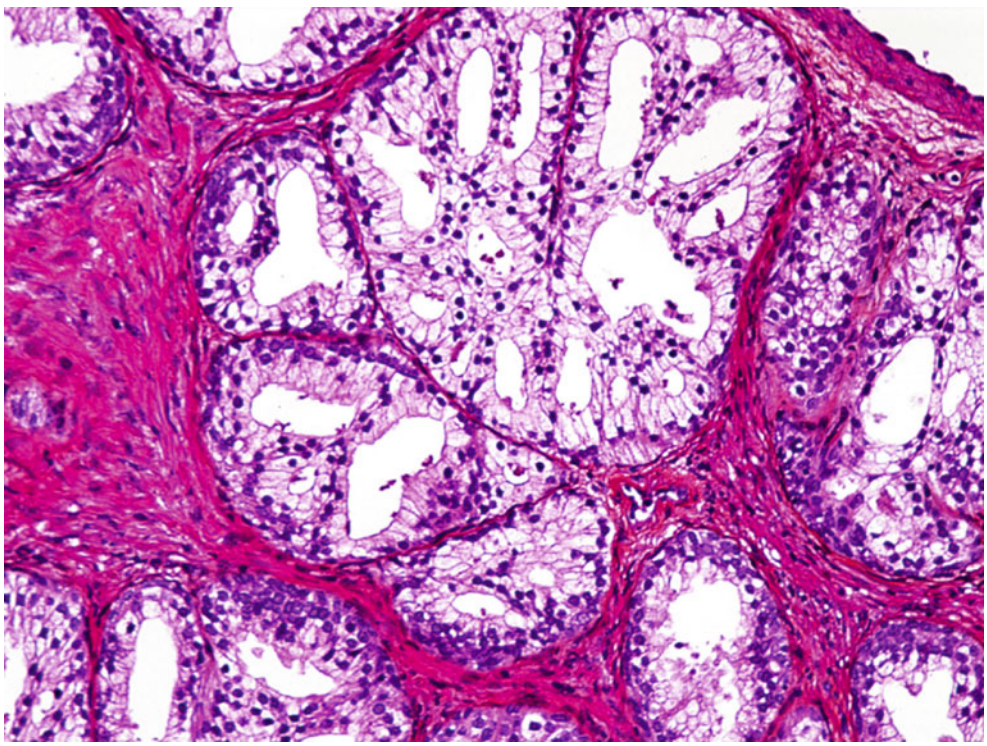

**Fig. 20.14** Clear cell cribriform hyperplasia, a mimicker of carcinoma. Note the intraglandular cribriform proliferation with clear cytoplasmic change. The nuclei are small, and there are no nucleoli. This is a benign lesion

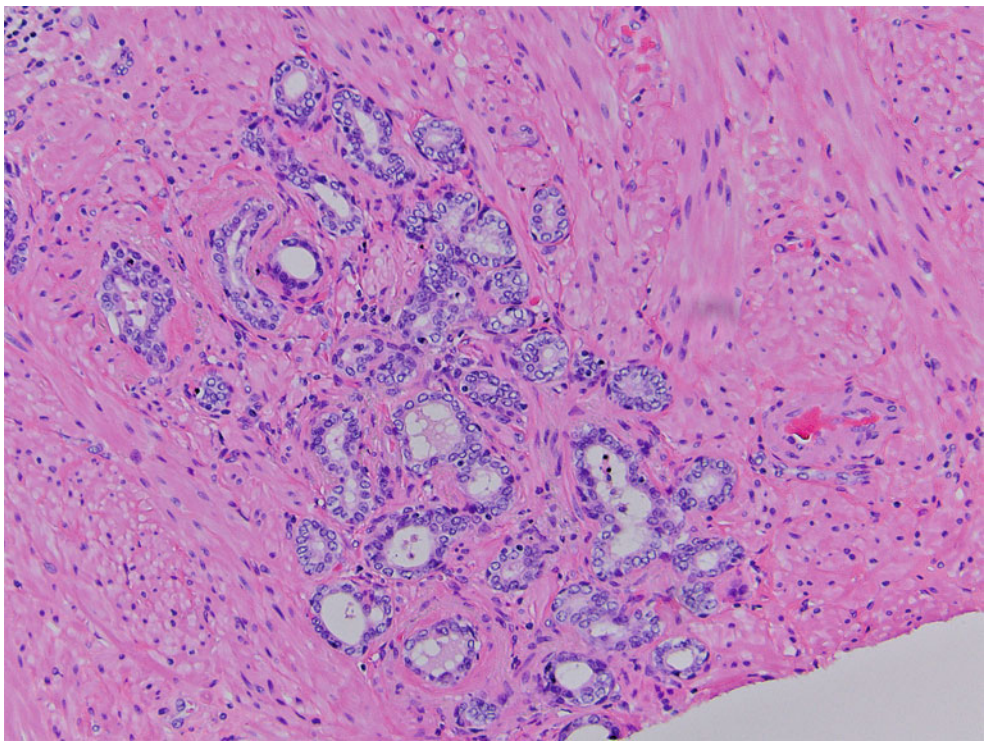

**Fig. 20.15** Partial atrophy. This lesion consists of microacini in a subtle lobular pattern. There are enlarged nuclei and occasional nucleoli

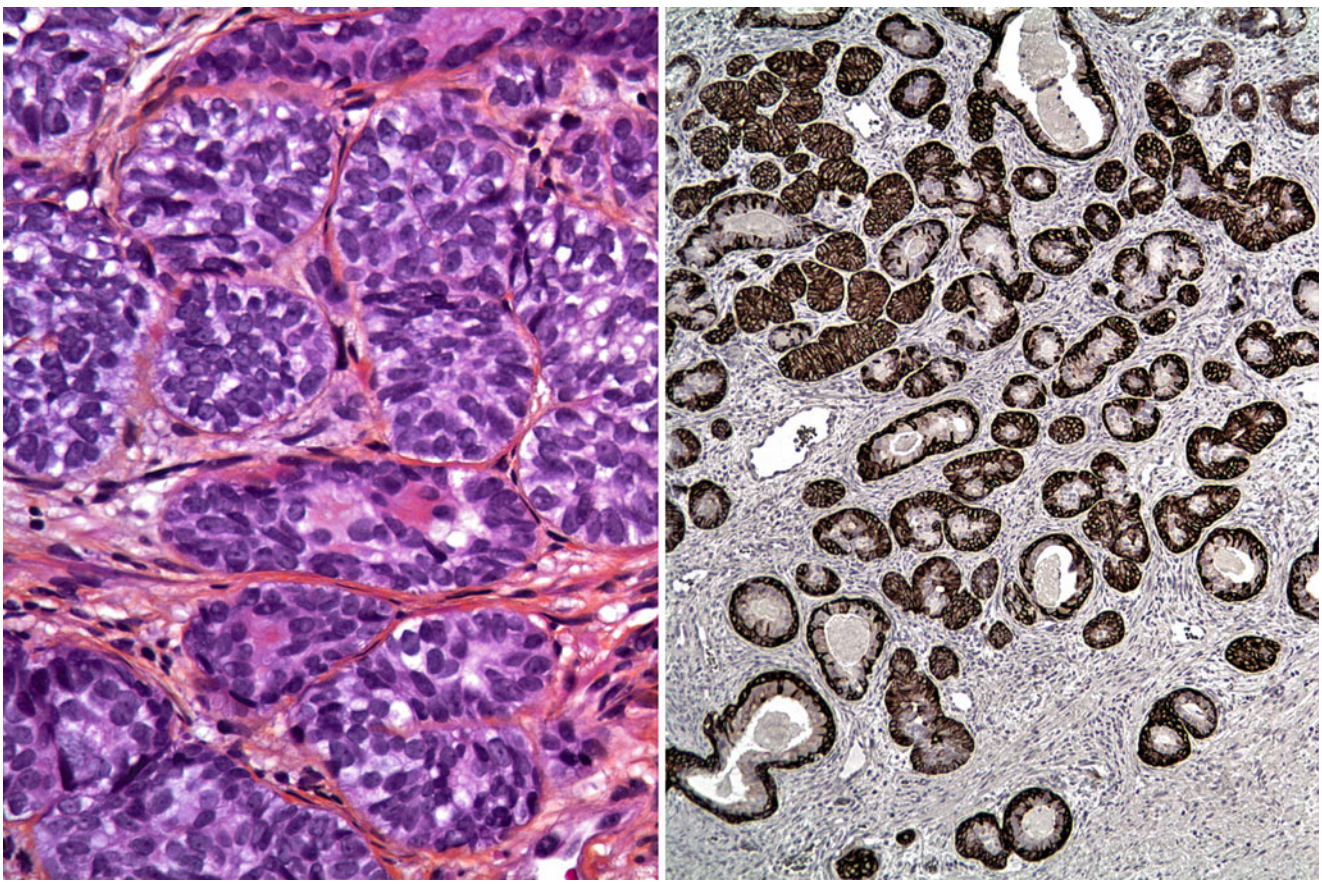

**Fig. 20.16** Marked basal cell hyperplasia in atrophic glands. These microacini are lined by a multilayered epithelium, with very hyperchromatic large nuclei, which contain nucleoli. The cytoplasm is sparse. HMWCK stain in the *right panel* shows intense staining of these proliferating basal cells

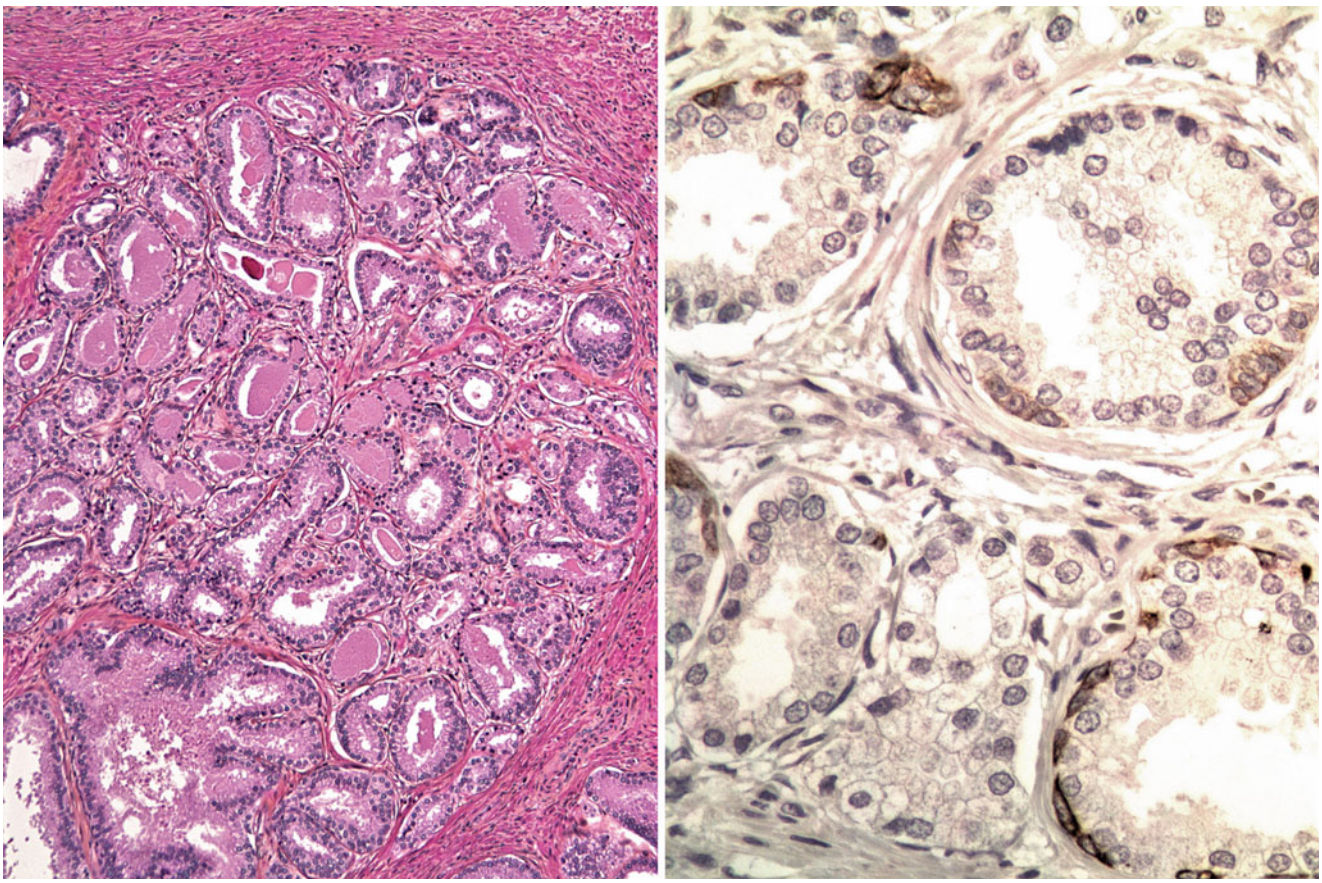

**Fig. 20.17** Atypical adenomatous hyperplasia (AAH). This lesion is architecturally abnormal because it consists of tightly packed microacini. It is also cytologically abnormal, as seen in the *right panel*, because there are large nuclei and a few large nucleoli. However, the HMWCK stain shows a few basal cells in these microacini. Please note that there is one unit, bottom middle, which is devoid of basal cells. However, it is part of this proliferation, and therefore the entire lesion, including this acinus, is benign. This type of lesion would pose diagnostic difficulty in a needle biopsy

surface changes. The entire specimen is then inked for histologic identification of margins. It is customary to use different colored inks, at least two to denote the left and right sides. The apex, para-apex, base, and para-base are sectioned and entirely blocked. The bases of the seminal vesicles are sectioned in continuity with their prostatic attachments. The remainder of the prostate is either blocked completely, or every other section is taken for initial review. If the prostate is incompletely sectioned initially, the remainder is kept for possible further examination. The gross description in the pathology report should indicate how the sections were taken, from where each section was taken, and if the entire prostate was sectioned.

## Pathologic Staging of Prostate Cancer

*Perineural invasion*, when identified in prostatectomy specimens, does not increase the risk of progression [26]. *Blood and lymphatic vessel invasion* is a significant negative risk factor for progression but is infrequently seen [27].

*Positive surgical margins* are most often identified at the apex and laterally. Frequently these positive margins are intraprostatic, in which case they do not raise the pathologic stage of the tumor; however, some expert uropathologists advocate staging these tumors as *pT2+* to indicate that extraprostatic extension cannot be entirely excluded. Regardless of whether they are intraprostatic or in an area of extraprostatic extension, positive margins are associated with a significantly increased risk of progression (Fig. 20.18).

The prostate does not have a true capsule. The area referred to as "capsule" consists of the compressed fibromuscular stroma of the prostate. *Extraprostatic extension* (*stage pT3a*) is diagnosed when malignant glands are identified in loose periprostatic fibroadipose tissue. In addition to diagnosing extraprostatic extension, many pathologists also indicate whether this extension is focal/localized or multifocal/established and its location/laterality (Fig. 20.18). Difficulties in determining the presence of extraprostatic extension may occur anteriorly toward the apex because in this location there is a fibromuscular ligament, which extends

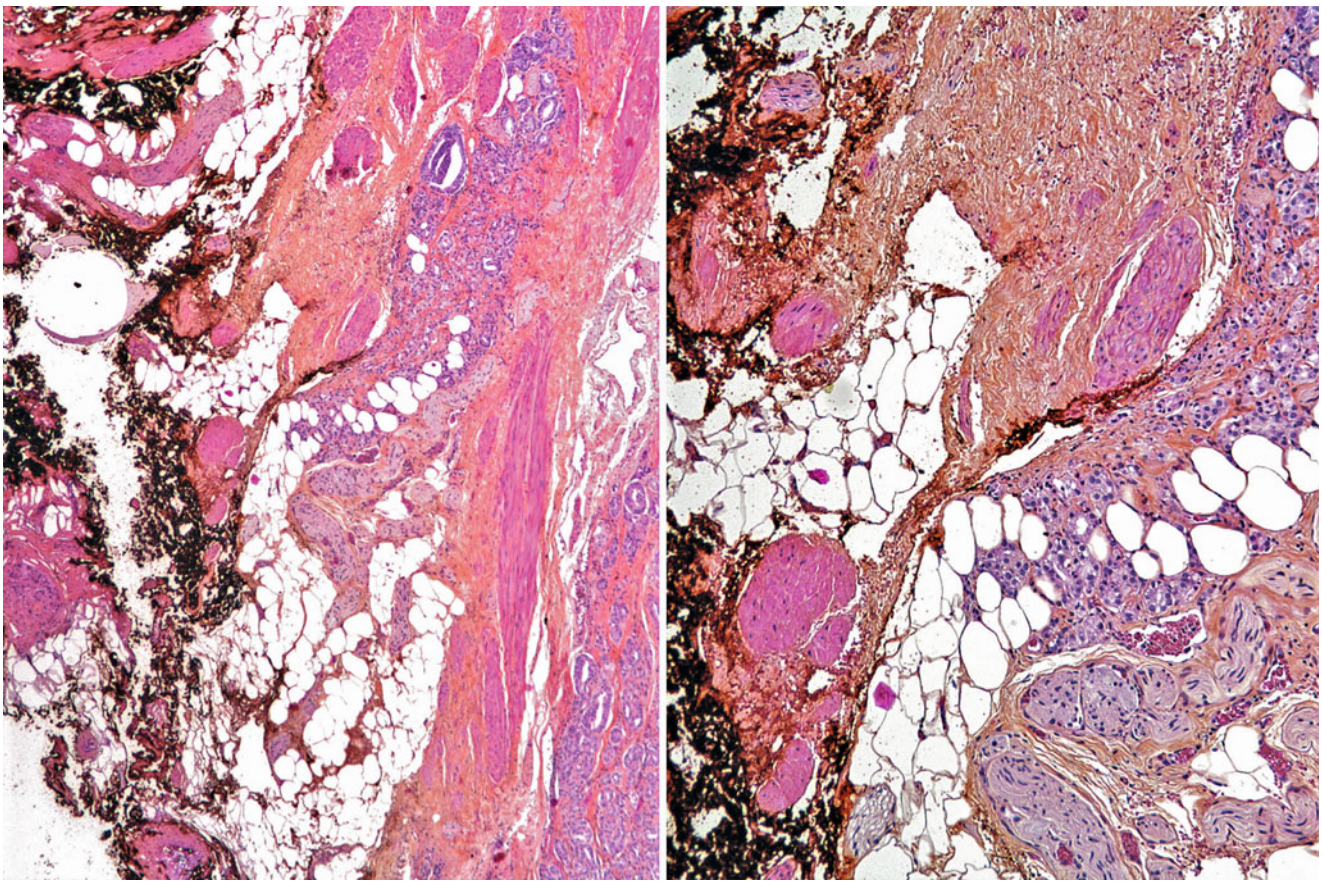

**Fig. 20.18** Extraprostatic extension of prostatic adenocarcinoma and negative surgical margins. Both the lower magnification *left panel* and the higher magnification *right panel* show malignant microacini infiltrating periprostatic adipose tissue, constituting a pT3a tumor. The inked margins are negative for tumor

from the fibromuscular "capsule" of the prostate, with little or no adipose tissue and no clear demarcation of the edge of the prostate (Fig. 20.19). Another potentially difficult area is posterior lateral, where there might be a fibrotic reaction in an area of periprostatic tumor extension, which might obliterate adipose tissue, making this area appear like part of the prostate. Pathologists use the contour of the organ with the adjacent benign glands as a guide. In cases in which a definite determination cannot be made, the pathologic diagnosis will be "suspicious for extraprostatic extension," or "extraprostatic extension cannot be excluded" [27].

*Seminal vesicle invasion* (*stage pT3b*) is diagnosed when prostatic carcinoma is identified in the muscularis propria or among the glands of the seminal vesicle (Fig. 20.20). Invasion of the small intraprostatic portion of the seminal vesicle does not constitute stage pT3b disease.

*Intraoperative lymph node evaluations* (*frozen sections*) are currently infrequent following several significant clinical observations. First, only two-thirds of micrometastases are identified in frozen sections due to sampling issues and because pelvic lymph nodes are fatty, which makes them technically difficult to section as fat does not freeze. Secondly, if the carcinoma is less than Gleason score 8, a prostatectomy provides a prolonged tumor-free survival even in cases with lymph node micrometastases. Therefore, the intraoperative lymph node evaluation would not alter the operative procedure [17].

The only cases in which lymph node frozen sections might be warranted are during surgeries for prostatic carcinomas with Gleason scores 8–10. Some of these patients can be cured by prostatectomy, if the lymph nodes are negative, and therefore lymph node status might be evaluated intraoperatively before prostatectomy is attempted [17].

## Low-Volume Prostatic Carcinoma

Low-volume carcinoma in prostatectomy specimens should not be considered a clinically insignificant tumor. El-Gabry et al. report that in their series of prostatic carcinomas of less than 0.5 $cm^3$, 35 % were Gleason score 7 or greater, 8 % had positive margins, and 2.5 % had biochemical failure in 1–66 months post-prostatectomy [28]. Similar findings were reported by other groups, including Cheng et al. [22].

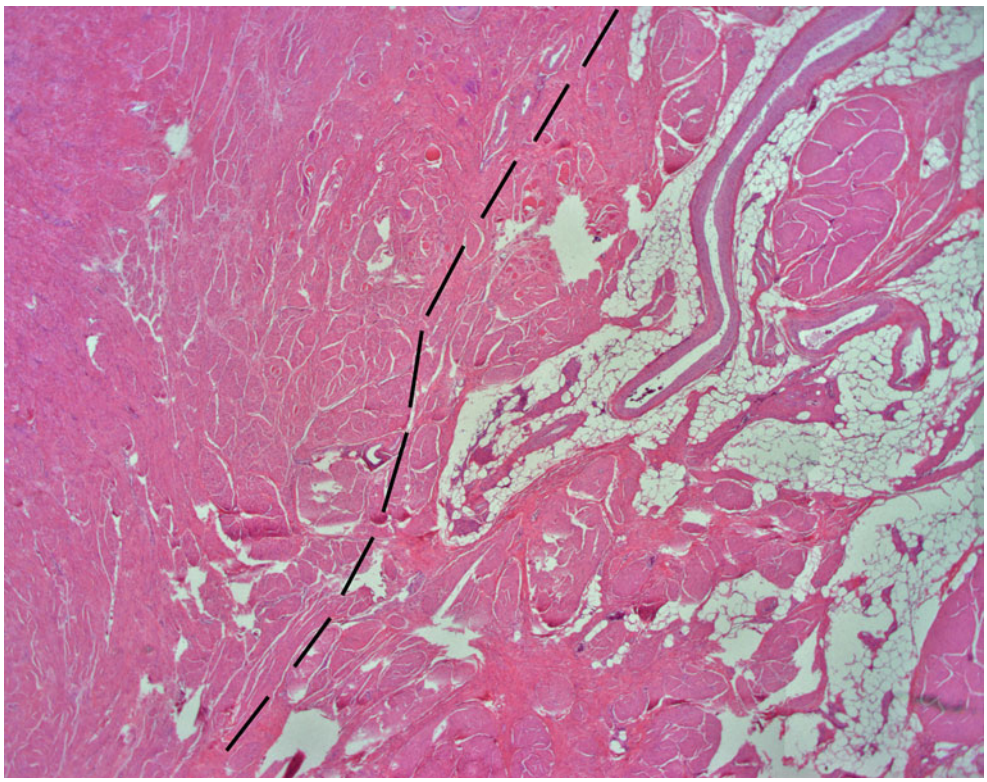

**Fig. 20.19** The fibromuscular tissue of the anterior ligament (*right side* of *dotted line*) is continuous with the fibromuscular stroma of the prostate (*left side* of *dotted line*), making demarcation of the beginning of extraprostatic tissue difficult. The placement of the *dotted line* in this image, which indicates the boundary of the prostate and extraprostatic tissue, is somewhat arbitrary

## Clinicopathologic Correlation in Prostatectomy Specimens

1. Gleason score is confirmed.
2. Pathologic stage is determined, including evaluation for extraprostatic extension, seminal vesicle invasion, and lymph node metastases.
3. Surgical margins are evaluated. Positive margins are most commonly found at the apex and laterally.
4. Frozen section evaluation of lymph nodes is not indicated in most cases.

## Problem Areas in the Pathologic Diagnosis of Prostatic Adenocarcinoma

### Treatment Effect

Hormone and radiation therapies have a profound effect on the histology of both benign and malignant prostatic tissues. In order to avoid misinterpretation of these changes, the pathologist should always be informed of the patient's treatment history.

*Hormone treatment* usually results in atrophy of the *benign* prostatic glands, often with basal cell hyperplasia and squamous metaplasia. *Malignant* glands showing hormone effect usually lose their glandular structure and frequently have pyknotic small nuclei without nucleoli. They can either be mistaken for infiltrating lymphocytes or histiocytes, or, if recognized as tumor, they may be diagnosed as a Gleason score 10 carcinoma. Both of these would be significant misdiagnoses. The consensus among uropathologists is that hormonally treated tumors should not be Gleason graded. Occasionally, there are tumor foci that do not show evidence of hormonal effect. These should be mentioned in the report, Gleason graded, and are considered an adverse prognostic sign.

*Radiation-treated benign* glands acquire cytologic atypia and nuclear pleomorphism, suspicious for carcinoma. A pathologic clue that there is radiation effect is that these changes are seen throughout the entire prostate in glands that are architecturally benign. *Malignant* glands are also affected, showing cytologic atypia or atrophy-like changes (Fig. 20.21). The consensus is that radiation-treated prostatic carcinoma should not be Gleason graded. If prostatic carcinoma is identified in the prostate 12–18 months post radiotherapy and particularly if it does not show significant radiation effect, the prognosis is poor [17].

### "Vanishing Carcinoma"

"*Vanishing carcinoma*" refers to the absence of carcinoma in the prostatectomy specimen after a definitive diagnosis on biopsy. This phenomenon has been recorded in the literature to occur in less than 1 % (close to 0.5 %) of cases. Most of these cases had a biopsy diagnosis of a Gleason score 6 adenocarcinoma on only one or two cores [29, 30].

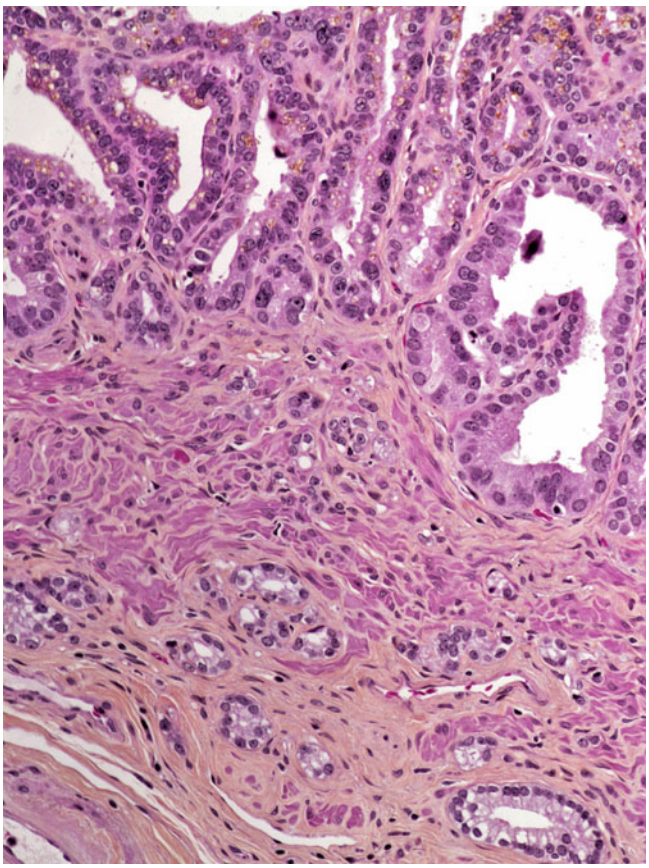

**Fig. 20.20** Seminal vesicle invasion by prostatic adenocarcinoma. The *upper portion* of the image consists of benign seminal vesicle glands. Note the small clustered glands with large hyperchromatic nuclei and the characteristic cytoplasmic golden-brown pigment. These glands are generally oriented perpendicular to a large lumen. In the *lower portion* of the image are infiltrating microacini of prostatic carcinoma, constituting seminal vesicle invasion, a pT3b tumor

## Clinicopathologic Summary

*Hormone and radiation-treated carcinoma*, "*vanishing*" *carcinoma*:

1. *Hormone and radiation* therapies have a profound *effect* on both *benign and malignant* prostatic glands.
2. *Radiation-treated benign glands* acquire nuclear atypia and *could be mistaken for carcinoma*.
3. *Hormone-treated* prostatic carcinoma may have small pyknotic nuclei and be *mistaken for histiocytes or Gleason pattern 5 carcinoma*.
4. *Radiation-treated* prostatic carcinoma may lose its glandular architecture, acquire pleomorphic nuclei, and *resemble Gleason pattern 5 carcinoma*.
5. Proper diagnosis by pathologists requires *adequate history of prior radiation/hormone therapy* from clinicians.
6. Carcinoma showing *treatment effect should not be Gleason graded*.
7. Carcinoma *without treatment effect* is reported, *Gleason graded*, and a *negative prognostic indicator*.
8. *Prostatectomies without carcinoma* following a positive needle biopsy occur at a *rate of 0.5 %*.

# Histologic Variants of Prostatic Carcinoma

## Morphologic Variants of Acinar (Conventional) Adenocarcinoma

The vast majority of acinar adenocarcinomas, which are derived from secretory epithelial cells, display the typical features described in the previous sections of this chapter (i.e., glandular structures comprised of cuboidal cells with amphophilic cytoplasm and round to ovoid nuclei having prominent nucleoli). Occasionally, acinar adenocarcinomas may show distinct histologic features that diverge from the usual morphology, and these variant morphologies may comprise anywhere from a small portion of a usual acinar adenocarcinoma to the tumor in its entirety. Some of these variants have been associated with a more favorable or unfavorable clinical prognosis; however, other variants have not been shown to portend a prognosis different from usual acinar adenocarcinomas of comparable grade, and the recognition of these variants is mainly of academic interest and to aid pathologists in the diagnosis of such carcinomas.

Acinar adenocarcinomas that contain abundant extracellular mucin (at least 25 % of the tumor being composed of pools of extracellular mucin) have been termed *mucinous* (*colloid*) *adenocarcinoma* (Fig. 20.22). If this strict diagnostic criterion is applied, these tumors are quite rare (0.2 % of prostate cancers). Mucinous carcinomas have a prognosis similar to comparable usual acinar adenocarcinomas. That being said, the majority of mucinous adenocarcinomas are moderately to poorly differentiated, with Gleason pattern 4 often predominating [31–33].

*Foamy gland carcinoma* denotes those tumors with abundant, pale, foamy cytoplasm (Fig. 20.23). These tumors often have small, round, pyknotic-appearing nuclei without prominent nucleoli, which can make diagnosis difficult on limited needle core biopsies. Immunohistochemistry to demonstrate the absence of basal cells (negative p63 and high molecular weight cytokeratin stains) is often necessary to make the diagnosis in many cases. Most of these tumors are Gleason score 6 (3+3) cancers, although they can be large volume, bilateral tumors, and sometimes of higher Gleason grade with an aggressive clinical course [34, 35].

Virtually all acinar adenocarcinomas will show some degree of neuroendocrine differentiation by immunohistochemical staining, even in the absence of light microscopic features of such differentiation [36]. However, these neuroendocrine cells are often single or in small clusters and scattered throughout the tumor. Occasionally, though, tumors will contain abundant cells with bright eosinophilic neurose-

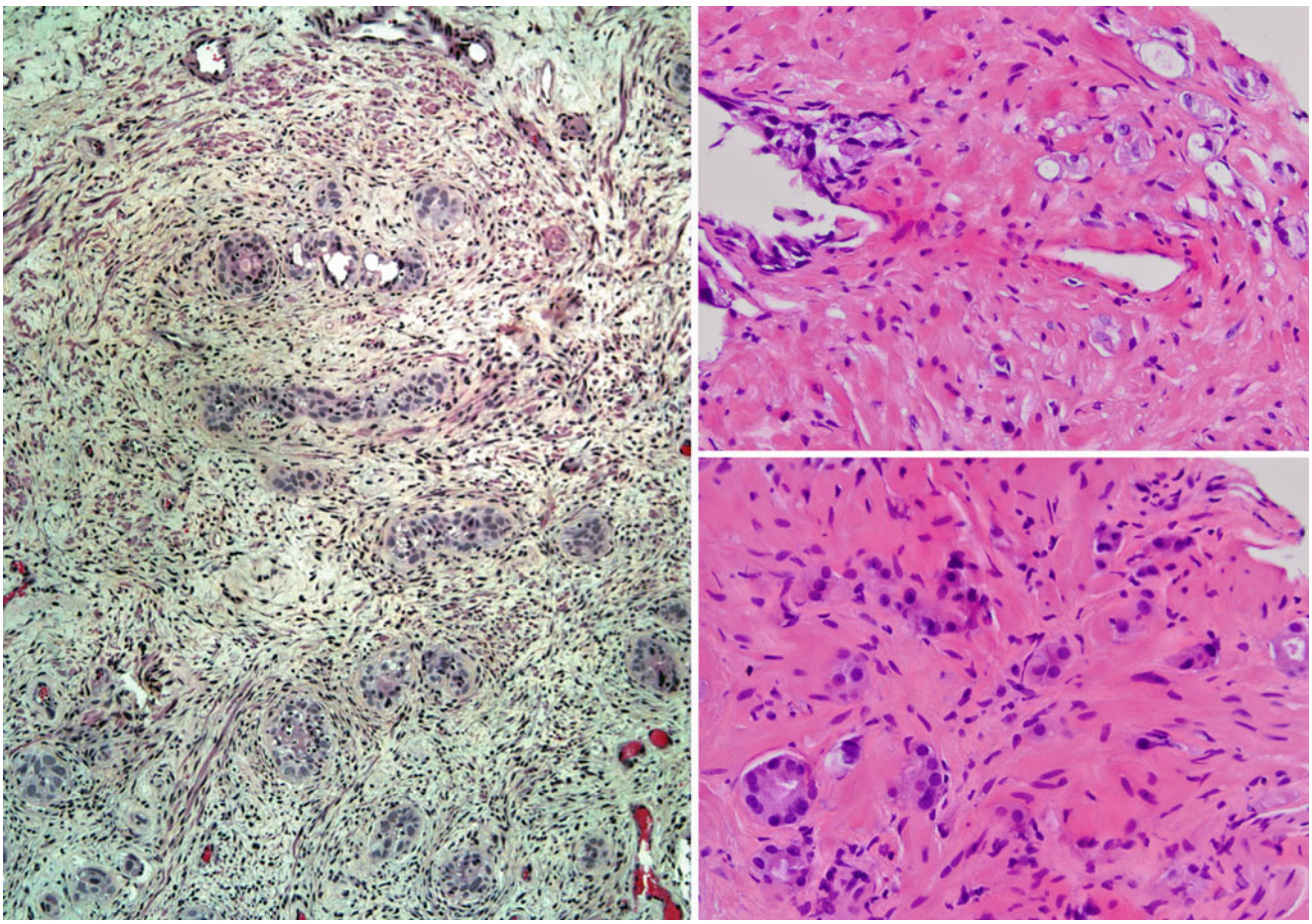

**Fig. 20.21** Radiation change of benign and malignant prostatic glands. In the *left panel*, note the glandular atypia, with nuclear pleomorphism of benign radiation-treated prostatic glands. These may be difficult to distinguish from carcinoma. On the *right* are two images of radiation-treated prostatic carcinoma. Note in the *top panel* that the carcinoma is pale, does not form glands, and may be missed or mistaken for histiocytes. The *lower right panel* shows the "single file" pattern, which would be diagnosed as a Gleason pattern 5 tumor, if the radiation history were not known

cretory granules within the cytoplasm (Fig. 20.24). These prostate cancers have been termed *prostatic adenocarcinoma with Paneth cell-like neuroendocrine differentiation*, given the resemblance to Paneth cells of the gastrointestinal tract. Although these tumors may appear high grade histologically in that they often grow as sheets, nests, or cords of cells, Tamas and Epstein reported a favorable prognosis for these cancers, and, therefore, Gleason grading is not recommended for areas of Paneth cell-like differentiation, as the assigned Gleason score will often not reflect the underlying biologic behavior [37, 38].

*Pseudohyperplastic carcinoma* denotes acinar adenocarcinomas characterized by large, dilated glands with branching or papillary luminal infolding. The cells often contain abundant, pale cytoplasm with the nuclei basally oriented. In contrast to foamy gland carcinoma, pseudohyperplastic carcinoma typically has prominent nucleoli, which also helps distinguish this variant of cancer from benign hyperplastic glands (Fig. 20.25). Nevertheless, immunohistochemistry is often necessary to definitively diagnose this variant of prostatic adenocarcinoma, especially on needle core biopsies. Most of these tumors are Gleason score 6 (3+3) and frequently are associated with conventional acinar adenocarcinomas of the same Gleason score [39, 40].

The *atrophic variant* of prostatic adenocarcinoma is composed of small malignant glands with scant cytoplasm, mimicking benign atrophy (Fig. 20.26). On needle core biopsy, the diagnosis of atrophic prostate cancer may be extremely difficult, with the diagnosis resting primarily on the infiltrative nature of the glands and occasional nuclear atypia beyond that seen in benign atrophy. The presence of non-atrophic prostate cancer, as is commonly present in cancers with atrophic features, is also useful in making the diagnosis. Clinically, most of these tumors are Gleason score 6 (3+3), but the biologic behavior of these tumors is likely dictated by

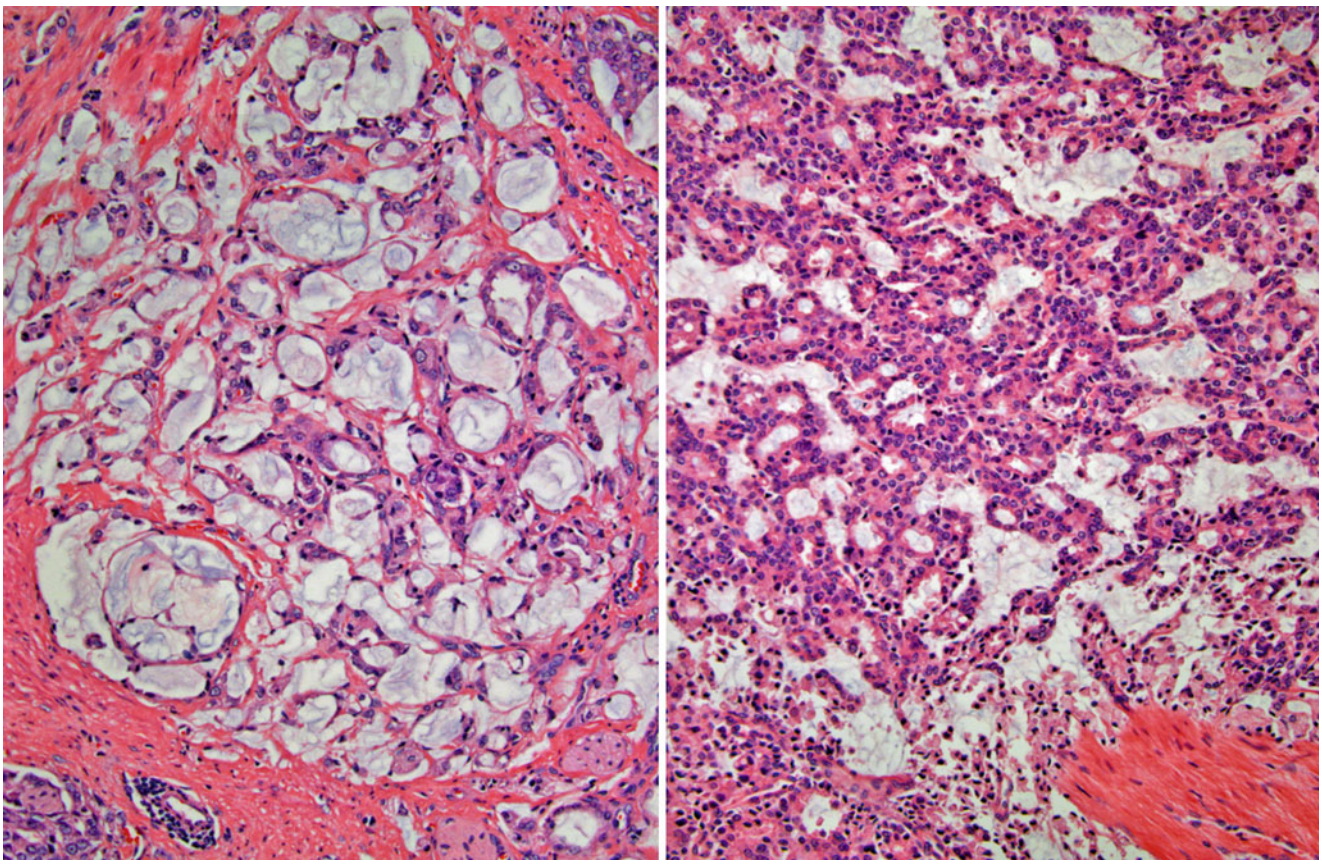

**Fig. 20.22** Mucinous (colloid) carcinoma. The *left panel* shows individual glands with abundant extravasated mucin surrounding each gland. On the *right*, extravasated mucin has coalesced to form a lake containing numerous cribriform glands

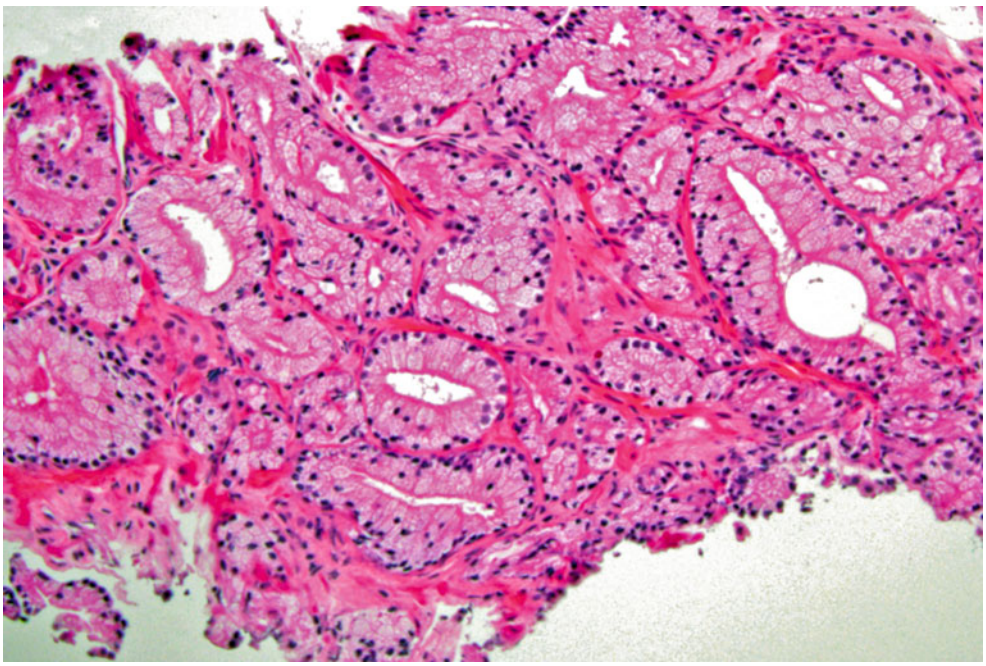

**Fig. 20.23** Foamy gland carcinoma. The glands have abundant pale cytoplasm with small, hyperchromatic nuclei that are basally oriented. Nuculeoli are usually absent at higher power examination

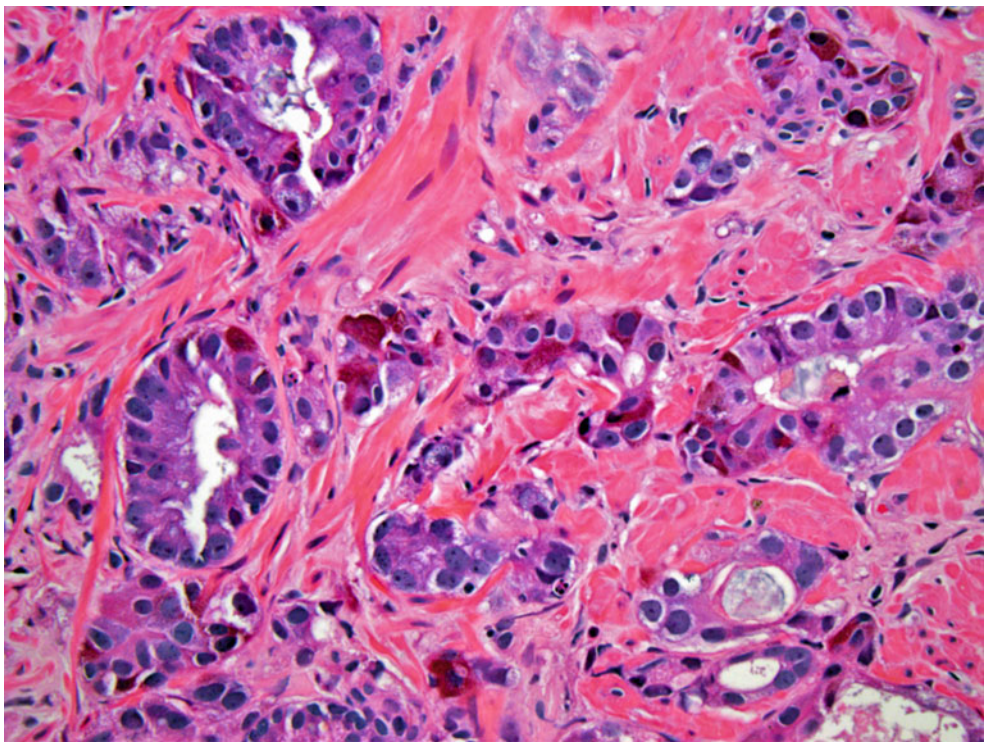

**Fig. 20.24** Paneth cell-like neuroendocrine differentiation in prostatic adenocarcinoma. The neuroendocrine cells contain bright, eosinophilic neurosecretory granules and appear similar to Paneth cells of the gastrointestinal tract. Even though many of the glands are poorly formed with even some single cells seen infiltrating through the stroma, these tumors are suggested to behave in a fashion similar to Gleason score 6 (3+3) conventional adenocarcinomas

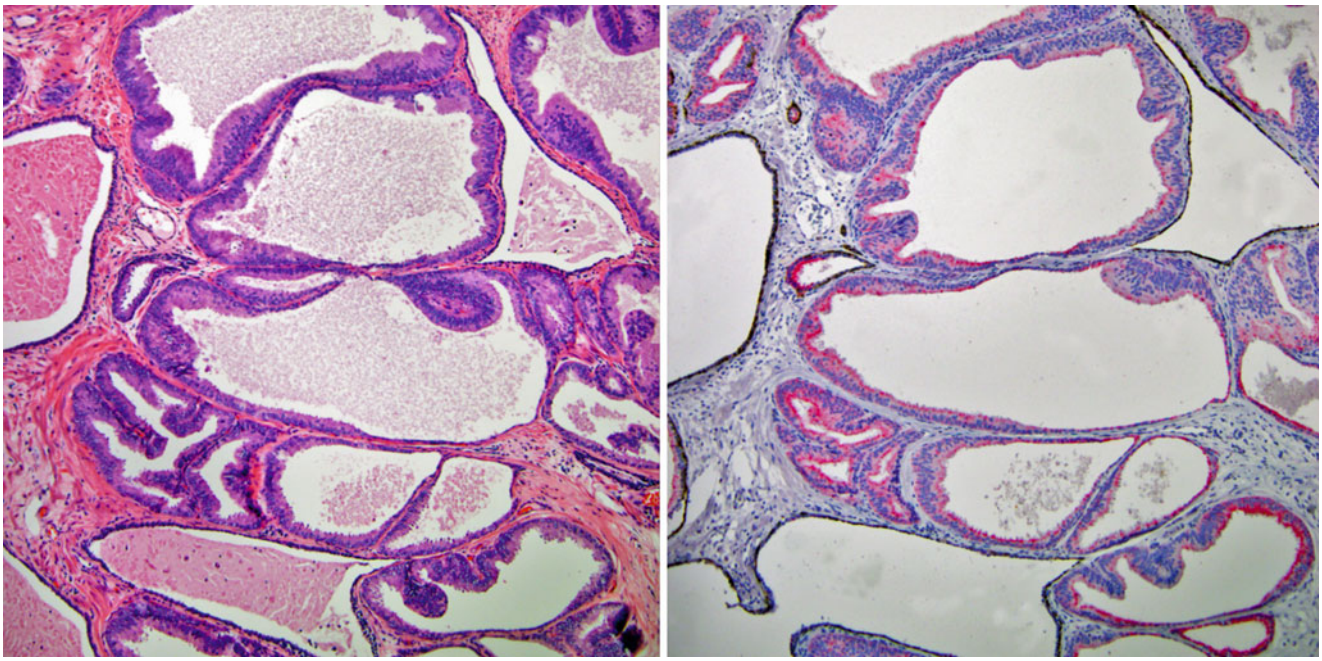

**Fig. 20.25** Pseudohyperplastic carcinoma. While large, dilated glands containing papillary infoldings (*left panel*, H&E) are typically a feature of benign prostate glands, in pseudohyperplastic carcinoma, the nuclear atypia (enlarged nuclei with prominent nucleoli) is beyond that seen in benign prostate. Cancer glands also demonstrate an infiltrative pattern characteristic of carcinoma, seen here as entrapped and dilated benign atrophic glands. Immunohistochemistry (*right panel*) is often necessary to confirm the diagnosis of pseudohyperplastic carcinoma, which demonstrates the absence of basal cells (*no brown staining* in the malignant glands) and the overexpression of AMACR (*red staining* in malignant glands)

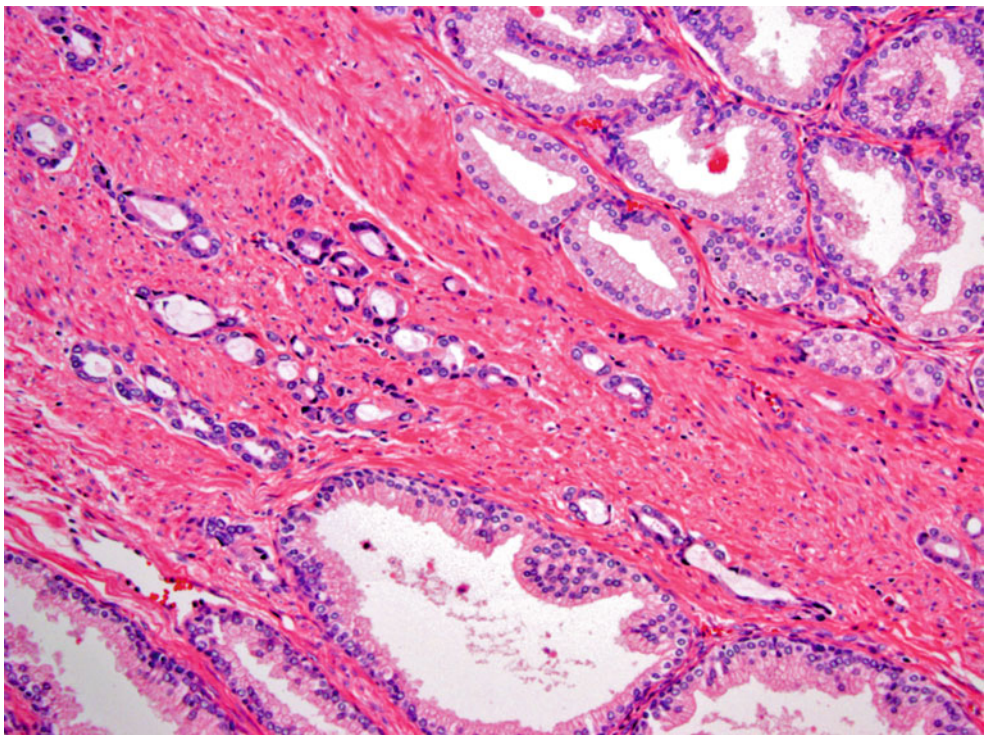

**Fig. 20.26** Atrophic variant of prostatic carcinoma. Malignant glands with scant cytoplasm and only mildly enlarged and hyperchromatic nuclei (*middle of image*) are seen infiltrating between benign glands (*top right* and *bottom left*). Only the infiltrative pattern and occasional nucleoli suggest malignancy as opposed to benign atrophy on H&E sections. Immunohistochemistry can be employed to confirm the diagnosis

the Gleason score of any higher grade non-atrophic cancer admixed with the atrophic variant [41, 42].

Although the term *PIN-like ductal adenocarcinoma* is used to describe prostate cancers that mimic high-grade PIN, these tumors are frequently cytologically and architecturally more similar to usual acinar adenocarcinomas than prostatic duct adenocarcinomas (described below). In addition, while prostatic duct adenocarcinomas are typically considered aggressive tumors, PIN-like adenocarcinomas have a more favorable prognosis and behave similarly to Gleason 6 (3 + 3) conventional acinar adenocarcinomas. Histologically, these tumors are composed of large glands with pseudostratified epithelium having amphophilic cytoplasm and enlarged nuclei with prominent nucleoli. In limited biopsy material, the diagnosis may be difficult to make, as the only distinction from PIN may be the crowded and/or infiltrative nature of the glands combined with the absence of basal cells on immunohistochemistry (Fig. 20.27) [43, 44].

## Clinicopathologic Summary

1. *Mucinous* (*colloid*) *carcinoma* often has significant component of *Gleason pattern 4*.
2. *Foamy gland carcinoma*, *atrophic carcinoma*, and *pseudohyperplastic carcinoma* typically have predominantly *Gleason pattern 3*.
3. *PIN-like ductal adenocarcinoma* and *prostatic adenocarcinoma with Paneth cell-like neuroendocrine differentiation* are usually considered Gleason pattern 3 and have a *favorable prognosis*.

## Intraductal Carcinoma of the Prostate (IDC-P)

Occasionally, conventional acinar adenocarcinoma cells may exist within preexisting ducts that immunohistochemically demonstrate retention of their basal cell layer (Fig. 20.28). This phenomenon has been termed *intraductal carcinoma of the prostate*, or IDC-P, and should not be confused with prostatic duct adenocarcinoma (see below), as the cells of IDC-P are acinar in morphology and not ductal. IDC-P is almost always seen in association with an invasive, high-grade (Gleason score ≥7) acinar adenocarcinoma. The presence of IDC-P on needle core biopsy, even in the absence of documented invasive adenocarcinoma, indicates a high likelihood of extraprostatic extension and/or seminal vesicle invasion at the time of radical prostatectomy [45, 46].

## Clinicopathologic Summary

*Intraductal carcinoma of the prostate*:
1. Associated with *high-grade acinar adenocarcinoma*
2. More frequently seen in *high-stage* (*pT3*) *tumors*

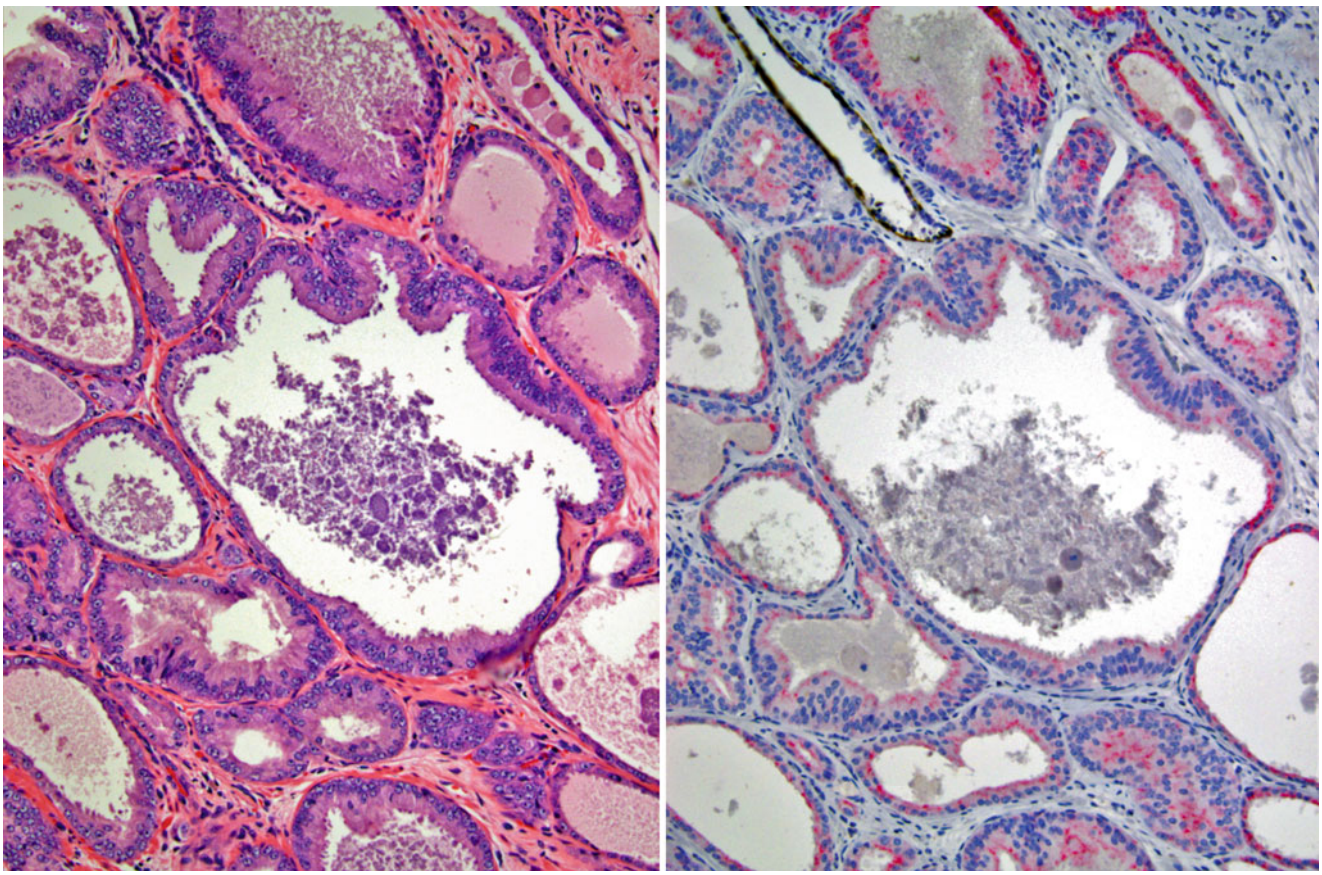

**Fig. 20.27** PIN-like ductal adenocarcinoma. On H&E (*left panel*), the glands of PIN-like ductal carcinoma resemble high-grade PIN in that they are large glands with tall columnar cells and pseudostratified nuclei. Immunohistochemistry (*right panel*) shows the absence of basal cells (*no brown staining*) in these large glands and an infiltrative pattern, whereby the cancer glands surround benign atrophic gland (*upper left corner*). AMACR (*red stain*) is also overexpressed in the cancer glands

## Prostatic Duct Adenocarcinoma

Pure *prostatic duct adenocarcinoma* (ductal adenocarcinoma) is a relatively uncommon form of prostate cancer, accounting for 0.2–0.8 % of all cancers. More commonly, ductal adenocarcinoma is seen admixed with conventional acinar adenocarcinoma, such that around 5 % of all prostate cancers are mixed ductal-acinar tumors. Histologically, these tumors display a cribriform, papillary, or solid growth pattern, and the tumor cells are tall and columnar with amphophilic cytoplasm. The nuclei are usually more elongate than acinar adenocarcinoma, and nucleoli are typically quite prominent (Fig. 20.29). Historically, these tumors were defined by their central location around and within the prostatic urethra; however, more recent studies have shown these tumors to involve only the peripheral zone in many cases and both the *peripheral and central zones* in an even greater proportion of cases, suggesting that central location is not necessary for diagnosis. Nevertheless, prostatic duct adenocarcinoma should be included in the differential diagnosis of any prostatic urethral mass [47–50].

Prostatic duct adenocarcinomas are considered poorly differentiated tumors. Although assignation of a Gleason score is not recommended by some authors, they are considered similar to Gleason score 8 (4 + 4) acinar adenocarcinomas. In cases of mixed ductal-acinar carcinoma, the ductal component is frequently considered *Gleason pattern 4 or 5*, depending upon the absence or presence of comedonecrosis, respectively. These tumors tend to present at a later, higher stage than comparable acinar adenocarcinomas, with some series reporting metastasis in up to 1/3 of patients at the time of diagnosis. At radical prostatectomy, nearly 2/3 of ductal adenocarcinomas have extraprostatic extension, and around 10 % show seminal vesicle invasion. The pattern of metastasis is similar to acinar adenocarcinomas, and treatment options are also the same. A recent study indicated that men with ductal adenocarcinoma of the prostate frequently present with lower serum PSA levels than comparable acinar adenocarcinomas, potentially complicating clinical diagnosis and contributing, at least partially, to the higher stage at presentation [4, 51–53].

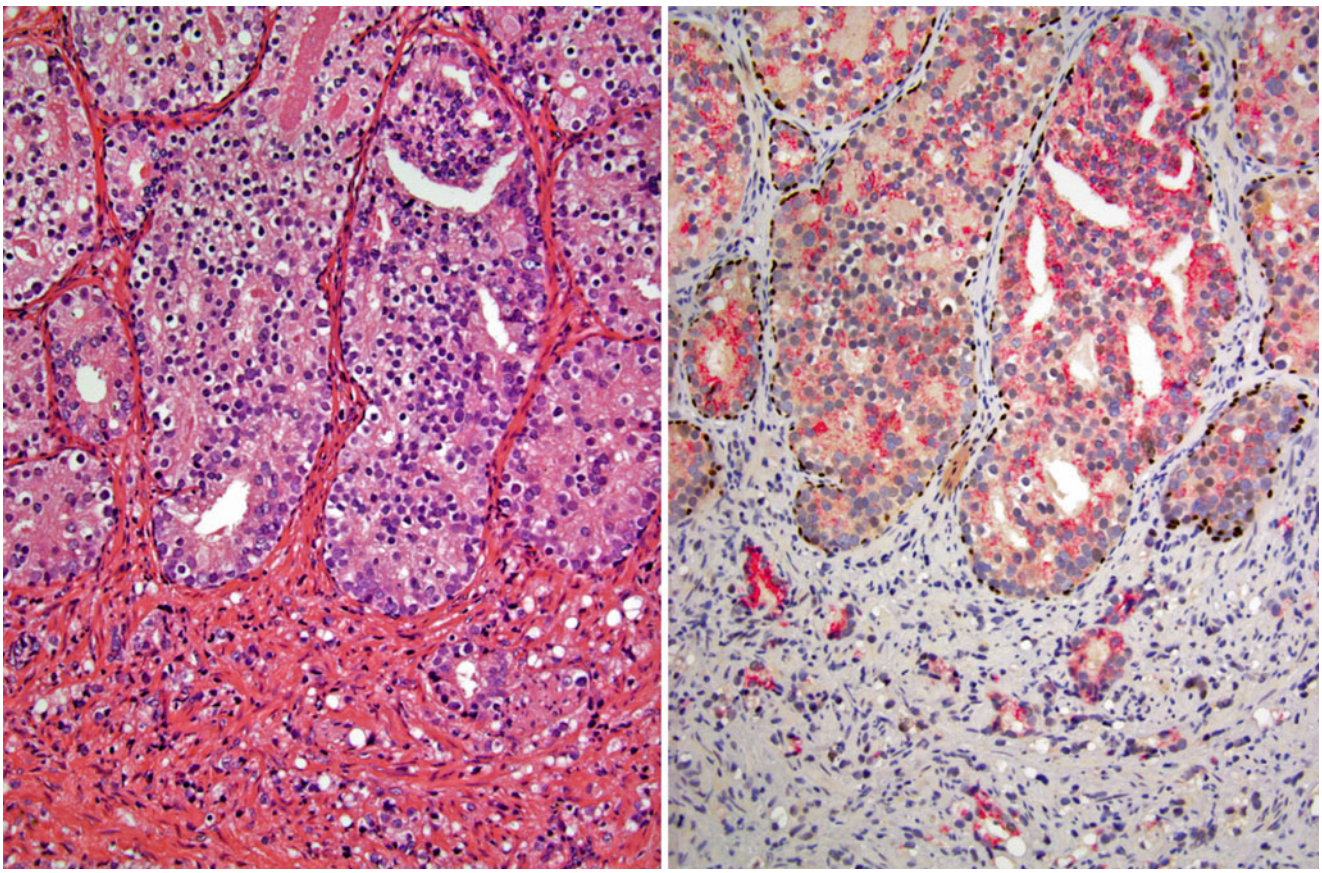

**Fig. 20.28** Intraductal carcinoma of the prostate (IDC-P). By routine H&E examination (*left panel*), IDC-P often resembles invasive cribriform carcinoma (Gleason pattern 4; *top half of image*). However, immunohistochemistry (*right panel*) reveals the presence of a basal cell layer surrounding these glands (*brown staining*). IDC-P is almost always seen in the context of invasive high-grade acinar adenocarcinoma, which can be seen at the bottom half of these images as single, infiltrating cancer cells (Gleason pattern 5). Both IDC-P and invasive cancer overexpress AMACR (*red staining*)

## Clinicopathologic Summary

*Prostatic duct adenocarcinoma*:

1. *High-grade*, *aggressive* variant of prostate cancer with frequent *extraprostatic extension*
2. May be *central* and/or *peripheral* in location
3. Frequently has a *conventional acinar adenocarcinoma component*

## Basal Cell/Adenoid Cystic Carcinoma

Prostatic carcinomas proposed to originate from the basal cells lining prostatic ducts and acini are termed *basal cell carcinomas* (also known as *adenoid cystic carcinomas*). These tumors are extremely rare, with fewer than 75 cases reported in the literature. Two major histologic growth patterns characterize this cancer, both of which may be present in the same tumor: (1) variably sized nests, cords, or trabeculae of cells with scant cytoplasm, vesicular nuclei, and peripheral palisading, similar to basaloid carcinomas of other organs (*basaloid pattern*; Fig. 20.30, left panel) or (2) nests of cells with a prominent cribriform architecture, wherein these microcysts contain eosinophilic basement membrane-like material or basophilic mucinous secretions, similar to the salivary gland tumors of the same name (*adenoid cystic pattern*; Fig. 20.30, right panel). As with all non-acinar adenocarcinomas of the prostate, a Gleason score is not assigned to basal cell carcinomas. These tumors may be locally aggressive with extensive bladder neck invasion, but they uncommonly metastasize to distant sites. Ali et al. found that the presence of necrosis, high proliferation index, and the

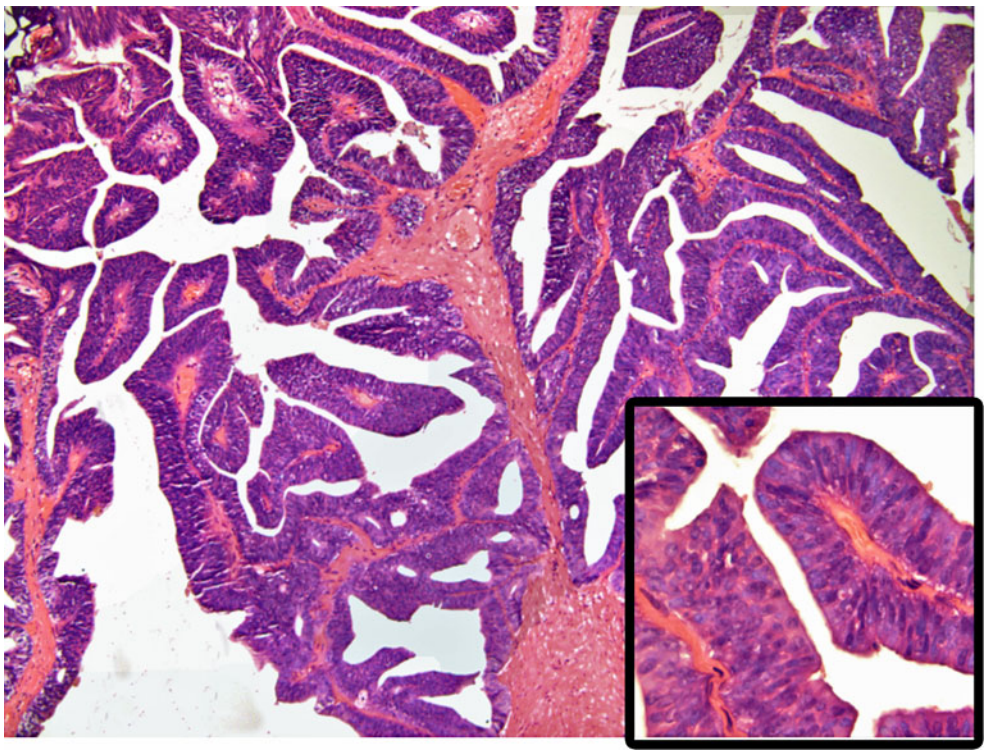

**Fig. 20.29** Prostatic duct adenocarcinoma. Ductal adenocarcinoma of the prostate typically grows in a solid, cribriform, or papillary architectural pattern, the latter of which is demonstrated in this image. Cytologically, the cells of prostatic duct carcinoma differ from acinar adenocarcinoma cells in that they are tall, columnar cells with ovoid or cigar-shaped nuclei that are pseudostratified (inset). Nucleoli are often prominent and may be multiple

solid pattern of basaloid growth were the most significant predictors of increased metastatic potential [54, 55].

## Clinicopathologic Summary

*Basal cell/adenoid cystic carcinoma*:
1. Rare tumor, often *locally aggressive*
2. *Necrosis* and the *basaloid pattern* are indicators of *metastatic potential*

## Sarcomatoid Carcinoma (Carcinosarcoma)

Similar to kidney, bladder, and other organs, malignant spindle cell proliferations that demonstrate epithelial origin by either light microscopy (e.g., concomitant adenocarcinoma) or immunohistochemistry (e.g., cytokeratin or p63 staining) have been termed *sarcomatoid carcinomas*. Some authors reserve the term *carcinosarcoma* for those rare subsets of sarcomatoid carcinomas containing foci diagnostic of a particular type of sarcoma, such as chondrosarcoma, osteosarcoma, or rhabdomyosarcoma (Fig. 20.31). Regardless of terminology, the spindle cell and/or heterologous elements share immunohistochemical, ultrastructural, and molecular characteristics with the associated epithelial component, indicating that the terms sarcomatoid carcinoma and carcinosarcoma likely reflect variations of the same entity, which should be *considered epithelial in origin*. The majority of sarcomatoid carcinomas occur in the setting of either *existing high-grade acinar adenocarcinomas* or in patients with a *history of prostate cancer*, most of whom have received hormonal and/or radiation therapy. Uncommonly, patients may present with pure sarcomatoid carcinoma in the absence of any previously documented adenocarcinoma. Clinically, these tumors behave aggressively, with frequent metastases and a mortality rate of 20 % within the first year [56–60].

## Clinicopathologic Summary

*Sarcomatoid carcinoma* (*carcinosarcoma*):
1. Epithelial-derived malignancies showing *spindle cell* or *heterologous elements*
2. *Aggressive* clinical course with *poor prognosis*
3. Most *associated with high-grade acinar adenocarcinoma* and/or *prior hormone or radiation therapy*

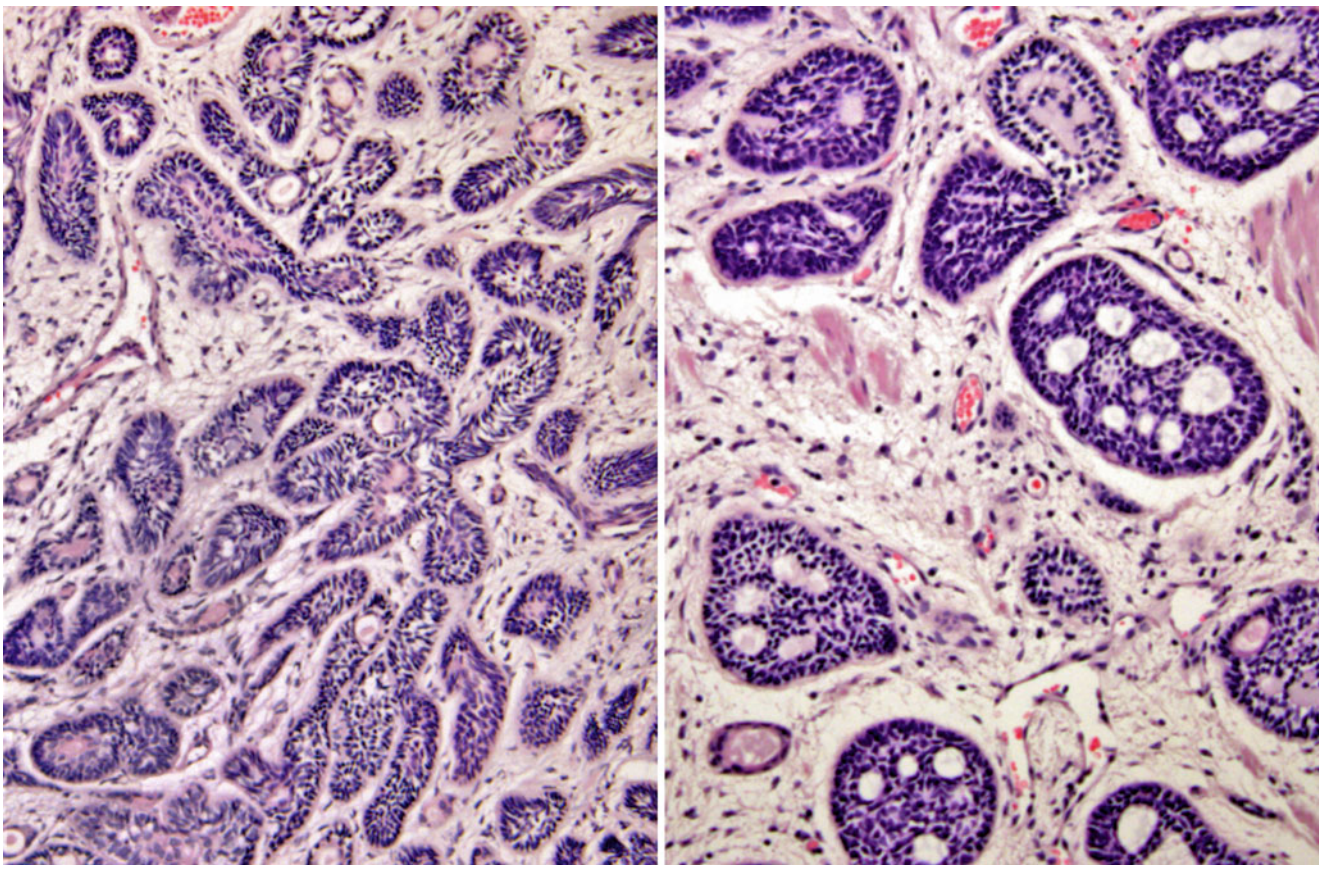

**Fig. 20.30** Basal cell/adenoid cystic carcinoma. The basaloid pattern (*left panel*) of this variant of prostate cancer grows as trabeculae and nests of tumor cells with peripherally palisading nuclei. The adenoid cystic pattern (*right panel*) exhibits cribriform growth pattern with blue mucin or pink basement membrane-like material within the cystic spaces. Both patterns may be present in a single tumor

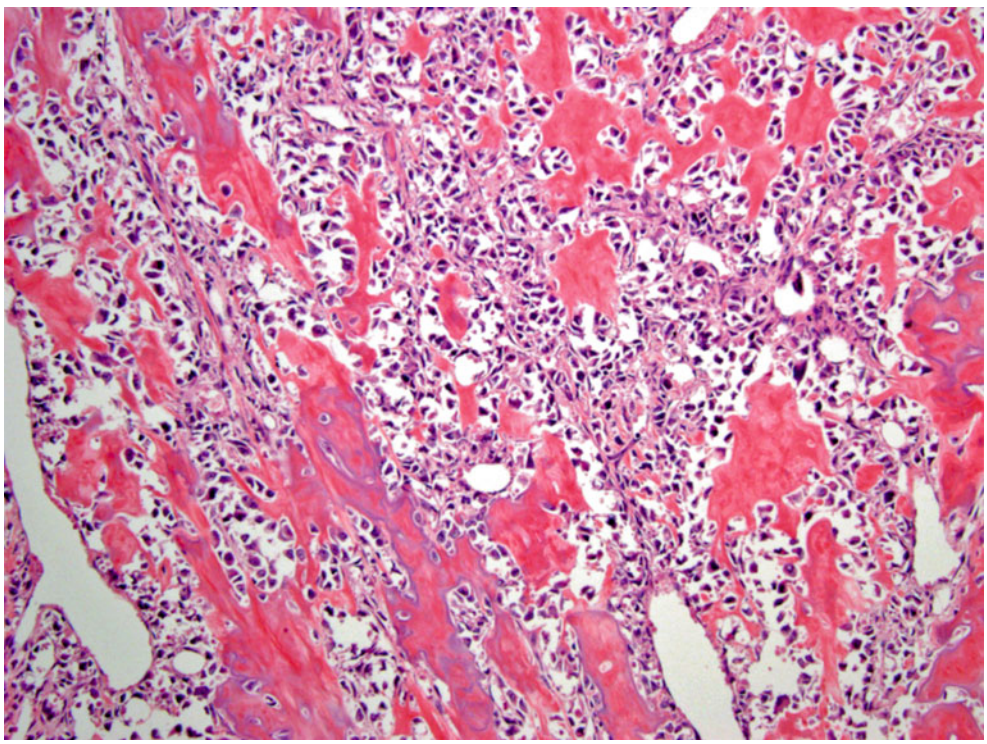

**Fig. 20.31** Sarcomatoid carcinoma (carcinosarcoma). Epithelial-derived malignancies, including prostate cancer, may show mesenchymal differentiation, usually manifest as nondescript spindled cells. In some cases, areas resembling true mesenchymal neoplasms, such as osteosarcoma (*shown here*), may be evident. Such carcinomas are termed sarcomatoid carcinomas, or carcinosarcomas

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# The Pathology of Non-epithelial Tumors of the Prostate

21

Maria M. Shevchuk and Brian D. Robinson

## Mesenchymal Tumors

### Prostatic Stromal Tumors

Tumors of specialized prostatic stroma are rare neoplasms with varied histopathologic patterns and clinical behavior. These tumors are classified according to the WHO as either *stromal tumors of uncertain malignant potential* (*STUMP*s) or prostatic *stromal sarcomas*, based upon histologic features [1]. Only a few large studies on these lesions have been published to date [2–4]. Both STUMP and stromal sarcoma stain immunohistochemically for CD34 and progesterone receptor, similar to nonneoplastic prostatic stromal cells, supporting the specialized stromal nature of these tumors.

#### Stromal Tumor of Uncertain Malignant Potential (STUMP)

*STUMP*s are the more frequent of the two lesions and generally have a good prognosis, with most following a benign clinical course. Occasionally, STUMPs may recur rapidly after resection or, rarely, progress to malignant stromal sarcomas with metastatic potential [2]. For these reasons, definitive treatment is often performed for STUMPs in younger men. However, due to their rarity and therefore the lack of reliable clinical data, the preferred treatment modality for these lesions is unclear.

Patients with STUMPs often present with symptoms of urinary obstruction, hematuria, hematospermia, or rectal fullness, while some cases are detected by digital rectal examination or elevated serum PSA levels. Patients tend to be in their sixth and seventh decades, with a mean age of 58 at presentation. STUMPs may involve either the transition zone or peripheral zone of the prostate and can be greater than 10 cm in size. They are tan-white on cut surface and can be entirely solid or have both solid and cystic areas, with the cysts containing blood, mucin, or clear fluid. Microscopically, four patterns of STUMP have been described. The most common pattern features hypercellular stroma with atypical, degenerative-appearing stromal cells and intermixed benign glands (Fig. 21.1). Other patterns include cellular stromal pattern, stromal predominant/myxoid pattern, and phyllodes pattern. In these latter three patterns, the stromal cells are typically cytologically bland. Mitoses are infrequent. A mixture of these four patterns is seen in many cases of STUMP, and various patterns of epithelial proliferation have also been described within these tumors [5].

#### Stromal Sarcoma

*Stromal sarcomas* may present similarly to STUMP, but stromal sarcoma patients tend to be younger, with approximately half of all cases occurring in men under the age of 50. They are typically solid lesions with a fleshy cut surface, typically greater than 2 cm in size. The diagnosis of stromal sarcoma is made when there is a solid or infiltrative proliferation of stromal cells with hypercellularity, cytological atypia (not degenerative type), mitotic figures (especially atypical mitotic figures), and/or necrosis (Fig. 21.2). Occasionally, stromal sarcomas may have a phyllodes growth pattern with leaflike glands and hypercellular atypical stroma. Stromal sarcomas may be locally invasive with extraprostatic extension, and metastasis from stromal sarcoma, such as to bone and lung, has been reported.

#### Clinicopathologic Summary

*STUMP* and *stromal sarcoma* are rare prostatic neoplasms derived from specialized prostatic stroma. Stromal sarcomas are malignant tumors with an aggressive clinical course, while many STUMPs behave in a benign fashion.

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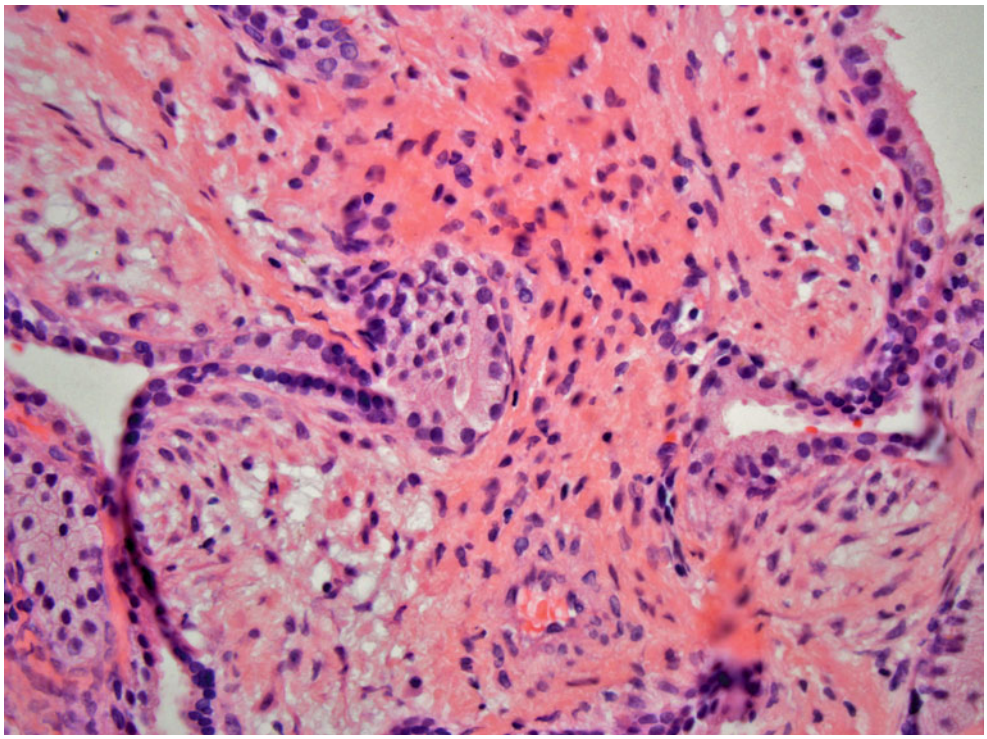


**Fig. 21.1** STUMP. Increased stromal cellularity and mild cytologic atypia of the stromal cells are features of the cellular stromal pattern of STUMP

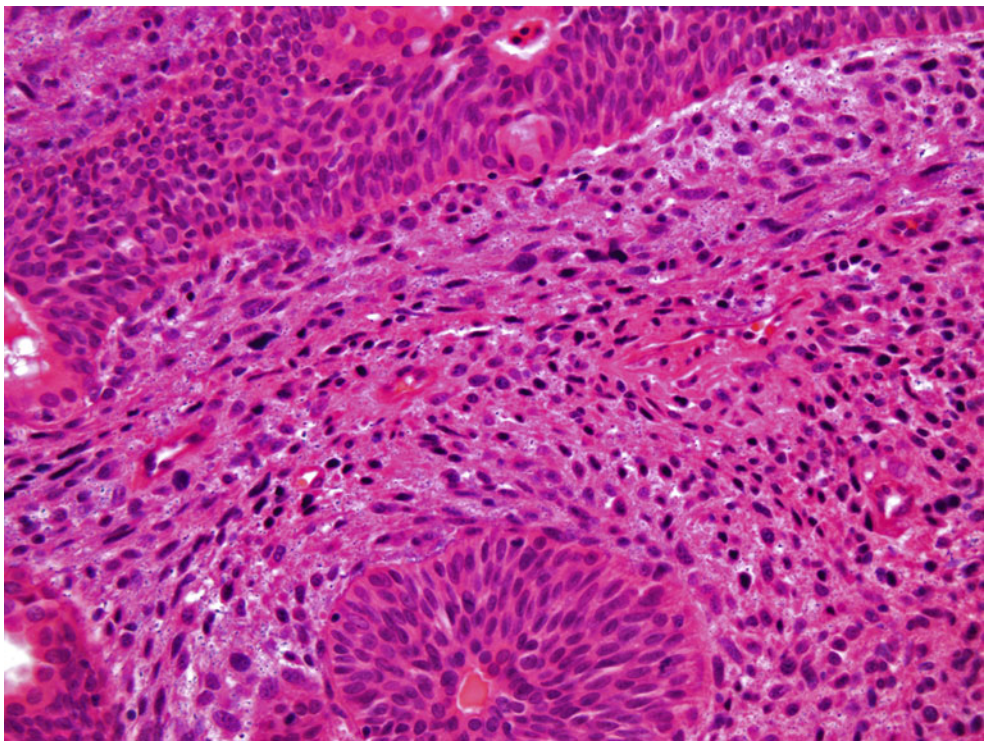


**Fig. 21.2** Stromal sarcoma. Stromal sarcomas typically have a highly cellular stromal component with cells that display severe cytologic atypia, including nuclear pleomorphism and hyperchromasia

## Smooth Muscle Tumors

### Leiomyoma

*Leiomyoma* of the prostate is rare, and the distinction between a leiomyoma and stromal nodule of BPH is difficult, making definitive diagnosis of leiomyoma nearly impossible. Indeed, some consider a prostatic "leiomyoma" to be an expression of stromal hyperplasia of BPH [6]. Others have recommended the diagnosis of prostatic leiomyoma only be made when there is a well-circumscribed proliferation of smooth muscle at least 1 cm in diameter [7]. Additional features that favor the diagnosis of leiomyoma include organized fascicular growth, hyalinization, and calcification [8].

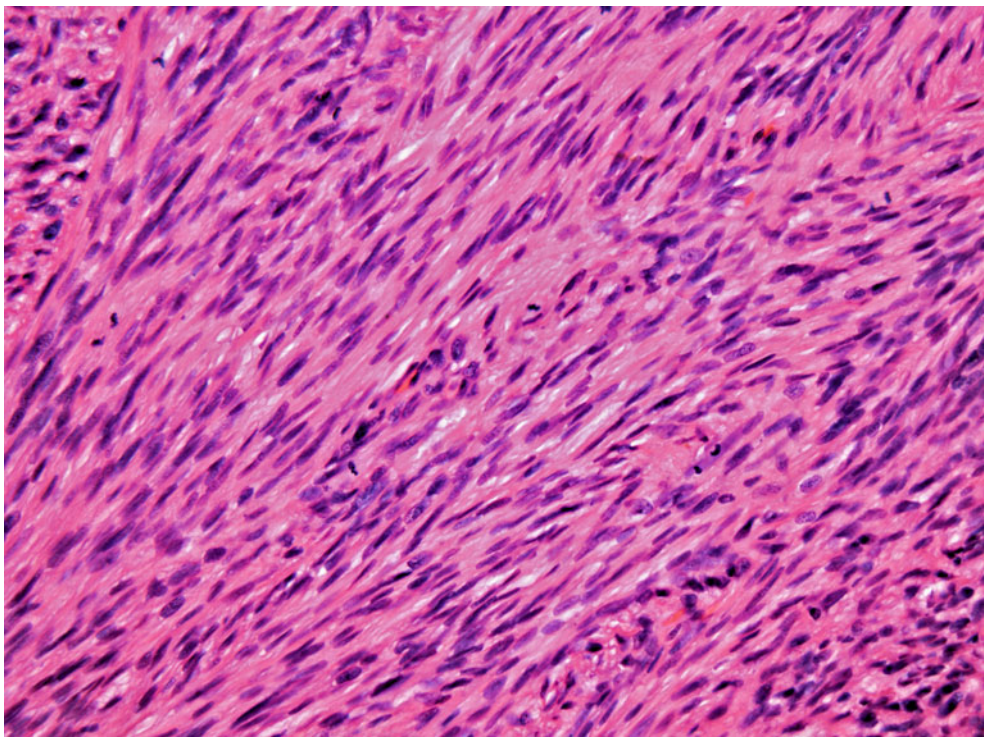


**Fig. 21.3** Leiomyosarcoma. Leiomyosarcomas are composed of intersecting fascicles of malignant smooth muscle cells. Mitotic figures are typically frequent, as seen in this case

## Leiomyosarcoma

Although still exceedingly rare, *leiomyosarcoma* is the most common sarcoma to occur in the prostate [9, 10]. It affects men typically in the fifth to eighth decades and is almost always high grade. Microscopically, the lesions are hypercellular, composed of spindled smooth muscle cells arranged in intersecting fascicles with moderate to marked atypia (Fig. 21.3) [1]. Frequent mitotic figures and necrosis are common features. Survival is relatively short, with patients often suffering from multiple local recurrences as well as metastatic spread, commonly to lung. More than half of men with prostatic leiomyosarcoma die within 5 years of diagnosis.

## Clinicopathologic Summary

1. *Leiomyosarcoma* is the most common sarcoma of the prostate, although still exceedingly rare. These malignant smooth muscle tumors are typically high grade and carry a poor prognosis.
2. *Leiomyoma* of the prostate is a controversial benign entity, with many considering these lesions to be part of the BPH spectrum.

## Inflammatory Myofibroblastic Tumor

*Inflammatory myofibroblastic tumors* (*IMT*s), also known as postoperative spindle cell nodules, pseudosarcomatous fibromyxoid tumors, inflammatory pseudotumors, myofibroblastomas, and pseudosarcomatous myofibroblastic proliferations, are benign tumors that may occur in the prostate. Previously, lesions that occurred following a surgical procedure, such as transurethral resection, were separated from similar lesions that occurred de novo. However, their overlapping morphological, immunohistochemical, and molecular features and identical clinical behavior have led to the unified classification and designation of all such lesions as IMTs [11–17].

Most IMTs of the prostate occur in men in the fifth to seventh decade and may be relatively small (<1 cm). Microscopically, they are identical to IMTs of the bladder and other organs. The tumors are composed of spindle cells with abundant dense eosinophilic to amphophilic cytoplasm. The cells are fibroblastic/myofibroblastic in appearance with long tapering processes in a loose myxoid stroma, which often contains chronic inflammatory cells. They are classically described as having a "tissue culture" appearance. They may be arranged haphazardly or in intersecting fascicles. Nuclei are not hyperchromatic, in contrast to sarcomatous lesions with which this benign entity should not be confused, and the chromatin pattern is delicate with only one or two micronucleoli (Fig. 21.4). Mitotic figures may be abundant, but this should not raise concern for malignant behavior, as virtually all IMTs behave in a benign fashion. They may recur, however, if incompletely resected. Positive ALK immunohistochemical staining, or detection of ALK gene fusion by fluorescence in situ hybridization (present in approximately three-fourths of all cases of IMT), can confirm the diagnosis [14, 17].

## Clinicopathologic Summary

*Inflammatory myofibroblastic tumors* are benign lesions that may occur de novo or following a surgical procedure. Their appearance may mimic a high-grade sarcoma, yet

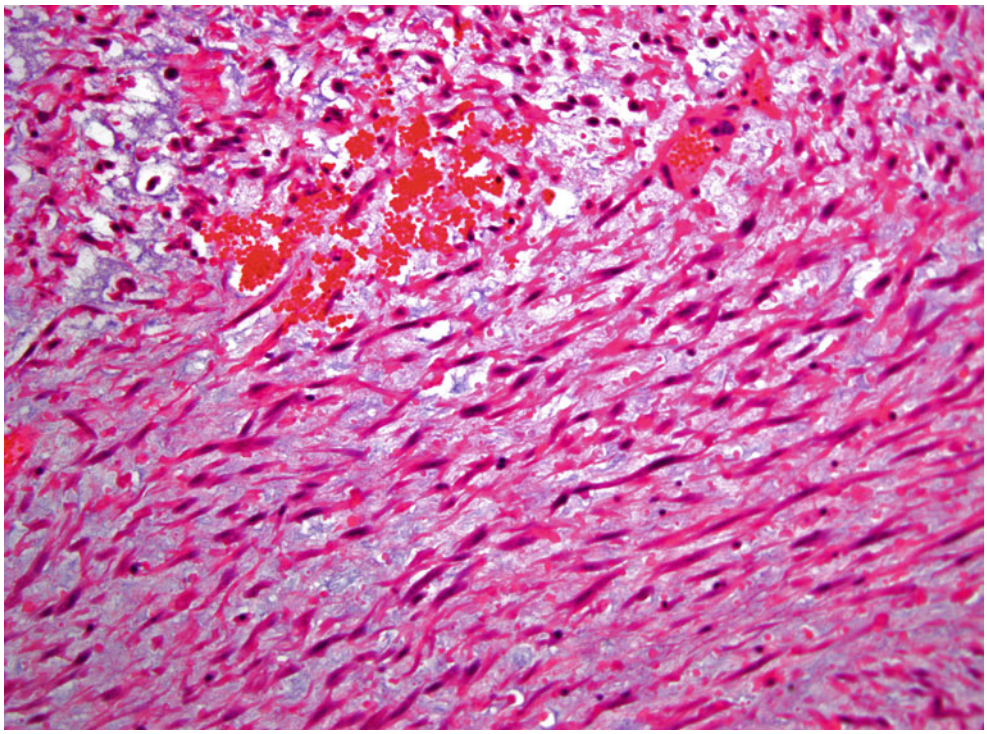


**Fig. 21.4** Inflammatory myofibroblastic tumor. IMTs are composed of cells with a spindled shape and long tapering cytoplasmic processes. The cells are embedded in a loose, myxoid stroma that frequently contains inflammatory cells and extravasated red blood cells

careful examination and ALK gene rearrangement status can help in difficult cases. Conservative complete resection is generally curative.

## Rhabdomyosarcoma

*Rhabdomyosarcomas* of the prostate occur almost exclusively in pediatric patients, and the mean age at diagnosis is 5 years [1, 18, 19]. Fewer than 20 adult cases of prostatic rhabdomyosarcoma have been reported [20, 21]. Tumors typically present at advanced stage, with gross disease remaining following incomplete resection or biopsy (stage 3) or metastasis (stage 4). Many patients with stage 1 or stage 2 disease may be cured with the use of effective chemotherapy, and even stage 3 patients often experience long periods of disease-free survival with only 15–20 % mortality. Stage 4 patients, on the other hand, have an extremely poor prognosis with most dying from this malignant tumor. Occasionally, it may be difficult to distinguish primary bladder rhabdomyosarcomas from prostatic rhabdomyosarcomas due to their often large size and advanced stage at presentation. In cases where chemotherapy and radiotherapy are unsuccessful, radical surgery is performed. While the majority of these tumors are of the embryonal subtype (rarely as *sarcoma botryoides*), it is clinically important to distinguish those rhabdomyosarcomas of the alveolar subtype, which have an unfavorable histology, so that more aggressive chemotherapy regimens may be administered [1].

### Clinicopathologic Summary

*Rhabdomyosarcoma* is the most common mesenchymal tumor of the prostate in pediatric patients. Although many patients present with advanced stage disease, current chemotherapy and radiotherapy regimens can offer long-term disease-free survival and even cure.

## Solitary Fibrous Tumor

Fewer than 20 cases of *solitary fibrous tumor* (SFT) of the prostate have been reported, and the largest case series included 13 patients [22–25]. While none of these has behaved in a malignant fashion, long-term clinical follow-up is recommended based upon the malignant potential of SFTs at other sites. They have been reported to occur in a wide age range of adult men, and a broad size range is also reported, with many larger than 5 cm. Microscopically, SFT of the prostate is similar to SFT of other sites, being composed of spindle cells with bland nuclei embedded within a ropy collagenous stroma. The tumor is classically described as having a "patternless" pattern to the cells. Hemangiopericytoma-like vessels are also a common feature (Fig. 21.5). Immunohistochemically, these tumors are diffusely positive for CD34, bcl-2, and vimentin, while typically negative for S100, CD117, and cytokeratins.

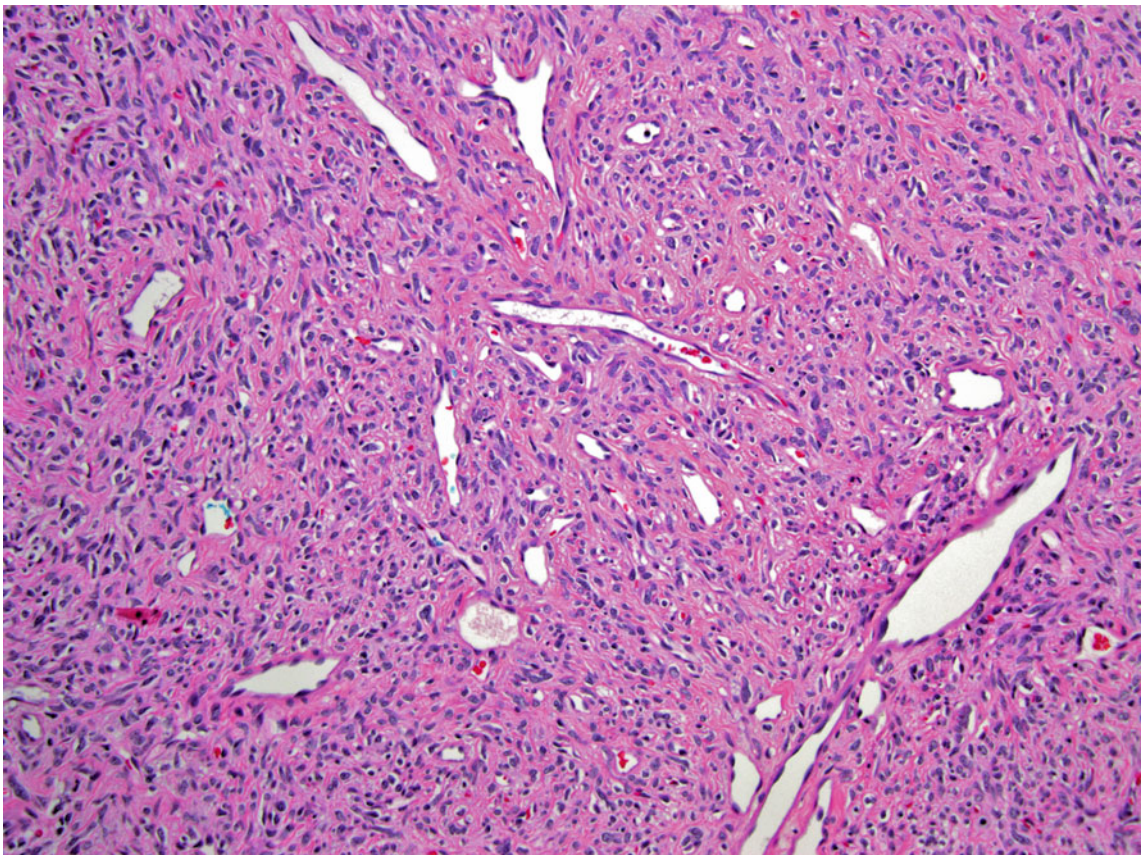


**Fig. 21.5** Solitary fibrous tumor. Features of SFTs include fibroblastic-appearing cells with dense pink cytoplasm embedded within a ropy collagenous stroma. The vessels typically have a staghorn appearance resembling those seen in hemangiopericytomas

### Clinicopathologic Summary

*Solitary fibrous tumors* of the prostate are uncommon neoplasms, and their appearance in the prostate is similar to those in other sites. While none has behaved in a malignant fashion, close observation is warranted based upon malignant behavior in other organs.

## Miscellaneous Non-epithelial Tumors

Several additional tumors have been reported to occur in the prostate, including melanocytic lesions. Primary *malignant melanoma* of the prostate has been reported only rarely [26, 27], and melanoma involving the prostate is more likely to be secondary and represents metastasis from a distant site. In our experience, these melanomas frequently demonstrate a spindle cell morphology.

*Blue nevus*, on the other hand, is a benign melanotic lesion that has been reported to occur in 4 % of prostates [8, 28–31]. Blue nevi appear microscopically as pigmented spindle cells filled with melanin within the fibromuscular stroma (Fig. 21.6a, b). Melanin deposition within glandular epithelium (glandular melanosis) is also seen in approximately 4 % of all prostates [8, 32, 33]. Neither blue nevi nor glandular melanoses have been reported to show malignant transformation.

Rectal *gastrointestinal stromal tumors* (GISTs) may be detected on transrectal prostatic needle core biopsy specimens, and occasionally rectal GISTs may radiographically appear to arise from the prostate gland [34–36]. However, to date, no GIST has been confirmed to arise from the prostate.

*Paraganglioma* (*extra-adrenal pheochromocytoma*) arising in the prostate has been reported in the literature in less than 30 cases [37–44]. The patients' ages were from 8 to 37, and most presented with the characteristic symptoms of hypertension and headache, along with hematuria. Sometimes these symptoms were exacerbated by micturition. The tumors measured 3–5 cm, and the treatment was usually a radical prostatectomy. Most of these tumors had a benign course, but lymph node metastases have been reported [45, 46].

*Germ cell tumors* have been described in the prostate. They probably arise from germ cells sequestered during migration, similarly to the cells that give rise to other extragonadal midline germ cell tumors. The diagnosis of a prostatic germ cell tumor is made only after the exclusion of a testicular primary. Most types of germ cell tumors have been

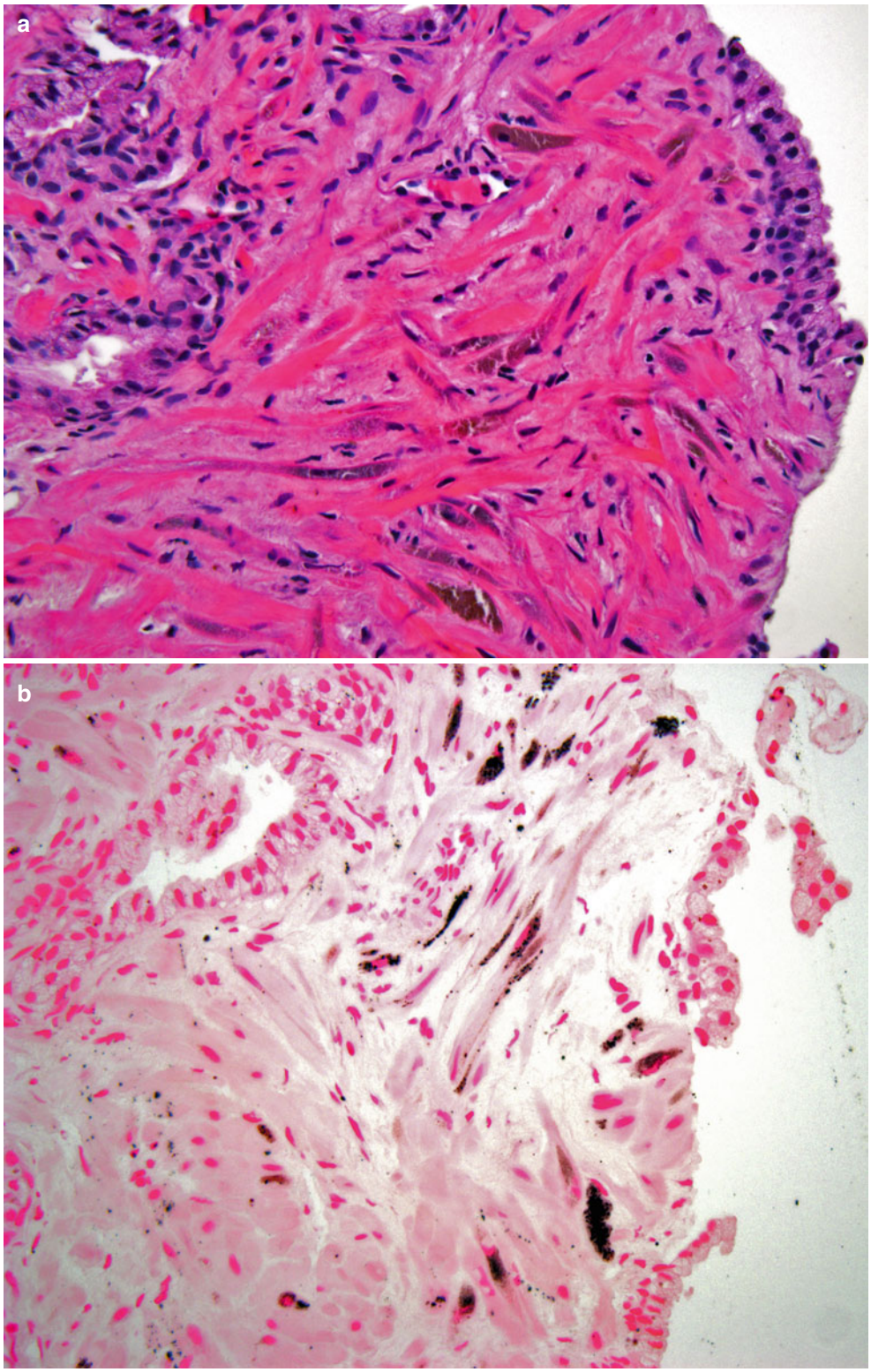



**Fig. 21.6** (**a**) Blue nevus. Melanin-containing spindled stromal cells are seen in *blue* nevi of the prostate. (**b**) A Fontana-Masson stain highlights the melanin pigment (*black*)

described, including *embryonal carcinoma*, *yolk sac carcinoma*, and *choriocarcinoma*, as well as *seminoma* [47–61].

*Angiosarcoma* [62], *peripheral neuroectodermal tumor* (*PNET*) [63, 64], *neuroblastoma* [65], *malignant peripheral nerve sheath tumor* (*MPNST*) [66], *synovial sarcoma* [67–69], *malignant perivascular epithelioid tumor* (*PECOMA*) [70], and *Wilms' tumor* [71] have all been reported to occur in the prostate.

### Clinicopathologic Summary

1. Melanotic lesions occur not uncommonly in the prostate; however, most of these represent benign *nevi* or *melanosis* without malignant potential. Rare primary *melanomas* of the prostate have been reported, but most melanomas involve the prostate only secondarily.
2. *Gastrointestinal stromal tumor* (GIST) has not been documented to occur in the prostate. Rectal GIST may be detected incidentally on needle core biopsy of the prostate.
3. *Paraganglioma* may occur in the prostate, most of which have a benign clinical course, though lymph node metastases have been reported.
4. *Germ cell tumors*, both seminomatous and non-seminomatous types, may rarely occur in the prostate, but diagnosis requires the exclusion of a testicular or mediastinal primary tumor.
5. Multiple additional benign and malignant lesions have been reported in the prostate as case reports or small series.

## Hematologic Neoplasms of the Prostate

### Chronic Inflammation

*Chronic inflammation* is frequently seen in prostates, particularly in specimens from benign prostatic hyperplasia with obstruction. The histologic spectrum ranges from individual scattered lymphocytes to large aggregates of chronic inflammatory cells, frequently centered on or surrounding prostatic glands. Characteristically, there is an admixture of small lymphocytes with plasma cells and histiocytes (Fig. 21.7a, b). Since chronic inflammation can be associated with a modest elevation of PSA, its presence is often noted in needle core biopsies. More importantly, cases of leukemic and lymphomatous infiltration of the prostate need to be distinguished from the common chronic inflammation and not overlooked (see below).

### Leukemia

#### Chronic Lymphocytic Leukemia (CLL)

*Chronic lymphocytic leukemia* (*CLL*)/*small lymphocytic lymphoma* (*SLL*) involves the prostate in 20 % of cases of disseminated systemic disease [72]. Occasionally, CLL presents in the prostate, often with symptoms of urinary tract obstruction, and a subsequent hematologic workup confirms the diagnosis of CLL [8]. Histologically, CLL involvement of the prostate consists of extensive infiltration of the prostatic stroma by sheets of monomorphic small lymphocytes, which spare the prostatic acini and glands (Fig. 21.7c). Marked chronic inflammation can be distinguished from CLL, because the former has an admixture of plasma cells and histiocytes, which the latter lacks. The diagnosis of CLL must always be corroborated by the proper hematologic workup.

#### Myeloid Sarcoma (Chloroma)

Rare cases of *myeloid sarcoma* (*chloroma*) have been reported in the prostate, usually in the context of known *acute myeloid leukemia* (*AML*) [73, 74].

#### Multiple Myeloma

*Plasmacytoma*, causing bladder outlet obstruction, has been reported in a few patients with *multiple myeloma*. There is a mass-like infiltration of prostatic stroma by atypical plasma cells. The diagnosis is confirmed by specific immunohistochemical and genetic studies, in the context of the appropriate hematologic evaluation [75–77].

### Lymphoma

#### Secondary Lymphoma

Most *lymphomas* of the prostate are *secondary* and part of disseminated disease. They are uncommon and usually present in older men, with an enlarged smooth prostate causing obstructive symptoms. Most of the different types of lymphoma have been described in the prostate, but by far the most common is the *diffuse large B-cell lymphoma* (Fig. 21.8a) [78, 79].

#### Primary Lymphoma

*Primary lymphoma* of the prostate is rare and its prevalence among extranodal lymphomas has been reported to be 0.2 % [80, 81]. The diagnosis of primary lymphoma of the prostate can only be made after excluding all other sites of involvement, with the possible exception of pelvic lymph nodes (whose involvement is accepted by some authors in cases of primary prostatic lymphoma) [81–83] (Fig. 21.8b–d). Most primary lymphomas of the prostate are *diffuse large B-cell lymphomas*; however, rare cases of other types of lymphoma have also been reported. Of particular interest are the reported cases of *mucosa-associated lymphoid tissue lymphoma—MALT lymphoma* (Fig. 21.9a–b) [84].

Histologically, both primary and secondary lymphomas consist of malignant lymphoid proliferations (specific to lymphoma type) infiltrating and expanding prostatic stroma, while preserving the prostatic glands.

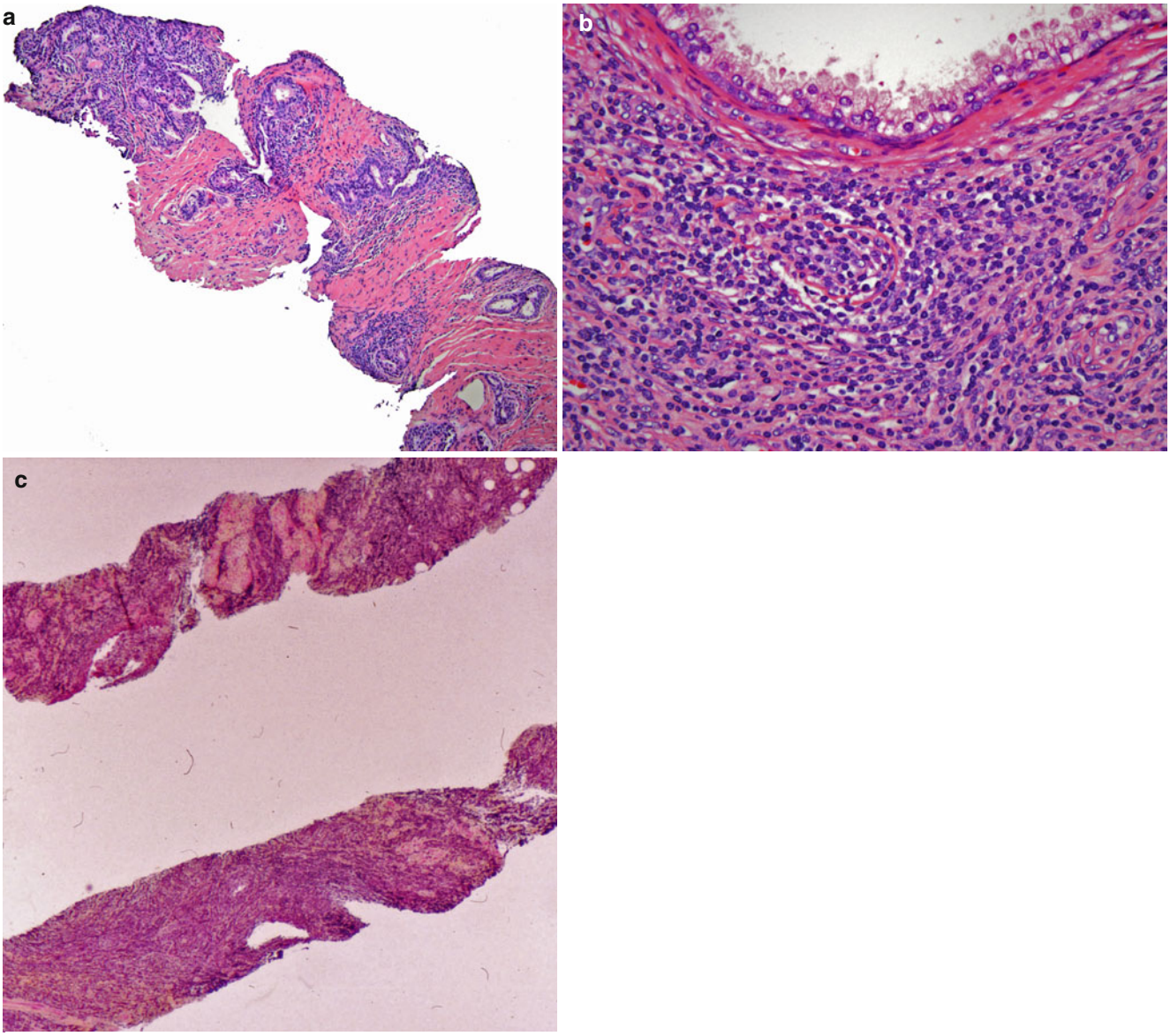



**Fig. 21.7** (**a**) Chronic inflammation of the prostate. Inflammatory cell aggregates are present primarily around prostatic glands. (**b**) Chronic inflammation of the prostate. Note that the inflammatory foci consist of lymphocytes, plasma cells, and histiocytes. (**c**) Chronic lymphocytic leukemia involving the prostate. Note the extensive diffuse stromal infiltration by neoplastic small lymphocytes

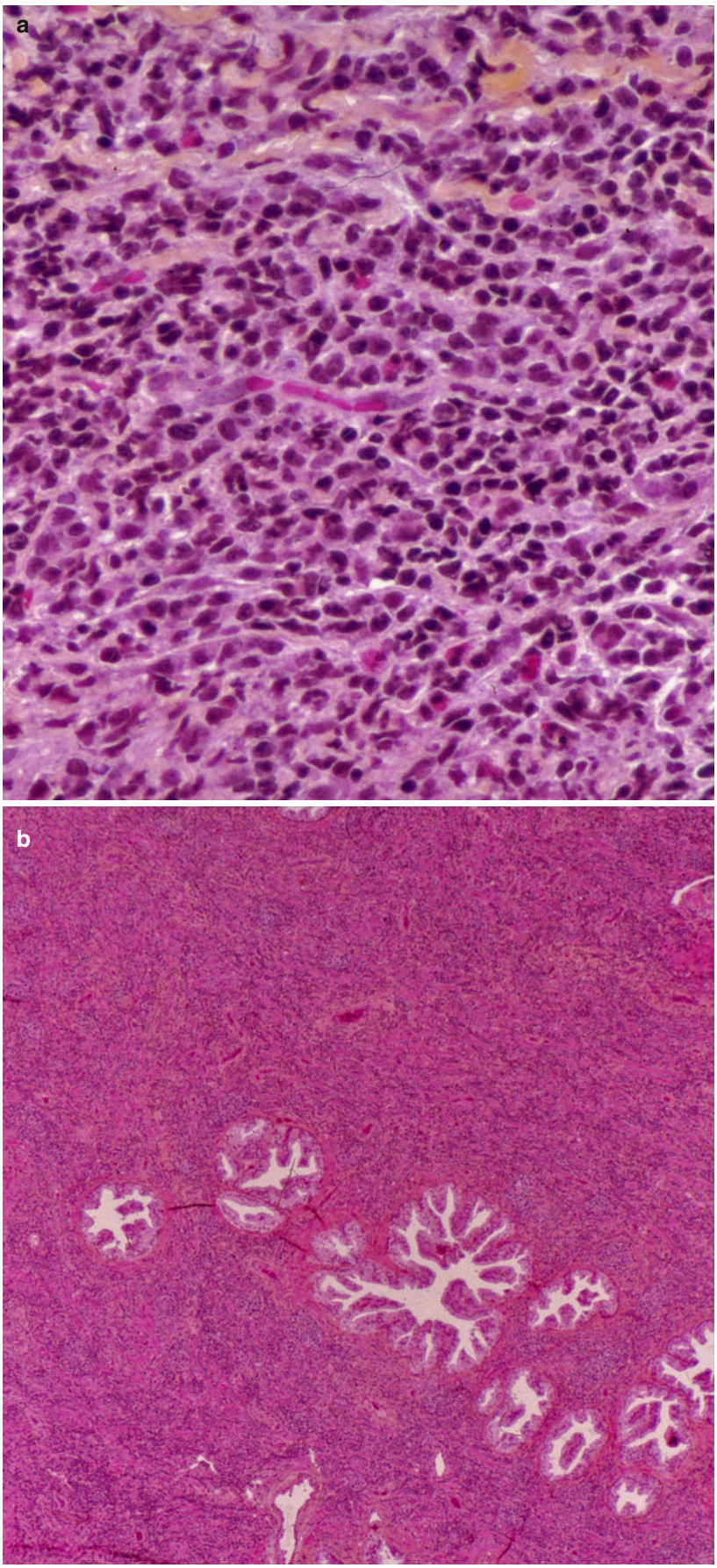
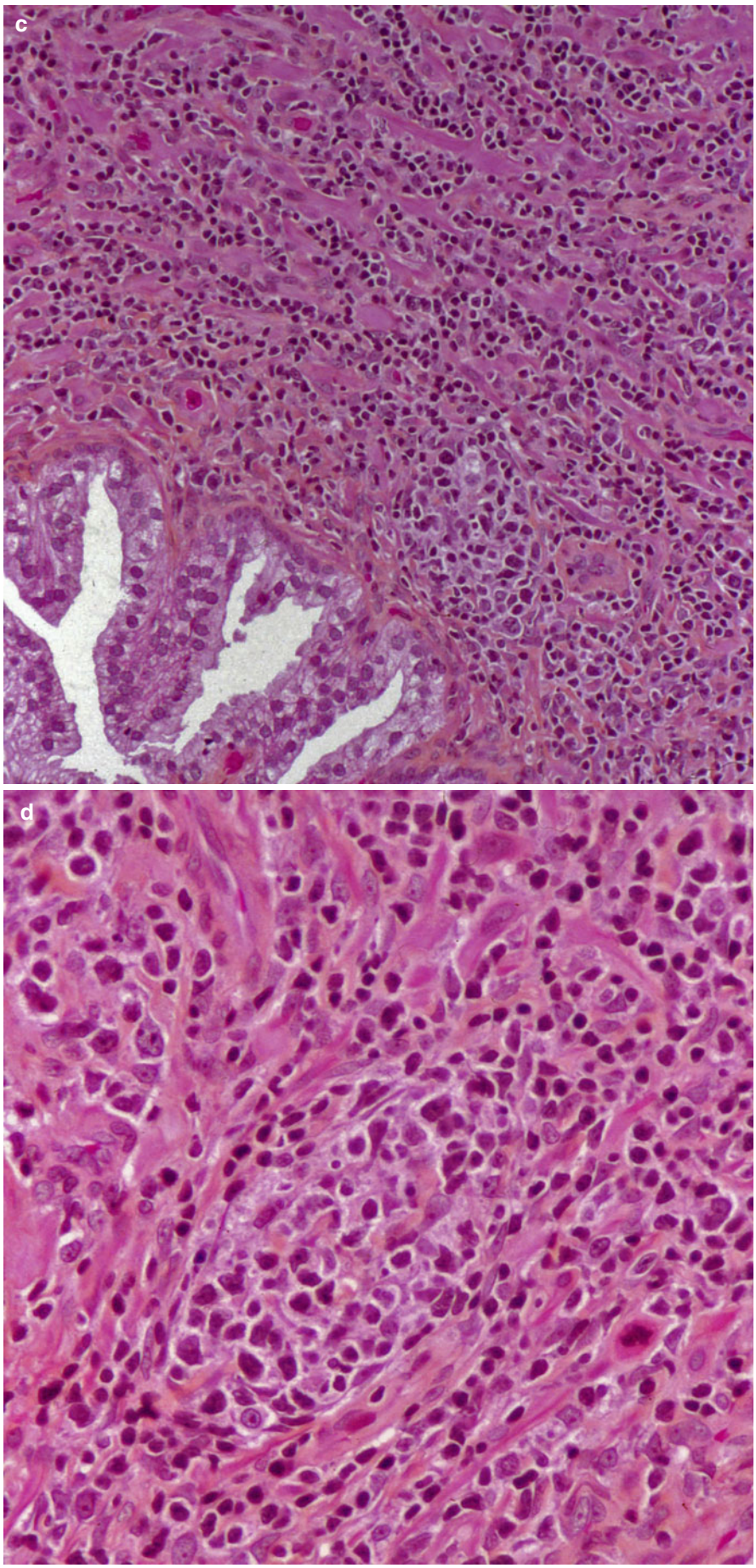



**Fig. 21.8** (**a**) Retroperitoneal diffuse large B-cell lymphoma, secondarily involving the prostate. Note the classic appearance of diffuse large B-cell lymphoma. (**b**) Primary diffuse large B-cell lymphoma of the prostate. Note the diffuse infiltration of prostatic stroma by the lymphoma, with sparing of prostatic glands (40×). (**c**) Primary diffuse large B-cell lymphoma of the prostate (200×). (**d**) Primary diffuse large B-cell lymphoma of the prostate (400×)

**Fig. 21.8** (continued)



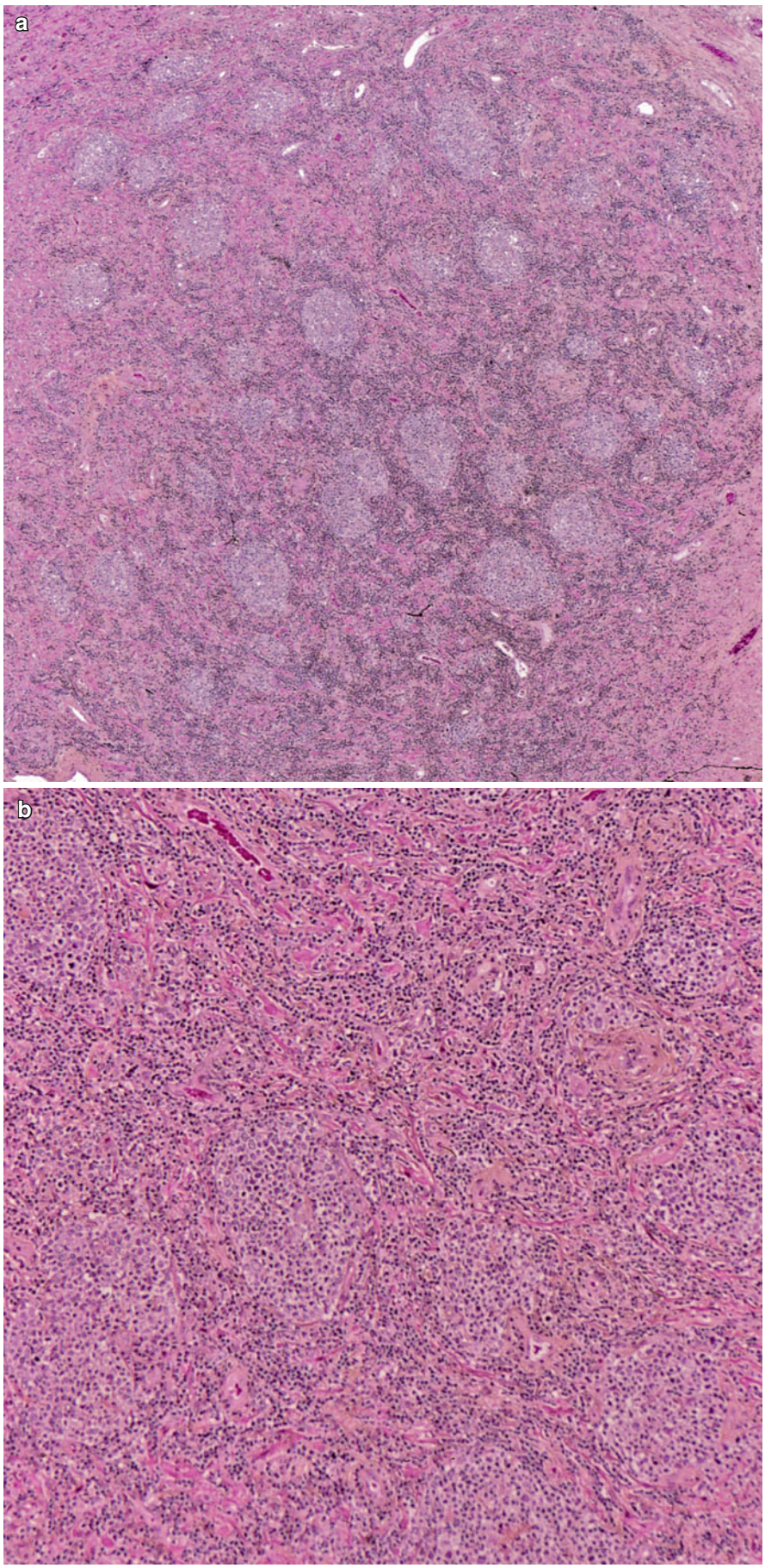



**Fig. 21.9** (**a**) Primary MALT lymphoma of the prostate. Note the numerous follicular structures characteristic of this lymphoma. (**b**) Primary MALT lymphoma of the prostate. Higher magnification of the neoplastic components of the tumor

## Clinicopathologic Summary

1. *Chronic inflammation* of the prostate is very common and consists of a mixture of chronic inflammatory cells. The pathologic diagnosis of "chronic inflammation" is preferable to "chronic prostatitis," which is a clinical term with treatment implications. Leukemic and lymphomatous involvement, especially CLL, has to be distinguished from chronic inflammation.
2. The presence of *leukemia/lymphoma* should be suspected in cases with extensive infiltration of the prostatic stroma by lymphoid or hematopoietic cells, particularly with the preservation of prostatic glands. A hematologic workup is required, and in most cases this is secondary involvement.

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# Neuroendocrine Prostate Cancer

# 22

Himisha Beltran, Juan Miguel Mosquera,
and Mark A. Rubin

Neuroendocrine prostate cancer (NEPC) is a highly aggressive subtype of prostate cancer that may either arise *de novo* or much more commonly after hormonal therapy for prostate adenocarcinoma. It is estimated that up to 30 % of late stage prostate cancers harbor a predominance of neuroendocrine differentiation [1]. However, due to a general lack of biopsy diagnoses for advanced disease, this may underrepresent the frequency of neuroendocrine PCa (NEPC). Since androgen deprivation therapy promotes the development of NEPC, its incidence is anticipated to escalate with the introduction of new potent hormonal agents into the clinical arena.

NEPC is more aggressive than prostate adenocarcinoma, does not secrete prostate specific antigen (PSA) or express androgen receptor [2], and can be suspected in patients with progressive disease despite a normal or modestly elevated PSA and/or elevated serum markers of neuroendocrine differentiation (i.e., chromogranin A or neuron-specific enolase (NSE)). These tumors are highly aggressive, with nearly all patients dying within 1 year of diagnosis [25].

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## Neuroendocrine Cells in the Normal Prostate

The epithelial compartment of the normal prostate gland is composed of basal cells, secretory (luminal) epithelial cells, and neuroendocrine (NE) cells. Prostate adenocarcinoma shows features of secretory cells. Basal cells are androgen insensitive and have recently been shown to display stem cell features [27].

Neuroendocrine cells are distributed throughout the normal prostate (<1 %), with a higher frequency in ducts compared to acinar tissue [3]. There are two types of NE cells: "open" cells with apical extensions that connect with the lumen and "closed" cells with dendritic-like processes that extend between adjacent cells and rest on the basal lamina in close relation to adjacent nerves. NE cells have features of epithelial, neural, and endocrine cells and act in a paracrine fashion to communicate with luminal and stromal cells via these extensions (or neurites) [4].

The physiological role of NE cells in the normal prostate is not well established, but they are thought to be involved in regulation of epithelial cell growth and differentiation. NE cells contain dense-core cytoplasmic granules that store peptide hormones and prohormones, including chromogranin A, NSE, chromogranin B, somatostatin, bombesin, and calcitonin gene family of peptides (calcitonin, katacalcin, and calcitonin gene-related peptide) [5, 6]. Normal prostatic NE cells lack the proliferation-associated Ki-67 antigen, are considered differentiated postmitotic cells, and do not express p63 or PSA. They lack androgen receptor (AR) expression and are thus androgen insensitive.

## Neuroendocrine Differentiation of Prostate Cancer

Focal neuroendocrine differentiation can be seen in 5–10 % of localized prostate cancers, and this proportion rises with disease progression [7]. The amount of neuroendocrine differentiation in prostate tumors correlates with the rate of

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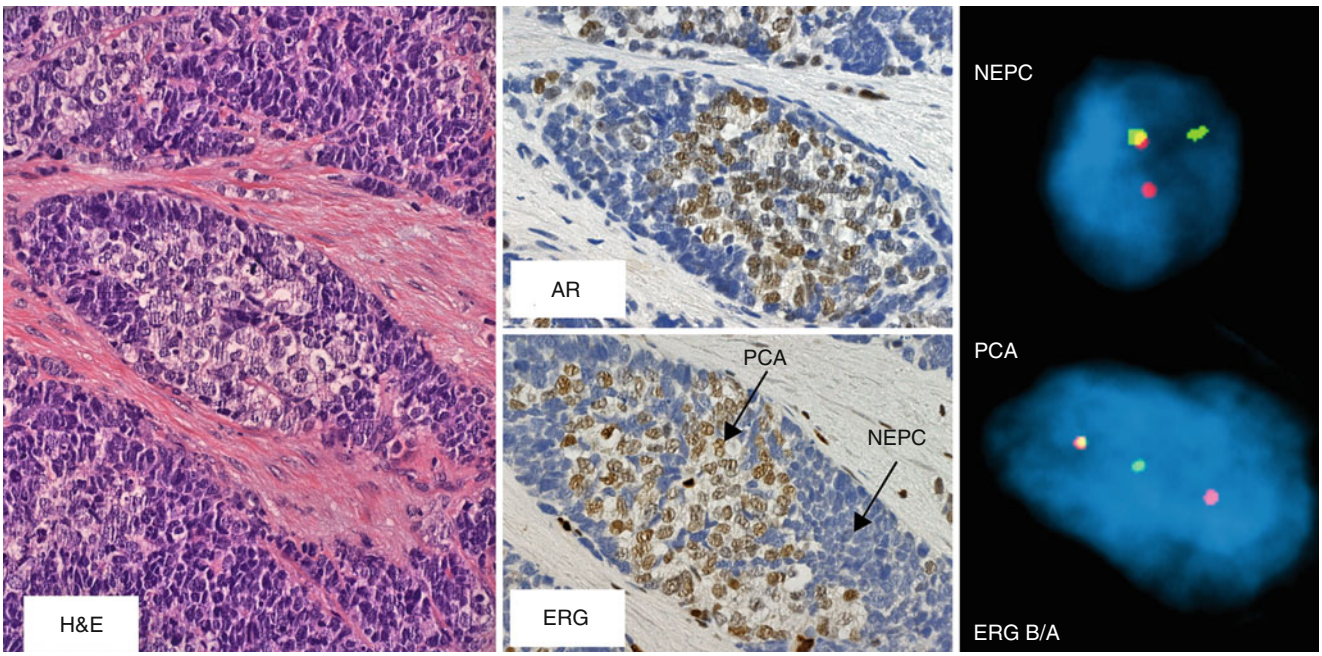


**Fig. 22.1** Hematoxylin and eosin (*H&E*) staining showing a tumor focus with mixed features of NEPC and PCA. Immunohistochemical analysis for androgen receptor (*AR*) and ERG, and FISH for ERG break-apart (indicating gene fusion) reveals that ERG gene fusion is present in both NEPC and PCA, but AR and ERG protein expression is positive in PCA and completely negative in NEPC

tumor progression, adverse outcome, and with surrogate markers of adverse outcome (such as tumor grade and stage) [8, 9]. NE cells may also contribute to a significant percentage of prostate cancers developing resistance to hormonal therapy. Elevated serum chromogranin A levels are associated with worse survival in men with metastatic PCa, adding prognostic information to clinical stage and Gleason grade [10]. Chromogranin A and PSA serum levels show a weak but positive correlation in many patients, supporting the presence and growth of both chromogranin A and PSA-expressing cells simultaneously. Neuroendocrine differentiation is becoming increasingly recognized as an independent prognostic factor, especially for patients with castrate-resistant prostate cancer (CRPC), though sequential measurement and calculation of chromogranin A kinetics in men with prostate cancer does not add prognostic value [11].

Prostate adenocarcinomas may eventually completely escape androgen blockade and become truly hormone refractory, associated with the development of a predominantly neuroendocrine phenotype. How this occurs is poorly understood. There is evidence that when prostate adenocarcinoma cells are exposed to various cytokines (IL6, IL8, heparin-binding EGF) or an androgen-depleted environment in cell culture, they are able to differentiate into neuroendocrine cells transiently and then revert back to their original phenotype when the inducer is removed [12]. Prostate adenocarcinoma cell lines (LNCaP) have also been shown to become "neuroendocrine-like" when stably transfected with the gene that encodes the transcription factor (and oncogene) N-myc (MYCN), with upregulation of neuroendocrine markers and downregulation of androgen receptor and androgen-regulated genes occurring via direct binding of N-myc to promoters of synaptophysin (SYP), NSE, and AR [28]. This suggests a transdifferentiation model of progression, with direct evolution of NEPC from adenocarcinoma cells. As opposed to normal prostate neuroendocrine cells, neuroendocrine cells in cancer express cytokeratin 18, bcl-2, and alpha-methylacyl-CoA racemase (AMACR) [13].

As further support of a transdifferentiation model of NEPC and clonal origin from prostate adenocarcinoma, the frequency of the prostate cancer-specific ERG gene rearrangement is similar to that of prostate adenocarcinoma [14]. Histologic evaluation of mixed tumors reveals that NEPC and prostate adenocarcinoma can coexist and intermingle within the same tumor focus, and tumors that are ERG fusion positive demonstrate rearrangement in both the NEPC and adenocarcinoma foci (Fig. 22.1). Since the upstream genes commonly involved in ERG gene rearrangements are androgen regulated (e.g., TMPRSS2), the downstream ERG protein expression is limited only to the adenocarcinoma component of mixed tumors. Thus, ERG fusion positive NEPC is AR negative and ERG protein negative.

It has also been suggested that the neuropeptides released by neuroendocrine cells in the prostate may facilitate the development of androgen independence, acting as autocrine and paracrine growth factors for malignant cells. In prostate cancer cells, neuropeptides have been shown to promote cell growth, migration, and protease expression [15]. For instance, the neuropeptides bombesin and gastrin-releasing peptide (GRP) transmit their signals through G protein-coupled receptors,

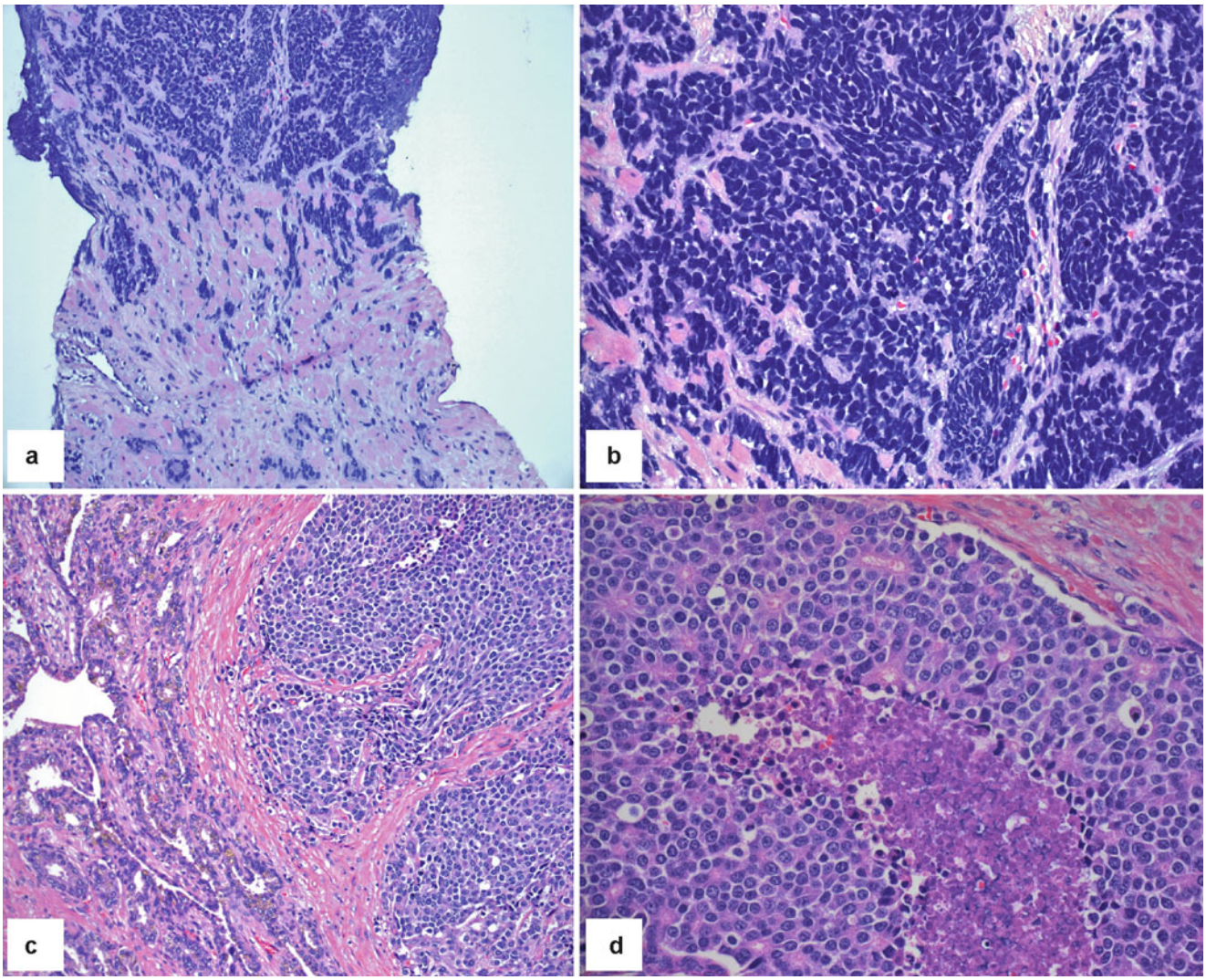


**Fig. 22.2** (**a**, **b**) Small cell carcinoma of prostate. Core biopsy (**a**) with poorly differentiated neuroendocrine carcinoma (*upper half*). Note the "crush" artifact at the edge of the tissue. Conventional acinar prostatic adenocarcinoma is also present (*bottom*). At higher magnification (**b**), tumor cells have hyperchromatic nuclei and nuclear molding, characteristic features of small cell carcinoma (Original magnification 20× and 40×). (**c**, **d**) Large cell neuroendocrine carcinoma of prostate. Section of prostatectomy specimen (**c**) with a neuroendocrine carcinoma (*right*) invading into the seminal vesicle (*left*). At higher magnification (**d**), the tumor is composed of larger cells with abundant eosinophilic cytoplasm, rosette-like structures, and necrosis (*center*) (Original magnification 20× and 40×)

which are often overexpressed in prostate cancer, and can aberrantly activate AR in the absence of androgen [16].

Thus, neuroendocrine differentiation and hormone-refractory disease seem to be an associated phenomenon: extensive neuroendocrine differentiation of a tumor renders prostate cancer androgen-independent, and androgen blockade induces neuroendocrine differentiation.

## Histology

Pure neuroendocrine prostate cancers resemble small cell carcinomas, large cell neuroendocrine carcinomas, or carcinoid tumors of other primary sites. Small cell carcinoma is composed of sheets and nests of uniform cells with scant cytoplasm, rounded hyperchromatic nuclei, coarse chromatin, and unapparent nucleoli (Fig. 22.2a,b). Mitotic figures are numerous, at a rate of 5–10 per high power field. Cells tend to be arranged without structure or cell-to-cell orientation. Microscopic or larger foci of tumor necrosis are evident, and there tends to be wide and diffuse infiltration with poorly circumscribed margins at the advancing edge. Lymphatic and blood vessel invasion is common. Electron microscopy of NE cells reveals small neurosecretory dense-core granules. Large cell neuroendocrine carcinoma is an unusual variant arising in the prostate. It consists of solid sheets and ribbons of cells with abundant cytoplasm, large nuclei with coarse chromatin,

brisk mitotic activity, rosette-like structures, and foci of necrosis (Fig. 22.2c,d). Both small cell and large cell neuroendocrine carcinomas are high-grade aggressive tumors and behave in a similar fashion clinically. On the other side of the spectrum, low-grade neuroendocrine carcinoma (carcinoid) can rarely arise in the prostate. This is a well-differentiated tumor composed of uniform cells arranged in an organoid pattern of nests, ribbons, or acini (not shown).

In secondary NEPC, adenocarcinoma tumor cells are adjacent or intermingling with NEPC cells (Fig. 22.1). The adenocarcinoma tends to be moderately to poorly differentiated, displaying microacinar or cribriform morphology. The amount of NEPC in the tumor focus can vary considerably and increases with clinical disease progression and in response to androgen deprivation therapy. Distinguishing NEPC from high-grade adenocarcinoma, especially Gleason pattern 5, may sometimes be challenging. The presence of rosettes, nuclear molding, "crush" artifact, and fine chromatin supports NEPC.

The diagnosis of NEPC is primarily based on morphology, though immunohistochemistry can support or confirm the diagnosis. Typically one or more of neuroendocrine markers, chromogranin A, synaptophysin, neuron-specific enolase, and CD56, are positive by immunohistochemistry. In a minority of cases (10 %), neuroendocrine markers are all negative, but the morphology still supports the diagnosis. Again, immunohistochemistry is negative for AR, PSA, and prostatic acid phosphatase (PAP), distinguishing NEPC from conventional prostate adenocarcinoma. The presence of the prostate-specific ERG gene fusion by FISH break-apart occurs in approximately 50% of NEPC, which rules out small cell carcinoma from other primary sites [17, 18].

## Neuroendocrine Differentiation of Clinically Localized Prostate Cancer

A number of studies have implicated the presence of neuroendocrine differentiation in localized prostate cancer as a prognostic biomarker. Evaluation of 104 prostatectomy specimens of patients with clinically localized prostate adenocarcinoma revealed that either histological grade or the presence of neuroendocrine differentiation predicted the development of biochemical recurrence [8]. Furthermore, the presence of neuroendocrine differentiation also distinguished tumors of Gleason sum ≥6 into groups with high and low risks for progression, independent of Gleason sum. Theodorescu D et al. also evaluated 71 prostatectomy cases and found the level of chromogranin A immunoreactivity to strongly predict disease-specific survival and was superior to standard pathologic prognostic factors (such as Gleason score, capsular penetration, seminal vesicle invasion, and percentage of tumor in the specimen) [19]. A multivariate analysis of neuroendocrine differentiation and cell proliferation (Ki-67 labeling index) on radical prostatectomy specimens found neuroendocrine differentiation to be the second most significant predictor of biochemical progression, after Gleason score [20].

## Clinical Presentation

Pure NEPCs, most commonly small cell prostate cancers, that arise de novo (primary NEPC) are rare (<1 %), tend to occur in younger patients and most patients present with overt metastases. There are no established risk factors. Patients that do present with localized disease usually have few symptoms. Distant spread is often to visceral organs (such as liver and brain) or lytic bone lesions, unlike prostate adenocarcinoma that tends to metastasize to bone and produce blastic lesions. Presenting symptoms may include constitutional symptoms, hydronephrosis, bone pain, abdominal pain, hematochezia, or hematuria. Paraneoplastic syndromes occasionally are present, due to ectopic production of hormones (such as adrenocorticotropic hormone, antidiuretic hormone, etc.) [21].

Distinguishing pure NEPC from small cell carcinomas of other primary sites can be challenging, especially if a patient presents with widely metastatic disease. Histologically, they appear similar and may have a similar immunohistochemical profile (negative for androgen-regulated genes and positive staining for neuroendocrine markers). Assessment of the presence of ERG gene rearrangement by FISH can be performed to help distinguish prostate adenocarcinoma from other sites, as it is positive in approximately 50 % of NEPC and is universally negative in small cell carcinomas of lung and bladder [17, 18].

Much more commonly, NEPC arises after therapy of prostate adenocarcinoma (secondary NEPC, also called treatment related NEPC or t-NEPC). It is believed that hormonal therapy accelerates the development of NEPC, as evidenced by increased chromogranin A expression in prostate or serum, while patients are on continuous androgen deprivation therapy [22], as well as preclinical studies showing transdifferentiation of prostate adenocarcinoma cells to NEPC in response to androgen depletion. Clinically, t-NEPC may be suspected in a patient with advanced prostate cancer showing evidence of progression (especially visceral metastases) without an appropriate rise in serum PSA. Serum markers of neuroendocrine differentiation, such as chromogranin A and NSE, are frequently elevated in advanced prostate cancer [23] but if extremely high may support the diagnosis of NEPC.

Similar to small cell lung cancer, pure NEPC is a chemosensitive and radiosensitive tumor. However, despite high initial response rates, all patients progress,

and average survival is less than 1 year [24, 25]. There appears to be no significant difference in survival between primary de novo NEPC and those that arise after treatment of prostate adenocarcinoma.

## Treatment

Since hormonal therapy promotes neuroendocrine differentiation, intermittent androgen deprivation therapies for hormone responsive prostate cancer theoretically may prevent or delay the development of NEPC though this has not yet been proven.

Localized NEPC that remains only in the prostate is rare at diagnosis, and data are limited on how to manage these patients. Positron emission tomography (PET) may be useful in confirming localized stage disease. If identified early, chemotherapy with concurrent or consolidative radiotherapy similar to limited stage small cell lung carcinoma may be considered. Surgical resection may also be considered, but data in this setting is scarce.

Patients with metastatic disease with mixed features of NEPC and PCA that have not yet had hormonal therapy are often started on androgen deprivation initially but usually progress rapidly since NEPC is hormone refractory and only the adenocarcinoma component would be expected to respond.

Patients with NEPC and castration resistance are treated with chemotherapy and often with platinum-based regimens similar to small cell lung cancer. Radiotherapy is sometimes added for local control or palliation of symptoms. Cisplatin and etoposide is commonly used, and other agents such as ifosfamide and doxorubicin have shown activity. Few prospective clinical trials have been conducted for patients with NEPC. In one phase II trial of 38 patients, the addition of doxorubicin to cisplatin and etoposide produced a 61 % response rate with 22 partial responses but was associated with greater toxicity than cisplatin and etoposide [25]. Median time to progression was 5.8 months, and overall survival was 10.8 months. Carboplatin and etoposide has also been evaluated, with similar survival rates [24]. An ongoing phase II trial is prospectively evaluating the combination of carboplatin and docetaxel for patients with known or suspected NEPC (clinicaltrials.gov/ct2/show/NCT00514540).

Pharmaceutical agents aimed at blocking neuroendocrine cancer cells, such as serotonin and bombesin antagonists, are under investigation. In addition, a Phase II trial evaluating the aurora kinase A inhibitor MLN8237 is planned.

Although elevation of serum chromogranin A and NSE levels is prognostic and can support the diagnosis of NEPC, following levels on therapy has not been shown to correlate with response to therapy [26]. Circulating tumor cells have not been evaluated in this specific population but are also under investigation.

## Molecular Alterations

Recent advances in understanding tumor biology, development of new diagnostic, prognostic, and predictive biomarkers, and identification of new therapeutic targets have come through sequencing efforts for a variety of tumor types. Similarly in prostate cancer, transcriptome sequencing and assessment of DNA copy number changes of both PCA and NEPC has brought new insight into NEPC pathogenesis. Despite clonal origin of NEPC from adenocarcinoma cells, there exist dramatic gene expression differences with nearly 1,000 genes showing differential expression [28]. In addition, the genome of NEPC is widely aberrant with frequent amplifications and deletions. There are subpopulations of PCA patients that demonstrate mixed molecular features and may be at high risk for progression to NEPC. For instance, co-amplification of the genes encoding the oncogenes Aurora kinase A (AURKA) and N-myc (MYCN) genes are frequently found in primary tumors of patients that later develop t-NEPC, and are infrequent in other primary prostate adenocarcinomas (Mosquera, Beltran et al, In Revision) and may predict patients at high risk for the development of t-NEPC. Prospective clinical validation of such of novel biomarkers will help identify high-risk populations for early intervention. Also from these types of analyses, targetable pathways implicated in NEPC pathogenesis have been identified and functionally validated. For instance, Aurora kinase A also cooperates with N-myc to directly promote the neuroendocrine phenotype in preclinical models, and Aurora kinase inhibitor therapy has shown dramatic and preferential effect against NEPC cell lines and xenografts. Further studies are underway, including clinical studies investigating Aurora kinase A and N-myc alterations as predictive and prognostic biomarkers, as well as a Phase 2 clinical trial evaluating the role of the aurora kinase A inhibitor MLN8327 for patients with NEPC.

## Summary

NEPC is a highly lethal form of prostate cancer that is believed to often progress from treated adenocarcinoma of the prostate but can also arise de novo. Chemotherapy used for other small cell neuroendocrine cancers is the mainstay of treatment; however, more targeted approaches are being developed based on an emerging understanding of this aggressive form of prostate cancer.

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# Part II

# Epidemiology, Screening, and Chemoprevention

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and Alexandre Zlotta

# Epidemiology of Prostate Cancer

23

Ankur M. Manvar, Raj S. Pruthi, Eric M. Wallen, and Matthew E. Nielsen

## Incidence

### United States

In the USA and worldwide, prostate cancer is the most commonly diagnosed non-dermatologic cancer in men and remains the second most common cause of cancer death in men in the developed world. In a lifetime, prostate cancer will affect approximately 1 in 5 American men [1].

Over the past several decades, changes in prostate cancer incidence in the USA can be contextualized by background trends in the diffusion of different technologies applied to the management of prostate disease. With the increased popularity of transurethral resection of prostate (TURP) to manage BPH in the 1970s followed by the advent of widespread population-based prostate-specific antigen (PSA) screening in the late 1980s, incidence rates started to increase dramatically after 1986. The incidence rate increased 108 % from then on and peaked in 1991 [2]. Interestingly, the incidence of distant disease decreased starting in 1991, with the most likely explanation being earlier detection and screening with PSA [3].

Recent reports have estimated that prostate cancer accounted for 28 % (217,730) of incident cases in men in the United States in 2010 [4] (Fig. 23.1). The peak incidence for both Caucasian and African American men in the USA was around 1986–1992. It is entirely unclear why the incidence started to decline after 1992; however, a likely explanation is the introduction and widespread use of the prostate-specific antigen (PSA) early detection test in 1989, with a "cull effect," in the context of the diffusion of a technology that increased the rates of diagnostic activity to detect latent disease in the population. This decline continued at a rate of 2.4 % per year from 2000 to 2006 and likely reflects several factors including a widespread use of PSA, an actual decrease in detection, or a reduced number of undiagnosed cases of prostate cancer [4, 5]. Although the benefit of the PSA screening on disease mortality remains the subject of controversy, it stands to reason that the advent and widespread adoption of PSA screening explains a substantial degree of the observed changes in prostate cancer incidence in recent decades. For prostate cancer, variation by state is like that of various countries in which incidence reflects differences in the use of screening tests as well as to differences in disease occurrence. For example, Arizona has the least incidence at 116.6 cases, and Michigan has the greatest at 186.4 cases per 100,000. Recent studies have suggested that the incidence rates be leveling off in the USA.

#### Racial Differences in US Prostate Cancer Incidence

African American men have the highest incidence of prostate cancer, not only in the USA, but also in the world. The relative incidence in these men was 1.6 times that of their Caucasian counterparts in the USA [6]. From 1986 to 1993, the overall incidence in African American men increased from 124 to 250 per 100,000, a 102 % increase [7]. Though incidence in Caucasian men rose over this same interval to a roughly proportional degree, the absolute rates were lower (from 86 to 179 per 100,000) [7]. In 1995, the Caucasian incidence decreased to 110 cases per 100,000, while the African American incidence decreased to 170 cases

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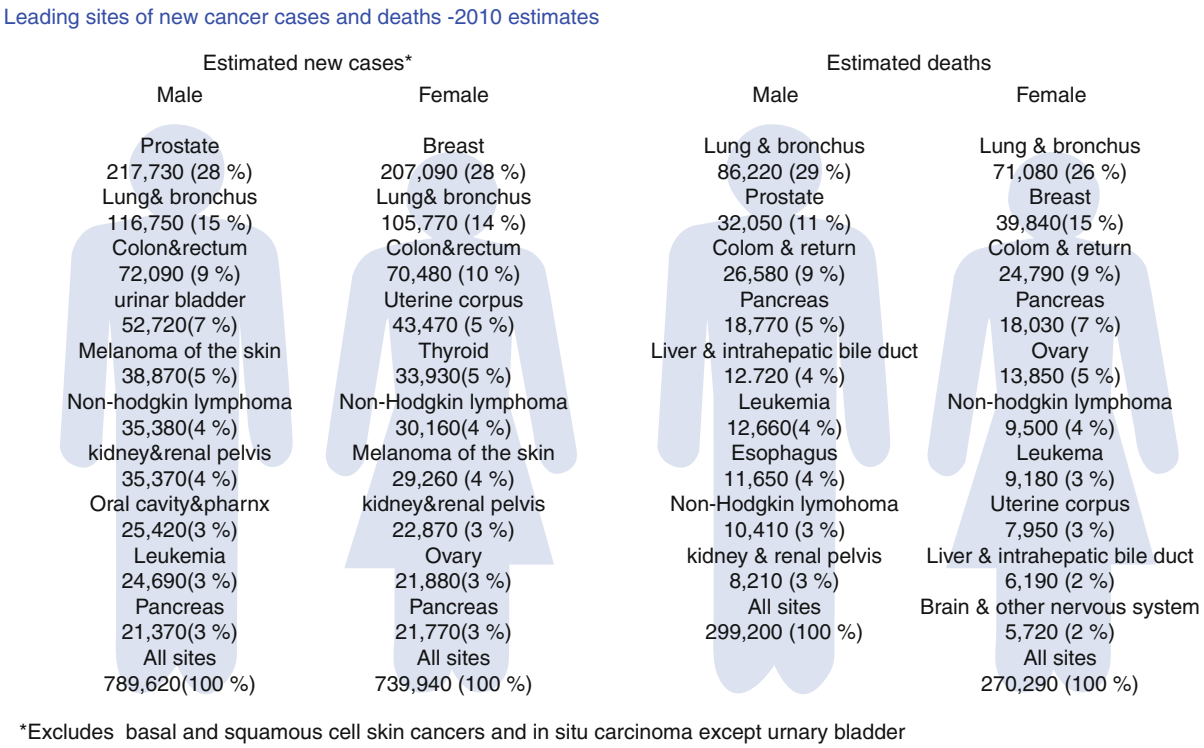



**Fig. 23.1** Estimated incidence and mortality rates in the USA in 2010 (©2010, American Cancer Society, Inc., Surveillance and Health Policy Research)

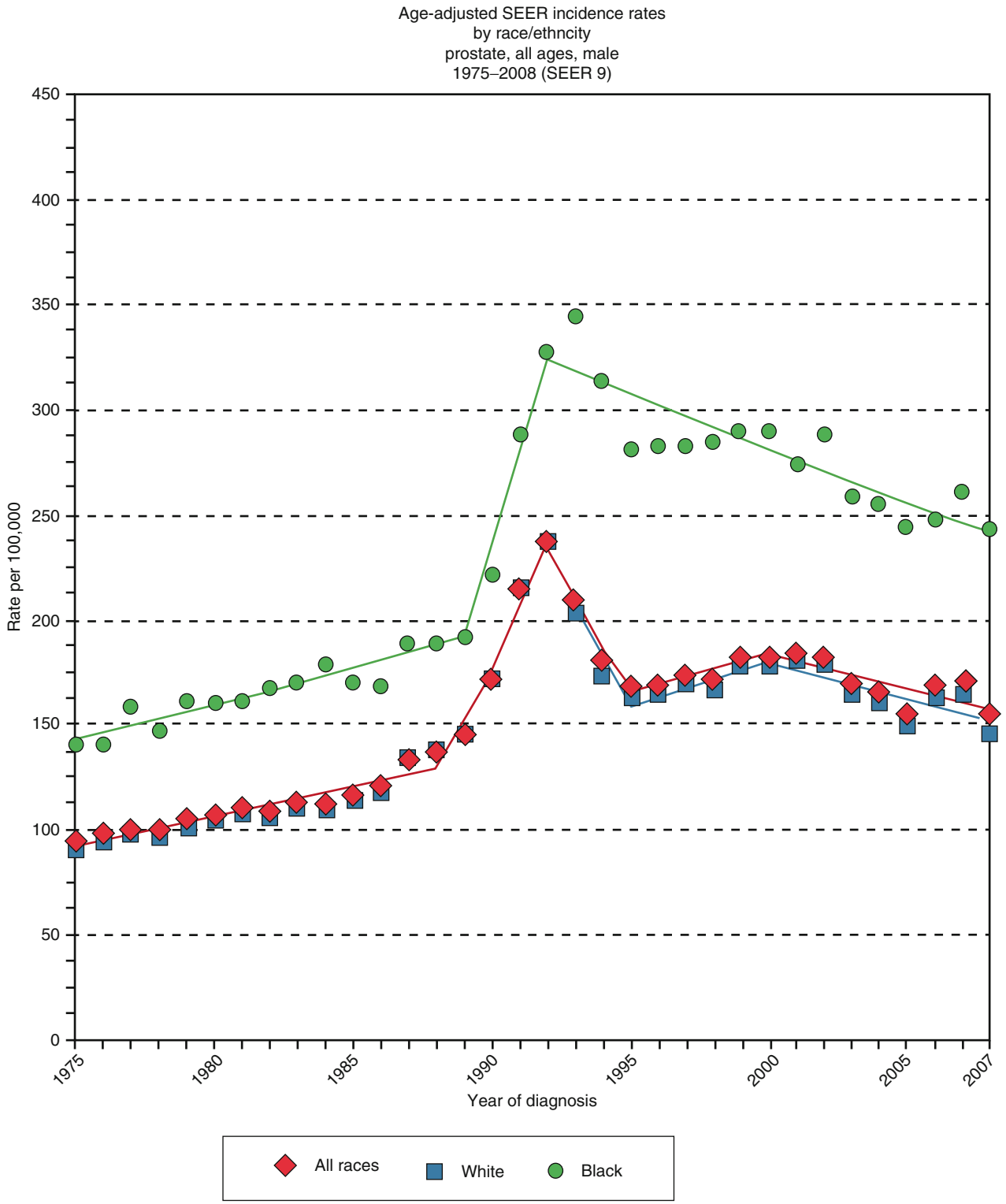
**Table 23.1** The burden of prostate cancer in the United States

| | Caucasian | African American | Total |
|---|---|---|---|
| Incidence | 164.3 | 272.1 | 170.1 |
| Mortality | 30.2 | 73.0 | 32.9 |
| New cases in 2005 | 201,320 | 30,770 | 232,090 |
| Mortality in 2005 | 25,300 | 5,050 | 30,350 |

per 100,000 [8]. The estimated lifetime risk of disease is 17.6 % for Caucasian men and 20.6 % for African American men, with a lifetime risk of death of 2.8 and 4.7 %, respectively [8] (Table 23.1, Fig. 23.2).

## Worldwide

In 2002, there were over 679,000 new reported cases of prostate cancer, making it the fifth most common cancer in the world and the fourth most common cancer in males worldwide [9]. Worldwide prostate cancer incidence rates vary almost 65-fold among countries reflecting, at least in part, variability in the adoption of screening and early detection programs in each country [7]. Interestingly, industrialized nations tend to have higher incidence and mortality rates than in developing nations. Prostate cancer comprised 11.7 % of all new worldwide cancer cases in 2002: 19 % in developed countries and 5.3 % in developing countries. There are several explanations for variations in prostate cancer incidence worldwide and among various ethnic groups, and such reasons would include differential genetic susceptibilities and environmental exposures and access to healthcare, as well as variably reliable ascertainment and reporting of cases in cancer. As incidence is clearly sensitive to the intensity of diagnostic activity, countries with widespread screening and early detection are likely to have a "higher" incidence level, though the true burden of latent cases in unscreened populations is largely unknown. For example, the USA, Scandinavian countries and Western European countries are high-incidence countries, but also have common screening protocols [9] (Fig. 23.3). East Asian countries like China and Japan have some of the lowest incidence rates in the world, around 4 cases per 100,000, and do not have widespread use of PSA test or other screening tools [8]. However, as Japan and China begin to become more Westernized, recent observed increases in incidence may be due to greater awareness of the disease or possibly an actual increase in the risk of occurrence [10]. According to the 2002 Global Cancer Statistics report, the average increase in the estimated age-adjusted incidence of prostate cancer worldwide between 1985 and 2002 was around 1.1 % annually. Though these estimates were largely driven by a surge in the USA after the advent of PSA screening, at this rate, the report predicted almost 900,000 cases worldwide per year by 2010 [9].




Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 us Std Population (19 age groups-Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.4.3. April 2010, National cancer Institute.

**Fig. 23.2** Prostate cancer incidence by race in US men, 1975–2007 (SEER)

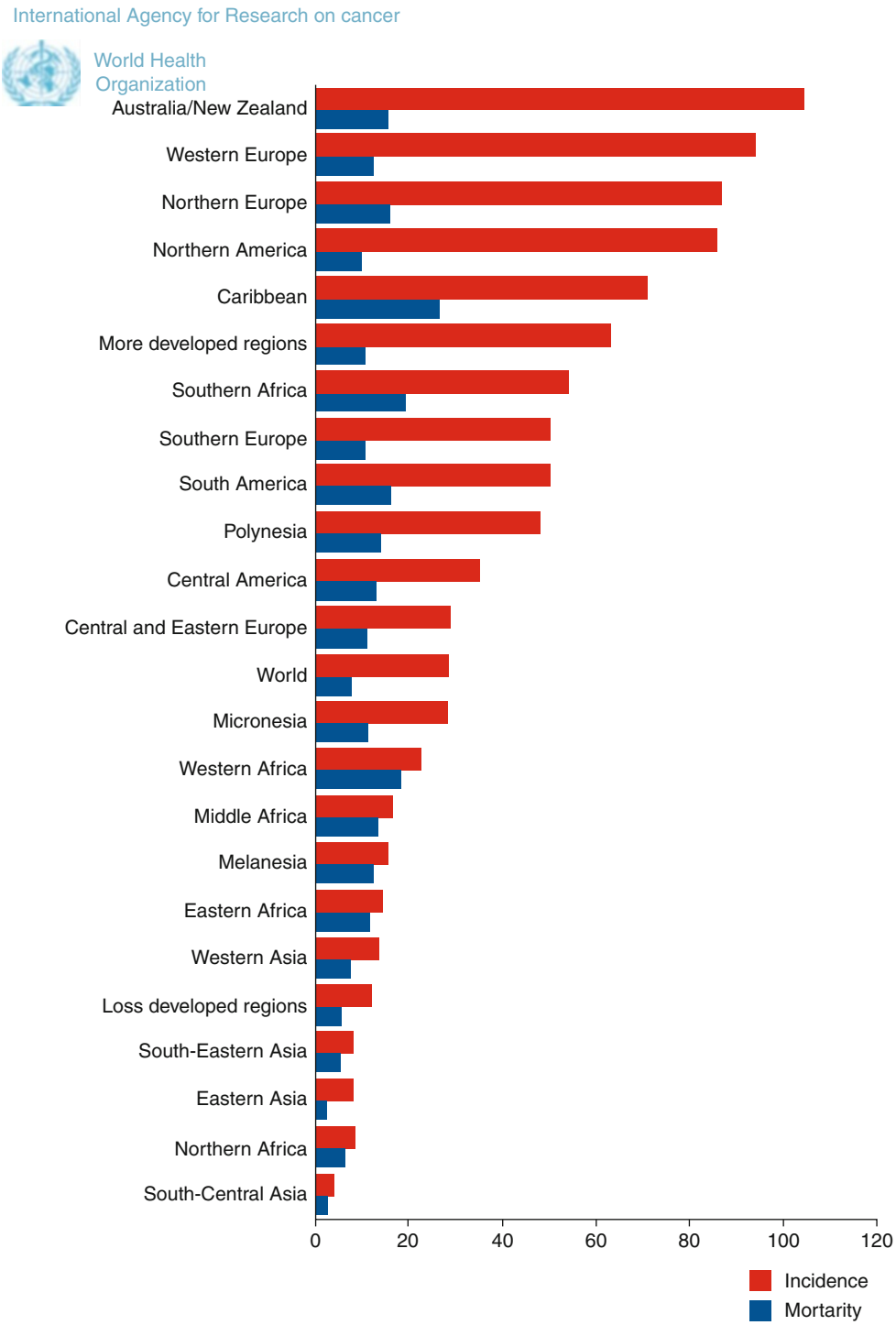



**Fig. 23.3** Global incidence and mortality rates for prostate cancer (GLOBOCAN 2008 (IARC)). Prepared by Cancer Research, UK. Feroy J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GOBCAN 2008 V1.2

## Age at Diagnosis

Prostate cancer is primarily a disease of men above the age of 65 with a median age of diagnosis at 67 years old [7]. It is comparatively rare for a man younger than 50 to be diagnosed with prostate cancer, and such cases account for less than 0.1 % of all cases. However, this number is recently increasing with an incidence rate of 1.9 % per year, likely attributable to PSA screening [8]. Based on the SEER report, a study comparing age at diagnosis in the pre-PSA era from 1980 to 1985 with PSA era (defined as 1990–1995) showed a lower mean age at diagnosis in the PSA era (1.7 year younger in Caucasian men and 1.3 year younger in African American men). Furthermore, African American men had a

younger median age at diagnosis than their Caucasian counterparts by 2 years. Incidence peaks in men between the ages of 70 and 74, with over 35 % of all cases between 65 and 74 years old [7] and 85 % of cases diagnosed after the age of 65 [11].

### Stage at Diagnosis

The stage distribution for prostate cancer in the USA from SEER data in 1999–2006 revealed that over 80 % of patients with prostate cancer were diagnosed as having confined, localized disease; 12 %, spread to regional lymph nodes; 4 %, metastasized to other sites; and 3 %, unstaged/unknown [7]. The large percentage of localized and regional stages may be attributable to the early onset of prostate cancer screening with PSA testing.

Since the introduction of the PSA test in 1986, there has been a huge shift in the stage of prostate cancer at diagnosis. The proportion of men diagnosed with stage IV prostate cancer decreased from 28.1 cases per 100,000 in 1988 to 12.3 cases per 100,000 in 2003, a 6.4 % annual decrease [12]. The decrease in late-stage distant metastatic prostate cancer at diagnosis was even greater and fell from 18.4 in 1988 to 6.7 cases per 100,000 in 2003, a drop of over 8.0 % annually [12]. The decrease continued around 12.5 % annually through 1995 [13]. The incidence of local and regional disease has increased, while there has been a decrease in late stage or metastatic stage of prostate cancer [7, 14]. On the basis of prostate cancer cases diagnosed between 1996 and 2004, an estimated 91 % of these new cases are expected to be diagnosed at local or regional stages. From 1988 to 1992, there was an increase of 18.7 % of locoregional disease and then almost a 10 % decrease through 1995 [13]. Interestingly, these trends are paralleled with an increase in the number of radical prostatectomies for local- and regional-staged patients [7, 13].

These trends in the stage of prostate cancer diagnosis can imply several important points, including the fact that a substantial stage migration has occurred, toward earlier diagnosis and away from late-stage diagnosis; that there is a shift in age of diagnosis; and that there is an increase percentage of men treated for clinically localized disease with a radical prostatectomy. It stands to reason that a major explanation for these observed trends is the widespread availability of PSA screening since the early 1990s.

### Lifetime Risk

Based on data from 2005 to 2007, almost 1 in 6 men (16.2 %) will be diagnosed with prostate cancer in his lifetime. As would be anticipated from the above-referenced figures, the lifetime risk for an individual varies significantly by race, with African American men having the highest lifetime risk. It should also be understood that this lifetime risk also varies by age group and that the older a man is, the higher risk he has of being diagnosed with prostate cancer. Recent data showed that 1 in 8 men above the age of 70 will develop cancer whereas 1 in 16 men between the age of 60 and 69 will develop prostate cancer [4]. Using lifetime risk, or the probability of developing cancer in a lifespan, enables a better understanding of risk disease from a public health standpoint and can influence screening programs within certain races or age groups.

### Migration Studies

Epidemiological studies of migrant populations have shown that men who move from low-incidence countries to high-incidence countries experience a shift in risk toward the rates observed in men in the high-incidence country. For example, individuals from Asian countries like Japan and China who immigrate to the USA have a higher risk for prostate cancer than men living in Japan and China [15]. The role of environmental factors, in particular dietary norms discussed in more detail below, of high-incidence countries is further supported by studies showing increasing incidence in Japan as the country has become more Westernized over the last decade [16]. Nevertheless, it is important to point out that the Japanese and Chinese men who immigrated to the USA still have lower incidence rates than Caucasian and African American men, underscoring the complex interactions of genetic and environmental factors in prostate cancer predisposition.

## Mortality

As important it is to assess prostate cancer incidence, it is equally, if not more important, to measure disease mortality. Mortality is expressed in terms of the number of deaths from prostate cancer per year over the number of men at risk in the same year. Calculating mortality for prostate cancer allows a clear gauge of the severity of disease from both a clinical and public health standpoint. While mortality is sometimes used as a quick index of the risk of disease in a given year, the long natural history of prostate cancer requires a longer time horizon to ascertain the ultimate effects of shorter-term changes in epidemiological trends [17].

### US Mortality

Since 1976, SEER has tracked trends of US prostate cancer mortality, and Table 23.2 shows that there was a statistically significant increase in the mortality rate at 3.0 % annually

**Table 23.2** US prostate cancer mortality trend for all races between 1975 and 2007

| Male | |
|---|---|
| Trend | Period |
| 0.9 | 1975–1987 |
| 3.0 | 1987–1991 |
| –0.5 | 1991–1994 |
| –4.1 | 1994–2005 |
| –2.6 | 2005–2007 |

from 1987 to 1991. The likely increase in mortality during these years can be attributed to several factors including an actual increase in the number of lethal prostate cancer cases, a decrease in the effectiveness of therapy, or a change in the management of patients that was not effective [18]. From 1991 the observed mortality rate started to decrease: first at a slow rate of 0.5 % per year through 1994 and then at a more rapid decline of 4.1 % annually per year from 1994 to 2005. The US prostate cancer mortality rate has since steadily decreased at 2.6 % from 2005 to 2007 [7]. Since mortality decreased after 1991, the decrease in effectiveness of therapy is an unlikely cause of the original increase in mortality [18]. In 2005, the US mortality was 32.9 cases per 100,000 for men of all races, and there were a reported 32,050 deaths from prostate cancer that same year [4, 11]. From 2003 to 2007, the median age of death from prostate cancer in the USA was 80 years old, with over 30 % of these deaths in men over the age of 85 [7]. The age-adjusted death rate from prostate cancer during the same period was 24.7 cases per 100,000 and varies significantly by race (discussed below).

Since 1995 for Caucasian men and 1997 for African American men, prostate cancer mortality rates have dropped below the 1986 levels, the first year the PSA test was introduced. Epidemiological evidence suggests that recent declines in mortality are strongly associated with the stage migration and, specifically, decreasing rates of stage IV disease in this time period [19]. These results are consistent with the suggestion that decreasing prostate cancer mortality is a result of earlier detection, with concomitant improved prognosis as a consequence of widespread PSA screening in the USA [19–21].

Hankey et al. further suggested that at least a portion of the observed decline in prostate cancer mortality in the USA may also a reflect misclassification in death certificates. They concluded that if men with another fatal disease in addition to prostate cancer were assigned as prostate cancer deaths, then the mortality rates would tend to rise and fall with the incidence rates [13]. Hence, it is difficult to attribute declining mortality rates solely to PSA testing or death certificates, but one should understand that it is a combination of factors that influence the declining rates.

In addition to the PSA test, advancements in prostate cancer treatment modalities for men with local and regional disease may also have contributed to the lower mortality rates in the USA in the recent past. This is validated in the SEER data since incidence-based mortality rates do not decline until 1997 [7]. Further, the SEER data classifies local tumors as regional disease, so improved treatments for patients with locally advance prostate cancer do not account for the decrease in mortality for men with distant disease [23]. However, since localized prostate cancer, the predominant stage detected by the PSA test, has a long natural history, the true mortality rates associated with widespread treatment of localized disease will not be appreciated for another decade [18]. Compared to patients diagnosed during the pre-PSA era, whose mortality levels are reflected in statistics from the 1990s, the long-term outcomes of patients diagnosed in the PSA era continue to accumulate. Additional follow-up is required to ascertain the longer term impact of widespread treatment of screen-detected disease with curative intent [18].

## Worldwide Mortality

As with the incidence trends, there is significant worldwide variation in prostate cancer-specific mortality trends. For instance, worldwide mortality has shown increases, especially in developed nations where there are already high-risk incidence levels. However, since the use of PSA testing, mortality has slightly decreased in developed nations, though not at rates comparable to the USA, which may be a result of screening and earlier detection testing [24]. Interestingly, however, prostate cancer mortality in the UK has declined, although there is neither a formal prostate cancer screening program in the country nor are there large increases in incidence [25]. On the opposite end of the spectrum, despite the existence of a formal screening program in Australia, there is no sign of decreasing mortality in the country [26]. Thus, we can infer that there are multiple causes for worldwide variations in prostate cancer, and not only screening programs but also the access and quality of healthcare affect mortality rates.

## Risk Factors

While the etiology and pathogenesis of prostate cancer are clearly complex and multifactorial, the variable risk in individuals and populations has revealed a number of important risk factors. In general, the risk of prostate cancer is increased by African American ethnicity, increasing age, strong family history, and behavioral risk factors such as diet and, to a lesser extent, smoking and alcohol consumption. Variations among high- and low-incidence countries are also attributed to genetic predisposition among different ethnic populations as well as with differences in diet and variety in the availability of healthcare, in addition to variable quality of available

**Table 23.3** Percent of US men who develop prostate cancer over 10-, 20-, and 30-year intervals according to their current age, 2005–2007 (SEER)

| Current age | 10 years | 20 years | 30 years |
|---|---|---|---|
| 30 | 0.01 | 0.32 | 2.49 |
| 40 | 0.31 | 2.52 | 8.30 |
| 50 | 2.30 | 8.30 | 14.40 |
| 60 | 6.62 | 13.36 | 16.11 |
| 70 | 8.50 | 11.97 | N/A |

cancer surveillance data. In this section, we review a selection of these risk factors in the context of relevant literature.

## Age

Typical of epithelial malignancies, it is well established that the risk of prostate cancer increases with age (Table 23.3). A diagnosis under the age of 40 years old is rare, and there is a probability of only 0.01 of men in this age group who are diagnosed with prostate cancer [4]. The probability slightly increases to 2.44 (1 in 41) between men 40 and 59 years old [4]. This is a significant difference when compared to men over 65 years old in which prostate cancer accounts for 70 % of cases in the USA [30]. The probability of prostate cancer increases to 12.48 (1 in 8) for men over 70 years old [4]. The table produced by SEER (below) shows the percent risk of developing prostate cancer for each age group over a time interval (table). Interestingly, prostate cancer is known to have a high prevalence as a subclinical disease as the risk of having histological evidence of prostate cancer in men >50 years old is 42 %, whereas the clinical manifestations of men in the same age group is only 9.5 % with a 2.9 % risk of mortality [31]. To further substantiate a subclinical prevalence, autopsy studies have shown that 10 % of men at the age of 20 have histological evidence of cancer in the prostate [32]. This number increases to nearly 80 % by 80 years old. These data underscore both the long natural history of disease and the substantial reservoir of disease in the population which may be detected with widespread screening programs.

## Familial/Hereditary Predisposition

The incidence of prostate cancer in men with a strong family history is two to four times higher when compared to control populations [33]. Specifically, men with a first-degree relative who has prostate cancer have a two- to threefold risk compared to individuals without affected family members. Furthermore, the risk increases with the number of affected men in the individual's family as well as with younger age at which a relative was diagnosed [34]. Furthermore, men are more likely to get prostate cancer if they have a brother with the disease than if their father has the disease, which suggests a recessive characteristic or X-linked association to prostate cancer [35]. Twin studies show a high concordance rate between monozygotic twins, bolstering the evidence for a familial predisposition to prostate cancer [36].

While it might be argued that the observation of an association of elevated prostate cancer risk among family members may be attributable to similar environmental exposures, there are strong data from multiple genetic studies implying a similar environment, alone, does not explain the prostate cancer risk observed among men with a family history. Linkage studies have identified chromosome loci that involve prostate cancer genes with high penetrance [37]. It is estimated that between 5 and 10 % of all prostate cancer cases have at least one relative who is also affected [38], with estimates of genetic factors in up to 40 % of those cases diagnosed before the age of 55 years old [39]. Additional indirect evidence supporting the significance of hereditary prostate cancer is the observation of diagnosis at an average of 7 years earlier than the sporadic form of prostate cancer, diagnosed in men without a family history [39]. Whereas only 5–9 % of prostate cancer cases meet the criteria for hereditary prostate cancer (three successive generations or at least three members of a nuclear family), approximately 20 % of all cases represent familial forms of the disease [39]. The prevalence of these familial and hereditary forms of this common malignancy supports the current guidelines' recommendations for earlier screening in individuals with a family history.

## HPC-1

Among candidate genes identified in linkage studies, the HPC1 locus on the long arm of chromosome 1 appears to be implicated in at least some kindreds with familial prostate cancer [40]. In families with prostate cancer linked to HPC1, the main features were that the disease was diagnosed at a younger age (usually <65 years old), more than one member was affected, and spanned two generations. In a separate study, higher grade tumors and greater rates of advanced stage disease in HPC1 families were two more distinguishing characteristics of hereditary cases [41].

## BRCA1 and BRCA2

BRCA1 and BRCA2 are also felt to be prostate cancer susceptibility genes. The risk in men with a BRCA2 mutation is approximately five- to sevenfold higher when compared to men with the general population [42]. The link between the BRCA1 mutation and prostate cancer is not well established, yet researchers have shown that there is approximately double the risk for prostate cancer for men <65 years

old compared to the general population [43]. The IMPACT (Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening in BRCA1/2 mutation carriers and controls) is a multicenter study that targets the utility of PSA testing for prostate cancer in men who are known to have a genetic predisposition to prostate cancer. Analysis from this study showed that men with BRCA1 and BRCA2 mutations have a relative that has a risk of prostate cancer of 1.82 and 4.65, respectively [44]. Not only does BRCA2 mutation have a higher relative risk, but also it is reported to lead to a more aggressive disease with a higher mortality rate than men in the general population [45, 46].

## Race

Race is a complex construct, including genetically discrete populations of individuals, as well as cultural and environmental characteristics of racial groups. Incidence and mortality rates, as previously discussed, vary significantly with race [27, 28]. Noteworthy, however, though incidence and mortality for African American men are consistently highest, there is no consistently reported difference in the grade distribution of prostate cancer among the races [47]. Migration studies, discussed below, suggest that behavioral and environmental moderate baseline population-based risk levels and that observed differences between ethnic populations are in fact multifactorial and, to a certain degree, potentially modifiable [29].

## Inflammation/Infection

The consequences of inflammation, infection, and oxidative stress in a spectrum of disease processes, and a number of investigators have elucidated potential mechanisms by which inflammation and infection may play a role in the pathogenesis and biology of prostate cancer. Chronic inflammation causes cellular hyperproliferation to replace and repair damaged tissues, and several well-established associations exist between infectious disease and cancer in other organ sites [48]. A number of candidate inflammatory and infectious mechanisms have been associated with prostate cancer risk and are briefly presented in the following section. A more detailed discussion of this topic area is addressed elsewhere in the textbook.

## Glutathione S-Transferase

Glutathione S-transferase (GST) is an enzyme involved in biosynthesis and metabolism of potential carcinogens and reactive metabolites associated with cigarette, diesel fuel, and grilled meat exposure [49]. Isoforms of GST, M1, T1, and P1, are expressed in the prostate, and genetic polymorphisms that activate these GST isoforms have been associated with activation of carcinogenic metabolites in the prostate, thus increasing the risk of prostate cancer [50, 51]. Results from a GST polymorphism study revealed that isoform T1 increased the risk of biochemical recurrence of prostate cancer in African Americans but not in Caucasians with both high-grade and high-stage tumors, whereas the inverse association was observed with the M1 isoform [52].

## Cyclooxygenase

Cyclooxygenase (COX) is a prostaglandin with two isoforms, constitutively active COX-1 expressed in several cell and tissues types and inducible COX-2 that is induced by cytokines and growth factors, some of which have been implicated as tumor promoters [53]. COX-2 is an enzyme involved in the conversion of arachidonic acid to prostaglandins and has been associated with several cancers and cancer cell lines, including prostate cancer [54].

## Anthropometric Risk Factors

### Obesity

Though obesity has clear associations with increased risk in the settings of breast and colon cancer, the association with prostate cancer is somewhat more complex. Some investigators have suggested an inverse relationship between obesity and prostate cancer risk, whereas others have suggested that morbid obesity is associated with higher grade tumors and biochemical recurrence rates after surgery [55–57]. A body of literature supporting the biological plausibility of obesity and the associated metabolic syndrome as a risk factor for prostate cancer is briefly reviewed here and discussed in greater detail elsewhere in the textbook.

On the one hand, obese men have in general a hormonal profile that might be presumed to be protective against prostate cancer, by having lower levels of testosterone and higher levels of estrogen due to peripheral conversion in fat cells [58]. At the same time, obesity can theoretically promote prostate cancer by leading to the metabolic syndrome, resulting in increased levels of both leptin and insulin-like growth factor one (IGF-1) [59].

### Height

The results of an anthropometric study on height, weight, and hip circumference showed only a slight direct association between height and prostate cancer risk, after adjusting for BMI [60]. However, these results were not statistically significant. There was a stronger correlation for men who were taller than >74 in., with almost a 6–70 % higher risk of advanced disease in these men compared to men shorter than

<68 in. [60]. Another study found no association between height and prostate cancer [55].

## Leptin

Leptin is an adipocyte-derived hormone that regulates satiety and energy expenditure while contributing to the control of body weight, representing a potential mechanism through which prostate cancer is associated with obesity. Leptin deficiency is associated with morbid obesity since there is no sense of satiety or communication with the brain when there is enough energy, or food intake [61]. Leptin receptors are highly expressed on the prostate [62], and increased levels of leptin are associated with angiogenesis and proliferation of prostate cancer cell lines in vitro [63]. Leptin is also known to have a hand in secondary organ growth during puberty, and thus it could play a role in prostate cancer development directly through cellular effects [64].

## Insulin-Like Growth Factor 1 (IGF-1)

IGF-1 is a peptide hormone produced in response to growth acting in both an autocrine and paracrine manner to promote normal cell growth and malignant cellular proliferation, differentiation, and apoptosis [65]. IGF-1 has been demonstrated to promote cell proliferation by acting locally through receptors on the prostate, suggesting a potential role in prostate cancer biology [66]. The major circulating binding protein for IGF-1 is insulin-like growth factor-binding protein-3 (IGFBP-3), which regulates the availability of plasma IGF-1 while also exerting its own pro-apoptotic properties on prostatic cells [67]. Interestingly, while IGF-1 increases proliferation of prostate cancer cell lines, IGFBP-3 decreases the growth-stimulating effects of IGF-1 and thus decreases prostate cancer development.

One study reported a 1.7–4.3-fold higher risk of prostate cancer in men with higher levels of IGF-1 [68]. Measuring IGF-1 could be one explanation for the higher incidence of prostate cancer in the USA, since a Westernized sedentary lifestyle and larger consumption of fats result in increased production of insulin and, in turn, IGF-1.

## Behavioral Risk Factors

### Smoking

There is no question that environment is an influential factor in prostate cancer rates worldwide; however, there are limited studies beyond diet that determine the link between these factors and prostate cancer. Cigarette smoking is suggested to be a risk factor for prostate cancer since it is a source of carcinogens which are associated with increasing levels of androgens and decreased estrogen in the body, causing oxidative stress and leading to prostate cancer progression [69]. Specifically, men who reported smoking more than 1 pack per day had a relative risk of 1.5 higher than men who did not smoke or smoked less than 1 pack per day [70].

### Diet

Ecological studies have suggested, and migration studies have affirmed, that prostate cancer is highly associated with a Westernized lifestyle including a diet consisting of high intake of fat, meat, and dairy. Particular components of the typical Western diet have been consistently associated with prostate cancer including α-linolenic acid (polyunsaturated fats found in vegetables and dairy products) and calcium [71]. One mechanism whereby high dietary fat may affect prostate cancer risk is α-methyl-CoA remarcase (AMACR), an enzyme involved in the oxidization of branched chain fatty acids, common in dairy products, and is upregulated in prostate cancer tumors. The oxidation of fatty acids produces reactive oxygen species which may exert carcinogenic effects in the prostate [72].

Diet has provided several explanatory hypotheses for the observed comparatively lower incidence of prostate cancer in Asian countries. Traditional Asian diets have less meat than traditional Western diets and instead have a higher consumption of soybeans and other dietary phytoestrogens [34]. Phytoestrogens have been observed to have an effect on prostate cancer by decreasing tumor size, increasing apoptosis, and decreasing secretion of PSA [73]. Isoflavonoids, a type of phytoestrogen, when metabolized in gut, undergo conversion into hormone-like compounds with weak estrogen. Soybeans and isoflavones work by inhibiting tyrosine kinase enzymes, which promote cellular proliferation and angiogenesis [74].

In the Physicians' Health Study, it was reported that men who had a higher than 600 mg intake of calcium per day were 1.32 times more likely to develop prostate cancer than men who consumed 150 mg or less of calcium per day [75]. Further, this association was found to be the strongest among patients with advanced and metastatic disease. Calcium may influence prostate cancer by downregulation of 1,25-dihydroxyvitamin $D_3$, a form of vitamin D that is protective against prostate cancer [76].

To the extent that oxidative stress is implicated in prostate cancer risk, foods with antioxidant properties may provide a means of mitigating these risks. Foods containing lycopene, including tomato-based foods, and other antioxidants have been associated with a reduced risk of prostate cancer. One study showed a 16 % lower risk of prostate cancer in men who consumed large amounts of lycopene when compared to men who consumed little to no lycopene [77]. Another study showed that increased consumption of tomato juice weeks prior to a radical prostatectomy resulted in a decreased

follow-up PSA, an increased lycopene in the prostate, and a decreased oxidative damage in the prostate [78].

Selenium and vitamin E are two nutrients also being studied in their influence on prostate cancer, and weak evidence shows that both reduce the risk of prostate cancer [79]. Selenium is a nonmetallic element with preclinical data suggesting antitumor properties mediated by antioxidant and pro-apoptotic effects in prostate cancer [80]. In one follow-up study, prostate cancer risk was 66 % lower in a group given selenium than a placebo group who did not receive selenium [81]. The potential of selenium as a primary preventive agent for prostate cancer was suggested by indirect evidence from the Nutritional Prevention of Cancer trial, which randomized patients with a history of skin cancer to oral selenized yeast versus placebo. The report showed a reduction in prostate cancer incidence in the group who had selenium supplementation and that reduction was strongest for men who had a PSA 4.0 ng/mL and lower [82].

Likewise, a Scandinavian study of vitamin E, a fat-soluble vitamin with antioxidant properties, showed a 40 % decrease in incidence and mortality of prostate cancer in men taking vitamin E compared to a placebo group [83]. New data emerging from the SELECT study, specifically designed to address these hypotheses, have cast some doubt on the potential benefit of this approach and will be discussed in greater detail in the chemoprevention section elsewhere in the book [84].

## Alcohol

The interest in alcohol consumption and the influence on prostate cancer is a popular topic because the risk of other cancers like oral, larynx, and pharynx is associated with excessive drinking. In this vein, one study evaluating total alcohol consumption reported a significantly increased risk of prostate cancer among heavy drinkers (>8 drinks/day), in whom the relative risk was 1.9 compared to nondrinkers or men with moderate levels of consumption [85]. These risks were similar among blacks and whites, and no differences were observed by alcohol type (beer or wine vs. liquor). In a slightly different vein, moderate red wine consumption has been the subject of epidemiological studies, given the antioxidant effects of polyphenols which have been associated with growth inhibition in prostate cancer cell lines in vitro [86]. The results of one study suggested that red wine consumption may be associated with a reduced risk in prostate cancer; however, further research is needed to evaluate the type of wine, red or white, to confirm these results [87].

## Vitamin D Link to Worldwide Incidence

Vitamin D deficiency is a worldwide health problem that affects both developed and developing nations alike. It has been estimated that there may be approximately 30–50 % risk reduction for developing prostate cancer by increasing vitamin D intake to more than 1,000 IU/day or increasing sun exposure to increase blood levels of $1,25(OH)_2D_3$. Recent theories have hypothesized that low levels of vitamin D may increase the risk for clinical prostate cancer [88]. The sun is the primary source for vitamin D, and a deficiency can lead to autoimmune, infectious, and cardiovascular diseases as well as cancers like prostate and colon cancer [89]. In the USA, India, Asia, Australia, and New Zealand, vitamin D deficiency is known to be common among young, middle-aged, and adult men [89, 90]. There is significant evidence suggesting the link between sun exposure, vitamin D level maintenance, and prostate cancer [22, 89]. Woo et al. [91] showed that men with stage IV prostate cancer who received 2,000 IU/day of vitamin D had a 50 % reduction in PSA levels after 21 months. Another study examined the geographic distribution of UV radiation and prostate cancer mortality and concluded that there is a significant north-south trend, with lower rates of prostate cancer in the more sun-exposed southern geographical areas [88]. This result has several implications and may be one explanatory hypothesis for the observation of higher incidence rates in more northern latitude countries like Norway and Sweden, whereas countries closer to the equator are low-incidence countries for prostate cancer.

## Vasectomy

Historically, there was some concern regarding a potential link between vasectomy and elevated prostate cancer risk. Though the exact mechanism is unknown, one study reported that a vasectomy influences prostate cancer by decreasing the amount of prostatic fluid secreted after the procedure or that there is a post-vasectomy immune response to sperm antigens, creating anti-sperm antibodies [92]. History of vasectomy was reported to have a relative risk of 1.56 compared to in men who did not undergo the procedure. Further, this risk increased with time, so that men who had a vasectomy at an earlier age had a higher risk of developing prostate cancer than men who underwent the procedure at an older age, with a relative risk of 1.89 among men who had a vasectomy >20 years prior to diagnosis [93]. Subsequent studies have suggested that the observed association may have in fact reflected healthcare usage patterns among men with an established relationship with a urologist [94].

## Sexual Activity

To the extent that prostate carcinogenesis has been associated with inflammation, there has been some interest in evaluating the possibility of a relationship between sexual activity and sexually transmitted infections as mediators of prostate cancer risk. Prostate cancer risk has been associated with earlier age at first intercourse, large number of sexual partners, and

history of STDs [95]. The odds ratio for prostate cancer diagnosis among men with a history of greater than eight sexual partners was 2.24 compared to men who had fewer than eight sexual partners. Another study on sexual behaviors reported that there was no relation between sexual orientation and prostate cancer, and the risk estimate increased directly with the number of female sexual partners but only slightly increased with the number of male partners [96].

In addition to sexual behaviors, infectious agents have been reported to increase risk for prostate cancer. Hayes et al. showed a significant 60 % increased risk among men who had a history of an STD [92]. Further, men who had three or more STDs had a threefold increased risk for prostate cancer compared to men who did not have a history for STDs, with the observation of a significantly increased risk in men with a history of gonorrhea but no association observed with a history of syphilis [95].

Observational data have suggested that higher ejaculation frequency may be associated with subsequent decreased prostate cancer risk [97]. This is substantiated by a study of Roman Catholic priests, assumed to be celibate, who had an above-average risk of dying from prostate cancer [98].

### Summary

Prostate cancer is a common condition with a complex and multifactorial etiological basis. Genetic studies have substantiated the existence of familial and hereditary forms of the disease, and geographic and racial disparities likely reflect, to a degree, variable baseline levels of risk in different populations. At the same time, a large body of literature describes the importance of environmental, nutritional, and dietary exposures as additional moderators of prostate cancer risk. These factors help inform not only our understanding of the potential mechanisms of the disease but also provide a basis for targeted screening, risk factor modification where possible, and potentially primary and secondary prevention strategies, outlined in greater detail elsewhere in the textbook.

## Molecular Epidemiology

Sex hormones are known to play an intermediary role between exogenous effectors, such as environment and diet, and molecular targets in the development of prostate cancer.

### Androgens

It is well established that male sex hormones, or androgens, and prostate cancer are strongly interrelated. Testosterone, the principal male androgen, is necessary for growth of secondary sex organs as well as for prostate epithelium formation, proliferation, and differentiation throughout adulthood. The prostate converts testosterone to dihydrotestosterone (DHT), the primary nuclear androgen and a substrate for hormone metabolism. Testosterone is also responsible for the production of prostate-specific antigen (PSA), and it has long been implicated as a promoter of prostatic cancer growth since castrated men or men with lower levels of testosterone have reduced incidence rates of prostate cancer [99].

Within the prostate, DHT binds to the androgen receptor to form an intracellular complex that binds to androgen-response elements in the DNA of prostate cells inducing proliferation. The potent action of DHT in the prostate is mediated by the androgen receptor. The receptor is encoded by the X chromosome and contains CAG repeats. CAG repeats decrease the transactivation of testosterone while it is bound to the androgen receptor [100], decreasing intracellular stimulation and cellular proliferation and providing a potential protective mechanism to prostate cancer. There is an inverse relationship between the number of CAG repeats and transcriptional activity of the receptor [101]. There is also a racial difference in CAG repeats in that African American men have a shorter mean of 20 repeats compared to 22 repeats for Caucasians [102]. It has been demonstrated that men who had fewer than 20 repeats were at a threefold increased risk compared to men who had more than 22 repeats [103]. Given these observations, this represents another possible mechanism for increased prostate cancer risk in African American men. Further, shorter CAG repeats have also been associated with a higher risk for advanced prostate cancer [104], and the data is still inconclusive for the influence of fewer CAG repeats on lower stage disease.

DHT binds to the receptor, forming an intracellular complex that binds to DNA in prostate cells and induces proliferation of prostatic cells. Non-androgenic hormones like estradiol, vitamin D, and IGF-1 can also trigger this pathway [105]. Similarly, coactivator proteins ARA, p160, and BRCA1 also enhance androgen receptor activity several-fold and cause cellular proliferation [106].

Differences in polymorphism frequencies for genes mediating testosterone metabolism, including CYP17 and SRD4A2, have also been studied as putative mechanisms for differential prostate cancer risk. One example CYP17 (encoding cytochrome P450c17, necessary for steroid biosynthesis) has a polymorphic T to C substitution in the 5′-untranslated region, giving rise to two alleles, A1 and A2. The base pair change at the promoter site may enhance transcriptional activity and influence the risk of prostate cancer [107]. Allele A2 is known to have a higher frequency in Caucasian men (70 %) who have prostate cancer compared to control patients (57 %) [108], whereas A1 is reported to have a higher risk of prostate cancer among Japanese men [109]. If the A2 polymorphism is considered to correlate with the racial differences in prostate cancer

incidence, then Japanese men with A2 should be hypothesized to have a higher incidence than African Americans and Caucasians, but that is the reverse of actual incidence rates. This underscores the complex interaction of genetic and environmental influences in racial differences in prostate cancer incidence.

In the prostate, testosterone converts to the more bioactive DHT by the enzyme catalyst 5α-reductase type II, which is encoded by the SRD5A2 gene. This gene is involved in androgen biosynthesis and metabolism, and polymorphisms of the gene have the potential to alter long-term androgen exposure and prostate cancer susceptibility. One polymorphism, V89L, replaces valine with leucine, causing a reduction in 5α-reductase activity, thus creating a decreased conversion to DHT and reduced risk for prostate cancer [110]. V89L is also associated with lower circulating AAG, a marker for SRD5A2 activity, in both Asian and Caucasian men [111], explaining the possible racial variation in prostate cancer incidence, particularly a lower risk in the Asian male population. V89L frequency was low in African Americans (22.1 %) but much higher (46.1 %) in Asians [111].

Despite convincing data that supports the role of androgens in prostate cancer growth, epidemiologic studies on serum levels of androgens remain inconclusive. One study with over 9,000 men reported no association between serum levels of testosterone and prostate cancer risk [112]. Differences in the study population, testing accuracy, and confounding factors could account for this discrepancy. More specifically, there was a slight association between low-grade disease and serum testosterone levels [113]. Even the largest study, the Prostate, Lung, Colorectal and Ovarian (PLCO), found no association with prostate cancer, but did report a higher testosterone to sex hormone-binding globulin (SHBG) ratio had an increased risk of prostate cancer in men >65 years old [114]. Of all serum testosterone studies, only one to date has found a significant inverse relationship between androstenedione concentration and the risk for advanced stage prostate cancer, in addition to a weak positive association between testosterone concentration and the risk of prostate cancer in younger men [115].

Testosterone deficiency is common among aging American males, and men suffering from testosterone deficiency may actually have a protective affect against prostate cancer. Evidence supports this hypothesis since African American men have 15 % high circulating testosterone than Caucasian men: a possible explanation for the higher level of prostate cancer incidence in African American men [116]. Though this link is established, the extent of testosterone deficiency and cancer risk is yet to be determined.

## Estrogens

To the extent, testosterone is linked to prostate cancer; it follows that estrogen may also have potential implications in prostate cancer biology. In vitro, estrogen has both stimulatory and inhibitory effects on prostate cancer cells [117], and estrogen-dependent transcriptional factors are found in both normal and cancerous prostatic tissue as well as in prostate cancer cell lines [118]. Estrogen receptor-α, ERα, promotes prostatic epithelial cell growth when estradiol binds to it, whereas estrogen receptor-β, ERβ, inhibits cell growth and loss of ERβ causes tumor progression [119]. Since both receptors are located on normal and malignant prostate epithelium, the imbalance of their expression may be a crucial factor that determines estrogens' effect on prostate cancer.

As discussed previously, individuals from countries with typical diets rich in phytoestrogens, including soybeans, have a comparatively low incidence of prostate cancer. In one study of American men, there was an inverse relationship found between soy milk consumption and prostate cancer risk. The association was strong with nearly 70 % reduction in disease risk in men who drank soy milk several times a day versus those who did not drink soy milk at all [120]. See risk factors for more information.

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# Racial Disparities and the Global Picture

# 24

James E. Ferguson III, Matthew E. Nielsen, Eric M. Wallen, and Raj S. Pruthi

## Objectives

1. To understand current trends in racial/ethnic disparities in prostate cancer outcomes
2. To understand the potential causes of these disparities; sociologic, and/or biologic
3. To understand the potential contribution of detection bias due to high prostate cancer prevalence and differences in screening penetrance as possible confounding variables to explain prostate cancer disparities between populations

## Introduction

Epidemiologic studies in prostate cancer have evaluated the impact of race and geographic location on prostate cancer risk and outcomes, with the goal of further understanding risk factors, molecular mechanisms, and the impact of potential differences in practice patterns between populations. Important epidemiologic differences in prostate cancer incidence and mortality have been discovered between different ethnicities and geographic regions with African American men (AAM) having one of the highest reported incidence rates in the world as well as much higher mortality than European American men (EAM) (Fig. 24.1). These data raise the following questions which are currently under investigation: (1) Are these differences representative of inherent environmental or biologic differences between ethnic groups? (2) Are they representative of different screening and treatment patterns between populations? and (3) Are they simply artifacts of data collection and cancer registry accuracy (i.e., increased attribution of mortality to prostate cancer due to increased detection)? If the answer to any of these questions is "yes," how can we use this information to improve our knowledge and better prevent and treat prostate cancer in all men? Each of these questions is addressed in this chapter, with particular attention to the first two questions.

A few caveats must be kept in mind when reviewing studies involving race/ethnicity, geography, and prostate cancer. First, prostate cancer is, among epithelial malignancies, a relatively slow-growing disease. Five-year survival rates in the USA are above 95 % in the PSA era. Thus, any changes in screening or treatment that affect the progression of the disease are unlikely to manifest in mortality differences until 10–15 years later. In addition, because prostate cancer incidence increases exponentially with age, any changes in life expectancy will drastically affect this measure. It is therefore critical to use age-adjusted incidence rates for accurate analysis and to ensure that the same age-adjustment standards are used when comparing different populations. Second, prostate cancer is extremely prevalent on autopsy, with close to 80 % of 80-year olds harboring the disease. Thus, reported prostate cancer incidence rates are highly sensitive to screening as well as other health care phenomena that result in histologic evaluation of prostate tissue (i.e., transurethral resection of the prostate for benign prostatic hyperplasia). PSA screening is not universally supported or implemented across the globe (or even the USA), with developing countries showing drastically lower penetrance of

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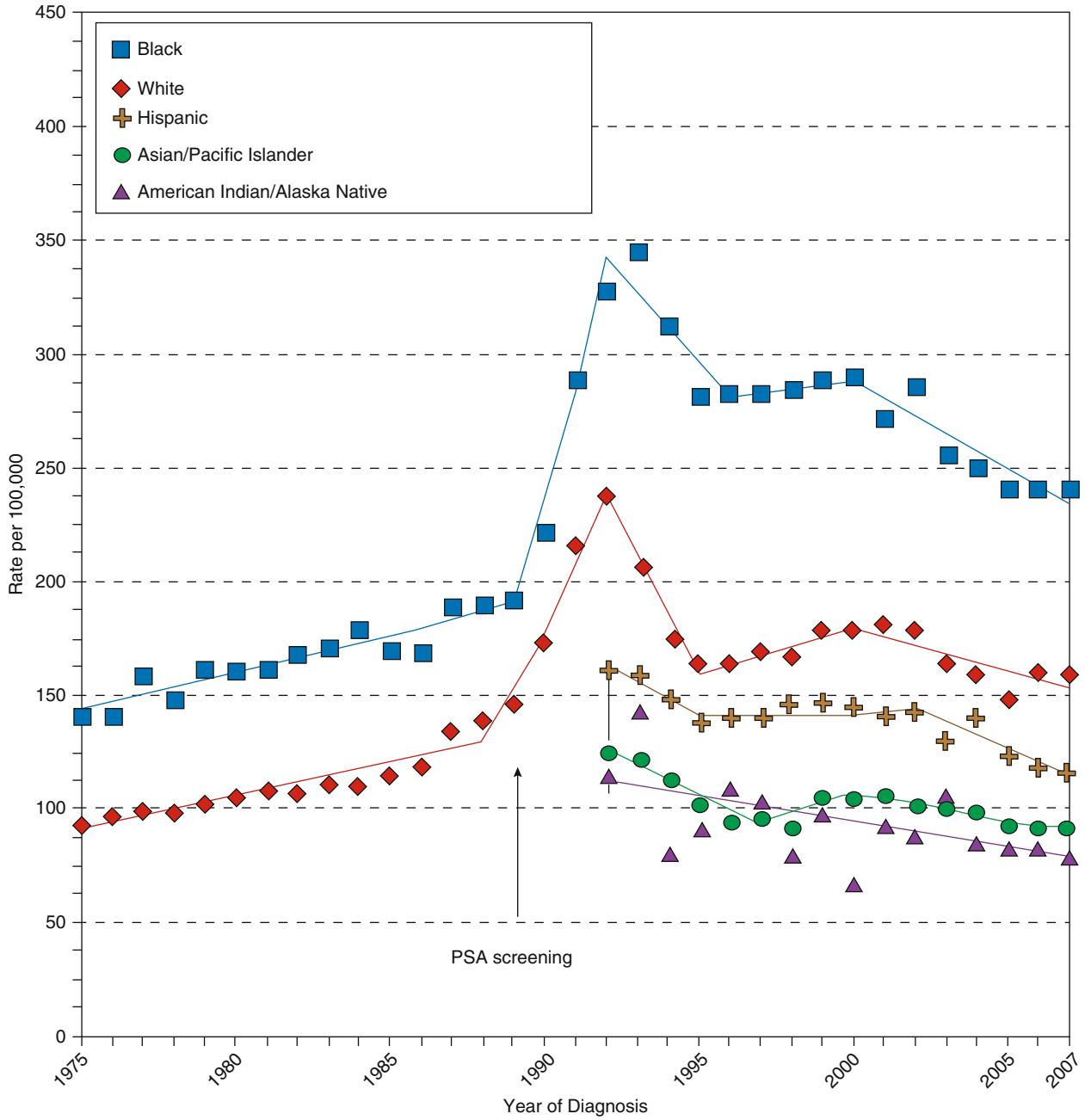


**Fig. 24.1** SEER incidence by race

PSA screening as well as other health care technologies including transrectal ultrasound and biopsy, pathologic evaluation, and surgical treatment of BPH. As these practices are adopted in developing countries, the incidence of prostate cancer (and likely, mortality attributed to prostate cancer) will undoubtedly rise. Finally, race/ethnicity is often a patient-reported attribute and is based more on cultural than biologic characteristics. While self-reported race/ethnicity may be appropriate for studies investigating the effects of cultural differences and barriers to care, it may not provide the resolution necessary to compare genetic variables in cancer outcomes [1]. These caveats must be kept in mind when attempting to glean meaningful and accurate inferences from the relevant literature [2].

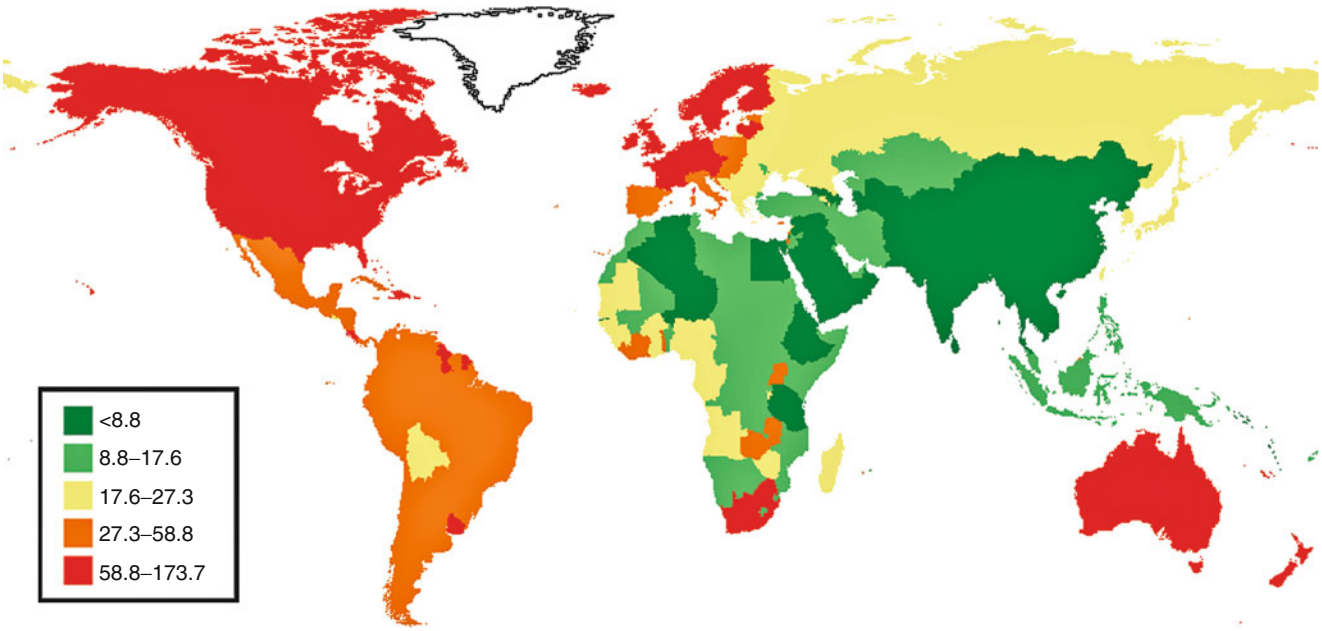


**Fig. 24.2** Worldwide incidence

## Epidemiology

### Overall Incidence

According to data from the United States National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database, it is estimated that 217,730 men will be diagnosed with and 32,050 men will die of prostate cancer in 2010 [3]. (For more details on overall prostate cancer epidemiology, see Chap. 20). Between 2003 and 2007, the total age-adjusted incidence rate was 157 per 100,000 men/year. However, there were significant differences between races with AAM showing the highest yearly incidence (235 per 100,000 men), EAM and Hispanics showing intermediate incidence (150.4 and 126 per 100,000 men, respectively), and Asians and American Indians showing the lowest incidence (90 and 78 per 100,000 men, respectively) (see Fig. 24.1).

The incidence of prostate cancer on the global scale varies widely and is highly affected by implementation of health care resources and epidemiologic resources as mentioned above [4]. While it is widely accepted that Asian countries have comparatively low rates (>10 per 100,000 men/year) and western/developed countries have higher rates (over 100 per 100,000 men/year), the actual incidence in developing countries in general, and Sub-Saharan African countries in particular has been difficult to accurately ascertain (Fig. 24.2) [5]. PSA screening, prostate biopsy, and TURP for BPH in these populations is comparatively low, as is general knowledge about prostate cancer [6, 7]. Incidence and mortality have been increasing in many African countries including Uganda and Nigeria, with rates now approaching those of AAM in some cases [8, 9]. While authors have postulated that this is due to a "Westernization" of lifestyle and associated dietary/environmental exposures, others have posited that it represents a combination of increased access to care, "Westernization" of health care (i.e., more TURP for BPH), and increased sensitivity of cancer registries, all in a population at high baseline risk [10]. While reliable data from Africa are relatively few, recent studies have found high incidence and mortality rates in populations of West-African decent on multiple continents and suggested a residual genetic link from the Transatlantic Slave Trade to explain the apparent racial disparity [10, 11].

### Mortality

In the United States, AAM die of prostate cancer more frequently than other races/ethnicities. According to the SEER database [3], the overall age-adjusted prostate cancer-specific death rate was 25 per 100,000 men/year, with rates for AAM higher than average (54 per 100,000 men/year), rates for EAM, American Indians, and Hispanics close to

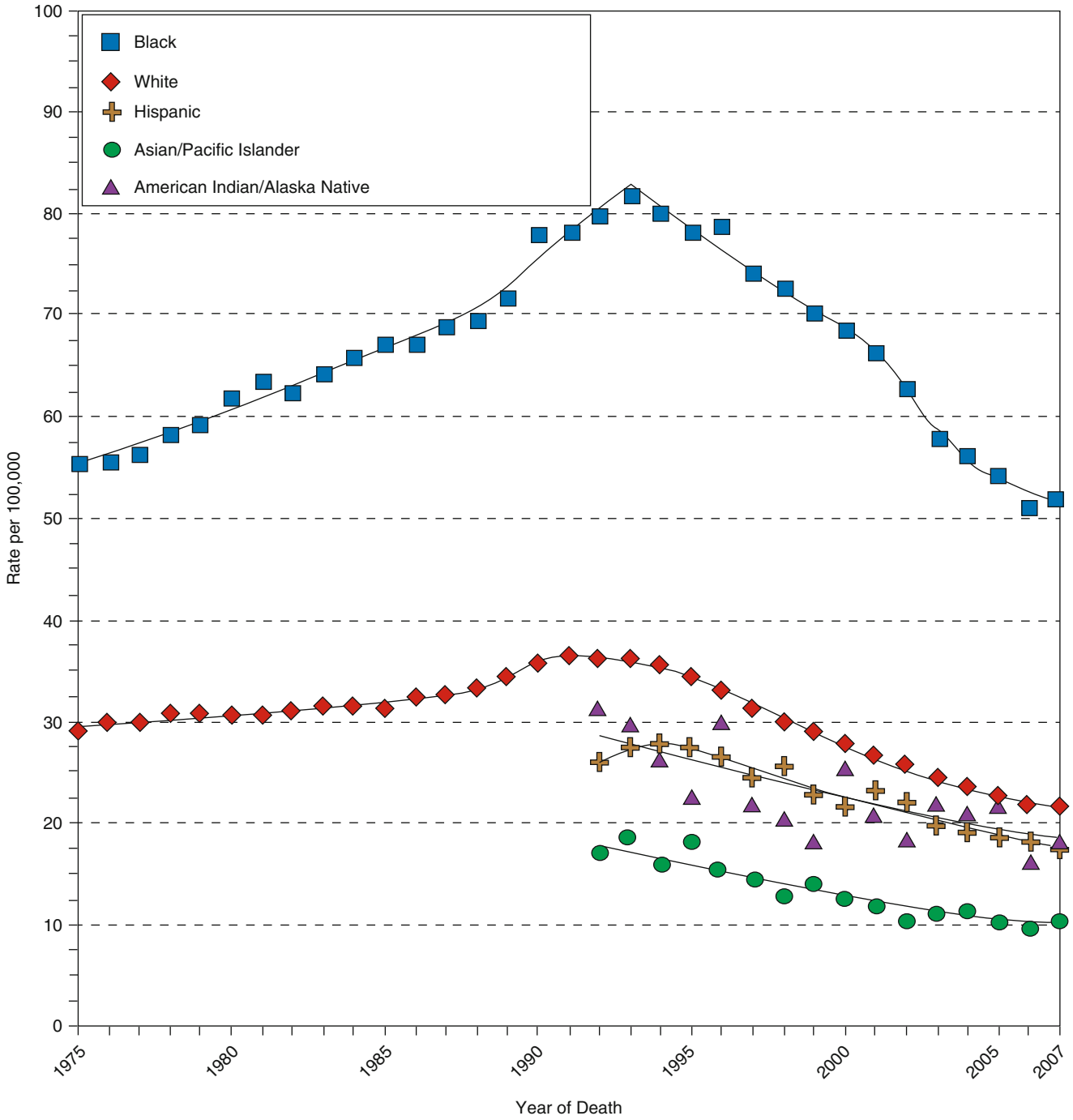


**Fig. 24.3** SEER mortality by race

average (23, 20, 19 per 100,000 men/year, respectively), and rates for Asian Americans lower than average (11 per 100,000 men/year) (Fig. 24.3).

These US racial and ethnic mortality trends are also reflected on the global scale with Asian countries showing relatively low prostate cancer-specific mortality rates (>5 per 100,000 men/year), and Sub-Saharan African countries showing higher mortality rates (~30 per 100,000 men/year), although the data from developing countries should be interpreted with caution (Fig. 24.4) [5]. Mortality remains highest in Scandinavian countries. It should be noted, however, that US and global data use different age-standards; thus, the point estimates between the two databases are not directly comparable.

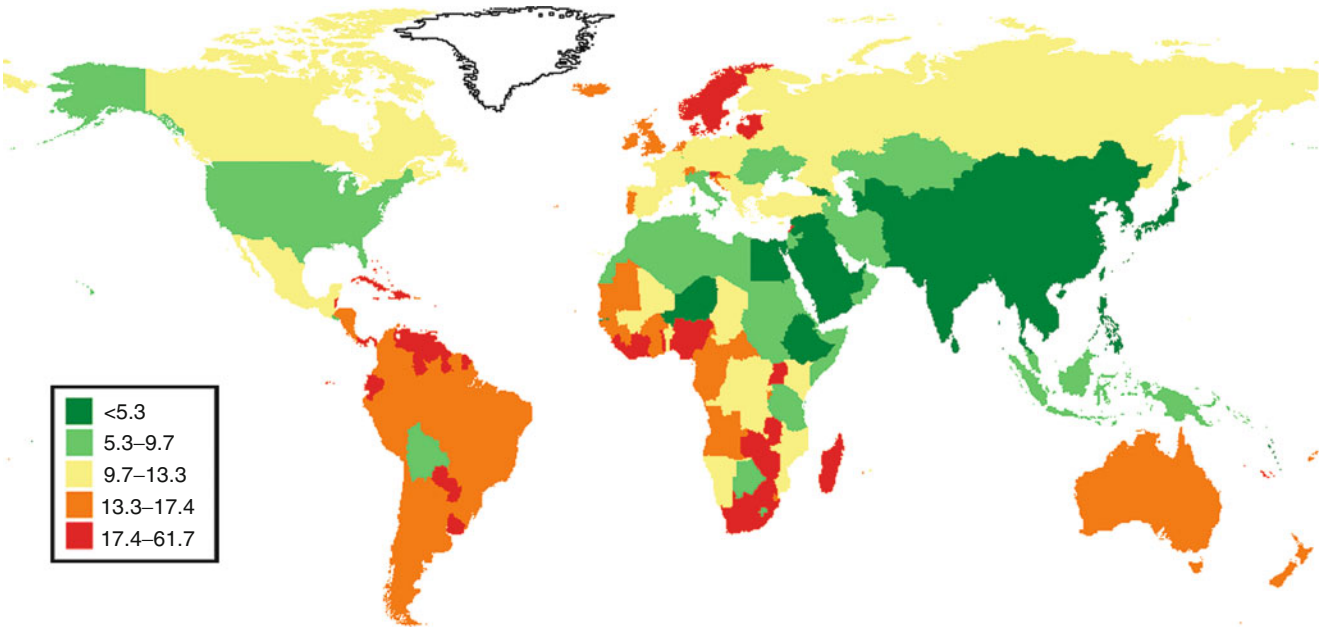


**Fig. 24.4** Worldwide mortality

## Trends in Incidence and Mortality

Importantly, these disparities are changing over time, and the gaps of both incidence and mortality between AAM and EAM appear to be narrowing since 1992, when the gaps were at their widest. When compared to 1975, however, the disparities have not changed. The exact causes of these observed trends are not entirely clear, but are likely due to a combination of factors including increased utilization of PSA screening, more effective treatment modalities, and perhaps changes in other-cause mortality in these populations. Whether the gap will continue to narrow, or will return to pre-PSA levels is debatable and requires further research.

Incidence rates in Sub-Saharan Africa are increasing with rates in Uganda rising 4.5 % annually between 1992 and 2005. This is likely due to changing access to care and increasing sophistication of medical care and cancer surveillance [12]. In fact, a similar pattern is seen across the globe where rates in developing countries are increasing and mortality rates in most developed countries are slowly decreasing [13].

## Prevalence, Disease Presentation, and Intermediate Outcomes

Autopsy studies have shown that the baseline prevalence of prostate cancer is quite high (31 % in fourth decade of life, increasing to over 80 % in the eighth decade) but is not different between AAM and EAM [14, 15]. In fact, even worldwide autopsy series have found similar prevalence rates between populations with very different incidence and mortality rates [16]. Despite this baseline similarity in prevalence, AAM have historically presented with higher tumor stage [17–19], higher grade [20–22], and a higher PSA level at diagnosis, although these differences at presentation appear to be diminishing in the last 10 years [23, 24]. Interestingly, in the UK, when compared to white men, black men only have higher PSA levels and show no difference in disease stage or grade [25]. Finally, when receiving treatment with curative intent for locoregional disease, AAM have higher recurrence rates and earlier failure after radical prostatectomy even after controlling for stage, grade, and PSA at diagnosis [26–29]. However, a separate study evaluating the influence of stage, age, and year of diagnosis suggested that these results are highly dependent upon the stage migration due to PSA screening, and that differences between black and white men over age 70 had disappeared by the late 1990s [24, 30].

## Potential Explanatory Variables for Observed Disparities

What differences between AAM and EAM can explain these differences in prostate cancer incidence and mortality? Are they sociologic, biologic, or both? If sociologic, are they due to behaviors/circumstances of the patients, behaviors/circumstances of the physicians and workup, or some combination? If biologic, are they environmental, genetic, or both? The remainder of this chapter will address these questions.

## Socioeconomic Factors and Patterns of Care

Access to care may play a central role in explaining part of these disparities, and many studies have attempted to control for socioeconomic status to evaluate the impact of this confounding variable, with varying results [19, 26, 31–38]. In fact, a recent systematic review and meta-analysis evaluating all of the studies that controlled for clinical predictors and socioeconomic variables found that while there was no longer a difference in overall survival, AAM still had increased risk of prostate-specific mortality and biochemical recurrence [39]. Other studies have been performed in "equal access" settings, with older studies showing differences between races, and more recent studies showing fewer differences [20, 40–43].

The processes of screening, diagnosis, and therapy for prostate cancer provide many opportunities for variations in care that may mediate observed differences in outcome between different population subgroups. The patterns of care between men of different races have been extensively investigated, with particular attention to PSA screening rates and choice of definitive therapy. In the early 1990s, various studies showed that EAM were significantly more likely to receive PSA screening than AAM, but this difference had essentially disappeared by the early 2000s [44–46]. In fact, in response to practice guidelines recommending AAM screening starting in the fifth decade of life, vastly more young AAM are screened by PSA [46]. However, the extent of mortality benefit due to PSA screening remains a contentious issue, and the effect of this closing screening gap, if significant, is unlikely to manifest itself until 10–15 years later. Furthermore, AAM showed higher prostate cancer incidence rates before and after PSA screening [3], suggesting that much of the mortality disparities historically cannot be attributed solely to screening differences. However, to the extent that black men truly have more aggressive disease, one might speculate that this group may experience a comparatively greater benefit from early detection through screening. Unfortunately, two large randomized controlled trials did not have the statistical power to address this question specifically for the subgroup of AAM [47, 48].

One group of investigators described that once elevated PSA levels are found, AAM are also less likely to undergo an ultrasound-guided biopsy than are EAM at all time points [49]. Data on treatment selection following diagnosis have been somewhat mixed. Multiple studies have documented treatment differences between EAM and AAM, with AAM less likely to undergo curative treatment for clinically locoregional disease [22, 43, 50–59]. In a few reports, these differences disappeared when controlling for age and poverty [31], or stage and grade [22]. Interestingly, in an "equal access" setting, the age-adjusted rate of radical prostatectomy for AAM in the VA system between 1998 and 2003 was nearly double that of EAM at all time points [49].

While the possibility of provider discrimination to explain these discrepancies has not been formally evaluated, patient behaviors have shown some differences. Some studies have pointed to access to care and educational differences between races/ethnicities [32]. Others have found that AAM are "well aware of their risk," and that the main barriers to diagnosis arose from "constrained opportunities for health care access and utilization, lack of long-term primary care, and reduced trust in physicians" [60]. This is likely reflected in an increased PSA screening interval which may result in later diagnosis of more advanced disease in AAM older than 65 [61, 62].

In summary, while the debate over the exact contribution of socioeconomic factors and patterns of care to disparities in prostate cancer outcomes remains contentious, there is good evidence to support that they play *some* role. Access to care and patient education is a major issue and should be attempted to be improved across all races/ethnicities, and the possibility that PSA screening and follow-up could preferentially aid AAM is a provocative but unproven concept. More research is needed to more accurately understand these effects, particularly with regard to choice of curative treatment between AAM patients and their physicians.

## Biologic Factors

Due to the inability of many retrospective trials to assign all of the increased prostate cancer risk of AAM to socioeconomic/behavioral factors, much work has been done to investigate the role of biology in determining this apparent elevated risk, with many studies illuminating potentially relevant biologic differences between men of different races and ethnicities that may explain some of the observed disparities.

### Androgen Axis

Since the pioneering work of Huggins and Hodges, prostate cancer has been understood to be exquisitely androgen-sensitive. In this context, many studies have evaluated various aspects of the androgen axis between AAM and EAM. Among college-age men, AAM have testosterone levels that are 15 % higher than EAM; however, this difference has not been found in older populations [63–67]. AAM have also been found to have differences in the gene encoding 5-alpha reductase, which could result in increased prostatic levels of dihydrotestosterone in AAM [68, 69]. Perhaps most convincing, androgen receptor (AR) expression is 21 % higher in benign prostates and 81 % higher in cancerous prostates of AAM versus EAM. ARs with shorter polyglutamine repeats are more highly expressed and bind testosterone and its metabolites with greater affinity. Interestingly, the length of polyglutamine repeats vary consistently among races/ethnicities and are inversely proportional to their overall prostate cancer risk [13, 70, 71]. If AAM truly have increased

activity in the androgen axis, they should theoretically be more sensitive to androgen blockade. However, there was no increased magnitude of 5 alpha reductase inhibitor prevention observed among black men in the PCPT or REDUCE randomized controlled trials, although these trials were not adequately powered to detect small differences in this subgroup (only 2 % of participants were AAM) [72, 73].

While the significance of the results of each of these studies individually may be debatable, the preponderance of the data clearly points toward an increase in androgen activity in AAM and may explain at least part of the higher incidence, PSA at diagnosis, HGPIN on autopsy, and mortality in these men. The recent elucidation of the role of androgen-sensitive topoisomerase-mediated DNA double strand breaks, and the resulting androgen-responsive TMPRSS2:ETS fusion genes in prostate cancer raises the interesting possibility of racial/ethnic differences in susceptibility to the molecular ramifications of this genetic rearrangement [74]. Early studies are finding some differences with Japanese men showing lower rates of rearrangements, but larger studies and longer follow-up will be needed to fully understand the contribution of these differences to prostate cancer incidence and mortality disparities [75–77].

## Diet and Environmental Factors

Migration studies have provided some insight that some of the geographic risk of prostate cancer may be environmental. In a study comparing Japanese-American immigrants to native Japanese men, Shimizu et al. found that immigrants had increased prostate cancer risk, but that their risk did not become equivalent to that of AAM or EAM [78–81]. The authors postulated that this increased risk is due to exposure to carcinogenic substances in the USA, either through diet or the environment, but could not exclude the contribution of differential health care practices between the populations (PSA screening, prostate biopsy, and TURP for BPH, etc.) [82].

Ecologic data reveal that the Asian and American diets are very different, with Asians consuming, on average, more fiber and soy protein and less saturated fats [83]. (The epidemiologic evidence of dietary risk factors for prostate cancer is reviewed in Chap. 20.) A number of epidemiologic studies have implicated diet in prostate cancer risk, especially a high intake of saturated fat, red meat, and dairy products [84–86]. In fact, differences in dietary fat are thought to account for approximately 10 % of the difference of prostate cancer incidence between AAM and EAM [87]. Specifically, omega-6 fatty acids are thought to act as promoters of prostate cancer while omega-3 fatty acids are thought to be protective, and the typical diet of AAM has been shown to contain the highest overall saturated fat and omega-6 fatty acid content in the world [88, 89].

Alternatively, increased dietary fat in AAM may simply be a surrogate for the conferred risk of obesity in prostate cancer. Obese prostate cancer patients present at younger ages, with higher Gleason grades and more advanced stages. AAM are more obese than EAM, which may explain some degree of their elevated risk [90, 91]. While the biologic processes underlying this observed association are not yet firmly established, obesity has been associated with hormonal alterations that may promote prostate carcinogenesis [90]. In particular, abdominal obesity is associated with lower levels of insulin-like growth factor-binding protein (IGFBP), resulting in higher levels of free IGF-1, a growth factor strongly implicated in prostate cancer growth. AAM have been shown to have lower IGFBP and higher concentrations of IGF-1 than EAM [92–94].

Finally, because AAM have darker skin pigmentation and because men at higher latitudes have the highest prostate cancer risk, it was postulated that vitamin D levels may be protective for prostate cancer. While the slim majority of studies have found lower vitamin D levels in AAM, especially at higher latitudes, other large cohort studies have failed to find racial differences in plasma vitamin D levels or associations with prostate cancer risk [95, 96]. Some authors have suggested vitamin D supplementation as a strategy to prevent prostate cancer, especially in high-risk populations such as AAM at high latitudes, though this strategy remains to be tested in large prospective trials [97].

### Conclusions

Prostate cancer incidence and mortality differences between ethnicities in the USA and across the globe are heavily influenced by health care utilization patterns, and are likely the result of a combination of environmental and genetic factors. However, the narrowing gap in mortality between AAM and EAM suggests that some of this disparity may be abrogated by continuing to increase access to care. It has been postulated that because of their higher risk, AAMs may receive the greatest benefit from PSA screening, and that efforts to aggressively screen this population will yield benefit regardless of biologic cause. Unfortunately, large randomized trials evaluating the efficacy of PSA screening have not shown racial-group-specific differences, perhaps because of insufficient statistical power [47, 48].

While it is hoped that the historical gaps of prostate cancer incidence and mortality between AAM and EAM will continue to narrow and perhaps close completely, most believe that the underlying bases for these disparities are complex and multifactorial, still exist, and remain incompletely addressed. Improving access to care remains an important and potentially actionable goal, and efforts should continue to understand and improve prostate cancer knowledge and quality of care in AAM. At the same time, further study investigating the molecular

susceptibilities of prostate cancer in AAM may ultimately result in a refined understanding of the biologic basis of prostate cancer which could lead to more accurate risk-stratification, and in turn, less over-testing and overtreatment in all men.

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# Natural History of Prostate Cancer

25

Nicholas J. Hegarty and Paul K. Hegarty

*For a patient with prostate cancer, if treatment for cure is necessary, is it possible?*

*Dr. Willet Whitmore Jr.*

## Introduction

The natural history of prostate cancer raises many questions as to the appropriate approach to diagnosis and treatment. While it remains one of the leading causes of cancer death, clinicians and patients are keen to limit the morbidity of treatment to those likely to benefit from it.

Prostate cancer is the most frequently diagnosed cancer and the most frequent cause of cancer-related death in men. In the USA, it accounts for nearly 30 % of all newly diagnosed male cancers with an estimated 240,000 men being diagnosed with prostate cancer in 2011. The lifetime incidence of prostate cancer is 30 % [1], with 10 and 15 years survival of 91 and 76 %, respectively [2]. Much of the increase in incidence and improved survival of prostate cancer over the past decades have often been attributed to prostate cancer screening and early detection. Definitive evidence supporting this relationship is, however, still awaited with alternative explanations such as improved treatment at advanced stages that could lower prostate cancer mortality.

## Establishing a Baseline: How Common Is Prostate Cancer?

The incidence of prostate cancer increases dramatically with age, rising from 1 in 10,000 in men <40 to 1 in 8 in those >80 (Fig. 25.1) [3]. Thus, in comparing incidences between countries, it is important to account for differences in life expectancy. The age-standardized worldwide incidence and mortality of prostate cancer are shown in Fig. 25.2. A very clear difference in incidence is seen between more and less developed regions of the world [4]. Certainly, differences in healthcare systems, public and physician awareness, and availability of screening contribute to this, while environmental and dietary factors have also been implicated. Prostate cancer incidence increases in populations who move from areas of low incidence to high-incidence areas, demonstrating an increase in incidence approaching that of their new location: increasing incidence is seen when Japanese migrate from their native country (low incidence) to Hawaii, with a further increase with migration to US mainland [5]. The amount of time spent in the new host country is also a factor with immigrant Chinese having a threefold greater incidence of prostate cancer if they have spent more than 25 years in the USA, compared to those who have spent less than 25 years [6].

Another limitation in determining the incidence of prostate cancer is that diagnosis is typically restricted to those in whom the diagnosis is suspected. In the Prostate Cancer Prevention Trial (PCPT), 15 % of men with "normal" PSA (<4 ng/mL) had prostate cancer [7]. These were diagnosed on the basis of sextant biopsy, which for many years was considered the standard. The introduction of additional lateral biopsies to TRUS biopsy protocols increased the detection rates of prostate cancer further. Saturation biopsies, by both the transrectal and transperineal routes, lead to higher yields [8], with 3D mapping strategies suggesting that better characterization may be made between significant and low-volume cancers [9].

A more in-depth analysis of the incidence of "histologic" prostate cancer is estimated by post-mortem findings. In looking at a predominantly African American population, Sakr et al. [10] showed foci prostate cancer in 27 % of men aged 30–39 and 34 % of men in their 40s. Similar findings are seen in international studies – in comparing the prevalence of microscopic disease with clinically detected prostate cancer in West Africa and in African Americans, Jackson

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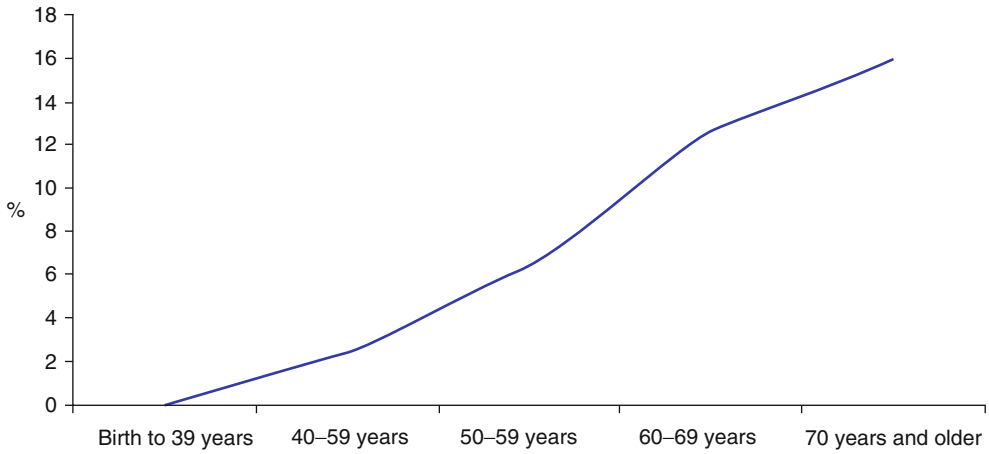


**Fig. 25.1** Probability of developing prostate cancer in different age groups (Jemal et al. [3])

et al. showed comparable incidence of microscopic disease, though a tenfold greater detection of clinical cancer in the American cohort [11].

What these studies have confirmed is that screening has led to the problems of overdiagnosis and overtreatment. It has been estimated that 1.3 million extra patients have received "unnecessary" treatments for prostate cancer since the introduction of PSA 3 decades ago [12]. In an attempt to clarify those needing treatment, a number of definitions of clinically significant or insignificant prostate cancer have been proposed. These generally include details as to clinical stage, tumor grade, and tumor volume.

Perhaps the most widely used is that proposed by Epstein et al. [13] who define clinically insignificant disease as:

Tumor volume < 0.5 mL

No Gleason grade 4 or 5 disease

PSA density > 0.15

The presence of less than 3 mm of tissue in a single needle core (Epstein et al. [13])

Using this definition of insignificant disease, Lucia et al. [14] explored the relationship between PSA and significant cancer in the Prostate Cancer Prevention Trial (PCPT). Among cancers detected, a little over half the subjects with PSA 1.0 ng/mL or less had an insignificant cancer, approximately one-third of those with a PSA between 1.1 and 2.5 ng/mL, falling to 17.8 % in those with PSA between 2.6 and 4.0 ng/mL, and 11.7 % in subjects with PSA between 4.1 and 10 ng/mL. In this setting, PSA can be seen to perform well in predicting significant disease at higher levels, though the majority of subjects with cancer and a "normal" PSA still harbor significant disease.

## Disease Progression

Much of what we know of the natural history of prostate cancer comes from longitudinal population studies prior to the introduction of PSA. Rates of progression of disease have consistently been shown to be dependent on prostate cancer grade. Chodak et al. [15] reported 10-year progression in 17 % of patients with low-grade disease increasing to 74 % in poorly differentiated cancer (Fig. 25.3) [15, 17]. Mortality is also related to cancer grade. Overall 15-year prostate-cancer-specific mortality is of the order of 20 % [16]. Studies from Albertson and Johansson [17, 18] report 6 % cancer-specific mortality at 15 years in low-grade disease rising to between 56 and 86 % in patients initially diagnosed with Gleason 8–10 disease (Fig. 25.4).

More recent data from the Prostate Intervention Versus Observation Trial (PIVOT) reported the mortality from prostate cancer at median of 9 years of 8.4 % in the observation group compared to 5.8 % in those undergoing following radical retropubic prostatectomy. The biggest difference was seen in those with high-grade disease where the operated group had an 8.4 % absolute reduction in prostate cancer mortality compared to the observation group [19].

## Natural History in the PSA Era

The emergence of PSA as a screening tool in the 1980s has impacted dramatically on the field of prostate cancer. An almost fourfold greater rate of decline in age-adjusted prostate cancer mortality was observed in the USA (where screening has been far more prevalent) compared to the UK where the uptake of PSA has been less widespread in the last two decades [20]. Improvements in survival in recent years must be interpreted with caution as PSA is thought to increase the lead time for prostate cancer between 5 and 11 years [21]. It was hoped for many years that the true value of PSA screening might come from large prospective randomized screening studies. The Prostate Lung Colorectal and Ovary (PLCO) Screening Trial looked at 76,693 men randomized to either annual screening (38,343 subjects) or nonscreening arms (38,350 subjects) between 1993 and 2001. After 7–10 years

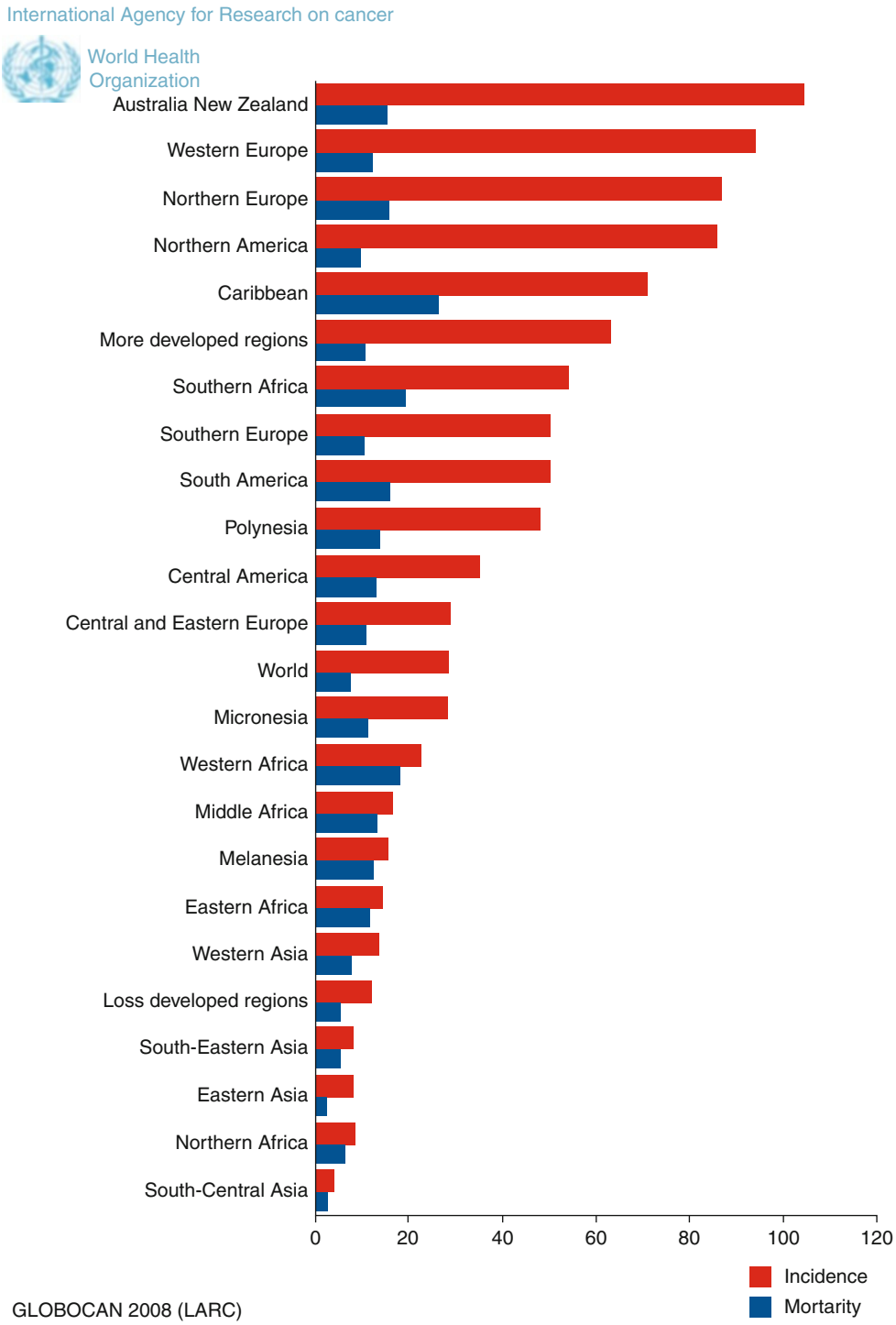


**Fig. 25.2** Estimated age-standardized rates (World) per 100,000 (WHO) [27]

follow-up, no conclusive benefit was seen to prostate cancer screening in terms of prostate cancer mortality. Mortality rates were low in both screened and nonscreened groups, and many in the nonscreening arm had PSA measurements performed leading to difficulty in interpreting the results [22]. The European Randomized Study of Screening for Prostate Cancer (ERSPC) looked at 182,000 men between ages of 54 and 74 years, with a core group of 162,243 between the ages of 55 and 69 years receiving more detailed study. Subjects were randomized to receive PSA screening on average once every 4 years or no PSA screening, with a median follow-up of 9 years. Contamination of the nonscreened group by PSA testing outside of the study was less of an issue than was seen in the PLCO, with the screened population showing a 20 % reduction in prostate-cancer-specific mortality. The number

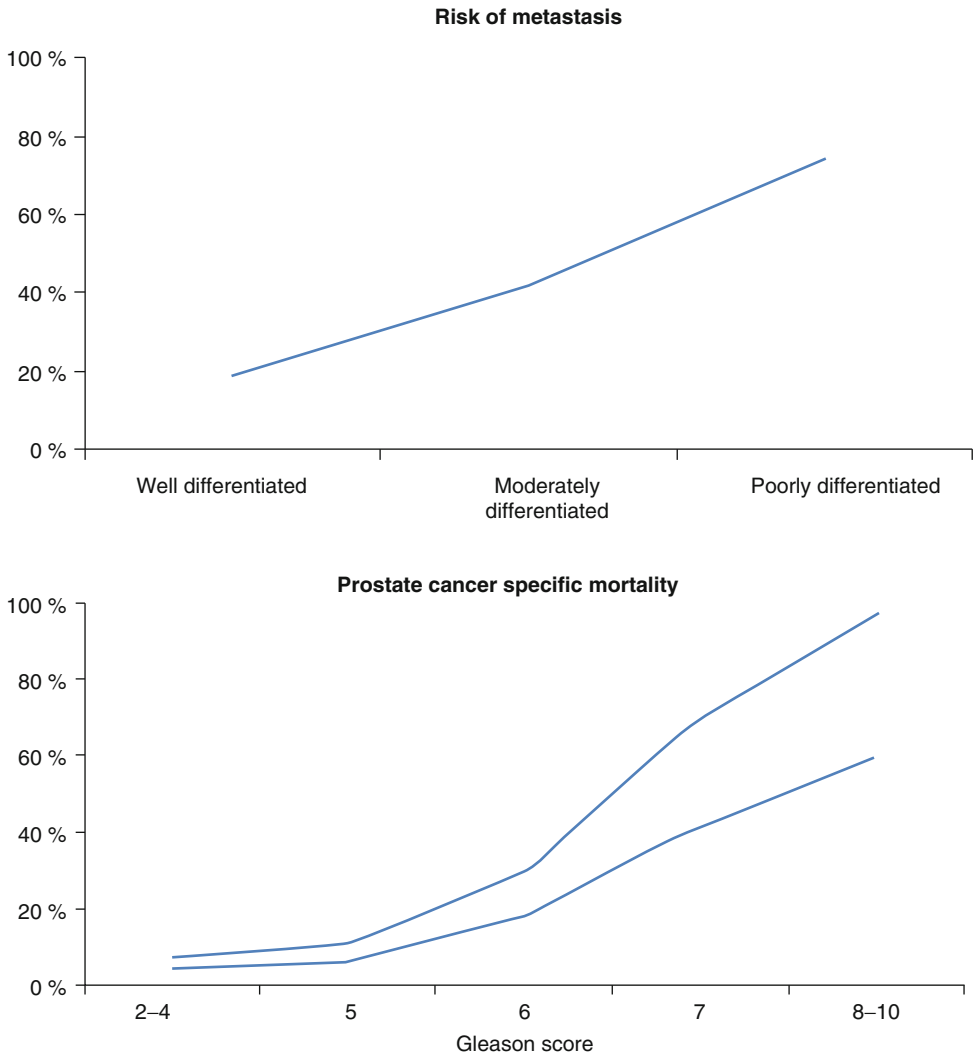


**Fig. 25.3** (**a**) Ten-year risk of developing metastases in men diagnosed with prostate cancer (Chodak et al. [15]). (**b**) Albertsen 15-year data [17]

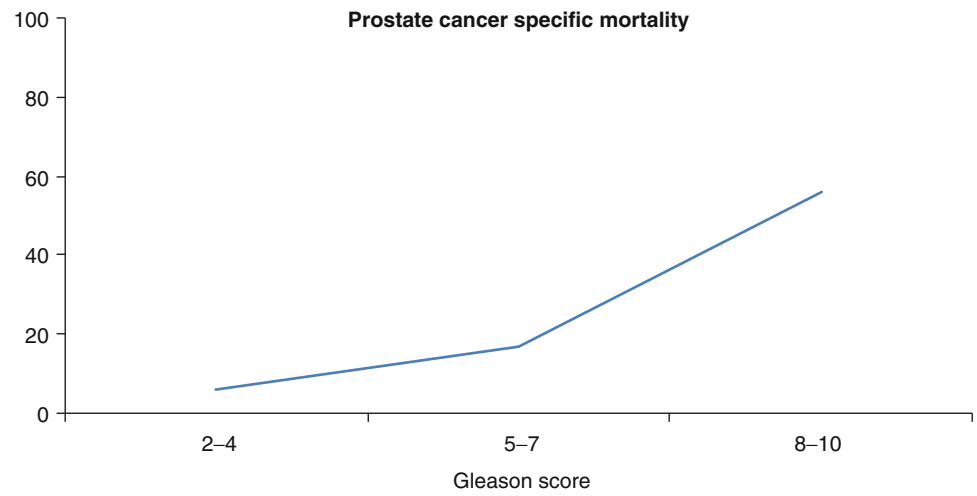


**Fig. 25.4** The 15-year cancer-specific mortality for men diagnosed with prostate cancer (Johansson et al. [18])

needed to screen on initial review was 1,410 and with an extra 48 cases requiring treatment to prevent one death from prostate cancer at 9-year median follow-up. The number needed to treat to prevent metastasis was lower at 24, suggesting smaller screening numbers will be required to achieve benefit with more prolonged follow-up [23].

## Natural History Following Treatment

An advantage of radical prostatectomy over radiation and other ablative treatments is that accurate pathological staging can be achieved. Combining this information with patient follow-up, several predictive algorithms have been constructed. Eggener developed a model derived from four institutions where 11,521 were treated by radical prostatectomy between 1987 and 2005 [24]. This was then validated using data from 12,389 patients from a separate institution treated over the same interval. Following radical prostatectomy, the 15-year cancer-specific mortality was 7 %. High-grade cancer (primary or secondary Gleason grade of 4 or 5), seminal vesicle involvement, and the year in which RRP was performed were all predictive for mortality. For those men with organ-confined disease with a Gleason score of 6 or less, only 3 of 9,557 (0.031 %) died of prostate cancer. Similar studies have been performed with radiotherapy cohorts, though histology is based on pretreatment biopsy rather than the final surgical specimen.

## Natural History of Biochemical Relapse (BCR)

PSA recurrence following radical prostatectomy is cause for worry for patient and physician alike. However, PSA recurrence is not necessarily a harbinger of inevitable disease progression. Pound et al. looked at a cohort of men who underwent RRP for localized disease at the Johns Hopkins Hospital between 1982 and 1997 by a single surgeon. Of the 1997 men operated, 315 (15 %) had BCR during a median follow-up of 5.3 years. Thirty-four percent of these men with BCR developed metastasis. In this group, the actuarial interval between PSA rise and development of metastasis was 8 years, and the time between metastasis and death was 5 years. Thus, for the 34 % of men who will progress, the time between BCR and death is an estimated 13 years [25].

A more recent retrospective review of 14,632 men who underwent radical prostatectomy between 1990 and 2006 at the Mayo Clinic identified 2,462 men (16.8 %) with BCR [26]. This series had very few node-positive cases, as they tended to receive early adjuvant treatment and were thus excluded from the cohort. Overall, 5.8 % of those with BCR died of prostate cancer during follow-up period (median 11.5 years). In this study period, the median progression-free survival and cancer-specific survival had not been reached. The 15-year cancer-specific survival following BCR was estimated to be 83.6 %. Factors that were predictive of death from prostate cancer were greater age, higher Gleason grade, higher stage, and rapid PSA doubling time. Of note, patients who received salvage therapy did not seem to have improved survival, in the retrospective study.

## Summary

Understanding the natural history of prostate cancer is fundamental to decisions on treatment in individual patients and recommendations with regard to screening and diagnosis of potentially curative cancers. The histological incidence greatly exceeds the proportion of individuals who will manifest overt disease, and while there has always been a desire not to misdiagnose those harboring cancer within the prostate, there has also been increasing focus on identifying patients who might be considered for surveillance. The introduction of PSA has impacted greatly on detection rates and our overall understanding of prostate cancer. Since its introduction, a stage migration has been observed with an increase in the proportion of patients presenting with early stage disease. Whether this has translated into an overall improvement in prostate survival remains controversial. Following a dramatic rise in the detection of prostate cancer and a brief increase in prostate cancer mortality rates in the 1990s, a reduction in prostate-cancer-specific mortality was then observed. This has been sustained with prolonged follow-up. The ERSPC appears to confirm that screening can reduce prostate cancer mortality. In confirmed cases, cancer-specific survival decreases from low- to intermediate- to high-grade cancer. The relatively low cancer-specific death rates seen in low-grade cancer mean that survival benefits from curative treatment strategies with medium-term follow-up have been modest at best. More definite benefit is seen in patients with high-grade disease who undergo surgery. Postoperative PSA testing remains important in determining the oncological outcome following treatment. Biochemical recurrence following surgery was thought to be synonymous with treatment failure. Almost two-thirds of patients with BCR however will show no evidence of disease progression. Median survival in those that progress is reported as 13 years.

Our knowledge of prostate cancer continues to evolve as we observe a continued increase in incidence with reducing mortality. PSA level and tumor grade remain two of the most important indicators of significant prostate cancer, the likelihood of progression, and the need for curative treatment. Improved imaging and better markers of disease progression have long been awaited, and it is hoped that these will facilitate the dilemma of avoiding or deferring cure in those that do not need it while not denying treatment to those who possess potentially lethal disease.

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# Population-based Health Systems as a Foundation for Prostate Cancer Control Research: The Cancer Research Network

26

Mark C. Hornbrook and Joan Holup

## Health Systems as Research Laboratories

This chapter describes the rationale and opportunities for collaborating with the Cancer Research Network (CRN) on prostate cancer research—prevention, screening, treatment, survivorship care, and end-of-life care. The CRN represents a consortium of population-based integrated health care delivery systems operating largely under capitation payment from a wide range of public and private payers. As such, their motivation for collaborating on prostate cancer research stems from a desire to improve the evidence base for prostate cancer prevention and treatment while providing affordable health care to prostate cancer patients and survivors. Prostate cancer is the leading cancer among men. Its incidence, at 156.9 per 100,000 males, is nearly twice as high as the second leading cancer for men, lung/bronchus, at 80.5 cases per 100,000 (see Fig. 26.1). These health plans view public-domain research as desirable because it stimulates critical thinking about the evidence foundations for clinical and managerial decisions among their clinicians and managers, contributes to advancing health care technology, and helps fulfill their social missions (a requirement for tax-exempt status). Defined representative populations, accountable care organizations, extensive informatics systems, and public-domain research programs represent the CRN's strategic assets. This chapter provides an overview of how these assets are pertinent to building research collaborations with the CRN. This chapter will also highlight the comparative advantages of integrated delivery systems as research laboratories serving multiple stakeholders—patients and families, physicians and other clinical professions, public and private purchasers, pharmaceutical firms, radiotherapy device manufacturers, health administrators and policymakers, and researchers. This chapter aims to strengthen the CRN's prostate cancer research program and facilitate translating research findings into clinical practice and improving patient well-being.

## Founding the Cancer Research Network

In 1997, the National Cancer Institute (NCI) announced a competition for funding [2] "to encourage the expansion of collaborative cancer research among health care provider organizations." NCI recognized that the only readily available automated data on cancer care came from the linkage of Surveillance, Epidemiology, and End Results (SEER) tumor registry data with Medicare claims data. The SEER-Medicare data link, however, excludes people under age 65 years unless they are disabled, has limited data for individuals enrolled in Medicare Advantage plans, does not permit direct contact with patients or providers, and lacks detailed data on cancer treatments. This realization foreshadowed later efforts to involve community-based health care organizations in research, primarily to support the translation and dissemination of findings into the delivery system [3]. The original CRN Request for Applications defined the desired health care provider organizations as being "oriented to community care, hav[ing] access to large, stable and diverse patient populations and able to take advantage of existing integrated data-bases that can provide patient-level information" [2]. Systems involved in the CRN meet these criteria in large part because they are integrated health care delivery systems. Specifically, CRN systems incorporate clinicians, care facilities, and insurance components into a system that facilitates coordinated delivery of a full range of health care services with explicit quality and cost management controls. These systems also emphasize preventive care and chronic disease management to improve long-term health outcomes and overall patient well-being. Member institutions of the HMO Research Network [4] collaboratively submitted a successful

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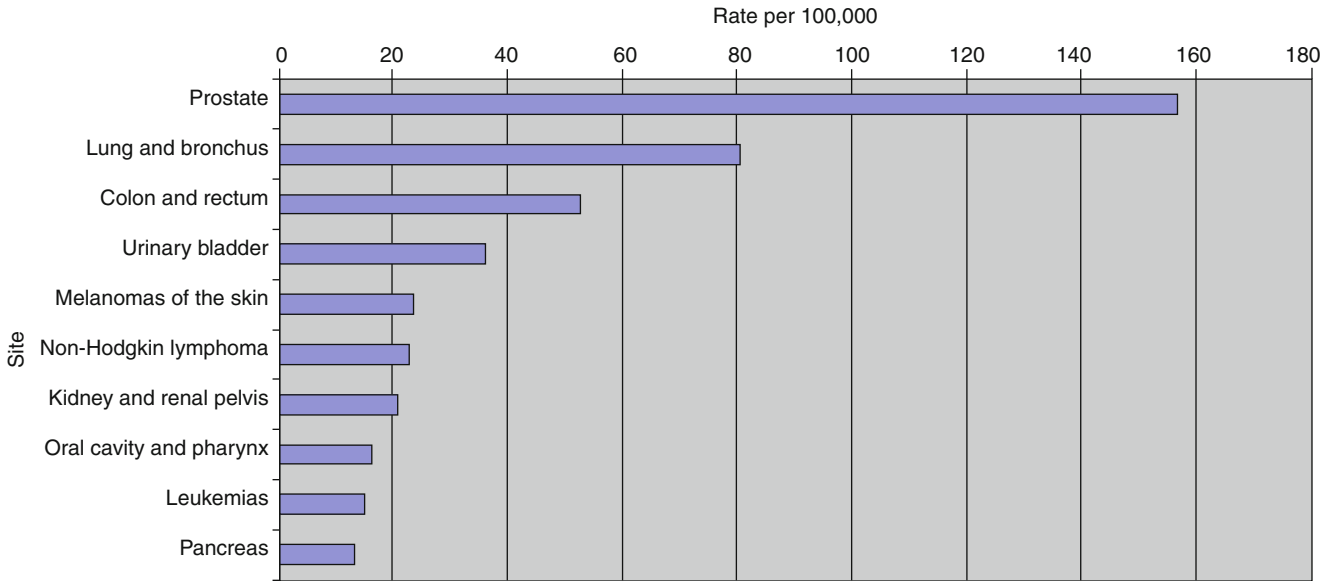


**Fig. 26.1** Age-adjusted invasive cancer incidence rates for the ten primary sites with the highest rates, males, all races, 2007( Source: Centers for Disease Control and Prevention [1])

application, resulting in the 1999 formation of the CRN. The CRN was granted a Certificate of Confidentiality from NIH to protect CRN research data from Freedom of Information Act disclosure requests. This step was essential for obtaining cooperation from participating medical groups in research on the effectiveness of cancer screening programs, especially determination of rates of missed diagnoses when cancer screening test results were reanalyzed [5].

The CRN has reapplied successfully for funding. The most recent funding announcement, [6] *Funding Opportunity Announcement, RFA-CA-11-502, would continue the network's funding until 2017*. The CRN has been funded through an NCI cooperative agreement that ensures substantial NCI involvement in attaining research goals and catalyzing new collaborations. AHRQ became a cosponsor of the CRN in 2003, which invokes the Agency's statutory protections on data collected for the purposes of research from being used for nonresearch purposes (such as malpractice case finding). The CRN is planning for continued operations into the future.

## CRN Setting and Structure

### Participating Health Systems

The CRN has included these integrated health care delivery systems and their associated research centers: Fallon Community Health Plan/Meyers Primary Care Institute (MPCI), Geisinger Health System/Geisinger Center for Health Research (GHS), Group Health/Group Health Research Institute (GH), Harvard Pilgrim Health Care/Harvard Medical School Department of Population Medicine (HPHC), HealthPartners/HealthPartners Research Foundation (HPRF), Henry Ford Hospital and Health System/Health Alliance Plan/Department of Biostatistics and Research Epidemiology and Center for Health Services Research (HFHS), Kaiser Permanente Colorado/Institute for Health Research (KPCO), Kaiser Permanente Georgia/The Center for Health Research-Southeast (KPG), Kaiser Permanente Hawaii/The Center for Health Research-Hawaii (KPH), Kaiser Permanente Northern California/Division of Research (KPNC), Kaiser Permanente Northwest/The Center for Health Research-Northwest (KPNW), Kaiser Permanente Southern California/Department of Research and Evaluation (KPSC), Lovelace Clinic Foundation Research (LCFR), and Marshfield Clinic Security Health Plan/Marshfield Clinic Research Foundation (MCRF). Figure 26.2 illustrates the CRN's geographic range. The CRN has been described more extensively elsewhere [7]. Collectively, these organizations provide care to diverse population of nearly 11 million individuals, possess extensive automated data, and employ scientists conducting research in the public domain [2, 8].

The CRN member systems include a variety of types of health systems, including group and network HMOs, independent practice associations, consumer-directed self-insured health plans, high-deductible health plans, and point-of-service option plans. This variety of arrangements reflects historical precedents as well as health plans' response to marketing opportunities. Kaiser Permanente represents a national-group-model HMO, as contrasted with the Henry

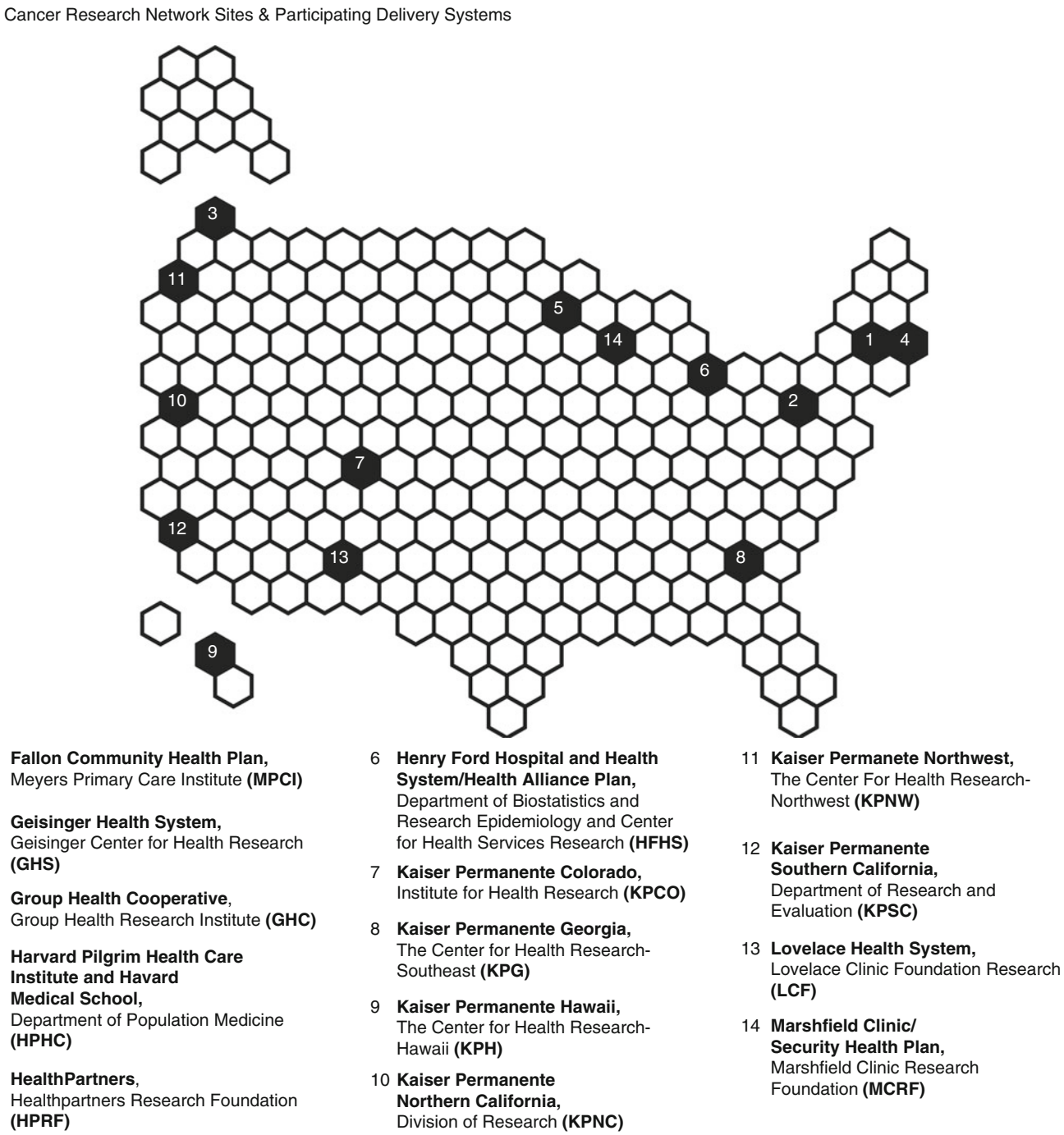


**Fig. 26.2** Sites and participating health care delivery systems that have been part of the CRN

Ford Health System Health Alliance Plan, an HMO insurance product that is offered by the Henry Ford Medical Group alongside its dominant fee-for-service system. CRN health plans offer a variety of benefit options that change with each open enrollment season in response to competitive pressures in the CRN members' markets. This means that consumers in CRN plans face varying out-of-pocket costs for health care services over time, which provides natural experiments on the effects of out-of-pocket costs on access to and use of medical care, including prostate cancer screening services. Clinicians in CRN plans also face varying financial incentives in making treatment decisions for their patients depending on their remuneration/reimbursement systems and the financial status of their health plans and medical groups. Key characteristics of the CRN members are highlighted in Table 26.1.

**Table 26.1** Cancer Research Network health systems—key characteristics relevant to prostate cancer research

| Characteristics | Fallon | GH | GHS | HPHC | HPRF | HFHS | KPCO | KPG | KPH | KPNC | KPNW | KPSC | LCRF | MCRF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total enrollment, in thousands | 171 | 540 | 267 | 805 | 620 | 295 | 462 | 286 | 225 | 3,260 | 487 | 3,190 | 240 | 175 |
| Members enrolled in integrated system, % | 53 | 80 | 28 | 20 | 64 | 65 | 100 | 90 | 100 | 100 | 100 | 100 | 90 | 85 |
| Retention of 2000 cohort, % | | | | | | | | | | | | | | |
| 1 year | 95 | 80 | 78 | 79[a] | 77 | 84 | 83 | 87 | 85 | 87 | 82 | 85 | 85 | 88 |
| 3 years | 92 | 63 | 55 | 55 | 57 | 68 | 66 | 67 | 72 | 75 | 66 | 71 | N/A | 73 |
| 5 years | 92 | 51 | 42 | N/A | 44 | 56 | 56 | 54 | 63 | 66 | 57 | 61 | N/A | 68 |
| Age, years | | | | | | | | | | | | | | |
| ≤24 | 29 | 30 | 26 | 33 | 36 | 30 | 30 | 32 | 32 | 30 | 31 | 34 | 34 | 31 |
| 25–64 | 53 | 57 | 54 | 60 | 56 | 57 | 56 | 61 | 57 | 56 | 57 | 54 | 54 | 50 |
| ≥65 | 18 | 13 | 20 | 7 | 8 | 13 | 14 | 7 | 11 | 14 | 12 | 12 | 12 | 19 |
| *Female*, % | 51 | 53 | 50 | 52 | 52 | 55 | 53 | 52 | 51 | 52 | 52 | 53 | 52 | 53 |
| Race/ethnicity, % | | | | | | | | | | | | | | |
| African American | 2 | 3 | <1 | 16 | 6 | 28 | 6 | 33 | <1 | 8 | 3 | 8 | 1 | <1 |
| Asian American | 3 | 6 | <1 | 5 | 5 | 2 | 2 | <1 | 63 | 17 | 5 | 10 | 1 | <1 |
| Latino/a | 8 | 4 | 1.4 | 4 | 4 | 1 | 15 | <1 | 3 | 19 | 6 | 41 | 38 | <1 |
| White | 87 | 82 | 96 | 75 | 85 | 67 | 75 | 63 | 25 | 51 | 84 | 38 | 55 | 97 |
| Other/unknown | <1 | 5 | 1 | <1 | <1 | 2 | 2 | 4 | 9 | 5 | 2 | 3 | 5 | <1 |
| Research center established | 1996 | 1983 | 2003 | 1969 | 1989 | 1987 | 1987 | 1988 | 1991 | 1961 | 1964 | 1975 | 1990 | 1959 |
| Research affiliation with NCI-designated Cancer Center | No | Yes | Yes | Yes | Yes | No | Yes | No | IP | No | Yes | IP | No | IP |
| Data resources, first year available | | | | | | | | | | | | | | |
| Cancer registry | N/A | 1974 | 1951 | 1982 | N/A | 1972 | 1987 | 2004 | 1973 | 1973 | 1960 | 1988 | 1999 | 1960 |
| Membership tracking | 1987 | 1988 | 1982 | 1969 | 1990 | 1980 | 1992 | 1995 | 1998 | 1970 | 1982 | 1988 | 1991 | 1986 |
| Electronic medical record | 2006 | 2005 | 1995 | 1969 | 2004 | 1988 | 1997 | 2006 | 2001 | 2005 | 1997 | 2006 | N/A | 1994 |
| Outpatient visit claims | 1987 | 1992 | 1993 | 1969 | 1990 | 1988 | 1992 | 1995 | 1995 | 1994 | 1987 | 1993 | 1999 | 1991 |
| Hospitalization claims | 1987 | 1979 | 1993 | 1990 | 1990 | 1989 | 1991 | 1995 | 1988 | 1979 | 1965 | 1981 | 1999 | 1991 |
| Pharmacy claims | 1987 | 1977 | 1985 | 1988 | 1990 | 1992 | 1993 | 1995 | 1992 | 1993 | 1986 | 1992 | 1999 | 1992 |
| Deaths | N/A | 1972 | 2006 | 1979 | N/A | 1990 | 1988 | 1995 | 1992 | N/A | 1979 | 1988 | N/A | 1992 |
| Oncologists within system[b] | 10 | 13 | 19 adult 3 peds | 8 | 9 | 38 | 6 | N/A | 6 | 83 | 12 | 81 | N/A | N/A |

Adapted from Wagner et al. [7]

*N/A* not available, *IP* in process, *Fallon* Fallon Health Care System, *GH* Group Health, *GHS* Geisinger Health System, *HPHC* Harvard Pilgrim Health Care, *HPRF* HealthPartners Research Foundation, *HFHS* Henry Ford Health System/Health Alliance Plan, *KPCO* Kaiser Permanente Colorado, *KPG* Kaiser Permanente Georgia, *KPH* Kaiser Permanente Hawaii, *KPNC* Kaiser Permanente Northern California, *KPNW* Kaiser Permanente Northwest, *KPSC* Kaiser Permanente Southern California, *LCRF* LCR Foundation, *MCRF* Marshfield Clinic Research Foundation

[a]HPHC = retention for 2002

[b]Includes adult and pediatric gynecologic, medical, radiation, and surgical oncologists, as of 2001

All systems participating in the CRN have research centers akin to academic departments in that they conduct research in the public domain, rely on external funding to support their studies, and disseminate their results through peer-reviewed publications. Professionally autonomous scientists within the centers have substantial expertise about their health care delivery system's patients, providers, scope of services, facilities, and informatics systems. These scientists lead their own studies and also actively collaborate with scientists from other institutions.

To support collaborative cancer research and help meet the CRN's goals, several systems have formal affiliations with NCI-designated Cancer Centers [8]. Many of the CRN systems also participate in clinical trials through national cooperative groups and the Community Clinical Oncology Program.

## Population Diversity

As of this writing, the systems fully involved in the CRN provide care for approximately 11 million people in the United States [8]. The cumulative population within the CRN has substantial age, gender, socioeconomic, racial, and ethnic diversity. Health plans with Medicaid risk contracts and contracts with state-subsidized health insurance risk pools have greater representation of lower socioeconomic status groups, which tend to have greater racial and ethnic diversity. The CRN cumulative population is similar with regard to gender and age distribution and has a higher portion of racial/ethnic minorities than the USA as a whole [9]. As an example, Table 26.2 shows the high degree of similarity in the distributions of KPNW members and the Portland, Oregon, metropolitan area for 2010. One notable discrepancy is that Hispanics are somewhat underrepresented among KPNW members.

The CRN includes population centers with relatively higher percentages of African Americans (Henry Ford Hospital and Health System, Harvard Pilgrim Health Care, and Kaiser Permanente Georgia), Asian Americans (Kaiser Permanente Hawaii, Kaiser Permanente Northern California, and Kaiser Permanente Southern California), Hispanics (Lovelace Health System, Kaiser Permanente Southern California, Kaiser Permanente Northern California, and Kaiser Permanente Colorado), and rural and underserved rural populations (Geisinger Health System and Marshfield Clinic). Racial, ethnic, and socioeconomic diversity is an important strength of the CRN, which permits studies emphasizing effectiveness research focused on these subpopulations [8]. The CRN has analyzed disparities among these populations in health behaviors, treatments, and outcomes [11–21]. Many HMORN health plans also cover large populations of Medicare/Medicaid and uninsured persons, further enhancing representativeness. While it is true that integrated delivery systems are not present in every community, approximately one in four US residents is enrolled in a health maintenance organization [22]. The CRN also includes settings that share features with integrated delivery settings, such as the Veterans Health Administration and primary care networks organized around academic medical centers. Thus, the CRN provides an opportunity to study the impact of clinical questions for nearly all demographic groups and insurance relationships within a unified health services delivery and health information system framework.

**Table 26.2** Distribution of KPNW membership and Portland, Oregon metropolitan area by race and ethnicity, 2010

| Race/ethnicity | KPNW | Portland |
|---|---|---|
| White alone | 86.17 % | 87.49 % |
| Black alone | 2.94 % | 3.10 % |
| American Native | 0.79 % | 1.00 % |
| Asian alone | 4.65 % | 5.43 % |
| Pacific Islander | 0.45 % | 0.36 % |
| Multiple races | N/A | 2.60 % |
| Unknown | 5.00 % | 0.02 % |
| Total | 100.00 % | 100.00 % |
| Hispanic | 6.02 % | 10.50 % |

Sources: KPNW membership data and Statistical Abstract of the US [10]

## CRN Research

Originally conceived as a "population laboratory" centered in community-based health care systems, the CRN is able to harness these organizations' data and health informatics systems, as well as their clinical staff and enrolled populations to conduct research. This allows for large, multicenter, multidisciplinary observational and intervention [11, 17, 23] research that starts from the foundation of integrated health care delivery systems with defined populations and comprehensive health informatics systems. This unique position allows the CRN to measure complete episodes of the spectrum of cancer control and care in support of studies of prevention [11, 13, 17, 23–30], early detection [5, 16, 21, 30–45], treatment [19–21, 46–55], survivorship [56–60], surveillance [15, 21, 61, 62], secondary preventive care [13, 53–55, 58, 60, 63], and end-of-life care [14]. One study conducted at five CRN sites found the retention rate among survivors for all cancers combined at 1 and 5 years after cancer diagnosis was 96 and 84 %, respectively. This ample proportion of enrollees diagnosed with cancer who remained enrolled and available for evaluation suggests that the CRN is well suited for studies of the quality of care for cancer patients, survivorship, and long-term outcomes [23, 57].

The CRN is also uniquely positioned to conduct multisite studies in geographically diverse community-based settings [5, 19, 20, 28, 29, 31, 37, 38, 40, 48, 52, 54, 55, 58–60, 62–64].

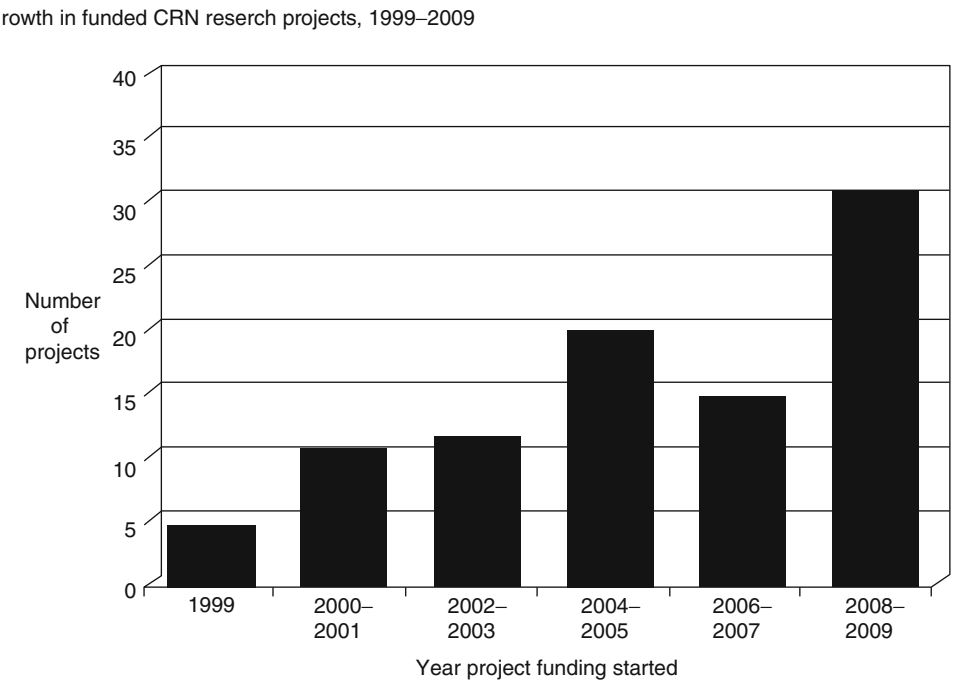


**Fig. 26.3** Growth in funded Cancer Research Network projects, 1999–2009

CRN research focuses on examining the characteristics of patients [14, 46, 59], clinicians [12, 13, 41, 45], and health care systems [37, 64, 65]. The CRN also develops and uses standardized approaches to data collection, data management, and analyses across health systems [66]. Since 1999, the CRN has conducted dozens of joint research projects and published over 200 peer-reviewed papers [8]. The number of funded CRN research projects has increased over time and reflects many successful efforts to address important cancer control questions in the CRN population laboratory (see Fig. 26.3). We hope this chapter stimulates growth in research collaborations focused on prostate cancer.

## CRN Data Systems

### Understanding CRN Data

All health systems have automated databases containing information on membership and utilization claims for outpatient visits, hospitalizations, surgical procedures, imaging, laboratory tests, pharmacy, home health, hospice, and durable medical equipment. These databases feed the Virtual Data Warehouse [66]. All but one health system have implemented an electronic medical record, most using the EpicCare™ system. All CRN research centers have developed procedures for collecting death certificate data for all individuals who have ever been members. Cancer registries and many other types of automated data can be analyzed independently of other information [20, 47, 57, 67, 68] or used in conjunction with other types of data [19, 46, 52, 53, 55, 59, 60, 62, 69–72]. The CRN has experience with many data collection modalities, including data extraction from medical records [5, 18, 19, 21, 24, 27, 29, 31–36, 38, 40, 42, 43, 47–55, 57, 62, 63, 66, 73], natural language processing of chart text [27, 74], online patient surveys [17], surveys of patients by mail [12, 26, 28, 58–60] and phone [37, 46], and physician surveys [12, 13, 41, 45].

The CRN's Virtual Data Warehouse (VDW) comprises a set of data-extraction programs at each CRN system that translate health care delivery system data from unique local data into a common format across the CRN, along with data-quality checks and documentation. The VDW increases study efficiency by facilitating access to data elements commonly used in research studies. VDW data-quality checks include comparisons of relationships among variables across health systems (e.g., inpatient days per 1,000 members by age and gender) to detect aberrant patterns, which in turn define a focus for investigation of potential data entry and processing errors.

Developing the VDW makes it appear that CRN data are relatively easy to use and interpret. It is not possible, however, to capture and summarize all of the information required to fully understand CRN data in the data dictionary. The essential reason for this disparity is that health plans are continually modifying their organizational structures, processes of care, contracting practices, and informatics systems.

An electronic medical record (EMR) system, for example, is updated multiple times annually, and each update incorporates new variables, tables, and functions and may eliminate some variables. The data systems reflect the dynamic nature of health care—from new technologies (new drugs, new surgical techniques, new imaging techniques, new genetic tests, new imaging modalities) to cost containment efforts (changes in health insurance eligibility, premium increases, changes in benefits, changes in facility staffing).

A major asset of the CRN is the sophisticated medical informatics systems supported by the health plans. These systems convey a comparative advantage for conducting clinical trials and biospecimen research, enable epidemiologic and health services research, and support translational research. With approval of health systems and their IRBs, research can be conducted using limited data sets without individual patient consent when projects are judged by the IRB to carry minimal risk to human subjects. The key components of the data systems are described below.

### Tumor Registries

Cancer registries are in place at most of the CRN's participating systems. CRN health systems have established procedures to capture new cancer diagnoses and assemble the data required by state tumor registries. Nearly all CRN health systems either operate or have access to a SEER (http://seer.cancer.gov/), State, or accredited internal tumor registry that covers all their enrolled members. Accredited tumor registries represent the preferred procedure for identifying cancer cases due to standardized definitions and medical record abstraction procedures. The National Association of Accredited Cancer Registries conducts regular accreditation reviews to enforce high data-quality standards (http://www.naaccr.org/). Tumor registries provide rigorous outcome measures for prostate cancer prevention and screening research (e.g., was an elevated PSA screening test followed by a new tumor registry record), as well as rigorous case definitions for clinical trials and epidemiologic, genomic, and health services research. Prostate cancer diagnoses extracted from claims and encounter information systems do not represent research-quality data because they are influenced by payment rules, use billing clerks rather than tumor registrars to extract data from patient charts, and are not verified by tissue examinations. Ensuring comprehensive cancer reporting for CRN populations is complicated by outside and patient self-referrals related to cancers diagnosed by non-HMO providers and cancers diagnosed while not an active HMO enrollee. Most tumor registries will not release identified data on tumors not reported by the HMO. However, comparison of tumor data for KP Hawaii with the Hawaii SEER Tumor Registry for the period 2000–2008 revealed that only 1.22 % of KPH members had tumors that were not identified in the KPH tumor registry. This reveals the high membership stability among cancer patients in HMOs.

### Tumor Specimen Repositories

CRN oncology departments maintain tumor specimen repositories (paraffin blocks and tissue slides) for legal and research purposes. These repositories are indexed by tissue accession numbers, which are linked to patient-identifying information. The KPNW tissue repository has been operating for more than 30 years. These samples deteriorate over time and some samples are used up by various research studies. For the future, the CRN needs to determine the feasibility of converting hard-copy tumor repository accession lists into searchable relational databases.

### Enrollment and Demographics Information Systems

CRN health systems tie health insurance and health care delivery. As such, they have enrollment and eligibility information systems that provide comprehensive enumeration of every individual who is eligible (e.g., at risk) for covered services. This enables population-based epidemiologic studies (incidence of prostate cancer) as well as studies of barriers to access and financial incentives related to copayments and travel time to care facilities for prostate cancer screening, treatment, and survivorship care. Residential address data enables geocoding to link census data and health care system attributes to describe the neighborhood context of prostate cancer patients. One potential research question is whether neighborhood housing and individual housing status is associated with prostate cancer risk, age at diagnosis, and tumor aggressiveness, operating through mediating factors such as diet, physical activity, and genetic polymorphisms and whether these relationships differ by race (prostate cancer is much more prevalent among African-American men than White men).

### Encounter and Claims Data Systems

Encounter data systems describe the activities of hospitals, emergency departments, and medical offices. Claims data systems describe the professionals' and facilities' billing processes and insurer payments for medical care services. These data systems support measurement of prostate-related diagnoses, procedures, utilization events, and medical care expenses. The rules for assigning diagnoses to insurance claims are not the same as for tumor registries. For example, diagnoses on claims for imaging services can represent the reason for ordering the imaging service not the disease detected by the image; hence, diagnoses on imaging and laboratory procedure claims represent unknown mixes of rule-out diagnoses.

### Electronic Medical Records Systems

All CRN health systems have installed some form of an electronic medical record system (EMRs), with the most common vendor being EPIC, Inc. (Madison, WI). All sites are working to obtain meaningful use certification for their EMR systems from the DHHS Office of the National Coordinator for Health Information Technology as of this writing [75]. CRN research centers are working to develop data-extraction programs to collect expanded information on medical care processes from EMRs. For cancer research, perhaps the most important advance is development of medical oncology EMR interfaces that provide detailed information on chemotherapy protocols and actual dosages delivered to patients (as compared to supplies delivered from the oncology pharmacy). CRN sites have started work on extracting and standardizing chemotherapy treatment data. One potential research opportunity is evaluating whether oncology EMR systems lead to more standardization of chemotherapy regimens for prostate cancers.

### Laboratory Information Systems

Data on PSA test results are required for research on prostate cancer screening programs. The CRN has developed a standardized Laboratory Results data file that includes PSA testing results. These data are also required for research on prostate cancer recurrence. Laboratory tests include genetic testing procedures. Unfortunately, for research purposes, the technology of genetic/genomic testing is advancing so rapidly that the Health Care Procedure Coding Systems (HCPCS) listing used by CMS cannot keep up. The newest tests carry "miscellaneous" procedure codes until CMS updates the HCPCS to include these tests, which is unfortunately a multiyear lag. This is relevant for future research on introduction of tests to identify genetic markers of prostate cancer risks.

### Vital Signs

EMR systems encode vital signs data routinely collected in ambulatory care settings—weight, height, systolic and diastolic blood pressure, respiration, and body temperature. These data are useful for identifying patients with uncontrolled hypertension, obesity (body mass index), infections, and sudden unexplained weight loss. As hospitals are converted to EMR systems, vital signs will be available for inpatients as well.

### Medication Dispensing Information Systems

Most CRN health systems operate internal pharmacies as a means of managing quality of pharmaceutical services and care and of controlling total expenses for prescription drug benefits. Internal pharmacy departments, staffed with clinical pharmacologists, drug information specialists (PharmDs), and clinical pharmacists, manage the health system's formulary, negotiate medication purchases with drug manufacturers and wholesalers, develop evidence-based prescribing guidelines in collaboration with physicians, and interact with patients at the point of dispensing. Drug dispensing information systems provide data on all outpatient medications dispensed to prostate cancer patients. Such medication records are needed to assess care processes for these patients, including oral chemotherapy agents, oral medications to treat the side effects of chemotherapies and radiotherapies, and opiates for management of cancer pain. In the context of prostate cancer research, medication systems provide measures of androgen deprivation therapy (ADT) so that relationships of ADT to bone fractures, cardiovascular disease, and diabetes can be studied. Medication systems also support pharmacoepidemiologic studies of the relationships between long-term exposures to selected drugs and prostate cancer risk.

### Infusion Information Systems

A new informatics development in the CRN is infusion information systems that track outpatient chemotherapy protocols and sessions. This EMR module allows oncologists to preload chemotherapy protocols into an online directory, select a protocol for a patient, tailor it to the patient's clinical needs, and track actual timing and quantities of mediations administered. The infusion module supports the entire infusion team and their work flow—oncologist (writing medication orders), pharmacist (setting up infusion bags), and nurse (administering infusions). Kaiser Permanente has preloaded over 600 chemotherapy infusion protocols for oncology, rheumatology, and gastroenterology. CRN researchers have developed a standardized extract of the infusion data tables for research purposes. One goal is to improve use of evidence-based protocols but also to enable research on individual differences among patients in their toxic and allergic reactions to a prescribed protocol and the modification strategies implemented by medical oncologists.

### Imaging Information Systems

Data on imaging procedures—x-rays, ultrasound, computed tomography, magnetic resonance imaging, positron emission tomography, and other nuclear imaging—are needed for research on prostate cancer diagnostic work-ups and surveillance for progression and metastases. Patients who show chemical recurrence through elevated PSA values after initial cancer treatment are usually scanned to identify the specific locations of metastatic tumors, which is information required to formulate a treatment plan. The CRN has developed standardized data files to identify the performance of all imaging procedures. Future research can access digital imaging libraries to reinterpret these images and examine clinical decision criteria for interpreting patterns as cancer, metastatic lesions, or other abnormal tissue structures.

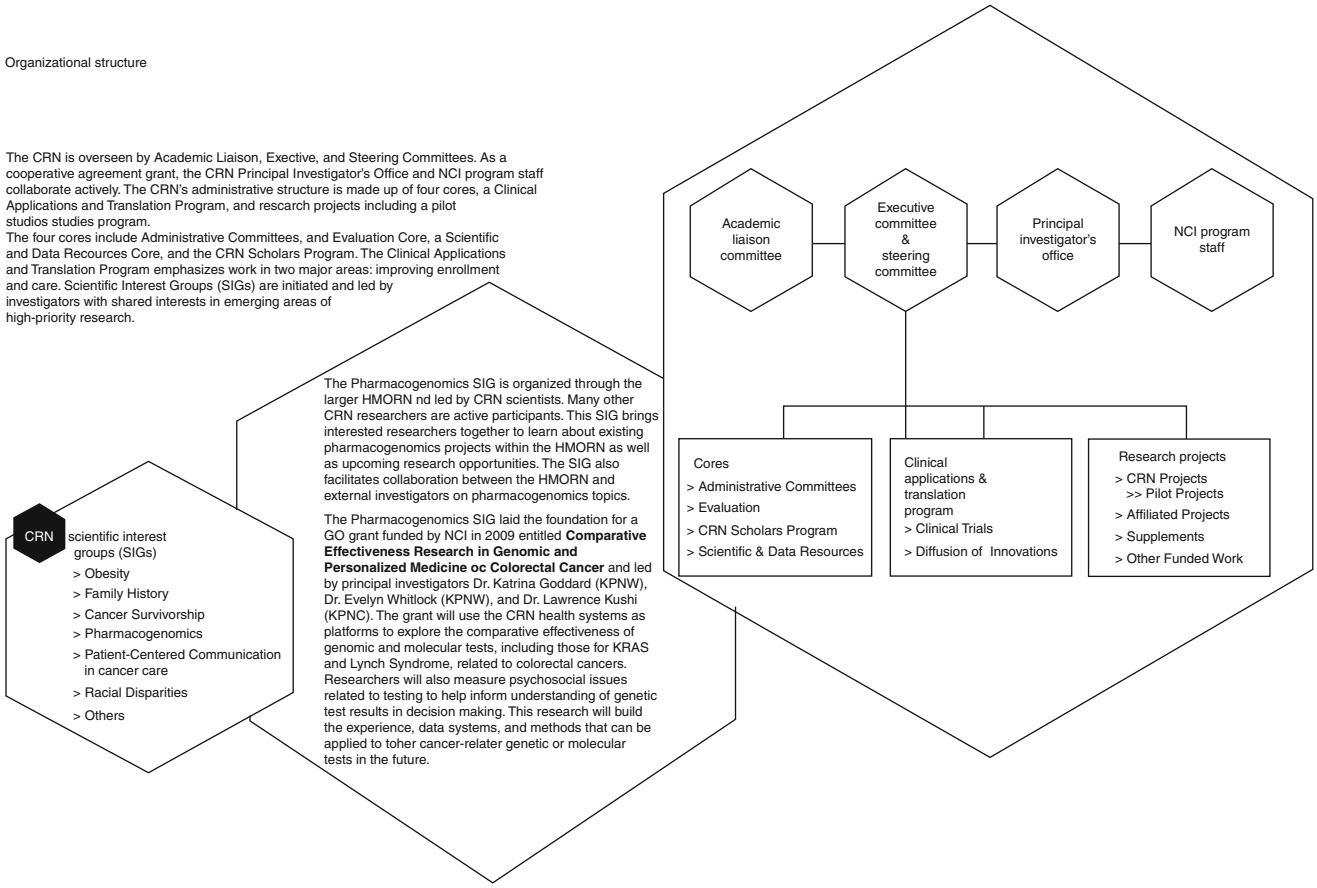


**Fig. 26.4** Organizational structure of the Cancer Research Network

### Home Health, Hospice, Palliative Care, and DME Information Systems

Prostate cancers are diagnosed throughout the last years of life. Hence, some patients will be institutionalized in long-term care facilities, terminally ill from another disease, or very frail with multiple chronic diseases. The CRN data systems enable tracking prostate cancer patients who require long-term and end-of-life care. A study of hospice use in CRN sites among men who were dying of prostate cancer revealed that the rate of hospice use exceeded 80 %, but the average length of stay in hospice was only 5 weeks [76].

## CRN Governance Structure

We provide a brief description of the CRN governance structure to illustrate the overall infrastructure that has been established to facilitate cancer research. This infrastructure supports collaborative research across multiple disciplines and CRN systems and other institutions and provides a foundation for future studies. A Steering Committee with representation from the NCI and each health system provides scientific and administrative leadership across the CRN. Four cores provide infrastructure. The Evaluation Core conducts an annual evaluation of CRN-wide and study-specific processes and productivity [77]. The Administrative Core includes three committees: a Communications and Collaboration Committee facilitates information exchange across systems and studies, and with researchers, advocates, and others outside the CRN; a New Proposals Committee ensures new proposals avoid overlap, are scientifically sound, and involve appropriate collaborators; and a Publications Committee encourages publications and presentations, advises studies on writing strategies and authorship issues, and verifies that submitted publications appropriately describe the CRN. The Scientific and Data Resources Core includes expertise in measurement, economics, and data and maintains the CRN's Virtual Data Warehouse [66]. The Research Training Core, known as the CRN Scholars Program, is designed to nurture and develop new talent through a 20-month training activity that helps junior investigators develop research independence [8]. Figure 26.4 provides a visual depiction of the CRN's organizational structure. This structure will likely change in response to the most recent NCI RFA issued to continue CRN funding.

## Developing Collaborations with the CRN

Scientists from all institutional affiliations are welcome to approach the CRN with ideas and are encouraged to allow ample time to establish collaborative relationships and design rigorous studies. Initial steps in this process include assessing whether an idea is well suited to the CRN, forming a partnership with at least one CRN-based scientist and submitting a concept proposal to the CRN New Proposals Committee. The process for external researchers who are interested in collaborating with the CRN is outlined in Fig. 26.5.

Developing collaborations with the CRN should begin early in the stages of formulating the research questions and specific aims. Inviting CRN scientists and sites to participate after funding has been obtained for a study is more likely to result in mutual disappointment because the project budget will not be adequate to cover the research costs. External investigators are not well-informed about the procedures and costs of conducting research in CRN environments. Early discussions of research questions enable full discovery of the needs for all parties to the collaboration as well as mutual understanding of the respective research priorities. The research questions that have the highest priority for health systems often diverge from the priorities developed by NIH. Thus, collaborations between academic and CRN scientists enable identification of translational research opportunities—why do observed patterns of practice diverge from current evidence standards; which evidence gaps carry the highest priority for practicing clinicians; which evidence gaps have the greatest impact on patient well-being.

## Nonconsented Versus Consented Data

Potential collaborators should be aware of a crucial distinction regarding properties of CRN data. Data that has been collected under express written consent from the patients included in the dataset are governed by the IRB-approved consent forms. As an example, it is possible to create public use microdata files on members of CRN health plans if each person contained in the files (or their power of attorney) has signed a consent form permitting use of their health information. However, one of the key strategic advantages of the CRN is the ability to use patient-level clinical data for legitimate minimal-risk research purposes when appropriate permissions have been obtained from IRBs and health plan officials. From a health plan perspective, patient-level data are proprietary because their commercial success depends on protecting their reputations. Therefore, access to CRN microdata requires a written research proposal (preferably peer reviewed), IRB approval, compliance with HIPAA regulations regarding PHI and data security, and approval from the participating health plans. All CRN members have well-established policies and procedures for obtaining these permissions. This is one reason we strongly recommend that CRN scientists be included on the investigator team of any collaborative research project.

## Human Subjects' Protections

The IRB system is a critical, but currently burdensome, part of the infrastructure to perform multicenter studies. Local IRBs feel simultaneous demands to review more clinical and translational research, but the requirements of federal regulations were not designed for multicenter studies. Several studies have looked at the problems arising from the review of multicenter projects by multiple IRBs. Greene and Geiger's review of challenges and strategies for IRB review of multicenter studies identified 46 key bibliographic sources for the review, including 40 peer-reviewed articles and 6 reports from commissions or advisory groups on this topic [78]. Recurring themes in the literature include delays and inconsistencies associated with multicenter reviews that result in questionable benefits but extract high-opportunity costs in terms of knowledge, time, and money [79]. To enable more efficient multisite research, the sites in the CRN recently adopted a model of facilitated IRB review, in which it is possible for a single site's IRB to serve as the IRB of record, and other participating study sites' IRBs can elect to cede to this "lead" IRB. The CRN is working to educate IRB chairs and members, as well as CRN scientists on the availability and desirability of the delegated IRB model.

## Clinical Trials

Nearly all CRN sites support cancer clinical trials research, and most are affiliated with national cancer clinical trials groups such as the Southwest Oncology Group, the Community Clinical Oncology Program, the Gynecologic Oncology Group, and the National Surgical Adjuvant Breast and Bowel Project. This means the presence of the following elements: (1) a formal administrative process for reviewing proposed clinical trial protocols for acceptability and implementability in the local setting; (2) a formal administrative process for obtaining IRB and HIPAA approvals for approved protocols; (3) electronic data systems covering the health plan membership to identify persons who are presumptively eligible for a specified protocol, which supports feasibility and desirability evaluations and enables direct recruitment of these persons, thereby reducing the costs of screening patients for trial eligibility; (4) trained research support staff to implement trial protocols, improve recruitment yields and

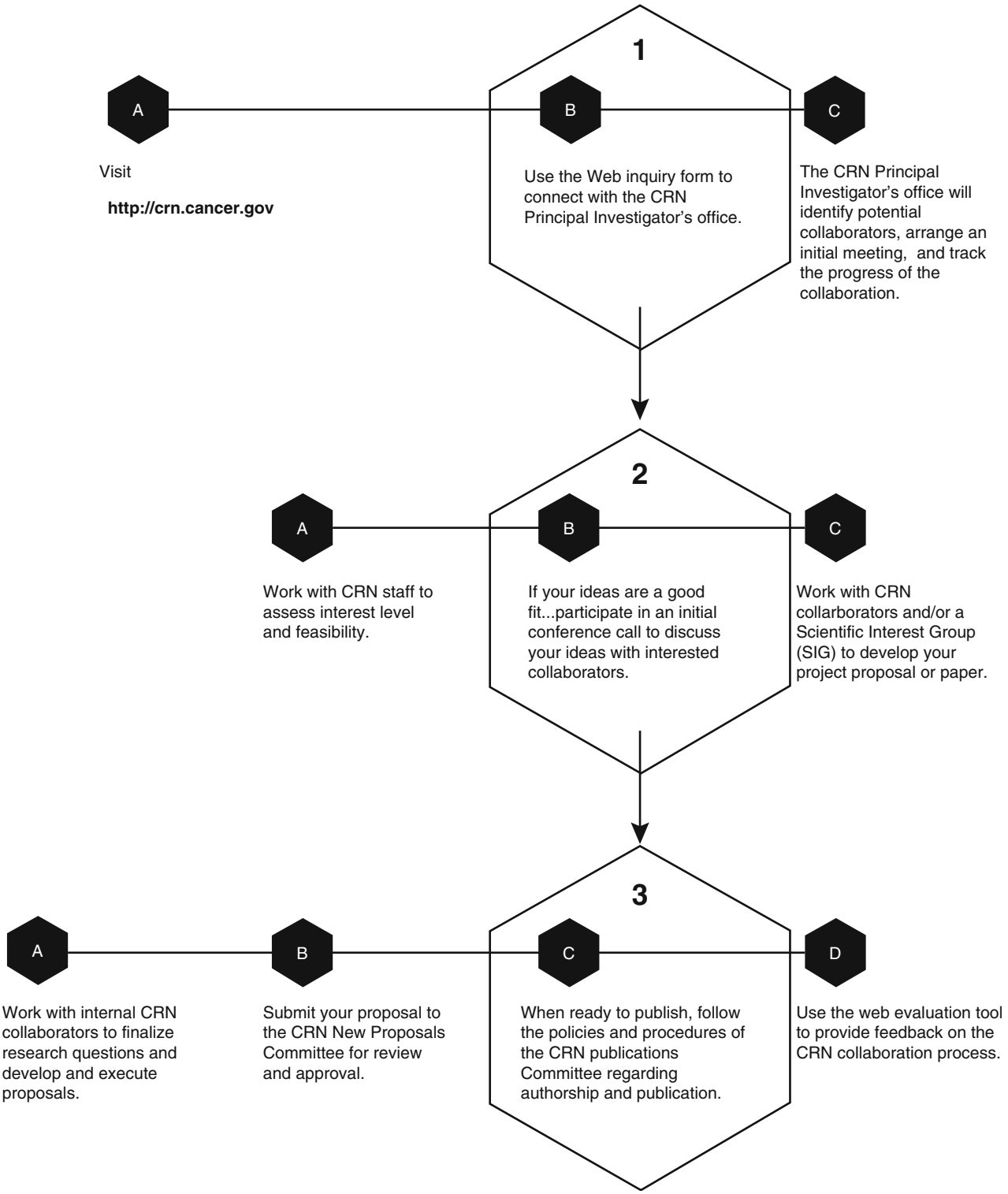


**Fig. 26.5** Avenues for developing collaborations with the Cancer Research Network

protocol fidelity, and reduce IRB violations; (5) clinical and utilization data systems to support identification of key clinical events post randomization; (6) expert data analysts to extract electronic clinical and utilization data on trial subjects from the EMR and other data sources; (7) oncology specialty pharmacies to manage blinding and prepare experimental medications; (8) mechanisms for communicating with all clinic staff across the health plan about the opening

of a new clinical trial and its target recruitment population; and (9) biostatisticians to consult on data safety and monitoring questions. Compared to advertising in the mass media, CRN members are able to conduct direct personal recruitment strategies—letters, e-mail, and telephone calls to health plan members from health plan research staff. Participation rates are substantially improved when potential subjects are contacted by their own health plan. Moreover, administrative approval of a trial protocol means that the health plan's clinical staff and managers are supportive of the trial.

## Practical Clinical Trials

Per regulations of the Food and Drug Administration, testing safety and efficacy of new pharmaceutical agents requires placebo-controlled clinical trials in order to obtain nonconfounded measures of rates of adverse events and poor outcomes. Usual-care controlled clinical trials are needed to answer the question of whether a new pharmaceutical agent performs better and/or has a lower risk profile than existing approved medications. One of the key features of controlled clinical trials is adherence to the trial protocol, for both administering the therapies and measuring the outcomes and adverse effects. Clinical trials impose strong controls on care processes that are not present in routing clinical care. Hence, outcomes for a usual-care control group are often better than regular nonresearch care.

The concept of practical clinical trials has been formulated to describe trial designs that are more flexible than the traditional rigidly controlled approach but still incorporate randomization [80–82]. One type of practical trial design is to recruit patients who are willing to be randomized to alternative initial treatment protocols, but let them cross over to another treatment if the one they are randomized to is not working to their satisfaction. For prostate cancer, men with early stage disease could agree to be randomized to alternative first-round treatments—prostatectomy, brachytherapy, external beam radiation, or cryotherapy. Randomization is a critical element here because it removes the problem of selection bias in treatment choice—unmeasured factors influence patient's choice of treatment and confound the attribution of outcome to the treatment.

## Comparative Effectiveness Research

In clinical scenarios where inadequate evidence is available on the relative effectiveness or cost-effectiveness of competing treatments and insufficient numbers of patients are willing to be randomized to competing treatments that are safe and effective, a tool for filling in this evidence gap is retrospective comparative effectiveness research (CER) using large samples of patients on whom complete clinical and utilization data are readily available. The key to CER is identifying large samples of patients who could have had equipoise between alternative treatments for their disease and for whom we have good data on pertinent attributes on which they vary. Equal preference among alternative treatments can arise when there is positive evidence of equivalence, when practice guidelines give equal weight to more than one treatment option, when there is no evidence to differentiate among treatments, or when variations in preferences for one treatment over others do not appear to result in different health outcomes. Statistical models can be estimated in an attempt to approximate randomization by controlling for measurable differences between the treatment groups. High-dimensional propensity scoring models are one statistical technique to reduce the effects of unmeasured factors that create selection bias with purposive choice of therapy [83]. The CRN, with its relatively large numbers of prostate cancer patients and strong informatics resources, is well suited to conduct retrospective comparative effectiveness studies of alternative screening and treatment strategies for prostate cancer.

### Conclusions

Nonprofit integrated health care delivery systems committed to public-domain research represent a highly strategic foundation for multisite collaborative research on prostate cancer. Their defined populations, sophisticated health informatics systems, and organized research centers are sources of efficiencies in prostate cancer clinical trials—targeting patients most likely to be eligible for a trial, reducing demands for primary data collection, and enabling strong fidelity to trial protocols. Defined populations with medical homes provide advantages to studies of prostate cancer screening—who is never screened, who is screened too frequently, and what happens to patients receiving false-positive and false-negative screening results? EMRs with embedded clinical decision support systems represent a means for rapid translation of new evidence into clinical practice as well as a means for identifying providers who are most resistant to drop practices demonstrated to be unsafe, ineffective, or too costly. Moreover, patients with higher continuity of primary care with a specific provider represent potential early adopters of improved cancer screening practices. In an insured population with a high degree of primary care access, continuity with a specific primary care physician was associated with greater likelihood of PSA testing [36]. CRN oncologists are interested in offering access to experimental treatments for prostate cancer patients who are eligible for such studies. EMRs and VDWs enable closer oversight of virtually every clinical activity, which eliminates medicine as a cottage industry (aka independent professional practice) and brings the health care

system under scientific controls. Health informatics also generates a synergy between research and clinical practice (the learning health care organization) and makes large-scale genomics research and comparative effectiveness research and cost-effectiveness analysis possible. A major challenge to clinical research is that only about 7 % of adult cancer patients in the CRN participate in clinical trials [84]. This represents an opportunity for developing and testing interventions to inform prostate cancer patients and their families about the role of clinical research and about how to become better prepared to deal with opportunities to participate in clinical trials should they arise.

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# Screening for Prostate Cancer

27

David R. Yates and John B. Anderson

## Introduction

In 2010, 217,730 men will have been diagnosed with prostate cancer (PCa) in the United States of America (USA), and around 32,730 will have died from the disease [1]. Depending on the extent of prostate-specific antigen (PSA) testing, similar ratios of incidence and mortality will be seen throughout Europe; PCa is the second commonest cause of death from cancer in men in the UK, and in the USA, it is estimated that a man aged 40 years has a 16 % chance of being diagnosed and a 3 % lifetime chance of dying from PCa [2]. Once diagnosed, the chance of a man dying from his cancer rather than other causes depends not only on the biological aggressiveness of the tumor and the age and comorbidity of the individual in question but crucially on the stage of the disease at diagnosis and, by definition, how early it has been detected. Screening for disease to allow early detection is now an integral part of modern medicine, and screening for breast, cervical, and colorectal cancer is now standard practice in some countries. Although PCa is an equally important health problem, PSA testing to screen for the disease, allowing earlier detection and thereby reducing the chance of a man dying from PCa, remains controversial with the medical community divided on whether this approach causes more harm than good.

## The Principles of Screening

### Definitions

Cancer screening aims to identify preclinical and asymptomatic cases of a disease in a population at risk rather than waiting to make a diagnosis once a patient presents at a later stage with signs and symptoms. The rationale behind screening is simple: to detect cancer at an early stage when it is still curable. Population-based screening programs aim to reduce cancer mortality and morbidity by detecting cancer at an early stage, on the assumption that earlier diagnosis and treatment will potentially improve prognosis and survival. The criteria against which any screening program is designed or critically assessed originate from the 1968 World Health Organization (WHO) document written by Wilson and Jungner [3], while the United Kingdom National Screening Committee has recently produced comprehensive standards to assess the efficacy and effectiveness of any screening program (www.screening.nhs.uk). Screening for cancer may take place in a variety of ways ranging from mass screening of a general population, through more selective screening by targeting "high-risk" populations, opportunistic screening which is incorporated as part of a medical consultation for other reasons, and simple case finding.

## Screening for Prostate Cancer

### General

As with any cancer screening program, the primary goal of screening for PCa is to reduce PCa mortality. Other potential benefits may be prolongation of life, prevention of advanced disease with less morbidity, and patient reassurance if the test is truly negative. Against these advantages, the often-cited negative criticisms of PSA-based screening which include too many unnecessary biopsies, an increased detection rate of "insignificant" cancer, dilemmas over active treatment versus surveillance, uncertain effects on morbidity and mortality, unclear cost-effectiveness, and psychological harm have to be balanced.

Screening for PCa has been debated for years and has divided opinion within the international urological community and the regulatory bodies of the USA, UK, and Europe. This is most obviously seen in the advocacy for PSA-based screening in the USA [4, 5], but not in the UK or Europe [6]. In the USA, 87 % of male physicians over the age of 50,

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21 % below 50, and 98 % of male urologists report having had their PSA measured [7]. It is estimated that >55 % of American men over 50 years of age undergo annual PSA testing, while up to 75 % have been tested at some point [8]. This compares to an overall annual rate of only 6 % in asymptomatic men aged 45–84 in the UK [9].

The assumption that underpins the potential introduction of PCa screening is that PCa can be diagnosed at an early stage by PSA testing and prostate biopsy, and patients with organ-confined PCa can be cured of their cancer by radical surgery or radiotherapy. Although serum PSA estimation has established itself as the primary screening test for PCa [10], the test is prostate specific, not disease specific, and therefore its operating characteristics as a PCa marker are not robust [11]. Nevertheless, the widespread use of PSA to diagnose PCa has resulted in a significant stage migration of the disease. Before the widespread introduction of PSA testing, only 27 % of newly diagnosed PCa cases were clinically localized. Now, with investigation of men who have a marginally elevated PSA (2–10 ng/ml) and normal DRE, the majority of cases diagnosed today (70–80 %) are confined to the prostate [12].

A big challenge to the assumption that PSA screening might reduce the PCa mortality rate is the heterogeneous behavior of this cancer. Although a man has been estimated to have a 10–20 % (1 in 6) risk of developing clinical PCa during his lifetime [2], the chance that he may harbor the disease may be as high as 60–70 % [13]. Furthermore, a man's lifetime risk of dying from PCa is only around 3–4 % (1 in 30) [2]. This observation gives substance to the often-quoted saying "men die with PCa, not of it." Autopsy studies of men who have died of non-cancer causes have been found to have a very high prevalence of cancer within the prostate with pathologists diagnosing disease in 3–43 % of men in their 40s, 14–70 % of men in their 60s, and 31–83 % of men in their 70s [14]. Since only 1 in 30 of these men will die from PCa, one can understand the complexity of early detection and screening for PCa. A credible screening program will need to provide evidence that the benefits of screening outweigh the main disadvantages of overdiagnosis and overtreatment (and its potential complications). Further unresolved controversies in PCa screening include the age range within which screening should take place, how often to screen (screening interval), the PSA threshold to prompt prostate biopsy, the development of risk-based strategies for early detection, and ideally the ability to differentiate "insignificant" PCa from more aggressive life-threatening disease.

## National Guidelines on PCa Screening

Evidence-based medicine together with guidelines and protocols is a key driver in the contemporary management of many health conditions including PCa. It is therefore interesting to see that the division of opinion among the urological community is reflected in the most recent viewpoints and guidance offered by the key regulatory bodies in the USA, UK, and Europe.

### American Urological Association (AUA)

The AUA published a "PSA best practice statement" in 2009 which remains in favor of PSA screening [4]. This was an update to the previous statement in 2000 but with two notable differences. Firstly, the 2009 statement abandoned the AUA's former position that "a single threshold value of PSA should prompt a prostate biopsy." The decision to proceed with a biopsy should now be a matter of individual choice based primarily on PSA and DRE results but also taking into account other factors that potentially increase an individual's risk of PCa, e.g., free/total PSA ratio, age, PSA velocity, PSA density, family history, race, comorbidities, and prior biopsy history. Secondly, the age at which a baseline PSA estimation is recommended has been reduced from 50 years to 40.

### National Comprehensive Cancer Network (NCCN), USA

The NCCN annually review online guidelines (www.NCCN.org) which have been developed for men who are considering PCa screening. Their guideline recommends offering a baseline PSA and DRE at the age of 50 along with information on the risks and benefits of screening. These are one of the few guidelines that have incorporated PSA kinetics (PSAV and % free PSA) into the various algorithms to aid in the decision-making process for men with a PSA 2.5–4 ng/ml or for men with a PSA >4 ng/ml but with significant comorbidity.

### American Cancer Society (ACS)

The 2010 ACS guidelines do not support routine population PCa screening for all men because "the benefits are unclear or unproven." Instead, it recommends that asymptomatic men over the age of 50 who have at least a 10-year life expectancy should have an opportunity to make an informed decision about PSA testing, together with their health care provider, after they have received information about the uncertainties, risks, and potential benefits of the test. They do recommend that men in higher-risk groups should be given this information before the age of 50 years [5].

### US Preventative Service Task Force (USPSTF), USA

In 2008, the USPSTF concluded that "current evidence is insufficient to assess the balance of benefits and harms of screening for prostate cancer in men younger than age

75 years." They are explicit that one should "not screen for prostate cancer in men age 75 years or older," which differs from the AUA and ACS guidance [15].

### European Association of Urology (EAU)

Following the publication of the European Randomized Study of Screening for Prostate Cancer (ERSPC) [16], the EAU produced a "position statement" where they concluded that "current data is insufficient to recommend adoption of population screening because of the significant overtreatment that would occur" [6]. This view is echoed in the latest EAU guidelines on prostate cancer which recommend that, in the absence of population screening, early detection (opportunistic screening) should be offered to the well-informed man aware of the risks and benefits of screening and individual risk assessment [17].

### United Kingdom National Screening Committee (UKNSC)

The UKNSC have defined 22 criteria for PCa screening largely based on the original WHO criteria (www.screening.nhs.uk) and recently published a document which concluded "the harms from screening using PSA are currently likely to outweigh the benefits and in this circumstance screening for PCa cannot be justified on current evidence" [18].

## PCa Screening Tools and Methods

### Digital Rectal Examination (DRE)

The sensitivity of DRE for diagnosing prostate cancer depends both on the stage of the tumor and the experience of the examiner. While DRE is of limited value in detecting tumors confined to the prostate gland, it remains a useful adjunct to PSA testing in identifying higher-risk cancer when the PSA is low. Twenty percent (20 %) of tumors detected by DRE when the PSA is less than 2 ng/ml are not organ confined [19]. Since the positive predictive value (PPV) of an abnormal DRE can be as high as 50 % and DRE screening tends to detect non-organ-confined disease not identified by PSA screening, the opportunity for cure with DRE screening alone however is limited.

### PSA and PSA Thresholds

PSA expression is prostate specific rather than PCa specific, and this makes it a less than ideal screening marker for PCa [20]. Although PSA lacks sensitivity and specificity for PCa, these parameters will vary depending on the threshold level employed to recommend a prostate biopsy. Furthermore, we are aware of the influence of increasing age on the development of benign prostatic hyperplasia which will raise the baseline PSA level, and this has led to age-specific reference ranges for PSA [21].

Traditionally, a PSA >4 ng/ml has been used as a common threshold above which a prostate biopsy should be considered since approximately 70 % of cancers will be detected using this cutoff. Up to 30 % of men with a PSA in the range 4–10 ng/ml will have PCa on biopsy [22]. However, Thompson et al. [11] have reported a high prevalence of PCa among men with a PSA ≤4 ng/ml and showed that at these levels many men can harbor clinically significant disease (in men with PSA 3.1–4.0 ng/ml, 26.9 % had PCa, and of these, 25 % were high-grade cancers). It is probably more useful, therefore, to consider a continuum of risk attributed to PSA values and not a "safe" value below which a man can be reassured he does not have PCa.

Altering the PSA thresholds to recommend prostate biopsies will obviously affect the sensitivity and specificity of PSA to detect PCa. Lowering the PSA threshold will lead to an increased number of prostate biopsies, a consequent increase in sensitivity (more cancers detected), but a decrease in specificity and PPV (more negative biopsies) [23]. Holmstrom et al. [24] have evaluated the validity of PSA as a screening test in order to see whether it could attain the standard necessary for large-scale population screening. They reviewed the PSA levels, some 7 years before diagnosis, from 540 men with PCa identified from their regional cancer registry and compared them with 1,034 age-matched noncancer controls. The area under the curve (AUC) for PSA was 0.84 (95 % CI 0.82–0.86), and the sensitivity of PSA to diagnose cancer at thresholds of 3, 4, and 5 ng/ml was 59, 44, and 33 %, respectively. The specificity at these thresholds was 87, 92, and 95 %. The positive likelihood ratios (+LR) for the same thresholds were 4.5, 5.5, and 6.4, respectively (a + LR >10 is needed to "rule in" disease), while the negative LRs (–LR) were 0.47, 0.61, and 0.7. (a – LR <0.1 is needed to "rule out" disease). PSA levels <1 ng/ml virtually ruled out a PCa diagnosis during follow-up, with a – LR of 0.09. The authors concluded that no single cutoff value for PSA reached a likelihood ratio formally required for a screening test.

### Age Range for Screening

A key criterion for any screening program is to define the population who are likely to benefit from screening, and therefore, we need to clarify the age at which to commence screening and the age at which to stop. While it is difficult to be prescriptive about the upper age limit of screening, the ACS have recommended men need a life expectancy of at

least 10 years if they are to benefit from screening and the upper age limit in most screening trials is 80 years.

With regard to the lower age limit for PCa screening, the current AUA guidelines have recently lowered the age threshold from 50 to 40 for men at average risk of PCa. Among men in their 40s and 50s, a baseline PSA above the median value for their age is a stronger predictor of future risk of PCa than family history or ethnicity. Studies have shown there is a significant association between baseline PSA at a younger age (40s or 50s) and the subsequent risk of PCa diagnosis, ranging from a threefold to a 7.6-fold increase, with the median PSA levels (ng/ml) for men in their 40s, 50s, 60s, and 70s being 0.7, 0.9, 1.2, and 1.5, respectively [25]. Vickers et al. [26] have examined the association of a single baseline PSA taken at age 60 in 1,162 men with PCa. The PSA level at 60 was associated with the risk of a clinical PCa diagnosis (AUC 0.76, 95 % CI 0.71–0.81, $p<0.001$), metastatic disease (AUC 0.86, 95 % CI 0.79–0.92, $p<0.001$), and death from PCa (AUC 0.90, 95 % CI 0.84–0.96, $p<0.001$) by the age of 85 years. Using a PSA cutoff of 2 ng/ml, the odds ratio (OR) for a clinical diagnosis of PCa was 13 (95 % CI 5.7–29), for metastatic disease 17 (5.2–57), and for death from PCa 26 (6.2–113). If the PSA is <1 ng/ml at 60, there is only a 0.5 and 0.2 % probability of developing metastatic disease and dying of PCa, respectively, by the age of 85. The authors concluded that if at the age of 60 years, a man's PSA is <1 ng/ml, then there is little need to screen any further. However, if the PSA level is >2 ng/ml, further regular PSA testing may be appropriate, while for men with a PSA between 1 and 2 ng/ml, an informed discussion about the relative merits of screening with PSA will allow an individual to make an informed decision according to his needs and wishes. Taking this approach, up to 50 % of men at age 60 can be reassured and excluded from long-term follow-up.

## Screening Interval

The ideal interval between separate rounds of screening for PCa has yet to be defined. The common intervals studied are every 1, 2, or 4 years although it has also been suggested that a single baseline PSA taken at a specific age and compared with the population median PSA levels would allow for a future screening interval to be determined according to risk [25, 26].

The downside of a shorter interval between rounds of testing is an increase in the number of negative biopsies, increased workload, cost, anxiety for the patient, and risk of overdiagnosis. However, if the interval is too long, one runs the risk of a cancer developing during the interval period, which can be important if the cancer is high risk and the opportunity for cure has been compromised.

Evidence from the Rotterdam section of ERSPC suggests that when using a 4-year interval, the average tumor stage and grade at diagnosis is lower among men whose cancer is not detected in the first round of screening. The interval cancer rate in this study was low (13 %), and since the screening protocol had a high sensitivity (85.5 %), the authors concluded that a 4-year screening interval is reasonable [27]. Roobol et al. [28] compared the interval cancer rate using a 2-year (Göteborg) and 4-year (Rotterdam) screening interval in the ERSPC trial. Reassurance was provided that of the 4,202 men screened every 2 years in Göteborg, the 10-year cumulative incidence of interval cancer was 31 (0.74 %) compared to 31 of 13,301 (0.43 %) men screened every 4 years in Rotterdam ($p=0.51$).

## The Evidence Base for Screening in Prostate Cancer

Along with the recent publication of two large international randomized controlled trials (RCTs) of screening [16, 29], there have been a number of other trials and studies that have helped to inform the debate about screening for PCa.

## The European Randomized Study of Screening for Prostate Cancer (ERSPC)

The ERSPC trial [16] was designed in the early 1990s to determine whether a reduction of 25 % in PCa mortality could be achieved by PSA-based screening alone. Seven European countries (Holland, Belgium, Switzerland, Italy, Finland, Sweden, and Spain) recruited patients from June 1991 to December 2003. Portugal had originally planned to include patients but withdrew in 2000 because of a lack of necessary data, and although France joined in 2001, their data was too immature to include in the 2009 publication. The screening protocol (eligibility, recruitment, randomization, and follow-up) differed slightly between countries leading to speculation that the ERSPC is actually a combination of different studies from seven centers. The ERSPC trial coordinators refute this, claiming that the ERSPC study group originally agreed on a common data set, centralized data collection, and other key matters at the inception of the trial in 1994. The target age group was 50–74, but the investigators also defined a "core group" within this of 55–69. The study had an 86 % power to show a 25 % reduction in death from PCa. Lateral sextant biopsies of the prostate were performed by the study groups, the pathology was not centrally reviewed, and after a diagnosis of PCa, the treatment decision and execution of that treatment were left to the regional health care providers.

182,160 men aged 50–74 (core 162,243) were randomized to screening with PSA every 4 years (82,816) or to a control

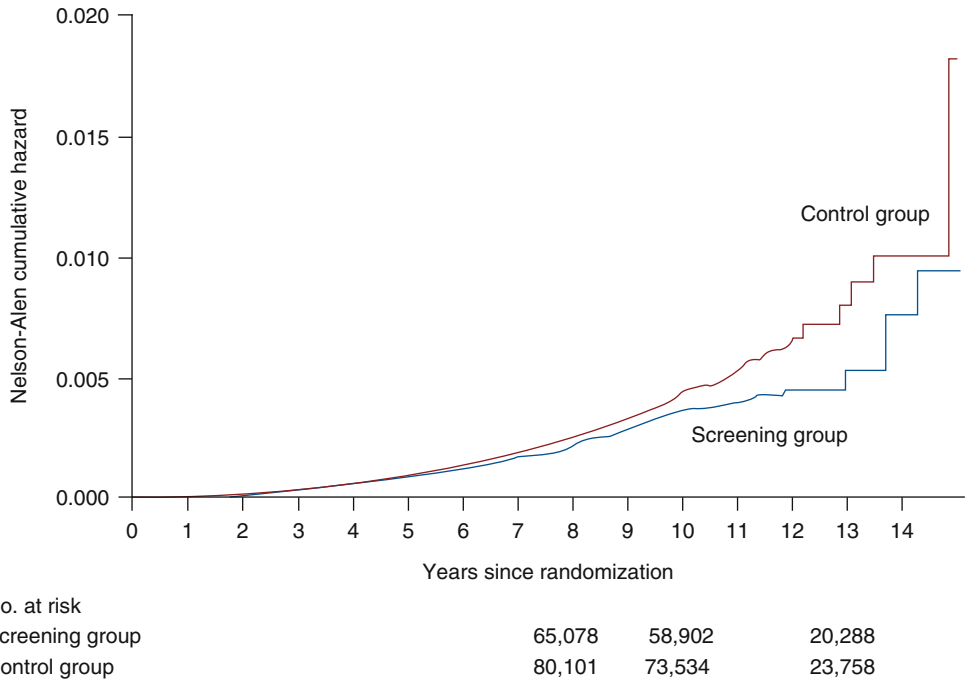


**Fig. 27.1** Cumulative risk of death from prostate cancer in ERSPC. The adjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95 % CI 0.65–0.98, $p=0.04$) (Reprinted from [16] with permission from *The New England Journal of Medicine*)

group (99,184). Originally, a PSA >4 ng/ml led to a recommendation of a prostate biopsy, but this threshold was subsequently lowered to >3 ng/ml in 1997. As well as differences in the age groups included in the trial, there was some variation in the interval between the screening events, the age when screening was discontinued, the PSA cutoff value used to determine a positive test, the use of ancillary screening for borderline positive tests (e.g., DRE, ratio of free to total PSA, transrectal ultrasonography), and the biopsy techniques. Local policies also guided treatment of newly diagnosed cancers.

The mean age at randomization was 60.8 years, and 82 % of men in the screened group accepted at least one offer of screening with compliance for biopsy of 85.8 %. 16.2 % of men in the screened group had a PSA >3 ng/ml, and of the men biopsied, 13,308 (75.9 %) had no evidence of cancer, i.e., a 75 % false-positive rate and a PPV of biopsy of 24.1 %.

In October 2008, the data-monitoring committee of ERSPC reported "a significant difference in PCa mortality in favor of screening." This was based on complete data follow-up to the end of 2006 (the time of the third interim analysis), and the study group followed self-imposed rules and published their findings. Among the 82,816 men screened, 6,830 cancers were diagnosed (5,990 in core group) compared to 4,781 (4,307) in the control group. This gave a cumulative incidence of PCa of 8.2 % and 4.8 %, respectively. After an average follow-up of 8.8 years, 214 PCa deaths had occurred in the screening arm versus 326 in the control arm. The rate ratio (RR) for PCa mortality in the screened group, compared to the control group, was 0.80 (95 % CI 0.65–0.98, $p=0.04$), i.e., a 20 % reduction in rate of death from (Fig. 27.1). The absolute difference in the number of PCa deaths was small at 0.71 deaths per 1,000 men. This means that 1,410 men (1,142–1,721) needed to be screened and 48 men would need to be treated in order to prevent one death from PCa. It is also worth noting that 41 % more men were diagnosed with metastatic disease in the control arm at 9 years compared to those who were screened, suggesting the possibility of further longer-term reduction in PCa mortality in the screened arm. The authors concluded that "PSA-based screening reduced the rate of death from prostate cancer by 20 % but was associated with a high risk of over-diagnosis." Based on previously published ERSPC trial data, Welch and Black have estimated this risk of over-diagnosis to be approximately 67 % [30].

Roobol et al. [31] have further analyzed the ERSPC results, adjusting for both nonattendance in the screened population and contamination in the control group, both of which have an effect on the intention-to-screen (ITS) analysis. Adjusting for nonattendance resulted in a RR of 0.73 (95 % CI 0.58–0.93), and then adjusting for contamination gave a RR of 0.69 (95 % CI 0.51–0.92), suggesting that PSA screening reduces risk of dying by up to 31 % in men who were actually screened. Although no overall survival advantage has been demonstrated for screening in this study, a mean follow-up of 9 years may be insufficient time to identify such a difference. It is planned to reanalyze the data once

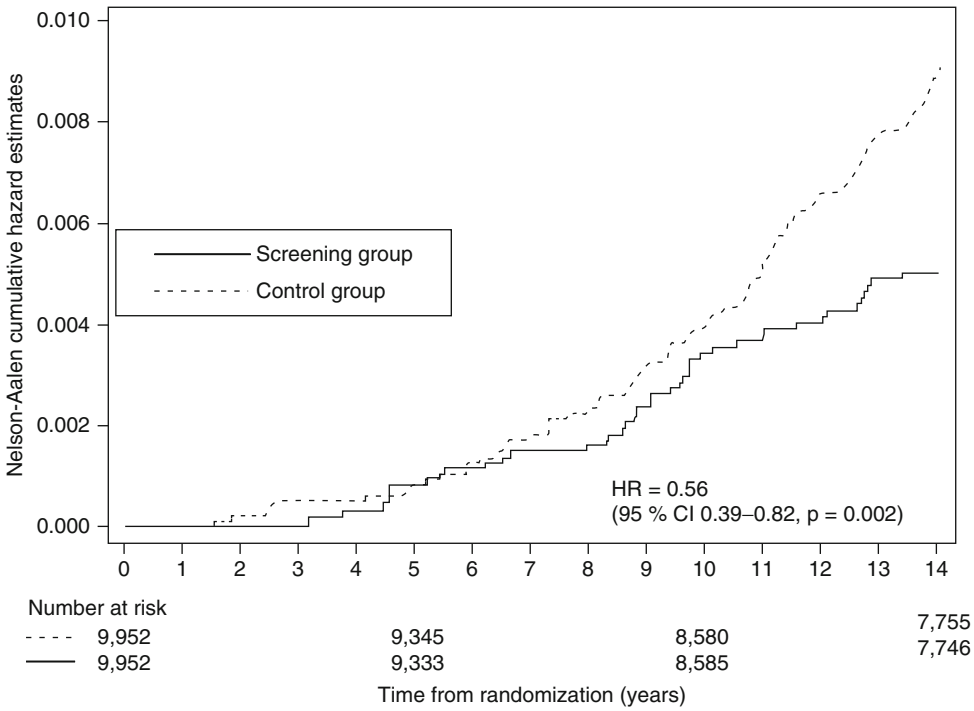


**Fig. 27.2** Cumulative risk of death from PCa in the Göteborg population-based screening trial. The RR for death from PCa was 0.56 (95 % CI 0.39–0.82, $p=0.002$) in the screening group compared to the control group (Reprinted from [33] with permission from Elsevier)

a mean follow-up of 11 years has been reached, and given the trend seen in the PCa mortality curves (Fig. 27.1), one might expect that the benefits of screening will become more apparent with longer follow-up.

## Göteborg Trial, Sweden, 2010

Biennial PSA testing in the Göteborg section of the ERSPC trial was originally reported to significantly reduce the risk of being diagnosed with metastatic prostate cancer after 10 years of follow-up [32], and in 2010, Hugosson et al. [33] reported the mortality results from this randomized population-based PCa screening trial. Started in 1995, 20,000 men (aged 50–64), randomly sampled from the population register, were randomized to either a screening group (invited for PSA testing every 2 years) or to a control group (not invited). Of the 9,952 invited to be screened, 7,578 (76 %) men attended at least one screening round. Only men with a raised PSA were offered DRE and prostate biopsy.

With a median follow-up of 14 years and seven screening rounds completed by 2008, 1,138 (11.4 %) men in the screened group and 718 (7.2 %) men in the control group had been diagnosed with PCa. The cumulative PCa incidence in the screened group and control group was 12.7 % and 8.2 %, respectively (HR 1.64, 95 % CI 1.50–1.80, $p<0.0001$). In the screened group, 44 men died of PCa compared to 78 deaths in the control arm. The cumulative risk of death from PCa fell from 0.90 % in the control group to 0.50 % in the screened group, giving an absolute risk reduction of death from PCa at 14 years of 0.40 % (95 % CI 0.17–0.64). The rate ratio for death from PCa was 0.56 (95 % CI 0.39–0.82, $p=0.002$) in the screened group (Fig. 27.2). The number needed to screen (NNS) to prevent one PCa death was 293 (177–799), while the number needed to treat (NNT) was 12, results which compare favorably with other established cancer screening programs, e.g., breast and colorectal.

This study is, in part, a subgroup analysis of the ERSPC trial, as it became associated with the ERSPC in 1996 without any changes in the protocol. 11,852 men had already been in ERSPC at the time of enrolment to this study, so one might reasonably ask why the RR for death from PCa should be so different in the Göteborg study (0.56 vs. 0.80 in the ERSPC). Certainly the median age of men in this study (56 years) was lower than ERSPC (>60 years), and this is important as advanced disease is less likely to be present at the time of screening in younger men thus leading to a higher cure rate if PCa is diagnosed. In addition, the overall median follow-up is longer for this study (14 years) compared to ERSPC (9 years), and it would appear that most of the benefit from screening occurs after 10 years (Fig. 27.2) which is what one would expect from a disease with a long lead time and a long natural history.

## Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, USA, 2009

The prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) [29] Cancer Screening Trial was designed to determine the effect of annual PSA testing *and* DRE on

mortality from PCa and randomized 76,693 men aged 55–74 to either screening or to "usual care" at 10 centers in the USA between 1993 and 2001. The age range was originally 60–74, but the protocol was changed in 1996 while also limiting pre-randomization PSA testing to one such event in the preceding 3 years. The study sample size and power calculations were based on 13 years follow-up after randomization from 2001. 38,343 men were randomized to screening which involved annual PSA testing for 6 years and annual DRE for 4 years. The control group consisted of 38,350 men who were managed as per "usual care" which interestingly "sometimes included screening"! A PSA >4 ng/ml or abnormal DRE triggered recommendation for a prostate biopsy, and regional health care providers made the final decisions on when to biopsy, the technique, and treatment choice after a positive diagnosis. The primary end point was causing specific mortality, and the investigators used an ITS method of data analysis. Assuming 100 % compliance, the study had a 91 % power to show a 20 % mortality reduction in men aged 60–74.

In contrast to ERSPC, the independent data-monitoring committee for the PLCO study terminated the trial early and recommended publication of results because of "a continuing lack of a significant difference in the death rate between the two study groups at 10 years (with complete follow-up at 7 years) and information suggesting harm from screening."

At 7 years, with 98 % full follow-up data, PCa was diagnosed in 2,820 of screened men vs. 2,322 in the control group (RR 1.22, 95 % CI 1.16–1.29), giving a crude incidence of PCa of 7.4 % vs. 6.1 %, respectively (RR 1.11, 95 % CI 0.83–1.5). This is an incidence of 116/10,000 person-years vs. 95/10,000, respectively, and is a relative 22 % increase in rate of PCa diagnosis in the screened arm. At 10 years (67 % complete data for mortality), 3,452 screened vs. 2,974 controls were diagnosed with PCa (RR 1.17, 95 % CI 1.11–1.22).

With regard to PCa mortality at 7 years, 50 deaths had occurred in the screened arm vs. 44 in control arm (RR 1.13, 95 % CI 0.75–1.7). This gives an incidence of 2/10,000 person-years vs. 1.7/10,000. By 10 years, 92 deaths had occurred in the screened arm vs. 82 in the control arm (RR 1.11, 95 % CI 0.83–1.5). The study concluded that the death rate from PCa was very low, and screening men aged 55–74 with annual PSA and DRE did not reduce the mortality rate from PCa when compared to a control group (Fig. 27.3).

Compliance for screening was high at 85 % for PSA and 86 % for DRE, but of those men with a positive PSA test or abnormal DRE, compliance with prostate biopsy was low in both the first and subsequent screening rounds (40.2 and 30.1 %, respectively). The PPV of the first biopsy, and subsequent biopsy was 44 and 33 %.

Although at 7 years, there was no statistical difference in PCa mortality between the 2 groups (RR 1.13), the 95 % confidence intervals (ranging from 0.75 to 1.70) are wide, and this means that the PCa mortality potentially ranged from a 25 % *reduction* in mortality (0.75) to as high as a 70 % *increase* in mortality (1.70). The lowest margin of the

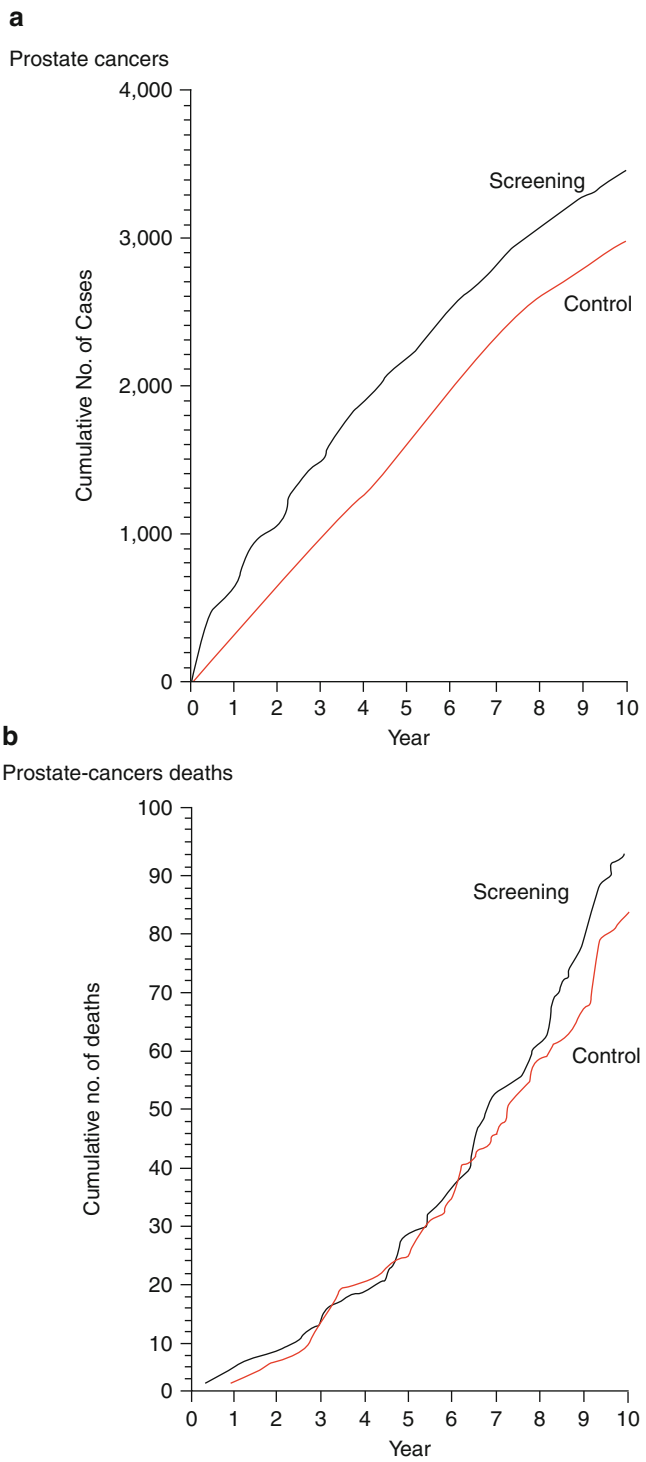


**Fig. 27.3** The number of diagnoses of all PCa (*panel* **a**) and number of PCa deaths (*panel* **b**) in PLCO. The incidence of PCa was higher in the screening group (RR 1.22, 95 % CI 1.16–1.29), but the rate of death from PCa did not differ significantly between the two groups (RR 1.13, 95 % CI 0.75–1.70) (Reprinted from [29] with permission from the *New England Journal of Medicine)*

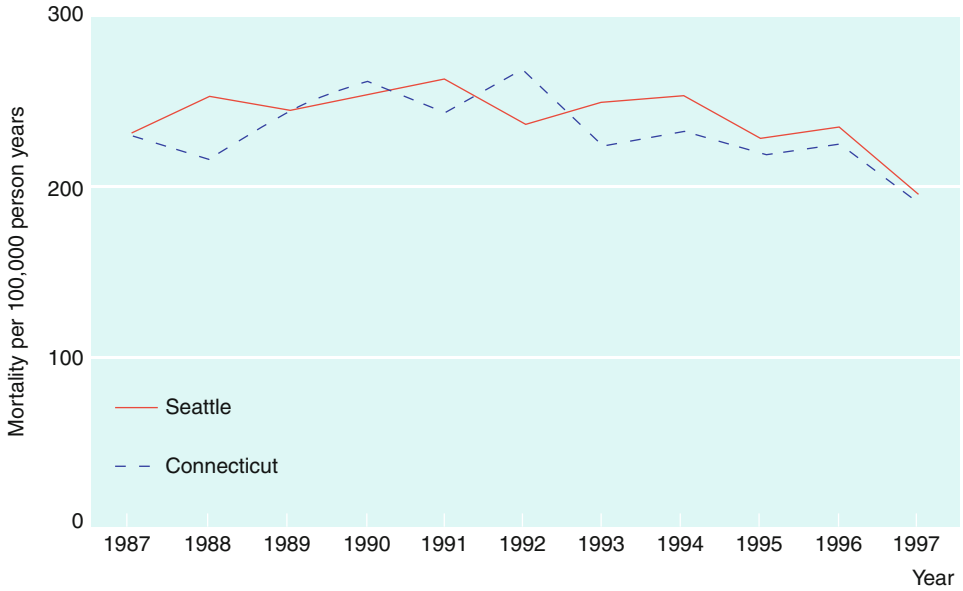


**Fig. 27.4** Age-adjusted prostate cancer mortality per 100,000 person-years for men in Seattle-Puget Sound and Connecticut, 1987–1997. Despite the increase rate of PSA testing and prostate biopsy leading to more men undergoing radical treatment for PCa in Seattle compared to Connecticut, no significant difference in PCa mortality existed during the 11-year follow-up period (RR 1.03, 95 % CI 0.95–1.11) (Reprinted from [35] with permission from BMJ Publishing Group)

95 % CI is 0.75 which is the same as the point estimate of the positive effect of screening with PSA in the ERSPC trial (0.73 for those actually screened).

There are a number of explanations for the discrepancy between the results from the PLCO, ESRPC, and Göteborg studies:

1. A PSA threshold of >4 ng/ml for recommending a prostate biopsy in the PLCO trial is higher than the ESRPC trial, and one could speculate that if the threshold had been lower, then more cancers would have been diagnosed in screened group.
2. There was substantial contamination (PSA testing outside of study) in the control arm of the PLCO study, increasing from 40 % in year 1–52 % by year 6 which may well have diluted the difference in cancer detection rates. The PCa incidence in the control arm of the ESRPC (4.8 % at 8.8 years) was lower than in the "usual care" arm of PLCO (6.1 % at 7 years), suggesting that contamination was much less common in the ERSPC study.
3. The PLCO reported their results after a median of only 5–6 years. Since the mortality curves did not diverge in the ERSPC trial for at least 7–8 years, this potentially premature reporting of the results may well explain why no difference was seen in the PCa mortality rates and represents a major limitation of the PLCO trial.
4. The power of the PLCO study was limited with only 174 PCa deaths overall compared to 540 deaths in the ERSPC trial.

When one considers the ERSPC and PLCO studies together and examines the trial differences in terms of goals, design, and results, one can see that the results may well be complementary rather than conflicting in nature [34]. Overall, one cannot state that population screening with PSA is either effective or ineffective. The most rational conclusion is that the PLCO trial did not demonstrate benefit at 10 years for more intense compared with less intense PSA screening combined with community standards of care during the study period. The ERSPC trial showed that PSA screening with a cutoff of 3 ng/ml in certain age groups led to a small improvement in cancer-specific mortality albeit with unknown effects on morbidity, costs, and quality of life and significant risks of overdiagnosis and overtreatment. Longer follow-up may well change this conclusion.

## Other Studies

### Seattle, USA, 2002

Lu-Yao et al. [35] examined the impact of aggressive screening and treatment on PCa mortality in two fixed cohorts of Medicare beneficiaries from the Seattle-Puget Sound area (94,900 men) and Connecticut (120,621) in an 11-year longitudinal study during the "early PSA era," defined as 1987–1990. During this time, the observed increased frequency of PSA testing, prostate biopsy, and radical prostatectomy (RP) among men in Seattle should arguably have led to an earlier and larger decline in PCa mortality when compared to Connecticut where aggressive screening did not take place. Prior to PSA testing, the age-adjusted PCa death rates were almost identical (115.5 vs. 155.6 per 100,000 person-years for white men aged 65–79 and 317.2 vs. 323.3/100,000 for black men aged 65–79, from 1977 to 1986). Between 1987 and 1990, the authors reported that the PSA testing rate and prostate biopsy rate in Seattle were 5.39 (95 % CI 4.76, 6.11) and 2.20 (1.81, 2.68) times greater than in Connecticut, respectively. The adjusted cumulative incidence of PCa was 93 % (81–107) higher in Seattle, and men in Seattle had a 5.9-fold (5.0, 6.9) higher rate of RP and 2.3-fold (2.2, 2.5) higher rate of radical radiotherapy. However, no significant difference in PCa mortality existed between the two cohorts (Fig. 27.4) with up to 15 years of follow-up (RR 1.03: 0.95, 1.11) [36].

This was termed a "natural experiment" in which the majority of men were over 70 years at diagnosis, and it should be noted that the outcomes of men in this age group do not represent the expected outcomes for men in the usual core age who are screened. Their older age at diagnosis along with competing morbidity may dilute any benefit from screening in this age group.

### Norrkoping Trial, Sweden, 2004

In 1987, 9,026 men aged 50–69 residing in the city of Norrkoping (Sweden) were identified from the national population register, and every sixth man ($n=1,494$) was randomly selected to be screened for PCa every third year over a 12-year period, leaving 7,532 men to act as controls. At the first two screening sessions (1987 and 1990), DRE was the sole screening method used, but from 1993, DRE was combined with PSA. Sandblom et al. [37] have reported on the outcome after 15 years of follow-up.

In the screened group, 85 (5.7 %) cancers were detected, 42 (49.4 %) of which were diagnosed in the interval between screening rounds. 292 (3.8 %) cancers were identified in the control group of which 26.7 % ($n=78$) were localized at diagnosis compared to 56.5 % ($n=48$) in the screened group ($p<0.001$). A lower incidence of metastases, regional lymphadenopathy, and higher-grade tumors were found in the screened group ($p<0.05$). Curative treatment was given to 25 % ($n=21$) and 14 % ($n=41$) of the screened and control groups, respectively. With regard to mortality, log rank testing did not show any significant difference in overall survival or cancer-specific survival for men who were screened, but at 15 years, 11 % of the screen-detected patients had died compared to 33 % of patients diagnosed in control group. There are a number of limitations to this study. Originally, it had been intended as a pilot to show how a screening program could be designed, and the study was insufficiently powered to provide a definitive answer. The rate of diagnosis in the screened group was lower than in ERPSC and PLCO, and this may be explained by the use of a fine-needle aspiration biopsy to establish a cancer diagnosis rather than standard needle core biopsy, the latter having a comparatively higher sensitivity for diagnosing PCa [38]. 48.8 % of the group with screen-detected tumors did not undergo treatment. It is unclear how men were randomized, there was no blinding to intervention or assessment of outcomes, and results from the study were disseminated via television, radio, and newspapers, increasing the chance of contamination and self-selection bias, with controls opting to be screened.

### Quebec, Canada, 2004

Labrie et al. [39], in 2004, reported 11-year follow-up data on a prospective RCT of men on the electoral roll of the Quebec City area, Canada. 31,133 men were randomized and invited by letter to annual screening for PCa, of which only 7,348 (23.6 %) accepted and were actually tested. 23,785 (76.4 %) men did not accept the invitation. Of the 15,353 men allocated to the control arm, 14,231 (92.7 %) remained unscreened. At the first screening visit, PSA and DRE were performed. A prostate biopsy was offered if PSA >3 ng/ml or the DRE was abnormal. Ten of the 7,348 screened men died from PCa compared to 74 deaths in the 14,231 unscreened control group. With a median follow-up of 7.93 years, the annual cause-specific death rate incidences were 19.8 and 52.3/100,000 person-years ($p<0.002$), equating to a 62 % reduction in cancer-specific mortality (RR 0.38, 95 % CI 0.20–0.73). The limitations of this study are self-evident including the low rate of acceptance in the screened group (24 %) potentially introducing significant bias, the uncertain level of contamination (PSA testing) in the control group, and, most importantly, the failure to use an intention-to-screen (ITS) analysis, and the study conclusion of a 62 % reduction in death rate has largely been discounted.

### Tyrol, Austria, 2006

Although not a "screening trial" but rather an "observational study," Oberaigner et al. [40] analyzed the PCa mortality over time in the population of Tyrol, Austria, comparing it to "Austria without Tyrol." The study design arose from the fact that PSA testing was introduced on a routine basis into the Tyrol in Austria in 1988–1989 and, since 1993, had been offered free to all men aged 45–74, leading to approximately 75 % of men having at least one PSA test. However, in "Austria without Tyrol," PSA was not offered in free health checks, and thus the study aim was to assess whether the mortality rate was lower in a region with a high rate of PSA testing. The analysis of mortality time trends was based on age-cohort modeling and Poisson regression for mortality data covering three decades, 1970–2003. The authors reported a significant reduction in PCa mortality in Tyrol during the last 5 years with a risk ratio (RR) of 0.81 (95 % CI 0.68–0.98). For "Austria without Tyrol," no reduction was seen with a RR of 1.0 (0.95–1.05), which led the authors to conclude "PSA testing offered to a population free of charge can reduce PCa mortality" (Fig. 27.5). However, due to the design of the study and lack of any prospective randomization of the intervention, the results cannot confirm that screening for PCa has any impact on mortality rates.

### Cochrane Review, 2010

There have been many other published studies examining whether screening for PCa reduces PCa mortality, most of which are of dubious methodological quality. Rather than continuing to try and keep abreast of all published studies on the subject, the epidemiologist Archie Cochrane saw the wisdom in establishing a "critical summary….adapted periodically… of all randomized controlled trials" on many different topics [41]. The initial Cochrane review on screening for prostate

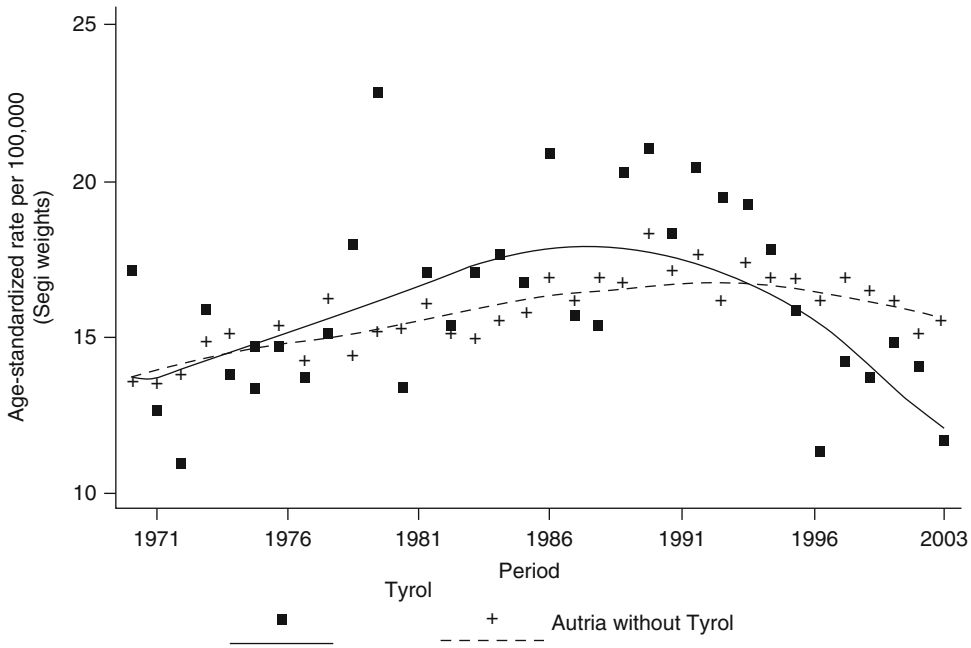


**Fig. 27.5** The age-standardized rate of PCa mortality in Tyrol and in "Austria without Tyrol," mortality data for Austria, 1970–2003. In the last 5 years of this period, there was a significant reduction in PCa mortality (RR 0.81, 95 % CI 0.68–0.98) in Tyrol, while no effect was seen for "Austria without Tyrol." (Reprinted from [40] with permission from Oxford University Press)

cancer was published in 2006 and was reanalyzed and republished in 2010 [42]. Two hundred five potentially relevant studies have been identified, but only 5 RCTs met the review inclusion criteria. The combined RCTs included 341,351 participants, although all but the ERSPC and the PLCO trials were judged to contain a high risk of bias. Reanalysis using the ITS principle and meta-analysis of the results from the 5 RCTs found no statistically significant difference in PCa mortality between men randomized for screening and controls (RR 1.01, 95 % CI: 0.8, 1.29), and the investigators concluded there was "insufficient evidence to either support or refute the routine use of mass, selective or opportunistic screening compared to no screening for reducing PCa mortality." Djulbegovic et al. [43] published their own update of the 2006 Cochrane review and included six RCTs. This meta-analysis of 351,531 patients demonstrated that screening was associated with an increased probability of being diagnosed with PCa (RR 1.46, 95 % CI 1.21–1.77, $p<0.001$) and being diagnosed with localized disease (RR 1.95, 95 % CI 1.22–3.13, $p=0.005$), but there was no effect of screening on death from PCa (RR 0.88, 95 % CI 0.71–1.09, $p=0.25$) or overall mortality (RR 0.99, 95 % CI 0.97–1.01, $p=0.44$).

## The Pitfalls of Screening for Prostate Cancer

Having examined the evidence, one can see the variety of reasons why many consider screening for PCa does more harm than good. There are confounding limitations to the RCT evidence including significant trial contamination, reduced compliance (nonattendance), and limited follow-up. In addition, there are inherent pitfalls of screening with three major types of bias which can occur with any screening program. It would seem appropriate to consider each of these types of bias further and identify how they relate to what we know about screening for PCa.

### Overdiagnosis or Detection Bias

Overdiagnosis is the identification of disease in patients in whom it would never have become apparent or symptomatic in their lifetime [44] or, in other words, disease that does not need diagnosing. Cancer overdiagnosis occurs either because the cancer never progresses or the cancer progresses sufficiently slowly that the patient dies of other causes before he becomes symptomatic. Overdiagnosis contributes to the problem of escalating health costs, and patients are subjected to unnecessary diagnostic tests and unnecessary treatment while also putting them at risk for physical or psychological harm.

Welch and Albertsen [45] obtained data on age-specific incidence from the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER) and on age-specific male population estimates from the US census to determine the excessive number of men who are diagnosed and treated for PCa each year following the introduction of PSA testing (1986–2005). Since 1986, an estimated additional 1,305,600 men were diagnosed with PCa of which 1,004,800 were definitively treated. Given the considerable time that has passed since PSA screening began, most of this excessive incidence is thought to represent overdiagnosis.

Draisma et al. [46] developed mathematical models of PCa detection and progression calibrated to incidence data from the SEER program to estimate lead times and the

proportion of overdiagnosed cancers due to PSA screening among US men aged 54–80 years between 1985 and 2000. Among screen-detected cancers that would have been diagnosed in the patients' lifetime, the estimated mean lead time ranged from 5.4 to 6.9 years, and overdiagnosis ranged from 23 to 42 % of all screen-detected cancers. The same authors had previously developed similar models based on the results from the Rotterdam section of the ERSPC trial. For a single screening test at age 55, the overdiagnosis rate was 27 %, and by age 75, the estimates had risen to 56 %. For a screening program with a 4-year screening interval from age 55 to 67, the estimated mean lead time was 11.2 years and the overdiagnosis rate was 48 %. For annual screening from age 55 to 67, the estimated overdiagnosis rate was 50 % and the lifetime prostate cancer risk was increased by 80 % [47]. Etzioni et al. [44] have reported similar computer modeling data based on the SEER database and have estimated that 29 % of cancers in white men and 44 % of cancer in black men are overdiagnosed.

The main threat posed by overdiagnosis is overtreatment of indolent disease. Overtreatment in PCa is a term used to describe the situation when a man undergoes radical treatment for a localized PCa which, untreated, would not have led to clinical detection or altered the man's life expectancy. In other words, we are treating disease that does not need treating or diagnosing in the first instance. This becomes extremely relevant when one considers the potential long-term morbidity of radical treatment, namely, urinary incontinence, erectile dysfunction, and bowel dysfunction [48].

### Lead Time Bias

Lead time bias can be defined as the time by which the date of diagnosis of PCa is advanced by screening from the date when the disease would have been diagnosed clinically. Screening leads to an earlier disease detection date, but the date of death is the same as nonscreened individuals and has no effect on life expectancy or the mortality rate. This causes survival to appear artificially increased given the "lead time" from screening diagnosis to clinical diagnosis. For PCa, the published lead time estimates range from 5 to 12 years [46]. Draisma et al. [47] have published estimates from the Rotterdam section of the ERSPC. For a single screening test at age 55 or 75, the estimated mean lead time was 12.3 years (range: 11.6–14.1) or 6 years (5.8–6.3), respectively. For a 4 yearly screening interval between the ages 55 and 67, the mean lead time was 11.2 years (10.8–12.1). The same authors have more recently estimated the lead time of PSA screening between 1985 and 2000 in the USA, a period that covers the early PSA era [46]. Using several different definitions of lead time and independently developed models, they calibrated each model to the US incidence of PCa during this time. The estimated lead time for cancers destined to be clinically diagnosed was 5.4–6.9 years, but this may be an underestimate. Since 2000, with the revision of national guidelines, there has been an increase in the number of first biopsies performed at lower PSA values, the traditional sextant biopsy technique has been replaced with more extensive core biopsy protocols, and more repeat biopsies are being performed. All of these factors will result in still further overdiagnosis.

### Length Time Bias

Length time bias is a term used to describe how screening overrepresents less aggressive disease. Aggressive, faster-growing PCa has a shorter asymptomatic period than a slower-growing tumor. Thus, they are less likely to be detected by a screening program and more by clinical presentation. However, aggressive PCa is also associated with a poorer prognosis, and this can lead to the overrepresentation of slower-growing tumors in screening programs. This, in turn, can mean screening tests are erroneously associated with improved survival, even if they have no actual effect on prognosis. Length time bias is more pronounced in screening programs with longer screening intervals.

## A Risk-Based Strategy for Early Detection

So where does this information on mass population screening leave the individual patient? An alternative to population screening, where age is the only factor determining whether you should be offered screening, is to target screening according to an individual's risk. Targeted screening may be more appropriate given that not all men with a predefined PSA threshold (whether >2.5 ng/ml, 3 ng/ml, or >4 ng/ml) need a biopsy, not all PCa needs to be diagnosed, and a diagnosis of PCa should not always lead to treatment. An individual risk-based approach improves PSA-driven detection of PCa [49], and tools now exist such as the PCPT risk calculator to guide risk prediction based on 5,519 men from the PCPT placebo arm who all underwent biopsy regardless of DRE and PSA [50].

The main risk factors for PCa include race, age, family history, genetic susceptibility, PSA kinetics (PSA velocity, PSA density, and % free/total PSA ratio), and previous prostate biopsy history. Ideally, all of these should be considered along with the conventional DRE and PSA when recommending further investigation with a prostate biopsy [51].

As the large RCTs of screening for PCa have failed to provide a definitive answer, individual risk assessment and a risk-based strategy in the early detection of PCa would appear to be a better way forward until more specific markers for prostate cancer become available. Furthermore, due to

the ever-expanding field of basic science and molecular biology, an individual's genetic susceptibility to PCa is now becoming more decipherable. There are now a number of candidate PCa susceptibility genes, and two of the best characterized are *HPC1* and *BRCA2* [52, 53]. Chapter 28 gives further information in this area. Studies of families with breast cancer have indicated that male carriers of BRCA2 mutations are at increased risk of PCa, particularly at an early age. Edwards et al. (53) found that 2 % of men with early onset PCa harbor a germline mutation in the BRCA2 gene, and the relative risk of developing PCa by age 56 in men with this mutation is increased 23-fold. The role of targeted PCa screening in men with BRCA2 (or BRCA1) mutations is the focus of ongoing research. Three hundred men aged 40–69, from families with BRCA 1 and BRCA 2 mutations, were offered annual PSA screening over 33 months and compared to 95 nonmutation controls. After baseline PSA screening, 7 % (21 men) have undergone a prostate biopsy for a PSA >3 ng/ml, and of these 21, 11 men have been diagnosed with PCa, giving a prevalence of 3.3 %. Of the 11 men with PCa, 9 (81.8 %) were mutation carriers and 8 (72.7 %) of the cancers were clinically significant [54]. The PPV of PSA screening in this cohort was 52.4 % and supports the rationale for continued screening in this group of high-risk men.

The recent advances in molecular biology and PCa genomics have now reached a point where some are advocating gene-based individualized screening for PCa [55]. Eeles et al. have conducted a genome-wide association study using blood DNA samples from 1,854 men with clinically localized PCa which was either diagnosed before the age of 60 years or where there was a strong family history of prostate cancer and compared this to 1,894 controls with a PSA below 0.5 ng/ml. They analyzed 541,129 single nucleotide polymorphisms (SNPs) and have identified seven new loci associated with PCa. Of the three newly identified loci containing candidate susceptibility genes, microseminoprotein-beta (MSMB) has been nominated as a new urinary biomarker in PCa [56]. Whitaker et al. [57] have demonstrated that in men who carry a specific risk allele, MSMB is significantly less likely to be found in the urine of men who have prostate cancer.

## Summary

The final chapter on screening for prostate cancer has yet to be written. Whether screening for PCa reduces mortality remains controversial and unresolved. We do know that PSA screening can reduce the PCa mortality rate, the presence of metastatic disease at the time of diagnosis, and increase the detection of localized cancer. Nevertheless, the disadvantages of overdiagnosis, overtreatment, and unproven cost-effectiveness, coupled with the probable but as yet unquantified effects on the quality of life of men who have been screened, are cogent reasons not to push for a PSA-based screening program at this time. As we await the development of better prostate cancer biomarkers, most men will still want to know their PSA and an informed risk-based approach to early PCa detection would appear to be the most rational way forward.

## Update

Due to the nature of the ever-evolving debate on prostate cancer screening and early detection, there have been recent amendments to the recommendations of some of the key international regulatory bodies, most notably from the US Preventive Service Task Force (USPSTF). In October 2011, the USPSTF released a controversial definitive position statement in contrast to their previous report which could be considered noncommittal. The USPSTF have concluded prostate cancer screening is not to be advocated for US men regardless of age, and the grade D recommendation states "the USPSTF recommends against prostate cancer screening. There is moderate or high uncertainty that screening for prostate cancer has no net benefit or that the harms outweigh the benefits" [58].

The 2011 update of the online version of the National Comprehensive Cancer Network (NCCN) Prostate Cancer Guideline for Early Detection (www.NCCN.org) also has become slightly more prescriptive. Using its algorithmic design, they continue to advocate thorough discussion between physician and individual patients about the pros and cons of screening, but they now make the following recommendations: (1) for men opting to participate in an early detection program, baseline DRE and PSA testing at 40 is useful; (2) annual follow-up is recommended for men who have a PSA value ≥1.0 ng/ml; (3) men with PSA ≤1.0 ng/ml should be screened again at age 45; (4) regular screening should be offered to all participants starting at age 50; (5) African-American men and men with a first-degree relative with PCa should commence screening at an earlier age ("in their 40s"); and (6) annual screening is also recommended for men receiving 5-alpha reductase inhibitors due to the reported association of high-grade cancer in men taking this medication for preventative reasons. This latter statement is the first time this population of patients have been identified as candidates for active screening due to their perceived risk.

Essentially, the publication of ERSPC and PLCO has probably created more confusion than clarity, but it has certainly stimulated long overdue international debate in the role of PSA as a screening tool, considering PSA is the "best available" serum PCa marker and was identified 40 years ago. However, on the whole, clinicians are unaware or

unwilling to acknowledge the limitations of PSA as a sensitive and specific marker for PCa. As with everything in life, opinions differ and the controversy of PSA-based screening will continue indefinitely or until a much needed improved biomarker for PCa is discovered.

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# Next Generation Screening Tests

# 28

Jack A. Schalken and Agus Rizal A.H. Hamid

## Introduction

Cancer screening intends to increase the chances of successful treatment through early cancer detection and then reduce cancer-specific mortality [1]. Cancer screening is performed on healthy/nonsymptomatic population. A cancer screening test must be considered as intervention protocol, so measurement of benefit and harm must be outweighed before introduced into the population [2–4]. Screening can be performed through three methods, which are mass (in entire population), selective (in high-risk populations), or opportunistic (incorporated as part of a medical consultation) [1]. Contrary to opportunistic screening, mass screening is endorsed by the health care officials and governmental bodies [5]. There are ten general requirements to be fulfilled to qualify a disease for a screening program (Table 28.1) [6].

Prostate cancer (PrCa) is one the most common cancers in men worldwide. PrCa has also become the second and third most common cause of cancer mortality in the USA and Europe [7–9]. These data indicate that PrCa is a major health problem that fulfills the first requirement as disease that needs screening [10, 11]. Even as it did not fulfill all disease screening criteria, almost all medical organization have encouraged PrCa screening. PrCa screening is then only recommended after a patient was clearly informed about the decision-making process, and as such it is not for mass screening [4, 12–18].

Currently, PrCa screening is based on the serum PSA test [19]. The incidence of PrCa has rapidly increased after the introduction of the serum PSA test. There is also a clear stage migration in that PrCa is predominantly diagnosed as localized disease [20]. PSA-based screening effects on PrCa specific mortality are still controversial. The European Randomized Study of Screening for Prostate Cancer (ERSPC) study showed a 30 % decrease in PrCa-specific mortality [21]. But this decrease in PrCa-specific mortality was also seen in countries with limited use of PSA screening [22, 23]. Another factor that should be considered is the improvement of effective localized PrCa treatment [23, 24]. Meanwhile, other randomized study did not show a beneficial effect probably because of poor methodology [25]. Even though the controversy on the effectiveness of population-based screening has not been resolved, it is clear that due to the overtreatment, the number needed to treat is unacceptably high, and there is no recommendation for screening by the European urological association (EAU) [16].

**Table 28.1** Criteria for disease that need screening program [6]

| |
|---|
| 1. The condition sought should be an important health problem. |
| 2. There should be an accepted treatment for patients with recognized disease. |
| 3. Facilities for diagnosis and treatment should be available. |
| 4. There should be a recognizable latent or early symptomatic stage. |
| 5. There should be a suitable test or examination. |
| 6. The test should be acceptable to the population. |
| 7. The natural history of the condition, including development from latent to declared disease, should be adequately understood. |
| 8. There should be an agreed policy on whom to treat as patients. |
| 9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole. |
| 10. Case-finding should be a continuing process and not a "once and for all" project. |

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**Table 28.2** Development screening marker phase [45]

| Phase | Step | Aim |
|---|---|---|
| Phase 1 | Preclinical exploratory | To identify promising marker |
| Phase 2 | Clinical assay and validation | To validate promising marker in clinical assay and assess its ability to distinguish subjects with cancer from subjects without cancer |
| Phase 3 | Retrospective longitudinal | To evaluate the capacity of the marker to detect preclinical disease |
| Phase 4 | Prospective screening | To determine detection rate, false referral rate, and practical feasibility in a relevant population |
| Phase 5 | Cancer control | To estimate the reductions in cancer mortality afforded by the screening test |

## The "PSA Dilemma"

The limited or conditional screening recommendation is due to several limitations of PSA as a screening test [1]. A major limitation of PSA is the low specificity (high false-positive rates). PSA levels are highly variable and influenced by several factors, such as benign enlargement, inflammation, and prostatic manipulation (i.e., catheterization and DRE) [11, 26]. The low specificity of the PSA test can lead to 70–80 % of negative biopsies [11, 21, 27]. In the "gray area" (PSA 4–10 ng/ml), the positive predictive value (PPV) was only 25 %. Furthermore, controversy about the PSA cutoff level to be used to distinguish PrCa from benign tissue is also unresolved [4]. The prostate cancer prevention trial (PCPT) study showed that 25 % of PrCa cases are found in patients with a PSA level below 4 ng/ml [28, 29]. This study recommended the PSA level was not a dichotomous value but it reflects a continuum for PrCa risk [30]. An attempt to discard all PSA cutoff level will result in more overdiagnosis and thus overtreatment, so different PSA-based nomograms are needed to decrease unnecessary biopsies and reduce over diagnosis/treatment [31, 32].

Risk of overdiagnosis in PSA-based screening was almost 50 % [1, 24]. This risk is higher than for any other cancer for which screening is commonly recommended. For example, the overdiagnosis probability is estimated to be about 10–25 % in breast cancer screening [33]. This overdiagnosis was due to the high incidence of latent PrCa and was in fact predicted by autopsy studies. Therefore, there is a large pool of indolent PrCa cases that could potentially be detected by screening [2, 24]. ERSPC study showed that one needed 1,410 cases to screen and 48 additional cases to treat to prevent one PC-specific mortality case [21]. False-positive results will increase anxiety, especially cancer-specific anxiety preoccupation with symptoms and increased use of health services. It might last long to reassure the diagnosis [24, 34, 35]. Overdiagnosis and overtreatment can also increase almost twofold of cost for repeated screenings, biopsy, and treatment [11, 36]. Thus, there are biomarkers needed to generate several ways to overcome these PSA limitation.

## Novel Biomarkers

It is clear that novel PrCa biomarkers are urgently needed that can identify patients with clinically significant PrCa. Current advancements in molecular profiling technology have enabled the discovery and development of novel biomarkers. Molecular alterations in cancer can be discovered by using these technologies that assess changes at the genomic/DNA level, its transcriptome (RNA), the production of proteins (proteome), or the synthesis of various metabolic products. Biomarkers can be categorized into DNA-based (genomic), RNA-based (transcriptomic), protein-based (proteomic), and metabolic-based (metabolomic) biomarkers [37–40]. By DNA microarray analysis, thousands of DNA variations can be assessed at high throughput as potential biomarker simultaneously. Then potential biomarkers should be further validated either by a quantitative measurement of DNA/RNA levels (northern blot, RT-PCR, or in situ hybridization) or protein levels (immunohistochemistry or Western blot) [41, 42]. Development of microdissection techniques can isolate particular cell populations for analysis and give more specific information. This technique can overcome disadvantages of the use of heterogeneous cells population used in the past [41].

However, the road from the initial discovery of a biomarker to widespread clinical application involves several steps [43]. Five conceptual steps of biomarker development have been suggested, as seen in Table 28.2 [38, 44]. Most common pitfalls in moving from the discovery phase to the validation phase are the need for a standardization assay and a well-designed multicenter prospective studies. Validation of biomarkers should also focus on "doing no harm" and includes psychosocial, ethical, and economic assessment [45].

The widespread use of the PSA test complicates novel biomarker evaluation because biopsy work-up is usually triggered by elevated PSA [46]. The observed sensitivities and specificities typically reflect the diagnostic value over and above the commonly used primary screening tests rather than the diagnostic value in a primary screening situation [47].

## PrCa Screening Biomarker Criteria

There are several basic requirements for a screening marker that are different from those for a diagnostic marker [10, 12, 38, 44]. These requirements are:

1. Highly specific
   Maintaining high specificity (low false-positive rates) is a high priority for screening test. It is due to the low prevalence of cancer in the general population, a lot of participants, and cost-effectiveness [44, 48, 49]. There are only 5–10 % PrCa cases detectable in a screening setting during life [2]. An almost absolute specificity (at least 95 %) and good sensitivity would be required for screening of an apparently healthy population. A simple calculation shows that in ideal conditions (1 % incidence of the disease, 99 % sensitivity and specificity), the frequency of false positive is already 50 % [48]. So ideally, a substance as potential marker must be secreted only from cancer tissue, not secreted by non cancer tissue [44].
2. Easily obtainable specimens/noninvasive
   Several substrates for a PrCa biomarker can be considered, that is, prostate tissue, blood, urine, or seminal fluid [50]. Serum and urine can easily be obtained. In contrast, prostate tissue sampling requires a minimally invasive procedure. Many studies though used tissue in phase 1 to identify the potential marker. The paradigm of direct detection of cancer cells in biological fluids then becomes opportune due to the expected specificity improvement. Detection of cancer cells in blood is considered to be specific for patients with advanced PrCa [51]. Prostatic cells and biomolecules, however, can be released directly into urine. Thus, urine was expected to have exfoliated cancer cell even in early cases. Manipulation of the prostate would mobilize PrCa cells into the urethra, so sediments from urine collected following a DRE would be enriched in prostate borne cells. Another advantage of urine is that it contains cancer cells that come from multiple foci within the gland. So urine sample was a yet-unexploited high-potential substrate for PrCa tests albeit that one had to anticipate the potential problems with respect to sample stability [27, 52, 53].
3. Simple and cost-effective test
   In a population-based setting, there are many participants and therefore considerable amounts of money are needed. So the test should be easily distributed to laboratories and readily interpretable by a clinician [49, 54].
4. Ability to differentiate indolent (low risk) from aggressive cancers
   Overdiagnosis is arguably the most important harm associated with early cancer detection. The impact of overdiagnosis can be lifelong and affects patients' sense of well-being, their ability to get health insurance, their physical health, and even their life expectancy. Recent criteria for indolent PrCa are no Gleason grade 4 or 5, organ confined, and cancer volume was less than 0.5 $cm^3$ [55]. It was found that indolent PrCa constitutes up to 30–50 % of all newly diagnosed PrCa [23, 49, 56].
5. Ability to detect PrCa at an early stage
   PrCa cases can be found at any PSA level. Novel biomarker should be significantly increased (or decreased) in the related disease condition and have no or limited overlap in values. It should also differentiate between healthy control subjects and untreated patients [38].

Recently, so many new markers have been suggested as PSA alternative. But there is only one PrCa specific marker that is already used in a clinical setting (PCA3) [57]. Furthermore, another PrCa specific gene rearrangement, commonly referred to as ETS gene fusions, has a high potential due to its PrCa specificity.

## PCA3

PCA3/DD3 was recently clinically implemented and is thus the first biomarker after PSA to predict outcome of prostate biopsies [58]. PCA3 as marker was identified in 1999 by using differential display analysis, a PCR-based technique that compares mRNA expression patterns. PCA3 is a noncoding RNA and is only expressed in the prostate. Its expression was much higher in PrCa than BPH or normal prostate tissue; hence, it is close to being PrCa specific. Because no protein product has been detected from PCA3 RNA, PCA3 assays were developed using RNA detection methods. The next big step forward was the detection of PCA3 transcripts in urine, which is a clear benefit for routine analytical procedures [59]. An RT-PCR-based PCA3 test was developed to evaluate the utility of PCA3 to detect PrCa cells in post-DRE urine [60]. The proof of principle was delivered with an early urinary RT-PCR-based test by Hessels et al.; PCA3 could be useful to predict biopsy outcome, with high specificity, in patients with a PSA <10 ng/ml. The assay was a robust RUO test, yet too time consuming for widespread implementation in clinical laboratories. The PCA3 test was then developed on an IVD technology platform based on transcription-mediated amplification (TMA). This technology is more simple, faster, and sensitive enough to be used in a clinical laboratory. All assay steps can be done in a single tube and completed within 6 h [54]. The PCA3 score was calculated by the ratio of PCA3 mRNA and PSA mRNA. PSA mRNA was used to normalize the PCA3 value for the expected variations in cell numbers in urine. The apparent specificity of PCA3 was 66–83 % in a population of patients that had a PSA >2.5 ng/ml. In the "gray PSA range," its specificity increased to 71–91 % [59, 61]. The commercial PCA3 test has already been studied in several multicenter studies and showed similar specificity as the RUO test [62].

In recent studies, the potential of the PCA3 test to predict the presence of clinically significant PrCa was tested. The PCA3

score correlated with PrCa volume measured in the subsequent radical prostatectomy specimen. This was confirmed by several studies and only one study failed to show a difference between PCA3 score and pathology outcome [63]. This might be attributed to the highly selected population typically seen in an academic referral situation. The general picture that emerges is that PCA3 can discriminate indolent from significant cancers, but that within the group of patients with significant cancers, there is no further discriminative value of the test. This could be explained by the fact that these significant cancers all shed cells in the urine and that the absolute expression levels do not vary much between Gleason grades [64]. The next phase was measuring effectiveness of PCA3 in a screening study. This has so far not been reported. The only study in a screening cohort (ERSPC) unfortunately used an already-multiple-times-prescreened population. In that study, a biopsy indication was used as PSA >2.5 ng/ml or PCA3 score >10. This study showed PCA3 decreased the number of missed PrCa cases compared to PSA. Adding PCA3 to the decision to biopsy resulted in detecting 64 % additional cases of PrCa in men with PSA levels <3.0 ng/ml, of which 15 % could be considered as potentially life threatening if detected at a later stage [61, 65]. There are still more general study to establish cutoff values before its use in screening test study [66]. The evaluation of PCA3 in a screening setting is thus still to be expected and eagerly awaited.

## TMPRSS2:ETS Gene Fusions

For over 30 years, genetic rearrangements have been recognized as key events in hematological malignancies and sarcoma development. A surprising report was that of the frequent occurrence of gene fusions in PrCa in 2005. This discovery was based on using microarray data, combined with a novel bioinformatic algorithm. Traditional microarray analysis methods only prioritize genes commonly activated across a class of cancer samples, and these methods will fail to identify rare/outlier events. A novel bioinformatic algorithm called the cancer outlier profile analysis (COPA) was developed to analyze outliers in gene expression profiles (those markedly overexpressed in a subset of cases). COPA identified high outlier profiles for the v-ets erythroblastosis virus E26 oncogene homolog (ERG) gene and the ETS variant 1(ETV1) gene. This high ERG or ETV1 outlier expression led to the identification of fusions of the 5-untranslated region of the prostate-specific-androgen-induced transmembrane protease serine 2 (TMPRSS2) gene to the ETS gene. This fusion is only found in cases with over expression of ETS gene and was not detectable in benign prostate tissues. TMPRSS2:ERG fusions in PrCa tissue have been reported in approximately 50 % cases, which represents the prevalence in PSA-screened cohorts worldwide [42]. These TMPRSS2:ERG fusions are highly specific for PrCa [67]. Based on detection of PCA3 in post-DRE urine, to detect PrCa, it was an obvious next step to measure gene fusions in urine. Detection of TMPRSS2:ERG transcripts by quantitative RT-PCR in post-DRE urine can be found in 42 % of PrCa cases. The gene-fusion-based test had a sensitivity of 30–50 % with specificity >90 % in PSA-screened cohorts [42]. Recently, gene fusion scoring using ERG mRNA expression and PSA mRNA expression was proposed. This score gave same sensitivity and specificity as previous results [68]. A review of the literature demonstrated an association between gene fusions to both more and less aggressive PrCa cases. Thus, there were conflicting results on associations between gene fusions and aggressive PrCa features. This discrepancy is yet not fully explored. The gene fusion based test is currently being evaluated for their positioning in the diagnostic armamentarium for PrCa.

## TMPRSS:ERG

Thus, it seems clear that none of the new tests is proven to be better than serum PSA measurements; however, based on the high specificity, the combination of the strengths of the serum PSA test with the PrCa specific PCA3 and gene fusion tests bears the promise to come to a better diagnostic algorithms for clinically significant prostate cancer that are so eagerly needed for PrCa.

## Targeting Screening on High-Risk Population

Screening can be targeted to a group of men who have a higher incidence of disease [69]. After an age, the strongest PrCa risk factor is a family history. Risk factor of family history has already been reported in 1974. There were approximately 10–20 % of PrCa cases having a significant family PrCa history [70]. One meta-analysis data showed the average PrCa risk will increase 2.5-fold if men had one first degree relative with PrCa. It will increase if men had more than one affected family member [71]. Although men who had a family history of PrCa are at a substantially greater risk for developing the disease, recent studies showed no difference in clinical presentation and prognosis by biochemical progression compared to sporadic cases, with the exception of PrCa cases among BRCA2 carriers (as describe below) [72, 73]. Meanwhile, an increased diagnostic activity among men with a family PrCa history had also contributed to a detection bias [74]. Thus, there is a controversy whether PSA-based screening should be offered to all men with a family PrCa history.

## Gene Variants

Many genetic linkage studies and genome-wide association studies (GWAS) have been reported to explain the hereditary basis of PrCa. These investigations enabled the prediction of

risk of men to develop PrCa based on gene variants [69, 75]. There are indications that up to 90 % of men that had a familial history of PrCa were interested in undergoing genetic testing [70].

GWAS try to identify genes involved in human disease using single nucleic polymorphism (SNP) covering the entire human genome. GWAS have identified at least 40 reported SNPs that are associated with PrCa risk [75–77]. But each SNP had very low odds ratio (OR) between 1 and 1.3. The combination of the 30 selected SNPs only explained 13.5 % of the total genetic variance in the European population associated with PrCa risk [78]. Another study showed that a combined set of SNPs associated with an OR of 2.5 was found in only present 1.3 % of the population [77]. Another challenge is more SNPs will be detected as sample sizes increase and additional populations are studied [75].

Recently, at least two risk prediction models using combined panel of SNPs and family history were tested. These models identified about 0.5–1 % of men have 41–52 % risk for developing PrCa between ages 55 and 74 years. The limitation of this risk prediction model still could not define aggressive PrCa risk. This was due to the fact that the panel of SNPs used was not correlated to aggressive PrCa features. It was expected that increasing novel SNP finding can improve risk prediction model [79].

GWAS also found at least six SNP variants that are related to PSA level. This study evaluated the combined relative effect of the SNPs variants primarily associated with PSA levels to variation in PSA levels among individuals. This study found that unnecessary biopsies are more likely to be performed on individuals with elevated PSA levels due to genetic variants factors. Then this study proposed a personalized PSA cutoff value, based on genotype variants, to decide a prostate biopsy [80]. Genetic variants test for PrCa risk is already commercially available, but it still needs further validation study. The cost-effectiveness and the utility for the individual patient remain the main challenge for SNP-based selection to identify high-risk populations.

## BRCA2 Carrier

Another gene that was shown to be related to PrCa risk is BRCA2. Men with BRCA2 mutations have been reported to have 4.7 relative risk of PrCa, more aggressive disease, and a high mortality rate. Men with BRCA1 mutations are reported to have lower relative risk of PrCa than those with a BRCA2 mutation. A large international study is ongoing to study the effect of PSA-based PrCa screening in BRCA mutation carrier men. Preliminary report of this study showed higher population incidence of PrCa, as observed particularly in BRCA2 mutation carriers, that can affect the PPV of screening [69, 81].

## Risk Calculator for Biopsy-Detectable PrCa

PSA was considered as a range of risk. PrCa occurs in men at all PSA ranges and a significant number of men with "normal" PSA levels (<2.5 ng/ml) have high-grade PrCa. PSA by itself may not be the only factor to consider when selecting men for prostate biopsy. This led to the development of a biopsy-detectable PrCa predictive risk calculators (or nomograms), which combined several risk factors with PSA level [30, 82, 83]. These combinations will improve the diagnostic value of PSA by increasing its sensitivity and specificity and provide individual risk estimation of having a biopsy-detectable PrCa [32, 84, 85]. Mathematically, a nomogram is a graphic calculating scale design to provide an approximate calculation of a function. In clinical practice, a nomogram is used as an algorithm to predict the probability of an outcome [86]. Recently, there are two online biopsy-detectable PrCa risk calculators available, which come from ERSPC study based on European population (http://www.uroweb.org or http://www.prostatecancer-riskcalculator.com/via.html) and PCPT study based on United States (US) population (http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp) [49]. These risk calculators have already proved to support in individualized clinical decision-making and reduced the number of unnecessary biopsies with a marginal loss of potentially aggressive PrCa [85].

The main limitation of these risk calculators is their development depends on population characteristic. It is well known that ERSPC risk calculator was based on Dutch section of ERSPC; meanwhile PCPT risk calculator was based on US population. PrCa characteristics may not be the same in Europe as in the USA [84]. Indeed, the PCPT risk calculator that had been applied retrospectively to the ERSPC has been found to be miscalibrated and gave a higher risk. It is also questionable whether the risk calculator based on European population can be applied to a US population. Thus, validation of the risk calculator on a variety of different population is needed [87].

Tools that were developed in a different era may not provide equally accurate predictions in contemporary patients. So this nomogram should be updated and developed [84]. The latest development in risk calculator is the use of a PCA3 score [49, 66, 82, 88]. As at least half of PrCa cases detection in screening was an indolent PrCa, more discussion recently also move to the development of risk calculator to predict indolent PrCa as effect of screening [49, 89].

### Conclusion

A rather diverse recommendation for PrCa population-based screening is due the low specificity of the serum PSA test. The way forward is to find new biomarkers that are better than PSA or can complement serum PSA in its weak characteristics, particularly the low specificity.

The development of new high-throughput molecular tools has given the way to find such novel markers. Biomarker assays for urine have expanded the (screening) marker panel for PrCa. It so far has taken a long time to bring a discovery of a new marker into the realm of routine clinical. For PCA3, for example, it has taken more than 7 years to develop it into a clinical test. However, the valuable experiences now enable a much faster translation from bench to bench, like for the gene-fusion-based tests. In the mean time, targeted population screening can be an option. The risk calculator approach is the closest option to overcome PSA limitation, integrate all clinical and laboratory parameters, and include new tests.

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# Diet and Prostate Cancer: A Holistic Approach to Management

29

Philippa J. Cheetham and Aaron E. Katz

## Introduction

Prostate cancer foci are believed to exist in 30% of men >50 years and in 75% of men >80 years [1]. Most of these foci remain latent and do not grow or spread to any significant extent, and the occurrence of such foci is fairly consistent worldwide.

There is now increasing evidence from epidemiologic surveys and from laboratory, intervention, and case-control studies that diet and lifestyle play a crucial role in prostate cancer biology and tumorigenesis. This applies to both the development and progression of prostate cancer, although in many cases the specific initiating factors in the diet are poorly understood. Many nutrients and herbs also show significant promise in helping to treat prostate cancer by slowing progression and reducing recurrence, ultimately reducing the risk of morbidity and mortality from the disease. Furthermore, for all grades of prostate cancer, nutritional interventions complement conventional treatment to improve response and quality of life.

With high incidence (currently affecting one in six men in the United States), a long latency period, and strong environmental influences, prostate cancer is an ideal target for chemopreventative approaches. In this context, the term chemoprevention is used to describe nutritional interventions (i.e., changes in diet and the use of specific nutritional supplements) to slow or reverse the progression of premalignant lesions (i.e., high-grade prostate intraepithelial neoplasia [PIN]). Reversing PIN with chemopreventative agents could be the best primary defense against prostate cancer, preventing it from occurring in the first place.

The information given in this review about prostate cancer chemoprevention will benefit the health of every man, whether he has prostate cancer or not. Most nutritional chemoprevention agents also have the added benefit of being beneficial for the cardiovascular system, bone health, and for the prevention of other cancers.

## Epidemiology

African American men in the United States have the highest risk of prostate cancer on the planet, with a much greater risk of advanced, invasive prostate cancer and prostate cancer death. Caucasian and African American men have a prostate cancer incidence that is 5–50 times greater than that of Japanese men residing in Japan [2, 3].

Furthermore, migration studies reveal that risk shifts in men who move from low-risk to high-risk countries. When a man adopts the lifestyle and diet of a high-risk country, his risk rises correspondingly. Risk of prostate cancer thus increases substantially within a single generation in lower risk men who relocate to the United States. The incidence of prostate cancer in Japanese immigrants to the United States is four times that of their native Japanese counterparts. The risk of prostate cancer in Indian men in the United States is comparable to that of native-born American men. These changes in risk are linked to changes in diet and lifestyle that most immigrants adopt when they make the United States their home. These men exercise less and eat a diet heavier in fats, alcohol, and meat and lower in fiber. As more of the planet eats like Americans, the incidence of prostate cancer is rising even in relatively low-risk countries. This, along with marked racial and cultural disparity, indicates that diet plays a strong role in prostate cancer risk.

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## Evidence for Dietary Intervention

In research conducted at the Preventive Medicine Research Institute at the University of California, San Francisco, Ornish et al. [4] demonstrated the power of diet and lifestyle changes in 87 men with prostate cancer (prostate-specific antigen [PSA] 4–10 ng/mL; Gleason score <7) who chose not to undergo conventional treatments during a 1-year period. Subjects were enrolled either in a program of extensive, comprehensive lifestyle changes, including a low-fat, vegetarian, soy-rich diet and nutritional supplements; exercise; psychosocial support; and stress reduction, or in a usual case-control group. Not one of the men in the experimental group required conventional treatment during the study period, but six control subjects required such treatment. This study and other research studies strongly suggest that if men who would otherwise be told to watch and wait were offered the information and motivation they need to enter into a focused chemoprevention program, we could have a significant impact on disease progression, as well as on other important aspects of men's overall health. Following a nutritional plan also gives men the power to do much more than watch and wait; active holistic surveillance that incorporates diet and lifestyle changes along with some of the herbs, supplements, and other holistic interventions to promote the body's natural defenses against cancer growth and spread gives men the tools they can use to heal themselves proactively.

## Diet and Prostate Cancer Risk

Fat content of the diet, overall caloric intake, the ratio of omega-6 to omega-3 fatty acids in the diet, and consumption (or lack thereof) of meat, antioxidants, and soy foods are the major factors that appear to correlate most closely with risk of prostate cancer and risk of death from this disease. These dietary factors may act as late-stage promoters rather than initiators transforming a relatively harmless, latent prostatic neoplasia into a more aggressive form.

### Dietary Fat

Fat intake, especially from animal sources, has been linked to an increased risk of developing prostate cancer in several studies. In a 31-country study, investigators also found a close correlation between fat intake and prostate cancer mortality [5, 6]. Within populations with a low risk of prostate cancer, such as Chinese men, the percentage of fat in the diet is strongly predictive of whether they will ultimately develop the disease [7]. Another case-control study, which was performed in Utah, found that men with high-fat intake had the highest risk of developing aggressive prostate tumors [8].

The exact mechanism by which dietary fat induces prostate carcinogenesis is unclear. Possible explanations include the effects of dietary fat on serum testosterone levels, oxidative stress, or increases in the hormone insulin-like growth factor-1 (IGF-1) with those on a high-fat diet having higher IGF-1 levels. On the other hand, more fat in the diet may boost conversion of testosterone to estrogens, which may have protective effects against cancer progression.

### Obesity

Men who are obese have an increased risk of developing prostate cancer. Obesity has also been strongly implicated as an independent risk factor for high-grade prostate cancer and prostate cancer mortality [9–11]. Obesity is not only a risk factor for prostate cancer; it can also increase the risk of recurrence. In some cases, obesity may be correlated to high-fat intake, although the more likely culprit is high-caloric intake.

### Physical Activity

The increased risk of prostate cancer in obese men is related to changes in hormone balance. Excess body fat alters estrogen and testosterone activity, and lower testosterone is associated with lower PSA at diagnosis. Tymchuk et al. [12] found that when obese men were put on a very-low-fat (<10% of calories from fat), high-fiber diet, and exercise programs, all of those men who had high PSA levels (>2.5 ng/mL) saw those values fall. Sex hormone-binding globulin (SHBG) rose and free testosterone levels dropped, possibly decreasing growth-promoting effects on the prostate. Another hazard of obesity—one that increases risks of all cancers, as well as heart disease—is that it exacerbates both inflammation and oxidative stress. Obese men are also more likely to have high insulin levels and high blood sugar levels.

Refined carbohydrates also fan the flames of chronic inflammation. Food sources rich in refined carbohydrates (or saccharides) include table sugar, corn syrup, fruit, white bread, white pasta, fizzy drinks, and cakes. Carbohydrates, particularly those with a high glycemic load, consumed in excessive amounts, result in a state of relative hyperinsulinemia and obesity. This has been postulated to increase the risk of developing prostate cancer through higher bioavailability of circulating estrogen and IGF-1 [13]. None of this bodes well for a man's prostate; it exacerbates both inflammation and oxidative stress. Further studies and randomized controlled trials are thus urgently required to investigate the potential role of carbohydrate consumption in prostate cancer in humans.

## Saturated and Trans Fat

Before the advent of highly processed diets, the ratio of omega-6 to omega-3 fats in typical diets was about two or three to one. Today's standard processed-food American diets, however, yield a ratio as high as 40:1. An American high-fat diet is high in omega-6 polyunsaturated fatty acids (PUFAs) and trans fats.

A high intake of saturated fatty acids (SFA) (from red meats, processed meats, egg yolks, whole fat dairy foods), trans fatty acids (from processed, hydrogenated vegetable oils), and omega-6 PUFAs, particularly arachidonic acid (AA) and linoleic acid (LA), have been associated with both an increase in the incidence of prostate cancer and of mortality. All authorities agree that trans fatty acids should be avoided completely. Saturated fats are probably not intrinsically carcinogenic. There are, however, chemical toxins found in most sources of saturated fat, as a result of modern factory farming methods. Toxins that can raise cancer risk concentrate in the fat of animals that eat a diet laced with pesticides and herbicides. Even higher concentrations of these toxins accumulate in dairy products and eggs.

Conversely, higher intake of the omega-3 fatty acids docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-linolenic acid (ALA) is associated with a reduced risk of prostate cancer. The protective effects of omega-3s (found in oily fish such as salmon and mackerel) may be prostate cancer protective by reducing inflammation. In a Swedish study, those subjects who ate oily fish more than three times a week had almost half the risk of metastatic prostate cancer compared with those who ate fish less than twice a month. Each additional daily intake of 0.5g of marine fatty acid from food was associated with a 24% decreased risk of metastatic cancer [14].

Unrefined vegetable oils rich in phytosterols, including beta-sitosterol and campesterol, are also believed to reduce the risk of prostate cancer; Asian and Mediterranean diets, both rich in phytosterols, thus confer reduced risk compared with the standard American diet, with its abundance of cholesterol, refined oils, and saturated fats.

Olive oil in the diet, a source of neutral omega-9 fatty acids, has been found to be protective against many cancers, including prostate cancer.

## Dairy Products

Clinical studies assessing dairy intake and risk of prostate cancer have shown conflicting results. A large meta-analysis of 45 observational studies showed no evidence of increased risk [15]. Other large meta-analyses have showed that men who consume more dairy products have an 11–39% higher risk of prostate cancer [16, 17]. The most likely explanation for this increased risk is a high dairy diet resulting in increased levels of plasma calcium, which in turn cause suppression of 1,25-dihydroxyvitamin D3 [18]. Other researchers have suggested that the increased risk is attributable to the high amount of saturated fat present in dairy, as well as increased circulating IGF-1 levels which have also been implicated in an increased risk of prostate cancer [13, 19, 20]. There is very limited data assessing the effect of dairy intake and prostate cancer progression, although some studies have suggested a low dairy diet may prolong PSA doubling time [21].

## Exercise and Weight Management

Studies demonstrated that physical activity is important in preventing prostate cancer. In one large prospective study, men over 65 who exercised the most had the lowest risk of prostate cancer [22]. Exercise also helps maintain normal body weight and obesity is a risk factor. In one study involving men who previously had prostate cancer, those with the highest BMI had the highest risk of developing the disease. Improving physical and psychological health has also shown promising results in prostate cancer survivors. Physical activity for at least 30 minutes a day and lifting weights or performing resistance exercises several times a week has a positive effect on reducing the side effects of androgen deprivation therapy (ADT). Exercise reduces the risk of weight gain, reduces insulin resistance, and minimizes bone loss, all of which are so prevalent in men on ADT.

## Meat

There is considerable evidence across populations that the more red meat a man eats, the higher his risk of developing prostate cancer. Meat contains high amounts of arachidonic acid. Some byproducts of arachidonic acid have promoted prostate cancer in animals [23]. Preliminary reports have suggested that frequently eating well-done steak or cured meats is a risk factor. Meat contains high concentrations of heterocyclic amines (HCAs) (in particular meat that has been cooked at high temperatures and is thus well done or charred, creating poly-aromatic hydrocarbons). Cured meats contain nitrosamines because meats contain amines, and sodium nitrite, a source of nitrosating agents, is added to cured meats as a preservative. These chemicals concentrate preferentially in the prostate gland, where they enhance free radical production and trigger carcinogenesis. Colli and Colli found strong correlations between prostate cancer mortality and intake of meat, reported in two retrospective population studies assessing prostate cancer mortality in 71 countries [24, 25]. Marinating meats in a mixture of olive oil, vinegar, and protective spices like garlic, rosemary, or turmeric reduces the

production of carcinogenic substances during cooking. Eating plenty of crucifer vegetables (broccoli, cauliflower, and cabbage) further helps by neutralizing the effects of heterocyclic amines in the body.

## The Ideal Prostate Cancer Chemoprevention Diet

Slowing the growth of latent foci of prostate cancer is best achieved with a combination of dietary and nutritional supplements. Current evidence supports the notion that the most effective prostate cancer protective diet is low in red meat and dairy and high in fruits, vegetables, whole grains, herbs (especially Asian herbs like turmeric and ginger), and green tea.

Overall, the best diet for prostate cancer chemoprevention most closely resembles the traditional diets of the southern Mediterranean and Japan. Fish and soy foods take the place of red meats, and dairy products are kept to a minimum. When oils and fats are called for, they are included in the form of oils that help reduce the omega-6 to omega-3 balance. Whole grains are favored over refined grains and foods made with flour and sugar. Both diets contain abundant fiber. Yet these two diets differ in many important ways: The Mediterranean diet is rich in tomatoes, which are the best source of cancer-fighting lycopene. Its main source of fat is olive oil, which (in its extra-virgin form) is high in important antioxidants. Olive oil is high in omega-9 fatty acids, which do not promote inflammation, and contains a compound called oleocanthal that has anti-inflammatory properties. The Japanese diet includes a variety of medicinal mushrooms that have great value for cancer prevention. Japanese diets also incorporate sea vegetables. Soy foods and ginger are important parts of Japanese cuisine; Mediterranean cuisine is often flavored with rosemary and oregano. All of these foods have cancer-fighting properties.

Fruits and vegetables have high concentrations of various phytochemicals, antioxidants, and fiber and are therefore promoted not only in healthy populations for the prevention of cancer but also in cancer survivors. Red meat should be a small part of the diet, if consumed at all, and grass-fed, organic beef, free-range poultry, game, eggs, and wild-caught ocean fish are the best options for flesh foods. Tempeh, tofu, and miso are good alternative protein sources.

Whole grains in the diet have an inverse relationship with prostate cancer risk. They are rich in fiber that helps remove carcinogens from the body. Grains should be chosen in a form as close as possible to the ones in which they occur in nature: brown rice instead of white and whole-grain or sprouted-grain crackers and breads, for example. Nuts and seeds are good additions to the chemopreventive diet; unrefined extra-virgin olive oil and ground flaxseeds are positive additions to the diet, particularly when stirred into organic, low-fat, and live-culture yogurt (the best choice of dairy product) or oatmeal. Flour and sugar intake should be minimized, as well as the consumption of trans refined fats and other highly refined vegetable oils, which promote the proinflammatory eicosanoid cascade.

Research suggests that the following natural substances may be of some benefit in prostate cancer prevention:

### Fruit and Vegetables

An antioxidant-dense diet made up primarily of whole plant foods (vegetables, fruit, whole grains, nuts, and seeds) provides a good antioxidant foundation. Certain foods like pomegranates, tomatoes, dark leafy greens, deeply colored fruits, and cruciferous vegetables (broccoli, cauliflower, and the like) are especially dense with protective antioxidants.

### Phytoestrogens

Phytoestrogens are a group of biologically active plant compounds with a chemical structure similar to estradiol, of which isoflavones are the most important. Foods rich in isoflavones include soy bean, tofu, kidney beans, lentils, chick peas, and peanuts.

There is conflicting information on soy and soy isoflavones and prostate cancer risk. Current evidence indicates a possible protective effect of dietary soy in prostate cancer prevention [26]. The effects of concentrated soy extracts and other phytoestrogens are less clear.

Differences in the level of consumption of traditionally prepared dietary soy foods (i.e., miso, tofu, tempeh, natto) is believed to contribute to the significant difference in prostate cancer incidence and mortality between Asian and American men. A large-scale epidemiologic study by Hebert et al. [27] of 59 countries found that soy-derived products offered highly significant protection against prostate cancer. Animal studies reveal that soy isoflavones, particularly genistein, inhibit prostate cancer growth in cell cultures [28]. In rat models, genistein has been found to offer significant chemopreventive activity against advanced prostate cancer. Possible mechanisms of action include estrogenic properties (binding to estrogen receptors thus suppressing cellular proliferation and promoting differentiation *in vitro* and in vivo) and inhibition of 5α-reductase (5AR). Soy foods contain protease inhibitors, saponins, and phytates, which have putative anticarcinogenic effects.

Some of the conflicting information on soy may be due to the fact that men eating a Western diet (full of meat and low in vegetables) have a different population of bacteria inhabiting their gut. These bacteria may not effectively break down soy into its active metabolite, genistein. Men eating a traditional Japanese diet tend to experience greater benefit from soy in

terms of preventing prostate cancer because they have been eating soy foods as a part of their daily diet for years. They are therefore more likely to have a population of gut bacteria that effectively metabolize soy isoflavones into genistein: men who incorporate soy foods in the diet abruptly may not receive the same benefit.

### Tomatoes and Other Lycopene–Rich Foods

Lycopene is a bright red carotenoid pigment found in tomatoes, watermelons, pink grapefruit, and papaya. A number of small studies indicate that regular consumption of lycopene (from eating raw tomato and cooked tomato products) may help prevent prostate cancer [29], as well as reducing the risk of progression in those who have the disease [13, 18–30] Cooked tomatoes and tomato sauce are better than raw tomatoes because cooking them releases lycopene from their storage sites. *In vitro*, lycopene has been shown to exert its antiproliferative effects on various cancer cell lines by causing cell cycle arrest and inducing apoptosis [31]. It also increases IGF-1 binding proteins thus resulting in a reduction in serum IGF-1, which has previously been associated with increased risk of prostate cancer [32]. However, no studies have proven that taking lycopene in supplement form can decrease the risk of prostate cancer. Further, well designed large-scale studies are required to establish the role of lycopene in the prevention and treatment of prostate cancer [33, 34].

### Silymarin

This phytochemical found in the herb milk thistle was shown *in vitro* to inhibit prostate cancer cell growth [35]. Silymarin actually refers to several different flavonoid compounds with similar structures: silibinin, the most prevalent form, has been entered into phase I and phase II clinical trials with prostate cancer patients [36].

### Delphinidin

Delphinidin from berries caused apoptosis of prostate cancer cells along with significant inhibition of tumor growth in an animal study [37].

### Quercetin

A preliminary cellular study in the journal of Carcinogenesis demonstrated that the flavonoid quercetin has potential as both a preventive agent and a complementary treatment for prostate cancer [38, 39].

### Fiber and Lignan Intake

Lignans are found in seeds, whole grains, vegetables, fruit, and legumes, but the richest dietary source of lignans is flaxseed. Diets rich in this and other fibers have consistently been associated with reduced prostate cancer risk [40]. Duke University investigators added 30g of ground flaxseed/day for an average of 34 days (21–77 days) to the diets of 25 patients scheduled for prostatectomy. The men were also placed on a 20% fat diet for the study's duration. During the study, testosterone and free androgen levels fell, proliferation rate fell, and cell apoptosis was enhanced [41]. To enhance lignan intake, patients may be advised to supplement their diets with three tablespoons of flaxseed daily; the seed meal can be added to yogurt, hot cereals, soups, stews, or nut butters. The seeds also can be ground in a coffee grinder, or they can be purchased already ground.

### Cruciferous Vegetables

Consumption of cruciferous vegetables from the Brassicaceae family, including broccoli, cauliflower, and cabbage, is inversely related to the incidence of prostate cancer. Broccoli in particular has been shown in clinical trials to help prevent prostate cancer. Sulfur-containing glucosinolate breakdown products indole-3-carbinol (I3C) and sulforaphane are phytochemicals found in crucifers, and both have been demonstrated to reduce the proliferation of prostate cancer in vivo in a dose-dependent manner. I3C reduces the proliferation of cancer cells and increases cell apoptosis; some investigations have found that supplemental doses of this nutrient chemosensitize chemoresistant prostate cancer cells, aiding in the treatment of hormone-resistant cancers [42]. Supplements of I3C and sulforaphane are available, such as BroccoProtect®; however, more research is needed to determine whether these supplements are more useful chemopreventives than the foods from which they are derived.

### Fish and Fish Oils

The long-chain ω-3 fats DHA and eicosapentaenoic acid (EPA) are abundant only in fish, crustaceans, and some forms of algae. They have been found to suppress cancer initiation, induce cell apoptosis, and decrease proliferation of several cancers including prostate cancer, causing decreased PSA doubling time in a mouse model. This appears especially true when the overall diet is altered to reduce intake of red meat, dairy products, hydrogenated oil, and highly unsaturated vegetable and seed oils, which are staples of the standard American processed-food diet and sources of saturated fats, ω-6 polyunsaturated fats, and trans fats [43, 44]. These

three classes of fat have been linked with increasing incidence of cancer in the prostate and breast.

The short-chain ω-3 fat found in plant foods such as flaxseeds, which contain ALA, has not matched DHA and EPA in its chemopreventive effects; to act as a substrate for the production of anti-inflammatory eicosanoids, ALA must first be converted to long-chain ω-3 PUFAs, an inefficient process. Flaxseeds, walnuts, and soybeans, the most important dietary sources of ALA, are still good foods to include in the chemoprevention diet, but they should not be relied upon as sole sources of ω-3 fats.

Numerous investigations have found that the consumption of fish three to four times per week confers a significant reduction in prostate cancer occurrence (a two- to threefold reduction in one study and a 40–44% reduction in risk in two other studies) [14, 45, 46].

The evidence in favor of fish oil supplementation is adequate to make general recommendations for patients to consume one each day and to use a fish oil supplement that has been purified (pharmaceutical grade or molecularly distilled), contains an antioxidant, such as vitamin E or rosemary oil, to prevent rancidity, and that comes from small, oily cold-water fish, such as anchovies or sardines. Current guidelines indicate that patients may benefit from 1,000 to 3,000 mg/day of combined EPA and DHA, with higher EPA than DHA content.

## Green Tea

Green tea is derived from the plant Camellia sinensis. The tea leaves are very rich in polyphenols, known as catechins, of which epigallocatechin-3-gallate (EGCG) makes up 10–50% of the total catechin content. EGCG inhibits cellular proliferation primarily by acting as a very potent antioxidant scavenging free radicals along with 51 other compounds present in green tea that have anti-inflammatory activity. Other modes of antitumorigenic action include apoptosis and cell cycle arrest via alterations in the mitogen-activated protein kinase, phosphatidylinositol-3-kinase (PI3K)/Akt, and protein kinase C pathways; inhibition of inflammatory pathways (nuclear factor-kB and cyclooxygenase-2(COX-2)); and modulation of the insulin-like growth factor and androgen receptor axes [47].

In oriental cultures in which green tea plays a major role in diet, the incidence of and mortality from prostate cancer is significantly lower. Several studies have confirmed green tea as a potent agent against many cancers, including prostate cancer [48]. A recent small double-blind human trial demonstrated that green tea was effective at treating high-grade prostatic intraepithelial neoplasia (HGPIN) with a significant reduction in the incidence of prostate cancer [49]. Researchers at Louisiana State University conducted a study involving 26 cancer patients. Prior to their scheduled surgery, the patients were given a green tea extract containing 800 mg of EGCG (equivalent to 12 cups daily) for an average of 34.5 days. The patients had significant reductions in blood levels of PSA, VEGF, and HGT, all of which are correlated with prostate cancer growth [50]. Furthermore, in a population study published in 2008, researchers looked at data on 49,920 men (ages 40–69) and found that consumption of green tea was linked to a dose-dependent reduced risk of advanced prostate cancer in men who drink more than five cups of green tea per day [51]. Most men will not drink 6 cups per day of green tea; therefore, supplementation with a concentrated extract appears to be an important aspect of herbal chemoprevention [49–52].

*Essiac Tea*—a combination of four herbs (*Rheum palmatum*, *Trifolium pretense*, *Arctium lappa*, *and Rumex acetosella*) has also been found *in vitro* to inhibit prostate cancer cell growth.

## Pomegranate Juice

Pomegranate is a rich source of polyphenolic compounds, including anthocyanins and hydrolysable tannins. It has a reportedly higher antioxidant activity than green tea and red wine as well as anti-inflammatory properties. Recent studies show that anatomically discrete sections of the pomegranate fruit acting synergistically exert antiproliferative and antimetastatic effect against prostate cancer cells. Furthermore, pomegranate fruit extract treatment of highly aggressive PC-3 cells resulted in a dose-dependent inhibition of cell growth/cell viability along with induction of apoptosis coupled with corresponding laboratory effects on prostate cancer *in vitro* cell proliferation and apoptosis, as well as oxidative stress [53].

Pomegranate juice has also been shown to increase mean PSA doubling time. A human clinical trial featuring men with rising PSA levels demonstrated that drinking just 8 oz of pomegranate juice daily was effective at stabilizing PSA levels up to four times longer than normal, potentially delaying the growth of prostate cancer cells [54].

## Eicosanoids and Anti-inflammatory Chemoprevention

Inflammation is mediated by hormone-like chemicals called eicosanoids. Some eicosanoids encourage chronic inflammation; others discourage it. They impact the action of the immune system as well as the constriction of blood vessels, blood clotting, stomach acid secretion, and the intensity and longevity of pain and fever. Eicosanoids are built from polyunsaturated fats. Fats dictate the action of

enzymes that build eicosanoids. Certain enzymes make "good," anti-inflammatory eicosanoids; others make "bad," proinflammatory eicosanoids. "Good" eicosanoids are made from omega-3 fats, found in fish, walnuts, flaxseeds, and leafy green vegetables. "Bad" eicosanoids are made from omega-6 fats, found in many vegetable oils used to make processed foods, including oils made from corn, soybeans, sunflower, safflower, and cottonseed. Meats and dairy products, which come mostly from animals that are fed a grain-rich diet, also are high in omega-6s. The body's production of eicosanoids depends in large part on the balance of these fats in the diet.

In prostate cancer, the eicosanoid-building enzymes that seem to have the greatest impact on progression are *cyclooxygenase-2* (COX-2), *5-lipoxygenase* (5-LOX), and *12-lipoxygenase* (12-LOX). These enzymes lead to the production of proinflammatory eicosanoids like *prostaglandin E2* and *leukotriene B4*. COX-2 overexpression is a predictor of a worse prostate cancer outcome [44].

Other studies have suggested that angiogenesis is orchestrated in part by increased COX-2 activity and ensuing prostaglandin production, a hypothesis supported by the effects of some COX-2 inhibitor drugs (i.e., celecoxib) on the biochemical measures of apoptosis.

The anti-inflammatory aspect of chemoprevention appears to be a pivotal one, particularly in cases of PIN, which can appear up to 10 years before diagnosable cancer and which coexists with cancer in >85% of cases. PIN also offers investigators the opportunity to apply chemopreventive measures when dysplasia is present and the point at which prostate carcinogenesis may be at its earliest stage.

Manipulation of proinflammatory eicosanoids can be achieved in two ways: (1) with manipulation of fatty acid intake, providing the body with increased substrate for the production of anti-inflammatory eicosanoids, which then competitively inhibits formation of proinflammatory eicosanoids and (2) with manipulation of COX and lipoxygenase (LO) enzyme isoforms, inhibiting those that promote the inflammation that encourages prostate carcinogenesis. So far, it appears that fatty acid intake is a safe and effective intervention in this regard. Manipulating COX and LO with pharmaceutical agents, however, has proven to be a less promising avenue for chemoprevention. Recent case–control studies have found significant risks regarding long-term COX-2 inhibitor therapy, with increases in mortality and risk of heart failure and gastrointestinal (GI) bleeding.

Herbal anti-inflammatory agents have a broader, less specific effect and the research community is beginning to recognize their therapeutic value. Many researchers have explored a variety of natural plant extracts and other natural products to elucidate their specific and nonspecific effects on COX and LO. Curcumin (turmeric), ginger, holy basil, resveratrol (concentrated in grape skins), and berberine (from barberry and Chinese goldthread) are among the most promising candidates in the burgeoning field of herbal anti-inflammatory agents.

A novel compound under further study, Zyflamend (New Chapter, Brattleboro, VT), is composed of these and a few other herbs, most of which have a nonselective COX inhibitory effect. Each of the mixture's components has been found to have anti-inflammatory, antioxidant, or antiproliferative effects; some are even antiangiogenic. In 2005, Bemis et al. [55] published the results of an analysis of Zyflamend's effects on LNCaP cells—significant decrease in both COX-1 and COX-2 activity; increased p21 expression; attenuated cell growth; and induced cell apoptosis. A phase 1 clinical trial is currently being conducted at Columbia University in men with PIN to determine whether Zyflamend can influence the progression of biopsy-proven high-grade PIN to prostate cancer. Preliminary results are promising [56].

## Curcumin

Curcumin, or turmeric, has been found to be a potent radiosensitizer that enhances radiation-induced clonogenic inhibition in tumor cells [57]. A recent in vivo study showed that curcumin can help prevent prostate cancer. Dorai et al. [58] found that curcumin modulates proteins that suppress cell apoptosis and interferes with growth factors that promote cancer progression [59].

## Ginger

Ginger flavors many cuisines and has been a herbal medicine since antiquity, used to treat nausea, motion sickness, upper respiratory infections, and intestinal parasites. Modern investigators have discovered >20 phytochemicals in this rhizome that inhibit COX-2 and 5-LO. Ginger constituents have potent antioxidant and anti-inflammatory activities; some, particularly shogaols and vallinoids [6]-gingerol and [6]-paradol, exhibit cancer-preventive activity in experimental carcinogenesis. The chemopreventive effects of ginger have been illustrated in a variety of experimental models [60].

Prostabel, a herbal combination containing extracts of pao pereira (an Amazonian tree) and Rauwolfia vomitoria (from the bark of a sub-Saharan plant), was created by the late molecular biologist Mirko Beljanski. These plants have been used in indigenous medical traditions for centuries; Beljanski found that they had anticancer activities in various cancer cell lines, including prostate cancer. Research has revealed that both Rauwolfia and pao extracts suppress prostate tumor cell growth in culture and in vivo. Patients with elevated PSA and negative biopsy results are now being

enrolled in a phase 1 study of this herbal medicine. Results are awaited [61].

The herbs discussed in this review are relatively free of interactions with prescription drugs. Turmeric, however may potentiate antiplatelet activity in patients on antiplatelet agents; ginger and turmeric may potentiate the effects of anticoagulants. Patients should be advised that herbs and drugs can interact in harmful ways and that they should reveal the use of all medications and supplements to their physicians so that these adverse interactions can be avoided.

## Individual Micronutrients as Chemopreventatives

Vitamins are a group of structurally and functionally unrelated organic compounds that are essential for the normal functioning of the body and are present in various different food sources. According to a survey by the American Institute of Cancer Research (AICR), roughly half of adults >45 years take multivitamins specifically to lower the risk of developing cancer. In this same survey, 23–36% of subjects reported using other supplements for the same purpose [62]. No single nutrient has been found to stand alone as a chemopreventive agent. Notwithstanding current evidence in favor of individual nutrients from animal and *in vitro* models, the synergistic action and interaction of wide spectrum of micronutrients are the most likely reasons for the health benefits of disease-preventive foods, not the isolated action of any one or two nutrients in those foods.

The evidence does point strongly to the supplemental use of a handful of nutrients, in addition to a diet composed of beneficial and nutrient-dense foods in prostate cancer prevention. Vitamin E, selenium, vitamin D, and calcium all appear to play roles in prostate health. Supplementation of some vitamins and minerals may be appropriate as part of a chemopreventive program.

## Vitamin E

Vitamin E is a general term referring to a class of related compounds, including α-, P-, Σ-, and ψ-tocopherol and α-, P-, Σ-, and ψ-tocotrienols. α-Tocopherol has the highest biologic activity of all these compounds. In foods, vitamin E exists as a mixture of these various compounds, each of which has unique and interactive effects. The inhibitory effect of vitamin E on prostate carcinogenesis is probably attributable to its potent antioxidant effect in membrane phospholipids. It is the major hydrophobic chain-breaking antioxidant that protects membrane lipids from oxidation. Animal and preclinical studies have found that vitamin E also has direct antiproliferative effects unrelated to its antioxidant capacity [63], including inhibition of protein kinase C (PKC) activity, which plays an important role in proliferation, adhesion immune response, free radical production, and gene expression. Vitamin E also appears to interfere with hormone signaling, which is particularly relevant to prostate carcinogenesis.

Several RCTs have evaluated the role of Vitamin E either alone or in combination with other vitamins. In the large α-Tocopherol, B-Carotene (ATBC) RCT study, 29,133 male smokers received daily doses of 50 mg α-tocopherol (Vitamin E), 20 mg B-carotene (Vitamin A), both, or a placebo for 5–8 years. Although B-carotene had no effect on prostate cancer risk and it increased the risk of lung cancer and total mortality in this cohort, α-tocopherol supplementation reduced the risk of prostate cancer by 32% [64, 65]. Other research by the same Finnish investigators found that higher circulating concentrations of α-tocopherol and ψ-tocopherol, the major vitamin E fractions, correlated with a reduced risk of prostate cancer [66]. A role for α- and ψ-tocopherol in prostate cancer chemoprevention is further supported by the results of serum case-control studies. Follow-up analysis of the cohort involved in the ATBC studies found that the risk ratio for prostate cancer rose again to 0.94 in the 6 years following the end of the supplementation protocol, suggesting that continual supplementation with vitamin E is necessary to maintain its chemopreventive effects in the prostate. Men should take a minimum of 240 international units (IU) of vitamin E daily as mixed tocopherols (α and ψ in particular).

The selenium and vitamin E chemoprevention trial (SELECT), the largest prevention trial ever undertaken using a drug or nutrient, involved over 35,000 men randomized to one of four arms (to receive either 200 μg selenium, 400 IU of Vitamin E, both nutrients, or two placebo capsules alone). This large double-blind placebo-controlled trial closed enrollment in 2004. The trial was terminated early as interim results failed to show any benefit with either of the components in reducing prostate cancer risk [67]. The evidence supporting vitamin E is a chemoprotective agent in prostate cancer thus remains controversial.

## Selenium

Selenium is an essential trace mineral that gives reduction/oxidation (redox) potential to vitamin E. It is found in Brazil nuts and certain seafoods such as tuna, swordfish, and oysters. Furthermore, the amount of selenium obtained in any diet can vary widely because of variations in the selenium content of soil in different parts of the world where food is grown. Population studies consistently show that men with higher intake of selenium have a lower risk of prostate cancer and that men with prostate cancer have lower selenium levels than men who do not have the disease.

In 1996, the nutritional prevention of skin cancer study found that although daily supplementation with 200 μg selenium did not prevent recurrence of skin cancer in men with a previous history of skin cancer, it did result in a substantial reduction in the incidence of prostate cancer [68]. Supplementation for 6.5 years correlated with a 60% reduction in the number of new cases of prostate cancer compared with placebo, and 7.5 years of supplementation yielded 52% fewer cases compared with placebo. These investigators used a form of selenium that had been fermented with *Saccharomyces cerevisiae* yeast, a process that increases the nutrient's bioavailability [68]. These results and the overall reduction in the risk of other cancers were so promising that the control arm of the trial was stopped early.

Other studies demonstrate that selenium supplementation alone may slow prostate cancer growth or aid in the prevention of recurrence. In one study, 974 men with a history of prostate cancer received 200 μg selenium/day or placebo. With about 4.5 years of treatment and a 6.5-year follow-up, the authors concluded that selenium treatment was associated with a 63% reduction in prostate cancer recurrence.

Laboratory studies have determined that selenium inhibits angiogenesis and cellular proliferation [69], as well as inducing apoptosis *in vitro* [70]. Selenium also potentiates vitamin E-induced inhibition of prostate cancer cell growth [71]. Vitamin E combined with selenium has been found to induce cellular arrest in abnormal cells. Five of six biomarker-based studies found an association between selenium intake and either a reduced risk of prostate cancer or a nonsignificant trend toward a lower risk of the disease [72–76].

The studies above initially raised the prospect of using selenium supplementation for chemoprevention of prostate cancer. The interim results of the SELECT trial, however [67] were disappointing, showing no benefit of selenium alone or when combined with vitamin E for prevention of prostate cancer, which led to the early closure of this trial, however, Recently, the results of another large multicenter phase III RCT using selenium vs placebo in men with HGPIN has proved equally disappointing with no benefit seen in the intervention group receiving selenium supplementation [77]. The role of selenium supplementation in men with an already established diagnosis of prostate cancer was recently studied by Chan et al. [78]. The authors concluded that selenium supplementation in certain patients may result in a more aggressive prostate cancer phenotype especially when patients have an altered genotype for the manganese superoxide dismutase (SOD2) enzyme. These results taken together now challenge the previous notion of a protective role of selenium supplementation with some studies even suggesting the converse. Further investigations into selenium for chemoprevention are ongoing [79–81].

## Calcium

Current guidelines for calcium intake for osteoporosis prevention recommend that men >50 years take 1,200 mg calcium daily. Yet, in epidemiologic studies of calcium intake from diet and supplements, men with the highest intake of calcium have a significantly elevated risk of prostate cancer [18, 82]. The calcium intake found to raise the risk of prostate cancer was >1,200 mg; however, calcium intake of >2,000 mg/day from food and supplements elevated men's risk of the disease to varying extents, with risk ratios for prostate cancer ranging from 1.2 in the 86,404 men enrolled in the Cancer Prevention Study II (CPS-II) Nutrition Cohort to 1.71 in the Physicians' Health Study. The risk ratio for metastatic disease was found to be 2.97 in the latter investigation. A small proportion of men (1% of study subjects) consumed enough calcium to raise their risk of prostate cancer, but the link does exist and it is consistent. Physicians should thus ensure that patients recognize the upper limit for calcium intake. If the patient consumes significant amount of dairy products along with a calcium supplement, it may be prudent to evaluate the patient's diet to reduce calcium intake.

The interplay between vitamin D and calcium is probably the reason behind this association. High calcium intake reduces the production of $1.25(OH)_2$ vitamin D, which has antiproliferative, differentiating, and antimetastatic effects [83].

## Vitamin D

Several studies have demonstrated that vitamin D can inhibit prostate cancer growth by promoting cellular differentiation and inhibiting proliferation, invasiveness, and metastases [84]. In areas of the world where sun exposure is low and thus vitamin D deficiency is more prevalent, prostate cancer rates increase [85] and geographical distribution of CaP mortality is the inverse of that of UV radiation [86].

An international placebo-controlled randomized trial is looking into whether vitamin D has benefits for those with prostate cancer. In a pilot study, PSA levels decreased or remained unchanged after patients were given 2,000 IU (50 mcg) of cholecalciferol daily. This was sustained for as long as 21 months. Also, there was a statistically significant decrease in the rate of PSA rise after administration of vitamin D. The doubling time for PSA was increased by approximately 50% in the men taking vitamin D [87, 88]. A recent study of 3,763 urology patients revealed that 68% were deficient in vitamin D [89]. It thus seems appropriate to measure 25-hydroxy vitamin D in patients to check they have normal levels between 30 and 70 ng/mL. Randomized phase III clinical trials are necessary to determine the optimal dose

and most optimal vitamin D analogue along with route and schedule of administration.

## Active Hexose Correlated Compound (AHCC)

Active hexose correlated compound (AHCC) is a mushroom mycelium extract derived from a liquid culture of basidiomycetous mycelia of *Lentinula edodes* (shiitake mushroom). It was developed by Amino Up Chemical Co. Ltd (Sapporo, Japan) in 1989 and has been used throughout the world for its antitumor effects through the purported upregulation of the innate and adaptive immune responses [90]. Its main active component is a mixture of oligosaccharides with an average molecular weight of 5,000 kDa, with about 20% of them being of the α-1, 4glucan type, which is likely to be the molecule responsible for the therapeutic effects of AHCC [91–93]. In studies to date, AHCC has been shown to have some biological response modifier-like activity in certain cancer patients.

AHCC has a number of effects at the cellular level on immune function. AHCC has been shown to significantly increase the number of total dendritic cells (DCs) [93]. AHCC has also been shown to have direct anticancer activity against certain tumor cell-lines [94] as well as increasing natural killer (NK) cell activity which is important in the elimination of tumor cells. AHCC was also found to increase production of IFN-y, TNF-α, and other cytokines important in the activation of effector cells, which translates into antitumor activity in the cancer microenvironment. These results may indicate that AHCC can improve immunological competence in cancer patients, many who are already on therapies that cause immunosuppression. Despite the relative lack of large-scale randomized controlled trials, the existing literature has shown AHCC to be effective in the treatment of numerous cancers including breast [95], liver [96], and prostate [97].

The only studies in the existing literature utilize the reduction of prostate-specific antigen (PSA) as the primary end point to indicate the effectiveness of AHCC in treating prostate cancer. Case reports, although not conclusive, have shown AHCC to be an effective treatment option for prostate cancer showing that PSA levels drop significantly as early as 1–2 months and reach normal levels by 4 months [94]. But the relatively small number of patients in AHCC studies, as well as lack of controls and statistical analysis, greatly limits their power.

Although based on the two small clinical studies, AHCC does not appear to lower PSA scores of the general population of prostate cancer patients, but it has potential to lower PSA levels in older patients and in patients with advanced disease, which should be confirmed in larger trials focusing on these population groups. Case studies also indicate that patients with certain characteristics may benefit from supplementation with AHCC. Besides looking at PSA values as a standard of efficacy, other clinical correlates should be analyzed, such as using imaging techniques to assess for resolution of cancer, as well as eliciting overall symptom response and assessment of patients' physical and psychosocial improvement. Given the strong safety profile of this natural compound and its apparent lack of side effects, supplementation with AHCC holds much potential to help certain prostate cancer patients, but further studies need to be conducted in order to support this.

Because, thus far AHCC has not been shown to be harmful and is not associated with any significant adverse effects, its clinical utility can still be assessed with little overall risk to the patient. Although AHCC appears to be a promising alternative treatment in patients with malignancy, there is a need to conduct randomized controlled double-blind trials on a larger scale to understand its true implications in prostate cancer patients. To date, PSA has been used as the primary outcome measure to quantify the effectiveness of AHCC, but the utility of this measure needs to be considered against other clinical outcomes. By performing studies with higher statistical power and including the measurement of other clinical end points while controlling for prostate cancer grade and stage, AHCC may be confirmed as a safe, natural, and effective alternative to standard medical therapy for prostate cancer.

### Conclusions

The popularity of complementary and alternative medicine continues to grow in prostate cancer management. Nutritional and herbal interventions in early prostate cancer and high-grade PIN have strong support in the published research. Furthermore, they show significant promise in helping to slow progression and reduce recurrence of prostate cancer. The interventions described in this review are beneficial for multiple body systems, including the endocrine, cardiovascular, immune, and central nervous systems. In all grades of prostate cancer, diet and supplements complement conventional treatment to improve response and quality of life and help empower the patient to be proactive and play their role in taking control of their disease.

In a series of studies, Demark-Wahnefried et al. [98] of the Duke University Program of Cancer Preventive, Detection, and Control Research have pointed out the growing role of oncologists as advisors and supporters of cancer patients who will greatly benefit from long-term diet and lifestyle changes. According to their review article on the subject, cancer survivors frequently initiate diet, exercise, and other lifestyle changes after the wake-up call of cancer diagnosis but that older men and less well-educated men are less likely to do so. In reviewing relevant studies from 1966 to the present, Demark-Wahnefried and

colleagues found that only 25–42% of cancer survivors consume adequate fruit and vegetables and that approximately 70% of prostate and breast cancer survivors are obese or overweight. They conclude that "oncologists can play a pivotal role in health promotion, yet only 20% provide such guidance."

With the number of cancer survivors continually rising as the result of early detection and improved treatments and with our increasing understanding of the benefits of dietary changes and nutritional interventions in early-stage cancers, the time has come for urologists to disclose all pertinent information regarding their knowledge of specific foods and nutritional supplements to their patients. Accountability and responsibility are required of both doctor and patient.

At this writing, clinical research into the use of such therapies in early prostate cancer and high-grade PIN is relatively new. Much more of this kind of research is imperative for the creation of consistent and effective protocols for chemoprevention, not just of prostate cancer but of other cancers as well. Recommendations for standardization and dosages of herbal medicines are often frustratingly difficult to determine because of the lack of this research. Even so, the benefits of herbal and nutritional chemoprevention appear to greatly outweigh any harm that could come to a patient, particularly in the earliest stages of detectable disease, in whom active surveillance would be the most likely first intervention.

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# Estrogens in Prostate Cancer

30

Giuseppe Carruba

## Introduction

Although prostate cancer represents a major health issue in men in Western countries, being a common cause of morbidity and mortality after the age of 50, it ought to be preventable and curable. Notwithstanding, despite the most recent advances in both basic and translational research, the molecular basis of prostate cancer remains poorly understood. In particular, the mechanisms underlying development and progression of this neoplasm appear to be complex: genetic and environmental factors (notably lifestyle and diet), along with endogenous sex hormones and host immune and inflammatory response, are likely to be interconnected in the pathogenesis of the disease.

As for breast cancer, dietary factors are thought to profoundly affect levels of endogenous hormones and their metabolism, eventually leading to prostate cancer development and/or progression [1]. In this context, sex hormones may act as intermediaries between exogenous factors, either environmental or nutritional, and biomolecular targets in both development and progression of prostate malignancies. Fascinatingly, breast and prostate cancer share many similarities, in terms of geographical distribution, risk factors, biomolecular determinants, and natural history. In a figurative way, cancer of the human prostate and breast can be viewed as brother and sister tumors, where dietary factors and hormones, especially estrogens, represent key interrelated players in many biological and pathological processes. In this framework, both breast and prostate cancer may be primarily considered, as elegantly proposed by Coffey [2], an acquired nutritional disease that could be prevented through changes of lifestyle and dietary habits.

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Although estrogen regulation of prostatic development, growth and function is generally recognized, the potential role of estrogens in human prostate cancer has been mistakenly neglected for decades and only recently reconsidered [3]. It has been long time remarked, but lately acknowledged, that neither androgens nor estrogens have a sexual selectivity, the former being implicated in breast and the latter in prostate, either normal or malignant, cell growth. This concept is nicely presented in a paper by Kuiper and colleagues where estrogen is described as a male and female hormone [4].

## Epidemiological Studies

Prostate cancer is the commonest non-skin tumor and the second leading cause of cancer death in men in the United States, with an estimate of 241,740 new cases and 28,170 deaths from this disease expected in the year 2012 [5]. Between the late 1980s and 1990s, incidence rates of prostate cancer have increased dramatically in USA, Europe, and in many other Westernized countries with a peak in 1992 as a consequence of the introduction of prostate-specific antigen (PSA) blood test as a diagnostic tool for prostate cancer screening. The causes of the subsequent decline of prostate cancer incidence, that is present solely in men aged 65 years and older, remain indefinite. In addition, mortality rates of prostate cancer have been consistently decreasing in Western countries since the late 1990s. Notwithstanding, human prostate carcinoma continues to represent a major health and socioeconomic issue especially because mechanisms underpinning prostate carcinogenesis and tumor progression are largely unclear and, hence, new strategies for prevention, early diagnosis, and personalized treatment have only been rarely developed and implemented in clinical practice.

Both incidence and mortality rates for prostate cancer vary greatly worldwide, with as much as 50-fold and a 12-fold [6] difference, respectively, between African American and Caribbean men and men in Eastern Asia (China, Korea) and Africa (Egypt, Somalia). In European

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countries, incidence of prostate cancer is markedly higher in Northern (80.1/100,000) than in southern Europe (44.7/100,000), with Sweden having the highest rates (139.3/100,000) and Greece the lowest (43.4/100,000).

Although several aspects may account for these large geographic variations, there is an overall consensus that lifestyle and, notably, diet play a key role, while environmental and genetic factors may only have a limited impact on prostate cancer incidence. A small proportion (5–9%) of prostate cancer cases can be in fact associated with heritable genetic defects, while familial prostate cancer may represent up to 20% of cases [7]. However, even in men who carry strong cancer-susceptibility genes, the contribution of environment and lifestyle appears to be critical for the manifestation of disease.

An increased risk of developing prostate cancer has been reported in relation to a high fat diet, high protein and energy intake, low intake of fiber and complex carbohydrates, and a sedentary lifestyle [8–10]. However, the statistical significance of this association is low, and age, ethnicity, and family history remain the few, well-established risk factors for prostate cancer [11].

Previous studies on migrant populations who moved from countries with low incidence/mortality rates of prostate cancer (i.e., China or Korea) to countries with higher prostate cancer rates (Unites States) showed, within a generation, a significant increase in prostate cancer incidence/mortality as compared with their peers in the countries of origin [12, 13]. On the other hand, prostate cancer incidence is rising rapidly in countries that have been historically characterized by low rates especially Asian countries such as China and Japan, as oriental populations gradually adopt Western diet and lifestyle. This evidence suggests that environmental and, especially, lifestyle factors play a dominant role in prostate cancer development.

Several studies have hypothesized that plant hormones contained in Asian diets, particularly the phytoestrogens present in soy products, might act as natural hormone antagonists and anticancer agents and that their intake could be associated with a decrease of prostate cancer risk. A recent review [14] of epidemiological studies on the association of soy and other nutrients containing phytoestrogens with the risk of developing prostate cancer showed contradictory results with only a few studies reporting a risk reduction associated with the intake of soy food, legumes, and isoflavones. In a meta-analysis of eight epidemiological studies, Yan and Spitznagel indicated that the consumption of soy food was related to a nearly 30% reduction of prostate cancer risk, despite only three studies in the analysis showed statistically significant lower risk of prostate cancer [15]. Several studies in Asian men have also reported a trend toward decreased prostate cancer risk with increased equol (a gut bacterial product of the isoflavone daidzein). In addition, lower equol concentrations or a lower prevalence of equol producers have been observed in Asian populations among men with prostate cancer compared with controls, whereas studies in European populations have reported no association [16].

Interestingly, after World War II, lifestyle and dietary habits in Asian countries, especially Japan, have drastically changed, and these changes have been accompanied by a marked increase of both testicular and prostatic tumors [17]. In particular, the introduction of milk in a no-meat/no-milk dietary culture produced a significant, unprecedented source of saturated fats and estrogens that could have, in turn, favored prostate cancer development and progression. In this respect, Ganmaa and colleagues claim that the 20-fold increase of milk consumption seen in Japan after the war should be taken into account to explain, at least in part, the increase of prostate cancer incidence and mortality that has recently occurred in this country.

An explanation of the linkage between environmental and/or lifestyle factors and prostate cancer risk may lie in the potential impact of these factors on both levels and biotransformation of endogenous sex steroids, particularly estrogens. It is noteworthy that environmental and dietary factors are highly likely to induce significant changes in circulating hormones, their intraprostatic levels and metabolic patterns, eventually leading to prostate cancer development and/or progression.

## Circulating Sex Steroids

Doubtlessly, the human prostate gland is dependent upon androgen for its development, function, and homeostasis. On the other hand, the potential implication of androgens in prostate carcinogenesis and tumor progression remains a common assumption (the “androgen hypothesis”), to such a point that prostate cancer is universally recognized as a prototype of age-related, androgen-dependent tumor. This assumption is based also on the fact that a high proportion of patients having locally advanced prostate tumors initially respond to hormone treatment, while they frequently develop an androgen-refractory condition after a relatively short time (usually within 2 years from presentation).

Both total and free serum testosterone significantly decline with age, eventually leading to an inverse relationship between testosterone levels in blood and prostate cancer risk. Thus, we are facing a seeming paradox whereby the higher the circulating testosterone, the lower the risk of developing prostate cancer.

In men, the balance between circulating levels of androgens and estrogens changes significantly with age [18]. In the aging male, a reduced production by the testes and increased levels of sex hormone-binding globulin (SHGB)

combine to lower free circulating testosterone. While plasma androgens decline, estrogen levels remain fairly constant, also as a consequence of an age-related increase of adipose tissue where estrogens are produced through the aromatization of androgens [19]. The ultimate result is a marked increase of the estrogen to androgen ratio and, hence, a potential increase of estrogenic activity on prostate gland that may eventually lead to abnormal growth and subsequent malignant transformation [20].

Apart from aging, males are exposed to relatively higher levels of circulating estrogens solely during in utero development. Several studies have indicated exposure of prostate cells to elevated estrogens early in uterine or perinatal life (a process referred to as developmental estrogenization or estrogen imprinting) may induce permanent disorders of prostate development that may in turn result in a higher propensity of prostate to develop precancerous or malignant lesions [21–23]. In addition, perinatal or neonatal exposure of prostate gland to endogenous estrogen and/or environmental estrogen-like endocrine disruptors may directly impair androgen-driven prostate development or result in functional and morphological prostate alterations that may in turn predispose the tissue to an earlier onset of disease, including cancer [24, 25]. One could speculate that developmental estrogenization generates important changes in the pool of embryonic stem cells that may, in turn, give rise to a population of adult "imprinted" prostate stem cells having a high susceptibility of developing cancer. All other things being equal, an increased adult prostate stem-cell pool would elevate the risk that one stem cell might become initiated [26].

The association between circulating androgens and prostate cancer risk has been explored by several studies, but the resulting data have been inconsistent and largely conflicting the "androgen hypothesis." None of the numerous prospective studies that have investigated the relationship between absolute plasma levels of testosterone and the risk of developing prostate cancer have shown any significant association. The subsequent meta-analyses by Eaton and colleagues [27] and Hsing et al. [28], respectively presenting quantitative reviews of the data from 8 and 12 available prospective studies, clearly revealed no significant differences in circulating hormones, either androgens or estrogens, between men who subsequently develop prostate cancer and those who remain free of disease. Only one study, the Physician's Health Study [29], reported a significant rise of prostate cancer risk with increasing plasma testosterone levels and an inverse association of estradiol with risk after adjusting for reciprocal levels and sex hormone-binding globulin (SHBG). However, this study found no significant difference in the risk of prostate cancer between men in the highest and the lowest quartiles of serum total testosterone.

Only a few earlier studies have investigated the correlation of serum levels of free testosterone and the risk of prostate cancer. Again, no significant association has been reported when the free fraction of this androgen was measured directly [30, 31].

The Rancho Bernardo study, conducted in California, revealed an association of elevated plasma estradiol and estrone with an increased risk of prostate cancer [32]. Two more recent nested case-control studies on serum levels of both androgens and estrogens failed to show any association with prostate cancer risk [33, 34]. Interestingly enough, one of the two studies has reported a positive association of plasma total testosterone with low-grade disease and an inverse association with high-grade disease [33].

Recently, a limited but significant decrease of prostate cancer risk has been associated with increasing serum levels of total testosterone [35]. In a study on hypogonadal men, Morgentaler and colleagues [36] reported that subjects with PSA levels <4.0 ng/mL had a 15% overall rate of prostate biopsies positive for cancer. Interestingly, subjects with plasma levels of testosterone <250 ng/dL had a prostate cancer rate of 21% as opposed to 12% for men with a testosterone level >250 ng/dL. Furthermore, the probability of cancer in men in the lowest tertile was over twice as much as that in men in the highest tertile of both total and free testosterone.

Several studies have scrutinized the relationship between pretreatment serum levels of testosterone with clinical stage of prostate cancer and patient survival, suggesting that low serum testosterone could be used as a negative prognostic predictor for this neoplasia. In the last decade or so, a number of papers have emphasized that low serum testosterone is associated with prognostically adverse characteristics of prostate cancer, including high-grade [37, 38], poor clinical outcome [39], advanced pathological stage at surgery [40, 41], and shorter survival [42].

Based on the above inconsistency, investigators have raised the question why it has been so problematical to demonstrate that plasmatic androgens are related to the risk of developing prostate cancer. The most obvious answer to this question is that circulating androgens are simply not associated with prostate cancer risk.

It should be taken into consideration, however, that several issues related to measurement of plasma steroids, both androgens and estrogens, could be contemplated to explain this large inconsistency of data. They include the low statistical strength of most studies, the limited number of incident cases in prospective studies, the minor differences in sex steroid serum levels between cases and controls, and the rather large intra- and inter-assay laboratory variations of serum hormone measurements [43]. On the other hand, several other variables, including obesity, physical activity, diabetes, metabolic syndrome, and benign prostatic hyperplasia, that might have an impact on serum levels of hormones and have been related to prostate cancer have not been adjusted for in previous nested case-control studies [44].

In any case, it is unlikely that a single assay of plasmatic androgens can be regarded as descriptive of average androgen levels over an etiologically relevant period of life. In this respect, since the length of prostate carcinogenesis and tumor progression can span 35–40 years or longer, the timing for the carcinogenetic activity of androgen and/or estrogen on human prostate should be counted 20–30 years (or even earlier) prior to the clinical manifestation of the disease, when serum androgens are higher and, hence, could be biologically relevant.

All the above issues might contribute to justify, at least in part, the inconsistency of data on the association of plasmatic androgens and prostate cancer risk. However, a major problem remains whether or not plasma levels of steroids can be considered representative of the respective intraprostatic concentrations. Intratissue levels of sex steroids in target organs, including breast and prostate, have been reported to be markedly greater (10- to 100-fold) than the respective values in plasma [45, 46]. Furthermore, both normal and malignant steroid target tissues are equipped with a repertoire of enzymes of steroid metabolism, including a superfamily of hydroxysteroid dehydrogenases, two 5α-reductases, several hydroxylases, sulfotransferases, sulfatases, and aromatase. A different expression and/or activity of these enzymes may result in a different accumulation of bioactive metabolites, eventually leading to patterns of intratissue steroids that may substantially diverge from the plasmatic figure. Simpson and colleagues [47] have emphasized that estrogens circulating in men and in postmenopausal women are not the drivers of estrogen action, but they represent a reflection of estrogen uptake and biotransformation at extragonadal sites, including prostate. In other words, they are *reactive* rather than *proactive* [48].

## Tissue Biosynthesis and Metabolism

As pointed out above, the balance between androgens and estrogens in individual target tissues may be significantly different from that in plasma, being dependent on several factors including uptake from the circulation, binding to steroid receptors and cofactors, and, notably, expression and/or activity of steroid enzymes, including 5α-reductase and aromatase. In this context, the ultimate biological impact of parent sex steroids and their derivatives could be assessed only through the evaluation of their local biosynthesis and metabolism. This issue has become increasingly important for a better understanding of the potential role of estrogens in breast and prostate cancer, also because abnormal levels of estradiol and/or estrone and, especially, of some of their hydroxylated tissue derivatives have been implicated in tumor development and progression [49].

As compared to breast, only a few early studies have assessed intraprostatic levels of sex hormones [50, 51]. Although these studies present some interesting preliminary observation on how prostate cells, either epithelial or stromal, metabolize androgens, they are largely insufficient and not significant enough to draw any conclusive inference.

In androgen target tissues, such as skin and prostate, testosterone is converted into its bioactive metabolite dihydrotestosterone (DHT). DHT binds in turn to androgen receptors and localizes in the nuclei of prostate epithelial cells as a dimer to regulate transcriptional activity of androgen-sensitive genes and DNA synthesis. The extent of DHT formation, that is governed by the 5α-reductase enzyme(s), produces DHT tissue levels markedly higher than those of testosterone, leading to a totally reversed testosterone:DHT ratio with respect to plasma (1:6 vs. 10:1, respectively) [52, 53]. In humans, two isozymes (type I and II) of the 5α-reductase exist, having distinct enzyme kinetics and tissue distribution. The type 1 isoform (encoded by *SRD5A1*) is expressed predominantly in skin and hair, while the type 2 enzyme (encoded by *SRD5A2*) is located primarily in androgen target tissues, including skin and prostate [54].

Results of the Prostate Cancer Prevention Trial (PCPT) indicate that the use of finasteride, a 5α-reductase inhibitor, for chemoprevention of prostate cancer results in a decrease of the overall number of incident cases but increases the proportion of high-grade prostate tumors [55]. Correspondingly, Nishiyama et al. [56] reported significantly lower levels of intraprostatic DHT in men with prostate cancer having a 7–10 Gleason score (GS) as compared with prostate cancer of ≤6 GS, suggesting that locally advanced, aggressive disease can progress even in a low-androgen environment. The authors also found no correlation between plasma levels of testosterone and/or DHT and intraprostatic levels of DHT. Indeed, Freedland and associates [57] have reported that circulating testosterone could not be mirroring intraprostatic androgenicity, and, hence, comparison of men having low and high testosterone levels could not be useful for a better understanding of the association between low androgen and aggressive prostate tumors.

Tissue estrogen biosynthesis occurs primarily through androgen aromatization. Since results of several studies suggest that human prostate gland is a primary target for estrogen action and that local synthesis of estrogen may be significant in prostate cancer, it would be important to determine whether or not aromatase is expressed in prostate tissues and to investigate the association between aromatase alteration and prostatic disease(s), including cancer. In this respect, the aromatase enzyme may act as a critical regulator of the balance between androgens and estrogens in target tissues and plasma. In the last decades, consistent evidence has accumulated to support the hypothesis that abnormal aromatase may play a critical role in development and/or

progression of human breast cancer. The *normal* prostate expresses aromatase in the stromal compartment, while aromatase expression is induced in malignant prostate through an abnormal promoter utilization, eventually leading to an altered T:E ratio that is associated with the development of disease [58]. Interestingly, lifelong exposure of aromatase knockout (ArKO) mouse to elevated androgens resulted in the development of prostatic hyperplasia, although no malignant changes could be detected in the prostate at any time, supporting a pivotal role of local estrogen biosynthesis in prostate cancer development [59]. In addition, significant expression and activity of aromatase have been detected in LNCaP, DU145, PC3 prostate cancer cells, and microdissected prostate epithelial tumor cells, while the enzyme could not be detected in *nonmalignant* prostate epithelial cells [60]. However, the potential implication of aromatase in either nontumoral or malignant human prostate remains today equivocal.

Estrogen patterns in target tissues and cells are much more assorted than one could expect on the basis of circulating estrogen profiles. The two major plasmatic estrogens, estradiol (E2) and estrone (E1), are readily interconverted in the tissue through the action of a superfamily of 17β-hydroxysteroid dehydrogenase enzymes (17β-HSDs) having distinct catalytic preferences and tissue distributions [61]. The hydroxylation of these "classical" estrogens at the C2/C4 positions through cytochrome P450 enzymes encoded by the CYP1A1 and CYP1B1 genes generates the so-called catecholestrogens (CCE), namely, the 2-hydroxy and 4-hydroxy derivatives of E2 and E1. Until are further metabolized by the catechol-O-methyltransferase enzyme into inactive methoxy derivatives, CCE may produce reactive oxygen species (ROS) that are in turn responsible of oxidative DNA damage.

Two mutually exclusive pathways, the 16α- and the 16β-hydroxylation, may act to produce a series of additional metabolites of either of as yet undefined biological activity. In particular, 16α-OHE1, along with other hydroxylated estrogens, has been repeatedly implicated in human breast carcinogenesis [49]. In a recent study, estrogen derivatives produced through either 16α-hydroxylation (e.g., 16α-OHE1 and 17-epiestriol) or 16β-hydroxylation (e.g., 16β-OHE1) have been reported to be comparable to classic E2 or E1 not only in terms of estrogenic potency but also for tumorigenicity in young adult mice [62].

Unfortunately, however, no direct unequivocal evaluation of estrogen intraprostatic levels has been so far provided.

In a recent randomized, dietary intervention study (the MeDiet study), we have ascertained that a traditional Mediterranean diet markedly reduces (over 40%) urinary levels of estrogens in healthy postmenopausal women [63]. It is of interest to note that, in this study, the majority of urinary estrogens was represented by hydroxy and methoxy derivatives of either E2 or E3 (notably 2-OHE2, 17-epiestriol, and 16-ketoE2), while *classical* estrogens (namely, E2 and E1) accounted for a mere 0.5% of total endogenous estrogens in urine. This pattern is cognate to what we have found by measuring intratissue levels of estrogens in both *nontumoral* and malignant human breast, whereby hydroxy estrogens accounted for the majority (more than 80%) of all estrogen metabolites in either condition [46]. In other words, metabolic profiles of estrogens in urine appear to be comparable to those obtained by measurement of their intratissue concentrations. This, incidentally, reinforces the suggestion that urinary estrogens can be used as indirect indicators of patterns of intratissue estrogens. In this respect, we have reported that a lower risk of developing prostate cancer is associated with a higher ratio of 2-hydroxyestrone (that has been originally proposed to act as anticancer estrogen and named accordingly *the good estrogen*, [64]) to 16α-hydroxyestrone (that has been claimed to be genotoxic, [65]) in urine [66].

Aiming to determine the impact of local metabolism on the distribution of bioactive steroids to malignant prostate cells, a few studies have assessed both expression and activity of key steroid enzymes in cultured human prostate cancer cells.

Recently, Vihko and colleagues [67], using both androgen-sensitive and androgen-independent LNCaP prostate cancer cells as a model system, have suggested that progression of prostate cancer to an androgen-refractory state is associated with a significant decrease of oxidative activity and a corresponding increase of reductive activity of the 17β-HSD enzyme(s). As a consequence, reduced bioactive estrogen (namely, estradiol) would accumulate in androgen-independent cells, while oxidized estrogen (namely, estrone) would become prevalent in androgen-sensitive cells.

We have originally established and optimized a rapid, simple approach to measure simultaneously the activity of several steroid enzymes in *intact* cultured cells [68]. Using this approach, we have assessed rates and direction of androgen metabolism in human prostate cancer cells [69]. Shortly, androgen-responsive LNCaP cells show consistent conversion of testosterone into the bioactive androgen DHT and its derivatives, 3α/3β-androstanediol, along with 17-βreduction of E1 to E2, while androgen-resistant PC3 cells exhibit a massive 17β-oxidation, leading to the predominance of oxidized androgen (androstenedione) and estrogen (estrone) derivatives. We have subsequently revealed that these highly divergent metabolic patterns are a consequence of a different expression and activity of several steroid enzymes, including 17β-HSDs, 3α-/3β-HSDs, and 5α-reductase, in the two cell lines [70]. This finding is of outmost importance since it corroborates the view that local steroid formation and metabolism is critical to determine the respective amounts of individual bioactive metabolites and, hence, the ultimate biological impact of sex steroids in target tissues and cells.

Our previous studies have revealed that aromatase activity is present in LNCaP prostate cancer cells even though to a significantly lesser extent than that observed in MCF7 human mammary carcinoma cells [71]. More recently, Ellem and Risbridger [72] have assessed aromatase RNA, protein, and enzyme activity in benign and malignant human prostate tissues, as well as in human prostate cancer cell lines. While aromatase was expressed solely in the stromal compartment of nontumoral prostate tissues, it was detected in microdissected epithelial tumor cells and prostate cancer cell lines.

Genes encoding for steroid enzymes are highly polymorphic in nature. Gene polymorphisms, along with epigenetic silencing or structural alteration, may all be associated with an increased risk of prostate cancer. To date, however, a relatively finite number of epidemiologic studies have been conducted to address this issue, and only limited, inconsistent evidence of the association between prostate cancer risk and gene polymorphisms has been provided.

As far as androgen metabolism is concerned, polymorphisms of genes involved in androgen biosynthesis (CYP11A1, CYP17A1, CYP19A1, CYP17A2), DHT formation (SRD5A2), and androgen inactivation and excretion (CYP3A4, HSD3B1, HSD3B2) have all been related to risk of developing prostate cancer [73–79]. In particular, several polymorphic regions are present in the SRD5A2 gene that encodes for the type 2 5α-reductase enzyme. Polymorphisms of this gene have been studied with special interest since its enzyme product presides over DHT formation in prostatic tissues. However, the present evidence indicates only a weak to modest increase of prostate cancer risk and, hence, does not apparently support the implication of DHT in prostate cancer development and progression [80].

As for estrogen metabolism, three different polymorphisms of the CYP1A1 gene, encoding the 2-hydroxylase enzyme, have been associated with an increased risk of prostate cancer, while only one single nucleotide polymorphism (SNP) has been reported to have an opposite impact by reducing prostate cancer risk in Japanese and a Caucasian-American population [81, 82]. Comparable finding was obtained for the CYP1B1 gene that encodes the 4-hydroxylase enzyme [83]. It is noteworthy that these polymorphisms result in a prolonged half-life and activity of either enzyme, and, hence, produce a sustained exposure of prostate cells to their products, respectively, 2- and 4-hydroxy estradiol, amplifying their carcinogenetic potential.

In a recent paper, Mononen and colleagues have identified a novel SNP of the CYP19A1 gene that encodes for a variant aromatase enzyme having higher activity and that is significantly associated with prostate cancer risk [79]. The reported evidence implies that this SNP results in lower androgen levels and greater amounts of tissue estrogens, supporting the potential implication of estrogen in prostate cancer development and growth.

Although some of these gene polymorphisms could be relevant in prostate carcinogenesis and tumor progression, their significance is still unclear and remains fairly speculative. Many issues may concur to make results of these studies inconsistent, but probably the most important is the lack of information on the combined effect of these polymorphic genes on prostate cancer risk [84]. Further studies on haplotypes and diplotypes are being conducted to determine the ultimate effects of polymorphic genes on the production and/or activity of steroid enzymes in relation to individual risk of prostate cancer.

## Estrogens in Prostate Tumor Development and Growth

Since the pioneering work of Charles Huggins, the concept that human prostate cancer represents a paradigm of androgen-dependent tumor has endured for decades against a bulk of experimental evidence suggesting that estrogens and other growth factors may be at least equally important in prostate carcinogenesis and tumor progression (reviewed in 3).

### Estrogens in Tumor Initiation

Recent experimental evidence suggests that prostate cancer originates from precancerous lesions, such as chronic proliferative inflammatory atrophy (PIA), as a consequence of prostate tissue injury [85]. Normally, in response to tissue injury, the prostate stem cell niche, that represents a minority (1–3%) of basal epithelial cells and has been located at the basement membrane of the prostatic glandular epithelium, would give rise a population of transit-amplifying/intermediate cells that would, in turn, terminally differentiate and generate luminal secretory and neuroendocrine epithelial cell types. It is speculated that tumor-initiating cells could arise during the prostate regeneration process within the pool of prostate stem cells when their differentiation ability is somehow impaired by a mutation activating oncogenic and/or abrogating tumor-suppressor signaling pathways [86]. The resulting progeny of cells would clonally expand and undergo the promotion and progression phases of the multistep carcinogenetic process, eventually leading to create a population of cancer stem cells featured by unrestricted replicative potential and reduced apoptosis. In this context, estrogens have been reported to upregulate both expression and activity of telomerase in human prostate epithelial cell lines, an event that is generally associated with unlimited cell proliferation [87].

Cavalieri and Rogan [88] have produced consistent experimental evidence in support of their hypothesis that selected tissue estrogen metabolites, notably the electrophilic catechol

estrogen-3,4-quinones, may react with DNA and generate depurinating estrogen-DNA adducts. After adducts are released from DNA, error-prone base excision repair of the resulting apurinic sites may eventually lead to mutations that can be critical to initiate breast, prostate, and several other human cancers.

## Experimental Animals

Early studies have reported that long-term administration of testosterone to rats induces the development of prostate tumors, suggesting that testosterone act as a complete carcinogen on the rat prostate, though in a limited proportion of cases and in some but not all rat strains [89–91]. However, when Noble rats were used as model system, the administration of testosterone and estradiol, in sequence or combined, resulted in the occurrence of both ductal and acinar epithelial dysplasia, followed within 1 year by the development of adenocarcinomas of the dorsolateral prostate in 90–100% of the animals [92]. If rats were treated with androgen alone, the incidence of prostate cancer dropped to 35–40% [93].

The mechanisms underpinning the hormonal carcinogenesis in the rat prostate remain largely undefined, but there is evidence to suggest that both receptor-mediated and *nonreceptor* effects may be implicated. As far as estrogens are concerned, the development of dysplastic lesions in the dorsolateral prostate of rats exposed for 16 weeks to a combination of testosterone and estradiol was almost completely abrogated by the simultaneous administration of the pure antiestrogen ICI-182,780 [94]. However, since ICI-182,780 also induces a block of the hyperprolactinemia produced in rats by estrogen treatment, it is difficult to establish whether the effects of this estrogen antagonist are a consequence of binding to estrogen receptor or not.

Other studies have revealed that Noble rats treated with testosterone and estradiol or with testosterone and the synthetic estrogen diethylstilbestrol (DES) for 16 weeks accumulate estradiol and the estrogenic androgen 5α-androstane-3β,17β-diol (3α-androstanediol, 3α-diol), respectively, in dorsolateral and ventral prostate [92, 95]. This evidence suggests that androgen and estrogen treatment of animals creates an estrogenic milieu in the rat prostates, eventually leading to the development of epithelial dysplasia and adenocarcinoma in the Noble rat prostate model. In an elegant study, Wang et al. [96] rescued pelvic organ rudiments of Rb KO mice and grafted them under the renal capsule of male adult nude mice to develop functional prostatic tissue. When Rb-/-prostate epithelium was combined with wild-type urogenital mesenchyme to construct chimeric tissue recombinants, dysplastic and malignant lesions occurred 5–8 weeks after host animals received silastic implants containing testosterone (25 mg) and estradiol (2.5 mg).

Although most studies on hormonal carcinogenesis of the prostate have been conducted on rodents, it ought to be emphasized that the rat prostate, consisting of dorsal, lateral, ventral, and anterior lobes, has embryology and anatomy distinct from human and dog prostates. Therefore, results of these studies should be interpreted with caution.

## Endocrine Disruptors

Accumulating evidence from both epidemiological and animal studies suggests that environmental exposure to endocrine-disrupting chemicals may be important for development or progression of human prostate cancer. These compounds may disturb estrogen signaling by interfering with either ER or enzymes of steroid metabolism, eventually leading to significant changes of levels of individual estrogen derivatives having distinct biological activity. Endocrine disruptors include pesticides, polychlorinated biphenols (PCBs), polyhalogenated aromatic hydrocarbons (such as bisphenol A, BPA), phthalates, arsenic, cadmium, and UV filters. Most of them have estrogen-like activity and are also referred to as xenoestrogens; many have been associated to an increase of prostate cancer risk (reviewed in [97]). The accumulation and the assortment of xenoestrogens in the environment have enormously increased in recent years, and this has also been related to the persistent increase of estrogen-related diseases, including breast and prostate cancer, neurodegenerative disorders, endometriosis, premature puberty, cryptorchidism, and many others. It is important to note that sensitivity of prostate tissues to endocrine disruptors appears to be prominent through critical developmental phases, notably in uterine life, at birth, and during puberty. A sustained exposure to xenoestrogens during these periods may be responsible for an increased susceptibility to develop prostate cancer later in life.

## In Vitro Studies

Both epidemiological and experimental evidences presented herein support the view that prostate cancer arises in the aging male in an estrogenic environment. However, the ultimate biological impact of sex steroids, particularly estrogen, on prostate cancer cells is difficult to dissect as it is strictly dependent upon several variables, including the estrogen:androgen ratio in both plasma and prostate, the expression and activity of steroid enzymes, the binding to intracellular and/or membrane receptors, the exploitation of genomic and/or nongenomic mechanism(s) of action.

Previous studies have assessed the proliferative effects of sex hormones in cultured prostate cancer cells. Although several reports have shown that androgens markedly stimulate

prostate cancer cell growth [98, 99], unequivocal evidence for a direct increase of DNA synthesis brought about by bioactive androgens in prostate tumor cell lines is surprisingly rare and often conflicting. The inconsistency of the results obtained in cell model systems does not allow to draw any truthful interpretation also because different variables including culture and experimental conditions, age of cultured cells, and exposure to endogenous hormones and growth factors may considerably affect the results.

Various in vitro studies carried out on LNCaP cells have indicated that both androgen and antiandrogen stimulate growth of these cells [100]. We have previously reported that exposure to physiological estrogen concentrations may either stimulate or decrease growth of androgen-responsive LNCaP or androgen-refractory PC3 prostate cells, respectively, and that these effects are predominantly receptor-mediated being completely abrogated by the simultaneous addition of the pure estrogen antagonist ICI-182,780 [101, 102]. This evidence implies that estrogen may affect proliferative activity of prostate cancer cells even if the cells have become androgen resistant. This finding is also corroborated by the significant rates of clinical response to the systemic administration of estrogens observed in prostate cancer patients having a metastatic, androgen-refractory disease [103]. Other authors have revealed that tamoxifen (mixed antiestrogen) and ICI-182,780 (pure antiestrogen) inhibit growth of both DU145 and PC3 prostate cancer cell lines and have cytotoxic effect on DU145 cells. This latter effect could be prevented by the pretreatment of cells with an estrogen receptor (ER) β antisense oligonucleotide, suggesting that antiestrogens may accomplish their antitumor effects also through this type of ER [104]. Based on the finding that the proliferative effects of estrogens on human prostate cancer cells in culture appear to be typically receptor-mediated, it would be important to assess ER content and the balanced expression of different ER types and their variants.

## Estrogen Receptors and Prostate Cancer

Several in vivo or in vitro studies have repeatedly pointed out that classical effects of sex steroids are mediated through specific intracellular receptors that belong to the superfamily of nuclear receptors [105]. However, there is accumulating evidence that estrogens and their receptors may combine or act unconnectedly to exploit an amazing array of both genomic and nongenomic, either ligand-dependent or ligand-independent, activities [106].

Two major ER types, the classical ERα and the more recently discovered ERβ, have been identified. The two receptor types are encoded by separate genes, respectively *ESR1* and *ESR2*, located on different chromosomes. In addition, several ERα and ERβ splicing variants and deletion mutants have been isolated in both *nontumoral* and diseased target tissues and cells [107]. However, these ER species are habitually coexpressed with wild-type receptors, and, hence, their potential role in either physiological or pathological processes is difficult to dissect.

The ERα and ERβ are characterized by tissue-specific distribution and exploit a variety of physiological activities in several human tissues [108]. Both receptors typically act as nuclear transcription factors with the ultimate biomolecular effect of estrogen on target cells being dependent on their respective expression levels and balance in individual tissues, ligand binding, heterodimerization, transactivation, and estrogen response element (ERE) activity. In this respect, an alteration of ERα and ERβ balance may be implicated in the etiology of various diseases, including prostate cancer.

Both ERα and ERβ are expressed in the adult human prostate, although ERα is generally located in the stromal compartment, while ERβ is located predominantly in the basal cell layer of the glandular epithelium. Various studies have inspected the expression of ERα and ERβ (at both transcript and protein level) in *nontumoral*, hyperplastic, and malignant human prostate tissues and cells. The resulting data have consistently revealed a marked decrease of ERβ expression in the malignant prostate as compared with benign (hyperplastic) or normal tissues, while ERα expression remains unchanged or even increased. There is convincing evidence that the two receptors are mutually regulated, with ERβ limiting cell proliferation by direct (ERβ-specific) effects on gene transcription and/or indirect activity through modulation of ERα. In this respect, loss of ERβ expression may represent a crucial step in estrogen-related mechanisms of prostate cancer progression (reviewed in [109]).

Previous studies based on estrogen receptor knockout (ERKO) mice model systems have provided important insights for a better understanding of ER role in both normal and diseased prostate. In particular, the adult ERβ knockout (βERKO) mouse has been associated with the onset of prostatic epithelial hyperplasia, while no prostatic alteration could be observed in the ERα knockout (αERKO) mice [110]. This evidence reinforces the assumption that ERβ may play a protective role against prostate malignant cell growth. Interestingly, both synthetic antiestrogen (toremifene) and natural phytoestrogen (genistein) prevent prostate cancer development in the transgenic adenocarcinoma mouse prostate (TRAMP) model acting as ERβ agonists [111, 112].

Cancer progression is hallmarked by the acquisition of genetic and epigenetic changes that eventually lead to the generation of a phenotypically diverse progeny of cancer cells. In this framework, hypermethylation of CpG islands in the promoter region of tumor-suppressor genes is a common mechanism of gene silencing during tumor progression. Loss of ERβ expression has been reported in both primary cultures

of human prostate cancer cells and prostate carcinoma tissues [113, 114]. Conversely, metastatic lesions of prostatic carcinomas frequently display high expression levels of ERβ [115]. This combined evidence apparently indicates that while loss of ERβ is an important event in prostate carcinogenesis, its re-expression in metastatic disease could even provide some survival advantage to prostate malignant cells. However, hypermethylation of the promoter region and silencing of the genes have been reported to occur for both ERα and ERβ in prostate cancer tissues and cells [116]. In addition, direct acetylation of ERα by the coactivator p300 at well-conserved lysine residues in the hinge/ligand domain of the receptor has been associated with both hypersensitivity to estradiol and contact-independent growth in cancer cells [117, 118]. All the above changes may be crucial in determining the net biological effects of estrogen in either normal or diseased prostate gland.

A few studies have investigated polymorphisms of both AR and ER genes in relation to prostate cancer risk. It has been experimentally observed that the length of the polymorphic glutamine (CAG) trinucleotide repeat in the AR gene affects both transactivation of AR and transcriptional activity of androgen target genes, hence having a potential on prostate cancer development and growth [119, 120]. In contrast, Platz and colleagues [33] revealed that neither circulating steroids nor length of the AR gene CAG repeat is associated with prostate cancer, supporting the view that these factors do not significantly contribute to prostate carcinogenesis and tumor progression.

A positive association with prostate cancer of the T/T variant of the PvuII site in the ERα gene and the TC or CC variant alleles of ERβ has been reported in case-control studies [121, 122].

Little is known about the expression and the functional meaning of splice or deletion variants of ER in the human prostate. There is evidence that two ERα splice variants, hERα46 and hERα36, are potent inhibitors of the wild type hERα66 transactivation. In particular, hERα46 is located almost exclusively in cell nuclei, while hERα36 is predominantly associated to the plasma membrane where it transduces both estrogen and antiestrogen signaling, including activation of mitogen-activated protein kinase [123, 124]. On the other hand, several relatively abundant ERβ isoforms have been described. In particular, hERβ2 and hERβ5 have been reported to inhibit transcriptional activity of ERα [125]. Presently, no ERα variant has been described in prostatic tissues, while both hERβ2 and hERβ5 have been detected in prostate cancer, with the combined expression of the two receptor variants being a prognostic indicator of patients having shorter disease-free survival [126]. In a recent report, Taylor and colleagues have indicated that expression of the ERαΔ5 deletion variant is significantly greater in tumor-adjacent prostate samples as compared to benign tissues [127].

Results of further studies on ER variants in both normal and malignant human prostate are awaited with interest to provide important insight into the role of ER and estrogen signaling in prostate cancer development and progression.

In the recent years, selective estrogen and androgen receptor modulators have attracted interest for their potential use in the management of various human diseases (reviewed in [128]). In particular, selective estrogen receptor modulators (SERMs) have been used to prevent bone fractures, to treat ER-positive postmenopausal breast cancer patients, and to induce ovulation in infertile women [129]. On the other hand, selective androgen receptor modulators (SARMs), a newcomer category of agents that are currently being investigated mostly at basic and preclinical level, have been proposed for both prevention and treatment of human prostate cancer [130]. SERMs, including raloxifene, lasofoxifene, and arzoxifene, selectively bind ERα and ERβ to accomplish either estrogenic or antiestrogenic activities in a variety of human tissues. It has been suggested that SERMs induce a conformational change of ER, dissociate the receptor from the heat-shock protein complexes, release ER in a monomeric form, and permit its translocation to nuclei of cells where it binds as a homodimer to the regulatory sequences of target genes to either initiate or suppress transcription [131]. Today, research on SARMs is largely in its infancy, with no SARM approved for clinical use and a few agents completing phase I and II trials. Their potential efficacy in prostate cancer remains to be established and again based on an "androgen hypothesis" that has been by far disputed more than convincing. On the other hand, the loss of ERβ expression during prostate cancer progression and its re-expression in metastatic prostate cancer cells raise the possibility of using ERβ-specific ligands in triggering cell death in these malignant cells. In this context, SERMs, along with synthetic estrogen receptor ligands and antagonists, have recently emerged as promising agents in both prevention and treatment of human prostate cancer [132].

## Perspectives

In spite of the recent, significant advances in the research on prostate cancer, mechanisms underpinning development and progression of the malignant prostate remain undefined. Several networked factors, including the balance of estrogen and androgen, changes and polymorphisms in the enzymes responsible for biosynthesis and transformation of intraprostatic hormones, alteration of hormone signaling or local balance between estrogen receptor types and variants, are all markedly affected by lifestyle factors (notably diet), genetic determinants, and exposure to environmental chemicals and may play a critical role in human prostate cancer.

Presently, the lasting conception that androgens are the key determinants in prostate carcinogenesis and tumor progression appears to be a never-ending persuasion that has, faultily, led to neglect different areas of research with promising perspectives for both treatment and prevention of this disease.

In particular, steroidogenic enzyme inhibitors [133], ER subtype-selective agonists/antagonists or SERMs [134, 135], have been in turn proposed as potential agents for both chemoprevention and treatment of prostate cancer.

In a recent intriguing paper, Williams [136] has combined apparently distant evidence from epidemiology, basic research, animal model systems, and clinics to design a unifying hypothesis for the increasing prevalence of global disease worldwide. The controversial breakthrough presented by the author proposes that several distinct factors may significantly affect hormone balance in the organism through upregulation of the P450 aromatase enzyme and the resulting unopposed excess of endogenous estrogen, alteration of insulin receptor machinery and leptins, and exposure to elevated environmental xenoestrogens. This unbalanced hormonal milieu may represent a common condition for development of life-threatening diseases, including cancer, diabetes, obesity, Alzheimer's disease, that are currently pandemic.

In this respect, we have been forerunner in approaching and emphasizing the potential implication of estrogen not only in endocrine-related tumors, including prostate cancer, but also in several other human diseases [137]. A better understanding of estrogen-driven mechanisms in different processes related to health and disease would be of primary importance to design and exploit original preventive and therapeutic strategies also in prostatic carcinoma.

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# Vitamin D and Prostate Cancer

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Naomi Smith and Alejandro Nolazco

## Introduction

Vitamin D was first recognized for its role in bone health. It is now known to have a number of important physiological effects, and vitamin D levels have been implicated in the pathology of a wide range of diseases including cardiovascular disease, hypertension, cancer, and autoimmune-based pathologies such as multiple sclerosis [1]. Aside from prostate cancer, vitamin D deficiency has also been linked to colorectal cancer [2], and there is evidence to suggest a role in skin and breast cancers. Elevated levels of vitamin D have been associated with worse outcomes from breast, esophagus, and pancreatic cancer [3].

The interest around vitamin D and prostate cancer began in 1990 when Schwartz and Hulka published epidemiological data describing the association between risk factors for vitamin D deficiency (black race, age, northern latitude) and clinically significant prostate cancer [4]. Schwartz and Hanchette subsequently published evidence demonstrating that mortality rates from prostate cancer in counties within the United States (US) were inversely correlated with the availability of ultraviolet (UV) radiation, one of the key factors in vitamin D production [5].

Considerable research has been carried out on the role of vitamin D in the pathophysiology of prostate cancer and its potential role in chemoprevention or as an adjunct to treatment. In this chapter, we will describe the physiology of vitamin D metabolism, the results of in vitro research with prostate cancer models, epidemiological research on the association between vitamin D and prostate cancer before finally reviewing the clinical trials of vitamin D in treatment of prostate cancer carried out to date.

## Vitamin D Metabolism

The term "vitamin D" is used to describe a group of fat soluble "secosteroids" (a steroid based structure with a broken ring). Physiologically, the two most important forms are vitamin D2 (ergocalciferol) available from fish, eggs, meat, and fortified dairy products and vitamin D3 (cholecalciferol) synthesized in the inner layers of the epidermis from 7-dehydrocholesterol in a reaction facilitated by UVB radiation, that is, sunlight exposure. Both forms are subsequently hydroxylated in hepatocytes by the enzyme D-25-hydroxylase to form the prohormone calcidiol (25(OH)D) which can be stored in tissues or released bound to alpha globulin [6]. It is calcidiol, a relatively stable circulating form of vitamin D which is usually measured in the serum since it has the advantage that it reflects both the vitamin D ingested as well as that produced in the skin. Circulating levels however may not always accurately reflect body stores, especially in obese individuals [7].

Calcitriol (1,25(OH)2D), the biologically active form, is produced by a further hydroxylation step carried out by 1-alpha-hydroxylase in the proximal tubules of the kidney and other organs including the prostate and colon [8, 9]. The conversion of calcidiol to this active form, calcitriol, is increased by parathyroid hormone (PTH) and low serum calcium or phosphate levels. The level of calcitriol is thus carefully controlled by these influences, falling only in very severe vitamin D deficiency.

The expression of renal 1-alpha-hydroxylase is upregulated by PTH and inhibited by calcitriol, forming a negative feedback loop. In contrast, extra renal 1-alpha-hydroxylase is thought to be constitutively active, suggesting that tissues

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expressing this enzyme, which could include certain tumors, may experience local levels of calcitriol which directly reflect circulating calcidiol levels rather than being under the tight control of the feedback loop [10].

Calcitriol is transported bound to vitamin D-binding protein (VDBP) and is the ligand for the vitamin D receptor (VDR). On binding this nuclear receptor, calcitriol promotes its association with the retinoic acid X receptor (RXR), and the complex formed acts as a transcription factor, binding to DNA sequences called vitamin D response elements (VDREs) and modulating the expression of target proteins such as calbindin (increases calcium uptake in the gut) [11] and osteoclastin (regulating bone metabolism) [12]. Many proteins affecting the cell cycle, cell proliferation, differentiation, and apoptosis have also been found to be VDREs, most notably the cell cycle regulator p21 [13], insulin-like growth factor [14], fibronectin [15], and tissue necrosis factor-alpha [16]. VDRs have been found not only in the gut but in the brain, heart, skin, gonads, prostate, and breast supporting the emerging evidence for the many and varied effects of this steroid hormone not just on calcium balance but on the immune system, insulin secretion, blood pressure regulation, and cell cycle, cell differentiation and proliferation.

## Vitamin D Deficiency

Severe vitamin D deficiency causing rickets in children and osteomalacia in adults is generally only seen with serum calcidiol levels of less than 10 ng/ml [17]. While levels of greater than 15 ng/ml have historically been considered sufficient for good health, this cutoff came from average levels found in healthy populations, and emerging evidence suggests that PTH levels and calcium absorption are not optimized until levels of approximately 30 ng/ml [18]. Using this value, it is estimated that approximately one billion people worldwide are vitamin D deficient [19].

People with dark skin, the elderly, pregnant and lactating women, and breast fed infants are at increased risk of deficiency. Certain medical conditions also predispose to vitamin D deficiency such as obesity, fat malabsorption syndromes, inflammatory bowel disease, and renal disease [19].

Conversely vitamin D toxicity, usually due to excessive supplementation, manifests as hypercalcemia and its clinical effects (gastrointestinal disturbances, renal stones, and bone pain). This is typically seen with calcidiol levels greater than 150 ng/ml and unlikely to occur in healthy people receiving less than 10,000 IU/day [20].

In November 2010, the US Institute of Medicine updated the dietary reference intake for vitamin D. The committee stated that the evidence for health outcomes other than bone health were not sufficiently robust to influence their recommendations and therefore advised 600 IU a day between the ages of 1 and 70 years and 800 IU a day for those 71 years and over (intake sufficient to achieve a serum calcidiol level greater than 20 ng/ml in at least 97.5 % of the population). In the European Union (EU), the recommended daily allowance is 5mcg per day (equivalent to 200 IU) [21].

## Effect of Vitamin D on the Prostate

Both in vitro and in vivo studies have provided evidence for the antitumor effects of vitamin D and its metabolites in prostate cancer cell lines and animal models.

Experiments with human prostate cancer cell lines have demonstrated that vitamin D has an antiproliferative effect and may also act to increase differentiation of tumor cells as suggested by an increase an in PSA secretion [22]. This effect is also shown by vitamin D analogs [23]. Furthermore, calcitriol and synthetic analogs have also been shown to decrease the invasiveness of prostate cancer cell lines, an effect that is probably mediated by a selective inhibition of type IV collagenase secretion [24].

These in vitro observations are supported by in vivo work using the Dunning rat model of prostate cancer. Both calcitriol and a synthetic analog inhibited tumor growth and decreased the number of lung metastases when prostate cancer cell lines were implanted into the flank of rats. Analysis of the treated cell lines showed a growth inhibitory and differentiating effect, with significantly more cells in the G0/G1 phase of the cell cycle compared with controls [25]. Using a murine model of prostate bone metastases, mice fed a vitamin D-deficient diet were found to develop larger lesions with increased mitotic activity [26].

In preclinical studies VDR ligands have been shown to potentiate the activity of many other antitumor agents. Calcitriol and its analogs act synergistically with conventional chemotherapeutic agents (e.g., docetaxel [27], paclitaxel [28], cisplatin, carboplatin [29], and mitoxantrone [30]) and enhance radiation-induced apoptosis [31] in prostate cancer models. Steroids [32] and nonsteroidal anti-inflammatory drugs [33] also increased cell cycle arrest and apoptosis in cell lines treated with vitamin D.

## Epidemiological Studies of Vitamin D and Prostate Cancer

A number of epidemiological studies have attempted to define the relationship between vitamin D and prostate cancer risk. These studies have focused on the dietary intake of ergocalciferol, sunlight exposure (known to be associated in a nonlinear fashion with levels of cholecalciferol), and serum levels of calcidiol. The results of these epidemiological studies remain contradictory. One of the key complicating factors

is that the association between the measurable variables is not related in a simple manner to the level of the active form calcitriol. Furthermore, there have been a number of confounding factors in these epidemiological studies that have been difficult to exclude, for example, reliance on self-reporting of dietary patterns and the use of single assessments of dietary intake or serum level may which may not adequately reflect lifetime exposure to vitamin D.

More recent research includes study of the role of polymorphisms in the genetic sequence of the vitamin D receptor and how these may influence the function of vitamin D hormone axis and the downstream effects of vitamin D in the prostate. Advancing techniques in genomics will no doubt continue to expand further into this field.

## Intake

In Schwartz and Hulka's 1990 paper proposing vitamin D as a risk factor for prostate cancer, they identify an increased incidence of prostate cancer in migrant Asians as they adopt a Western diet and decrease their intake of oily fish (rich in vitamin D). Hanchette and Schwartz later highlighted a ten-fold difference between prostate cancer rates in the United States and Japan where the traditional diet is high in fatty fish rich in both vitamin D and omega-3 fatty acids (which raise serum levels of active vitamin D metabolites by dissociating them from their binding proteins).

Many subsequent studies carried out to investigate the influence of dietary vitamin D on prostate cancer risk have included other food groups which may affect risk indirectly via their effect on vitamin D levels. For example, low serum levels of calcium and phosphate promote production of calcitriol, fructose can transiently reduce circulating phosphate levels, and high animal protein intake lowers serum pH, decreasing the activity of 1-alpha-hydroxylase [34].

A number of large questionnaire-based studies have failed to show an association between vitamin D intake and prostate cancer but have found associations with dairy intake and vitamin D from supplemental sources.

The National Health and Nutrition Examination Epidemiologic Follow-up Study included 3,612 men, 131 of whom developed prostate cancer during the 8–10-year study period. Increased risk was associated with dietary calcium (third tertile compared with first: RR 2.2, 95 % CI 1.4–3.5, $p=0.001$) and dairy intake (third tertile compared with first: RR: 2.2, CI 1.2–3.9, $p=0.05$). Low fat milk was associated with increased risk, while whole milk was not. Neither vitamin D nor phosphorus was independently associated with risk [35].

These results are supported by EPIC, a large multinational observational study (153,457 male participants across ten European countries), which found a significant association between prostate cancer and dairy protein intake and with calcium from dairy products [36]. The Multiethnic Cohort Study (82, 483 men; 4,404 prostate cancer patients were identified over 8 years) found no association between prostate cancer risk and calcium or vitamin D intake, but in the food group analysis, the risk of localized low-grade tumors was found to be increased with low fat and decreased with whole milk [37].

Interestingly the Prostate, Lung, Colorectal and Ovarian Screening Trial (29,509 patients; 1,910 developed prostate cancer) found that dietary vitamin D was not associated with prostate cancer risk, but that a greater intake of vitamin D from supplemental sources was associated with a decreased risk. In men who took >600 IU of vitamin D in the form of supplements, the risk of developing prostate cancer was 40 % lower [38]. However, the Prostate Cancer Prevention Trial examined nutritional risk factors in 9,559 participants using a questionnaire and serial PSA and digital rectal examinations (prostate biopsy was recommended to patients if either was abnormal and offered to all participants at the end of the study; 1,703 cancers detected). There was no association found with supplement use of any kind. Dietary calcium was positively associated with low-grade cancer but inversely associated with high-grade cancer (quartile 4 vs. quartile 1, OR 1.27, 95 % CI 1.02–1.57 and OR 0.43, 95 % CI 0.21–0.89, respectively) [39].

The reported association of prostate cancer with dairy intake remains controversial. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (27,062 Finnish smokers) found no association with any of the studied food groups, nutrients, or minerals in the entrance food use study questionnaire and the 183 incident prostate cancers diagnosed in the study period [40].

A review meta-analysis conducted in 2008 including 26,769 patients from 45 observational studies looking at dairy products, calcium, and vitamin D intake in relation to prostate cancer risk found no relationship between vitamin D intake and prostate cancer risk [41].

## Serum Levels

Large trials carried out to investigate the association between serum calcidiol and calcitriol concentrations have not shown a consistent association with prostate cancer risk.

Li and colleagues working in the United States carried out a nested case–control study within the Physician's Health Study. Comparing serum calcidiol and calcitriol levels between 1,066 prostate cancer patients and 1,618 controls (matched for age and smoking status), they concluded that men with calcidiol and calcitriol levels below the median had a significantly increased risk of aggressive prostate cancer (OR = 2.1 95 % CI 1.2–3.4). As expected median plasma levels of calcidiol varied for season (25 ng/ml in winter or spring and 32 ng/ml in summer or autumn) but serum levels of calcitriol did not [42].

However, a nested case–control study within the multinational European Prospective Investigation into Cancer and Nutrition (EPIC) compared serum calcidiol levels in 652 prostate cancer patients with 752 age-matched controls over 4 years and found no significant association with prostate cancer risk (highest vs. lowest quintile: odds ratio = 1.28, 95 % confidence interval: 0.88–1.88) [43].

In a large, nested case–control study carried out within the prospective Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial that included 749 cases and 781 controls, there was no trend between serum calcidiol levels and rates of nonaggressive prostate cancer. However, serum calcidiol levels greater than the lowest quintile were associated with aggressive disease ($p = 0.05$ for trend) [44].

Further evidence to support the possibility of a J- or U-shaped association between calcidiol serum levels and prostate cancer risk comes from a 2004 Scandinavian study which compared serum calcidiol levels in 622 prostate cancer patients with 1,451 matched controls. Low serum calcidiol levels (<19 nmol/L) were associated with an increased prostate cancer risk (RR 1.5, 95 % CI 0.8–2.7) as were high levels (>80 nmol/L) (RR1.7, 95 % CI 1.1–2.4) [45]. The J-/U-shaped association hypothesis is also supported by work in other cancers [3].

A meta-analysis of publications investigating the relationship between circulating levels of calcidiol (14 studies) or calcitriol (7 studies) and prostate cancer risk published in 2010 found little evidence to support a role for vitamin D in the risk of or progression of prostate cancer. Using $I^2$, a statistical test of heterogeneity in meta-analyses, the authors concluded that differences in the analyzed studies were unlikely to be genuine [46]. They suggested that differences the analyzed studies were instead attributable to variation in study design and other factors [47].

## Sunlight Exposure

Hanchette and Schwarz's 1992 publication analyzed the relationship between the distribution of UV radiation and prostate cancer mortality in 3,073 United States counties. They reported a significant inverse correlation ($p < 0.0001$)[5] [5]. This association has subsequently been supported by numerous further investigations.

Thirteen thousand five hundred and forty-one skin cancer patients from the Netherlands were found to be at decreased risk of developing prostate cancer compared with the general population (standardized incidence ratio (SIR) 0.89, 95 % CI 0.78–0.99). The risk of advanced cancer was significantly decreased (SIR 0.73, 95 % CI 0.56–0.94), suggesting a possible "antiprogressive" effect of UV radiation on prostate cancer [48].

Using mathematical models to calculate UVB levels from forecasted ozone levels, cloud levels and elevation researchers in the United States found an inverse correlation between UVB levels and prostate cancer incidence and mortality in white men (RR-0.42, $p < 0.01$: RR-0.53, $p < 0.001$), but only for prostate cancer incidence in black men (RR-0.40, $p < 0.05$). Interestingly these correlations were strongest with UVB levels in autumn and winter for white men and for UVB levels during the summer for black men [49].

## Vitamin D Receptor

The existence of genetic factors in the pathogenesis of prostate cancer is well accepted and supported by evidence from twin studies and familial clustering of disease [50, 51]. Given that the effects of calcitriol, the active form of vitamin D, are mediated via the vitamin D receptor, it is biologically plausible that VDR gene polymorphisms could affect the binding of vitamin D to its receptor and its downstream effects. The genetic differences in the VDR could also contribute to some of the differences seen in prostate cancer between ethnic groups.

The six most studied VDR polymorphisms are the restriction sites: *Apa*I, *Bsm*I, Cdx2, *Fok*I,*Taq*I, and the poly( A) microsatellite. Early findings of such differences were observed in the 1990s including an association between the *Bsm*I VDR polymorphism and both circulating levels of calcitriol and bone density in 1994 [52], the first report of a VDR polymorphism in prostate cancer in 1996, and subsequently a case–control study showing the presence of the *Taq*I tt genotype in 8 % of 108 men undergoing a radical prostatectomy compared to 22 % of controls [53].

Subsequent research has yielded often contradictory results, and a meta-analysis performed in 2006 of 26 heterogenous studies (1996–2005) looking primarily at *Taq*I but also at *Apa*I, *Bsm*I, *Fok*I, and the poly( A) found no significant association between VDR polymorphisms and prostate cancer susceptibility [54]. Similarly a population-based case–control study published in 2009 analyzed 48 single nucleotide polymorphisms (SNPs) in genes coding for the VDR, vitamin D-activating enzyme 1-α-hydroxylase, and deactivating enzyme 24-hydroxylase in 827 prostate cancer patients and 787 age-matched controls. Researchers found no association between these SNPs and the risk of prostate cancer or tumor aggressiveness [55].

It may be that VDR subtypes play a greater role in disease susceptibility when other environmental factors are taken into account. For example, Luscombe et al. found positive associations between *Fok*I,*Taq*I, and *Bgl*I in men with ultraviolet radiation exposure above the median arguing for an important gene-environment interaction [56].

## Vitamin D in Treatment of Prostate Cancer

A number of clinical trials have been carried out to investigate the potential for calcitriol, the biologically active form of vitamin D, and other vitamin D derivatives as therapeutic agents in prostate cancer.

In vitro research results suggest that expression of proteins with antitumor effects caused by the activated VDR bound to its ligand occur at high calcitriol concentrations and in a dose-dependent manner [57]. In vivo achievable concentrations are limited by the hypercalcemia and hypercalciuria associated with high doses of calcitriol. However, phase I clinical trials suggested that the tolerable dose could be increased by varying the dosing schedule. The first trials used doses of 0.5–2.5 μg daily with reported effects, showing considerable variation [58, 59]. Weekly oral calcitriol allowed significant dose escalation (up to 2.8 μg/kg), achieving plasma concentrations of 3.7–6.0 nM without dose-limiting toxic side effects, but the pharmacokinetics of the available formulation were found to be nonlinear at higher doses [60, 61].

Novacea Inc. subsequently developed DN-101, a calcitriol formulation available in larger dose capsules and with linear pharmacokinetics over a wide dose range. Concentrations up to 14.9 nM have been achieved with this preparation. ASCENT, a placebo-controlled randomized trial, compared DN-101 and docetaxel to placebo and docetaxel in 250 androgen-insensitive prostate cancer patients. PSA response rate, the primary end point, showed a trend toward the experimental arm (63 % compared to 52 %) but did not reach statistical significance ($p=0.07$) [62]. However, survival (secondary end point) was improved in the treatment group (HR 0.67).

A phase 3 trial ASCENT-2 commenced recruitment and was to compare 45 μg DN-101 and 36 mg/m$^2$ of docetaxel with 75 mg/m$^2$ and prednisolone. This trial was halted early due to an excess of deaths in the experimental arm, and the Food and Drug Administration placed a temporary hold on the studies of DN-101 [63]. Unfortunately due to changes in clinical practice, this study did not compare similar chemotherapy regimens, making interpretation difficult.

Given the potential side effects of calcitriol when used as a therapeutic drug for prostate cancer, there has been interest in synthetic VDR ligands. Researchers in Israel have reported the development of a synthetic calcitriol analog (BGP-15) which has shown anti-tumor activity in androgen-dependent prostate cancer cell lines (LNCaP). BGP-15 is derived from calcipotriene, a synthetic calcitriol analog which is already in use for the treatment of psoriasis and does not show any calcium-related side effects with long term use [64].

Phase I clinical trials of another synthetic vitamin D analog 1-alpha-hydroxyvitamin D2 found that 12.5 mg did not cause any toxic side effects. A phase II trial subsequently recruited 70 patients with androgen-insensitive prostate cancer and randomized them to receive docetaxel with or without 1-alpha-hydroxyvitamin D2. The response rates, time to disease progression, and toxicity were similar in both arms of the study [65].

### Conclusion

Evidence exists for the antitumor effects of vitamin D in prostate cancer cell lines and animal models and the inverse association of UVB exposure and prostate cancer incidence. However, epidemiological research has failed to define the association between vitamin D intake or serum levels and the risk of prostate cancer or its subsequent clinical course. The many and varied effects of vitamin D on different health outcomes and emerging evidence that response to vitamin D may follow a "J- or U-shaped curve" make the potential use of vitamin D a complex issue.

Clinical trials of high levels of vitamin D in the treatment of prostate cancer were initially promising but complicated by the outcome of the ASCENT-2 trial. Clearly there is a need for further large-scale research studies in this area.

Currently there is insufficient evidence to recommend vitamin D supplementation to the general population or prostate cancer patients.

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# The Role of 5α-Reductase Inhibitors (5-ARIs) in Prostate Cancer Chemoprevention

32

David Margel and Neil Fleshner

*Prostate cancer (PCa)* is the most common male malignancy in the Western world. The traditional treatments, such as surgery or radiation, are associated with significant adverse events and can negatively affect the quality of life of patients and their families [1–3]. The negative effects of the treatments combined with potentially long latency of the disease, late-age onset, and high prevalence make PCa an ideal target for disease prevention.

*5α-reductase inhibitors* (*5-ARIs*). The rationale for the specific use of 5-ARIs as chemopreventive agents is based on the androgenic nature of prostate cancer and the uniform absence of prostate cancer among men with congenital deficiency of 5α-reductase [4]. The enzyme 5α-reductase resides in prostatic tissue and converts circulating testosterone to localized dihydrotestosterone (DHT), a more potent agonist of androgen receptors in prostatic cells. 5α-reductase has two isoforms: Type II 5α-reductase is the isoform common in benign prostatic tissue; type I predominates in localized PCa [5]. Finasteride is a selective inhibitor of the type II enzyme, while dutasteride inhibits both isoforms [6].

*Preventive medicine or preventive care* refers to measures taken to prevent diseases, (or injuries) rather than curing them or treating their symptoms. Preventive medicine strategies are typically described as taking place at the primary, secondary, and tertiary levels:

1. *Primary prevention* strategies intend to avoid the development of disease.
2. *Secondary prevention* strategies attempt to diagnose and treat an existing disease in its early stages before it results in significant morbidity.
3. *Tertiary prevention* aims to reduce the negative impact of established disease by restoring function and reducing disease-related complications.

In this chapter, we will consider the role of 5-ARIs in chemoprevention of prostate cancer at the primary and secondary levels. Whether primary PCa prevention is truly primary or tertiary can be debated, given that histological evidence suggests that microscopic disease can be found in 1 of 3 men in their 30s—well before the average PCa patient is diagnosed [7]; but for the purposes of this chapter, "primary prevention" refers to the prevention of clinically detectable disease.

*5-ARIs for primary prevention*. There are two published large, prospective randomized controlled studies examining the role of 5-ARI in PCa prevention. The first was the Prostate Cancer Prevention Trial (PCPT) [8]. The PCPT randomized 18,882 men with low risk for prostate cancer development (normal digital rectal examination and prostate specific antigen [PSA] ≤3.0 ng/ml) to 5 mg finasteride daily or placebo for 7 years. Primary analysis demonstrated a 25 % reduction in the prevalence of prostate cancer among men treated with finasteride compared to the control arm. Secondary analysis showed an unexpected greater absolute number of high-Gleason-grade cancers in the finasteride arm. To put it simply, for every 1,000 men, finasteride reduced the number of prostate cancers from 60 to 45; however, the number of high-grade cancers would increase from 18 to 21[9]. This has raised concern of the potential causal relationship of finasteride to high-grade cancer. Does the increase in high-grade cancers reflect a real risk of finasteride or merely confounding factors?

Several subsequent analyses addressed this question. At first, the reliability of the Gleason score in patients treated with a hormonal agent such as finasteride was questioned. There was some concern that morphologic changes caused by finasteride may mimic high-grade cancer and therefore produce a false higher Gleason reading. However, pathologic review eliminated the questions of morphologic artifact [10].

The next possible explanation was sampling error induced by the recognized effect 5-ARIs have on prostate volume.

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Finasteride decreases prostate volume by approximately 30 % [11, 12]. Indeed, modeling studies incorporating prostate volume suggest that the increase in high-grade cancers in the PCPT may be accounted for by higher detection and not tumor transformation or induction [13]. In fact, in the pathologic specimen of subjects who underwent radical prostatectomy in the placebo and finasteride arms of the study, the rates of more aggressive disease were not in concordance with the biopsy results [14]. A higher number of patients in the placebo arm than in the finasteride arm displayed high-grade disease (8.2 % vs. 6.0 %) [14].

The third hypothesis by which high-grade tumors were seen more frequently has to do with the differential effects of 5-ARIs on PSA between men with low- and high-grade diseases. In the PCPT, PSA was corrected according to a changing ratio to keep for-cause biopsies similar among both treatment arms. Post hoc analyses revealed that the utility of PSA is better for higher grade disease [15]. The implication of this is that men randomized to finasteride and had high-grade disease were more likely to get a for-cause biopsy than men with low-grade disease. Although one might think that these cases would be found at study exit biopsies, in fact, fewer men randomized to finasteride had exit biopsies. Despite these hypotheses, a causal relationship between high-grade PCa and finasteride treatment cannot be eliminated. Although, most believe that a true causal association is unlikely.

The results from the PCPT provided the proof in principle for 5-ARIs as an effective prostate cancer chemopreventive strategy. The next big step was the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial [16]. This trial was a large prospective randomized controlled study, published in the New England Journal of Medicine 2010. It was designed to assess the specific benefit of dutasteride, a 5-ARI that inhibits both type 1 and type 2 isoforms of 5α-reductase, in the prevention of PCa. As mentioned earlier, the type 1 isoform of 5α-reductase is enhanced during prostate cancer development. Table 32.1 displays the main differences between PCPT and REDUCE. The primary end point for both PCPT and REDUCE was prostate cancer incidence. The REDUCE patients were a higher risk population. Specifically, eligibility criteria included men aged 50–75 years with a baseline PSA level between 2.5 and 10 ng/ml, a prostate volume of less than 80 $cm^3$, and a prior negative biopsy performed "for cause" within 6 months before enrollment. Unlike the PCPT trial, the REDUCE trial required subjects to have a negative prostate biopsy [no PCa, high-grade prostatic intraepithelial neoplasia (PIN), or atypical small acinar proliferation] within 6 months of starting the trial. This requirement aimed to limit for-cause biopsies (protocol independent). Perhaps, one of the most important design features was the plan to require biopsies at 2 and 4 years to further minimize for-cause biopsies as a result of the increased PSA and DRE sensitivity previously noted with therapy using 5-ARIs. In REDUCE, approximately 12 % of patients had a for-cause biopsy, compared with 35 % of patients in the PCPT.

**Table 32.1** Comparison between 5-ARI primary prevention trials

| | PCPT trial | REDUCE trial |
|---|---|---|
| Population | | |
| Age (at entry) | Over 55 | 50–75 |
| PSA (at entry) | 3 or less | 2.5–10 |
| DRE (at entry) | Normal required | Normal not required |
| Biopsy (at entry) | None required | Negative biopsy within 6 months |
| Number of patients | 9,060 | 6,729 |
| Exposure | Finasteride vs. placebo | Dutasteride vs. placebo |
| Follow-up period | 7 years | 4 years |
| Biopsy | | |
| For cause | 34 %—5-ARI arm<br>35 %—placebo arm | 10 %—5-ARI arm<br>14 %—placebo arm |
| End of study | Yes(6 cores at 7 years) | Yes (6–12 cores at years 2 and 4) |
| Primary outcome | PCa detection | PCa detection |
| Results | | |
| High-grade PCa (%) | 6.4 %—5-ARI arm*<br>5.1 %—placebo arm | 6.7 %—5-ARI arm<br>6.8 %—placebo arm |
| Urinary symptom improvement | Yes | Yes |

*Statistically significant $p<0.01$

The results of the REDUCE trial parallel those of the PCPT (Table 32.1). The 22.8 % reduction in PCa diagnosis with dutasteride at the end of 4 years was similar to that with finasteride (24.8 %) at the end of 7 years. Consistent with the PCPT trial, the effect of dutasteride on PCa incidence occurred in all subgroups (age, PCa family history, body mass index, prostate volume, etc.) suggesting good utility in a wide range of men. Men randomized to dutasteride also demonstrated significantly better outcomes with respect to benign prostatic hyperplasia, such as decreased prostate volume, fewer episodes of urinary retention, fewer episodes of urinary tract infections, and decreased benign prostatic hyperplasia-related surgery. Dutasteride was generally well tolerated with a small but significant decrease in libido, loss of libido, and increased erectile dysfunction in the dutasteride arm when compared with those receiving placebo. Of concern was an increase in all types of cardiac events in the dutasteride arm. Nonetheless, when compared with the total number of patients in each arm, the absolute numbers were very small (30 of 4,105 in the dutasteride group, 16 of 4,126 in the placebo group), and this outcome, a composite of several cardiac-related conditions, was not homogeneous.

In the REDUCE trial, there was no statistically significant overall increase of high-grade cancer among patients receiving dutasteride, although in the 4-year arm, there were more high-grade tumors in the cohort of men receiving dutasteride. The REDUCE authors noted that, by 2 years, 141 more patients with Gleason 5–7 disease were removed from the placebo arm than from the dutasteride arm as a consequence of PCa diagnosis. Conceivably, a significant number of those patients would have advanced to Gleason 8–10 if continued in the study for another 2 years, thereby offsetting the higher number of Gleason 8–10 patients in the dutasteride arm. In addition, like the Prostate Cancer Prevention Trial, men receiving 5-alpha-reductase inhibitor had a lower incidence of high-grade PIN (prostatic intraepithelial neoplasia) and in REDUCE, a lower incidence also of ASAP (atypical small acinar proliferation). Both ASAP and high-grade PIN are considered to be precancerous or precursors of prostate cancer.

Unpublished reanalysis of the REDUCE results (personal communication with Dr Fleshner, 2012) using the modified Gleason (as opposed to the traditional system) scoring system has revealed a slightly higher statistically significant rate of high-grade cancers among men randomized to dutasteride.

The results of these trials prompted a combined American Urological Association and American Society of Clinical Oncology guidelines and a systematic review on PCa prevention with 5-ARIs [17]. The panel arrived at the following conclusions:

1. Asymptomatic men with a prostate-specific antigen (PSA) less than 3.0 ng/mL who are regularly screened with PSA or are anticipating undergoing annual PSA screening for early detection of prostate cancer may benefit from a discussion of both the benefits of 5-ARIs for 7 years for the prevention of prostate cancer and the potential risks (including the possibility of high-grade prostate cancer).
2. Men who are taking 5-ARIs for benign conditions such as lower urinary tract [obstructive] symptoms (LUTS) may benefit from a similar discussion, understanding that the improvement of LUTS relief should be weighed with the potential risks of high-grade prostate cancer from 5-ARIs (although the majority of the panel members judged the latter risk to be unlikely).
3. A reduction of approximately 50 % in PSA by 12 months is expected in men taking a 5-ARI; however, because these changes in PSA may vary across men and within individual men over time, the panel cannot recommend a specific cut point to trigger a biopsy for men taking a 5-ARI. No specific cut point or change in PSA has been prospectively validated in men taking a 5-ARI.

Recently, the Oncologic Drugs Advisory Committee (ODAC) of the US Food and Drug Administration (FDA) recommended against PCa chemoprevention labeling for the 5α-reductase inhibitors finasteride (Proscar) and dutasteride (Avodart) because both agents increase the likelihood of high-grade tumors when given as preventive agents to healthy men.

Panelists and FDA reviewers shared 3 main concerns about the drugs:

1. The risk of exposing currently healthy people to an increased risk for high-grade tumors.
2. The fact that risk reduction was only in low-grade tumors.
3. The doubt that the supporting clinical studies are generalizable to clinical practice in the American population.

We believe that both the REDUCE and PCPT provide level I evidence to the following:

- 5-ARIs prevent biopsy-detected prostate cancer.
- These drugs are generally safe, with reversible sexual dysfunction as the major AE.
- The performance of PSA and DRE for the diagnosis of prostate cancer is improved with 5-ARIs.

At present, we believe that it is reasonable to offer 5-ARI chemoprevention to patients who are at increased risk for developing prostate cancer, especially men with concomitant symptoms due to prostate enlargement. The decision to pursue 5-ARI chemoprevention must be made in concert with the patient and must take into consideration the benefits and risks associated with treatment. During this discussion, patients must be made aware of the potential sexual-related side effects associated with treatment. In addition, patients must be willing to accept the burden of cost of the medication.

*5-ARIs in secondary prevention*. A more appealing strategy than exposing healthy men to long-term medication would be to use 5-ARIs to delay progression in those men already diagnosed with PCa. There are currently two studies examining the role 5-ARI to prevent progression in men with low-risk, localized prostate cancer. The first study is a single-institution retrospective cohort study comparing men taking a 5-ARI versus no 5-ARI while on active surveillance for PCa [18]. The primary end point was pathologic progression defined as Gleason score >6, maximum core involvement >50 %, or more than three cores positive on a follow-up prostate biopsy. A total of 288 men on active surveillance with a median follow-up of 38.5 months were included in the analysis. Men taking a 5-ARI experienced a lower rate of pathologic progression (18.6 % vs. 36.7 %; $p=0.004$) and were less likely to abandon active surveillance (20 % vs. 37.6 %; $p=0.006$). On multivariable Cox proportional hazards analysis, lack of 5-ARI use was most strongly associated with pathologic progression (HR: 2.91 95%CI 1.5–5.6).

This concept of the use of 5-ARIs to prevent clinical progression in patients on active surveillance for low-risk PCa was also studied in a randomized controlled study. Our group has led the Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial [19]. In this trial, 300 subjects with biopsy-proven, low-risk, localized

prostate cancer were randomized to receive dutasteride 0.5 mg/day or placebo for 3 years while on active surveillance. Eligible men were between 50 and 80 years of age, had clinical stage T1c–T2a prostate cancer, a Gleason score of less than or equal to 6, and serum PSA less than or equal to 10 ng/mL. Entry biopsy of at least ten cores had to be performed within 6 months of screening and was repeated at 1.5 and 3 years. The primary end point of REDEEM was time to disease progression. This was a composite outcome defined as the earliest of the following events: receipt of primary therapy for prostate cancer (e.g., prostatectomy, radiation, hormonal therapy) or pathologic progression (≥4 cores involved, ≥50 % of any core involved, or any Gleason score ≥7). The initial results of this study were presented as an abstract in the 2010 SUO [20]. Forty-nine percent (71 patients) progressed in the placebo group compared to 38 % in the dutasteride group (51 patients), translating to a relative risk reduction of 38.9 %. Furthermore, subjects treated with dutasteride were more likely to have no cancer detected on follow-up biopsies (23 % in the placebo arm vs. 36 % in the dutasteride arm). The authors conclude that among men followed up for prostate cancer with active surveillance, dutasteride may delay the time for cancer progression and may provide a useful adjunct to active surveillance.

In summary, the concept of prevention dates back to Benjamin Franklin, whose aphorism—"an ounce of prevention is worth a pound of cure"—has withstood the test of time. 5-ARIs seem ideal drugs for cancer prevention since they are safe with only minimal side effects which seem to disappear upon drug discontinuation. The question remains who is the ideal candidate for PCa prevention and in what setting should we offer such a strategy. For example, 5-ARIs have been demonstrated to be effective in men older than 50. However, primary prevention should most probably start earlier in life, since PCa starts its growth during a man's fourth decade. Secondary prevention, preventing progression in men already diagnosed with PCa, may be a more appealing option. We believe 5-ARIs show great promise in secondary prevention and may in the future have a role in any active surveillance protocol.

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# Other Pharmaceutical Agents in the Chemoprevention of Prostate Cancer

33

Vivekanandan Kumar

## Introduction

Prostate cancer is the most commonly diagnosed cancer in the Western world and second commonest cause of death in males. Clinically significant prostate cancer takes two decades to develop. This long natural history of the disease lends itself well to modification by agents—dietary and therapeutic. Prostate cancer represents an ideal target for nutritional prevention due to its long latency, high incidence, tumor marker availability (prostate-specific antigen, PSA), and identifiable preneoplastic lesions and risk groups.

There are three broad categories of chemoprevention for prostate cancer: hormonal, dietary, and anti-inflammatory. Most studies have focused on hormonal interventions, which manipulate sex steroid hormone pathways, and dietary interventions, which alter the balance of nutritional intake. As 5-ARI's role is discussed in the previous chapter, we will restrict this chapter to chemoprevention by statins, anti-inflammatory drugs, dietary supplements, and estrogen pathway modulators.

## Statins

### Rationale and Mechanism

Statins work by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting step in the biosynthesis of cholesterol.

Studies have shown a possible role for statins in prevention of cancer. Statins reduces mevalonate synthesis which is a product of HMG-CoA reductase. Mevalonate is indirectly responsible for the activation of RasG protein. Lack of mevalonate inhibits further downstream molecules like farnesyl pyrophosphate and geranyl pyrophosphate, which are responsible for translocation of Ras and Rho to cell membrane—essential component for cell proliferation and migration. Further cholesterol is a main component of cell membrane, and its lack affects key regions (lipid rafts) involved in cell growth, survival, and migration. Protein kinase B is important in intracellular signaling pathway, the level of which gets altered on statin therapy. p21 and p27 also accumulates in cells, due to inhibition of cyclin-dependent kinase 2 by statins, resulting in growth inhibitory effect, retarding cancer cell mitosis.

### Epidemiological Studies

Some observational studies support the role of statins in prostate cancer. Graaf et al. found a nonsignificant reduction in incidence of prostate cancer (risk reduction 65 %) among 300,000 Dutch residents who were on statins [1]. Similarly, Shanon et al. found 65 % reduction in risk of prostate cancer among 100 prostate cancer patients compared to controls who were recruited upon referral for biopsy [2]. The risk reduction was with patients with Gleason score $\geq 7$. Similarly, in a retrospective review of veterans database, Singal et al. found that statin use was associated with protective effect on prostate cancer (OR 0.46).

In the Finnish Prostate Screening Trial [3], long-term statin use appears to support a lower total incidence of prostate cancer in relatively dose-dependent fashion. A factor that confounds these analyses is that long-term statin use appears to decrease serum prostate-specific antigen. While this seems to be the case, it is unlikely to be the cause of the observed differences in lowering the risk of aggressive or overall prostate cancer. From the studies, it also appears that short-term statin use is probably not sufficient to have any impact on the development or treatment of prostate cancer.

Dale et al. performed a meta-analysis of 26 randomized trials involving statins with a mean duration of follow-up

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of at least 1 year, enrolling a minimum of 100 patients, and reporting data on either cancer incidence ($n=20$ studies) or cancer death ($n=22$ studies) [4]. In the meta-analyses, there were 6,662 incident cancers and 2,407 cancer deaths. Statins did not reduce the incidence of cancer (OR, 1.02; 95 % CI, 0.97–1.07) or cancer deaths (OR, 1.01; 95 % CI, 0.93–1.09). No reductions were noted for any individual cancer type. This null effect on cancer incidence persisted when only hydrophilic, lipophilic, naturally derived, or synthetically derived statins were evaluated. The strength of this study includes large patient numbers, multiple randomized studies, and rigorous methodology. There were few limitations for this meta-analysis as well. Variation in cancer reporting and surveillance strategy among different studies included could have had an effect on the results. The authors have excluded the cancer incidence from Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) from this analysis because it only reported the cumulative number of cancer diagnoses. Further, the study was not standardized for confounding factors like smoking, though randomization would have distributed these factors evenly.

Breau et al. [5] analyzed the data from a longitudinal population-based cohort. The statin intake was self reported, and the prostate biopsy and cancer-related information was obtained through community records [5]. Statin use was associated with a decreased risk of undergoing prostate biopsy (HR 0.31; 95 % CI, 0.24, 0.40), receiving a prostate cancer diagnosis (HR 0.36; 95 % CI, 0.25, 0.53), and receiving a high-grade (Gleason 7 or greater) prostate cancer diagnosis (HR 0.25; 95 % CI, 0.11, 0.58) (Figs. 33.1 and 33.2). Statin use was also associated with a nonsignificantly decreased risk of exceeding a prostate-specific antigen threshold of 4.0 ng/ml (HR 0.63; 95 % CI, 0.35, 1.13). In addition, a longer duration of statin use was associated with a lower risk of these outcomes (all tests for trend $P \leq 0.05$). In this study, the authors have suggested that longer duration of statin use is associated with protective effect, and the RCTs/ cohort studies which did not show the association typically had 3.9–6 years of exposure to statins. In their study, they also found strongest association in patients who were on statins for more than 9 years. This study also had detailed discussion on limitations including bias on screening, selection, and standardization of the groups.

Dietary fat intake has been shown in observational studies to increase the risk of prostate cancer. Hence, the effect of statins could be merely due the effect of treating hyperlipidemia than direct effect of cancer cells. However, a study comparing statin group versus bile acid-binding resin group showed a positive association for only statins in reducing prostate cancer risk.

**Conclusion**

Statins are widely used, and initial research demonstrates they may have a role in prostate cancer prevention. Further research is needed before clinical recommendations.

## COX-2 Inhibitors

### Rationale

Evidence of chronic inflammation is found in the prostate along with prostate cancer commonly. It is possible for the prostatic inflammation to contribute to the etiology of prostate cancer. Chronic inflammation can cause oxidative stress which could lead to accumulation of DNA damage during the aging process which has been implicated in the genesis of malignancy. Inflammatory cells in the prostate produce a number of compounds such as superoxide, hydrogen peroxide, oxygen-free radicals, and peroxynitrite that cause DNA damage. The inflammatory response also results in the production of bioactive lipids such as prostaglandins. Cyclooxygenase enzymes (COX-1 or COX-2) catalyze the rate-limiting step in prostaglandin synthesis, which is the conversion of arachidonic acid to PGH2. COX-2 expression is highly inducible and regulated by a number of inflammatory or mitogenic stimuli, such as bacterial lipopolysaccharides, proinflammatory cytokines (IL-ip, IL-2), tumor necrosis factor, epidermal growth factor, and androgens. Prostaglandins generated at sites of inflammation mediate a variety of responses to tissue injury and hypoxia, including inhibition of apoptosis, cell growth, increased cell migration, inhibition of the immune response, and stimulation of angiogenesis [6].

### In Vitro Studies

Epithelial proliferation has been shown to arise in the inflammatory foci, and it has been found that COX-2 is expressed at high levels at these sites [7]. However, the presence of COX-2 in prostatic lesions is highly variable [8]. The studies on expression of COX-2 in prostate cancer had shown conflicting results. NSAIDs have been shown to exert growth inhibitory effects through non-COX-2 inhibition effect like inhibition of proinflammatory gene induction by arachidonic acid metabolites in prostate cultures as well [9]. These studies show possible inhibition of prostate carcinogenesis by NSAIDs.

## Epidemiological Studies

A Canadian nested case–control study had shown NSAIDs/coxibs were associated with a reduced likelihood of prostate cancer occurrence (odds ratio [OR], 0.71; 95 % confidence interval [CI], 0.58–0.86), as was exposure to aspirin (OR, 0.84; 95 % CI, 0.74–0.96) in patients over 65 years of age. Longer duration exposure to NSAIDs increased the protective effect [10].

A systematic meta-analysis performed in 2004 and subsequently in 2006 identified 24 studies examining the association between NSAID use and prostate cancer [11, 12]. Ten of them were cohort, and 14 were case–control studies. There were no randomized control trials. Majority of the studies assessed the intake of drugs once only by asking the patients. Studies that assessed the effect of aspirin use on total prostate cancer had a pooled odds ratio (POR)

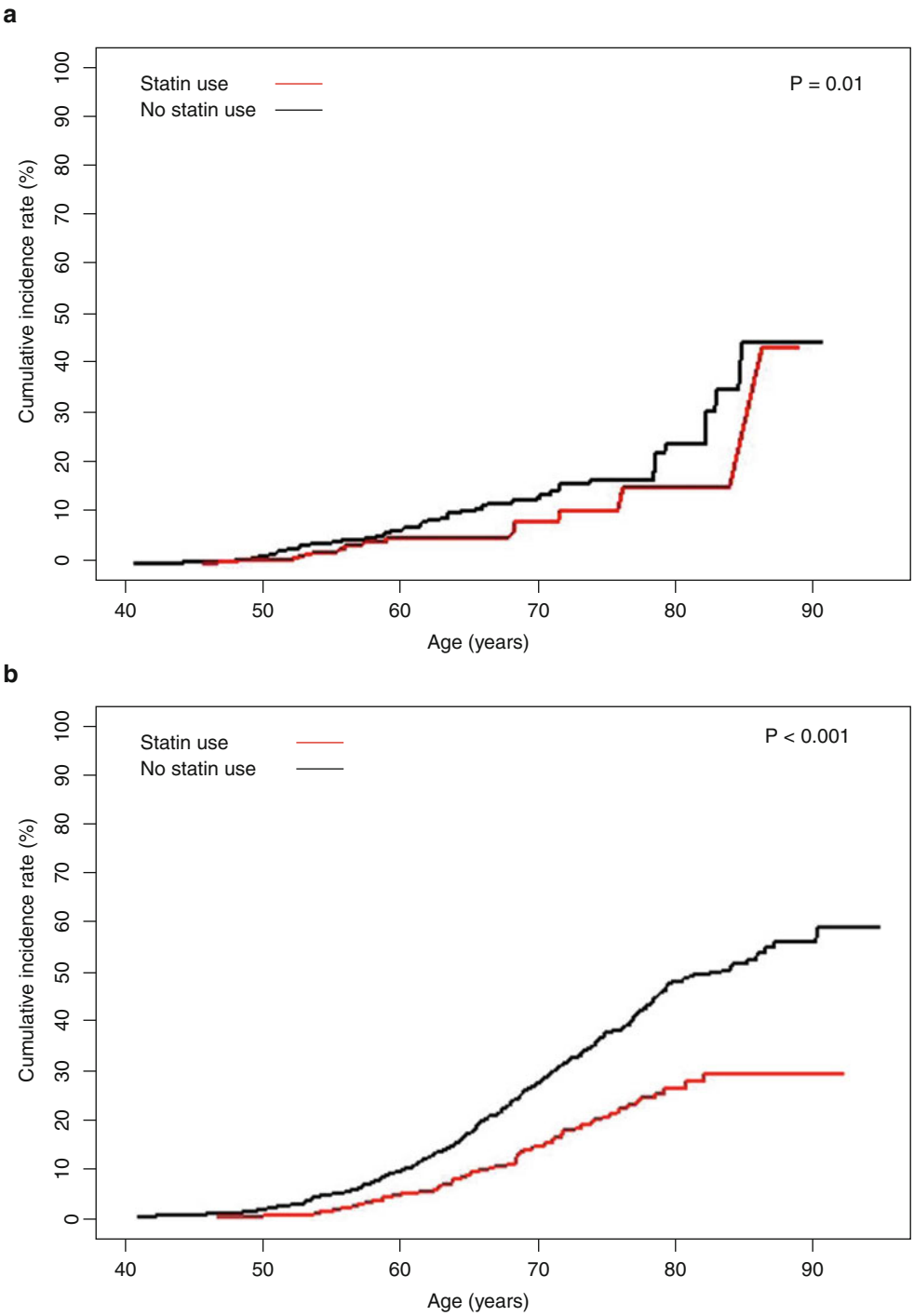
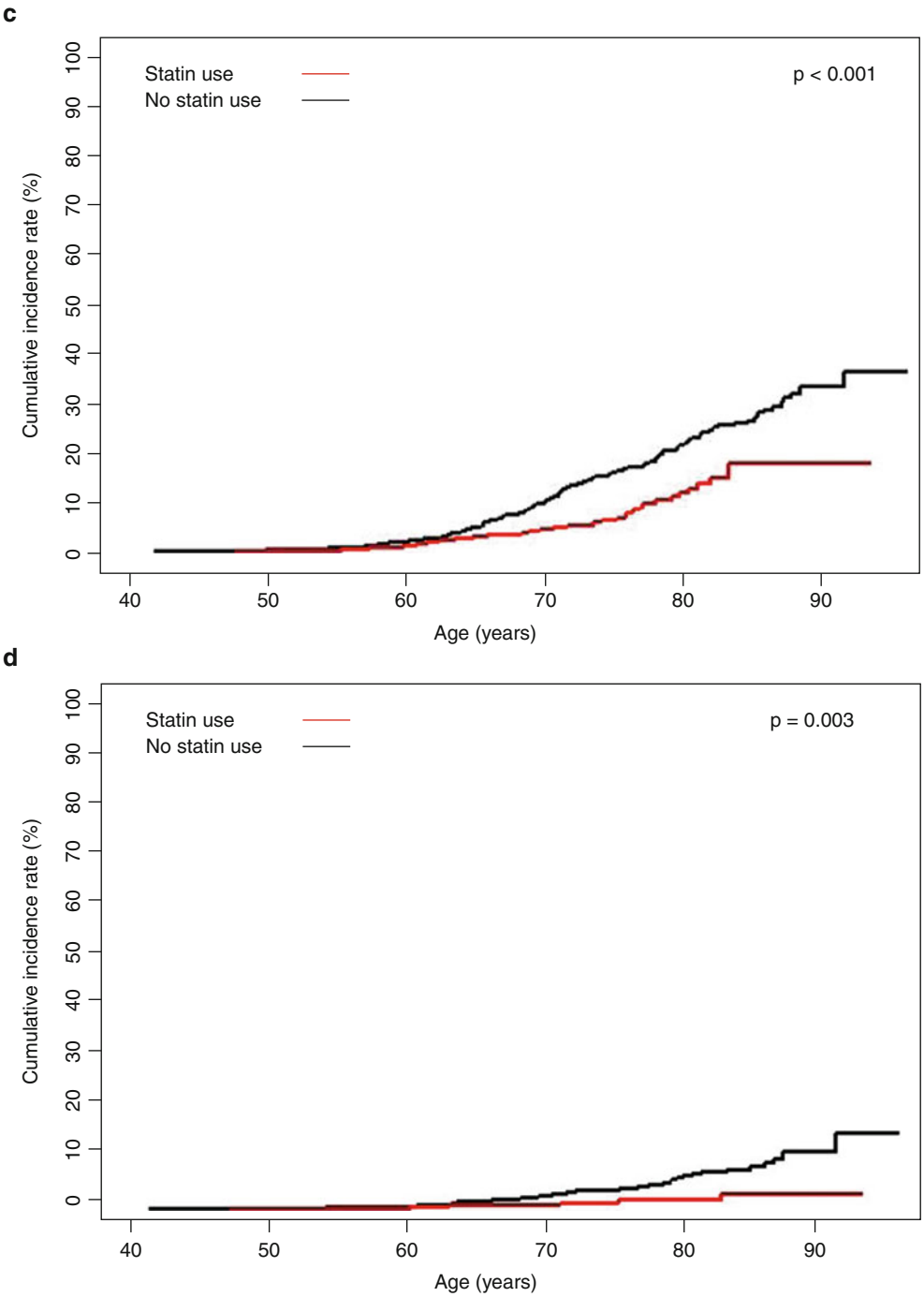



**Fig. 33.1** Cumulative incidence of exceeding age-specific PSA reference range (**a**) of prostate biopsy (**b**), of prostate cancer (**c**), and of high-grade prostate cancer (Gleason 7 or greater, **d**) (Reproduced from [5])

**Fig. 33.1** (continued)




of 0.83 (95%CI: 0.77–0.89), whereas those that assessed the effect of aspirin on advanced prostate cancer had a POR of 0.81 (0.72–0.92). Studies that examined the effects of nonaspirin NSAIDs or all NSAIDs were less consistent but still suggestive of reduced risks. Exposure misclassification, limited information on dose and duration of drug use, and the possibility of uncontrolled detection bias are limiting factors (Fig. 33.3).

## Conclusion

NSAIDs are a commonly used group of drugs, and they cause various gastrointestinal side effects, namely, dyspepsia, gastric ulceration, and bleeding. Every year, there are several reported cases of death due to these side effects. Selective COX-2 inhibitors (coxibs) were developed to reduce these side effects, and they indeed reduced the gastrointestinal side effects by 50 %. However, in

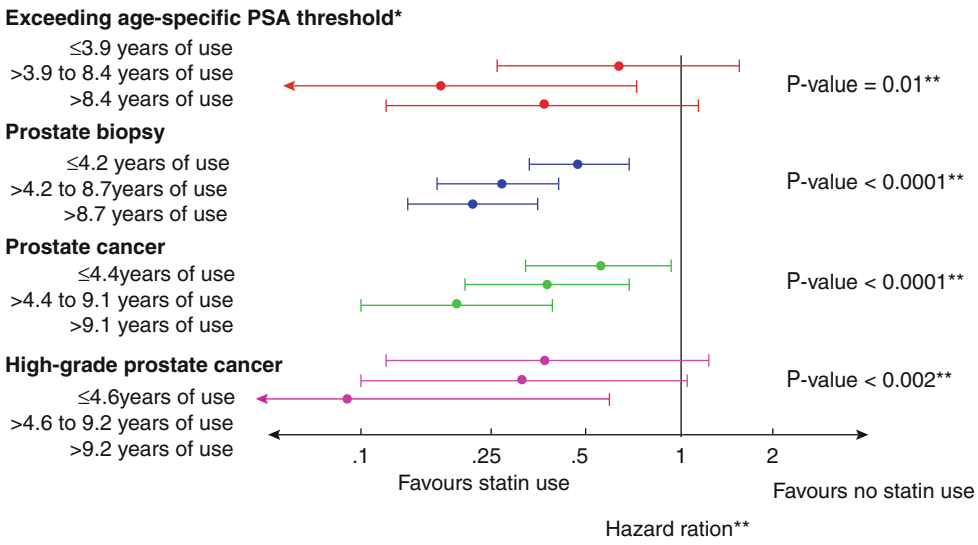



**Fig. 33.2** Associations between duration of statin use (stratified by tertiles) and outcome using nonstatin users as referent group. *P* values represent tests for trend. *Asterisk* indicates PSA outcomes only for 634 men who participated in in-clinic examinations. *Double asterisk* indicates adjusted for age, diabetes, hypertension, CHD, and NSAID, 5-alpha-reductase inhibitor, and α-blocker use (Reproduced from [5])

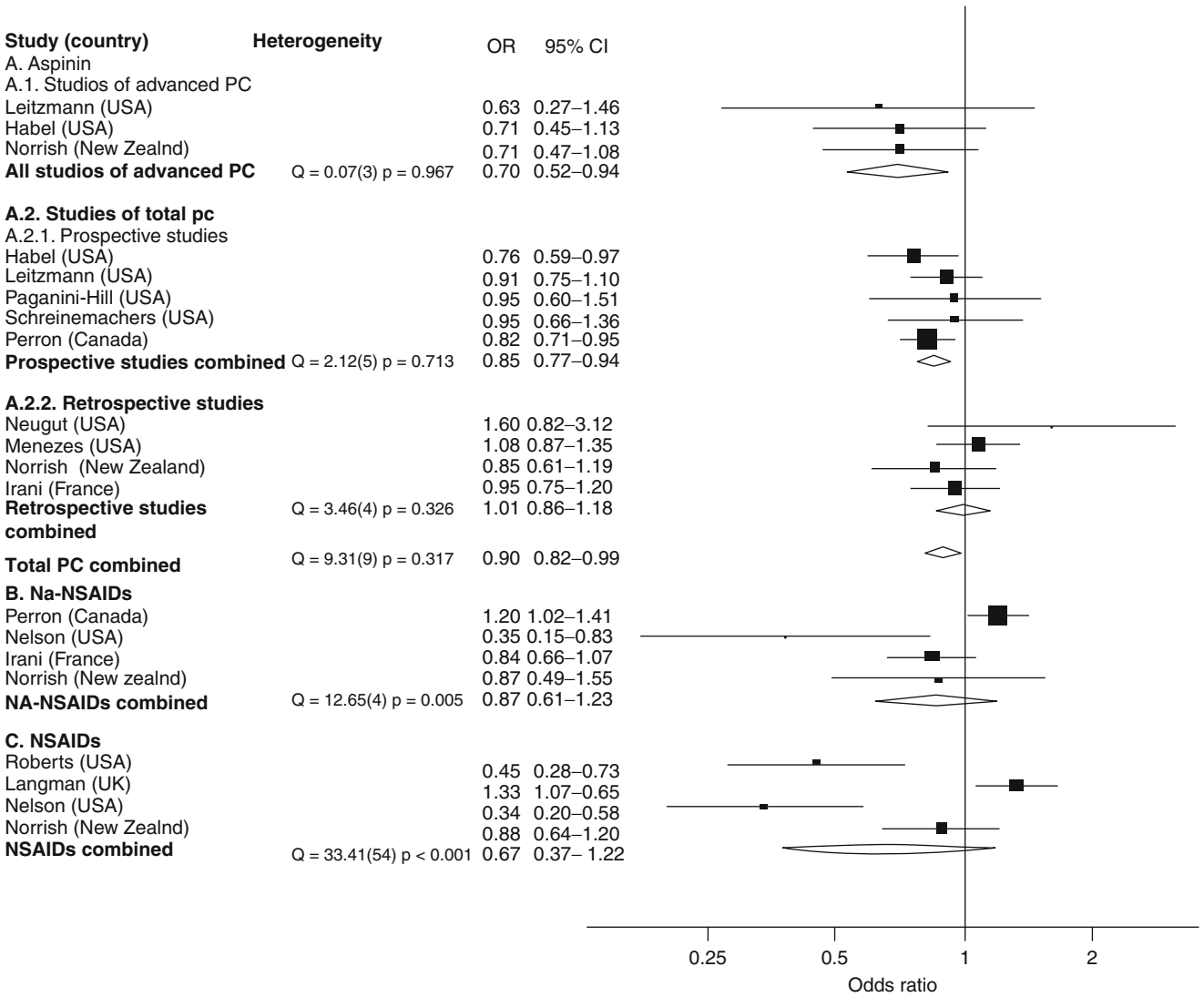



**Fig. 33.3** Relative risk estimates and summary of odds ratio by NSAID type (Reproduced with permission from [12])

cancer prevention studies, selective COX-2 inhibitors were found to be associated with increased risk of cardiovascular toxicity. This has caused a great deal of concern and hampered the progress in this field. Moving forward, it seems that a balance between the risk of disease and risk of taking NSAIDs or aspirin should be carefully taken into account when formulating recommendations.

## Selenium and Vitamin E

### Rationale

*Vitamin E* is used to refer to a group of fat-soluble compounds that include both tocopherols and tocotrienols (ref). There are many different forms of vitamin E, of which γ-tocopherol is the most common in the North American diet. γ-Tocopherol can be found in corn oil, soybean oil, margarine, and dressings. α-Tocopherol, the most biologically active form of vitamin E, is the second most common form of vitamin E in the North American diet. This variant of vitamin E can be found most abundantly in wheat germ, sunflower, and safflower oils. It is a fat-soluble antioxidant that stops the production of reactive oxygen species formed when fat undergoes oxidation.

*Selenium* is a nonmetal chemical element found in sulfide ores such as pyrite, where it partially replaces the sulfur. The chief commercial uses for selenium today are in glassmaking and in chemicals and pigments. Selenium salts are toxic in large amounts, but trace amounts are necessary for cellular function in many organisms. It is a component of the enzymes glutathione peroxidase and thioredoxin reductase (which indirectly reduce certain oxidized molecules in animals and some plants). It is also found in three deiodinase enzymes, which convert one thyroid hormone to another.

Preclinical and epidemiological data have suggested that selenium, vitamin E, and beta-carotene prevent prostate cancer. Cell line studies have shown that vitamin E inhibits the growth of LNCaP prostate cancer lines [13]. Further studies have also shown that selenium causes apoptosis in DU145 prostate cancer cell lines [14] and has an effect on prostate cancer cell growth [15].

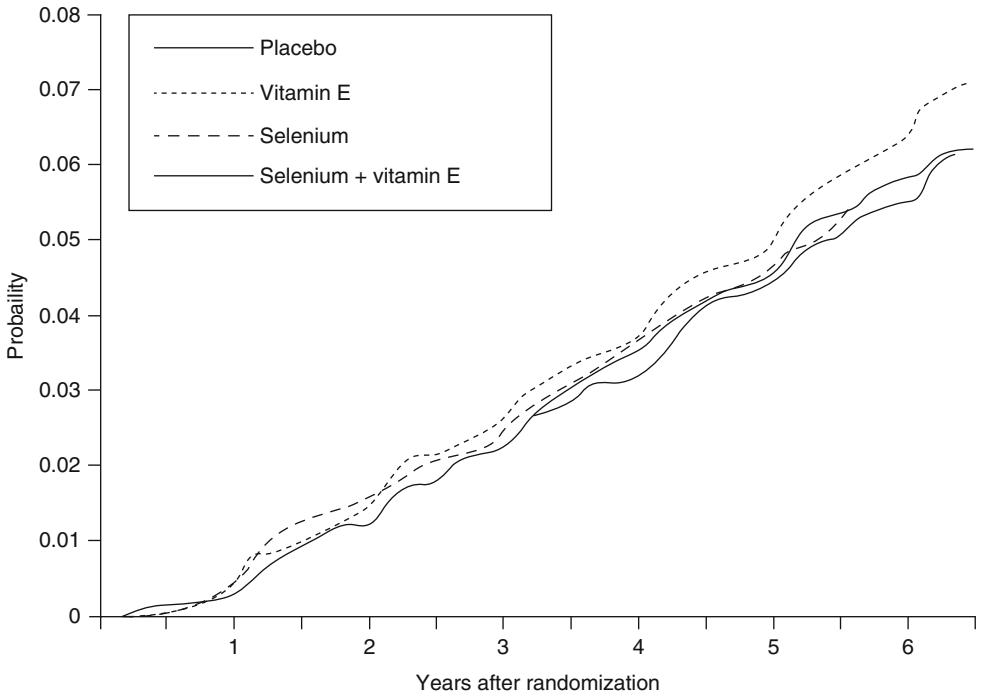
### General Cancer Prevention Studies

Nutritional Prevention of Cancer: This was a North American randomized, placebo-controlled, crossover cancer prevention trial. 1,312 subjects with nonmelanomatous skin cancer were randomized to placebo or 200 μg of selenium. Patients were treated for a period of 4.5 years and mean follow-up of 6.4 years. Results from secondary end point analysis suggested that supplemental selenium reduced the incidence of several cancers including prostate cancer. However, selenium did not protect against development of skin cancers [16].

ATBC Cancer Prevention Study: A randomized, double-blind, placebo-controlled, primary-prevention trial to determine whether daily supplementation with alpha-tocopherol, beta-carotene, or both would reduce the incidence of lung cancer and other cancers. A total of 29,133 male smokers, 50–69 years of age from southwestern Finland, were randomly assigned to one of four regimens: alpha-tocopherol (50 mg/day) alone, beta-carotene (20 mg/day) alone, both alpha-tocopherol and beta-carotene, or placebo. Follow-up continued for 5–8 years. As a secondary end point, the participants who received alpha-tocopherol had fewer cancers of the prostate and colorectum than those who did not receive alpha-tocopherol, whereas more cancers of the bladder, stomach, and other sites combined were diagnosed in the participants who received this supplement [17].

### Specific Prostate Cancer Prevention Trials

A randomized, placebo-controlled trial (Selenium and Vitamin E Cancer Prevention Trial [SELECT]) of 35,533 men from 427 participating sites in the United States, Canada, and Puerto Rico randomly assigned to four groups (selenium, vitamin E, selenium and vitamin E, and placebo) in a double-blind fashion. Baseline eligibility included age 50 years or older (African-American men) or 55 years or older (all other men), a serum prostate-specific antigen level of 4 ng/mL or less, and a digital rectal examination not suspicious for prostate cancer. Intervention included oral selenium (200 μg/day from L-selenomethionine) and matched vitamin E placebo, vitamin E (400 IU/day of all-rac-alpha-tocopheryl acetate) and matched selenium placebo, selenium and vitamin E, or placebo and placebo for a planned follow-up of minimum of 7 years and a maximum of 12 years. At a median overall follow-up of 5.46 years (range 4.17–7.33 years), hazard ratios (99 % confidence intervals [CIs]) for prostate cancer were 1.13 (99 % CI, 0.95–1.35; $n=473$) for vitamin E, 1.04 (99 % CI, 0.87–1.24; $n=432$) for selenium, and 1.05 (99 % CI, 0.88–1.25; $n=437$) for selenium and vitamin E versus 1.00 ($n=416$) for placebo. There were no significant differences (all $P=0.15$) in any other prespecified cancer end points. There were statistically nonsignificant increased risks of prostate cancer in the vitamin E group ($P=0.06$) and type 2 diabetes mellitus in the selenium group (relative risk, 1.07; 99 % CI, 0.94–1.22; $P=0.16$) but not in the selenium and vitamin E group. Selenium or vitamin E, alone or in combination at the doses and formulations used, did not prevent prostate cancer in this population of relatively healthy men (Fig. 33.4).




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 8689 | 8553 | 8328 | 8039 | 7389 | 4892 | 2516 |
| vitamin E | 8732 | 8610 | 8373 | 8096 | 7401 | 4867 | 2537 |
| Selenium | 8750 | 8597 | 8341 | 8083 | 7393 | 4848 | 2558 |
| Selenium + vitamin E | 8700 | 8585 | 8371 | 8097 | 7428 | 4894 | 2580 |

**Fig. 33.4** Cumulative incidence of prostate cancer detected each year by intervention group. Compared with placebo, there was as statistically nonsignificant increase in prostate cancer in the vitamin E group ($P = 0.06$) and not in the selenium + vitamin E group ($P = 0.52$) or the selenium group ($P = 0.62$) (Reproduced from [18])

**Conclusion**

SELECT suggested vitamin E, alpha-tocopherol, or combination did not prevent development of prostate cancer in spite of strong secondary evidence. There could be several reasons to account for this. The dosage (vitamin E dose of 400 IU vs. 50 IU) and formulations (L-selenomethionine vs. selenized yeast) used in the SELECT were different from ATBC or NPC. Nevertheless, the authors had a strong clinical evidence to use the dosage and formulations used in SELECT. Further, the results of NPC could be skewed due to low sample size, and the result could be chance finding due to multiple testing.

## Estrogen Receptor Modulators (Also See Chap. 30)

### Rationale

Estradiol contributes to the development of HGPIN and prostate cancer. Toremifene is an estrogen receptor modulator and has the potential to reduce the incidence of HGPIN and prostate cancer [19, 20]. Animal studies in transgenic mice had shown toremifene reduced the incidence of HGPIN and prostate cancer [21].

### Epidemiological Studies

A phase II dose-finding double-blind study involving 514 subjects had been conducted in subjects with HGPIN but not biopsy-proven prostate cancer. This was a 12-month prospective study, and patients were randomized to daily dosage of 20, 40, or 60 mg of toremifene. There had been 22 % reduction in cumulative risk of prostate cancer in patients on 20 mg of toremifene compared to placebo (24.4 % vs. 31.2 %, $P < 0.05$). The point incidence of prostate cancer was reduced by 48.2 % with 20 mg of toremifene compared to placebo in patients who did not have biopsy evidence of prostate cancer at baseline and 6 months [22]. Although it is unclear why only the 20-mg arm showed a significant reduction in the risk of prostate cancer, the authors hypothesize that it was the greater selectivity and inhibition of a subtype of the estrogen receptor which stimulate prostate growth.

**Conclusion**

A phase III study is ongoing comparing toremifene 20 mg with placebo, and the initial results indicate no statistically significant difference in incidence of the prostate cancer between the two groups [23]. However, final results are awaited. Until then, given current clinical recommendations for HGPIN, toremifene should not be considered for prostate cancer prevention at this time [24].

## Lycopene

### Rationale

Lycopene is a carotenoid that gives tomatoes their red color. Although lycopene is the major bioactive compound, there is a possibility of synergistic action with other compounds like glycoalkaloids (tomatine), phenolic compounds (quercetin), salicylates, phytoene, and phytofluene. Although it is established that lycopene is readily taken up by the prostate, most of the lycopene in the human prostate gland has been found to be primarily in the cis form, despite being available largely in the trans form in the food sources, although the significance of the transformation is still poorly understood [25, 26].

### Mechanisms

Lycopene exerts its effect by several possible mechanisms. It is an antioxidant and prevents oxidative damage to cellular protein, lipid, and DNA. Lycopene had been shown to modulate intercellular communication. Some studies have shown increased gap junction intercellular communication, decreased oxidative damage to DNA, and increased apoptosis. Lycopene had been shown to inhibit both androgen dependent and independent cell lines. Lycopene has been shown to impact IGF-I signaling, cell cycle progression, and cellular proliferation and to have an inhibitory effect on deoxyribonucleic acid (DNA) synthesis in primary prostate epithelial cell cultures in vitro [27].

Although in vitro studies have demonstrated several cellular effects, which are both genomic and nongenomic, to date, the molecular mechanism for the cancer-preventive effects of lycopene is not clearly understood. This may be due to the fact that chemopreventive agents have multiple chemoprevention-associated molecular activities. Some of these activities may be interrelated. Also, a single activity, even if it is the agent's predominant pharmacologic activity, may not be the most important or the only one effecting chemoprevention. Thus, although observing chemopreventive effects at the cellular and tissue levels is a key approach to identifying potential chemopreventive agents, future clinical trials must complement these studies by examining the molecular targets of these agents.

### Epidemiological Studies

Ten epidemiological studies have been found to be examining the relation between lycopene and prostate cancer. Six of them investigated the relation between dietary lycopene intake and risk of prostate cancer. Four studies examined the relation between blood lycopene levels and prostate cancer risk. Eight out of the ten studies have shown inverse association between lycopene and the risk of prostate cancer.

The possible importance of dietary lycopene in the etiology of prostate carcinoma was highlighted by the Health Professionals Follow-up Study. This showed that of all the dietary factors investigated, including several carotenoids and vitamin E, only high levels of dietary lycopene were associated with a decreased risk of developing prostate cancer.

Giovannucci reviewed the role of lycopene and lycopene-based dietary factors in relation to the risk of various cancers including prostate cancer [28]. Among 72 studies identified, 57 reported statistically significant inverse associations between tomato intake or blood lycopene level and the risk of cancer in defined anatomic sites including the prostate [29]. The Physicians' Health Study revealed lycopene was the only antioxidant found at significantly lower mean levels in patients with cancer than in matched controls [30]. None of the associations was confounded by age, smoking, body mass index, exercise, alcohol use, multivitamin use, or plasma cholesterol level. Furthermore, early clinical trials of short-term lycopene supplementation, either in the form of an oleoresin or in tomato pasta sauce, in patients before radical prostatectomy have shown significant decreases in PSA level, together with evidence of downregulation of cancerous cell activity.

However, in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, the intake of 25 tomato-related foods in 29,361 men was prospectively assessed, and lycopene intake was not associated with prostate cancer risk nor were reduced risks found for total tomato servings or for most tomato-based foods, although inverse associations were suggested for some processed tomato products commonly cooked with fats [31]. No association was observed between serum lycopene and total prostate cancer, whereas high serum beta-carotene concentrations were associated with increased risk for aggressive PCa [32].

A systematic review of lycopene supplementation on post diagnostic prostate cancer progression identified

eight interventional studies [33]. Five studies did not have a control, and one had unmatched control. There were two randomized studies. The studies also had widely different groups of patients and included a range of different outcome measures. The outcome measures reported in the studies include changes in PSA levels, cancer-related symptoms, evidence of progression from bone scans, survival, and toxicity. Six of the eight studies showed inverse association in biochemical response with PSA on lycopene supplementation. Kucuk in a small RCT examined short-term supplementation of lycopene for 3 weeks before radical prostatectomy, and he did not find significant change in percentage PSA. However, in a larger RCT, Ansari et al. examined the effect of lycopene supplementation on metastatic cancer patients treated by orchidectomy [34]. They used lycopene at a dose of 4 mg/day for 2 years. The intervention arm showed a significantly low mean PSA ($P < 0.001$) compared to nonintervention group and complete PSA response in 78 % versus 40 % in nonintervention group ($P < 0.05$). One RCT and another before–after study showed amelioration of cancer-related symptoms, namely, bone pain [35] and urinary symptoms [34] objectively. They have also shown higher proportion of patients with complete response by bone scan with corresponding decrease in bone pain and use of analgesics. The before and after study by the same group had shown 25 % reduction in overall metastatic lesions. Ansari group also reported survival advantage at a mean follow-up of 25.5 months. Out of 19 deaths, 12 happened in control group compared to seven in the intervention group ($P < 0.001$). However, there was no information on long-term survival.

Toxicity was examined in six out of eight studies. None of the studies reported severe intolerance according to the National Cancer Institute Common Toxicity criteria. In the RCTs, no adverse effect was reported during and after supplementation. The common side effects reported in the before–after studies were GI related, including nausea, vomiting, diarrhea, flatulence, anorexia, and dyspepsia. As these studies did not include control, it is difficult to definitely attribute the side effects to lycopene.

**Conclusion**

Studies indicate that lycopene is well tolerated and is not harmful. It is premature to recommend lycopene in primary chemoprevention of prostate cancer due to heterogeneity of the studies. However, lycopene supplements are already available in the market with specific reference to prostate cancer and men's health.

The trails considered so far do not provide sufficient evidence to recommend the use of lycopene supplements in routing clinical practice for patients diagnosed with prostate cancer. Further research should also consider other active components in tomato apart from lycopene.

## Zinc and Citrate

### Rationale and Mechanism

The primary function of the prostate gland is the production and secretion of prostatic fluid. The major component of the prostatic fluid is its extraordinarily high concentration of citrate, which ranges from ~40 to 150 mM as contrasted with ~0.2 mM citrate in blood plasma. The function of prostate citrate production is achieved by the activity of highly specialized glandular epithelial cells. The prevention of citrate oxidation by the prostate cells is the key event that is responsible for net citrate production. The cellular accumulation of zinc results in high levels of mitochondrial zinc that inhibit m-aconitase activity and citrate oxidation resulting in high prostatic citrate level. The inhibition of m-aconitase truncates the Krebs cycle at the first step of citrate oxidation, which provides the most efficient metabolic alteration for synthesized citrate to accumulate for secretion.

It is now well established that citrate and zinc levels [36] are markedly decreased in malignant versus normal prostate tissue (Figs. 33.5 and Table 33.1). In the absence of high cellular zinc levels, m-aconitase activity is no longer inhibited, and citrate oxidation proceeds via the Krebs cycle. Thus, zinc-accumulating citrate-producing normal prostate epithelial cells get metabolically transformed into citrate-oxidizing cells that have lost the ability to accumulate zinc. Zinc accumulation in normal prostatic epithelial cells results in citrate production, inhibits respiration and terminal oxidation of prostate mitochondria, inhibits growth and proliferation of prostate epithelial cells, induces apoptogenesis, and inhibits the invasive capabilities of malignant prostate cells. These effects of zinc accumulation are inhibitory to and incompatible with the prostate malignant process and can be defined as "tumor suppressor" effects of zinc. This leads to a rational expectation that the restoration of zinc accumulation in the malignant prostate cells should arrest the malignancy and cause the death of the tumor cells. Moreover, if zinc accumulation is restored in the neoplastic/premalignant stage, overt malignancy should be prevented.

### Epidemiological Studies

Based on this experimental evidence, several studies that relate the use of dietary zinc supplementation to prostate

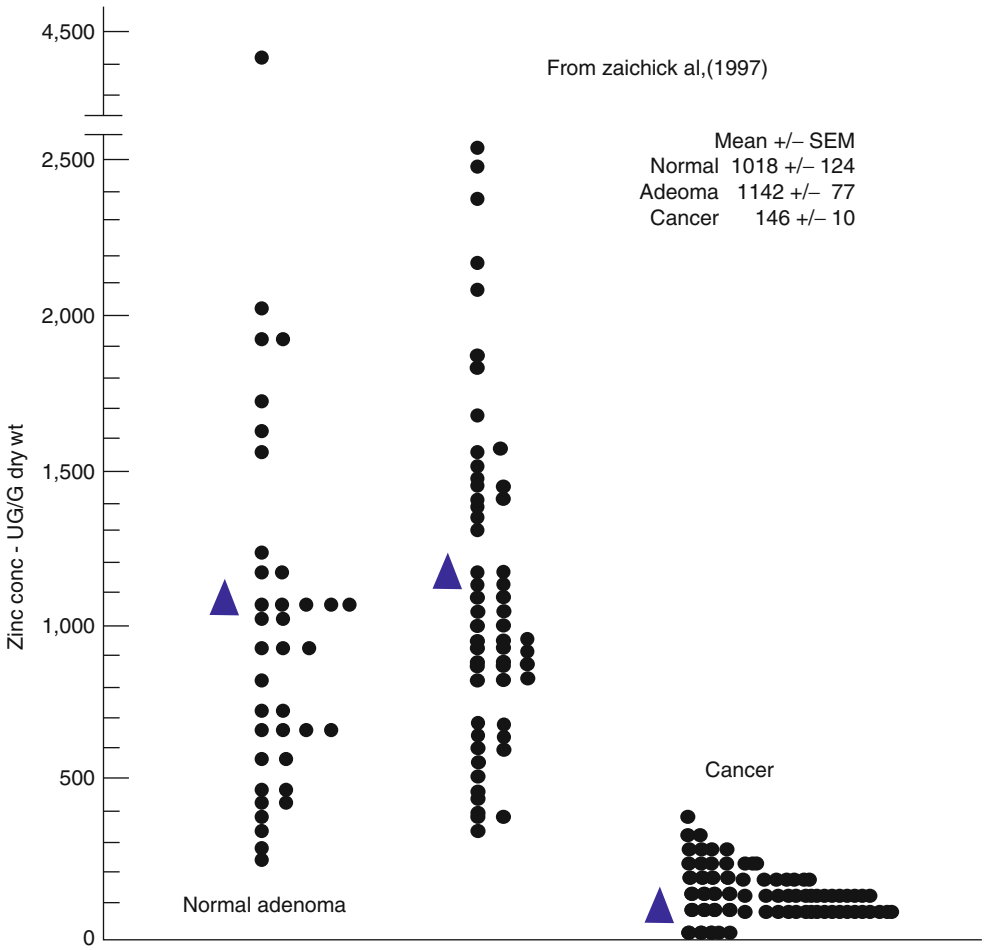



**Fig. 33.5** Zinc levels in normal, benign, and prostate cancer tissues (Reproduced from [37])

**Table 33.1** Zinc level in prostate from 17 published studies

| | Mean values | % Change from |
|---|---|---|
| Normal | Mean ± SEM | Mean (SEM) |
| Normal | 755 ± 158 | – |
| BPH | 1,270 ± 273 | +65 (45)% NS |
| PCA | 276 ± 48 | −68 (3)% $P < 0.001$ |

Reproduced from [37]
% Change from normal is obtained from the sum of the changes observed in each study that included normal values (15 reports)

cancer have been reported. Epidemiological studies regarding dietary zinc effects on prostate cancer have been conflicting and confusing. One study demonstrated that in vivo treatment of zinc increased zinc accumulation and citrate production in PC-3 cell-induced tumor tissues and inhibited tumor growth in nude mice [38]. Excess intake of zinc, especially with individual supplements, may however have the potential to encourage the transition of prostate conditions from benign prostatic hyperplasia to cancer. Health Professionals Follow-up Study examining the risk of prostate cancer in 46,974 supplemental zinc users found supplemental zinc intake at doses of up to 100 mg/day was not associated with prostate cancer risk. However, compared with nonusers, men who consumed more than 100 mg/day of supplemental zinc had a relative risk of advanced prostate cancer of 2.29 (95 % confidence interval = 1.06 to 4.95; $P$ trend = 0.003), and men who took supplemental zinc for 10 or more years had a relative risk of 2.37 (95 % confidence interval = 1.42 to 3.95; $P$ trend < 0.001) [39]. Large doses of zinc can inhibit the benefits of bisphosphonate drugs [40], increase testosterone level, increase cholesterol, reduce levels of "good cholesterol" (high-density lipoprotein), and can promote immune dysfunction [41].

## Conclusion

More research is needed in this area, but in the meantime, the intake of larger concentrations of zinc for most individuals need to be discouraged until adequate research resolves this controversial issue [42]. There is a consis-

tency in all the reports that the use of moderate levels of zinc supplement does not impose any additional risk; and in some reports, it could be efficacious against prostate cancer. In the elderly male population, supplemental zinc would be efficacious in maintaining a normal plasma zinc level. This should be incorporated into or along with any other interventions [37].

## Green Tea

### Rationale

Green tea is obtained from drying fresh tea leaves from tea plant *Camellia sinensis*. More than two-thirds of the world population consume this beverage. It contains characteristic polyphenol compound epigallocatechin 3-gallate (EGCG). EGCG is a more potent antioxidant, and it is 25–100 times more potent than vitamin C or E [43]. Many studies have shown decreased risk or reduced progression of prostate cancer [44, 45] associated with consumption of green tea.

### Mechanism

EGCG in prostate cancer cell lines have shown growth inhibition and induction of apoptosis primarily through p53-dependent pathway [46]. Combination of EGCG and a COX-2 inhibitor resulted in expression of pro-caspase-6 and pro-caspase-9 and poly(ADP-ribose) polymerase (PARP) cleavage, inhibition of peroxisome proliferator activated receptor (PPAR)-γ, and inhibition of NF-κB compared with the additive effects of the two agents alone, suggesting a possible synergism[47]. EGCG also specifically inhibited proteasomes resulting in accumulation of proteasome substrates KIP1/p27 and IκBα followed by growth arrest in the G(1) phase of the cell cycle[48].

### Animal Studies

Animal studies have been done employing TRAMP (transgenic adenocarcinoma of the mouse prostate) mice. Oral infusion of GTP at human achievable dose (six cups of green tea/day) significantly inhibited prostate cancer development and increased tumor-free and overall survival of mice. In the TRAMP mice ventral prostate, EGCG significantly reduced cell proliferation, induced apoptosis, and decreased androgen receptor (AR), insulin-like growth factor 1 (IGF-1), IGF-1 receptor, phospho-ERK1/2, COX-2, and inducible nitric oxide synthase (iNOS) [49]. In athymic nude mice, implanted with CWR22Rυ1 cells, treatment with GTP, water extract of black tea, EGCG, and theaflavins resulted in significant inhibition in growth of implanted prostate tumors, reduction in the level of serum PSA, induction of apoptosis accompanied with upregulation in Bax and decrease in Bcl-2 proteins, and decrease in the levels of VEGF protein [50].

### Epidemiological Studies

Six studies examined the role of green tea in prostate cancer. The trial setting, study design, population studied, and the end points were highly heterogeneous. Two studies have shown minimal or limited antineoplastic activity in castrate-resistant prostate cancer [51, 52]. In a phase II trial, tumor response, defined as a decline in the baseline PSA value, occurred in a single patient or 2 % of the cohort and was not sustained beyond 2 months. The median change in the PSA value, from baseline for the cohort, increased by 43 % at the end of the first month. Green tea toxicity, usually grade 1 or 2, occurred in 69 % of patients; however, six episodes of grade 3 toxicity and one episode of grade 4 toxicity also occurred. In a Japanese public health study, green tea consumption was associated with dose-dependent decrease in incidence of advanced prostate cancer. The multivariate relative risk was 0.52 for men drinking five or more cups/day compared with less than one cup/day. Green tea was not associated with localized prostate cancer [53]. A phase II proof of principle clinical study on HGPIN volunteers, green tea catechin (GTC)-treated men showed no significant change in PSA but a decreased incidence of prostate cancer and improved IPSS in patients with coexistent BPH. Further prostate mapping was done for 2 years in these subjects. It showed long-lasting inhibition of prostate cancer progression after 1 year treatment with GTC [54]. A Chinese case–control study examined the association between green tea intake and prostate cancer in 130 prostate cancer patients and 274 controls. Green tea intake was assessed using structured questionnaire by interview. The prostate cancer risk declined with increasing frequency, duration, and quantity of green tea consumption; and the dose–response relationships were also significant, suggesting that green tea is protective against prostate cancer.

There were no randomized studies examining the association of green tea and prostate cancer. There were very few or no studies examining the risk of prostate cancer in high incidence geographical locations like Europe or North America.

**Conclusion**

Further studies are needed to determine the role, if any, of green tea in prostate cancer prevention.

## Phytotherapy

### Rationale

Soya product intake is one of the major differences in diet between East and West inversely correlating with incidence of prostate cancer. A limited amount of clinical evidence points to a beneficial role of soy products in reducing male sex hormone levels and exhibiting weak estrogen and antiestrogen-like properties [55, 56]. The beneficial effects of soya product have been attributed to isoflavanoids. Experimental evidence is available regarding antitumor effect of isoflavanoids, namely, genistein and daidzein. Phytochemicals differ from what are traditionally termed nutrients because they are not a necessity for normal metabolism nor will their absence result in a deficiency disease.

### In Vitro Studies

Genistein blocked the cell cycle progression at G1, inhibited PSA expression, and modulated cell cycle gene regulation [57]. Genistein also inhibited endothelial cell proliferation and angiogenesis and induced apoptosis in androgen-dependent cell lines.

Aronson et al. demonstrated a reduced growth rate of LNCaP cells in nude mice fed with low fat plus soy protein and isoflavone extract [58]. In animal models, genistein has been demonstrated to inhibit angiogenesis through inhibition of endothelial cell proliferation and several enzymes promoting cell growth (e.g., tyrosine kinase, topoisomerases I and II).

### Animal Studies

A study with Lobund–Wistar rats that received a high-isoflavone diet showed a significant reduction of prostate tumor growth compared to the control group receiving a low-isoflavone diet [59]. Another study with TRAMP mice fed on a genistein-rich diet also found reduction of tumor incidence [60].

### Epidemiological Studies

The first prospective cohort study was conducted in 1994 and showed that flavonoid intake was not associated with mortality from cancer [61]. This was confirmed in a cross-national study of seven countries with 16 cohorts. A positive effect on coronary heart disease but not cancer mortality might be attributed to flavonoid intake [62]. Another cross-national study [63] which is a case–control study was done in 59 countries ($n = 24{,}213$). It showed that soy products are found to be significantly protective with an effect at least four times as large as any other dietary components. A substantial review of studies that have assessed the direct relation between the individual dietary intake of soy products and the risk of prostate cancer was done by Ganry in 2005 where he analyzed epidemiological studies providing data on (1) dietary soy intake or flavonoid intake, (2) urinary excretion of isoflavones or lignans, or (3) blood measurements of isoflavones or lignans. Soy was used as a marker for isoflavone intake. Overall, the results of these studies did not show protective effect. Only four of these studies were prospective, and none of them found statistically significant prostate cancer reductions [64].

Perabo et al. reviewed the role isoflavones in prostate cancer patients [65]. There were no randomized studies examining the relationship. Ten studies analyzed the relationship between isoflavone intake and prostate cancer. Four of them were case–control studies, and six of them were cohort studies. All the studies had few patients, short duration of isoflavone intake, and variable end points, some of which were not clinically relevant. All of them suggested isoflavones are well tolerated with minimal low-grade toxicity. The end points include PSA response (50 % PSA decrease, % change in PSA levels), cholesterol level, p105erB-2 proto-oncogene level, serum DHT level, micronucleus frequency, and serum isoflavone levels. De Vere White et al. determined if supplemental dose of isoflavone would lower the PSA by more than 50 % and found 0 % complete response and 17 % partial response and 67 % disease progression among 62 prostate cancer patients. To date, major prospective interventional randomized studies are lacking in this area to have any meaningful application in day-to-day clinical practice.

#### Conclusion

The protocols chosen for the clinical phase I and II trials make interpretation of data quite difficult. Dose and concentrations of the drug/substance used in the studies were empirically derived, and the manufacturing and preparation of the product were not standardized. Some analysis combined patients without stratification for androgen-dependent and androgen-independent tumors; some had small patient numbers, short treatment duration (6 months), or did not have sufficient statistical power. It is difficult to make definite statements or conclusions because of the great variability and differences of the study results. Although some results from clinical genistein studies seem encouraging, reliable data on tumor recurrence, disease progression, and survival are unknown. A major setback remains the problematic design and definition of end point criteria assessing the value of genistein in cancer therapy. The presented data may potentially allow recommending patients in favor of the use of genistein with the intention to prevent development of prostate cancer. At this stage, there is not enough

clinical evidence by clinical trials that genistein has an effect in the treatment of prostate cancer [64, 65]. To establish the influence of a nutritional compound such as genistein on cancer genesis, promotion, or progression, carefully designed, larger scale, prospective randomized trials should further support the epidemiological and experimental data.

## Conclusion

We have reviewed salient agents that were examined in chemoprevention of prostate cancer. Some of them are commonly used medications, and the remaining are dietary-derived products. All of them showed promising results in the experimental studies. Some of them have showed promising results in both epidemiological and observational studies. However, none of them have shown a significant chemopreventive effect in well-designed randomized control studies with clinically relevant end points. Selenium, vitamin E, isoflavones, and cyclooxygenase inhibitors are not recommended for chemoprevention until any future RCT suggests an association. The role of green tea and lycopene in chemoprevention is promising though the former was not examined in a randomized setting. Both these dietary derivatives are well-tolerated and well-designed RCTs needed to provide appropriate recommendation. Supplemental zinc has not shown consistent protective effect on prostate cancer. However, the association between zinc and prostate cancer is more complex than simple deficiency. The epidemiologic studies cannot and should not be interpreted as evidence that contradicts the clinically and experimentally established relationships. Intraprostatic zinc deficiency does contribute to the development of prostate cancer. More research is needed to elucidate the genetic/metabolic relationships in prostate malignancy and to provide an understanding of the onset of prostate cancer. Further research concentrating on intracellular transportation of zinc and other approaches in alteration of prostate metabolism also needs to be performed. Similarly, vitamin D deficiency is found to be associated with prostate cancer. However, the complex relation between sunlight, exogenous vitamin D intake, calcium intake, and endogenous vitamin D synthesis needs to be clearly understood in relation to prostate cancer. Large prospective observational and randomized studies are needed targeting these areas to fully utilize this unique compound in chemoprevention of prostate cancer.

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# Part III

# Diagnosis and Staging

Peter Carroll and Gary Dorfman

# Early Detection and Patient Risk Stratification in Prostate Cancer

34

Rajesh Nair, John Withington, Sukanya Ghosh, and Alastair Henderson

## Introduction and Philosophy of Early Detection of Prostate Cancer

Prostate cancer (PCa) is a significant health problem both for individuals, doctors, and public health systems. The received wisdom for the management of cancer problems in general has been that the earlier that a cancer diagnosis is made, the better the outcome for the patient. While it is true that the time to cancer death may often be increased, there has also been much debate about whether the increases in life expectancy after diagnosis of a cancer problem by screening simply represent a lead-time bias where life expectancy after diagnosis is increased by moving the time of diagnosis back to an earlier time point rather than a genuine increase in length of life.

While individuals and their physicians may believe that they would be best served by early diagnosis and treatment, this may not be an essential part of successful PCa management. Indeed, the impact of screening for prostate cancer using digital rectal examination and serum prostate-specific antigen (PSA) has been modest with number needed to screen, in the order of 1,410 unselected men screened to save 1 life [1].

The impact of treatment on mortality in screen-detected prostate cancer has also been questioned. Twelve-year follow-up data presented in the 2011 AUA meeting from the PIVOT study of 731 men treated for screening-detected prostate cancer showed no benefit in terms of cancer-specific or overall survival to men randomized to radical treatment over watchful waiting [2]. However, the benchmark SPCG-4 study [3] demonstrated a survival advantage to radical prostatectomy in clinically detected cancers in the pre-PSA era. This advantage equated to one life saved for seven patients undergoing radical prostatectomy in the under-65 age group. These data suggest that an unselective screening and treatment process may increase the number of patients treated and hence dilute the effects of treatment by increasing the number of treatments for clinically indolent disease. It will also increase the number of men exposed to the toxicities of treatment including the potential for erectile dysfunction, incontinence, or other urinary problems and psychological morbidity.

Taking these data as a whole might suggest that PSA-based screening is not justified. This is the conclusion of the European Association of Urology (EAU) and United Kingdom National Screening Committee (UK NSC) and the United States Preventative Services Task Force (USPSTF). Other bodies in the USA have generally supported the slightly stronger statement that PSA screening may be attempted in well-informed men with the necessity to proceed with the test and/or biopsy determined after an appropriate discussion with the patient (discussed in Chap. 27).

Early diagnosis (using newer methods other than digital rectal examination and serum PSA followed by a transrectal ultrasound and prostate biopsy) may however offer both alternatives to PSA screening and a further additional determination of risk prior to proceeding to biopsy or treatment. Costs and the morbidity of treatment and/or investigation are the major barriers to an effective screening/case-finding program. Thus, a "smarter" approach with both novel markers of risk and a more effective assessment of patient risk of non-cancer mortality may help us to deliver more individualized prostate cancer treatment in the future.

In addition, early detection using sensitive techniques is usually applied to patients who are undergoing their first tests for prostate cancer but may equally be applied to men with initial negative biopsies and men who have received treatment with curative intent but where there is a suggestion of recurrence.

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## Current Areas for Development of Early Detection Include

1. Whether newer biomarkers (serological, urinary, and histopathological) could give prognostic information on risk of cancer diagnosis, morbidity, or mortality
2. Whether newer imaging modalities can provide prognostic information to risk stratify early-stage disease
3. Whether standard 12-core transrectal ultrasound-guided biopsy gives adequate diagnostic yield to detect clinically significant cancers compared with transperineal prostate biopsy

## Prostate-Specific Antigen, Biomarkers, and Early Detection

Since its discovery over 30 years ago, the use of prostate-specific antigen (PSA) has transformed the detection, surveillance, and follow-up of patients with PCa worldwide. Because PSA is specific to prostatic epithelial tissue rather than purely to PCa, it is often that elevated PSA is due to pathology unrelated to cancer such as infection or inflammation due to instrumentation or urinary retention. Thus, PSA, while an excellent marker of advanced disease or of recurrence after radical surgery or effective ablation where there is no benign tissue left, is less helpful in differentiating prostate cancer from inflammation of the prostate in an early-diagnosis situation.

When an "abnormal" PSA value is chosen, it is necessarily a compromise between sensitivity and specificity where when one rises, the other falls. In order for a PSA screening program to produce the reductions in metastatic and advanced disease that have been identified by studies of screening such as the ERSPC [1], early-stage disease must be identified which means choosing a value with reduced specificity.

Efforts to allow sensitivity to be maintained while increasing specificity have led to studies of variations in PSA kinetics/metrics (Table 34.1). These include age adjustment, PSA density, free to bound PSA ratios, PSA doubling time, and PSA velocity [22].

These and a number of alternative markers (Table 34.1) have been developed with the aim of reducing the number of patients who need to proceed to prostate biopsy and to monitor disease activity. Nevertheless, in current clinical practice, the only widely used markers have remained PSA and PCA3.

## Prostate Cancer Antigen 3 (PCA3)

PCA3 is a commercially available, prostate-specific, non-coding messenger RNA detected in the urine after vigorous prostate massage. It has been used as a primary diagnostic tool with a reference value chosen which offers increased specificity for the same sensitivity values as PSA. This has recently been extended to secondary diagnostic use (in patients with prior negative prostate biopsy) with or without the addition of ETS fusion gene analysis. The PCA3-RNA complex is mapped to chromosome 9q21-22 [23], and under normal circumstances, a low level of the biomarker is expressed specifically by prostate tissue compared to other tissue types [24].

Groskopf et al. evaluated the PCA3 molecular urine test by collecting whole urine specimens after digital rectal examination from three groups: men scheduled for prostate biopsy, healthy men (<45 years with no known prostate cancer risk factors), and men who have undergone a radical prostatectomy. PCA3 and PSA were isolated, amplified, and quantified in each group. PCA3 results yielded a sensitivity of 69 % and specificity of 79 % in the pre-biopsy cohort compared to 28 % specificity with serum PSA assay. PCA3 and PSA were both undetectable in the cohort of recurrence-free post-prostatectomy urine specimens [25]. Data published by Hesse in 2008 demonstrated that PCA3 reference ranges could be chosen that offered additional specificity above F/T PSA but that this information added additional value to that offered by F/T PSA in that a high PCA3 assay result conferred greater positive predictive value in the low F/T PSA ratio group of patients who were identified as already being at greater risk of a cancer diagnosis [26].

PCA3 performance in different groups of men has also been used to determine whether synergistic use of the PCA3 score with other clinical information can predict biopsy outcome. It found that PCA3 is independent of prostate volume, serum prostate-specific antigen level, and the number of prior prostate biopsies. The percent of biopsy-positive men identified increased directly with the PCA3 score. An adapted quantitative PCA3 score correlated with the probability of a positive biopsy. Logistic regression results showed that the PCA3 score could be incorporated into a nomogram for improved prediction of biopsy outcome [27]. This is now clinically available via the PCPT nomogram website [28], and a similar nomogram has been published by Chun [29].

Interestingly, there is no correlation between PCA3 score and Gleason score or the expression of the immunohistochemical markers for PCa biological aggressiveness, though it was associated with clinical T2 (vs. impalpable) disease [26, 30]. PCA3 is probably advantageous to use as in combination with PSA; however, it requires prostatic massage to test which adds physician as well as laboratory costs to diagnostic workup which may represent as much as a tenfold cost increase in clinical practice. This is likely to limit its clinical utility in all but the best-funded health-care systems. It is also disappointing that there is, as yet, little evidence that the metrics of PCA3 predict outcome after prostate cancer diagnosis better than standard care once the diagnosis has been established.

**Table 34.1** Biomarkers in early prostate cancer

| Marker type | Marker | Sensitivity/specificity | Current uses | References |
|---|---|---|---|---|
| Serum/plasma markers | PSA | Sensitivity: 90 % | PSA continues to be the primary diagnostic investigation in the diagnosis of prostate cancer. As a continuous parameter: the higher the value, the more likely is the existence of prostate cancer | [4, 5] |
| | | Specificity: 10–31 % | Several modifications of serum PSA value have been described, to improve specificity of PSA. They include:<br>PSA density<br>PSA density of the transition zone<br>Age-specific reference ranges<br>PSA molecular forms<br>However, these derivatives have limited usefulness in the routine clinical setting | |
| | PSA isoforms | *Free to total PSA ratio*<br>Sensitivity: 90 %<br>Specificity: 10–45 % | The free to total PSA ratio is the concept most extensively investigated and most widely used in clinical practice to discriminate between benign prostatic hyperplasia and prostate cancer | [4] |
| | | *Human kallikrein 2/pro-PSA*<br>Sensitivity: 90 %<br>Specificity: 31 % | Limited studies/utility when PSA value is greater than10 ng/mL | [5, 6] |
| | | *Combination of total PSA, percentage-free PSA, and percentage sum – proPSA*<br>Sensitivity: 90 %<br>Specificity: 44 % | | [7] |
| | PSA kinetics | *PSA velocity*: (cutoff of 0.75 ng/ml/years) | PSA velocity and doubling time useful in monitoring patients with treated prostate cancer | [8–10] |
| | | Sensitivity: 72 % | Limited role in prostate cancer diagnosis due to background noise (total volume of prostate, BPH), the variations in interval between PSA determinations, and acceleration/deceleration of PSA velocity and PSA doubling time over time | |
| | | Specificity: 95 % | Prospective studies have shown that these measurements do not provide extra information compared to PSA alone in the diagnosis of prostate cancer | |
| | | *PSA doubling time:*<br>Sensitivity: 36.6 %<br>Specificity: 60.7 % | | |
| | Early prostatic cancer antigen (EPCA) | Sensitivity: 94 % | EPCA was specifically in prostatic intraepithelial neoplasia in addition to prostate cancer | [11, 12] |
| | | Specificity: 92 % | Although EPCA appears not to be present in patients devoid of prostate cancer, it has been detected in surroundings tissue, adjacent to the cancer | |
| | | | Currently, further investigation is needed to further characterize the protein as a suitable biomarker to diagnose prostate cancer | |
| | Circulating nucleic acids (microRNA) | Sensitivity: 60 % | Currently is used as a noninvasive diagnostic tool and for disease monitoring | [13] |
| | | Specificity: 87–100 % | The search for microRNA biomarkers for prostate cancer is still in its infancy, and only a small number of microRNA profiling studies using clinical samples have been published to date | |
| | | | A research tool only to date | |

(continued)

**Table 34.1** (continued)

| Marker type | Marker | Sensitivity/specificity | Current uses | References |
|---|---|---|---|---|
| Urine markers | DNA markers: hypermethylation, glutathione S-transferase P-1 (GSTP1) | Hypermethylation of GSTP1 has been detected in more than 90 % of prostate tumors | Reduced expression of the GSTP1 gene due to hypermethylation of the promoter has been shown consistently in prostate cancer and has been measured in urine sediment to determine the need for biopsy | [14] |
| | | Sensitivity: 73 % | GSTP1 has been shown to be acutely sensitive in detecting the presence of prostatic intraepithelial neoplasia and prostate cancer, thereby distinguishing patients with these diseases from patients with benign prostatic hyperplasia | |
| | | Specificity: 98 % | This assay has predominantly been used in the research setting although assays are increasingly filtering through to clinical practice | |
| | RNA markers: prostate cancer antigen 3 (PCA3), E-twenty-six (ETS) gene fusions | *PCA3*:<br>Sensitivity: 67 %<br>Specificity: 83 % | PCA3 alone as a diagnostic tool is limited in clinical practice. Increasingly, it is being used combined with serum PSA and/or urinary alpha-methylacyl-CoA racemase (AMACR). Both have shown improved sensitivity and accuracy | [15] |
| | Protein markers: sarcosine, telomerase, metalloproteinases (MMPs), urinary PSA | Sarcosine:<br>Sensitivity: <7 %<br>Specificity: 100 %<br>Telomerase:<br>Sensitivity: 58 %<br>Specificity: 100 % | Although early data has shown promise for sarcosine as a urinary marker, subsequent research has concluded that measuring sarcosine in urine fails as a marker in prostate cancer detection and identification of aggressive tumors. Subsequent review of the literature reached a similar conclusion | [16, 17] |
| | Alpha-methylacyl-coenzyme A racemase (AMACR) | Pairwise comparisons demonstrate significant differences in staining intensity between clinically localized prostate cancer and benign prostate tissue<br>Sensitivity: 82–100 %<br>Specificity 79–100 % | This is one of the few gene products consistently detected, with a high specificity for prostate adenocarcinoma. Considerably more enhanced sensitivity and specificity in prostate cancer patients with mid-range PSA levels have been observed with AMACR antibodies than that with PSA. However, it is a specialized technique limited to few research institutions where it is expensive, and currently, its sensitivity varies from laboratory to laboratory | [18, 19] |
| Tissue markers | Basal cell markers | High molecular weight cytokeratin (HMWCK, 34βE12) and p63 have been demonstrated to be the negative markers that can aid in diagnosis of prostate cancer | Immunohistochemistry plays an important role in diagnosis of prostate cancer | [20, 21] |
| | | The positive 34βE12 or p63 staining in prostatic basal cells may render a definitive diagnosis of benign glands | It helps to differentiate malignant glands from benign lesions, especially for morphologically equivocal glandular alterations in small-core biopsy specimens | |
| | | | Its use has been restricted to larger institutions with the expertise and equipment to process and interpret the data. A combination of HMWCK and AMACR is of great value in combating the morphologically suspicious cases | |

## Prostate Biopsy Techniques and Rates of Detection

The aim of prostate biopsy is to detect those prostate cancers with the potential to cause harm, rather than to detect all prostate cancers [31]. With this in mind, the standard of care for initial biopsy is transrectal ultrasound plus biopsy [31]. Transperineal template prostate biopsy represents a more recent development with a range of potential applications.

## Initial Prostate Biopsy

The UK Prostate Cancer Risk Management Programme and National Institute for Health and Clinical Excellence (NICE) recommended a multiple-core biopsy technique involving at least ten cores, covering all parts of the prostate and performed under ultrasound guidance [32].

Validated nomograms have been developed which predict outcome of biopsies based on preceding PSA and DRE [33], and these may be used to aid a decision on the appropriateness of the biopsy intervention. Total number of biopsies may be varied according to the total size of the prostate. The Vienna nomogram represents a system for deciding on number of cores in proportion to prostate size and inverse proportion to age [34].

The number of cores taken must also take into account the fact that higher numbers of cores seem to result in higher complication rates. A 2006 systematic review suggested that the balance between optimum diagnostic yield and complication rate occurs at 12 cores [35]. Thus, though a higher biopsy number on initial biopsy set (particularly via a transperineal route) might increase the diagnostic yield, there is as yet insufficient evidence that this should be done on a routine basis.

## What Is the Efficacy of Different Forms of Prostate Biopsy?

The first study to compare the two approaches to prostate biopsy was a prospective study of 107 patients with elevated PSA, who underwent both transrectal biopsy (six cores) and transperineal biopsy and suggested superior detection rates from transperineal biopsy [24]. However, a subsequent randomized controlled trial of 246 patients undergoing initial investigation by transperineal template biopsy or transrectal biopsy (12 cores each) reported cancer detection rates of 42 and 48 %, respectively [25]. While these reports confirm the practicality of the transperineal approach, they do not address the need to increase core number when the whole of the prostate gland is targeted with a transperineal template biopsy scheme.

As evidence is as yet lacking in the setting of primary assessment, transperineal template biopsy is not recommended by NICE in preference to the transrectal approach for initial biopsy [36]. However, good evidence is available that increasing core numbers (above 12) do not significantly improve cancer detection with the TRUS route [37].

## When Initial Biopsy Negative but Clinical Suspicion of Prostate Cancer High

Transperineal template prostate biopsy has been shown to be of increased diagnostic yield in patients with negative transrectal biopsy but in whom there remains a high clinical suspicion of prostate cancer. It is under these circumstances that NICE recommends transperineal biopsy [36].

An extended biopsy protocol using the transperineal approach may also be appropriate in cases where there is a rising PSA but equivocal results from transrectal biopsy, including prior biopsies containing higher risk features such as atypical small acinar proliferation [38].

## Transperineal Template Biopsy as a Reference Test for Emerging Imaging Techniques

At present, there is no imaging test that can reliably diagnose prostate cancer. Given its relatively close Gleason score agreement with radical prostatectomy specimens, transperineal template biopsy has become used as a reference test for emerging imaging techniques in the research context [31]. It offers an opportunity to diagnose men within the therapeutic window for radical treatment, particularly in the difficult anterior-only prostate cancer group; however, as with the other described tests, it may increase the chances of diagnosing low-volume low-risk disease which may require monitoring rather than definitive treatment as an initial strategy.

## Emerging Imaging Techniques

MRI scanning and other emerging modalities including computer-aided ultrasonography and PET-CT have been used to assess and stage early-prostate cancer with the hope that eventually less-invasive means to diagnose or risk stratify prostate cancer than biopsy may become available. The ideal test might take men at risk of cancer and identify only those with clinically significant disease for confirmatory biopsy and treatment.

## MRI in Prostate Cancer Early Diagnosis

Until recently, the role of MRI in detecting prostate cancer was limited to providing some evidence on the extent of distant metastasis. The development of multiparametric MRI

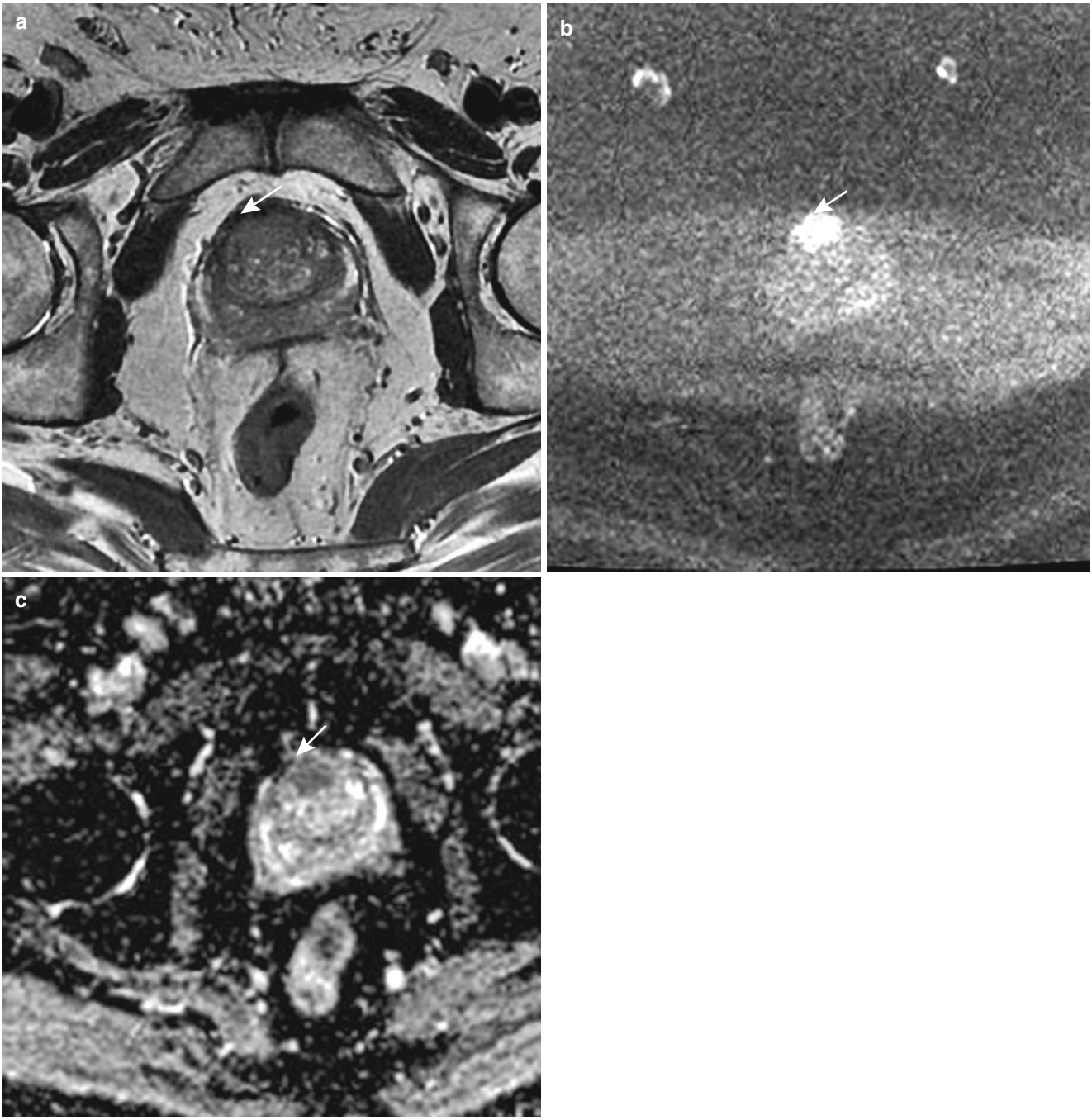


**Fig. 34.1** (**a**) A 70-year-old man presented with repeated negative TRUS biopsies but rising PSA. T2-weighted image demonstrates low signal changes in the bilateral peripheral glands which are negative on TRUS biopsy. (**b**) DWI demonstrates a small area of focal high signal uptake in the right transitional zone. (**c**) ADC demonstrates restricted diffusion in the correlating right anterior transitional zone suggesting tumor, hence explaining the negative TRUS biopsy and rising PSA

which includes both T1- and T2-weighted images, dynamic contrast enhancement, diffusion-weighted imaging (DWI), and proton spectroscopy has extended the use of MRI in the diagnostic pathway of prostate cancer [39].

While histological proof of prostate cancer based on prostate biopsy remains the gold standard, even the most invasive regimes of biopsy by either transrectal or transperineal routes have a false-negative rate [40, 41]. The latest iterative improvements in MRI give some indication of an ability to solve clinical problems in identifying tumor in those patients who have a rising PSA but repeatedly have had negative TRUS biopsies. This is particularly true in the anterior tumor (T2-weighted images Fig. 34.1a, diffusion-weighted images (DWI) Fig. 34.1b, apparent diffusion coefficient (ADC) map shown in Fig. 34.1c).

## Tumor Localization

Published results by Hricak et al. reported an MRI sensitivity of 96 %; however, this study excluded transitional zone tumors, and the analysis was by the presence or absence of tumor in a hemi-prostate.

It is now well established that although transitional zone tumors may be less aggressive, they account for 30 % of prostate cancers [42]. The anterior prostate is a region not biopsied by conventional TRUS biopsy. It is possible to use MRI as a primary "screening tool," decreasing morbidity and costs from patients undergoing TRUS biopsies and directing patients with anterior-only disease on MRI to a primary template biopsy. Clearly, the major disadvantage of this is the potential for false-positive reporting and the additional cost of adding a relatively expensive test or tests into the diagnostic pathway of all patients who are identified as at risk on basic investigation set of PSA and digital rectal examination.

## MRI with Contrast

Dynamic contrast imaging (DCI) techniques can be used to distinguish tumors in the peripheral zone from benign prostatic hypertrophy. Several studies [43, 44] demonstrate that the prostate cancers enhance earlier than the peripheral zone. Ito and Hara et al. have demonstrated 68 % sensitivity and 86 % specificities for detecting prostate cancer in the peripheral zone using dynamic contrast imaging using MRI [45]. Figure 34.2 illustrates the phases of DCI-MRI.

## Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI)

DW-MRI can be a useful in identifying PCa [46, 47]. The cellularity of viable tumor is higher than that of benign tissues, and there may be restricted diffusion of water molecules. Tumors of the peripheral and transitional zone show decreased apparent diffusion coefficient (ADC) compared with their surroundings (see Fig. 34.1c).

In 2005, a study by S*hifousa* showed an increased accuracy for detection of cancer using both DW-MRI and T2W-MRI, using biopsy for confirmation [48].

## Tumor Burden

Studies have confirmed that MRI best detects lesions >10 mm. Only 5 % of tumors <5 mm in diameter were detected compared with 89 % of those >10 mm [49].

## Limitations of MRI

It has been recommended that MRI should be performed 6–8 weeks post biopsy to avoid the hemorrhage artifact, but evidence demonstrates that the hemorrhage is only resolved in 50 % of cases and may delay treatment [50], though the clinical significance of this except as regards psychological morbidity is probably limited. Clearly, pre-biopsy MRI avoids biopsy artifact but increases costs within the patient pathway. In addition, the limited sensitivity of MRI confers problems as 11 % of lesions above 10 mm will be missed, and thus current practice is to use both tests.

The techniques described above, in combination with the advances in technology of 3-T MRI or endorectal coil imaging using a 1.5-T MRI scanner, have extended the potential use of MRI beyond local staging post biopsy . Prospective studies are planned where pre-biopsy MRI is routinely performed before prostate biopsy using the transrectal and transperineal routes. It is hoped that these will confirm the extent of additional information that these techniques add for patients either in the primary diagnostic assessment or in the setting of a negative prostate biopsy with persistent evidence of possible disease such as rising PSA.

## Computer-Aided Ultrasonography

HistoScanning™, or computer-aided ultrasonography, has been assessed as a technique for identifying prostate cancer [51]. Early results suggest that HistoScanning™ may offer more information than standard B-mode ultrasound on cancer size, location, and extent. This may act as a basis for conducting effective biopsy and risk stratification. In a small preliminary study of 29 patients, HistoScanning accurately detected cancer foci of greater than or equal to 0.50 mL (HS).

Detailed scrutiny of the potential for transrectal ultrasound to detect small tumor foci is partially limited by protection of certain proprietary information, regarding, for example, three-dimensional resolution of the ultrasound machine used. Braeckmann et al. [52] point out that there are specific limitations to the HistoScanning algorithm; it is adversely affected by the presence of dense calcification and in the anterior component of a very large gland in which the signal is poor. Further confirmatory publications are still awaited 3 years after the publication of initial study data.

## Positron Emission Tomography (PET)-CT

A recent innovation has been the combination of morphological modalities with functional imaging. Positron Emission Tomography (PET), which can be combined with standard X-ray computed tomography, offers a noninvasive

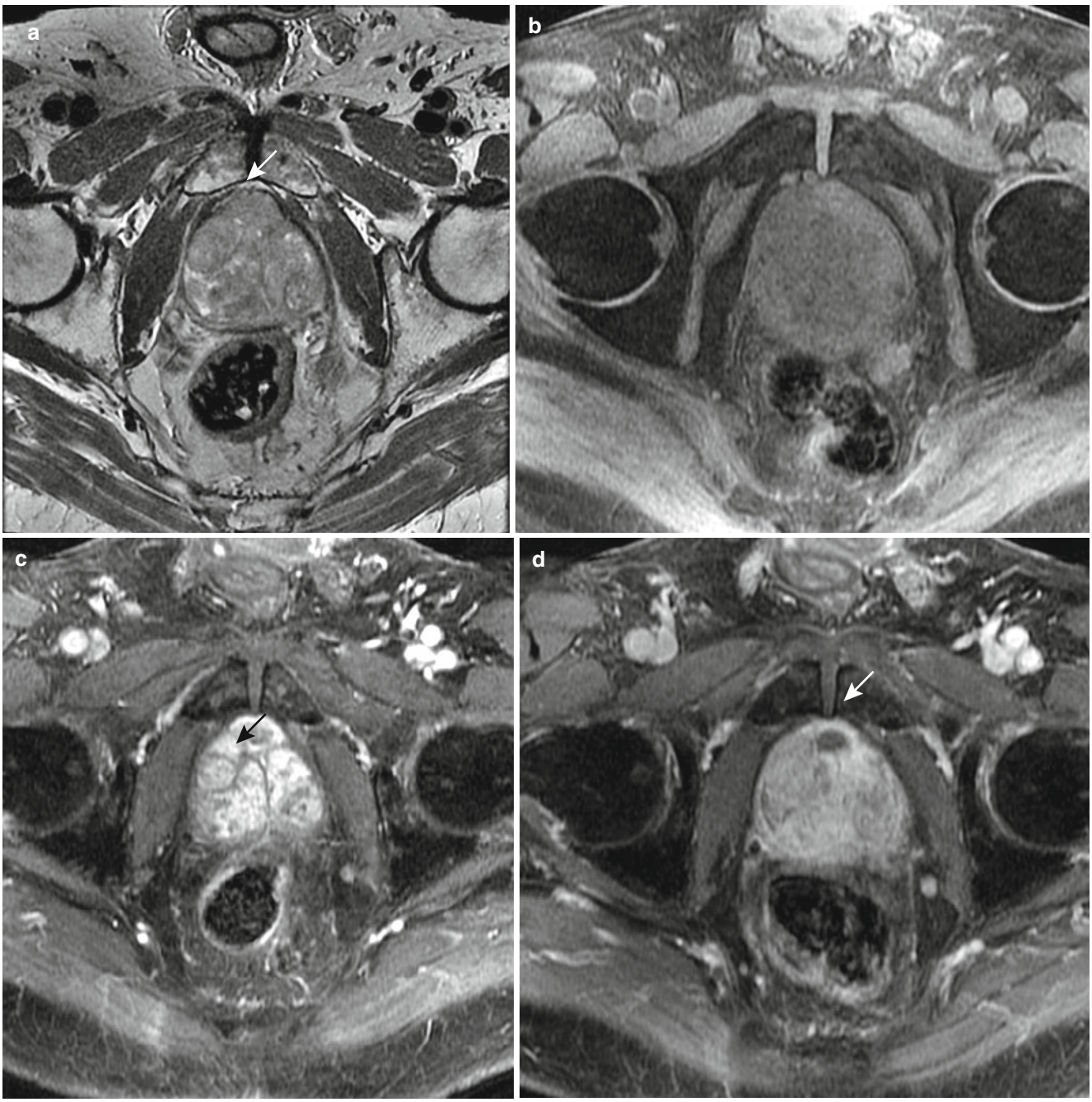


**Fig. 34.2** (**a**) T2-weighted image of low signal in the anterior transitional zone. (**b**) Pre-contrast image of the prostate. (**c**) 30–90-s enhancement of the anterior transitional zone tumor. (**d**) Washout of contrast confirming tumor in the 3–5-min phase of imaging

whole-body modality. PET and PET-CT have been evaluated at various points in diagnosing and treatment planning in prostate cancer, including tumor characterization and staging, restaging (in recurrent prostate cancer), and the monitoring of disease and treatment efficacy (review).

A variety of radiopharmaceuticals continue to be assessed in PET imaging in prostate cancer. $^{18}$Fluorodeoxyglucose is of particularly limited use in imaging the prostate, while $^{11}$C-choline PET has shown the greatest efficacy overall and particularly in the restaging setting. Choline PET-CT now has an established role in restaging prostate cancer, which should be triggered by an increase in PSA following radical treatment for prostate cancer, particularly after radical radiotherapy. Further, it may have a role in the disease and treatment monitoring, though further studies are required.

## Imaging Summary

At the current time, choline PET is useful only in relatively advanced disease, which is rarely present in the setting of early detection. HistoScanning requires further evaluation

before entering routine clinical use, but multiparametric MRI offers additional information, which may be useful in routine practice.

## Patient Factors in Risk Stratification for Early Disease

The assessment of non-prostate cancer related factors in the management of the patient considers the benefits of radical treatment over observation or indeed of watchful waiting. The simplest interpretation of the data from the SPCG-4 study [3] would be that radical prostatectomy has been established as a proven treatment with improved efficacy above watchful waiting.

However, for a number of patients, there will be limited benefit to radical treatment. Grossly, the SPCG-4 showed at a median of 12.8 years follow-up that in the over-65 age group, a significant dilution of the treatment effect occurred. In the over 65 s, no statistically significant treatment effect on all-cause mortality, cancer-specific mortality, or metastasis occurred. It is likely given the 12-year follow-up findings of the PIVOT study that for disease which is predominantly low-volume low-risk disease, there was no significant treatment effect for radical prostatectomy over watchful waiting [2].

Current best practice should choose to consider patient comorbidity as well as chronological age. In the United Kingdom, median life expectancy at age 65 in 2003–2005 was 16.8 years [53] with similar figures of 17.7 years on the Swedish population [54] and in men from the USA (17.2 years) [55]. One might therefore feel it likely that the benefits of treatment for men with limited life expectancy due to their comorbidities might be similarly reduced as they are for the group of older chronological age. While it can be argued that appropriate assessment of comorbidity is what dedicated physicians and surgeons have been doing for many years, it may be the case that there have been relatively limited efforts to risk stratify non-prostate cancer mortality risk in patients with early prostate cancer [56].

In the past, surgical studies have often reported the American Society of Anesthesiologists physical status score to measure comorbidity. Clearly, while these scales have a great practical use in the breadth of surgery, in general, any system which uses only six points to score comorbidity, only four of which relate to planned surgery are so broad that they are unlikely to be helpful in the assessment of chronic disease. Nor do they easily describe differences in outcome from an elective surgical patient group or for patients who are functioning well but have chronic illness.

Other studies have reported Eastern Cooperative Oncology Group (ECOG) performance status [57], which is commonly used in chemotherapy trials to describe comorbidity. ECOG is limited in the assessment of potential surgical or radiotherapy patients as they are generally in good health, and the ECOG scale has only six possible outcomes between completely healthy and dead, which lacks sensitivity in the prostate cancer patient who is being assessed prior to potentially curative treatment. In practice, only three levels of health classification would be likely to apply to any man deemed suitable for treatment of nonmetastatic prostate cancer (healthy – normal activity for >50 % of waking hours). Karnofsky scoring is a less frequently used version which was a precursor of the ECOG system which though it had a greater number of classes has no improvement in sensitivity in the surgical setting [58].

Charlson scoring [59] is a slightly more sensitive system which describes the likelihood of death from 22 serious conditions including solid cancers, heart disease, and diabetes. It allows predictions of estimated 10-year mortality from comorbidities and may also be adjusted for chronological age.

This sort of metric which is more sensitive and robust may help to add objective measures of comorbidity in the clinical trial setting but might also the patient some perspective on the competing risks of their non-cancer diagnoses [60].

In a recent sample of men with low-intermediate-risk prostate cancer, adjusted Charlson score > 3 had a threefold comparative risk of non-cancer death compared with men over age > 75. Despite this in the study of US patients in the Veterans Administration System, the patients with a Charlson score > 3 had fivefold greater risk of receiving radical treatment attempting cure than those of age > 75 [56].

Recently, further work by Litwin's group at UCLA has refined the Charlson score to address other-cause mortality risk in the prostate cancer population [61]. While these calculations demonstrate that current non-cancer mortality risk stratification (based on chronological age and clinical assessment) on when to offer radical treatment is not always based on logical and proportionate assessment of life expectancy, they as yet do not show that any of the scoring systems can be used to tell patients that radical treatment is or is not indicated at their level of risk. The problem with clinical trials may be that they may not include enough patients with comorbidities to allow for accurate risk stratification. It is however encouraging that trial data such as that from the PIVOT study is starting to report and adjust for Charlson score [2]. It is to be hoped that further data will be made available to allow patients and their physicians to make more accurate assessments of the competing risks to their health of prostate cancer and other common comorbidities.

### Conclusion

Early diagnosis of prostate cancer via unselected population screening with currently available tools is unlikely to be either cost-effective or to save significant numbers of lives. However, for well-informed men with good general health and particularly those with increased risk factors

for developing cancer such as a family history, PSA testing may be performed. In this scenario or when initial biopsies are negative but PSA kinetics suggest prostate cancer, the use of cutting-edge tools in early diagnosis can help to separate confirm the diagnosis and risk stratify progression due to higher volumes of cancer or higher Gleason grade.

The combination of more advanced methods of diagnosis and risk stratification of prostate cancer with assessment of the comorbidities of the patient offer the possibility to individualize the treatment of prostate cancer, though once strategies for using these modalities in combination have been developed, they will require testing in large-scale clinical trials with adequate follow-up to establish that they are robust.

They do however offer hope that in future radical therapy may both be applied earlier in clinically significant disease and also less frequently to men at low risk from cancer death either because of indolent disease or marked comorbidity.

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# Tumor Markers

35

Diederick Duijvesz and Guido Jenster

## Introduction

A tumor marker in a biomedical setting can be defined as "a biological object present in human tissue and/or body fluids that is capable to differentiate between normal and abnormal biological conditions." The National Institutes of Health added that it should be measured objectively and is evaluated as an indicator of pathogenic processes or biological responses to a therapeutic intervention. With this definition, a wide range of characteristics can be used as a tumor marker, such as easily observable skin lesions or more inconspicuous variables such as proteins or RNA present in tissue, serum, or urine. Nowadays, the term tumor marker is inextricably linked to molecular markers.

So far, different kinds of tumor markers have proven to be a useful diagnostic or prognostic tool for medical doctors when assessing a certain disease, especially within the field of oncology. The presence or an elevation of a marker could indicate the existence of a malignant tumor. Furthermore, it could also have the ability to predict outcome before and after treatment. Also with prostate cancer, tumor markers have been widely used in daily clinical practice. This chapter will discuss multiple types of tumor markers for the diagnosis and prognosis of prostate cancer and will review a selection of markers that have been validated to some extent or are of high interest.

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## Different Types of Markers

Tumor markers can be classified into several categories with their own specific purpose. The different kinds of markers can describe the chance of getting a disease (risk marker), the presence of disease (diagnostic marker, early detection, or screening marker), how the course of the disease will be (prognostic marker), and how to estimate the chance of success of a certain treatment (predictive marker) [1]. Furthermore, markers can also be applied to observe therapy efficacy during or after treatment (monitoring marker).

- When using a marker for risk assessment, the disease is not yet (clinically) present or cannot be detected with conventional techniques. Such a marker would be mainly suitable for life-threatening diseases that are typically diagnosed too late. In addition, risk markers can be implemented to identify a subpopulation for regular checkup or screening. In recent years, much research has been dedicated to the identification of genomic changes using genome-wide association studies (GWAS) to identify single-nucleotide polymorphisms (SNPs) associated with the development of a disease [2]. For prostate cancer, it is evident that many of such SNPs are linked to disease development, although none of them individually have a very strong correlation [3].
- Diagnostic markers have the ability to determine the presence or type of malignancy. Such a marker is often used in immunohistochemical examination on tissue specimens or in specific protein/mRNA analysis of patient-derived body fluids.
- Prognostic markers become very useful when it is possible to stratify patients in groups that have different outcomes. Based on this stratification, the physician can choose a specific therapeutic option in order to individualize treatment. Next to the choice of treatment, if aggressive subtypes can be identified, treatment can be initiated earlier [4]. One of the best prognostic markers for prostate cancer is Gleason score, a representation of the organization of tumor glandular architecture [5].

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**Table 35.1** Expression of different kind of markers in healthy tissue as compared to malignant tissue

| Healthy tissue | Malignant tissue | Type of dysregulation | Example marker |
|---|---|---|---|
| + | +++ | Upregulated in cancer | AMACR/PCA3 |
| + | + | New distribution due to cancer | PSA |
| – | + | Mutation, oncogene | TMPRSS2:ERG |
| + | – | Mutation, tumor suppressor | PTEN |
| +++ | + | Downregulated in cancer | GSTP1 |

- Predictive markers are used to foretell the responsiveness to or outcome of a specific treatment. Although some markers have been described that predict the efficacy of hormone, radiation, or chemotherapy, these markers are not yet utilized in clinical practice.
- Monitoring markers are measured before, during, and after treatment to determine effectiveness of therapy. Prostate-specific antigen (PSA) is a highly effective and established monitoring marker for efficacy of radical prostatectomy, hormone therapy, and/or radiotherapy [6].

The occurrence, elevation, or modification of tumor markers can be caused by several biological processes. Endogenous cellular products are produced and shed at a greater rate by the abnormal cancerous cells. Also, these markers are released due to a higher apoptosis and necrosis rate in cancer. Furthermore, markers can reveal themselves when the environment of the cells becomes aberrant. An example is PSA, where higher levels in serum can be detected when the blood-prostate barrier is affected. Besides that, products of newly created genes in cancerous cells, such as the TMPRSS2:ERG fusion transcript, are applicable as a marker. Regarding prostate cancer, DNA (genomics), mRNA (transcriptomics), proteins (proteomics), and metabolites (metabolomics) have been the biochemical analytes investigated that could contribute to a better and more precise diagnosis and prognosis.

## Biological Materials for Tumor-Marker Analysis

When searching for new tumor markers, it is important to choose which biological material to explore. The most logical material is the one for which eventually a clinical applicable assay can be generated [7]. Therefore, materials derived with noninvasive techniques and those easily obtainable, such as blood or urine, are the most obvious. Blood is widely used, mainly because of the traditional availability and of the idea that biochemical analytes in plasma might provide important insight in disease-specific characteristics. Unfortunately, discovery of tissue- or cancer-specific marker is hampered by the abundances of all kinds of different analytes. The abundant proteins are identified preferentially and are generally not useful cancer markers. Probably, the most interesting new tumor markers are present in the low abundance range. Unfortunately, for certain technologies such as mass spectrometry, the high-abundance analytes overshadow the detection of the low-abundant ones. This problem is in essence the so-called "dynamic range problem." As an example, the proteome in blood has shown to consist of 3,000 proteins so far, but many more have to be identified. The 22 most abundant proteins account for 99 % of the complete proteome, so the search for new and low-abundant tumor markers is like searching for a "needle in a haystack" [8].

Another issue that arises when using materials such as blood is the origin of the marker. Like most clinically applied cancer markers, it is expected that the disease-specific markers are derived from the cancer cells or organ of origin. When candidate tumor markers are identified in serum, it is difficult to determine from which tissue these markers originate. It becomes slightly less complicated with the use of urine or prostatic fluids/seminal fluids. These materials are more specifically related to the prostate, and the abundance and variety of analytes is generally much less (Table 35.1).

## Identification and Validation of New Markers

### Discovery Phase

Discovery of new markers is an open and unselective search by which the differential expression of specific biochemical analytes between states is first defined [7]. If one wants to identify a specific marker, optionally, two separate states have to be compared without the influence of confounding factors. This comparison and eventual identification are typically performed with state-of-the-art technologies such as mass spectrometry or microarray analysis by using a small training set of samples. Drawbacks from this phase are the costs and the limited number of samples that can be analyzed. Because of the limited number of samples and the large number of analytes tested, many top candidate markers will be false positives, and some genuine markers will not be significantly different (false negative) [7]. With statistical calculations for false discovery rate and multiple testing corrections, these false positively identified analytes can be trimmed down. Eventually, after a list of potential tumor markers is generated, a more focused approach has to be taken where the most promising candidate markers must be validated.

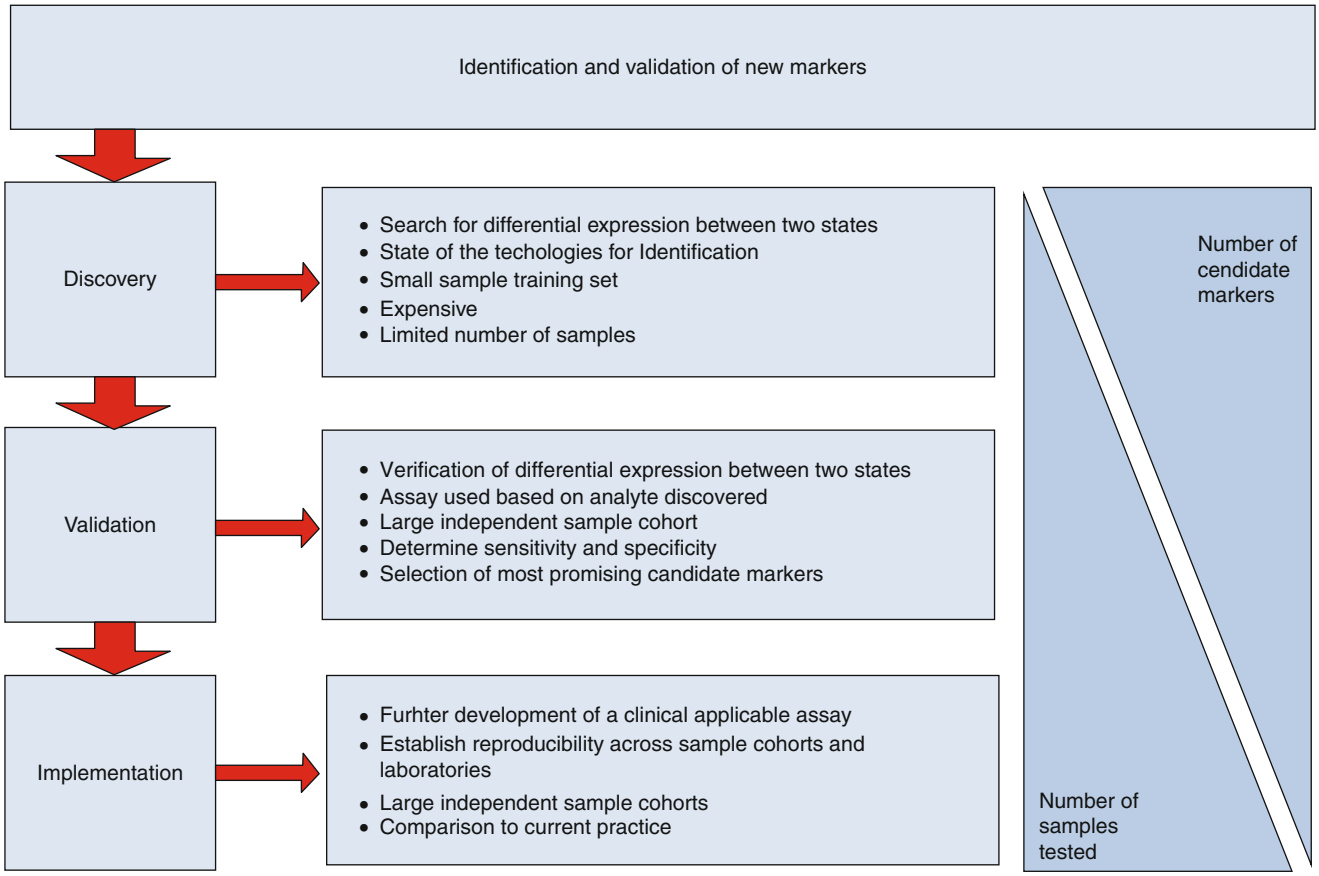


**Fig. 35.1** Identification and validation of new markers

## Validation Phase

The validation phase verifies the differential expression between samples and will give the opportunity to test the candidate tumor marker on an independent cohort (validation set). For this phase, an assay has to be developed that is capable of accurately measuring the candidate markers. The assay that is preferentially used is based on the specific analyte that has been discovered. For example, if a specific protein is identified, an ELISA (enzyme-linked immunosorbent assay) is a very sensitive and reliable test. When RNA is the marker of interest, most likely, the assay that will be used is qPCR (quantitative polymerase chain reaction). Besides these already established and widely used tests, novel techniques can be developed in order to more easily or more accurately detect the new tumor markers [9, 10]. Finally, with a specific and reliable test available, it has to be administered to larger study cohorts in order to test the most promising candidate markers. This cohort has to contain more variables in order to evaluate its restrictions and indicate the exact disease characteristics for which this candidate marker is most suitable. These experiments aim at confirming the previously discovered markers and will show their sensitivity and specificity for that particular disease they have been identified for. Eventually, from this validation step, only a few promising candidate tumor markers submerge. The ones that show a positive correlation with disease-specific characteristics will be used for the development of a clinically applicable assay. Normally, the whole process extends over a time line of at least 5 years, where initially 100–1,000 analytes are identified in the discovery phase. Unfortunately, only very few, if any, will survive the validation phase and reach the clinical implementation phase.

## Implementation Phase

In this phase, the main focus is the further development of a clinically applicable assay that can be used to further validate and implement the tumor marker. With the assay development, it is important to establish reproducibility across independent cohorts and laboratories [11]. By using this test, its operating characteristics are evaluated and a certain clinical cutoff value further tested and adjusted in multicenter prospective studies and compared to current practice. Only after this last phase, a specific test will gain wide acceptance and eventually be applied in a clinical setting (Fig. 35.1).

**Table 35.2** Tumor markers for prostate cancer

| Marker | | Biological function | Biochemical analyte | Marker ability |
|---|---|---|---|---|
| PSA | Prostate-specific antigen | Serine protease with diverse physiological functions | Protein | Screening/diagnosis/prognosis |
| %fPSA | Percentage-free PSA | | Protein | Diagnosis/prognosis |
| PSAD | PSA density | | Protein | Diagnosis/prognosis |
| PSAV | PSA velocity | | Protein | Diagnosis/prognosis |
| [-7],[-5],[-4],[2]ProPSA | PSA isoforms | | Protein | Diagnosis |
| hK2/KLK2 | Human kallikrein 2 | Peptidase, cleaving proPSA to mature PSA | Protein | Diagnosis |
| PCA3 | Prostate cancer antigen | Noncoding mRNA without a functional protein | RNA | Diagnosis |
| ETS | E twenty six gene family | Chromosomal rearrangement without a function | DNA | Prognosis |
| TMPRSS2:ERG | Transmembrane protein serine 2 (TMPRSS2) and ETS-related gene (ERG) | | DNA<br>Protein (ERG) | Prognosis |
| AMACR | Alpha-methylacyl-coenzyme A racemase | Metabolization of fatty acids and bile acid biosynthesis | RNA<br>Protein | Diagnosis/prognosis |
| GSTP1 | Glutathione S-transferase pi 1 (methylated) | Detoxification of carcinogens | DNA | Diagnosis/prognosis |
| PSMA (FOLH1) | Prostate-specific membrane antigen | Peptidase, hydrolyzing peptides in prostatic fluids | RNA<br>Protein | Prognosis |
| PSCA | Prostate stem cell antigen | Membrane-based glycoprotein | RNA<br>Protein | Diagnosis/prognosis |
| CgA | Chromogranin A | Proteolytic protein | Protein | Prognosis |
| B7-H3 | Transmembrane protein family B7, member H3 | Regulation of T lymphocytes | Protein | Prognosis |
| CAV1 | Caveolin-1 | Molecular transport, cell adhesion, and signal transduction | Protein | Diagnosis/prognosis |
| GOLPH2 | Golgi phosphoprotein 2 | Sorting and modification of proteins through the Golgi apparatus | RNA<br>Protein | Diagnosis |
| CRISP3 | Cysteine-rich secretory protein 3 | Unknown | RNA<br>Protein | Diagnosis/prognosis |
| Sarcosine | | Metabolite produced after enzymatic transfer of a methyl group from S-adenosylmethionine to glycine | Protein (metabolite) | Prognosis |
| Exosomes | Nano-sized vesicles, 100 nm in diameter containing RNAs and proteins | Intercellular communication, part of degradation pathway | RNAs and proteins | Diagnosis/prognosis |

## Tumor Markers in Prostate Cancer

Novel tumor markers for prostate cancer are still needed to improve the ability to detect prostate cancer, predict prostate cancer-related morbidity and mortality, and monitor response to treatment. Current markers used in research and even in the clinic remain controversial [12]. The most widely applied biomarker in prostate cancer is PSA. Because of its limitations, multiple new markers have been evaluated to compensate for these limitations. Unfortunately, many of these markers have not made it into the clinic, which shows that identification of better markers remains a challenge [13] (Table 35.2).

### PSA

Since its discovery in 1970, PSA has revolutionized the diagnosis and management of prostate cancer [12]. Subsequently, after its application in urological practice, it has proven to be a valuable tool for (early) detection, staging, and monitoring of men diagnosed with prostate cancer [14, 15]. Especially,

the use of PSA as a screening tool has increased the identification of prostate cancers and also improved curability with treatment.

PSA, also known as KLK3 or hK3, is a member of the human kallikrein family. This gene family consists of 15 members and is described with a distinct nomenclature [16]. The first three members (hK1, hK2, and hK3) encode for serine proteases that have diverse physiological functions. Expression of PSA and some other kallikrein members is androgen regulated. PSA protein has a half-life of 2–3 days and is secreted by prostatic epithelial cells into seminal fluid. Most likely, through tissue leakage, PSA can be found in serum but with a concentration of about $10^6$ times less as compared to seminal fluid.

Initially, PSA is produced as a 261-amino acid preproenzyme with a 17-amino acid signal peptide that is removed during synthesis [17]. After this step, proPSA is formed which contains 244 amino acids, from which subsequently 7 amino acids are cleaved, so it is processed to PSA that contains 237 amino acids. When shed in serum, PSA is unbound (free PSA or fPSA, 5–35 %) or bound (complexed PSA or cPSA) to complexes with the antiproteases α(alpha)1-antichemotrypsin (PSA-ACT), α(alpha)2-macroglobuline (PSA-A2M), or α(alpha)1-protease inhibitor (PSA-API) which inactivate its function [18]. In seminal fluids, it functions as a protease that liquefies semen by interacting with semenogelin and fibronectin [19, 20]. Although PSA is highly specific for prostate epithelial cells, in much smaller concentration, it can be measured in malignant breast cells, salivary gland, bowel, other urological tissues, and renal carcinoma cells [21–23]. Nevertheless, for practical and clinical purposes, PSA is organ specific because after removal of all prostate tissue, PSA values become immeasurable in serum. Although PSA is organ specific, it cannot be ascribed as prostate cancer specific because other urological conditions such as benign prostate hyperplasia (BPH), prostatitis, or mechanical damage also contribute to aberrant PSA values in serum [24]. It is noteworthy that the production of PSA by prostate cancer cells is not higher than benign prostate epithelial cells, but higher serum values are a result of an altered prostate-blood barrier [25]. In fact, production of PSA by prostate cancer cells is generally lower [26].

Large studies showed that 97 % of all men older than 40 years have PSA serum levels lower than 4 ng/mL, which gave rise to the idea that this value should be the threshold when it is used in a diagnostic setting [27]. Furthermore, it was shown that PSA serum values could increase when prostate cancer is present [28, 29]. Initially, PSA was used as a reliable marker to prove residual disease or progression after radical prostatectomy for prostate cancer [30]. Patients with lower values preoperative had higher rates of organ-confined disease [31, 32].

In a screening setting, it has been shown that PSA can increase the detection rate of prostate cancer in men without symptoms [33]. By using PSA, the percentage of men who were found with metastases at diagnosis was reduced from 16 to 4 %, but also late-stage disease and prostate cancer-related mortality was observed to be less [34]. During the last decades, it is shown that with the use of PSA, the detection of prostate cancer has increased dramatically but that prostate cancer mortality was only reduced with 20 %. Therefore, it was concluded that using PSA for the detection of prostate cancer results in a substantial overdiagnosis and overtreatment [35].

As a diagnostic tool, PSA has a high sensitivity but low specificity for prostate cancer, where the positive predictive value (>4.0 ng/mL) is limited to 25 % [36, 37]. Serum PSA levels are influenced by tumor grade, volume, and site of origin (primary tumor or metastases), and it is capable to predict pathological features [24]. On the other hand, in 15 % of men with low PSA levels, prostate cancer is present [38]. So, in order to improve identification of prostate cancer and gain specificity, changes in variant forms of PSA have been investigated and introduced into the clinic.

## Free PSA

The proportion of free PSA (%fPSA) is lower when compared to total PSA in healthy men or men with BPH [39–41]. Therefore, %fPSA has been suggested as a marker for prostate cancer [42]. The exact cause for this occurrence is not fully understood, but it is thought that in patients with prostate cancer, PSA "escapes" proteolytic activity and stays bound to ACT, A2M, or API. An extensive meta-analysis that compromised 66 studies showed that %fPSA and cPSA have better diagnostic potential compared total PSA (tPSA) in the intermediate range of 2–10 ng/mL [43]. In studies where %fPSA is combined with serum PSA levels between 2.5 and 4 ng/mL, more specificity can be obtained in diagnosing prostate cancer [44]. The use of %fPSA could contribute to a more reliable diagnosis and therefore maybe reduce biopsies by 20 % and lessen the overdiagnosis [45]. Furthermore, a better stratification could be made of patients who are more eligible to undergo active surveillance and therefore decreases overtreatment.

As a prognostic marker, high %fPSA correlated with smaller and lower grade prostate cancer [45]. Vice versa, low %fPSA resulted in a more aggressive form of prostate cancer, even when measured up to 10 years before diagnosis [46]. Prostate cancers with Gleason scores of >7 and extra capsular extension also showed a correlation with low %fPSA [47, 48].

## PSA Density

In a majority of men with slightly elevated PSA levels, the main contributor is probably BPH and, only in a small percentage

of men, prostate cancer [47]. To differentiate better between these two conditions, a method was introduced that compensated for the increase of serum PSA levels by prostate enlargement [49]. This measurement, PSA density (PSAD) where serum PSA is divided by prostate volume (>0.15), has shown to have a direct relationship with the probability of having prostate cancer, especially with intermediate PSA levels and no abnormalities on DRE (digital rectal exam) [50, 51]. Although these primary reports embrace promising results, this measurement has shortcomings. When PSAD was compared to PSA, it was not able to enhance the predictive value of PSA alone [52]. Furthermore, PSAD is not sensitive enough for prostate cancer detection; almost 50 % of all cancers are missed [53]. The most plausible interpretation of these conflicting results is most likely the heterogeneity of prostate volumes in prostate cancer and BPH. Because PSAD is influenced by prostate volume, the number of epithelial cells has to be a correction for these factors. Correction for transition zone size has shown to be a very specific and sensitive technique to detect prostate cancer, but because of the variability of ultrasound measurements, it has not gained wide acceptance in daily practice [54]. Also as prognostic marker, increased PSAD values were correlated with Gleason scores >7 and a greater risk of organ-confined disease [55].

### PSA Velocity

Another approach for detecting prostate cancer in the intermediate range of serum PSA is by using PSA velocity (PSAV), where the rate of PSA change between two separate measurements is taken into account [56]. As a diagnostic tool, an increase of 0.75 ng/mL or more per year is correlated with the presence of prostate cancer, which has a high specificity with PSA values between 4 and 10 ng/mL (up to 90 %) [56, 57]. To obtain a reliable PSAV result, the interval between the two separate measurement should be at least 18 months [57]. This interval seems not to be optimal for clinical daily practice because it can cause a delay in treatment. Furthermore, based on the characteristics of this marker, its use is limited. When initial PSA values are less than 4 ng/mL, the sensitivity and specificity is dramatically reduced [58]. As a prognostic marker, increased PSAV is significantly related to aggressiveness. One study showed that preoperative PSAV values of >2.0 ng/mL/year resulted in a nine times higher chance of prostate cancer-related mortality after prostatectomy or external beam radiotherapy [59, 60]. A recent study revealed that even a PSAV of >0.35 ng/mL/year correlated with a significant higher chance of biochemical progression [61]. On the other hand, when values of <0.4 ng/mL/year were used, it increased the likelihood of insignificant prostate cancer [62]. Besides these promising results, the exact role of PSAV in the stratification and characterization of specific subgroups of prostate cancer patients remains not fully elucidated. More research has to be performed to maximize its potential as a tumor marker and to establish the most ideal cutoff PSAV value for diagnosis and determining prognosis.

### PSA Doubling Time

Closely related to PSAV, PSA doubling time (PSADT) could also harbor some interesting capacities as a tumor marker. PSADT is defined as the time that serum PSA levels are doubled. As a diagnostic tool, so far, no reports have been published. Nevertheless, the predictive abilities of this tumor marker has been the focus of multiple research efforts, but their results show no relationship between pretreatment PSADT and posttreatment outcomes [63]. As a prognostic marker, it has mainly been measured post prostatectomy and was correlated with survival results. The first study showed that fast PSADT values (<10 months) correlated with lower metastasis-free survival [64]. Others showed that if PSADT was <3 months within a period of 24 months after radical prostatectomy, there was an associated lower cancer-specific survival [65].

### PSA Isoforms

ProPSA is an inactive precursor of PSA that is cleaved by hK2 or hK4, converting it into its active form [66]. The precursor form of PSA contains a 7-amino acid proleader peptide and is therefore named [-7]proPSA. Incomplete cleavage of proPSA results in other subforms, such as [-2], [-4], or [-5]proPSA. Elevated levels of proPSA and its truncated forms were observed in prostate cancer tissue [67, 68]. A possible explanation for this finding was the observation that proPSA is higher expressed in the peripheral zone of the prostate [68].

Mainly in the intermediate range (2.5–10.0 ng/mL) of PSA, ProPSA could early detect more prostate cancers [69–71]. Even when these isoforms were used, it could avoid 59 % of all biopsies taken, as compared to 33 % when only %fPSA was used. Unfortunately, in a prognostic setting, proPSA does not seem to be superior to %fPSA, but when combined, it is correlated with higher Gleason scores and non-organ-defined prostate cancer [72]. All the single subisoforms of proPSA have been investigated and showed no better correlation in diagnosing or determining prognosis as compared to total proPSA or %fPSA [71] (Fig. 35.2).

## KLK2

Human kallikrein 2 (hK2 or KLK2) is also a member of the kallikrein family and shares 80 % homology with PSA. It functions as a peptidase, cleaving proPSA to mature and active PSA [73, 74]. Like PSA, it is highly and specifically expressed in the prostate and is androgen regulated. hK2 levels show a distinct expression pattern on immunohistochemical analysis, which was also observed in serum. These

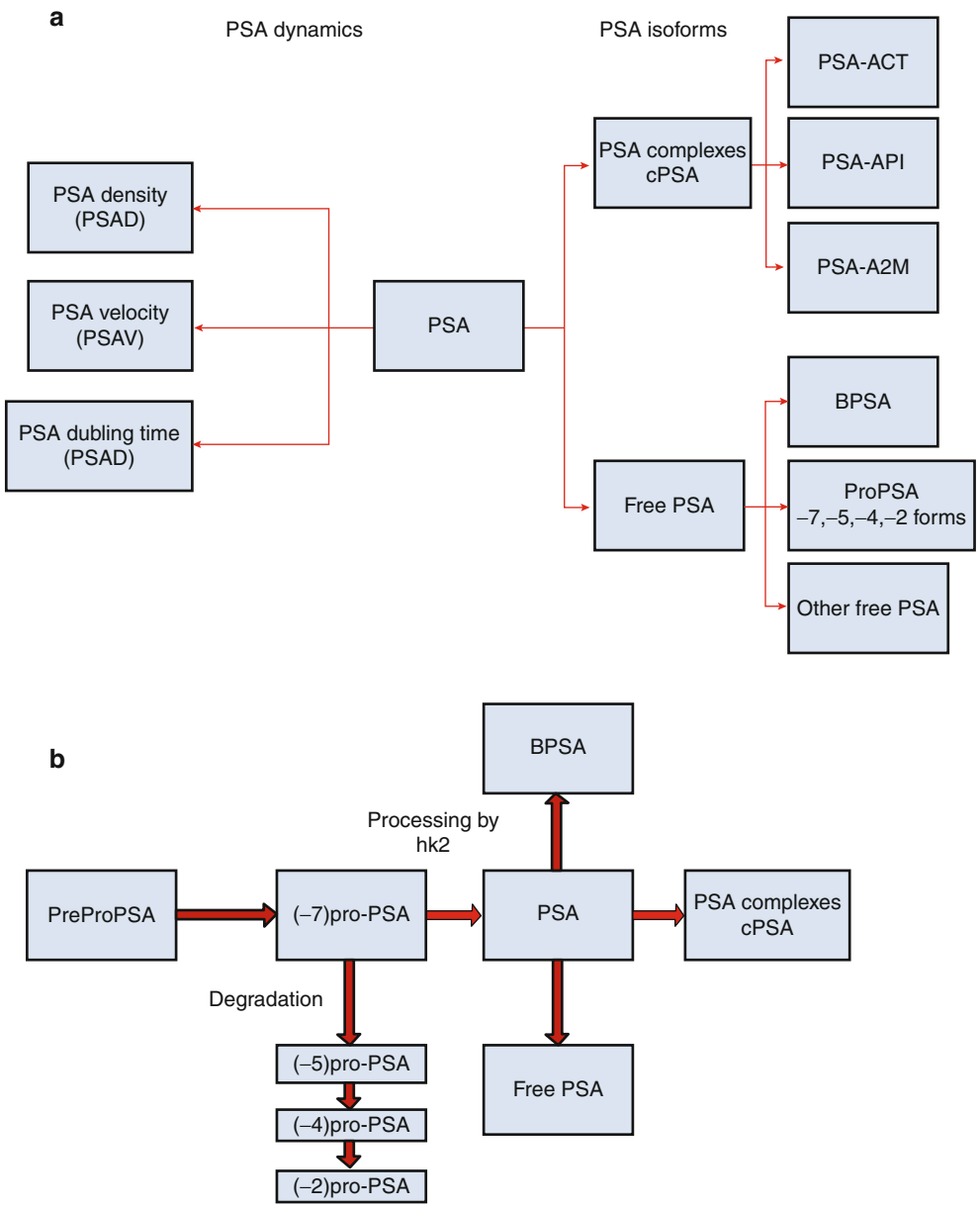


**Fig. 35.2** (**a**) Different measurements contributing PSA including PSA dynamics. (**b**) Processing of PSA to its subforms [295]

findings indicated that this marker could be indicative, independent of PSA [75, 76]. The first studies on hK2 showed no correlation of this marker with prostate cancer. [77–79] Nevertheless, a review that also included all studies on hK2 performed in a later stage revealed a significant higher expression of hK2 in serum from prostate cancer patients [71]. Especially for the intermediate elevated PSA values, it showed a better discrimination as compared to %fPSA. As a prognostic marker, hK2 is capable of differentiating between low and high Gleason scores and also for extraprostatic growth, even prior to radical prostatectomy [80–82]. Unfortunately, when this marker was analyzed in a multivariate model, it had a very limited improvement on prognoses as compared to Gleason score alone [83, 84]. One study revealed that hK2, together with other variables, was significantly predictor of biopsy outcome [85].

## Urinary PSA

In almost all reports, PSA as a tumor marker for prostate cancer was measured in serum. In contrast to serum PSA, also urinary levels of PSA were evaluated as a potential tumor marker for prostate cancer [86]. Although the first report was published in 1985, less is known about this PSA measurement. Just as serum PSA, it was shown that

elevated urinary PSA after radical prostatectomy was correlated with disease recurrence and therefore was suggested as a monitoring marker [87]. In a diagnostic setting, when a ratio was taken of urinary and serum PSA expression, it was shown that it produced higher sensitivity and specificity as compared to serum PSA alone, especially in the intermediate range [88, 89]. Unfortunately, reports on urinary PSA levels are few, and more research is needed to fully elucidate if urinary PSA has any potential as a marker for prostate cancer.

## PCA3

The PCA3 transcript (prostate cancer antigen 3) was discovered in the late 90s as a new promising candidate marker for prostate cancer [90]. The PCA3 gene is located on chromosome 9q21–22 producing a (noncoding) mRNA that does not encode a protein [91, 92]. After its discovery, it was named DD3 (differential display clone 3) as a result of a differential display analysis that was used to compare mRNA expression between healthy prostate tissue and prostate cancer tissue [93]. Ninety-five percent of prostate cancer specimens highly expressed PCA3, compared to no expression in normal prostate, BPH, or other types of cancerous tissues. High-grade PIN also revealed higher expression, up to 96 % of the cases [94, 95]. PCR on similar samples showed a 66-fold increase in PCA3 expression in prostate cancer samples with a sensitivity of 94 % and specificity of 98 % [96, 97]. Furthermore, the expression of this marker is not influenced by age, prostate volume, and infections [93]. The current PCA3 test is mRNA based, and the outcome is a ratio between PCA3 mRNA and PSA mRNA multiplied by 1,000 [97]. This test is preferentially performed on urine samples that are collected after digital rectal examination or prostate massage [98]. When this test is performed on serum, it has less accuracy [99].

Initially, the PCA3 test was launched to predict presence of PCa after negative biopsies. Subsequent reports on the urine test showed a sensitivity of 54–82 % with a specificity of 66–83 %, where PSA has a sensitivity of only 22–47 % for the diagnosis of prostate cancer [93, 95, 97, 99–101]. Multiple studies have shown that increased PCA3 is statistically significantly correlated with more tumor volume [102–104]. PCA3 also outperformed the diagnostic accuracy of %fPSA. This diagnostic accuracy can even further be increased when PCA3 is combined with other (clinical) variables such as PSA, physical characteristics during digital rectal examination, age, and family history [105]. In a screening setting, PCA3 was capable of improving the performance characteristics and identification of serious disease compared with PSA [106].

Although many reports describe the relation and prognostic features, such as histopathological outcome, generally no correlation could be observed between PCA3 and Gleason score and pT staging [107]. With these data, it was suggested that PCA3 could be applied to predict histopathological outcome after biopsy, especially in patients with elevated PSA and a negative biopsy [101, 107, 108]. Furthermore, it was suggested that PCA3 could be used to determine multifocality of prostate cancer lesions and patients that are candidates for active surveillance [93, 109–111]. The exact role of PCA3 in determining diagnosis and prognosis of prostate cancer remains to be further investigated. Since the PCA3 detection assay is RT-PCR (reverse transcriptase PCR) based, the assay needs to be performed by expert labs and is much more expensive than protein-based ELISAs.

## ETS

In prostate cancer, chromosomal rearrangements affecting the ETS (E twenty six) gene family members are common events; around 60–70 % of all cases exhibit such an alteration [112, 113]. In a majority of the rearrangements, there is a fusion between the genes TMPRSS2 and ERG, the so-called TMPRSS2:ERG fusion gene, which is unique for prostate cancer. Both TMPRSS2 and ERG genes are located in the same orientation on the long arm of chromosome 21. They are spaced by approx three million base pairs, and a deletion of this interstitial region can cause fusion of the two genes. Because the TMPRSS2 gene is androgen regulated, a fusion of this gene with ERG results in the androgen-regulated and high expression of ERG. So far, this fusion is never observed in normal tissue and unique to prostate cancer [114].

Multiple gene fusion partners that are related with either the TMPRSS2 part or the ERG part have been identified [115]. Other fusions of the TMPRSS2 gene occur in fewer cases with ETV1, ETV4, and ETV5. Although the TMPRSS2 gene is most often involved, other fusion partners such as the SLC45A3, ACSL3, HERV-K, FOXP1, EST14, KLK2, CANT1, and DDX5 genes can rearrange with ETS family members [116]. All these gene fusions are unique to prostate cancer and seem to play an important role in the biogenesis and development of this disease. Therefore, they could function as marker for diagnosis and prognosis. Recent studies showed that the fusion of TMPRSS2 to ERG is present in the precursor lesions PIN (prostatic intraepithelial neoplasia) and therefore must be an early event in cancer development [117, 118]. Multiple studies that address the prognostic value of this marker have been performed, with several opposing conclusions [113, 116]. Two studies examined 114 and 150 prostates after radical prostatectomy and revealed that expression of ERG or TMPRSS2:ERG correlated with a reduction of biochemical progression [119, 120]. Gleason score are thought

to be lower when TMPRSS:ERG is present [121]. No correlation was observed by other five studies that compromised similar-sized study cohorts [117, 122–125]. Also, the presence of ETV1 rearrangements failed to correlate with progression of disease [126]. Most reports reveal an unfavorable correlation of gene rearrangements with outcome after treatment (radical prostatectomy). These studies showed an increased rate of biochemical recurrence, formation of metastases, or even death [125, 127–135]. Interestingly, one study showed that ERG rearrangement alone was associated with low-grade prostate cancer; present with seminal vesicle invasion, there seemed to be a poorer prognosis [116, 133]. Expression of the TMPRSS2:ERG fusion gene was shown not to be able to predict response to endocrine treatment in hormone dependent and lymph node-positive prostate cancer [136, 137].

Rearrangements of genes from the ETS family are potentially very useful diagnostic markers due to their prostate cancer-specific occurrence if they can be measured in serum or urine. Like for PCA3, a test has been developed to measure fusion transcripts in urine. For prognostic or predictive purposes, fusion gene-based tumor markers remain controversial.

Because measurements of the fusion transcripts and genes are performed with RT-PCR or FISH (fluorescent in situ hybridization) techniques, implementation in daily clinical practice is hampered. Recently, an antibody against the ERG protein was generated that can be used for immunohistochemistry [138, 139]. Although the antibody has some cross-reactivity with FLI1, it gives the opportunity to easily and quickly assess 1,000 of retrospective and prospective patient samples. All three techniques (ERG antibody on protein level, RT-PCR on mRNA level, and FISH on DNA level) provide their own unique information on the status of the fusion event and are likely complementary in their diagnostic and prognostic value.

## AMACR

AMACR (alpha-methylacyl-coenzyme A racemase) is an enzyme that is encoded by the P504S/AMACR gene. In cells, this protein is located in the mitochondria and peroxisomes, and although the function has not been revealed completely, it is related to the metabolization of fatty acids and bile acid biosynthesis [140–142]. The AMACR transcript and protein are known to be highly expressed in a variety of cancers with a very high (up to nine times higher) expression in 86 % off all prostate cancers [143–145]. In 2002, AMACR was introduced as a new marker for prostate cancer [146]. A meta-analysis of multiple mRNA expression arrays revealed that AMACR is overexpressed in prostate cancer with high sensitivity and specificity [147, 148].

In a diagnostic setting, the use of the AMACR protein on immunohistochemical analysis of prostate biopsy samples has been limited to a valuable complement to other known markers [149]. Unfortunately, samples that did not contain prostate cancer also had AMACR expression but generally lower compared to the cancer samples [150]. In 18 % of the prostate cancers, AMACR is false negative [151]. When unusual histopathological subgroups of prostate cancer had to be identified, the increased expression was only limited to 62–77 % [143, 152].

In a prognostic setting, it has been shown that untreated metastasis and hormone-refractory prostate cancers were strongly positive for AMACR. In this specific prostate cancer stages, AMACR has a sensitivity of 97 % and a specificity of 92–100 % [146, 153]. Furthermore, decreased expression of AMACR has been shown to have prognostic value in predicting biochemical recurrence and prostate cancer-related death [154].

In order to assess this marker in noninvasive-derived patient materials (not biopsies) such as serum or urine, expression of AMACR mRNA could also be identified in 69 % of the cases. Unfortunately, AMACR is not specific to cancer of the prostate, because serum levels can also be elevated in other urological disorders like BPH or autoimmune diseases [155]. When used in a diagnostic setting as an additive to PSA, sensitivity and specificity can be increased when measured in urine, especially when the PSA is in the mid-range (4–10 ng/mL) [156–158]. Unfortunately, when AMACR mRNA was normalized to PSA mRNA, AMACR did not accomplish to be a statistically significant predictor of prostate cancer [159]. New promising serum tests for prostate cancer which comprehend the AMACR gene are evaluated. With these tests, a ratio is calculated between the expression of the AMACR gene and the PSA gene [142]. Until now, one report has been published where it was shown that the AMACR protein is detectable in serum with an ELISA, but elevation of this protein was not specific for prostate cancer [160]. Although more research has to be performed, it is also shown that circulating antibodies against the AMACR protein in combination with PSA could function as a useful tool for diagnosis [157, 161].

## GSTP1

During aging, DNA damage occurs as a result of oxidative stress, exposure to chemical substances, or ionizing radiation [162]. These damages can result in mutations or alterations of oncogenes and tumor suppressor genes. In healthy cells, the cytoplasmic enzyme glutathione S-transferase pi 1 (GSTP1) plays an important role in detoxifying the cell from carcinogens. GSTP1 is a member of the glutathione S-transferase family, which contains four different classes.

All these classes are expressed in prostate tissue [163]. Although GSTP1 expression is increased in various cancers, in prostate cancer, GSTP1 is downregulated [164]. This is caused by hypermethylation of the GSTP1 promoter, a mechanism well known in cancer to decrease expression of tumor suppressor genes. Hypermethylation of GSTP1 was observed in all stages of prostate cancer, from high-grade PIN to metastases [165, 166]. Such methylation was not observed in benign prostate epithelial cells [162]. Based on these findings and the presence of methylation in 90 % of prostate cancers and 67 % in high-grade PIN, it was concluded that GSTP1 methylation might function as a tumor marker for prostate cancer [167, 168]. Subsequently, methylation of this gene could be observed in serum, urine, and ejaculate of prostate cancer patients when analyzed by methylation-specific PCR, which gave rise to the idea that it could even be applied in a clinical setting [169–172].

As a diagnostic marker, it was shown that GSTP1 DNA methylation in urine has a sensitivity of 75 % (after DRE) and a specificity of 98 % for prostate cancer and is comparable to its expression in biopsy specimen [173]. Similar values for sensitivity and specificity were observed in other studies. It is notable that sensitivity in urine is increased by collection directly after digital rectal exam or prostate massage and functions independent of PSA [174–176]. To increase sensitivity even more, a relative ratio of GSTP1 methylation over methylated MYOD6 can be determined [164].

For prognostic purposes, 100 % of the locally advanced or metastatic tumors showed hypermethylation. Biochemical recurrence after prostatectomy seems to appear more and faster when the epigenetic alteration is present [177]. In a small study cohort, it was shown that methylation of GSTP1 is a statistically significant predictor for time to recurrence [178]. Androgen-deprivation therapy does not seem to influence GSTP1 methylation in 87 % of the cases [179]. Unlike other genetic alterations, methylation of this gene is reversible after therapeutic intervention. Because no reports have been published which describe this effect, more research is needed.

Methylation of GSTP1 seems to function very well as a diagnostic and prognostic tool, but because the number of reports describing this marker is lacking, we should be careful in jumping to conclusions. As more results are being published, more allusions are made regarding the use of a set of hypermethylated genes for optimal diagnosis and determining prognosis in prostate cancer patients.

## PSMA

PSMA (prostate-specific membrane antigen), or also known as FOLH1, is an androgen-regulated gene that encodes a type II transmembrane glycoprotein. PSMA belongs to the M28 peptidase family and has an intracellular and extracellular domain [180]. Its function is limited to hydrolyzing peptides in prostatic fluid and generating glutamate and also acts as a folate hydrolase [181, 182]. This protein is expressed in a number of tissues such as prostate, nervous system, and kidney [183, 184]. Furthermore, it has been shown to have a higher expression in prostate cancer. This finding could possibly be related to its enzymatic activity and thus invasiveness growth of prostate cancer [185, 186].

In the field of prostate cancer, PSMA has been the focus of many research groups. It has mainly been suggested as a prognostic tool [187]. Immunohistochemical analysis in a group of 232 patients showed higher expression in prostate cancer (79.3 %) and metastases (76.4 %) as compared to benign prostate tissue (46.2 %) [188]. Other studies showed an increased expression in progressive prostate cancer and hormone-independent prostate cancer [189–194]. In serum from prostate cancer patients, the PSMA protein is increased, with a higher expression in advanced stages of cancer [195–197]. Nevertheless, contradicting studies show that PSMA is not prostate cancer specific and does not discriminate between localized prostate cancer and advanced disease [198]. A possible explanation for these different findings could be the fact that in those studies, different types of antibodies have been used in various assays. Also, studies that investigated the expression of PSMA mRNA have shown varying and inconclusive results, probably because of different assays used. The sensitivity of diagnosing prostate cancer with PSMA mRNA is more or less similar to that of PSA mRNA [185]. As a prognostic marker, no correlation was observed between PSMA mRNA, Gleason score, pT staging, and serum PSA. In a study on patients with clinically localized prostate cancer, a combined PSMA/PSA mRNA analysis in peripheral blood samples showed that this could be an independent predictor to biochemical progression after radical prostatectomy [199].

Although PSMA seems to be not prostate and prostate cancer specific, there is an upregulation of PSMA in prostate cancer and probably more in its aggressive forms. Therefore, its function as a marker for prostate cancer is limited. A more promising feature of PSMA is its application in tissue-targeted therapy such as prostate-specific cancer vaccine therapy or radioimmunotherapy [200, 201].

## PSCA

Prostate stem cell antigen (PSCA) is a gene that encodes for a membrane-based glycoprotein. PSCA has been found to be relatively highly present in prostate but also in other cell types such as bladder, placenta, and gastrointestinal tissues [202]. The expression is also elevated in malignant tissues such as prostate cancer, bladder cancer, and gastrointestinal

cancers [203, 204]. In prostate, the expression of the PSCA mRNA is influenced by puberty, androgen deprivation, and androgen restorement [205]. Although the exact involvement of PSCA in prostate cancer is fairly unknown, it was shown that PSCA protein and mRNA are higher expressed from high-grade PIN through all stages of prostate cancer [206, 207]. Nevertheless, knockout of the PSCA gene in mice resulted in a normal urogenital development without an increased risk of prostate cancer [208].

As a diagnostic or predictive marker, it was shown that expression of PSCA in negative biopsies before TURP (transurethral resection of the prostate) is associated with higher risk of having prostate cancer in the TURP specimen, especially when serum PSA levels >4.0 ng/mL or with a suspicious DRE [209].

In a prognostic setting, immunohistochemical analysis showed that expression of the PSCA protein was present in 94 % of all tumors and was significantly associated with adverse prognostic features, such as high Gleason score and extracapsular extension [210, 211]. Furthermore, PSCA was identified in bone metastases and lymph node metastases [212, 213]. These findings suggest that there is a positive correlation of the PSCA protein with advancement of disease status in prostate cancer. When PSCA mRNA was measured in peripheral blood, it corresponded with a reduced disease-free survival time [214]. Compared to PSA and PSMA, it was noticed that specificity and independent prognostic value were very high [214]. Unfortunately, this transcript could only be identified in 13.8 % of the patients, which limited its ability to differentiate between benign and malignant prostate tissue. When this marker was investigated for its post-treatment monitoring value, it was shown that after EBRT, PSCA mRNA is decreased [215]. Therefore, it was proposed as in interesting marker for follow-up after treatment.

Besides the properties of being a possible diagnostic or prognostic marker for prostate cancer, it has also been found that PSCA is a possible target for prostate-specific virus therapy [216, 217]. When PSCA is used, it was possible to inhibit tumor growth and formation of metastases.

## Chromogranin A

Chromogranin A (CgA) is a gene that encodes for a proteolytic protein that is a member of the chromogranin/secretogranin family of neuroendocrine secretory proteins. CgA is one of the most frequently produced proteins in neuroendocrine cells in the prostate and can be easily measured by a radioimmunoassays [218]. Serum levels of chromogranin A could reflect neuroendocrine activity of prostate malignancies, therefore it holds an interesting potential to function as a marker for prostate cancer and especially for neuroendocrine differentiation [219, 220]. Unfortunately, chromogranin A is not prostate specific; it is also elevated in various neuroendocrine tumors and neuroblastomas [221–224]. The exact function of chromogranin A in prostate cancer is unknown, but it has been shown that it influences the growth of prostate cancer cells [225].

Despite conflicting results as a diagnostic tool, when measured in serum, high chromogranin A levels seem to correspond with the presence of (organ-confined) prostate cancer. [216] In combination with PSA, a better diagnostic accuracy could be established [226]. An interesting report showed that chromogranin A is able to predict conversion of hormone-naïve prostate cancer to hormone-refractory disease and the presence of hormone-independent prostate cancer itself [227, 228]. A small prospective study on 50 prostate cancer patients showed that high chromogranin A serum levels prior to radical prostatectomy were able to predict higher Gleason scores, extra capsular extension, and eventually treatment failure [229–231]. Especially in patients with hormone-independent prostate cancer, this marker correlates with adverse outcomes and decreased overall survival [232]. Furthermore, this marker could function as a predictor for chemotherapy response in hormone-independent prostate cancer [233]. In a prognostic setting, high levels of CgA correspond with factors such as a higher Gleason score, advanced pT stage, and metastases [234, 235]. Immunohistochemical analysis showed similar results [236, 237]. No decrease in chromogranin A serum levels were observed after radiotherapy or hormone therapy, therefore the use of this marker as a monitoring tool seems not to be useful [238, 239]. Specific antibodies against chromogranin A can suppress its function through apoptotic pathways, leading to programmed cell death. Therefore, chromogranin A antibody-mediated apoptosis was suggested as an alternative treatment for prostate cancer [225]. A derivate of this marker, chromogranin A velocity was introduced as a marker for predicting time to androgen independence after hormonal treatment [239].

## B7-H3

The transmembrane protein family B7 has gained publicity with its role in regulation of T lymphocytes [240]. Subsequent reports showed that a total of four subtypes (B7-H1, B7-H2, B7-H3, and B7-H4) could be identified in cancers and might play a role in the mechanism by which human malignancies evade host immune responses [241–243]. Higher expression of some of these subtypes are correlated to more aggressive behavior and poor clinical outcome [244, 245]. The B7-H3 has also been identified in healthy placenta and malignant tissues [246]. Although there was expression in benign tissue, the expression in cancerous lesions was significantly higher [241].

B7-H3 could be identified as an independent prognostic factor in 338 patient samples after radical prostatectomy that were followed with a median of 3.9 years. The patients which showed elevated B7-H3 expression had a shorter time to cancer progression [247]. This indicated that B7-H3 could function as a prognostic marker. Furthermore, B7-H3 expression is higher in metastases and hormone-refractory prostate cancer. The expression is not hampered by hormone treatment [248]. Also, this marker could have prognostic value for biochemical recurrence after salvage radiotherapy, especially with low primary TNM staging, low Gleason score, and low pre-radiotherapy PSA [249]. Because this marker is membrane bound in cells, it also harbors a function in targeted therapy. Chemotherapy or radionuclide therapy that is directed against B7-H3 makes it possible to specifically engage prostate cancer cells.

## CAV1 (Caveolin-1)

Caveolin-1, is a major structural component of caveolae. These caveolae are specialized membrane invaginations that are abundant in adipocytes, endothelium, and smooth muscle cells. Caveolae are involved in molecular transport but also in cell adhesion and signal transduction [250, 251]. Caveolin-1 has been linked to prostate cancer since the late 90s, where it was identified as a marker [252]. The exact relation of caveolin-1 and prostate cancer remains unclear, but it is known that caveolin-1 in prostate acts as a tumor suppressor by keeping Akt dephosphorylated in the Akt-pathway [253]. Subsequently, it was shown in in vitro experiments that downregulation of the expression of this gene resulted in cells turning from androgen independent to androgen dependent [254]. This implicated that there is a role for caveolin-1 in the development of castration resistance. It is also known that this protein plays a role in the malignant characteristics of prostate cancer cells by changing the microenvironment and promoting angiogenesis [255]. Studies showed that caveolin-1 is also expressed in normal prostate stromal cells but minimally expressed in normal epithelial cells [256]. The protein expression of caveolin-1 is higher in prostate cancer cells compared to normal prostate epithelial cells [252]. The expression of this marker in epithelial cells upregulates when prostate cancer grading increases [256]. Furthermore, the protein caveolin-1 also has higher serum values in patients with prostate cancer, which makes it possible to measure it with a very sensitive and reproducible ELISA [257]. Median serum caveolin-1 levels are significantly higher in localized prostate cancer compared to men with BPH.

Caveolin-1 levels could harbor a predictive potential in men undergoing radical prostatectomy [258]. Higher expression of caveolin-1 was correlated with an increased risk of developing aggressive recurrent tumors after surgical treatment. Preoperative high caveolin-1 serum levels resulted in a 2.7-fold higher risk of developing biochemical recurrence [259].

When caveolin-1 was investigated as a prognostic tool, in samples retrieved after radical prostatectomy, it was shown that a positive immunohistochemical staining correlates with a significant worse prognosis [260]. In patients with lymph node-negative prostate cancer, caveolin-1 expression is an independent prognostic factor for a Gleason score >7, extraprostatic extension and positive surgical margins. When combined in a multivariate model with other variables such as Gleason score, it is possible to more accurately predict the chance of biochemical recurrence. Unfortunately, another study showed in 1,458 cases no correlation between high postoperative caveolin-1 values in serum and aggressiveness of prostate cancer or adverse prostate cancer events [261].

## GOLPH2

GOLPH2 (Golgi phosphoprotein 2), also known as GOLM1 or GP73, is a type II Golgi membrane protein and involved in the sorting and modification of proteins that are exported from the endoplasmatic reticulum through the Golgi apparatus. Recent findings suggest that changes in structure and function of the Golgi apparatus may play an important role in the development or behavior of malignant cells. This protein has already been shown to be elevated in liver diseases as a result of viral infections but also as a potential marker for hepatocellular carcinoma [262, 263]. Immunohistochemical experiments on prostate cancer samples revealed that the GOLPH2 protein also is upregulated in prostate cancer [264, 265]. An interesting finding was that this specific marker is present, even when AMACR is negative. Therefore, it was mainly introduced as an additive protein marker for prostate cancer, next to other known markers. Preceding mRNA profiling studies, research already showed that GOLPH2 mRNA is upregulated in prostate cancer tissues [266, 267]. When this gene transcript is used in a marker profile to detect prostate cancer in urine, it seems to be capable to outperform PSA measured in serum [159].

## MYO6 (Myosin IV)

Myosin IV is a Golgi apparatus-associated protein that is involved in intracellular vesicle and organelle transport and is required for the structural integrity of the Golgi apparatus. Furthermore, the protein has been suggested as an important factor for cell migration and even cancer invasion [268–270]. Based on a microarray experiment, it was discovered that the

MYO6 mRNA is upregulated in prostate cancer, next to GOLPH2 [271]. Interestingly, expression of the transcript goes down in androgen-independent and more aggressive prostate cancers [271]. With Immunohistochemical analysis, it was shown that a strong protein expression is present in a PIN, the majority of prostate cancer cells, and weak or absent expression in neighboring benign prostate cells [265].. In a prognostic setting, no differences were observed between the different Gleason scores or other pathological indicators for aggressiveness [271]. Based on these results, the transcript could be used as a diagnostic marker, but further research has to be performed to reveal the true potential of this marker and to assess its possible role in prognosis.

## CRISP3

Cysteine-rich secretory protein 3 (CRISP3), also known as specific granule protein 28 (SGP28), has recently been implicated as potential marker in prostate cancer. Relatively, little is known about its function and role in prostate cancer. The CRISP3 mRNA has shown to be present in high concentrations in salivary glands, pancreas, and prostate [271–273]. Furthermore, its expression has been shown in secretory epithelium in the male urogenital tract, including the epididymis and the ampulla of the ductus deferens [274]. Regarding prostate cancer, multiple studies have shown that the expression of the CRISP3 mRNA is higher [275] (20–300 times) in prostate cancer as compared to healthy prostate tissue [273, 276, 277]. Also on the protein level, CRISP3 was shown to be higher expressed [278]. The protein also has been identified by ELISA in multiple bodily fluids, such as serum, saliva, and seminal plasma [279]. Unfortunately, serum concentrations were not different between prostate cancer samples and healthy controls.

As a prognostic marker, immunohistochemical analysis of prostate cancer specimen showed an increase in expression when Gleason scores increased. Expression in normal prostate epithelial cells was weak or absent. A similar analysis on radical prostatectomy samples revealed that expression of CRISP3 eventually positively correlated with biochemical recurrence [280]. In a multivariate analysis, this protein was still associated with recurrence. Nevertheless, when this marker was added in a model with other known markers, such as PSA, no improvement was observed. With the results acquired so far, CRISP3 does not seem to be a good prognostic marker for prostate cancer [275, 281].

An interesting observation was the decrease of CRISP3 after orchiectomy in some patient samples. This could reflect that CRISP3 could be partially androgen regulated and might function as a monitoring marker.

## Sarcosine

The discovery of sarcosine as a marker for prostate cancer has only recently been made. Since a large number of research groups are exploring changes on the level of genomics, transcriptomics, and proteomics, changes in the metabolomic field are novel and few. Sarcosine is a metabolite that is produced by the enzymatic transfer of a methyl group from S-adenosylmethionine to glycine. This reaction is catalyzed by the enzyme glycine N-methyltransferase (GNMT), which is highly expressed in prostate, liver, and pancreas. The first report on sarcosine in prostate cancer showed that sarcosine stimulates malignant growth of prostate cancer cells and has prognostic value [282]. With mass spectrometry, they analyzed blood, urine, and tissue samples from different well-characterized prostate cancer patients and explored them for metabolites. In a relatively small patient cohort, a total of 1,126 metabolites were identified. Sarcosine was highly increased during prostate cancer progression to metastasis and could easily be identified in urine [282]. Subsequently, they showed a decrease in disease progression when glycine N-methyltransferase was knocked down.

Although these results look very promising, subsequent reports showed that sarcosine as prognostic marker is debatable. On tissue samples, the expression in cancerous samples was 7 % higher compared to benign prostate samples. Unfortunately, no statistical differences were seen regarding prostate cancer progression [283]. A drawback of this study was the fact that metastatic samples were not included. Also, sarcosine as a urine marker, normalized to creatinine, could not reproduce the original finding that sarcosine functions as a prognostic marker. [284] When compared to PSA, urine-derived sarcosine was not able to outperform serum PSA on itself. When added to an algorithm with PCA3 or %fPSA, diagnostic performances could be improved [285].

Although sarcosine was promoted as a promising new marker for prostate cancer, its exact clinical value and applicability is unclear. The conflicting reports are mostly based on a limited number of samples with limited follow-up and different technologies to measure this metabolite. In order to resolve these contradictions, we need to control some of the variables, such as the study cohort and tumor marker assays [286].

## Exosomes

Exosomes are small vesicles (50–150 nm) that are shed by almost all cell types in the human body into almost all body fluids. Initially, exosomes were discovered during studies on the loss of the transferrin receptor in sheep reticulocyte maturation [287]. Exosomes are formed by inward budding of the cellular membrane which results in the formation of a large endosome. After formation of the endosome, it is

subjected to a second step of inward budding. During this second step, cytoplasmic content is taken up in small vesicles. When the endosome (now referred to as multivesicular body) is filled with small vesicles, it fuses with the cellular membrane, and the small vesicles, or so-called exosomes, are shed in the extracellular space [288, 289]. Because of this biogenesis pathway, exosomes contain proteins and RNA that are specific for the cell from which they are derived and thus represent the state of the cell [290]. By isolating prostate (cancer)-derived exosomes, one is able to search for new and specific tumor markers for prostate cancer. The reports on exosomes in prostate cancer are limited. One of the first clinically related studies showed their potential. The quantity of exosomes isolated from urine is higher in prostate cancer patients as compared to healthy controls [291]. Unfortunately, in this study, nothing was reported about differences in exosomal content. RNA expression analysis revealed that known markers of prostate cancer such as the TMPRSS2:ERG fusion mRNA and PSA mRNA could be identified in exosomes [290]. This finding emphasizes their function as tumor marker-containing structures [288, 292].

Although the reports are limited and the study populations and the variation in number of exosomes are very small, exosome research in prostate cancer could accelerate tumor marker discovery. Because they are present in body fluids, noninvasive technique can be applied to isolate exosomes and use them to diagnose or monitor the course of prostate cancer [293]. Unfortunately, when isolating exosomes from serum or urine, no distinction can be made between the different tissues from which the exosomes are derived. Therefore, more research has to be done to specifically isolate and profile prostate (cancer)-derived exosomes.

## Summary

Currently, PSA is the best and most widely accepted prostate tumor diagnostic and monitoring marker we have available for daily medical practice. Nevertheless, its limitations cause a need for new and more accurate markers. From the many discovery endeavors, there seems to be an inexhaustible source of new potential tumor markers that are being explored. Unfortunately, most of these candidate tumor markers still need to be evaluated more thoroughly to validate their diagnostic or prognostic value and demonstrate their added value over current practice.

Because of the heterogeneity of prostate cancer, there is a fairly good chance that the use of single tumor marker will not cover all aspects of the disease, and a combination of two or more markers is needed. In addition, multiple markers will be needed to address the different types of relevant clinical decision points, ranging from risk assessment, diagnosis, and personalized therapy [294]. Importantly, different technologies including mass spectrometry and microarrays are being introduced into the clinical practice to measure novel markers and extend the types of markers from the typical proteins to metabolites, DNA, and RNA.

Despite the large efforts invested in prostate cancer marker research in the past decade, the number of clinically valuable markers is very limited. We have learned that open and unselective searches in a discovery phase generally result in many new candidate markers but also that most of these are not validated in independent and larger cohorts. It has become painfully clear that the complexity of body fluids and tissues, a selection bias and inadequate number of samples for discovery, and the variation between individuals are some of the major hurdles in the ongoing quest for novel markers. Despite these challenges, more accurate and reproducible technologies, more focused explorations, and the growing number of samples in (consortium) tissue banks improve the essential steps of excluding false positive candidates in an early stage and robustly validate novel markers.

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# Prostate Specific Membrane Antigen-Based Diagnostics

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## Introduction

At present, prostate cancer imaging is performed for lesion localization, detection of recurrent and/or metastatic disease, and staging. Despite significant efforts, conventional imaging of prostate cancer does not contribute to patient management as much as imaging performed for other common cancers. In addition, these imaging tests yield no information to differentiate aggressive from indolent disease that is a very important distinction in prostate disease management. In the absence of a clinically useful initial diagnostic imaging modality, biochemical tests (prostate specific antigen (PSA)), digital rectal exam, and TRUS (Transrectal Ultrasound)-guided biopsy have been widely adopted for initial diagnosis. The first post-diagnostic imaging test is often an extent-of-disease evaluation with magnetic resonance imaging (eMRI-endorectal coil). Computed tomography (CT) has a role in higher risk patients to evaluate locoregional lymphadenopathy, solid organ, or bony involvement. Bone scintigraphy with $^{99m}$Tc-MDP or, more recently, $^{18}$F-NaF is widely used as an adjunct for detecting bone metastases. Positron emission tomography (PET) with fluorodeoxyglucose (FDG) has no role in early diagnosis and a limited role in late-stage prostate cancer because of low and heterogenous utilization of glucose by prostate carcinoma. Other nonspecific PET agents such as acetate and choline ($^{11}$C and $^{18}$F-labeled) or MR-based nanoparticles, diffusion-weighted imaging, and spectroscopy may have a future role; however, the performance of these agents remains to be determined in controlled clinical trials.

One future direction in prostate cancer imaging involves the development of imaging biomarkers and the exploitation of existing biomarkers to improve the accuracy of detecting prostate disease at every stage. One biomarker that has significant promise is PSMA (prostate specific membrane antigen) because of the high specificity of the antigen and new accompanying technology that has improved our ability to detect its presence. Other than capromab penditide (Prostascint®), most PSMA imaging are investigational and require validation and comparison to current conventional imaging techniques, which currently are in various stages of clinical trials. Therefore, it is important to understand not only the current state of conventional imaging but also existing pathway to developing safe and economical development of PSMA-targeted agents.

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## In Vivo Imaging of Prostate Cancer

### Conventional Imaging

#### TRUS

TRUS is the most prevalent imaging technique utilized in the initial evaluation of prostate cancer. Although TRUS has a low sensitivity/specificity for detecting tumor foci within the prostatic bed, it readily outlines the zonal anatomy and serves as a guide for biopsy. The sensitivity of prostate cancer detection with TRUS in B mode has been reported as ranging from 17 to 57 % [1, 2]. The classic description of a cancer focus on US is that of a hypoechoic lesion. However, experience has shown that hypoechoic lesions may represent benign disease [3]. In addition, small tumor foci are often isoechoic and cannot be distinguished from the subjacent normal glandular tissue. In addition, TRUS has not proven to be a valuable technique in determining local extent of disease (i.e., extracapsular extension or invasion of the seminal vesicles). In fact, significant spread of disease must be present in order to be detected by US. Color or Power Doppler is thought to add some value when compared with grey scale US alone, however, the primary tumor foci are often so small that they remain undetected by color US.

More recently, contrast-enhanced TRUS has been evaluated in prostate cancer diagnosis. Some of these studies have reported a higher sensitivity of this technique when compared with conventional TRUS, however, other disease processes (such as prostatitis) demonstrate enhancement and confound the confident cancer diagnosis [4]. Also, contrast microbubbles are relatively large which limits leakage into the tumor bed. Taymoorian K et al. reported a sensitivity of 100 % for reliably differentiating prostate cancer from subjacent normal glandular tissue but demonstrated a poor specificity (48 %) in patients with previous negative biopsies in the setting of rising PSA [5]. Clearly, US has its limitations in evaluating for the presence of prostate cancer foci within the gland as a stand-alone technique.

#### CT

CT has long been used as an imaging technique for staging more advanced stages of prostate cancer. The technique employs a contrast-enhanced study as permitted by renal function, with axial slices through the abdomen and pelvis. Other body regions may be included if there is clinical suspicion of more disseminated disease. The limitations of CT include lack of clear zonal delineation and difficulty with soft tissue contrast especially in the prostatic bed and region of the seminal vesicles. Small tumors within the prostate are often missed and local extension is difficult to discern. Major advancements in CT technology have generated limited advancements in prostate cancer evaluation [3, 6].

#### MR

MR imaging of the prostate gland has shown the most promise in recent years. MRI offers superb soft tissue contrast when compared with conventional CT or US imaging. The prostatic zonal anatomy is clearly depicted. The margins of the prostate gland are easier to evaluate as well as the contours of adjacent structures. There has been some debate in the literature regarding the use of endorectal coils. In general, endorectal coils are thought to reduce noise and improve diagnostic accuracy on 1.5T MRI machines. On 3T MRI machines, the use of endorectal coils to limit degradation of the images by noise appears less crucial but beneficial [7]. The standard MRI of the prostate includes multi-planar T1 and T2 images. Neoplastic lesions are classically visualized in the peripheral zone as low-signal T2 foci. T1-weighted sequences are useful for detecting post procedural hemorrhagic foci (to avoid misdiagnosis as tumor foci) as well as for evaluating surrounding structures and fat planes. However, the sensitivity and specificity for diagnosis on MR is low. Other benign processes such as prostatitis, atrophy, BPH, and posttreatment changes can have similar appearance to cancer on T2-weighted images. The reported sensitivity and specificity of T2-weighted MRI for tumor detection has been reported to be in the range of 50–85 % and 44–72 %, respectively [8]. The vast range in sensitivity and specificity is likely related to nonuniform imaging techniques, different machines, and varied experience in reading prostate MRI.

Of the conventional imaging techniques, MRI is the most useful in evaluating local disease. Extension of tumor into the periprostatic fat, prostatic capsule breakthrough, and seminal vesicle invasion can be performed on T2-weighted images. The morphologic appearance of the neurovascular bundle can also convey information of local extension. Functional MRI techniques have also shown significant promise in improving the diagnostic accuracy of MRI. These techniques include diffusion-weighted imaging, MR spectroscopy, and dynamic contrast-enhanced MRI sequences. Each technique explores different tumor characteristics that differentiated normal tissue form pathologic foci. For example, dynamic contrast-enhanced imaging shows early enhancement and rapid washout of contrast in neoplastic foci when compared with normal tissue or benign processes.

### Functional Imaging

#### MR Spectroscopy (MRS)

MRS in addition to MRI of the prostate for prostate cancer is thought to increase the specificity of tumor detection and localization [9]. This technique allows one to evaluate the amount of certain proteins in a voxel of tissue chosen by the MRI operator before the analysis. Of particular interest for

prostate imaging are the level of citrate, choline, and creatine. Normal glandular tissue utilizes citrate as an energy substrate. The choline levels in normal tissue should be low due to low cellular proliferation or turn over. However, choline level will be elevated in the setting of tumor. The ratio of (choline + creatine)/citrate in a voxel can be utilized to distinguish malignant foci from normal tissue. Muller-Lisse et al. reported a PPV of 80–90 % when MRI and MRS were employed together [10].

## PET Radiotracers

As FDG-PET has not demonstrated promise as a functional molecular imaging tracer, particularly in early stage disease, the focus in functional PET imaging to date has been choline and acetate with occasional use of other investigational tracers. The most commonly used PET radiotracer used in prostate cancer detection is radiolabeled choline ($^{18}$F- or $^{11}$C-). Choline is a component of the phosphatidylcholines, a class of biologic membrane phospholipids that are incorporated into malignant cells at an accelerated rate. Since prostate cancer is characterized by upregulated choline kinase activity, this has translated to a number of successful studies characterizing its use in detection of malignant foci.

Acetate is a substrate for the tricarboxylic acid (TCA) cycle with uptake increasing proportional to fatty acid synthesis. In a direct comparison of $^{11}$C-choline and $^{11}$C-acetate, Kotzerke et al. demonstrated that both tracers performed nearly identically in prostate cancer patients [11]. Recently, acetate has also been labeled with $^{18}$F. One investigational tracer of note is $^{18}$F-ACBC as it has been recently introduced into clinical trials and appears to be a practical ligand for imaging prostate cancer.

$^{18}$F -ACBC is a synthetic amine tracer whose uptake is likely related to sodium-independent L large-neutral amino acid transport system in prostate cancer cells [12]. Early results demonstrated significant uptake in vitro tumor cell lines as well as in rodent models. It was also noted that the degree of bladder activity is more significant than expected with conventional FDG-PET/CT, which was thought to improve diagnostic accuracy of locoregional disease [13].

Goodman et al. [44] found that anti F18-FACBC PET CT demonstrated significant uptake in primary, metastatic, and recurrent tumor foci. This technique often localized tumor foci in the setting of a negative In$^{111}$-capromab-pentetide scans. It also localized lymph involvement in lymph nodes that were not enlarged by CT and MRI criteria. The results were compounded by the fact that some radiotracer uptake was noted in inflammatory lymph nodes. Although the initial results are promising, further larger clinical trials are needed to establish the diagnostic utility of this technique.

## PET: Primary Diagnosis/Staging

There are many conflicting reports regarding PET/CT and the primary diagnosis and staging of prostate cancer as they are all investigational studies being compared to a dynamic standard-of-care. It is important, however, to highlight a few of these efforts to understand the potential of these imaging tracers in the future. Schiavina et al. utilized preoperative $^{11}$C-choline PET/CT and radical prostatectomy with extended pelvic LN dissection in patients at intermediate risk ($n = 27$) or high risk ($n = 30$) for preoperative lymph node (LN) staging [14]. The diagnostic sensitivity and specificity with $^{11}$C-choline was 60.0 and 97.6 %, respectively, while the lesion-based analysis was 41.4 and 99.8 %. $^{11}$C-choline PET/CT for LN metastasis detection performed better than clinical nomograms, with equal sensitivity and better specificity. Husarik et al. [15] used $^{18}$F-FCH PET/CT for correlation with lymphadenectomy for initial N-staging. Histopathological work-up was performed on $^{11}$5 LN sampled from 25 patients [15]. Only one of these LNs showed pathological $^{18}$F-FCH accumulation and was proven to be a metastasis measuring more than 1 cm. Four lymph nodes that did not show $^{18}$F-FCH accumulation turned out to contain metastatic cells, with an overall tumor load measuring less than 0.5 cm. The results obtained using $^{18}$F-FCH PET/CT for initial N-staging were discouraging, especially in terms of its inability to detect small metastases (micrometastases). The role of PET/CT in N-staging remains to be evaluated in larger clinical trials.

## PET: Disease Recurrence

One promising study evaluated suspected LN metastases before salvage LN dissection in 15 consecutive patients with rising PSA [16]. Although the group was limited in size, $^{11}$C-choline PET demonstrated value in this clinical scenario. In another small study of recurrence of prostate cancer, $^{11}$C-choline PET/CT was found useful for detection but unfortunately a limited positive predictive value (PPV) for locating pelvic LN metastases [17]. Reske et al. assessed the value of $^{11}$C-choline PET/CT for localizing occult relapse after radical prostatectomy in 49 patients [18]. PET/CT was judged negative for local remission in 12/13 of the controls and positive in 23/33 of the patients with histological verification of local recurrence. Husarik et al. [15] used $^{18}$F-FCH PET/CT for restaging of prostate cancer in 68 patients (mean PSA 10.81 μg/l) and demonstrated local recurrence in 36 patients. Overall sensitivity to detect recurrent disease was 86 % demonstrating that Fluorocholine may yield similar results to $^{11}$C Choline. More extensive clinical trials will be needed to demonstrate that this more practical tracer will also be as efficacious.

## Antigen-Based Imaging

Given the lack of specificity in conventional imaging techniques, one possible solution is to screen for specific, tumor-related antigenic targets and generate monoclonal antibodies (mAbs). In the case of prostate cancer, initial attempts in the 1980s began with mAbs to PSA and prostatic acid phosphatase (PAP) [19]. While the relevance and specificity of these antigens was appropriate, PSA and PAP are secreted antigens precluding cell-associated antibody binding. Furthermore, the presence of PSA and PAP in plasma effectively blocks specific antibody binding at the tumor site. Another murine mAb, 7E[11], ([111]In-capromab) was developed based on its recognition of prostate specific membrane antigen (PSMA). PSMA is not a secretory protein but undergoes constitutive internalization (residualizing) [20] and is a highly restricted prostate epithelial-cell membrane antigen.

## Monoclonal Targeting of PSMA Expression

### PSMA Antigen

PSMA is a type II membrane glycoprotein (Fig. 36.1) (100–120 kDa) with an intracellular segment (amino acids 1–18), a transmembrane domain (amino acids 19–43), and an extensive extracellular domain (amino acids 44–750) [19]. The PSMA gene has been cloned and sequenced and the three-dimensional crystal structure has been solved. PSMA has two unique enzymatic functions, folate hydrolase and NAALADase (catalyzing N-acetyl-aspartyl-glutamate by removing glutamate) [19]. NAAG is concentrated in neuronal synapses, and its role in releasing glutamate has assisted in characterizing PSMA and in the design of small molecule antagonists for imaging.

Although first thought to be entirely prostate-specific, PSMA is also expressed at a 100–1,000-fold lower level than in prostate tissue in the salivary glands, small intestine, proximal renal tubules, and tumor neo-vasculature. The intracellular location in these normal cells (brush border/luminal location) is not typically exposed to circulating antibodies which has significant consequences on the choice of imaging and therapeutic options. As circulating whole antibodies appear to best preserve the prostate specificity, it is these antibodies that have been the focus in therapies, suggest reference to Chapter 37.

PSMA has several optimal characteristics for targeting by antibodies. First, it is a highly expressed prostate-restricted non-secreted protein anchored to the plasma membrane. Second, its expression increases as tumor grade increases with concurrent increases in metastatic sites and androgen-independent disease. In addition, the 19 amino acid cytoplasmic domain contains a novel MXXXL internalization motif resulting in its internalization and endosomal recycling which increases the deposition of conjugated radiometals into the cell which potentially improves both imaging and therapeutic efficacy [21].

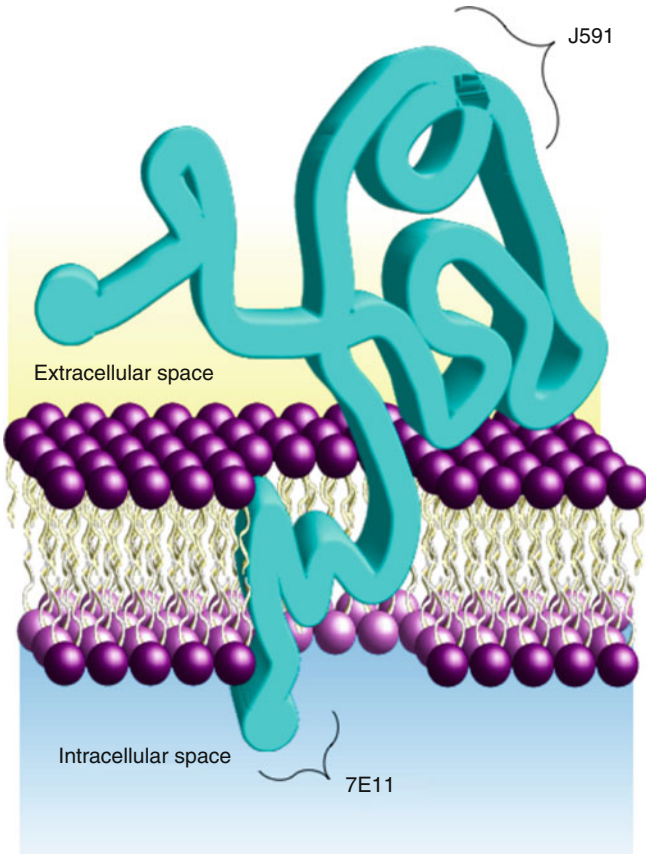



**Fig. 36.1** Schematic representation of prostate specific membrane antigen (PSMA) and epitopes of 7E11 (Capromab) and J591

### PSMA: Intracellular Epitope Imaging

With its FDA approval in 1996, [111]In-capromab pendetide (ProstaScint®, EUSA Pharma) became the first clinical agent targeting PSMA in prostate cancer. The mAb has affinity directed toward the short intracellular epitope of the protein (amino acids 1–18) and consists of an intact murine monoclonal antibody (mAb 7E[11]), labeled with [111]In. The molecule was developed for presurgical staging and the evaluation of PSA relapse after local therapy.

In presurgical patients with high-risk disease but negative conventional imaging, capromab was able to identify a subset

of patients with occult local nodal disease. It was assumed that this upstaging of disease and sparing of unnecessary surgery would lead to diverging outcomes, but no studies have been performed to determine whether high-risk patients with negative capromab scans fare better. In fact, since capromab scans fail to image bone metastases which are frequently the initial site of metastasis in 72 % of patients, one can assume a significant false negative rate in the setting of PSA relapse.

These finding highlights the main controversy with capromab detection. Since the intracellular portion is not normally accessible to circulating antibodies and the agent must internalize prior to binding, the antibody is thought to bind only to damaged cells greatly limiting the apparent sensitivity [22]. The utility of capromab will be discussed in detailed clinical context below, but the average sensitivity of 60 %, specificity of 70 %, PPV of 60 %, and NPV of 70 % are overall limitations of the technique. In 2009, capromab was used in a SPECT study which suggested higher sensitivities could be obtained, also the limitations in bony lesions remained [23]. Nevertheless, PSMA remains promising as the next generation antibodies and small molecule antagonists that target the extracellular domain will likely provide significant benefits to the imaging of prostate cancer.

### PSMA: Extracellular Epitope Imaging

Over the last 15 years, other monoclonal antibodies have also been developed to the extracellular domain of PSMA. These second- and third-generation humanized PSMA binding antibodies have the potential to overcome some of the limitations inherent top capromab pendetide. One example is the humanized monoclonal antibody J591 (huJ591) that has been developed primarily for therapeutic purposes but may also have interesting imaging characteristics including the identification of bone metastasis. J591 has been studied extensively in preclinical models where it has demonstrated excellent binding characteristics and tumor-to-background signal in prostate cancer xenografts.

In addition to J591, three additional mAbs (3/A12, 3/E7, and 3/F11) have been characterized [24]. The three IgG mAbs bind to different epitopes of the extracellular domain and have slightly different pharmacokinetics, but all have some potential for future development [25]. These antibodies (3/A12 in particular) have been labeled with $^{64}$Cu and have demonstrated good in vivo tumor-to-background rations required in a PET ligand [26]. Finally, another new mAb, 3C6, targeting the extracellular epitope of PSMA has been labeled with $^{111}$In- for imaging of prostate cancer xenographs and eventually patients in a clinical setting [27].

### PSMA: Small Molecule Inhibitors

The major disadvantage of whole mAb for imaging is slow target recognition and background clearance in an appropriate timeframe for diagnostic imaging. In general, radiopharmaceuticals that have thrived in the clinic have superior safety profiles, low radiation dose, and allow for administration and imaging in the same day. Based in part on homology to the PSMA receptors enzymatic moiety to NAALDase, Maresca et al. described the design and synthesis of a series of small molecule inhibitors of PSMA with the potential to image prostate cancer with improved pharmacokinetics.

To this end, radiolabeled PSMA inhibitor N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-S-[$^{11}$C]methyl-L-cysteine (DCFBC) has been successfully used for PET imaging of human PSMA-expressing xenografts [28]. This work has been extended by preparing and testing a PSMA inhibitor of the same class labeled with $^{18}$F [29]. Biodistribution and imaging studies showed high uptake of $^{18}$F-DCFBC in the PSMA-positive tumors with little to no uptake in PSMA negative tumors. Urea-based compounds may also present promising agents for prostate cancer imaging with SPECT and PET [30]. Two such urea-based small-molecule inhibitors targeting PSMA, MIP-1072 and MIP-1095, have exhibited high affinity for PSMA [31]. The uptake of $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095 in prostate cancer xenografts was successfully imaged with favorable properties amenable to human trials.

Functionally, PSMA is a proteolytic enzyme with high affinity to γ-glutamyl folic acid derivatives and N-acetylaspartylglutamate, as well as dipeptides similar to these compounds. Another class of PSMA inhibitors was created by utilizing and editing the above reference dipeptide motif and systematically pruning the molecule to pseudo-irreversibly bind to PSMA (Fig. 36.2). These phosphoramidates localize, bind, and internalize in PSMA-positive cells in vitro and have been fluorinated to function as a PET tracer in a murine xenograft model, and biodistribution data in murine xenografts have been reported [32].

## Clinical Role of PSMA-Targeted Imaging

### $^{111}$In-Capromab Imaging of Metastatic Disease

The initial excitement following capromab imaging was that the antibody would be able to detect sites of soft tissue primary disease and for presurgical staging or following biochemical relapse. The following clinical studies were designed in the context of standard-of-care management to assess performance in defined cases where the sensitivity,

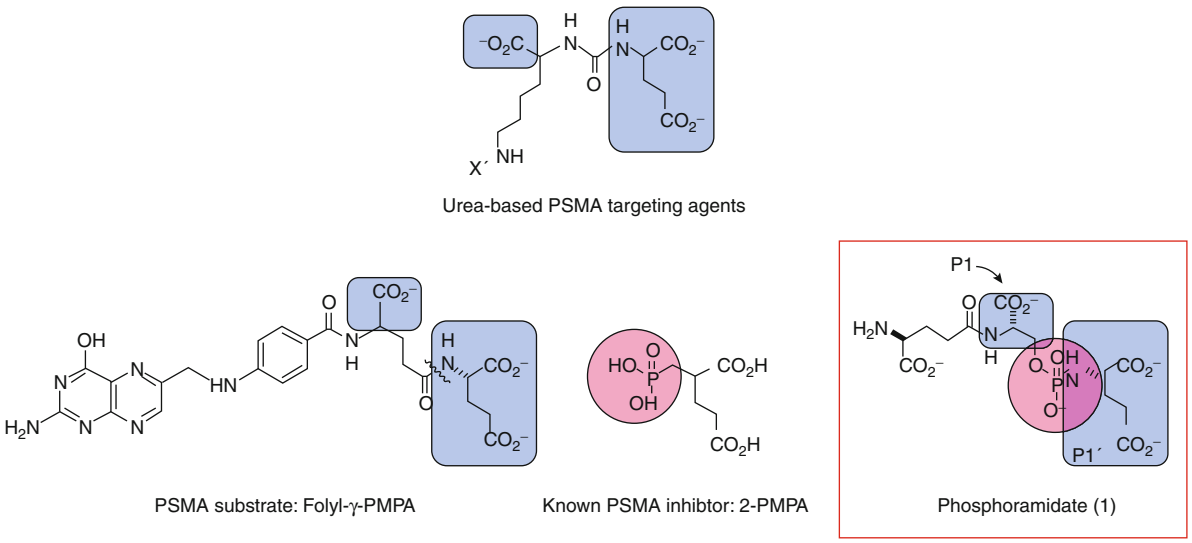



**Fig. 36.2** Structural elements of known PSMA substrate and inhibitors, compared with phosphoramidate (1). Highlighted portions indicate structural features similar to phosphoramidate design [32]. Reprinted with permission from *The Journal of Nuclear Medicine*

specificity, and positive/negative predictive value could be ethically determined. $^{111}$In-capromab scans were first compared to conventional imaging modalities in patients with known metastatic prostate cancer (MPC). In a phase I trial, 40 patients with MPC and bone and/or CT scan were evaluated and compared with contemporaneous capromab scans. In the trial, 38/40 patients had positive bone scans and 6 had soft tissue disease evident on the CT scan. In the positive bone scan fraction, only 5/38 (13 %) demonstrated all of the lesions and 17/38 had no evidence of disease (FN). $^{111}$In-capromab only detected 4/6 of the patients with CT-detected soft tissue disease. Another study with 7E11 radiolabeled with $^{111}$In and therapeutic nuclide Yttrium-90 demonstrated a similar relationship with conventional imaging in patients with known MPC. In the study, 11/12 had a median of 10 bone lesions seen on bone scan and 5/12 with demonstrable lympadenopathy on CT. In 5/12 patients imaged with $^{111}$In and $^{90}$Y, the lesions were not seen by either agent (FN) [33]. In 5/11 (45 %) patients with positive bone scans, none of the bony lesions were identified.

## $^{111}$In-Capromab in Patients with Biochemical Relapse and Negative Conventional Imaging

Although $^{111}$In-capromab failed to detect many of the bone scan positive lesions and CT-positive soft tissue lesions, there are somewhat counter-intuitive successes of capromab in the setting of otherwise negative imaging. These studies include patients who have a lower burden and prevalence of disease. The main two clinical settings are presurgical staging and postsurgical PSA relapse. In the presurgical studies, capromab was compared to surgical pathology on resected lymph nodes only with no attempt to identify possible bony lesions. In studies on high-risk patients (high presurgical PSA, high Gleason score/clinical stage) such as Manyak et al. [34], capromab's performance was significantly better than CT. In this study, 152 patients' (64/152 with positive nodes on pathology) capromab scans showed a sensitivity of 62%, specificity of 72%, PPV of 62%, NPV of 2%, and an overall accuracy of 68%. In comparison, CT has sensitivity of 4% and specificity of 100%, while MRI has sensitivity of 15% and specificity of 100% based upon the definitions used in the studies. Interestingly, the 62% sensitivity in these soft tissue lesions that are too-small-to-characterize lesions on CT/MR is similar to the sensitivity in the large lesions in the MPC studies. This would suggest that the main indication for $^{111}$In-capromab is to detect diminutive soft tissue lesions. Once the lesions are large or within the bones, the advantage disappears as anatomic imaging becomes more relevant. It would stand to reason that improved visualization of these scintigraphic findings either by improved radiotracer detection or antibody affinity would increase the relevance of PSMA imaging dramatically.

## $^{111}$In-Capromab in Extent-of-Disease Analysis

The second relevant clinical setting for capromab imaging is distinguishing local versus systemic extent of disease in

patients with a PSA relapse after radical prostatectomy. Approximately 30 % of patients develop PSA relapse following prostatectomy and are faced with the clinical dilemma of whether to initiate salvage external beam radiotherapy (EBRT) to the pelvis or whether systemic therapy should be initiated. This quandary exists because to date there is no reliable way to determine extent of disease on relapse in prostate disease. In most other cancers, PET/CT and MRI are reliable modalities to make this distinction, and frequently some determination of disease aggressiveness can be made. Currently, the accepted clinical endpoint is the PSA response after EBRT. In a study of 32 men with residual biochemical evidence of disease after radical prostatectomy, Kahn et al. used capromab scans to attempt to identify men most likely to have EBRT-induced PSA response [35]. Subjects were irradiated regardless of capromab scan findings, and the results were obtained by comparing patients whose scans were interpreted as having local or distant metastatic disease. The capromab scan demonstrated 9/32 (28 %) with disseminated disease and 23/32 with local disease. Of the patients with local disease, 61 % had a durable EBRT response while only 22 % with disseminated disease had a similar response. This result was highly suggestive of a role for capromab for extent-of-disease selection, however, the size of the cohorts and questions about how similar the groups of responders and non-responders were continue to plague this study. A similar study by Levesque et al. produced similar results suggesting that capromab is useful in selecting patients for salvage EBRT. Unfortunately, other studies have been contradictory [36]. In Wilkenson's study, 42 patients had rising PSA levels after prostatectomy with 15/42 with limited disease. Unlike the prior studies, only 7/14 (42 %) had a durable PSA response at follow-up. Similarly, in Thomas's 192-patient study with 30 receiving salvage radiotherapy, there was no statistically significant difference between the findings of the capromab scan and the likelihood of responding to salvage radiotherapy.

### $^{111}$In-Capromab SPECT/CT Imaging

The next generation of studies focused on the use of $^{111}$In-capromab SPECT/CT fusion imaging and/or fusion of SPECT images with contemporaneous MRI to enhance lesion detection [37]. Schettino et al. performed 58 capromab scans and compared the readings of the capromab only to the capromab-MR/CT fusion to determine whether greater accuracy is conferred [38]. The study revealed a significant difference in the reads in 47 % of patients (27/58). Interestingly, 46 % were reclassified as negative uncovering a high false positive rate rather than decreasing the known false negative rate. Sodee et al. suggest that with experience in over 600 cases and a detailed case report of five patients, this technique is likely to improve the high false negative rate, but there is scant pathology proven evidence to the contrary. Using the fusion techniques, Ellis et al. have reported a sensitivity of 79 % and specificity of 80 % when the capromab-CT.

## Clinical Trials and Future Prospects

### J591 Imaging

While no formal prostate imaging studies of humanized J591 have been completed, two independent phase I therapy trials have been completed where imaging was performed. [39]. The primary goal of these trials was to define the maximum tolerated dose of the therapeutic nuclides $^{90}$Y and $^{177}$Lu conjugated to J591. In these trials, imaging scans were performed to assess antibody targeting with respect to known sites of metastasis seen on conventional imaging. Compared to the known limitations of capromab scans, J591 demonstrated superior targeting. In fact, in a recent study by Bander et al., all known soft tissues and bone metastatic lesions were identified in the 30 patients enrolled. As the antibody was humanized/deimmunized, this also allowed for serial injections of the tracer over time to both treat and monitor progression over time [39].

In a few selected cases, J591 demonstrated lesions that were not apparent on the bone scan but were identified on MR or were subsequently seen on conventional imaging as the lesion progressed [40].

As all of the described work has utilized SPECT and therapeutic nuclides, the next generation of J591 imaging will require the conjugation of a PET nuclide such as $^{89}$Zr as was done in a murine Model by Holland et al. [41]. Other PSMA antibodies have been conjugated with a PET nuclide as was done in Regino et al., but huJ591 currently is the lead agent as the antibody has extensive safety data in human subjects and has been deimmunized [27].

## Small Molecule Inhibitors

The small molecule inhibitors of PSMA are now being evaluated in phase I human trials. As these are in progress and only minimal safety data is available, it will be a few years before it is known whether these agents will surpass whole antibodies and proceed to FDA approval.

As discussed above, several small molecule inhibitors of PSMA developed by Molecular Insight Pharmaceuticals

(MIP) are now in early stage clinical trials for SPECT imaging of PCa, including the $^{123}$I-MIP-1072, $^{123}$I-MIP-1095, $^{99m}$Tc-MIP-1404, and $^{99m}$Tc-MIP-1405. All four of these compounds bind PSMA with high affinity and are internalized in PCa cells. In vitro biochemical studies of -1072 and -1095 demonstrated that they inhibit NAALADase activity in lysates from PSMA-expressing tumors. Binding studies with intact PSMA-expressing cells demonstrated that both $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095 exhibit saturable and competitive binding. In contrast, no binding was observed in cells that do not express PSMA. Furthermore, a time- and temperature-dependent increase in cell association of MIP-1072 and MIP-1095 indicated internalization via endocytosis.

The ability of $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095 to selectively localize in PSMA-expressing tumors was studied in vivo using mouse xenograft models [31]. The results of these studies demonstrated that both $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095 localized to and were retained in PSMA-expressing tissues in vivo. Uptake in PSMA-expressing tumors and tissues was antagonized in vivo using known antagonists of PSMA, indicating that $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095 behave similarly in vivo. In addition, the rapid uptake and clearance from non-target tissues should permit the detection of PSMA-expressing tumors reliably in prostate cancer patients.

The pharmacokinetics and tissue distribution of $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095 were studied in conscious rats. Radiolabel was detected at varying levels in all tissues examined and decreased steadily over time. In the blood, after reaching $C_{max}$ at the first time point, blood concentrations of both $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095 rapidly declined, with $^{123}$I-MIP-1072 being cleared from the vascular compartment three times faster than $^{123}$I-MIP-1095. As anticipated, due to the mechanism of action of both compounds, uptake and exposure were greatest in the kidney which expresses high levels of PSMA. After reaching $C_{max}$ 2 h postinjection, kidney concentrations of both compounds declined with $^{123}$I-MIP-1072 being five times faster than $^{123}$I-MIP-1095. The clearance of $^{123}$I-MIP-1072 was renal, while the clearance of $^{123}$I-MIP-1095 was mixed renal and hepatobiliary. This is in stark contrast to whole antibody such as Prostascint which does not accumulate in the kidney and has a more traditional antibody-based dosimetric profile.

In vitro metabolism studies showed no substantial biotransformation of MIP-1072 or MIP-1095 occurring in hepatic microsomes of mouse, rat, nonhuman primate, or human origin indicating no monooxygenase-dependent metabolism. $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095 are stable in rat plasma and bind significantly to plasma proteins.

In initial Phase 1 clinical trials in patients with histologically confirmed metastatic prostate cancer, $^{123}$I-MIP-1072 and $^{123}$I-MIP-1095 detected both bone and soft tissue prostate cancer metastases at 1–4 h postinjection. An example of a prostate cancer patient imaged with $^{123}$I-MIP-1072 is shown in Fig. 36.3. Two potential metastatic lesions were detected in this patient; one lesion corresponded to a known lumbar spine metastasis detected by bone scan, the other is a suspected periaortic lymph node metastasis which was not of sufficient size to be detected by CT. Similar images were obtained with $^{123}$I-MIP-1095. A series of high-affinity radiolabeled PSMA inhibitors have been developed that localize specifically to PSMA-avid prostate cancer in preclinical models, two of which were shown to detect both bone and soft tissue metastases in prostate cancer patients. These radiopharmaceuticals, which are currently in clinical trials, may be valuable for patient management including the diagnosis, staging, and potential treatment of prostate cancer [42].

The similar preclinical safety profile, superior physical decay characteristics, and shorter half life of $^{99m}$Tc- and ease of logistics may give $^{99m}$ Tc-labeled PSMA inhibitors practical and clinical advantages over radioiodinated analogs. Initial proof of concept studies in humans of $^{99m}$Tc-MIP-1404 and $^{99m}$Tc-MIP-1405 are being conducted under an exploratory IND. This early phase 1 investigation is designed to evaluate the safety, pharmacokinetics, and biodistribution of $^{99m}$Tc-MIP-1404 and $^{99m}$Tc-MIP-1405 in patients with confirmed metastatic prostate adenocarcinoma and in healthy volunteers (ClinicalTrials.gov Identifier: NCT01261754).

## Conclusion

Imaging is an emerging component of diagnostic and therapeutic management of prostate cancer. While advances in conventional imaging will continue, antibody and small molecule imaging exemplified by PSMA targeting have the greatest potential to improve diagnostic sensitivity and specificity. To date, the most successful targeted prostate cancer imaging has been demonstrated with PSMA, but it is likely that additional candidate biomarkers will be identified.

$^{111}$In-capromab remains the only FDA-approved imaging agent for prostate cancer imaging, but indirect evidence demonstrates clear inferiority to the multiple investigational PSMA-targeted agents. Its inability to image bone lesions, the most common and the earliest site of metastatic spread, is hindrance to clinical metrics and the agents' future development.

Early experience with a mAb to the extracellular domain of PSMA confirms that an antibody to an extracellular epitope will have superior in vivo detection of tumor although the experiment directly comparing these

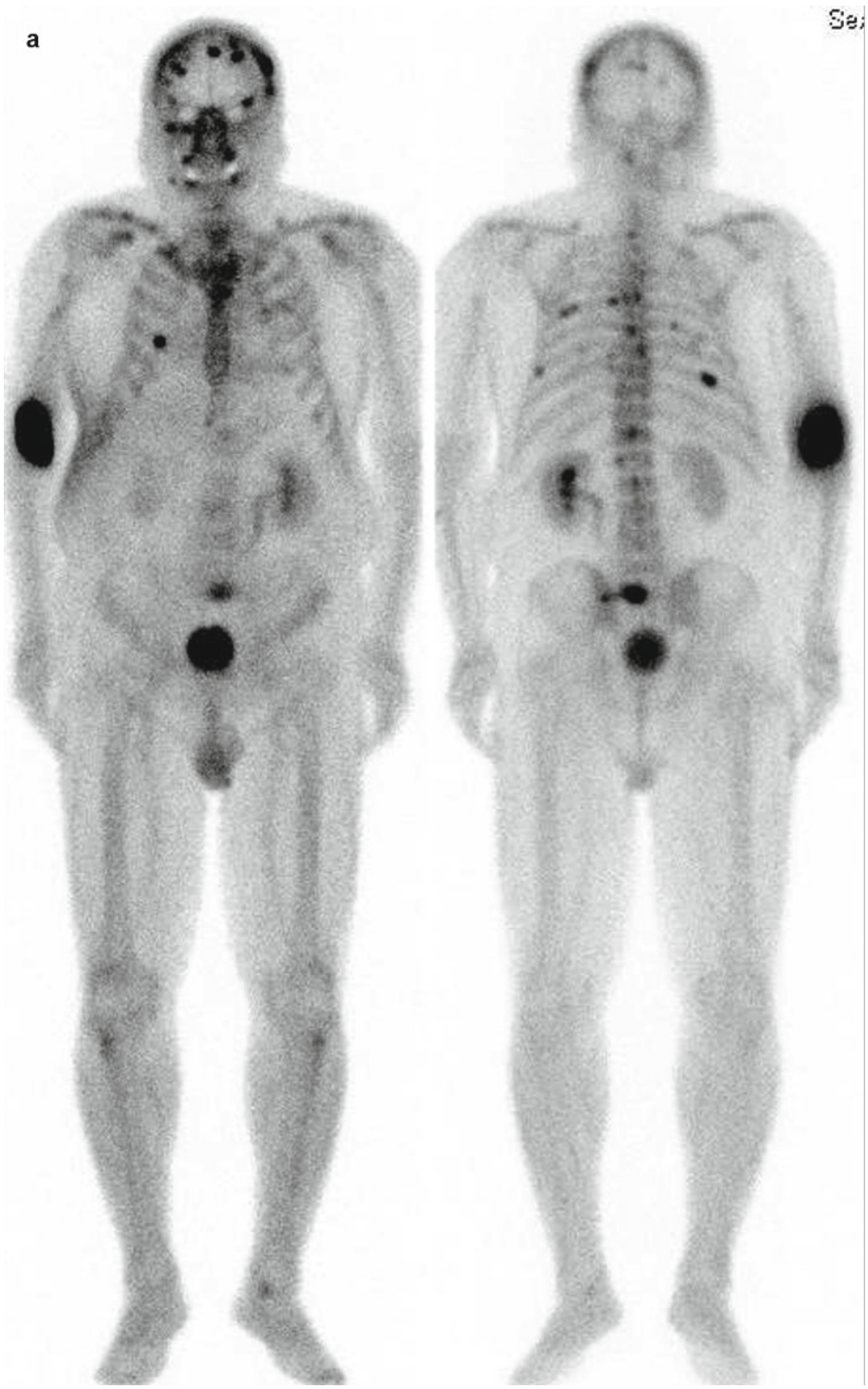
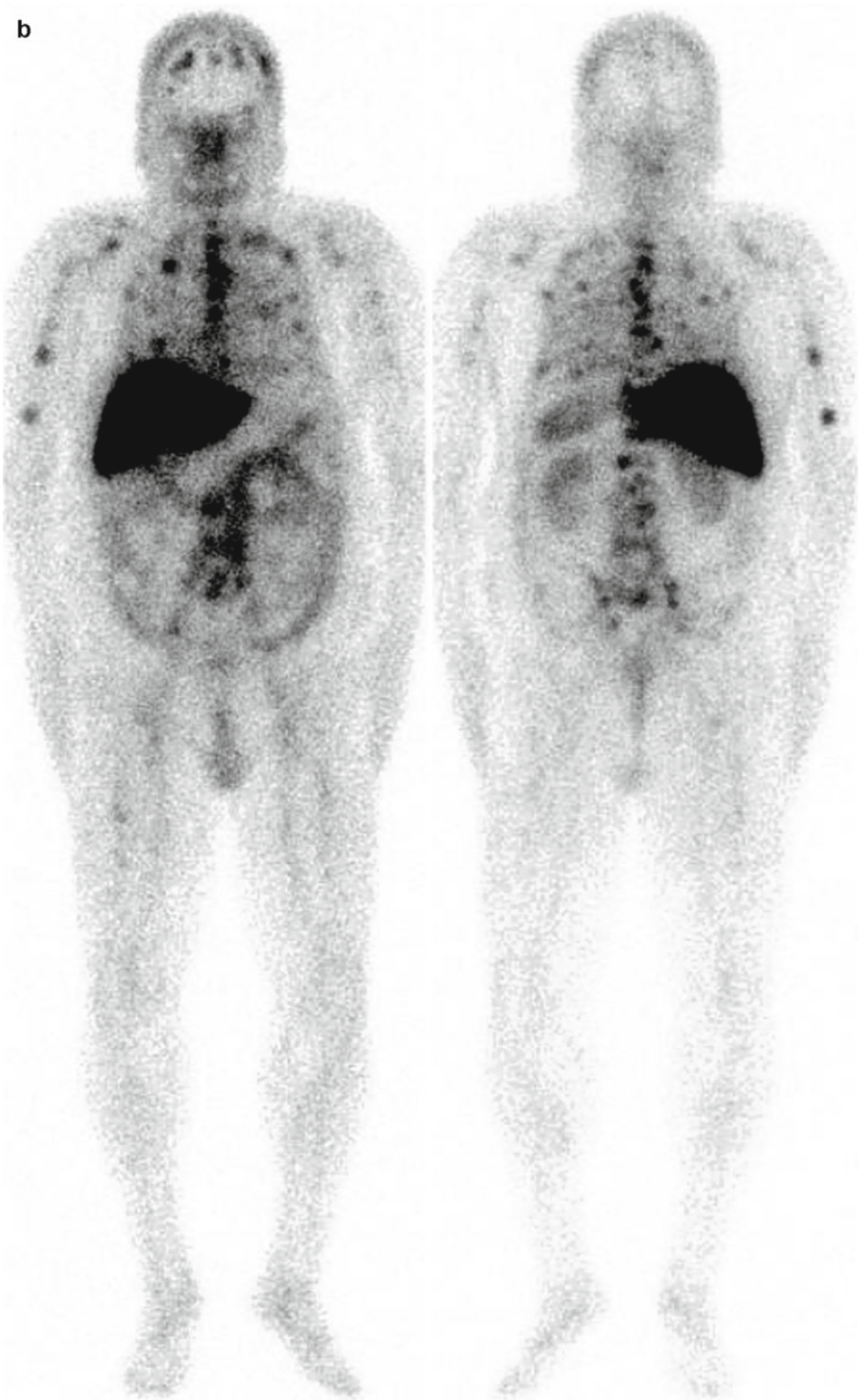



**Fig. 36.3** (**a**) Anterior and Posterior planar 99mTc-MDP Bone Scan demonstrating multifocal osseous metastasis. (**b**) Anterior and Posterior planar $^{177}$Lu-huJ591 demonstrating excellent tumor targeting to sites clearly seen on the bone scan and a few that are not clearly identified on bone scan. Abdomino-pelvic uptake was suspicious for soft tissue metastasis. (**c**) Axial (*top*) and Sagittal reconstruction after treatment dose of $^{177}$Lu-huJ591 SPECT/CT demonstrating localization in retroperitoneal lymph nodes as well as lumbar vertebrae

**Fig. 36.3** (continued)



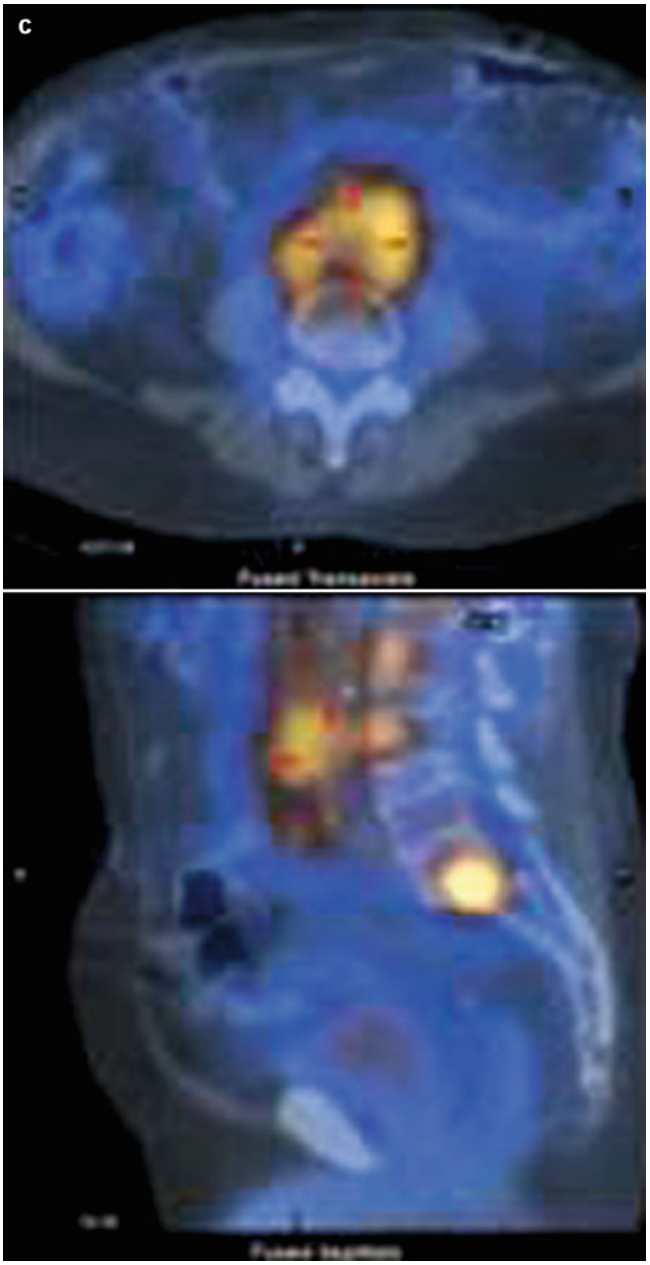



**Fig. 36.3** (continued)

entities has not been performed. Ultimately, a direct comparison of $^{111}$In-capromab and $^{111}$In-huJ591 on the same patients contemporaneously will be required to establish the superiority of the agent. Ideally, the next step will be a direct comparison of $^{111}$In-huJ591 and $^{89}$Zr-J591 to determine whether immunoPET will confer greater lesion detection and ultimately quantitative information about tumor targeting which has been indirect to date.

When whole antibody imaging has been optimized in human subjects, the questions in the future will likely include a comparison between whole antibodies and small molecule agents: Which is more practical for clinical use, which has better imaging characteristics, and which agent is better suited to guide therapeutic options. In a similar timeframe, nonspecific investigational agents may have been FDA-approved or at least deemed worthy of regular use in prostate cancer patients and some of the MRI-based or optical imaging tracers such as quantum dots.

## Update

Imaging is an emerging essential component of diagnostic as well as therapeutic management of PC. While advances in conventional imaging continue, antibodies and small molecule imaging exemplified by targeted PSMA agents have the greatest potential to improve imaging accuracy.

The most successful PC-specific imaging agent is $^{111}$In-capromab, which remains the only relevant FDA-approved imaging agent. Multiple studies now indirectly demonstrate that radiolabeled J591 is a superior imaging agent in PC. All of these studies on J591 have used SPECT and therapeutic nuclides with the promise that the next generation of J591 imaging will require the conjugation of a PET nuclide such as $^{89}$Zr as exhibited in a murine model by Holland et al. [41]. Other PSMA antibodies have also been conjugated with a PET nuclide as was done in Regino et al., but huJ591 currently is the lead agent in development as it is supported by extensive safety data in human subjects and has been deimmunized [27].

$^{89}$Zr-DFO-labeled mAbs show exceptional promise as radiotracers for immunoPET of human cancers as it displays high tumor-to-background tissue contrast in immunoPET and can be used to delineate and quantify PSMA-positive PC in vivo [41].

Urea-based small molecules are also proving to be an efficacious option for imaging of PC. Preclinical studies with PSMA-positive LNCaP cells and xenografts demonstrate that $^{99m}$Tc-MIP-1404 and $^{99m}$Tc-MIP-1405 bind to PSMA with high affinity. In early Phase I human studies, these molecules localize in tumors rapidly and identified a greater number of lesions than bone scans and rapidly detected soft tissue PC lesions including sub-cm lymph nodes (Osborne JR, asco gu 2012) [43]. Given the apparent high sensitivity of these agents, future work is planned in patients with high-risk localized PC to more accurately assess the accuracy of these agents for occult disease.

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# Prostate Specific Membrane Antigen-Based Therapeutics

37

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## Prostate Specific Membrane Antigen

Prostate specific membrane antigen (PSMA) is the single most well-established, highly restricted prostate epithelial cell membrane antigen known [1–6]. The PSMA gene has been cloned, sequenced, and mapped to chromosome 11p [2, 7]. Although first thought to be entirely prostate-specific [1–3], subsequent studies demonstrated that PSMA is also expressed by cells of the small intestine, proximal renal tubules, and salivary glands [5]. However, the level of expression in these non-prostate tissues is 100–1,000-fold less than in prostate tissue [6], and the site of PSMA expression in these normal cells (brush border/luminal location) are not typically exposed to circulating intact antibodies. In contrast to other well known prostate-restricted molecules such as PSA and prostatic acid phosphatase (PAP) that are secretory proteins, PSMA is a type II integral cell-surface membrane protein that is not secreted, thereby making PSMA an ideal target for monoclonal antibody (mAb) therapy. Pathology studies indicate that PSMA is expressed by virtually all prostate cancers [7]. Moreover, PSMA expression increases progressively in higher grade cancers, metastatic disease, and castration-resistant prostate cancer [3, 4, 8, 9].

Prostate specific membrane antigen has been found to have folate hydrolase and neurocarboxypeptidase activity [10]. Although its role in prostate cancer (PC) biology is unknown, the consistent finding of PSMA upregulation correlating with increased aggressiveness of the cancer implies that PSMA has a functional role in PC progression. Inhibition of enzymatic activity in vitro or in xenograft models has not demonstrated significant growth inhibitory effect (Bander NH unpublished data). Nevertheless, the expression pattern of PSMA makes it an excellent target for mAb-based targeted therapy of prostate cancer.

PSMA has been validated as an in vivo target for imaging utilizing radiolabeled mAb 7E11 (CYT-356, capromab) [11, 12]. Capromab pendetide imaging was approved to evaluate extent of disease in high-risk patients presenting with Gleason sums of 7 or more and in patients with rising PSA following prostatectomy. Though improvements have been made with single-photon emission computed tomography (SPECT) and SPECT/CT imaging, because of suboptimal sensitivity and specificity, capromab penditide imaging has not been widely adopted [13, 14]. As the antibody could target some sites of disease, treatment studies were initiated (see chapter 36) [15, 16].

Molecular mapping revealed that 7E11 targets a portion of the PSMA molecule that is within the cell's interior and not exposed on the outer cell surface [5, 17, 18] and cannot bind to viable cells [1, 18]. Recognition of these features by Bander and colleagues at Weill Cornell Medical College led to the development of mAbs to the exposed, extracellular domain of PSMA which in theory would have the potential to significantly improve in vivo targeting likely resulting in

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enhanced imaging and therapeutic benefit [18–20]. These antibodies (J591, J415, J533, and E99) demonstrated high affinity binding to viable PSMA-expressing LNCaP cells in tissue culture and are rapidly internalized [18, 19]. Among these antibodies, J591 is the most highly developed clinically. J591 is a deimmunized IgG monoclonal antibody (mAb) which binds the extracellular domain of PSMA followed by rapid internalization [18, 19, 21].

## Radioimmunotherapy: Background and Rationale for Prostate Cancer

Monoclonal antibodies and peptides can be labeled with radionuclides, usually beta-emitters in clinical practice. Radioimmunotherapy (RIT) is a technique by which a radionuclide is linked to a mAb or peptide and is typically delivered in a systemic fashion. This "targeted" form of radiotherapy allows radiation delivery to tumors while sparing normal organs. Although the initially investigated form of RIT utilized radiolabeled antibodies against carcinoembryonic antigen for solid tumors, the most studied form of radioimmunotherapy to date targets the CD20 antigen ($I^{131}$ tositumomab or $Y^{90}$ ibritumomab tiuxetan) in non-Hodgkin's lymphoma, demonstrating safety and efficacy in phase I–III trials, leading to FDA approval. While mostly used in the relapsed setting, it appears that these therapies may have their greatest impact in the minimal disease setting [22–27]. RIT for solid tumor malignancies has been slower to develop. Reasons for this are multi-faceted, including lack of specific antigens and antibodies optimized for RIT, difficulties in stably linking radionuclides to existing mAbs, shortfalls in existing (and readily available) radionuclides, and difficulty in clinical use (coordination between different specialties) [28]. However, clinical trials utilizing RIT in solid tumor malignancies have been increasing.

Prostate cancer is an ideal solid tumor malignancy for which RIT may be utilized. It is a radiosensitive tumor with typical distribution to sites with high exposure to circulating antibodies (bone marrow and lymph nodes). Although sometimes clinically problematic, early readouts of efficacy can be examined using serum prostate specific antigen (PSA) levels. In preclinical and clinical prostate cancer settings, radionuclides have been linked to antibodies and/or peptides against mucin, ganglioside (L6), Lewis Y ($Le^y$), adenocarcinoma-associated antigens, and prostate specific membrane antigen (PSMA) [15, 16, 29–37]. Of these, prostate specific membrane antigen is the most specific and has been studied most in clinical trials.

The most common radionuclides employed have been $^{90}Y$ and $^{131}I$, with $^{177}Lu$ being used more recently. Based upon the physical properties of each radionuclide, there may be more optimal tumor types and clinical situations for each one [38]. The higher beta energy particles of $^{90}Y$ may be good for bulky tumors, but it may not be necessary or even suboptimal for small tumors and especially bone or bone marrow metastases. The relatively low-energy beta particles of $^{131}I$ are better suited to small volume tumors. However, if conjugated to internalizing antibodies and peptides, in vivo dehalogenation is a significant disadvantage. The low-energy beta and gamma emitter $^{177}Lu$ has been utilized more recently. Its low energy and short range mission are ideal for small volume tumors and cumulative doses are usually higher in comparison to $^{90}Y$ because of much lower radiation dose to bone marrow compared to $^{90}Y$. In addition, due to longer physical half-life (compared to $^{90}Y$), the tumor residence times are higher. As a result, higher activities (more mCi amounts) of $^{177}Lu$ labeled agents can be administered with comparatively less myelosuppression. In addition to the favorable properties for small volume tumors described above, $^{131}I$ and $^{177}Lu$ have gamma emission, enabling imaging to be performed using the treatment dose (as opposed to using $^{111}In$ followed by $^{90}Y$). A representative planar gamma camera image of radiolabeled J591 is displayed in Fig. 37.1.

Radioimmunotherapy can be delivered in a single dose or in multiple fractions. The degree of antitumor response following the administration of radiolabeled mAbs depends on several variables, especially total (cumulative) radiation dose to the tumor, dose rate, and tumor radiosensitivity. As with conventional external beam ionizing radiotherapy, dose fractionation may result in the ability to deliver a higher tumor dose with less toxicity. Fractionated-dose RIT may decrease the dose to bone marrow while increasing the cumulative radiation dose to the tumor at an optimal dose rate [39–41]. Preclinical data have shown that dose fractionation or multiple low-dose treatments can decrease toxicity while increasing the efficacy [42–44]. Early clinical studies have supported the ability to increase the cumulative maximum tolerated dose by dose fractionation [45–47].

It is clear that external beam radiotherapy can be combined with cytotoxic chemotherapy. Though there may be increased toxicity, efficacy of concurrent chemoradiotherapy may be superior to sequential use. This may be especially true when utilizing chemotherapeutic agents with radiosensitizing effects. Combining RIT with cytotoxic chemotherapy has also been investigated [31, 32, 48]. These combinations have the possibility of increasing the therapeutic yield of RIT, particularly in the face of bulky, metastatic solid tumors.

With "targeted" therapy in general, patient selection can be important. While our ability to preselect optimal patients based upon expression of a target may be limited, in some cases, other biomarkers can be quite helpful either in selecting patients more likely to respond or by eliminating patients with a very low chance of response. For example, although epidermal growth factor receptor (EGFR) expression as

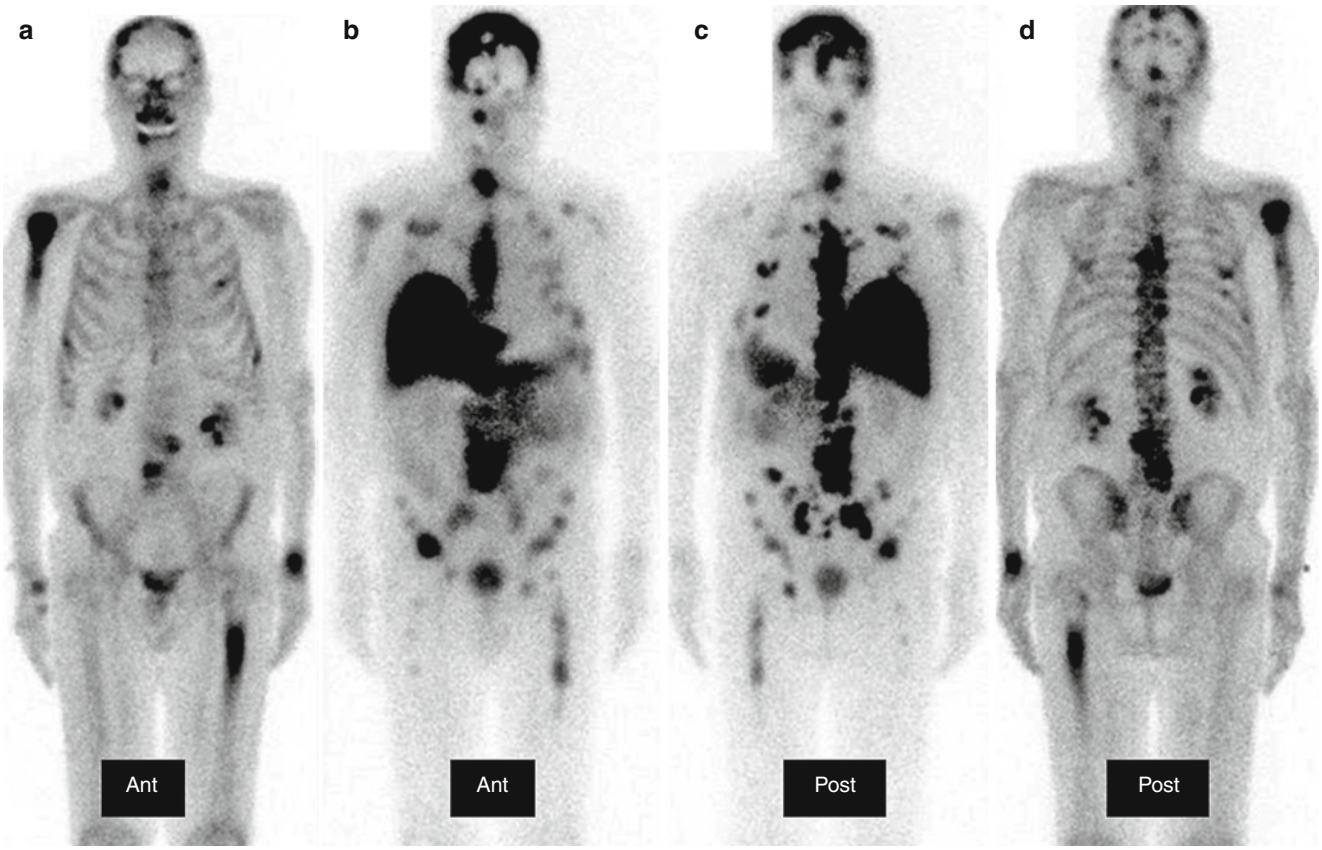


**Fig. 37.1** Radiolabeled J591 imaging. The outer images demonstrate anterior (**a**) and posterior (**d**) images of pretreatment bony metastases on $^{99m}$Tc-MDP bone scan. The central images demonstrate anterior (**b**) and posterior (**c**) total body images obtained via dual head gamma camera of sites of uptake 7 days after $^{177}$Lu-J591 administration (*Note*: antibody is partly cleared via the liver resulting in nonspecific $^{177}$Lu localization)

measured by immunohistochemistry is not helpful in selecting patients for anti-EGFR monoclonal antibody therapy in advanced colorectal carcinoma, excluding those with mutated K-ras has become helpful in clinical practice [49]. In performing studies developing predictive biomarkers, one must remember that prospective validation is important, as development of a "targeted" therapy may be thwarted by a suboptimal biomarker [50].

## Anti-Prostatic Specific Membrane Antigen-Based Radioimmunotherapy

Based upon its apparent clinical ability to target some sites of disease, treatment studies were initiated utilizing radiolabeled capromab (CYT-356). In a phase I dose-escalation study, 12 patients with metastatic castration-resistant prostate cancer (CRPC) received $^{90}$Y-CYT-356 after biodistribution studies with $^{111}$In-CTY-356 [15]. As expected with RIT, myelosuppression was the dose-limiting toxicity. No objective responses (PSA or radiographic) were noted. A subsequent phase II study utilizing $^{90}$Y-CYT-356 was performed in men with biochemically recurrent prostate cancer [16]. The study was stopped early after significant toxicity (myelosuppression) and lack of efficacy (no PSA declines) were seen in the first eight patients.

As it was determined that capromab is not able to bind to viable prostate cancer cells, phase I clinical trials of radiolabeled J591 were performed using Yttrium-90 ($^{90}$Y) or Lutetium-177 ($^{177}$Lu) linked to J591 via a DOTA chelate in patients with metastatic CRPC [35, 36]. Each of these studies was designed to deliver a single dose of radiolabeled J591 intravenously followed by planar gamma camera imaging +/− SPECT (in the case of $^{90}$Y-J591, imaging was performed after $^{111}$In-J591 administration). These trials defined the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) and further refined dosimetry, pharmacokinetics, and HAHA of the radiolabeled mAb conjugates and demonstrated preliminary evidence of antitumor activity. As expected, based upon the physical properties as described above, the MTD of single-dose $^{177}$Lu-J591 was higher (70 mCi/m$^2$) than that of $^{90}$Y-J591 (17.5 mCi/m$^2$) [35, 36].

A phase II study was subsequently performed with $^{177}$Lu-J591, confirming safety, efficacy, and tumor targeting ability [51].

In this dual-center study, men with progressive metastatic CRPC received a single dose of $^{177}$Lu-J591 intravenously followed by gamma camera imaging 1 week later with the primary endpoint of PSA and/or radiographic response. Though the MTD in the phase I study was 70 mCi/m$^2$, [36] based upon discussions with the FDA, an initial cohort of 15 patients was treated with 65 mCi/m$^2$ followed by 17 patients treated with 70 mCi/m$^2$. All patients progressed after 1–4 hormonal therapies, and the majority (56 %) also progressed after at 1–4 lines of chemotherapy including at least docetaxel.

Overall, 3 (9.4 %) experienced ≥50 % decline in PSA, 10 (31.3 %) experienced ≥30 % decline, and 19 (59.4 %) experienced any PSA decline lasting a median of 12 weeks (range 8–47 weeks). PSA declines were associated with longer overall survival ($p=0.01$). Patients receiving 70 mCi/m$^2$ experienced more PSA declines (71 % overall, 45 % with ≥30 % decline) and lived longer (19.8 months). The majority (94 %) demonstrated accurate targeting of known sites of metastatic disease. As demonstrated in the phase I studies, myelosuppression was the most significant toxicity. All experienced reversible hematologic toxicity with grade 4 thrombocytopenia occurring in 47 % (nine received platelet transfusions) without significant hemorrhagic complications. Those receiving 70 mCi/m$^2$ had more grade 4 hematologic toxicity. No serious drug-related non-hematologic toxicity occurred.

Based upon the phase I and phase II data, a single dose of $^{177}$Lu-J591 was well-tolerated with reversible myelosuppression. Accurate tumor targeting and PSA responses were seen with preliminary evidence of dose–response. PSA declines were associated with prolonged survival.

In aggregate, these trials provide support that radiolabeled J591 is well-tolerated with reversible myelosuppression, accurately targets prostate cancer metastatic sites, demonstrates efficacy, and is non-immunogenic. However, as discussed above, there are limitations of RIT for solid tumors, and the physical properties of $^{177}$Lu should be suboptimal in treating the population treated to date (men with progressive metastatic CRPC were treated, many of whom had bulky disease). Additional studies to improve the therapeutic profile were, therefore, activated.

A Department of Defense sponsored study utilizing fractionated-dose $^{177}$Lu-J591 has recently been completed with initial results presented [52]. Men with progressive metastatic CRPC received 2 fractionated doses 2 weeks apart. Doses were escalated in cohorts of 3–6 subjects, with cohort 1 receiving 20 mCi/m$^2$ × 2 and each successive cohort undergoing dose escalation by 5 mCi/m$^2$ per dose (10 mCi/m$^2$ cumulative dose increases per cohort). The primary endpoint was to determine DLT and the cumulative MTD of fractionated $^{177}$Lu-J591 RIT with pharmacokinetics and dosimetry and secondary endpoints of efficacy. Dose-limiting toxicity was defined as severe thrombocytopenia (platelet count <15 or need for >3 platelet transfusions in 30 days), grade 4 neutropenia >7 days, febrile neutropenia, or grade >2 non-hematologic toxicity. Twenty-eight subjects received treatment with cumulative doses of up to 90 mCi/m$^2$ (highest planned dose). The median age was 72 years with median baseline PSA 49 ng/mL; the majority had Eastern Cooperative Oncology Group (ECOG) performance status 1 and had bone metastases. The study confirmed the hypothesis that fractionated dose would allow higher cumulative doses of $^{177}$Lu-J591 to be administered with less toxicity with evidence of antitumor activity.

Following progression on primary hormonal therapy, chemotherapy can offer symptomatic improvement as well as incremental survival benefit [53, 54]. However, responses are transient and all men eventually suffer from progression of disease. As described above, single-agent anti-PSMA-based RIT has demonstrated efficacy in the treatment of metastatic CRPC, but the results are limited, and all men treated to date with mature follow-up have suffered from progression of disease. The combination of taxane chemotherapy with radiotherapy has been used in several diseases because of the radiosensitizing effects of taxane-based chemotherapy [55–57]. The combination of taxane chemotherapy with radioimmunotherapy has also been studied in preclinical and early clinical studies [31, 32, 48]. In addition to favorable results from fractionated radioimmunotherapy and the radiosensitizing effects of taxane-based chemotherapy, it is hypothesized that the additional debulking by chemotherapy will overcome some of the limits imposed by the physical characteristics of $^{177}$Lu. Based upon this data, a phase I trial of docetaxel and prednisone with escalating doses of fractionated $^{177}$Lu-J591 is ongoing [58].

As discussed above, the most studied form of RIT to date targets the CD20 antigen ($^{131}$Itositumomab and $^{90}$Y ibritumomab tiuxetan) in non-Hodgkin's lymphoma. While approved in the relapsed setting, it appears that these therapies have their greatest impact in the minimal disease setting [22–27]. The vast majority of relapses after local therapy for prostate cancer are initially "biochemical" only, that is, with a rising PSA despite no evidence of cancer on imaging, affecting approximately 50,000 men per year in the United States alone [59, 60]. Although there is no proven overall survival benefit in a prospective randomized trial, radiotherapy as a salvage regimen can lead to long-term survival in selected individuals [61–64]. Unfortunately, most subsequently suffer systemic progression because of subclinical micrometastatic disease outside of the radiation field.

Based on the demonstrated ability of J591-based therapy to successfully target known sites of disease and apparent clinical efficacy in the advanced setting, it is now under investigation in the salvage setting [clinicaltrials.gov NCT00859781]. "Targeted radiotherapy" in the form of

radioimmunotherapy is an attractive option with the possibility being a higher yield therapy in the minimal disease (biochemical only) setting. The primary objective of this trial is to prevent or delay radiographically evident metastatic disease. Radiolabeled J591 imaging will also be explored as a possible way to detect sites of disease in these patients with biochemical relapse and no evidence of disease on standard scans ($^{99m}$Tc-MDP bone scans and computed tomography or magnetic resonance imaging) [65].

## Anti-Prostate Specific Membrane Antigen Antibody-Drug Conjugates

Rather than linking a radionuclide to a monoclonal antibody, a drug or toxin can also be linked, forming an antibody-drug conjugate (ADC) [66]. In this form of therapy, drugs may be delivered to target cells, sparing normal cells from toxicity. Many advances have been made in ADC technology. Gemtuzumab ozogamicin is an anti-CD33 monoclonal antibody conjugated to calicheamicin which was approved by the US FDA for relapsed acute myeloid leukemia in older patients in 2000, though has recently been withdrawn from the market. Many others are in late stage development, including trastuzumab-DM1 (anti-Her2 for breast cancer), inotuzumab ozogamicin (anti-CD22 for non-Hodgkin's lymphoma), and brentuximab vedotin (anti-CD30 for Hodgkin's lymphoma).

MLN2704 is an antibody-chemotherapy conjugate designed to target PSMA. J591 is conjugated to maytansinoid 1 (DM1), which is a potent microtubule-depolymerizing compound. Preclinical activity was demonstrated [67], leading to a phase I trial designed to explore single ascending doses of the conjugate to define DLT, MTD, and PK [68]. Twenty three subjects with progressive castrate metastatic prostate cancer received MLN2704 at doses ranging from 18 to 343 mg/m$^2$ in an accelerated dose-escalation scheme; 18 received at least 3 doses. Grade > 3 toxicities occurred in two subjects, including one episode of uncomplicated febrile neutropenia and transient grade 3 elevation of transaminases. One subject (treated at 343 mg/m$^2$) achieved a >50 % decline in PSA, and another (treated at 264–343 mg/m$^2$) experienced a PR by RECIST along with a >50 % decline in PSA.

A subsequent multicenter phase I/II study was initiated based upon the above results [69]. Sixty-two subjects received multiple doses of MLN2704. Because of neurotoxicity at every 1- or 2-week doses, the study was amended to include every 3-week dosing and dosing on days 1 and 15 of 42-day cycles. Of the four schedules tested, PSA declines were most frequent at 330 mg/m$^2$ every 2 weeks (2/6 had PSA decrease >50 %, 2/6 had PSA stabilization). However, grade 2–3 neuropathy was dose-limiting and could not be predicted by prior taxane-based chemotherapy, diabetes, or prior neuropathy. Although response was modest and treatment was limited by toxicity, this trial demonstrated proof of principle that an immunoconjugate utilizing a PSMA antibody and work is in progress utilizing new linkers to J591 designed to improve selective targeting.

Based upon PSMA's selective expression in prostate cancer and the principle above, others have also begun clinical work on PSMA targeting with toxin-conjugates. Another mAb recognizing the external domain of PSMA has been conjugated to monomethylauristatin E (MMAE) with demonstrated preclinical activity [70]. This work has led to a phase I dose-escalation study which has been tolerated at the initial dose levels [71]. Additional early stage clinical work has involved utilizing enzymatic activation to release cytotoxic substances in PSMA positive cells [72].

## Anti-Prostate Specific Membrane Antigen Immunotherapy

Immunotherapy has been utilized in oncology over many decades, but it has been only relatively recently that an autologous cellular immunotherapy agent (sipuleucel-T) has been approved for clinical use [73]. Many of the attempts to utilized immunotherapy in prostate cancer have focused on PSA [74, 75]. However, as discussed above, based upon its restricted sites of expression, PSMA is clearly an attractive target. Therefore, multiple vaccine approaches have been utilized in preclinical models and have moved to early stage clinical trials [75–80].

In addition to the de-immunization process in the transition from murine to human antibody, mAb J591 was engineered to interact with human immune effector cells and trigger antibody-dependent cell-mediated cytotoxicity (ADCC). In some of the initial studies with "cold" or "naked" J591 (unconjugated J591 with or without small doses of trace-labeled $^{111}$In-J591 for imaging purposes), stabilization of previously rising PSA occurred [81, 82]. In a dose-escalation study in patients with progressive CRPC, evidence of a dose–response relationship between mAb mass delivered and induction of ADCC was observed [83]. One patient who received 100 mg of J591 had a >50 % reduction in PSA.

Interleukin 2 (IL-2) promotes the proliferation and enhances the secretory capacity of all major types of lymphocytes, including T, B, and NK cells [84]. In addition, through its effects on NK cells, IL-2 stimulates antigen-nonspecific host reactions that involve an interplay between NK cells and monocytes. Based on these functions, IL-2 may be useful as an immune stimulant, particularly in the setting of cancer immunotherapy [85]. Within 2 weeks of low-dose IL-2 treatment, selective expansion of human CD3$^-$, CD56$^+$, and NK cells is seen with a plateau after 4–6 weeks of therapy [86, 87]. Based upon the hypothesis that J591 plus IL-2

would work together to affect a positive immune response against prostate cancer, a combination study was initiated [88]. Seventeen patients with recurrent prostate cancer received continuous low-dose subcutaneous IL-2 ($1.2 \times 10^6$ IU/m$^2$/day) daily for 8 weeks with weekly intravenous infusions of J591 (25 mg/m$^2$) on weeks 4–6. Therapy was well-tolerated with a trend for those with significant NK cell expansion to be non-progressors.

In summary, PSMA is the most highly restricted prostate cancer cell-surface protein known. Prostate cancer represents an ideal disease for monoclonal antibody-directed therapy, with PSMA as an optimal target. Current strategies to improve upon past successes in utilizing anti-PSMA mAbs to deliver toxic payloads to prostate cancer cells, minimizing damage to normal organs, include developments with anti-PSMA radioimmunotherapy and antibody-drug conjugates. Additional work in early stages of development includes anti-PSMA vaccines and utilizing PSMA-targeted therapy with or without other immune modulators to stimulate anti-PSMA antibody-dependent cell-mediated cytotoxicity.

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# Presentation and Symptomatology of Prostate Cancer

38

Agnieszka Michael and Hardev Pandha

Prostate cancer can present at any stage of the disease and very frequently does not cause any symptoms at all. Most cancers arise in the periphery of the prostate gland and cause symptoms only when they have grown to compress the urethra or invade the sphincter [1]. In recent years, more and more of prostate cancer patients from the western hemisphere are diagnosed at an earlier stage due to rising prevalence of prostate-specific antigen (PSA) testing [2]. A study by Cooperberg et al. analyzed trends in clinical presentation in 2,078 men diagnosed between 1989 and 2001. The proportion of patients with low-risk tumor characteristics rose from 29.8 % in 1989–1992 to 45.3 % in 1999–2001 [3]. Studies based on the Department of Defense Center for Prostate Disease (CPDR) found downward migration at higher stage [3]. The percentage of patients presenting with locally advanced (T3 to T4) disease fell from 19.2 % in 1988 to 4.4 % in 1998; rates of metastatic disease at diagnosis likewise declined from 14.1 % in 1988 to 3.3 % in 1998.

There is some evidence that presentation of prostate cancer at a more advanced stage may be related to literacy and race [4]. Bennett et al. analyzed 212 low-income men who received care in an American center and concluded that low literacy may be an overlooked but significant barrier to the diagnosis of early-stage prostate cancer among low-income white and black men. Many studies conducted in America show that African-American patients are more likely to present with advanced prostate cancer than the white population [5]. A study by Hoffman et al. analyzed 3,173 men diagnosed with prostate cancer between 1994 and 1995. The results showed that clinically advanced-stage prostate cancers were detected more frequently in African-American (12.3 %) and Hispanics (10.5 %) than in non-Hispanic whites (6.3 %). A similar study analyzing men with prostate cancer in Jamaica [6] also found that presentation of prostate cancer at a more advanced stage is more common than in their white counterparts. In the study of 1,121 cases diagnosed between 1989 and 1994, 30 % of patients presented with acute urinary retention, 16 % presented with bone metastases, and 15 % had gross hematuria at the time of diagnosis. This type of presentation in the Western world is nowadays infrequent.

1. Common Symptoms Related to Urinary Tract Obstruction (LUTS)

   The symptoms of prostate cancer will commonly be related to the stage of cancer at presentation with T1 tumors that are clinically silent, T2 tumors only palpable rectally, and T3 and T4 tumors likely to cause symptoms due to invasion of surrounding or distant structures (see chapter regarding staging).

   When prostate cancer is large enough to compress the urethra or if it arises in a condition leading to the enlargement of the prostate, patients will present with symptoms related to urine flow obstruction. These symptoms are generally described as lower urinary tract symptoms (LUTS). Although many of the LUTS have recently been standardized [7], they are defined from the individual's perspective and cannot be used as a diagnostic tool. Many benign conditions that cause enlargement of the prostate and in particular benign prostate hyperplasia (BPH) will present with LUTS, and only a small proportion of those patients will have prostate cancer. One in four men over the age of 40 will suffer from BPH whereas the lifetime risk of a prostate cancer diagnosis is one in ten men (half of them will be over 70 years of age) [8].

   LUTS are divided into three groups that are related to storage of urine, voiding, and post-micturition symptoms [7] (see Table 38.1).

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**Table 38.1** Lower urinary tract obstruction symptoms (LUTS)

| Storage of urine | Voiding | Post-micturition |
|---|---|---|
| Daytime frequency | Slow or intermittent stream of urine | Feeling of incomplete emptying |
| Nocturia | Hesitancy | Post-micturition dribble |
| Urgency | Straining | |
| | Dribble | |

(a) LUTS symptoms related to storage of urine
Storage symptoms are experienced during the storage phase of the bladder and include daytime frequency of urine and nocturia. Daytime frequency is described from patient's perspective as a need to void too often during the day; nocturia, on the other hand, means having to wake up at night one or more times to void. Another symptom related to the storage phase of the bladder is urgency, a feeling of having a sudden compelling desire to pass urine, which cannot be deferred.

(b) LUTS symptoms related to difficulties with voiding
Voiding symptoms are experienced during the voiding phase and include slow or intermittent stream of urine (urine flow which stops and starts during micturition), hesitancy, straining, or dribble. Hesitancy is described as difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine.

(c) LUTS symptoms occurring post micturition
Post-micturition symptoms are experienced immediately after voiding and include a feeling of incomplete emptying and post-micturition dribble, which is described as an involuntary loss of urine immediately after an individual has finished passing urine, usually after they leave the toilet. Symptoms such as pain or bleeding from the urethra are rare.

A number of studies have tried to determine whether there is a difference in presentation of prostate cancer and benign conditions such as BPH [9–11] but no clear pattern has been distinguished.

Two Swedish studies looked into the presenting symptoms as reported by patients in self-administered questionnaires [10–12]. The most commonly reported LUTS in both prostate cancer and controls without cancer were hesitancy (22–38 %), leakage of urine (14–30 %), urgency (14–35 %), dysuria (3–12 %), weak stream (43–49 %), and frequency. Although symptoms such as hesitancy, urgency, leakage, and frequency were more prevalent in prostate cancer patients than controls, none of the reported symptoms was characteristic for malignant disease. A systematic review of studies looking into the prevalence of prostate cancer in men with LUTS concluded that there is no data to suggest that men with uncomplicated LUTS have an increased risk of prostate cancer [9].

2. Prostate Cancer Presenting with Sexual Dysfunction
Some patients will present with signs of sexual dysfunction. Cancer and its treatments impact sexuality and intimacy, regardless of age, race, sexual orientation, gender, or socioeconomic background [13]. The causes of sexual dysfunction are often both physical, due to treatment and progression of disease, and psychological [14]. In prostate cancer patients, these issues become particularly difficult following treatment; however, in some cases (in particular when patients present with advanced disease) patients may present with sexual dysfunction due to LUTS, general tiredness, and pelvic pain. Very occasionally, the presenting symptoms may be hematospermia; this is, however, a rare occurrence. In a prostate cancer screening population of 26,126 men, only 139 men (0.5 %) presented with hematospermia, while prostate cancer was diagnosed in 1,708 men (6.5 %) [15].

3. Presentation of Advanced Prostate Cancer
Advanced prostate cancer can present with symptoms of metastatic disease before any of the LUTS appear. These symptoms can include tiredness, loss of weight and appetite, or bone pain, often related to the metastatic spread of prostate cancer to the bones (see Fig. 38.1). Patients may complain of pain in the back, hips, and pelvis; however, these symptoms are frequently caused by common medical conditions such as arthritis, and a diagnosis of prostate cancer may only be reached following more through investigations such as X-rays or bone scan.
Spinal cord compression has been recorded as a presenting symptom of prostate cancer, but it is a lot more common in patients with known metastatic malignancy. In a large series of 478 prostate cancer patients treated for spinal cord compression, only 1 % of patients (5) had no previous diagnosis of cancer [16]. Patients can present with neurological symptoms, back pain, or symptoms of bladder dysfunction such as urinary retention. The commonest presenting symptom of spinal cord compression is back pain [17, 18]. Majority of urinary retention symptoms in Rosenthal series were acute in presentation with a median duration of 2-week neurological symptoms of spinal cord compression.

Some patients can present with pelvic pain and perineal pain. This may be somatic or neuropathic in nature [19]. Somatic pain arises from stimulation of nociceptors in the periphery where they reside in the integument and supporting structures, striated muscles, joints, periosteum and bones, and nerve trunks, which can be invaded by malignant growth by direct extension, through fascial planes, and through its lymphatic blood supply [19]. Malignant infiltration of the perineal nerves results in lumbosacral plexopathies and leads to pain or the feeling of numbness, burning, crawling sensation, or tightness.

With the changing pattern of prostate cancer presentation and widespread PSA testing, most patients present at an early stage when the symptoms are mild. On the other hand, the luck of symptoms in early disease will often mean that very early tumors such as T1 and T2 commonly

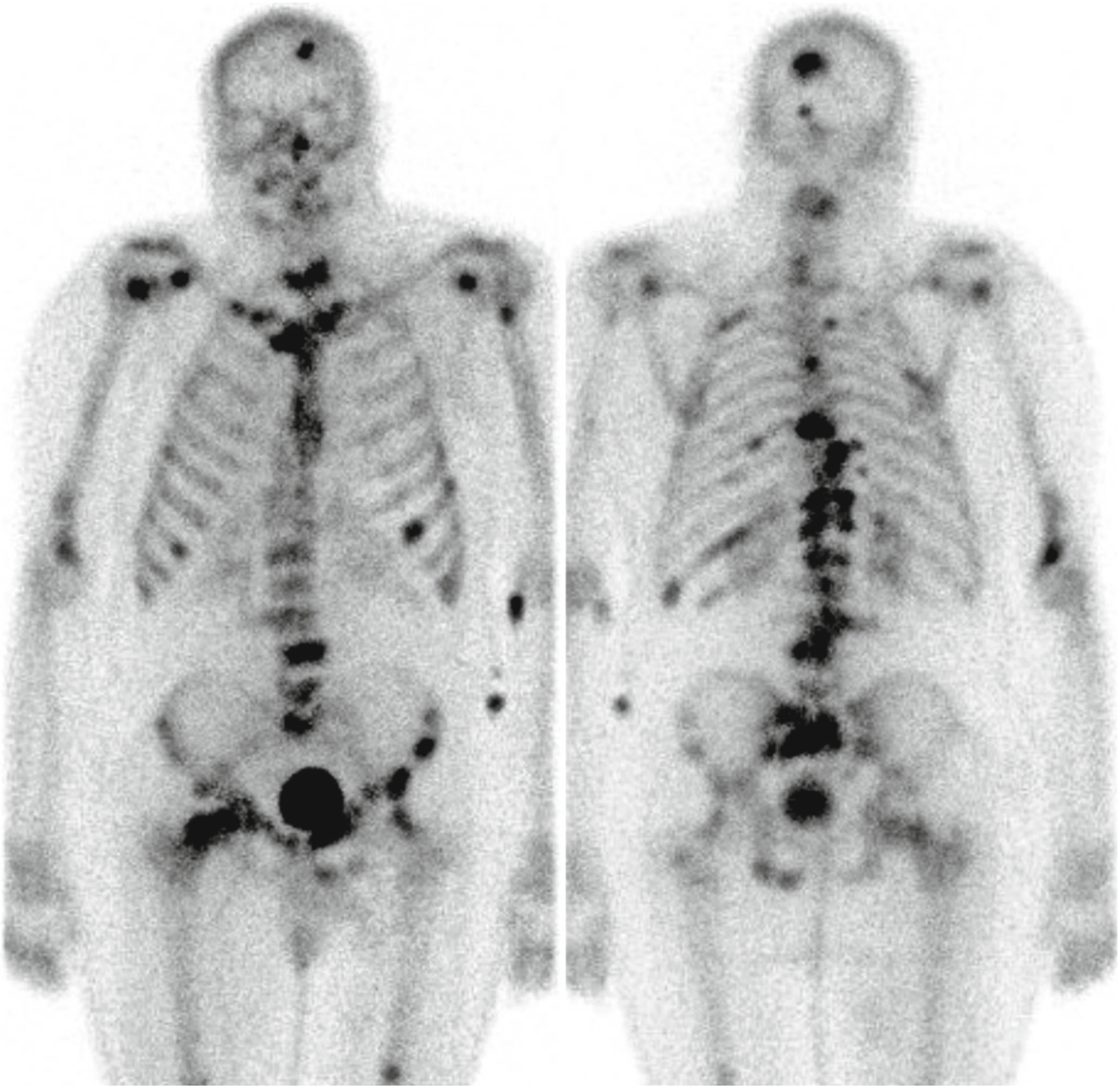
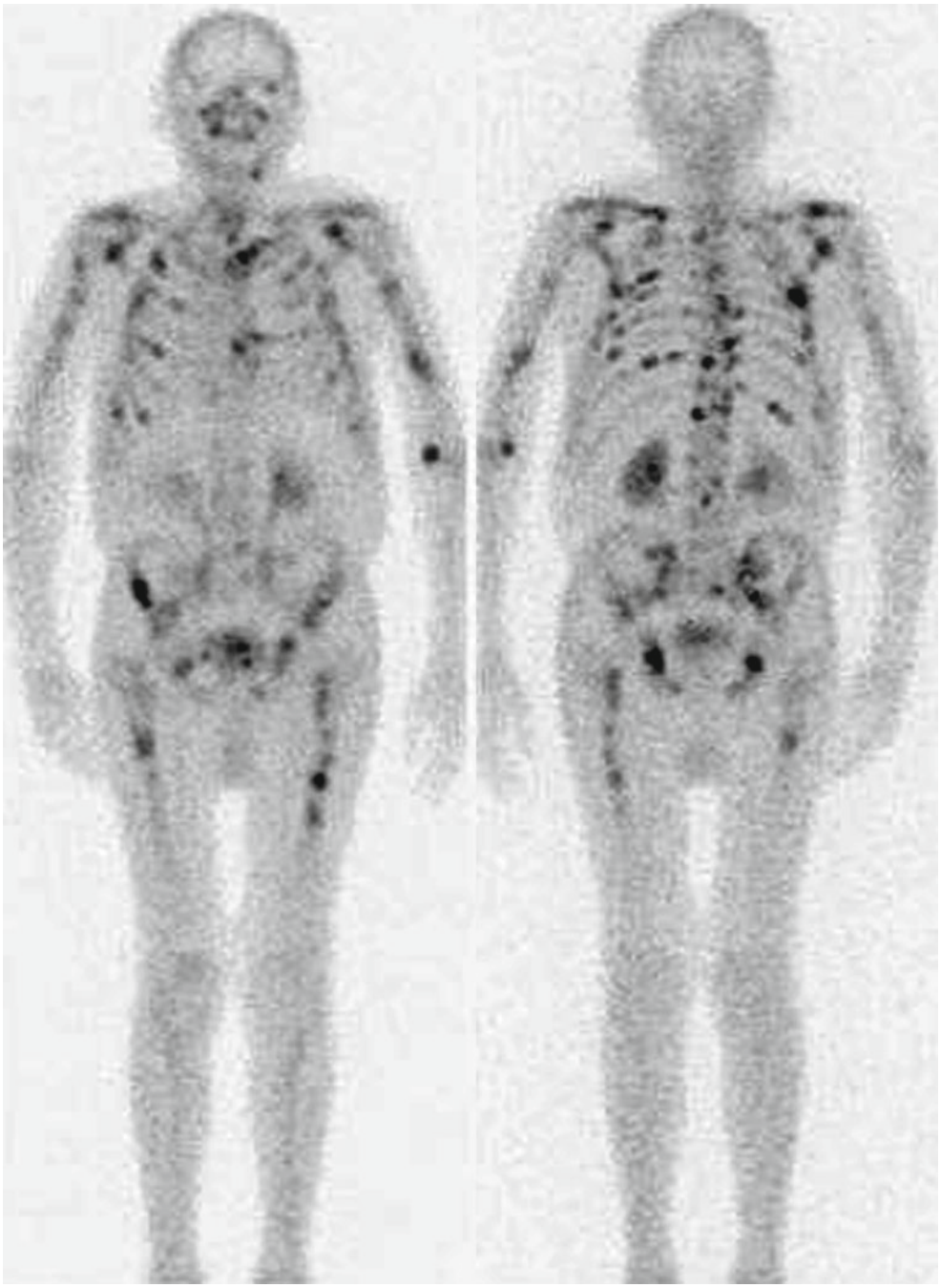


**Fig. 38.1** Multiple bone metastases from prostate cancer leading to bone pain (isotope bone scan)

**Fig. 38.1** (continued)



remain undetected. LUTS are most common in benign conditions; however, presence of LUTS may alert physicians to undertake further investigations.

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# The Role of Ultrasonography

# 39

Suzanne van den Heuvel, Paul C.M.S. Verhagen,
and Chris H. Bangma

## Introduction

Prostate cancer is the most common malignancy in the Western world, affecting approximately one in every six men. It is the second leading cause of cancer-related deaths in American men [1]. The main diagnostic tools used to look for evidence of prostate cancer include digital rectal examination (DRE), serum concentration of prostate-specific antigen (PSA), and transrectal ultrasonography (TRUS)-guided biopsy [2].

In this chapter, we review the clinical role for TRUS and recent ultrasonography developments in the detection and diagnosis of prostate disease.

## History

TRUS was initially used as a technique to evaluate rectal abnormalities, but in 1963, Takahashi et al. were the first to use this technique for evaluation of the prostate [3]. However, medical ultrasound was rather in an early phase at this time, so images created with this technique were of poor quality and they carried little medical utility [4]. The first clinically meaningful images of the prostate obtained with TRUS were described in 1974 by Watanabe et al. [5]. They used a 3.5-MHz transducer, which was at that time considered to be state of the art, to detect abnormalities of the prostate and measure prostate size. As ultrasound technology has become more refined, the use of TRUS increased.

## Conventional Gray-Scale Transrectal Ultrasonography

TRUS has revolutionized our ability to examine the prostate. Today, it is the most commonly used modality to detect prostate pathology and to assess prostate volume [6]. Furthermore, TRUS has become a mainstay for imaging-guided prostate interventions, including prostate needle biopsies, brachytherapy, cryotherapy, and high-intensity focused ultrasound (HIFU) [7].

TRUS provides an excellent visualization of the prostate. Advantages of TRUS include the ability to direct the biopsy needle precisely into regions of interest or to provide a uniform spatial separation of biopsy cores [8]. For these reasons, most prostate biopsies are taken under TRUS guidance. The greatest challenge for TRUS, however, remains the early and valid detection of prostate cancer [9, 10]. TRUS is highly operator dependent and thus is unsuitable as a screening test. Even in experienced hands sensitivity and specificity to detect prostate cancer is only has high as 50 % [11].

The low reliability of TRUS to identify early, small volume prostate cancer has led to the recommendation to perform random systematic biopsy of the prostate. Systematic sextant biopsy introduced by Hodge and coworkers in 1989 used to be the gold-standard technique [12]. It involved three cores from each lobe in a parasagittal plane at the base, midgland, and apex of the prostate. However, sextant biopsy misses 10–30 % of biopsy-detectable cancers [13–15]. Therefore, different and various biopsy strategies have been devised to increase the diagnostic yield of prostate biopsy including more lateral placement of the biopsies, anterior biopsies, and obtaining an increased number of cores (up to 45) [16, 17].

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At this moment, both the European Association of Urology (EAU) and the American Urological Association (AUA) guidelines recommend to sample at least eight laterally directed cores at a glandular volume of 30–40 cc. More than 12 cores are not significantly more conclusive [17–19]. Additional biopsies of suspect areas on TRUS may be useful [20–22].

### Transabdominal/Transperineal

Although the transrectal route is the current standard for ultrasound imaging of the prostate, other techniques like a transabdominal and transperineal approach are available. Due to a larger distance between the probe and prostate and therefore low resolution, the techniques provide images inferior to TRUS. Still, it can be used as a rapid, simple, and noninvasive method to measure prostate volume, especially in patients with anal diseases such as hemorrhoids, anal fistula, or a history of abdominoperineal resection [23–26].

## Imaging Techniques

### Patient Preparation

Patients are typically scanned in the left lateral position, with the hips and knees being flexed 90°. The examining physician sits on a mobile stool; one hand used to manipulate the ultrasound probe and the other to make scanner adjustments. The patient may also be placed in the knee-chest, prone jackknife, or dorsal lithotomy position. These positions give better appreciation of asymmetry as compared with the left lateral decubitus position.

### Probes

Currently, the most widely used probe is a high-frequency transducer (6–12 MHz), which can produce images of the prostate with high resolution. Commercially available endorectal probes come in side-fire and end-fire models (Figs. 39.1 and 39.2). An end-fire probe is particularly suitable for apical biopsies because the biopsy guide for end-fire imaging is placed immediately behind the imaging array. This ensures the shortest possible biopsy path to the apex [27]. Some of the currently available biplane probes provide simultaneous sagittal and transverse imaging modes, which is valuable for targeting biopsies more precisely.

### The Principles of Ultrasound Scanning

A frequency of 2 MHz means that the ultrasound wave generates 2,000,000 cycles/s. The lower the frequency of ultrasound, the greater the ability to penetrate deeper into the tissue, but because the wavelength becomes longer with decreasing frequency, the resolution will be lower. Conversely, increasing the frequency yields increased resolution, but the proportion of the image that is in focus is closer to the probe. Due to this relationship between resolution and penetration, the general rule for ultrasound scanning is that the frequency used should always be as high as possible, taking into account how deep in the tissue the target organ is situated. For very superficial organs, like penis and testis, frequencies above 10 MHz are used. For organs like kidneys, more penetration is needed; therefore, lower frequencies (3.5–5 MHz) are recommended. For transrectal prostate scanning, frequencies between 6 and 12 MHz must normally be used [28].

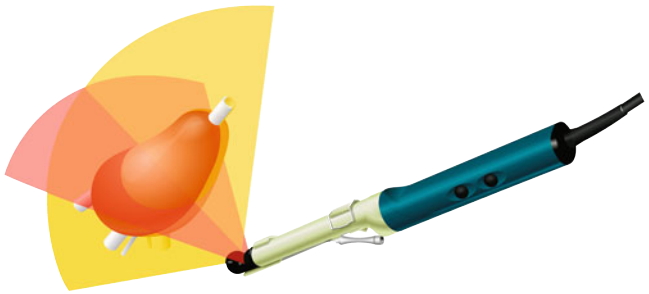

**Fig. 39.1** Illustration of biplane imaging with simultaneous transverse and sagittal plane (Provided by Dr. S. Torp-Pedersen, Dept. of Radiology, Frederiksberg Hospital, Denmark)

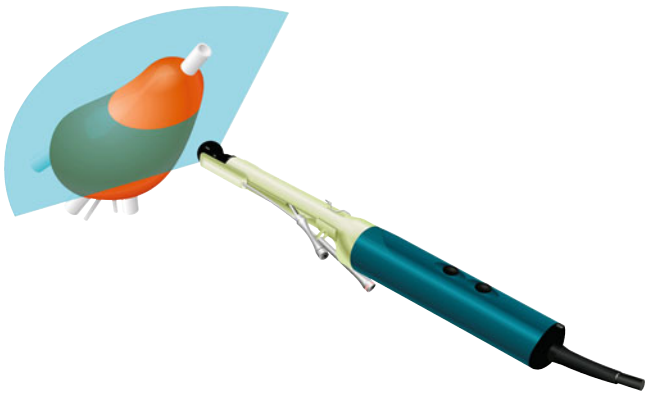

**Fig. 39.2** Illustration of the scan plane when the transducer is used in end-fire mode (Provided by Dr. S. Torp-Pedersen, Dept. of Radiology, Frederiksberg Hospital, Denmark)

Ultrasound is reflected when it passes through different tissues. How much is reflected depends on the change in impedance between two kinds of tissue. If most of the ultrasound wave is reflected by a structure, the echo on the image will be very bright (hyperechogenic) in this part of the ultrasound image (such as bony structures and calcifications). Liquid collections like cysts and the gallbladder will appear black [29].

### A-Mode and B-Mode Scanning

A-mode scanning (amplitude-mode scanning) is the simplest type of ultrasound. A single transducer scans a line through

the body with the amplitudes of the echo plotted on screen as a function of depth.

In B-mode scanning (brightness-mode scanning), a linear array of transducers simultaneously scans a plane through the body, and the amplitudes are converted into different gray levels. The gray levels in the different parts of the tissue being scanned are displayed with varying gray-scale levels on a map with depth of the tissue on the *y*-axis and the position along the transducer surface as the *x*-axis. B-mode scanning normally uses a gray-scale resolution of 256 levels.

### Attenuation

An important concept of ultrasound physics is attenuation. As ultrasound travels through a media, it loses energy to the surrounding tissues. This loss of energy is mostly in the form of heat. Loss of signal intensity results in degraded image quality of deeper structures. The higher the frequency of the ultrasound system, the more attenuation will occur.

With the gain function, it is possible to compensate for attenuation. The intensity of the returning signals can be amplified by the receiver upon arrival so that the displayed image is brighter and more visible on the screen. Gain can be adjusted for the entire field (overall gain) or for the near field to far field with time gain compensation (TGC) function. Without TGC, the image will be darker and darker as the distance from the transducer increases. Excessive increase in gain will add "noise" to the image [29, 30].

### Focus

Beam focus and image quality is best at the focal zone. Most ultrasound machines allow the operator to focus the ultrasound beam on the area of interest. This focused area represents the narrowest part of the three-dimensional ultrasound beam, and these narrow beams produce the best images.

## Artifacts in Ultrasound

### Shadowing

Shadowing happens due to decrease of echogenicity from tissues behind a zone with strong reflectivity or attenuation. This artifact occurs behind strongly reflecting structures like calcifications.

### Enhancement

Enhancement is increased echogenicity from tissues behind areas with low attenuation. This type of artifact is normally seen behind cystic or other liquid collections, such as bladder, lymphocele, and ascites. Enhancement could help to identify a structure as a true cyst. The increased echogenicity could be misinterpreted for a calcification; however, a true calcification will cause a shadow.

### Reverberations

When two or more strong reflectors are present, multiple reflections between these reflectors and the transducer surface may occur. The reverberations are caused by internal re-reflections in the tissue or between the transducer and a reflector in the tissue [31].

### Refractions

If the ultrasound beam does not hit an interface at perpendicular angle, the direction of the beam will be altered. The equipment assumes straight line propagation when it calculates the image, so a reflector may not be displayed in the correct position. These artifacts can often be avoided by trying to scan at a perpendicular angle.

Refraction is frequently seen during TRUS of the prostate. Ultrasonic beams hitting the prostate near the neurovascular bundles will hit the prostatic border in a tangential manner. Therefore, a significant part of the beam will be reflected in other directions than the direction of the original ultrasound beam. As a result, a lower intensity will be received by the transducer, and, due to attenuation, the echoes from these areas will be displayed as darker areas. This could be mistaken for suspicious hypoechogenic areas [28].

### Mirror Artifacts

If the ultrasound beam hits a strong reflector, a mirror image of the real structure is seen in the other side of the reflector. This artifact can usually be avoided by changing the position of the transducer.

## Volume Calculation

Diagnostically TRUS is also used to estimate the volume of the prostate gland, an important factor in calculating PSA density (serum PSA divided by gland volume) [32]. Several formulas have been used to calculate prostate volume, but most common one is the ellipsoid formula, which requires a measurement of three prostate dimensions. First, in the transverse plane, the width and the height are measured at its largest diameter. The length is measured in the sagittal plane just off the midline because the bladder neck often obscures the cephalad extent of the gland. The ellipsoid volume formula is then applied as follows: volume = height × width × length × $\pi/6$ (Figs. 39.3 and 39.4). In the same way, as described above, it is possible to determine the volume of the transition zone [33]. It must be noted that the elliptical volume is accompanied by considerable interobserver variation over repeated measurements [34, 35].

When a more accurate determination of gland volume is needed, such as during brachytherapy, planimetry may be used. The probe is mounted in a stepping device, and serial transverse images are obtained at set intervals (3–5 mm)

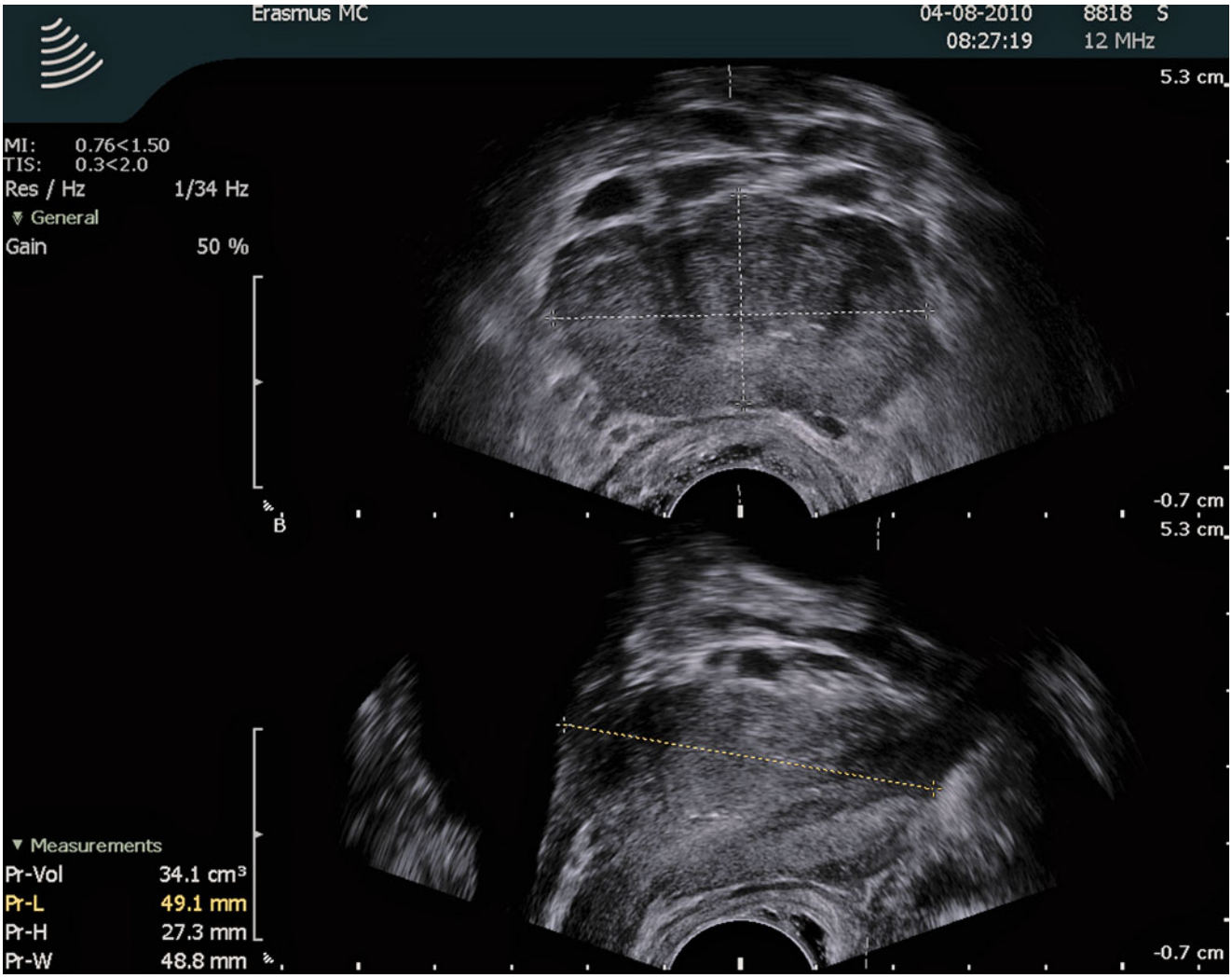


**Fig. 39.3** Volume measurement with biplane probe (Provided by Dr. M. Busstra, Dept. of Urology, Erasmus University Hospital Rotterdam, the Netherlands)

through the entire length of the gland. The surface area of each serial image is determined, and the sum of these measurements is then multiplied by the total gland length to yield the prostate volume [36].

## Sonographic Findings

### Overview of Prostate Anatomy

During the third month of gestation, the prostate gland develops at the base of the bladder from epithelial invaginations from the posterior urogenital sinus under the influence of the surrounding mesenchyme. This interaction forms the basis of the adult gland, which compromises a mixture of epithelium and stroma. During the prepubertal period, the constitution of the human prostate remains more or less identical but begins to undergo morphologic changes into the adult phenotype with the beginning of puberty. The gland enlarges continuously in size to reach the adult weight of approximately 20 g by 25 years of age [37, 38].

The adult prostate is a walnut-shaped organ enveloped in a fibrous capsule. The prostate lies between the bladder neck and the urogenital diaphragm, just anterior to the rectum, an ideal position to be imaged via TRUS. The prostatic urethra traverses the gland, which is the main reference point of the prostate. The verumontanum is a longitudinal ridge in the prostatic apex where the ejaculatory ducts enter the urethra. Anterior, the fibrous capsule thickens at the level of the apex to form puboprostatic ligaments, which attach the prostate to the back of the symphysis pubis. The dorsal venous complex (Santorini plexus) runs along these puboprostatic ligaments. The prostate gland lies beneath the endopelvic fascia. Posterior, the two layers of Denonvilliers fascia separate the prostate from the rectum. The rectourethralis muscle attaches the rectum to the prostatic apex [39].

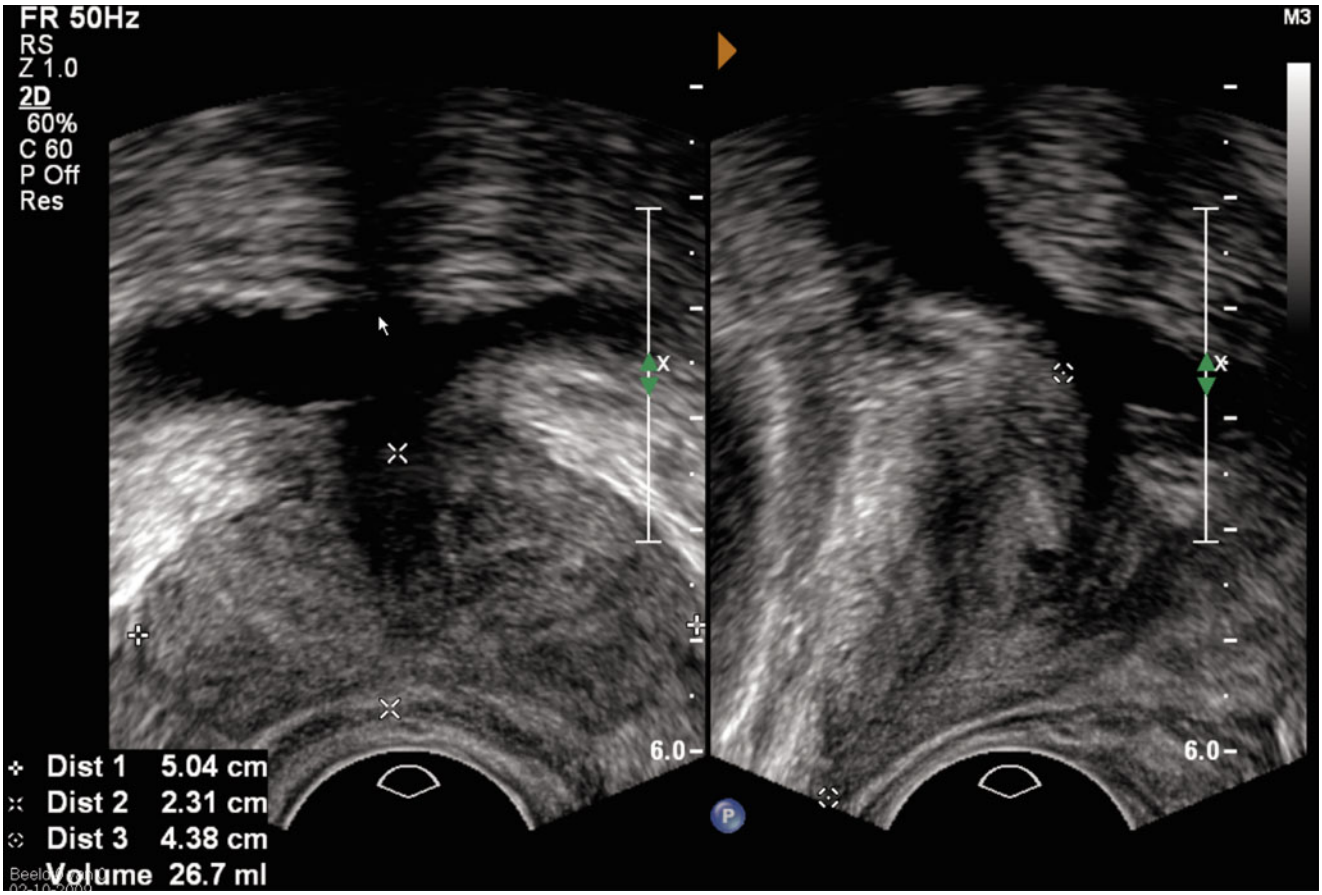


**Fig. 39.4** Volume measurement with end-fire probe. Note the images do not appear simultaneously in real time. The transverse plane is freezed first, then the probe is turned to show the sagittal plane

## Normal Sonographic Anatomy

According to the classic work by McNeal, five anatomical zones can be identified: three glandular (peripheral, transition, and central zone) and two nonglandular (periurethral zone and fibromuscular stroma) (Figs. 39.5 and 39.6) [40].

In young men, the peripheral zone constitutes almost 75 % of the prostate gland, the transition zone 20 %, and the central zone 5–10 %, but with age these ratios change. Most men develop benign prostate hyperplasia (BPH), which arises from the transition zone and eventually may occupy most of the gland [35, 41]. Conversely, the majority (70–80 %) of prostate cancers arise from peripheral zone [42], whatever the gland volume and zonal volume percentages.

When starting to scan in the transverse plane at the deepest part of the prostate, the seminal vesicles can be identified bilaterally. They have a smooth, saccular appearance and should be symmetrical. The ampullae of the vas deferens run on either side of the midline just above the seminal vesicles. Before entering the prostate, they fuse with the ducts of the seminal vesicles to form the ejaculatory ducts.

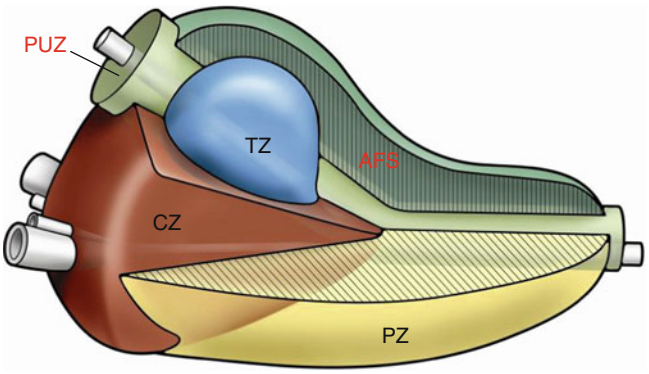


**Fig. 39.5** Zonal anatomy of the prostate. *TZ* transition zone, *PZ* peripheral zone, *CZ* central zone, *AFS* anterior fibromuscular stroma, *PUZ* periurethral zone (Provided by Dr. S. Torp-Pedersen, Dept. of Radiology, Frederiksberg Hospital, Denmark)

Next, the base of the prostate is imaged where central zone comprises the posterior part of the gland and often is hypoechogenic. Parallel to the prostatic urethra, the ejaculatory ducts traverse through here.

The midgland is the widest portion of the gland. The echogenicity in peripheral zone is described as isoechogenic

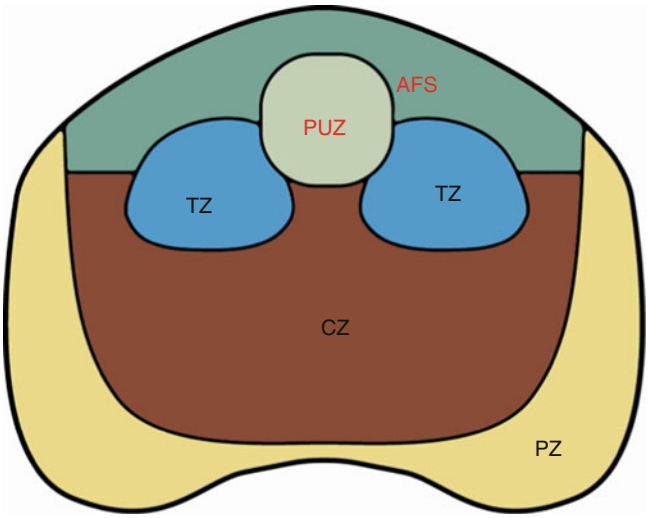


**Fig. 39.6** Zonal anatomy of the prostate, transverse plane. *TZ* transition zone, *PZ* peripheral zone, *CZ* central zone, *AFS* anterior fibromuscular stroma, *PUZ* periurethral zone (Provided by Dr. S. Torp-Pedersen, Dept. of Radiology, Frederiksberg Hospital, Denmark)

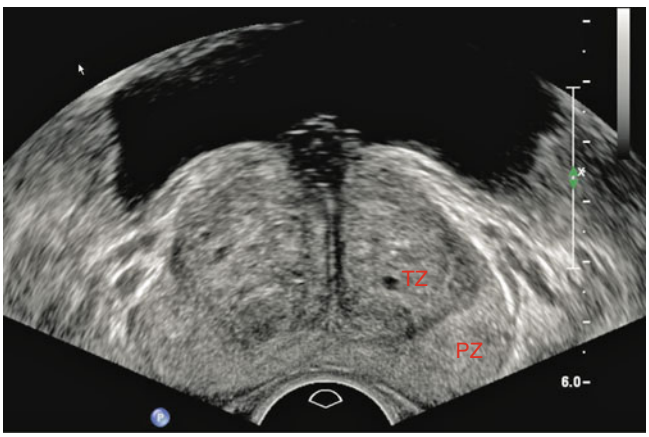


**Fig. 39.7** Mid prostate scanned in transverse plane with transitional zone (*TZ*) and peripheral zone (*PZ*)

and closely packed. The transition zone in the central part of the gland itself is moderately hypoechogenic when compared to the peripheral zone. The junction of the peripheral and transition zones is usually distinct and characterized by a hypo- or hyperechogenic border; see Fig. 39.7 [42, 43].

To identify the urethra, it helps scanning at the level of the verumontanum and observing the tower-like appearance. The apex, the part distal to the verumontanum, is mainly composed of peripheral zone. The several hypoechogenic structures anterior to the prostate gland are the prostatic venous plexuses. The neurovascular bundle can be identified as a hypoechogenic vascular complex, within which blood flow could be confirmed using Doppler imaging.

Imaging in the sagittal plane allows simultaneously visualization of the entire course of the urethra. In this plane, the median lobe of the prostate can be visualized [35].

## Benign Prostatic Hyperplasia

Prostate weight remains essentially constant with increasing age unless benign prostatic hyperplasia (BPH) develops. Early development usually occurs after the age of 40 years [44]; by the age of 60, its prevalence is greater than 50 %, and by 85 years, it is as much as 90 % [41].

BPH arises from the transition zone in close relation to the smooth-muscle sphincter. Although the hyperplastic transition zone is generally hyperechogenic, there is significant variability in the echogenic patterns of BPH. The stromal areas of the prostate appear hypoechogenic, whereas the appearance of glandular areas is more hyperechogenic, showing dense, lamellar patterns. The heterogeneous echogenic pattern of BPH makes the identification of transition zone carcinoma difficult. In BPH, small calculi that surround the transition zone can further obscure the images. Cystic degeneration is frequently seen, particularly associated with larger adenomas [45].

## Prostatitis

Histological evidence of prostatitis is most commonly encountered in the peripheral zone. In acute prostatitis, the glands appear enlarged, uniformly hypoechogenic, and symmetric. Other features may include the presence of hypoechogenic halo in the periurethral area, a heterogeneous echo pattern in the gland parenchyma due to multiple echo-poor areas. In contrast, in chronic prostatitis, there may be seen a nonhomogeneous echotexture often associated with the presence of canaliculi as well as hypoechogenic peripheral zone lesions. A prostatic abscess appears as a localized echo-poor area, with internal echoes being visible within the cavity [46].

## Cystic Lesions of the Prostate

Cysts of the prostate are not uncommon and in most cases diagnosed accidently during ultrasound. Cystic lesions are rarely associated with cystic carcinoma of the prostate. On TRUS, they generally appear as echogenic masses with clearly defined borders. The distal wall is often acoustically enhanced (Fig. 39.8a, b). Cysts are a phenomenon related to BPH, inflammatory conditions, anatomical variants (utricle), or focal atrophy.

Cysts of the prostate gland can be classified into six categories, including (1) isolated medial cysts (Müllerian duct cyst or cystic utricle), (2) cysts of the ejaculatory duct, (3) simple or multiple cysts of the parenchyma (Fig. 39.9), (4) complicated cysts (infectious or hemorrhagic), (5) cystic tumors, and (6) cysts secondary to parasitic disease. Treatment should be reserved only for men who are infertile

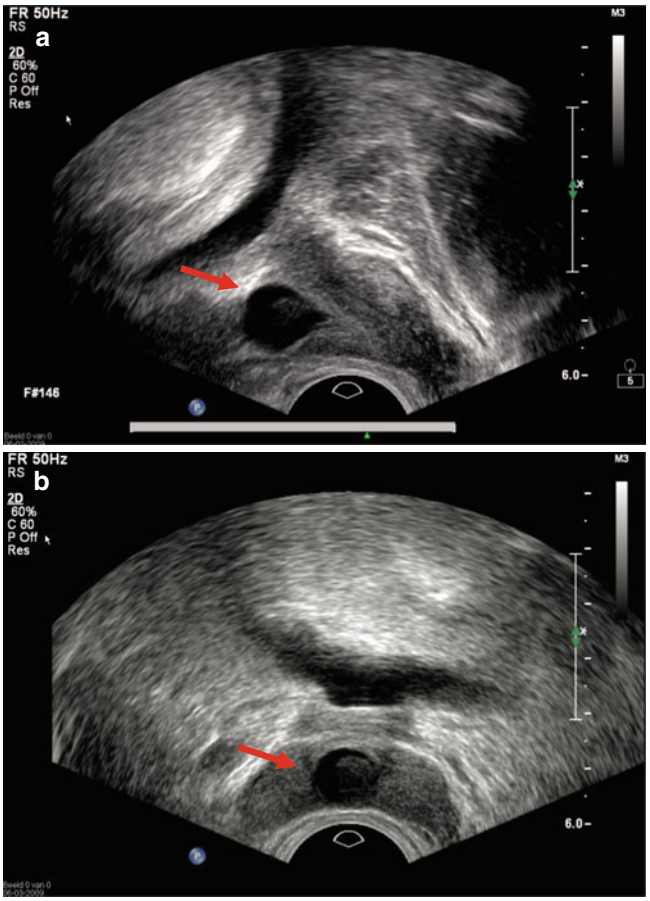


**Fig. 39.8** (**a**) Thirty-year-old male with hemospermia. Visible in a sagittal plane a congenital medial prostate cyst. The distal wall of the cyst is acoustically enhanced (*red arrow*). (**b**) Same cyst in transverse plane

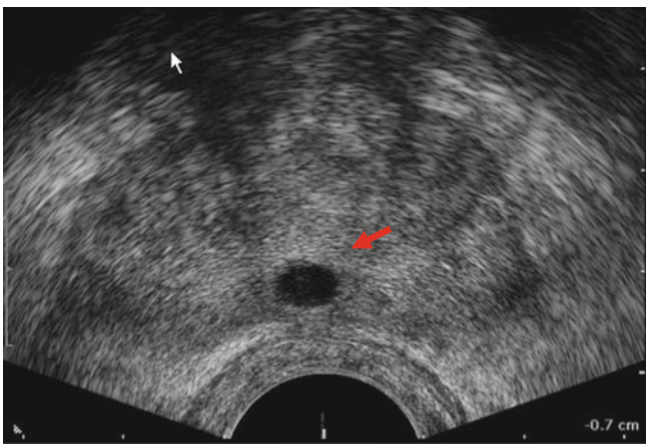


**Fig. 39.9** Midline cyst (*red arrow*) (Provided by Dr. M. Busstra, Dept. of Urology, Erasmus University Hospital Rotterdam, the Netherlands)

or who have symptoms or infection (type 4). The diagnosis of rare tumor cysts (type 5) is difficult preoperatively, and it is made only on biopsy or transurethral resection pathological specimens [47–49].

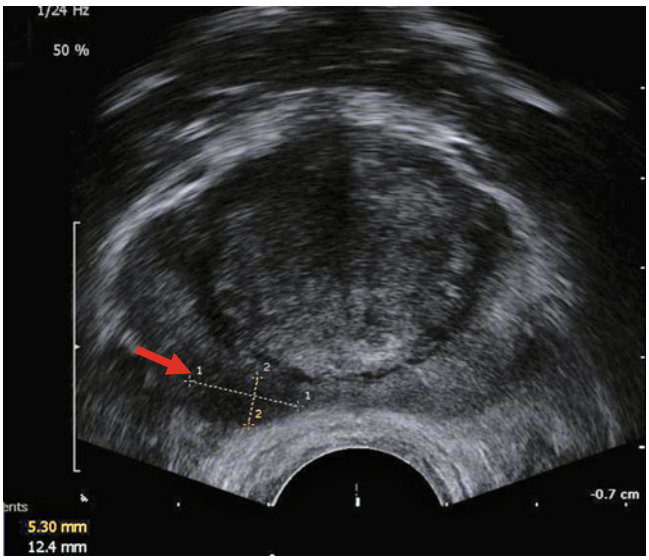


**Fig. 39.10** Hypoechogenic lesion (*red arrow*) mid prostate right side (Provided by Dr. M. Busstra, Dept. of Urology, Erasmus University Hospital Rotterdam, the Netherlands)

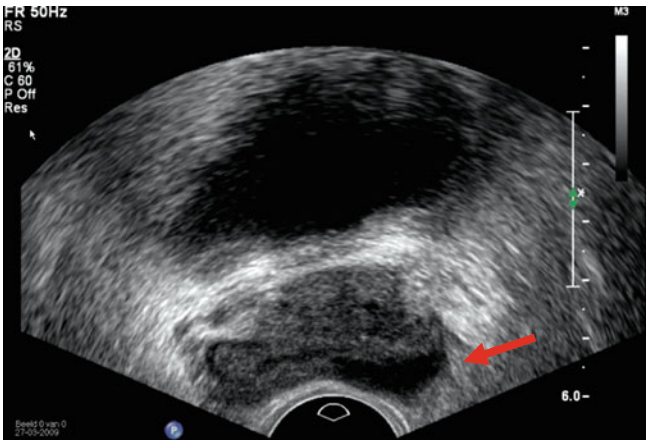


**Fig. 39.11** Hypoechogenic lesion (*red arrow*) in 73-year-old male with PSA level of 2.1 ng/ml, DRE T3 left side. Biopsy was positive in all cores on the left side (Gleason 3+4 and 3+5), cores right side benign

## Prostate Cancer Imaging

Prostate cancer, depending on size, grade, and location, usually appears hypoechogenic relative to the normal peripheral zone of the prostate (Figs. 39.10, 39.11, and 39.12). But prostate cancer may also appear hyperechogenic or isoechogenic. The sensitivity of B-mode TRUS for the detection of prostate cancer ranges from 35 to 91 % and the specificity from 24 to 81 % [20, 50–53]. In men with a PSA level of 4–10 ng/ml, about half of all prostate cancer lesions are invisible by gray-scale TRUS [10].

With the shift toward smaller, early stage cancers, many cancers detected at biopsy are not visible at TRUS (low

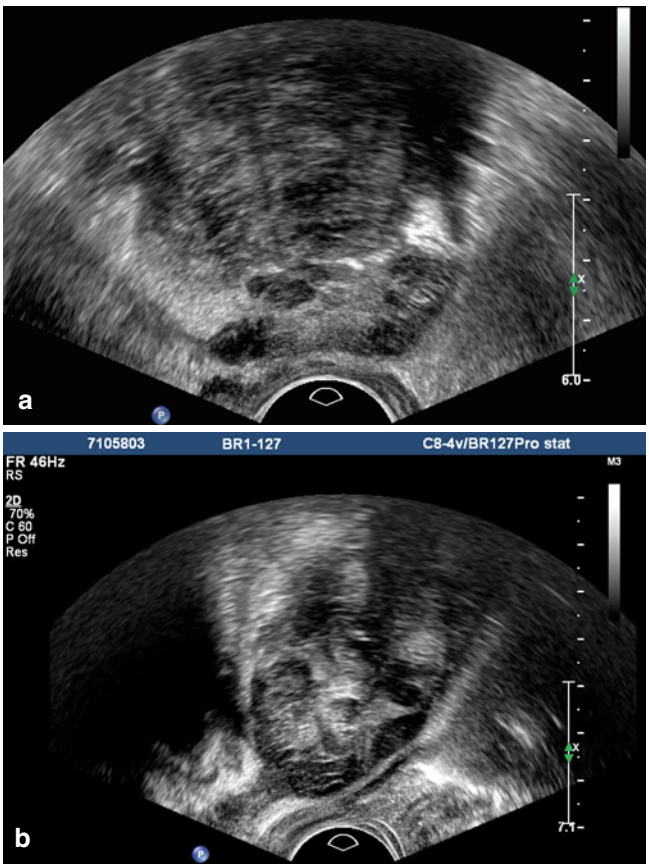


**Fig. 39.12** (**a**) A TRUS image of prostate with several hypoechogenic areas in 63-year-old man with a PSA level of 68 ng/ml. Biopsy showed in 10 out 12 biopsies Gleason 5 + 5. (**b**) Sagittal plane same patient

sensitivity). Also, prostatitis and benign prostatic hyperplasia mimic the gray-scale appearance of prostate cancer, lowering the specificity. Therefore, TRUS alone, without the addition of biopsy, has limited value in the detection of cancer.

Prostate cancer is often multifocal, with predominant localization in the peripheral zone (approximately 80 %). A large histopathology study of Chen et al. showed that transition zone foci are often small and almost always occur together with peripheral zone foci. This might explain the lack of effectiveness of transition zone biopsies in detecting additional cancers during screening [42].

The value of TRUS for local staging is controversial. Some studies have established criteria for distinguishing extracapsular extension on TRUS, including bulging or irregularity of the capsule adjacent to a hypoechogenic lesion, as well as the length of contact of a lesion with the capsule [54, 55]. Seminal vesicle invasion is suspected by a visible extension of a hypoechogenic lesion at the base of the prostate into a seminal vesicle [56].

## Developments in Transrectal Ultrasonography

### Color and Power Doppler Ultrasonography

Sensitivity and specificity of TRUS can be improved by using color or power Doppler ultrasound. Prostate cancer tends to have increased vascularity compared with healthy prostatic tissue due to the formation of new vessels or an increase in the capacity of existing vessels [57]. Also, hypervascularity correlates with higher Gleason scores [58, 59].

Color Doppler has been applied to evaluate the vascularity within the prostate and the surrounding structures. Color Doppler imaging measures blood flow velocity and direction. Three different flow patterns may be associated with prostate cancer: diffuse flow, focal flow, and surrounding flow. The most frequently identified flow pattern is diffuse flow within the lesion [59, 60].

Power Doppler ultrasonography is an amplitude-based technique for detection of flow. In power Doppler, the nuance and brightness of the color signal represent the total energy of the Doppler signal, which is related to the number of red-blood cells producing the Doppler shift. This technique is more sensitive to slow flow and is less angle dependent than color Doppler [61].

Rifkin et al. [60] found that up to 86 % of men with prostate cancer greater than 5 mm size had a visible increased flow in the area of tumor involvement. In addition, hypervascularity was also seen in patients with more difficult to identify, isoechogenic and hyperechogenic lesions. Color and power Doppler complement gray-scale imaging and could be used as a routine part of TRUS imaging of the prostate to improve detection and targeting of lesions [62, 63]. However, subsequent studies suggested that the combined application of gray-scale and Doppler ultrasound will still miss some cancers and is insufficient to preclude systematic prostate biopsy [61, 64].

### Contrast-Enhanced Ultrasonography

Recently developed ultrasound contrast agents can improve the detection of low-volume blood flow by increasing the signal-to-noise ratio. Intravascular contrast agents allow a more complete delineation of the neovascular anatomy, by enhancing the signal strength from small vessels [65].

Ultrasound contrast agents consist of small (2–8 μm) encapsulated gas bubbles that are administered intravenously and remain intravascular. The microbubbles that have been used most frequently in prostate cancer reports are Sonovue® (sulfur hexafluoride, Bracco, Milan, Italy) and Levovist® (galactose-palmitic acid, Schering, Berlin, Germany). The various agents differ regarding the gas substance and coating,

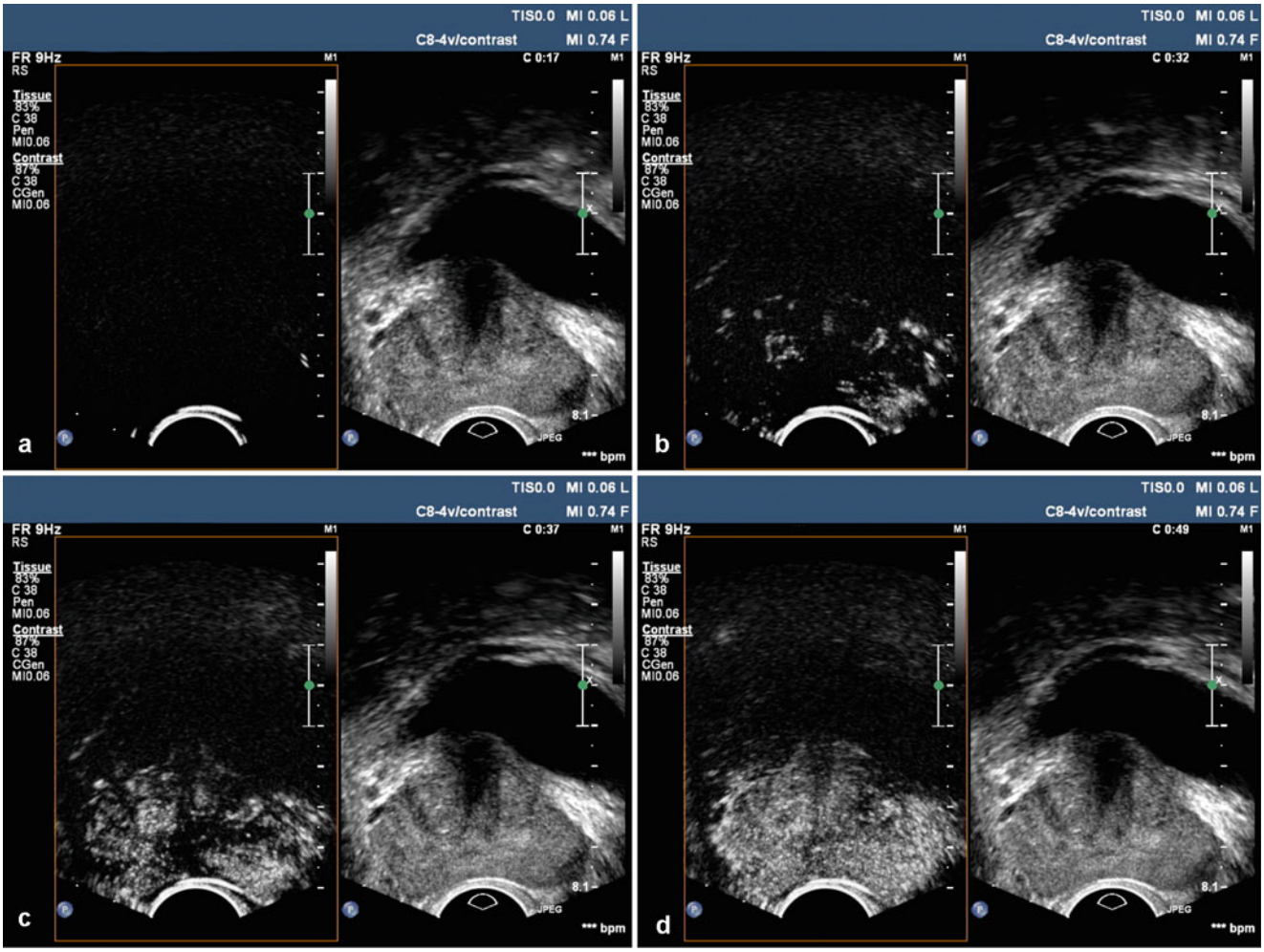


**Fig. 39.13** CEUS of the prostate: contrast only (*left*) and tissue only (*right*) images are presented. (**a**) Enhancement is shown as function of time. There is still no contrast visible in the prostate 17 s after injection. (**b**) First (early) enhancement 32 s after injection. (**c**) Enhancement 37 s after injection. (**d**) 49 s after injection (**b**, **c**) suspicious lesion is seen on the left lobe at the peripheral zone (Provided by prof. Dr. Ir. H. Wijkstra, Dept. of Urology, Academic Medical Centre, Amsterdam, The Netherlands)

which ultimately determine the behavior and longevity of the microbubble [66].

Adding microbubbles as additional reflectors into the bloodstream increases the sensitivity of color Doppler and power Doppler imaging. However, these techniques use relatively high ultrasound energy levels, and, as a result, a large proportion of the microbubbles are destroyed as they are imaged [67]. New signal transmission and reception techniques have been developed that enable sensitive microbubble imaging even in the microvasculature. First, low mechanic index imaging allows the ultrasound probe to emit ultrasound waves with a lower level of energy. The low mechanical index imaging prevents disruption of the microbubbles. Second, contrast-harmonic imaging, a novel signal reception technique, takes advantage of the microbubble's emission of relatively unique frequencies that are multiples (harmonics) of the frequency emitted by the ultrasound probe due to their nonlinear contracting and expansive behavior in response to ultrasound waves. Thirdly, altering between the modes of high and low mechanical index imaging, termed intermitted scanning, allows the operator to briefly increase the mechanic index and destroy microbubbles in the imaging plane, and after returning to low mechanical imaging visualize the repeated first-pass effect of the microbubbles through the vasculature (Fig. 39.13) [68–70].

A number of studies have examined the role of contrast-enhanced ultrasound (CEUS) and targeted biopsy [71–74]. All these studies demonstrated that the percentage of patients diagnosed with prostate cancer did not differ between systematic biopsy (23–28 %) and contrast-enhanced targeted biopsy (24–27 %). However, the percentage of positive biopsy cores was significantly higher for targeted biopsy (10–33 %) compared to systematic biopsy (5–10 %).

Two more recent studies, both from the same research group, showed for the first time that contrast-enhanced targeted prostate biopsy did significantly increase the overall detection rate. Mittberger et al. [75] showed in a prospective randomized trial on 100 patients a 32 versus 26 % difference in cancer detection by a limited number of targeted biopsies (5) compared with 10-core gray-scale biopsy. They also published a retrospective, single-center study of 1,776 men undergoing 10-core systematic biopsy and 5-core targeted biopsy between 2002 and 2006. Note that of the ten systematic cores, eight cores where taken from the peripheral zone and two cores from transition zone, which is not currently standard. CEUS targeted biopsy detected a significantly higher number of patients with prostate cancer (27 %) compared with systematic biopsy (23 %) [76]. Multicenter approaches are necessary to confirm the available results. No studies have been published on the application of microbubbles in local disease staging.

## Elastography

A significant number of pathological conditions are associated with changes in the rigidity and elastic properties of biological tissues. Nowadays, palpation is routinely used in most medical specialities, and many breast and prostate cancers are still detected by this means. The wide range of elastic tissue properties and the difference in elasticity of tumors and the adjacent tissues have provided motivation for developing elasticity imaging techniques [77].

Ultrasound-based real-time elastography imaging observes the differences in tissue strain produced by free hand compression. Using elastography, the investigator is able to discriminate hard from soft tissue regions within the prostate. The phenomenon is based on the fact that the backscattered ultrasound signal changes its local characteristic pattern only if the insonified tissue is slightly compressed and decompressed during the examination. Stiffer tissues show less displacement than normal soft tissues. For observation, stiffness values are marked in different colors and shown in real-time images. Following the hypothesis that solid tumors differ in consistency compared with the adjacent normal tissue, elastography has been investigated as a novel tool for detecting prostate cancer. Promising results have been recently reported in small cohorts.

Pallwein et al. [78] reported on 15 patients with histological proven prostate cancer who underwent elastography prior to surgery. Twenty-eight out of 35 cancer foci found at histopathology were correctly identified with real-time elastography. This adds up to a sensitivity and specificity of 87 and 92 %. In 2008, Salomon et al. [79] reported on 109 men in a similar study design. They found a sensitivity and specificity of elastography in detecting prostate cancer of 75 and 78 %, respectively. A comparison of stiff lesions at elastography with systematic biopsy outcomes in 492 screened volunteers revealed a sensitivity of 86 and 72 % specificity in detecting prostate cancer [80].

Only a few studies reported on elastography targeted biopsy. A study of 137 patients compared 6-core systematic prostate biopsy with targeted biopsy using gray-scale, color Doppler, and real-time elastography [81]. The cancer detection rate per core was significantly higher for the elastography targeted approach versus the systematic approach (12.7 vs. 5.6 %). Unfortunately, no abnormality on elastography or other sonographic modality was seen in 53.8 % of positive systematic biopsy cores. Eggert et al. [82] evaluated 351 men who were randomized in a control group with 10-core systematic biopsy or in a group with elastography-guided 10-core biopsy. In their study elastography did not improve the cancer detection.

In summary, real-time elastography seems to be a feasible, reproducible tool to improve prostate cancer detection in ultrasound investigations. However, future studies have to determine if it can be used to develop a targeted biopsy scheme that is at least as sensitive in tumor detection as an extended biopsy scheme.

## Imaging-Based Tissue Characterization

Prostate HistoScanning™ is a novel technique for tissue characterization and visualization, designed as an aid for ultrasound-based diagnostic techniques. Theoretically, malignancy will induce changes in the ultrasounds' backscattered signal, and mathematical analysis will detect these changes in the raw ultrasound data. HistoScanning processing of the ultrasound data is based on a theoretical estimation of how cancerous tissue, as opposed to none cancerous tissue, may cause a difference in the reflected acoustic waves. The development process relies on clinical data (ultrasound data and pathological data) collected from patients with cancer. The clinical data is used to translate the theory, of how the difference in tissue will influence the ultrasound reflections, into a set of mathematical measurements and criteria. Wide range of statistical measurements was applied to collected ultrasound data. These measurements have been classified, using methods of nonlinear pattern recognition, as "typical" of cancerous or noncancerous tissue behavior. What falls under "typical" is determined by matching the ultrasound data with detailed histopathology samples of the tissue of interest.

The first published papers on Prostate HistoScanning by Braeckman et al. [83, 84] described a study where 3D sets of ultrasound data from 29 patients were collected just before undergoing radical prostatectomy. Prostate HistoScanning analysis of that data showed close correlation with whole

mount pathologic findings. Tumor localization and prediction of their cross-sectional size matched with good accuracy as well were the predictions on multifocality, bilaterality, and extraprostatic extension. Further studies are being conducted in order to determine the roll of Prostate HistoScanning in management of prostate cancer patients; e.g., in selection of men with elevated PSA to undergo prostate biopsy, men suitable for local treatment procedures or for the selection and follow-up of men on active surveillance (Fig. 39.14).

## Conclusion

TRUS will remain an important imaging modality in prostate cancer diagnosis, grading, and staging. As hypoechogenic lesions are becoming less pathognomonic in the PSA-screening era, TRUS should not be used as biopsy guidance alone. Advances in ultrasound like CUES, elastography, and HistoScanning may improve the diagnostic performance in prostate cancer diagnosis.

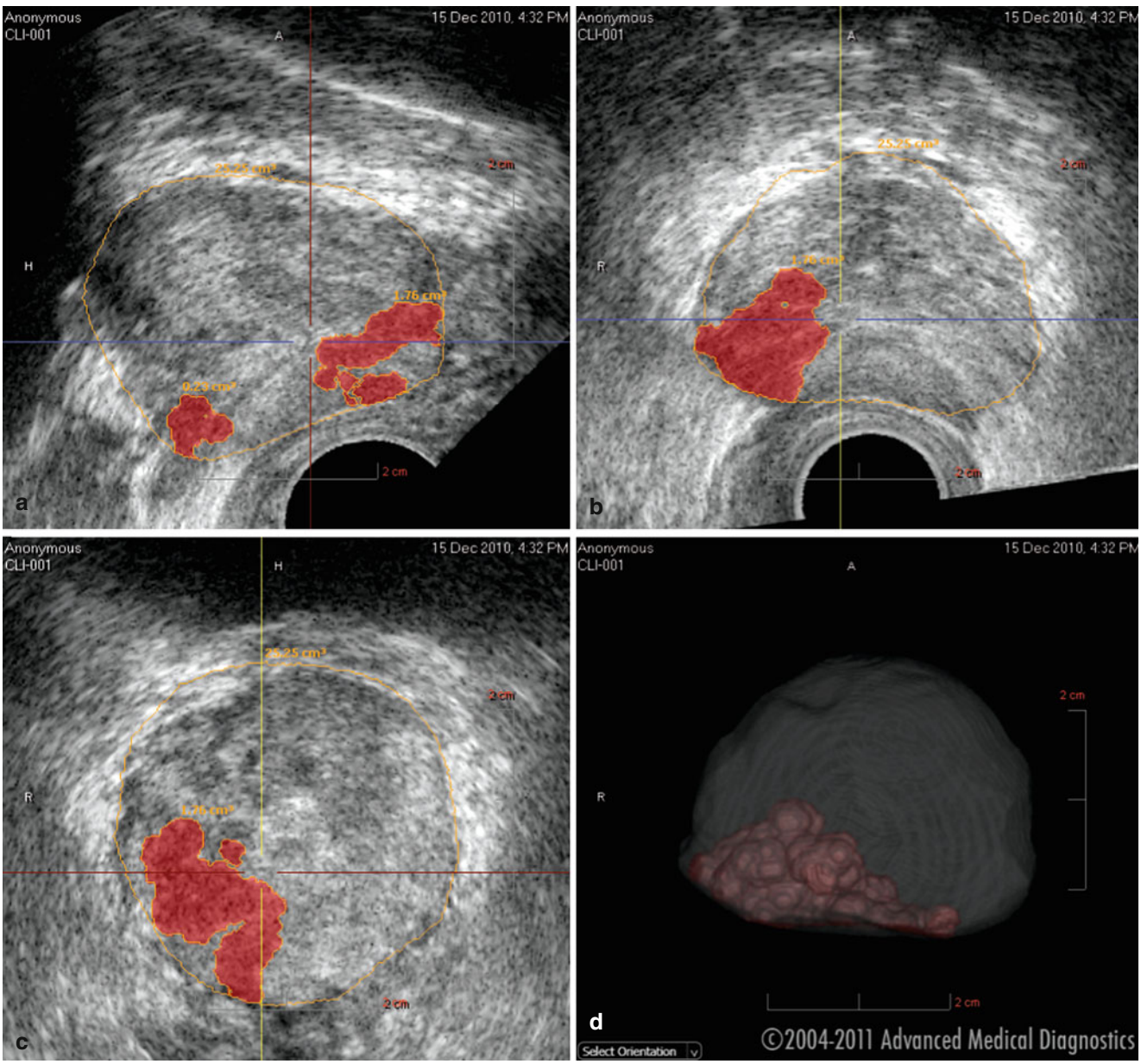


**Fig. 39.14** Prostate HistoScanning image of a patient with elevated PSA. The suspicious areas are represented by red areas in sagittal plane (**a**), axial plane (**b**), coronal plane (**c**), and in 3D (**d**) and confirmed at histopathology (**e**) (Provided by Advanced Medical Diagnostics SA, Waterloo, Belgium)

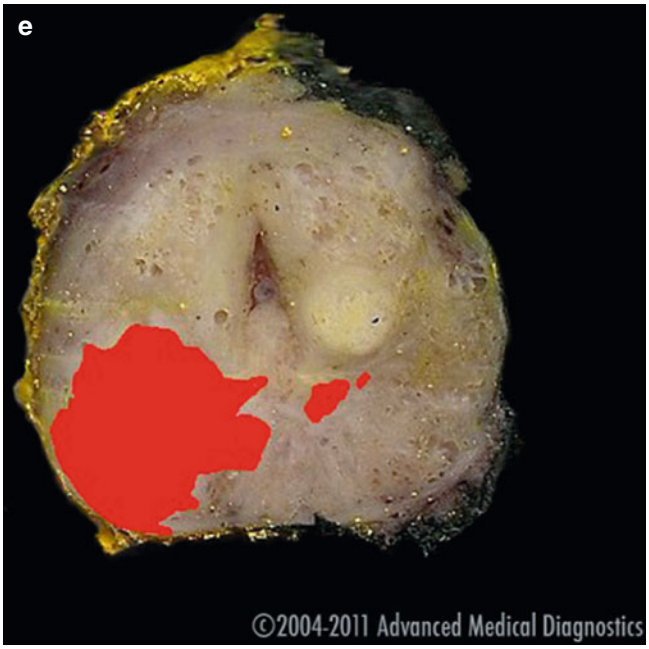


**Fig. 39.14** (continued)

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# The Use of Magnetic Resonance Imaging in the Management of Prostate Cancer

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In the current era, the use of magnetic resonance imaging (MRI) has become routine for the evaluation and management of prostate cancer (PCa), with most patients undergoing a 1.5-T MRI. There is a direct relationship between magnet strength and spatial resolution of the image: the higher the magnet, the higher the spatial resolution. In a 3-T MRI, a phased array pelvic coil is used instead of an endorectal coil, which could decrease patient refusal to undergo MR imaging due to avoidance of the discomfort associated with an endorectal coil. Multiparametric MRI (mpMRI) has become the gold standard in PCa scanning and is more reliable than T2-weighted (T2W) MRI alone [1]. The T2-weighted MRI sequence has a lower specificity due to a high frequency of low signal intensity foci, which causes false positives. In standard practice, multiparametric imaging modalities are based on the combination of T2-weighted (T2W-MRI), dynamic contrast enhancement (DCE-MRI), and diffusion-weighted imaging (DW-MRI) to improve detection, location, and characterization of PCa. Due to its time-consuming nature, another technique known as MR spectroscopy (MRSI) is likely to be restricted for scientific purposes.

Dynamic contrast-enhanced MRI (Fig. 40.1) consists of comparing the kinetics of tissue perfusion within PCa, benign prostatic hyperplasia and the normal tissue, by using an IV injection of gadolinium contrast. Imaging is carried out using a multiphase T1-weighted sequence. The analyzed parameters are the inflow of the agent contrast within the prostatic tissue (wash-in) and its return to the blood after organ perfusion (wash-out). This variable enhancement is related to the neovascularization of PCa causing avid early enhancement within the tumor tissue compared to a normal gland. Prostate cancer in the peripheral zone, with volume >0.5 cc, can be detected with a higher sensitivity than T2-weighted imaging alone, ranging from 60 to 97 %, and with a specificity of 85 % [2]. Dynamic contrast-enhanced MRI is still limited by prostatitis and BPH, causing false positives due to hypervascularity. However, it serves as a useful adjunct to the other sequences involved in mpMRI.

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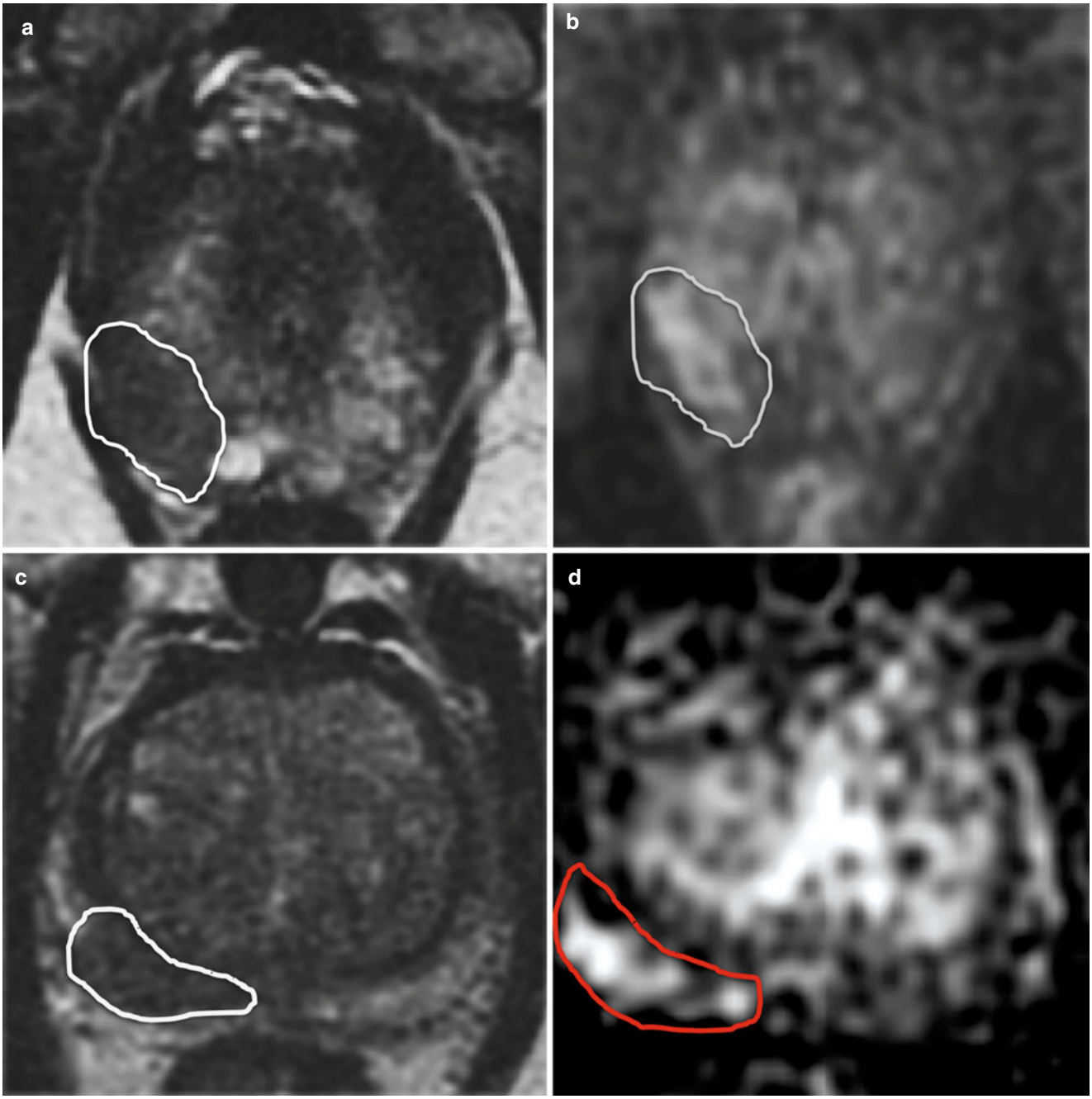


**Fig. 40.1** Dynamic contrast-enhanced magnetic resonance images. (**a**) Axial T2-weighted magnetic resonance (MR) image shows low signal within the right peripheral zone of the prostate (*outlined in white*). (**b**) Axial dynamic MR image of a prostate shows enhancement within the corresponding area suspicious for PCa (*purple circle*). The wash-in causes an early enhancement within the tumor due to the neoangiogenesis related to the PCa. (**c**) Axial T2-weighted MR image shows well-defined low signal in the right peripheral zone (PZ) (*outlined in green*). (**d**) The corresponding axial dynamic contrast-enhanced MR image shows an early avid enhancement due to the inflow of the gadolinium which is suggestive of PCa (*outlined in red*)

Diffusion-weighted MRI (Fig. 40.2) is based on measuring the Brownian movement of water within tissue. The diffusion of water molecules is free in liquid areas and restricted in high cellular density zones. The relative decrease in the free diffusion of water molecules can then be quantified, using a unit called the Apparent Diffusion Coefficient (ADC). Prostate cancer results in a higher cellular density, replacing the normal prostatic tissues, resulting in restricted diffusion of water molecules and, thus, a lower ADC. Diffusion-weighted MRI is a short sequence (<5 min), simple to use, and with a higher specificity (85 %) than DCE-MRI within peripheral zones to detect PCa. However, DW-MRI is very sensitive to technical factors such as patient motion and field inhomogeneities. DW-MRI remains the most practical

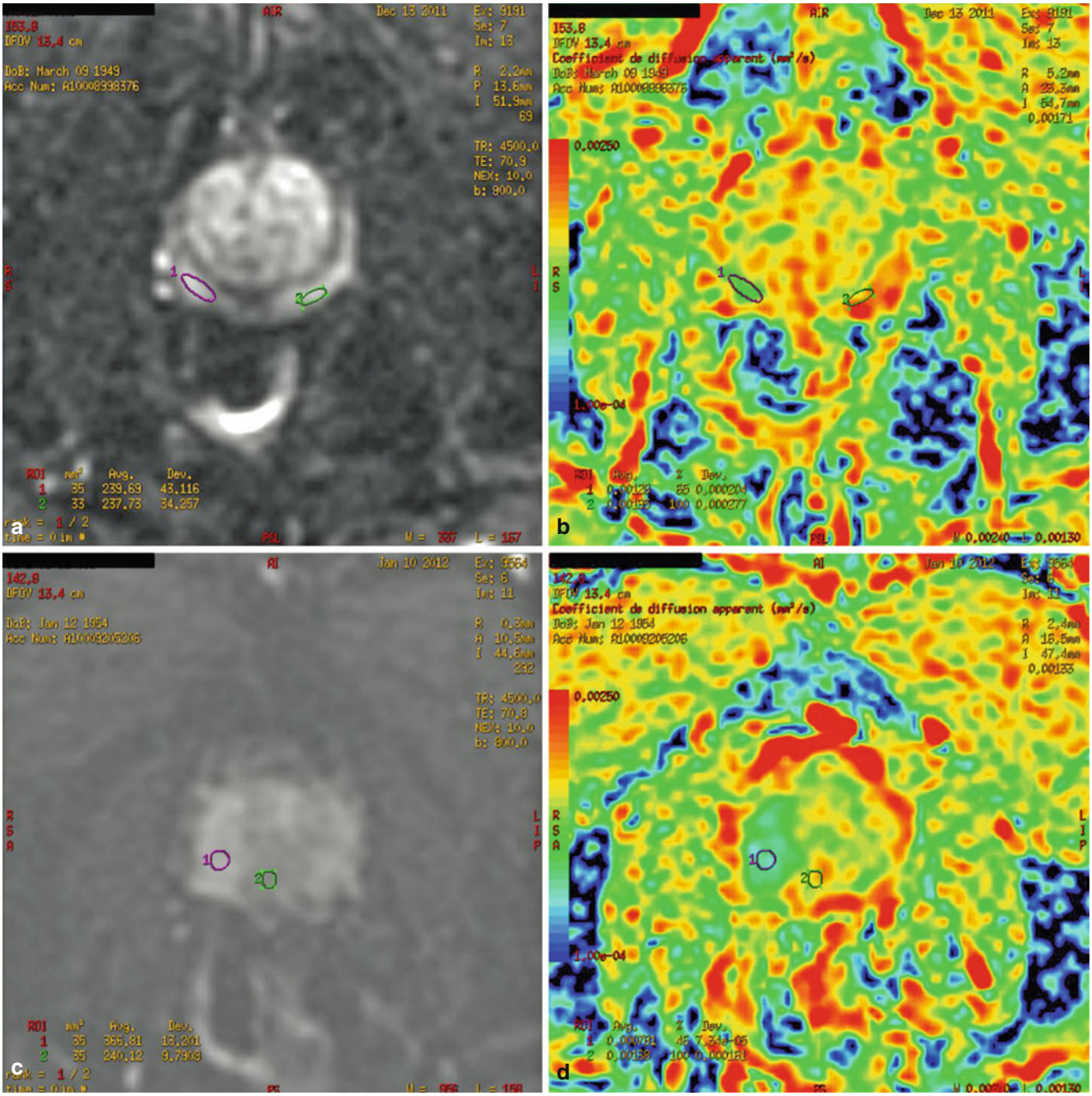


**Fig. 40.2** Diffusion-weighted magnetic resonance images. (**a** and **c**) Axial diffusion-weighted magnetic resonance (MR) images (**B**, 800) of a prostate show high signal intensity in the right peripheral zone (*purple circle*). The signal intensity is high when the diffusion (water motion) is low due to high cellularity, integrity of cell membrane, and high viscosity (e.g., cancer). The regions of interest (ROIs) are positioned manually by reader. One is located within the area suspicious for PCa (*purple circle*) based on the complement sequences (both T2-weighted MR image and dynamic contrast-enhanced MR image). One is located within the benign tissue (*green circle*). (**b**, **c**) The corresponding ADC mappings of the axial diffusion-weighted MR images (**a** and **c**, respectively). The ROIs indicate the ADC values. ADCs represent the degree of water molecular diffusion. The degree of restriction to water diffusion in biological tissues is inversely correlated to the tissue cellularity and the integrity of the cell membranes. ADC of ROI 1 (**b**) is 0.128 $cm^2/s$ and ROI 1 (**d**) is 0.078 $cm^2/s$ for ROI 2 of 0.195 $cm^2/s$ (**b**) and 0.168 (**d**) corresponding to a decrease of 35 and 54 % (**b** and **d**, respectively). The incremental value of diffusion-weighted MR image is to approach a correlation between the ADCs and histological grading

supplement to DCE-MRI in order to give the highest mpMRI reliability today.

Magnetic resonance spectroscopic imaging (MRSI) collects chemical data from reflecting concentrations of different prostatic metabolites such as citrate, choline, and creatine, within voxels (three-dimensional volume elements). In PCa, the ratio of choline + creatine to citrate is used to distinguish PCa within normal prostatic tissue, in the peripheral zone; a

ratio higher than 0.75 is described as prostate cancer foci [3]. The major restrictions of MRSI include the long acquisition time, the specific skills needed in both establishing and fine-tuning a department's protocol, as well as in the interpretation of the results. Magnetic resonance spectroscopic imaging is also limited by the impact of postbiopsy changes and prostatitis leading to an increase in the ratio, causing false positives. At this time, MRSI is not routinely used in practice due to these limitations; however, its usefulness in conjunction with DWI and DCE is well established.

Currently, MRI is recommended for staging of PCa after diagnosis. But the focus of mpMRI interest has neatly shifted from simply detecting advanced disease to its ability in targeting subsequent biopsies, to include and monitor patients in active surveillance (AS), to check patients with prostate-specific antigen (PSA) relapse, to assist grading evaluation, and even to help mapping before focal therapy.

## Characterizing Significant Prostate Cancer in Men with Positive Biopsy (Location, Volume, Extraprostatic Extension)

Today, MRI model has been accepted as the best imaging system to diagnose PCa with both higher sensitivity and specificity [4]. 1.5-T MRI is a significantly better tool to accurately locate PCa than transrectal ultrasound (TRUS). Mullerad et al. [5] demonstrated that the receiver operator curve area under the curve (ROC AUC) was meaningfully larger with 1.5-T MRI in any region of the prostate, except at the apex where TRUS was more accurate. Three-T imaging with an endorectal coil is likely to be of further value in improving the quality and localization and to achieve higher sensitivity ranging from 50 to 100 % [6, 7].

In a study examining the local staging accuracy of 3-T MRI, Fütterer et al. reported high accuracy levels of 94 and 81 %, sensitivities of 88 and 50 %, and specificities of 96 and 92 %, for an experienced and a less experienced radiologist, respectively [8]. Although there has been a wide variation in the reported accuracy of prostate cancer staging by MRI, it has improved widely because of increased reader experience, maturation of MRI technology (faster imaging sequences, more powerful gradient coils, and postprocessing image correction), and improved understanding of morphological criteria to diagnose extraprostatic extension (EPE) and seminal vesicle involvement (SVI).

The combination of multiple sequences (Fig. 40.3) results in improving the accuracy of the prostate peripheral zone (PZ) tumor volume measurement. Mazaheri et al. [9] investigated 42 patients with at least one PZ cancer larger than 0.1 $cm^3$ at final histological finding after radical prostatectomy. Patients underwent 1.5-T mpMRI prior to surgery. The radiologist identified 43 lesions out of 60. Concordance correlation coefficients (CCCs) assessed the association between volume measurements from the reader and the pathologist. The CCC of combined T2-weighted and DW-MRI was significantly higher ($p = 0.006$) than the T2-weighted imaging alone.

Magnetic resonance imaging is more sensitive for the detection of tumors in the PZ than transitional or central zones; it can also detect extracapsular extension of tumors and seminal vesicle invasion (Fig. 40.4). There is limited benefit for using MRI in the detection of T3a PCa because it is not accurate enough for decision-making. On the other hand, suspicion for pT3b PCa provides adequate reasoning for imaging. A low signal within the seminal vesicle (SV) with early enhancement and low diffusion (low ADCs) is indicative of possible SVI. Thus, preoperative MRI is a crucial component of PCa diagnosis and treatment.

## Targeting Patients with Persistent High PSA (Negative First Biopsy) for Repeated Biopsy

For patients having a high persistent PSA with no positive biopsy, the threat of disease is a heavy daily burden. In certain regions of the organ, particularly the anterior zone [10], it is not easy to find good placement for TRUS-guided prostate biopsy. For prostate evasive anterior tumor syndrome (PEATS), the assistance of MRI to localize the PCa might be a solution [11].

In targeted biopsies, MRI, performed prior to the TRUS, is used to direct biopsies toward suspicious lesions. Targeting biopsies provides the advantage of detecting prostate cancer that may not have been detected by systematic sampling alone, particularly those outside the peripheral zone [12, 13].

Regardless of cost/benefit, it has been shown that targeted biopsies may improve the diagnosis yield to a greater degree than increased number of biopsies [14]. The sensitivity of MRI to detect a PCa is tumor size dependent. In particular, sensitivity for small low-risk cancer is poor, leading to many false negatives; however, a negative MRI cannot eliminate a PCa diagnosis, and, hence, MRI cannot be used as a surrogate for biopsy in diagnosis.

Moreover, with an intention-to-treat, diagnosis must be certain; in other words, the negative predictive value (NPV) should be as high as possible; the fewer false positives, the higher the NPV. This is quite important for patients with persistent high PSA when the first biopsy is negative and causes a high suspicion of missed cancer.

While TRUS is not accurate enough to independently localize tumors, MRI-guided prostate biopsies do tend to reduce false negatives and have a higher NPV, which is essential for safe treatment. In a prospective study of 180 men with prostate cancer, Sciarra et al. [15] assessed the role of MRSI and DCE-MRI in targeting biopsies in patients displaying persistently elevated PSA levels with a prior negative biopsy and compared the results with those obtained with second TRUS-guided biopsy. On repeated biopsy, pros-

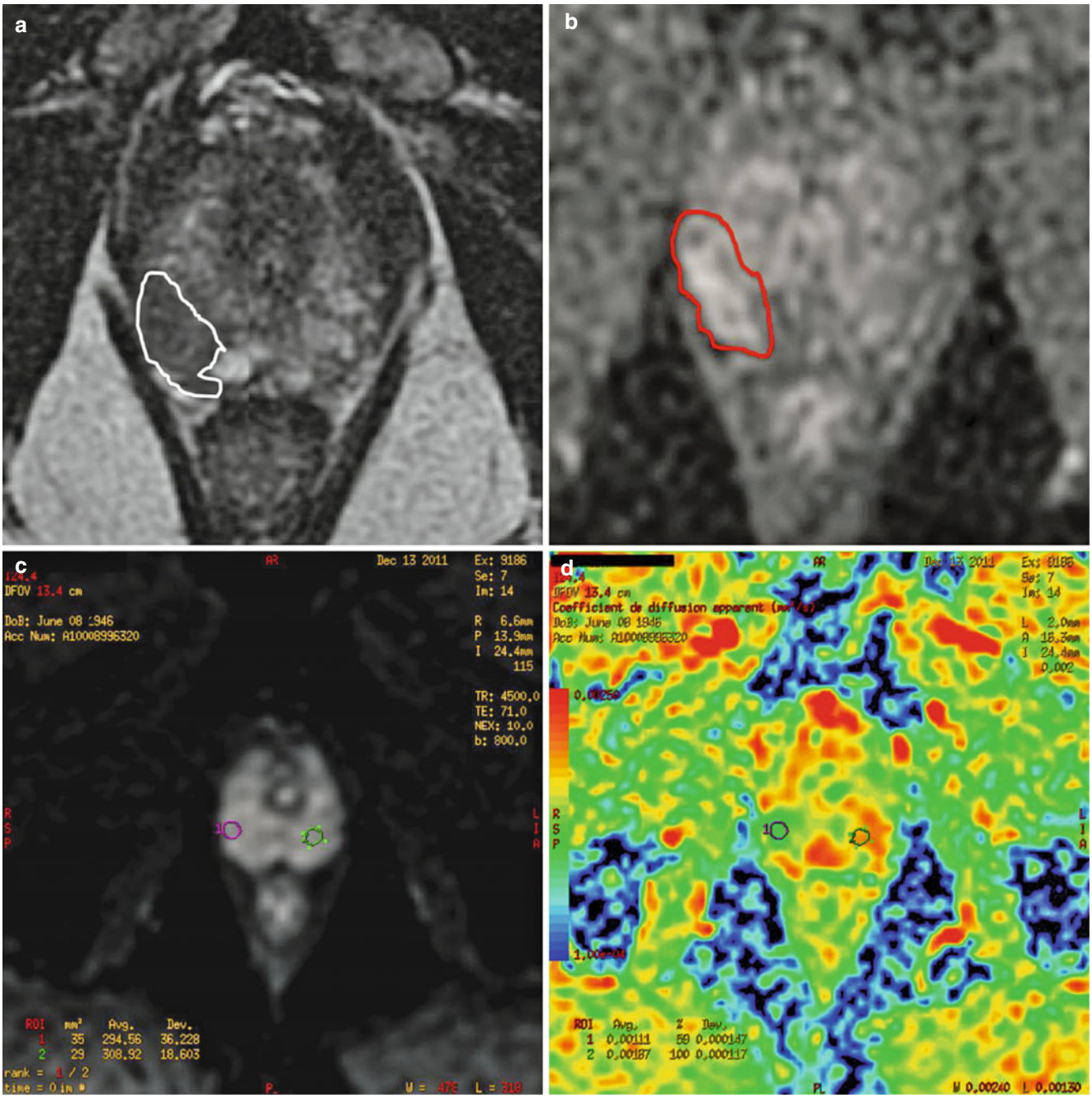


**Fig. 40.3** Combination of multiparametric magnetic resonance images. Patient (age: 65 years) with prostate-specific antigen level of 16.0 ng/ml; unsuspicious findings at digital rectal examination. Histology at transrectal ultrasound-guided biopsy showed prostate adenocarcinoma (PCa) on 3 cores out of 12, Gleason score 7 (3+4) in the right-side samples; histology at robotic radical retropubic prostatectomy showed Gleason score 7 (4 at 60 %+3 at 40 %) right PCa with extracapsular extension (ECE) indicating stage pT3a N0. (**a**) Axial T2-weighted magnetic resonance (MR) image shows low signal intensity at the right apex broadly in contact with the capsule (*outlined in white*), which is suggestive of PCa lesion. (**b**) Axial dynamic contrast-enhanced MR image shows early enhancement within the suspicious area for PCa with irregularity of the capsule (*outlined in red*). (**c**) Axial diffusion-weighted MR (B 800) shows the region of interest (ROI) 1 located within the suspicious area for PCa (*purple circle*) and the ROI 2 within the benign tissue (*green circle*). (**d**) ADC mapping results in the difference in ADCs'. ADC ROI 1 (0.111 $cm^2/s$) is lower than ADC ROI 2 (0.187 $cm^2/s$) leading in a difference of 41 % of decrease suspicious for PCa within the right apex

tate cancer was found in 22 out of 90 men (24.4 %) who had second TRUS-guided biopsy, compared to 41 out of 90 (45.5 %) ($p=0.01$) men who had MRSI-DCE-MRI targeted biopsy. Magnetic resonance spectroscopy had 92.3 % sensitivity, 88.2 % specificity, 85.7 % positive predictive value (PPV), 93.7 % NPV, and 90 % accuracy; DCE-MRI had 84.6 % sensitivity, 82.3 % specificity, 78.5 % PPV, 87.5 % NPV, and 83.3 % accuracy; and the association of MRSI

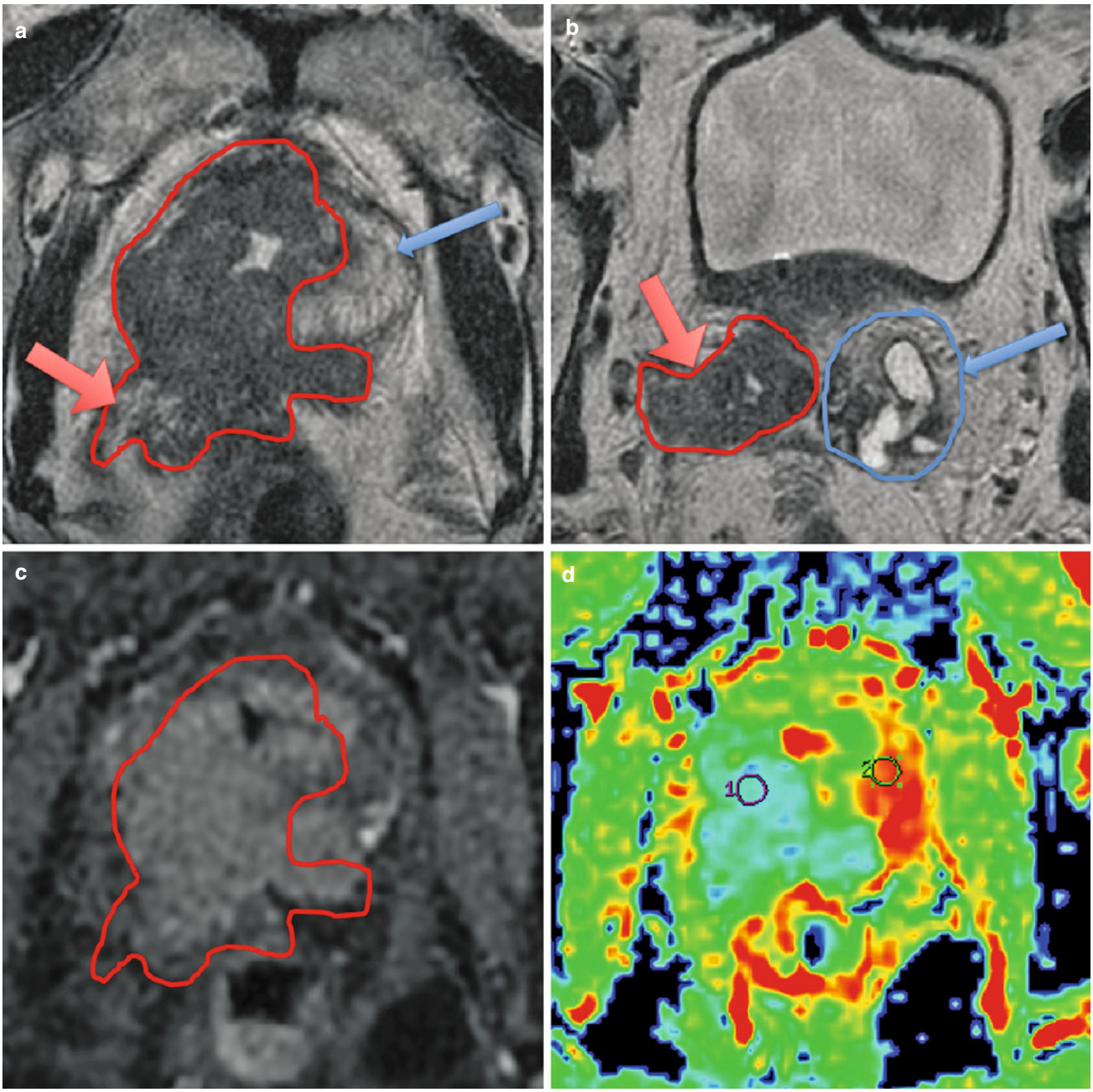


**Fig. 40.4** Seminal vesicle involvement images. Patient (age: 70 years) with prostate-specific antigen level of 6.48 ng/ml; bilateral suspicious findings at digital rectal examination. Histology at transrectal ultrasound-guided biopsy showed prostate adenocarcinoma (PCa) on 5 cores out of 10, Gleason score 7 (3+4) in right-side; histology at robotic radical retropubic prostatectomy showed Gleason score 7 (4 at 60 %+3 at 40 %) bilateral PCa with the right seminal involvement (SVI) indicating stage pT3b N0. (**a**) Axial T2-weighted image in a patient with advanced local stage prostate cancer. On the axial image, the entire right-side tumor is seen as a hypointense region in contrast to the normal appearing hyperintense left central zone (*small blue arrow*), with tumor also showing right SVI (*large red arrow*). (**b**) Axial T2-weighted image shows the right SVI within the hypointense area (*large red arrow*), just under the full bladder, in sharp contrast to the contralateral benign seminal vesicle in the left hyperintense area (*small blue arrow*). (**c**) Axial dynamic contrast-enhanced image shows an avid early enhancement within the right-side tumor prostate, involving the right seminal vesicle (*red circle*). (**d**) ADC mapping with region of interest 1 (*purple circle*) within the area highly suspicious for tumor based on both T2W-MR and DCE-MR images and the second region of interest (*green circle*) located within the appearing benign tissue. ADC ROI 1 is 0.747 $cm^2/s$, while ADC ROI 2 is 2.28 $cm^2/s$, resulting in a sharp drop of ADC values of 68 % between ROI 2 and ROI 1 highly suspicious for high-grade tumor, indicating preoperative stage pT3b Nx

plus DCE-MRI had 92.6 % sensitivity, 88.8 % specificity, 88.7 % PPV, 92.7 % NPV, and 90.7 % accuracy for prostate cancer detection. Therefore, the combination of MRSI and DCE-MRI leads to a greater potential for targeting cancer foci during a biopsy in patients with a previously negative TRUS biopsy.

Although these outcomes are encouraging, missing the cancer still remains a risk with TRUS, due to less visibility. As a result, software systems have been developed to intuitively guide the biopsy placement directly with MRI, but that is still in a testing phase [16, 17].

## Ruling Out Patients with Persistently High PSA

Regarding patients with persistently high PSA after negative transrectal biopsies of prostate, an ideal diagnostic test would provide a high NPV in order to avoid needless subsequent biopsies. Irrespective of the management chosen to find a positive PCa biopsy, a high PSA with negative biopsies presents dilemmas as to when further testing can be discontinued. Prostate-specific antigen values are very sensitive with low specificity [18], which means that there is a high false-positive rate but with most PCas being detected. If the threshold was decreased, the risk would be that cancers would be missed in greater frequencies. Despite PCa being screened with such sensitivity, the numerous false positives limit the precision of the screening tool, with a consequent delay in treatment. With a high positive predictive value (PPV), however, the false-positive rate can be reduced, and patients with a high risk of PCa can be excluded.

Established strategies for managing such patients include a repeat biopsy scheme (10–12 cores), saturation/template biopsy (>12 cores), or continued PSA monitoring. None of these strategies are ideal. The first two are invasive and may still miss significant cancer, while the third method does not address the necessary steps to take if the PSA continues to rise. A noninvasive imaging modality would constitute a major breakthrough in prostate cancer diagnostics. Magnetic resonance imaging shows promise in this area. Studies have shown that an MRI in patients with one set of negative biopsies and rising PSA levels is better than a repeat TRUS biopsy. In a screening population of 92 patients, Comet-Batlle et al. demonstrated 80 % sensitivity, 76.1 % specificity, 55.6 % PPV, 91.1 % NPV, and 77.2 % accuracy for MRI, compared to 85 % NPV for a negative octant biopsy for prostate cancer [19]. Cheikh et al. reported 82.6 % sensitivity and 100 % NPV for T2-weighted MRI when evaluating visible suspicious areas prior to repeat TRUS prostate biopsy [20]. An MRI showing "no evidence of disease" in a patient with a marginally raised PSA would seem to offer a similar level of reassurance as two sets of prostate biopsies reporting "no cancer detected."

To rule out cancer in a patient with a persistent high PSA score and no positive histologic results, one should work toward reducing the number of false positives and confirming the value of true negatives. When these goals are achieved, PPV and NPV will increase, respectively. Thus, a negative MRI result should increase the NPV of a set of negative biopsies and may eliminate the need for repeat biopsy.

## Diagnosing PSA Level Relapse After Definitive Treatment Ranging from Local to Distant Metastasis

A computed tomography (CT) scan has inferior diagnostic value in patients considered for salvage therapy, who typically have low PSA levels. Nomograms are useful for populations, but not highly relevant for an individual patient. Recently, MRI has proven capable of detecting local recurrence in many patients with a rising PSA, but who have no palpable tumor on digital examination. Silverman and Krebs have demonstrated the potential of MRI in the evaluation of local recurrence following prostatectomy with excellent sensitivity (100 %; 95 % confidence interval [CI] = 89–100 %) and specificity (100 %; 95 % CI = 69–100 %) [21].

Sella et al. confirmed the high efficacy of MRI (sensitivity for detecting a recurrence was 95 % and specificity 100 %). In patients with recurrent cancer after radiation therapy, MRI has shown reasonable accuracy in tumor detection, including the detection of extraprostatic extension (ECE) and seminal vesicle seminal involvement (SVI) [22]. Moreover, MRI has been shown to be superior to TRUS in detecting local recurrences of prostate cancer. In addition to detection of local recurrence in the perianastomotic and retrovesical regions (the sites also well identified on TRUS) [23], it can also detect recurrences occurring elsewhere in the pelvis, such as at the site of retained seminal vesicles or at the lateral and anterior surgical margins, which together account for 30 % of local cancer recurrences. Magnetic resonance imaging, therefore, has the potential to direct a transrectal biopsy to these sites and, thus, may lead to a better diagnostic yield than TRUS. An additional benefit of MRI over TRUS and CT scans is the ability to concomitantly evaluate pelvic lymph nodes and osseous structures, thus detecting most sites of pelvic relapse in a single examination.

## Assistance in Defining the Aggressiveness of Tumors

The Gleason score of the tumor is not necessarily truly represented by the biopsy results. For the low-risk PCa, DRE and TRUS results are unreliable. Based on first positive biopsy, some patients assigned to an active surveillance (AS) program ultimately die of disease or experience a worse outcome. Error comes from incorrect enrollment in AS, which is caused by poor selection. Some potentially highly aggressive PCas are not detected and are confused with some indolent ones.

To optimize eligibility of patients in AS, Bergund et al. [24] recommend repeated biopsy for patients, including those in AS, within 3 months of their first biopsies. Twenty-seven percent of patients experienced upgrading or upstaging after repeated biopsies. Among those patients finally treated by

radical prostatectomy (RP), all showed higher pathologic stage and grade than those who had not undergone RP. In the literature, more than 40 % of patients experience upgrading from pretreatment staging to definitive histologic staging of the specimen. In Bergund's study, the procedure was systematic and, even if MRI was performed, no target was defined by using MRI. So, tracking PCa first with MRI and targeting the more accurate biopsy in order to decrease the risk of undergrading might be a strategy that can improve results.

Multiparametric MRI, on its own, could also be a source of information for grading. Thanks to mpMRI, with assessment of metabolism, water diffusibility, and vascularity, we can expect to get more information about Gleason score. Further accuracy in Gleason scoring would enable more appropriate decision-making regarding radical treatment versus AS for individual patients and their doctors.

It is well established that Gleason score may be upgraded by 40 % [25] after RP. Hence, it is important to strengthen enrolment processes into AS programs by complementary tool that facilitates more accurate grading. Multiparametric MRI might contribute to defining aggressiveness of tumor, aiding in the decision-making process for patients. The incremental value of MRI/MRSI to the staging nomograms for predicting organ-confined prostate cancer has been assessed in a retrospective study (Wang et al.) [26]. This results in significant incremental value ($p \leq 0.02$) to the nomograms in the overall study population. The contribution of MRI findings was significant in all risk groups but was greatest in the intermediate- and high-risk groups ($p < 0.01$ for both). However, at that time, no significant benefit with MRSI relative to MRI has been found.

Furthermore, MRSI has shown promise in assessment of aggressiveness of tumor by revealing an increasing choline + creatinine/citrate ratio, parallel to Gleason score, as declared in the study of Shukla-Dave et al. [27]. The comparison was established from statistical models, based on clinical features (DRE, PSA, biopsies, etc.), developed to predict indolent PCa. The ROC AUC ranged up to 0.79 suggesting good accuracy. Ultimately, it was found that adding MRI with MRSI increases the predictive accuracy, improving the AUC from 0.803 (MRI model) to 0.854 (MRI/MRSI model).

Additionally, Franiel et al. [28] investigated whether mpMRI is helpful in differentiating the low-grade (Gleason score ≤ 6) and the high-grade (Gleason score ≥ 7) PCa. Promising results were achieved in correlating grading areas of PCa between MRI and histologic outcomes of RP specimens: in 32 patients scheduled for RP, 41 areas of PCa have been correlated with the RP specimens. No correlation could be found for the other 10 patients in the study. Low-grade PCa had significantly higher mean blood volume, longer mean transit time, and lower mean permeability than high-grade PCa. These features, achieved by using 1.5-T mpMRI, could be used to properly assess tumor aggressiveness and better manage the patient undergoing AS.

Villeirs et al. [29] have investigated the ability of MRSI to predict high-grade PCa, defined by Gleason ≥ 4 + 3, performed on 1.5-T MRI, by correlations with histologic findings of biopsies. This study enrolled 356 men with a rising PSA. With a very short follow-up (mean 21.3 months), 220 patients had PCa confirmed by positive biopsy (41 high-grade and 179 low-grade). Results revealed a significant ability to eliminate high-grade PCa with a NPV of 98.4 %. Few false positives have been found with only 7.3 %, with suspicion of PCa by combined MRI within cancer-free men (136). As reported, MRI and MRSI are reliable tools to exclude high-grade tumors with high sensitivity (92.7 %) but are still lacking sensitivity for low-grade PCa (67.6 %).

Those conclusions could involve a way of selecting and following up patients in AS programs but currently need more investigation of the low-grade PCa, by using more powerful magnets or different sequences of MRI to optimize their sensitivity of detection.

## Focal Therapy Planning of Prostate Cancer

Currently, new modes of therapy exist to treat just a part of the organ in order to spare nerves and to prevent voiding disorders that largely stem from curative treatment modalities and affect the sphincters or the neck of bladder. These technologies include brachytherapy, high-intensity focused ultrasound, cryotherapy [30], stereotactic radio surgery, and vascular-targeted photodynamic therapy [31]. Although PCa has been well demonstrated to be a multifocal disease, it has been shown that the biologically significant tumor is often a solitary, dominant lesion, with the secondary lesions being of limited malignant potential [32]. Since MRI has been found to be accurate in localizing a tumor with a high NPV, it could be used to map such dominant lesions, and thus could assist in planning for focal therapy [33]. Focal therapy could be a viable alternative to potential undertreatment associated with AS and potential overtreatment associated with radical therapies [34].

In theory, focal therapy extends its benefits by having the great potential to minimize treatment-related toxicity without compromising a cancer-specific outcome. Local cancers and unilateral tumors could be managed in a focal therapy program [35]. As encountered in AS, the difficulty lies in reliably finding these patients. Multiparametric MRI appears to be the best tool with its high NPV and its accuracy to target lesions. However, for the small low-risk cancers, mpMRI is still not as sensitive as required, resulting in missing many diagnoses (false negatives). For larger tumors and/or the more dangerous tumors, mpMRI has a much better sensitivity. Thus, mpMRI could still miss some small PCa, but it can eliminate the multifocal tumors and the bigger PCa. So, this may be of value in planning treatment areas for focal therapy [36].

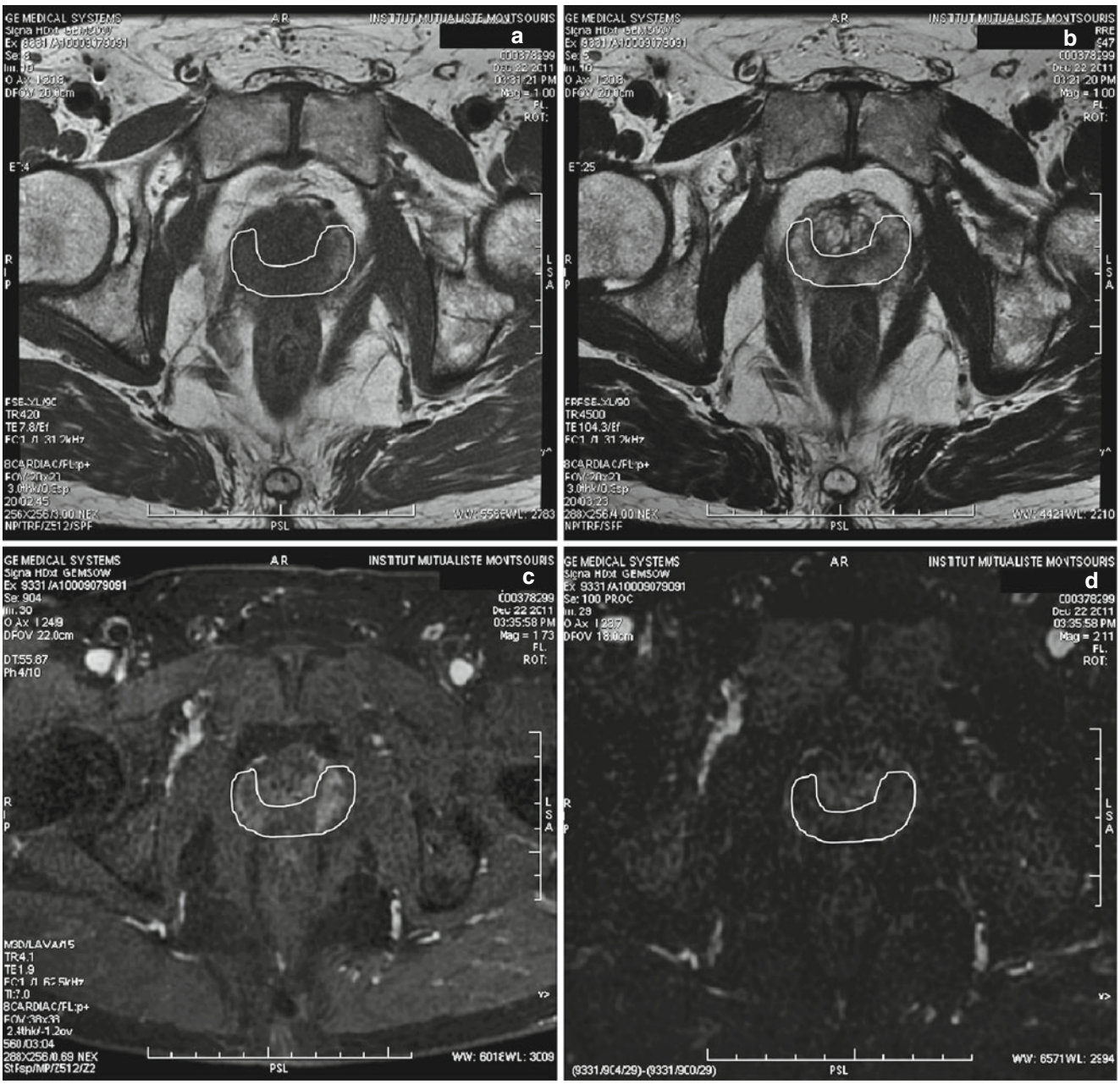


**Fig. 40.5** Posthemorrhage artifact images. Patient (age: 57 years) with prostate-specific antigen level of 6.01 ng/ml; suspicious findings at digital rectal examination on the right. Histology at transrectal ultrasound-guided biopsy showed prostate adenocarcinoma (PCa) on 3 cores out of 18, Gleason score 6 (3 + 3) in the right-side samples; histology at robotic radical retropubic prostatectomy showed Gleason score 7 (3 at 80 % + 4 at 20 %) bilateral PCa with extracapsular extension (ECE) in the right apex peripheral zone (PZ) indicating stage pT3a Nx. (**a**) Axial T1-weighted magnetic resonance (MR) image shows high signal intensity both in the right and left PZ (*outlined in white*), which is suggestive of postbiopsy hemorrhage artifacts. (**b**) Axial T2-weighted MR image shows low signal intensity both in the right and left PZ (*outlined in white*), which is suggestive of PCa lesion. (**c**) Axial dynamic contrast-enhanced MR image suspicious for early enhancement in both PZ (*outlined in white*). (**d**) Subtraction dynamic contrast-enhanced MR image results in no enhancement (*outlined in white*). Posthemorrhage must be screened on T1-weighted MR and leading to restrict any conclusion

## Limitations of MRI

Current MRI technology is limited by its low sensitivity for small PCa < 3 mm or containing less than 30 % cancer cells. As low risk CaP is increasing in both incidence and prevalence, it would be of high utility if MRI was more sensitive in picking up these lesions. Benign prostate hyperplasia (BPH) and postbiopsy hemorrhage (Fig. 40.5) are also real artifacts, restraining the accuracy for localizing PCa. A conventional time frame of 6 weeks is required after biopsy before MRI examination to try and minimize these artifacts. This is a long period and, even if respected, some lesions are

still visible as a hyper signal on T1-weighted images, resulting in false positives on DCE-MRI.

Furthermore, there are several limitations in the widespread adoption of mpMRI. First, equipment and protocols of MRI are not universal, with inconsistent uptake between centers, even those considered centers of excellence. In addition, there is no reliable trial today to investigate the cost/efficiency balance of mpMRI. In addition, the use of an endorectal coil is considered a barrier [37] by patients and limits compliance. A possible solution would be to increase the signal-to-noise ratio by using a more powerful magnet and thus avoiding the using of endorectal coil altogether.

## Future Prospects for MRI in Prostate Cancer

Currently, clinical magnets have field strengths in the range 1.5–3.0 T. Future studies should investigate whether a new generation of 7-T MRI could provide better discrimination in selecting and surveying patients in AS protocols. Several studies with 3-T MRI have recently led to improving the general performance of imaging [38]. Augustin et al. have demonstrated 3-T MRI imaging is meaningfully more accurate in pretreatment staging for clinically localized PCa than the Partin tables. It is actually common to think the higher is the magnet, the more accurate is the imaging. Moreover, at 3-T MRI, the signal-to-noise ratio improves. This leads to enhanced spatial, spectral, and temporal resolution, resulting in a more accurate anatomic imaging [39]. Further, increasing magnet strength would allow patients to avoid the endorectal coil.

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# The Role of Functional Magnetic Resonance Imaging Techniques

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## Introduction

Magnetic resonance imaging (MRI) has an increasing role to play in the diagnosis and staging of prostate cancer but is also valuable in the noninvasive assessment of tumor aggressiveness, in treatment monitoring, and in the diagnosis of tumor recurrence. Although morphologic T2-weighted (T2W) MRI is an essential first step in the diagnostic evaluation of the prostate, additional functional techniques such as magnetic resonance spectroscopy (MRS), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) MRI can boost the diagnostic, staging, and grading performance of MRI beyond the limits of what is achievable with T2W imaging alone. They can be used separately or in combination in a so-called multimodality approach.

In this chapter, MRS, DWI, and DCE-MRI will be discussed in detail, and reference will be made to some new applications and further refinements of these techniques.

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## Magnetic Resonance Spectroscopy

MR spectroscopy (MRS) provides information about the prostate metabolism by measuring the relative concentrations of metabolites such as citrate, choline, polyamines, and creatine.

In normal aerobic cells (outside the prostate), citrate is an important intermediary in the cellular metabolism through its mitochondrial synthesis and oxidation in the Krebs cycle (also called citric acid cycle or tricarboxylic acid cycle) [1, 2]. It is involved in the metabolism of carbohydrates, proteins, and fats and provides a major source of cellular energy through the generation of adenosine triphosphate (ATP). The oxidation of citrate is mediated by the enzymatic activity of mitochondrial aconitase (m-aconitase).

Normal prostate secretory epithelial cells, however, exhibit a totally different metabolism. Instead of oxidizing citrate, they actively accumulate and secrete very high levels of citrate into the prostatic fluid (about 500 times higher than in blood plasma), where citrate is assumed to play a role in the maintenance of acidity, in the chelation of cations, and in the energy provision and capacitation process of sperm [1, 3]. The citrate accumulation is the result of extraordinary high levels of intramitochondrial zinc, which inactivates m-aconitase and therefore aborts the normal operation of the Krebs cycle [4]. Prostate secretory epithelial cells actually adopt alternate, although energetically much less efficient, metabolic pathways for their energy requirements. Nonoxidized citrate accumulates within the mitochondrion and in the cytoplasm and is ultimately secreted into the ductal lumen.

Early in the pathogenesis of malignancy, even before the appearance of histopathologically identifiable malignant changes, neoplastic prostate cells lose their ability to accumulate zinc [1]. As a consequence, m-aconitase activity is restored, with resulting citrate oxidation and ATP production to fulfill the neoplastic energy requirements through a resumed Krebs cycle. In addition, citrate is utilized in an accelerated lipogenesis, which is important in the process of

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malignant membrane synthesis. Both phenomena provide a metabolic explanation for the lower citrate concentration in prostate cancer tissue. Furthermore, the citrate-containing secretory ductal compartment is gradually replaced by an increasing volume of citrate-poor metaplastic cells, especially in Gleason patterns 4 and 5, adding further evidence to the observed decrease of citrate in malignant tissue [5, 6].

An increased choline peak has been observed in spectroscopic evaluation of tumors in the brain, breast, and prostate [7]. Choline compounds are involved in the cellular membrane synthesis and degradation. Free choline enters the cell via membranous choline transporters and is phosphorylated to phosphocholine by the enzymatic activity of choline kinase. Further enzymatic activity results in the formation of the major membrane component phosphatidylcholine. In membrane degradation, the breakdown of phosphatidylcholine into phosphocholine, free choline, and glycerophosphocholine is mediated by several catabolic enzymes (e.g., phospholipase A2, C, and D) [8, 9]. In tumors, an increased choline concentration may thus be caused by several mechanisms, including altered choline transport, increased choline kinase activity, and/or increased catabolic activity [8–11].

Polyamines play a role in the regulation of cell proliferation and differentiation. In the prostate, spermine is the most important polyamine. It favors cellular differentiation rather than proliferation and is proportional to the epithelial secretory state [12, 13]. Spermine levels are therefore high in normal prostatic tissue and benign hyperplastic nodules but are reduced or absent in prostate cancer [12].

The creatine concentration in the prostate tends to be low and is not substantially different in normal prostate tissue than in prostate cancer [14, 15].

During a spectroscopic examination, a three-dimensional data set is acquired with spectra from small voxels throughout the prostate peripheral zone and central gland, using a 3D chemical shift imaging (3D-CSI) acquisition protocol [15, 16]. Signal contributions from water and fat are selectively suppressed, and several outer-voxel saturation bands are applied close to the prostate margins to reduce contamination from surrounding structures, especially periprostatic fat. Each voxel measures the relative concentration of metabolites that resonate at distinct frequencies in the spectrum [14, 17–19] (Fig. 41.1). The citrate peak resonates at 2.6 ppm and has a doublet-like shape at 1.5 T and a quadruplet-like shape at 3.0 T. The total choline peak resonates at 3.2 ppm and is a singlet that is actually composed of several choline-containing compounds such as phosphocholine, glycerophosphocholine, and free choline. In vivo spectroscopy at 1.5 T, however, cannot resolve their separate peaks. The creatine singlet resonates at 3.0 ppm and is difficult to resolve from choline at 1.5 T. Because of its position close to choline, its spectral contribution is usually added to the choline peak to ease the quantification of choline compounds. Polyamines,

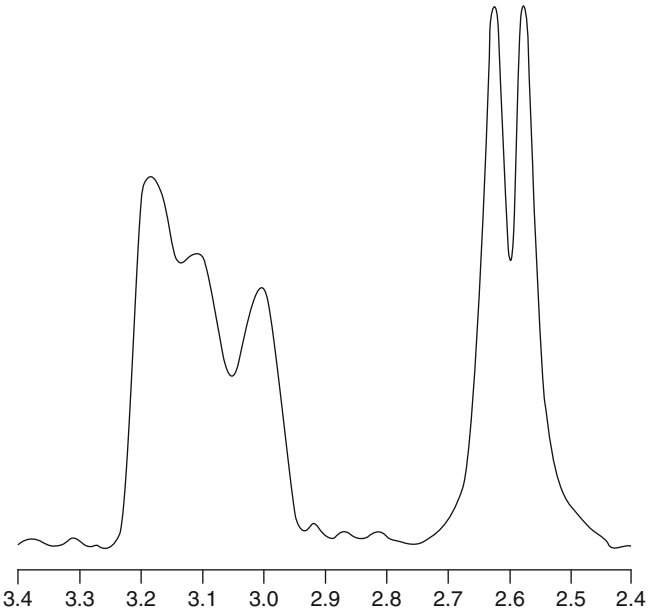


**Fig. 41.1** MR spectrum of healthy prostate tissue. MRS measures the relative concentration of metabolites that resonate at distinct frequencies in the spectrum. The citrate peak resonates at 2.6 ppm and has a doublet-like shape. The total choline peak resonates at 3.2 ppm, and the creatine singlet resonates at 3.0 ppm. Polyamines, including spermine, resonate in between choline and creatine and present as a variable multiplet resonating at 3.1 ppm

including spermine, resonate in between choline and creatine and present as a quite variable multiplet resonating at 3.1 ppm. At 1.5 T, the creatine, polyamines, and choline peaks are difficult to resolve separately, but at higher field strengths, the polyamine peak can occasionally be better resolved from choline and creatine.

The complementary changes of these metabolites are used to predict the presence or absence of prostate cancer. The choline-plus-creatine-to-citrate (CC/C) ratio integrates metabolic information of both citrate and choline into one parameter. Since malignancy is associated with higher choline peaks and lower citrate peaks, higher CC/C ratios are increasingly more suggestive of prostate cancer [15, 20, 21]. In addition, a choline-to-creatine (C/C) ratio can be calculated, especially at 3 T, and higher C/C ratios are associated with prostate cancer [22].

Polyamines are usually included in the numerator of the CC/C ratio at 1.5 T, but if they can be resolved at 3 T, a reduced peak height or even absence of the polyamine peak will be indicative of malignancy [12].

Metabolite peaks and ratios can be evaluated quantitatively or qualitatively. In the quantitative analysis, a measured metabolite peak is compared with prior knowledge files of how a standard metabolite peak looks like, and a mathematical curve is constructed that fits this given peak as closely as possible. On the basis of this mathematical curve, measurements such as peak height, peak width, and area

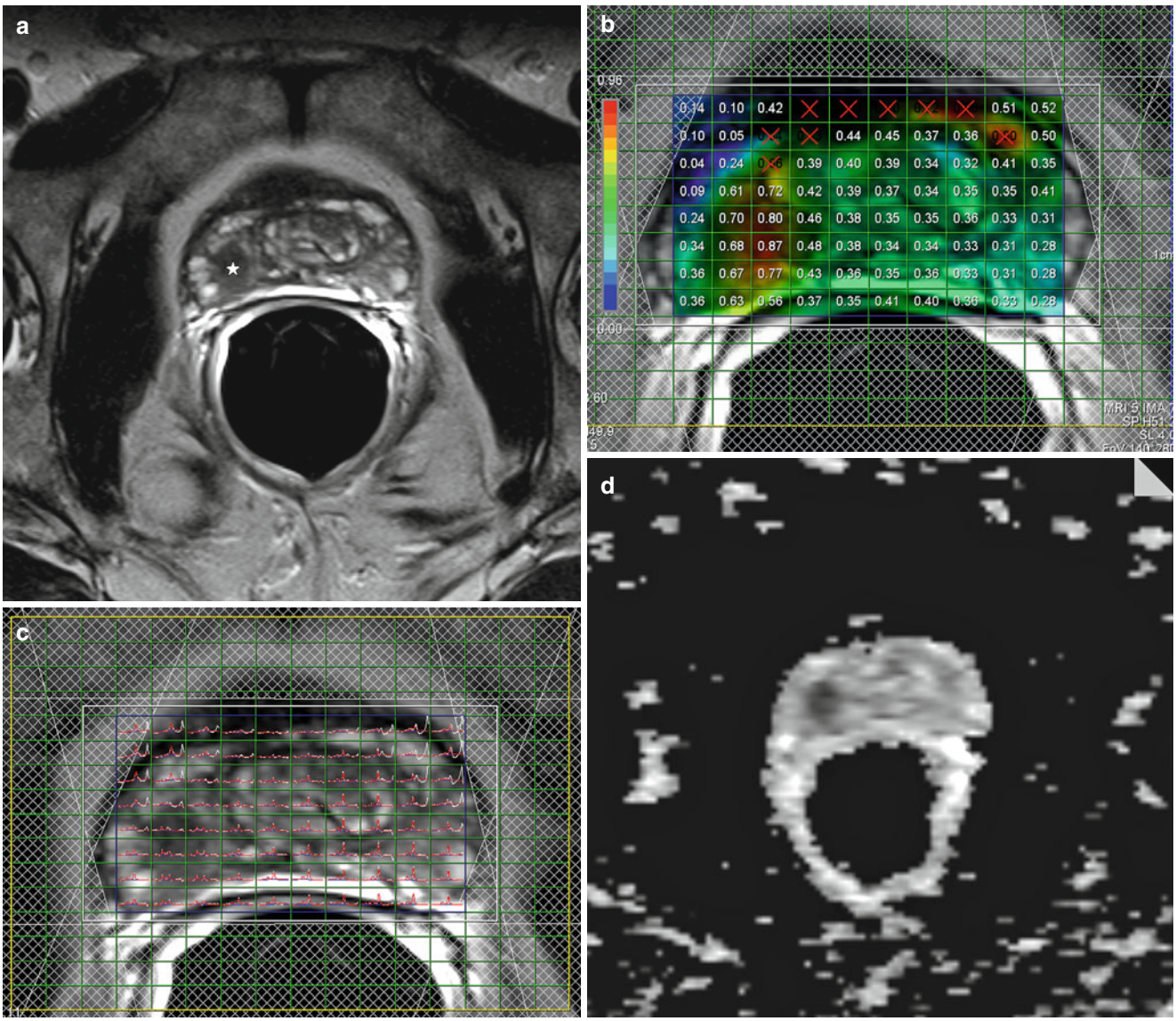


**Fig. 41.2** Multimodality approach with T2W, MRS, and DWI for primary tumor detection in a 61-year-old patient with elevated PSA. On a transverse T2W image (**a**) the prostate cancer is demonstrated as a nodule with low signal intensity on the right side of the midprostate (*white star*). MRS shows suspicious metabolite indices in this tumoral region. In the quantitative evaluations, metabolite peak area under curves is calculated in each voxel throughout the prostate and is visualized in a color-coded map (**b**, at the same level as **a**). In the qualitative evaluation, the peak heights of citrate and choline are visually compared. The prostate cancer on the right side of the midprostate shows elevated choline peak heights, exceeding the lower citrate peak heights in more than three adjacent voxels. In the left half of the prostate, normal metabolite concentrations are demonstrated (**c**, at the same level as **a** and **b**). On DWI, the prostate cancer shows restricted diffusion, resulting in a low-signal intensity lesion on the ADC map (**d**, at the same level as **a**–**c**)

under curve can be performed, and metabolite ratios can be calculated. At least 2–3 adjacent voxels with CC/C ratios exceeding 2 (possible cancer) or 3 (definite cancer) standard deviations above the mean ratio in normal peripheral zone tissue and exceeding 3 (possible cancer) or 4 (definite cancer) standard deviations above the mean ratio in normal central gland tissue are considered indicative of malignancy [15, 20, 22–24].

In the qualitative analysis, on the other hand, the measured peak heights of citrate and choline are visually compared using a pattern recognition diagnostic scale. An area in which choline peak heights exceed the citrate peak heights in at least three adjacent voxels is considered indicative of malignancy [25, 26] (Fig. 41.2).

Diagnostic accuracies up to 70–90 % for MRI combined with MRS have been reported, yielding a 10–20 % improvement compared to morphologic T2WI alone [17, 18, 27–30]. A very interesting application, however, is its ability to noninvasively predict tumor aggressiveness. The prostate cancer Gleason grade has been reported to correlate with both MRI

[31] and MRS [27], and the combination of both techniques has shown to better predict the probability of insignificant prostate cancer than clinical models (clinical stage T1c or T2a, primary and secondary biopsy Gleason grades 1–3, pretreatment PSA level <20 ng/ml, ≤50 % of biopsy cores positive) [32]. Furthermore, combined MRI and MRS has shown to be successful in predicting presence or absence of a high-grade tumor (Gleason 4+3 or higher), with a sensitivity of 92.7 % and a negative predictive value of 98.5 %, respectively [33]. This is of particular importance in patients with persistently elevated PSA and repeatedly negative prior biopsies, in whom a negative MRI+MRS may reduce the need for rebiopsy but a positive MRI+MRI warrants systematic rebiopsy, supplemented with biopsies targeted at the suspicious areas. Furthermore, the exclusion of high-grade tumors with MRI+MRI may support the choice for active surveillance in a prostate cancer patient in whom active therapy is deemed inappropriate.

MR spectroscopy can be a very helpful adjunct to image-guided radiotherapy for prostate cancer. It has been reported that tumor recurrences after treatment failure usually originate at the primary tumor location [34] and that the probability of local relapse after radiation therapy increases with increasing Gleason grade of the primary tumor [35]. It may thus be justified to focus a high radiation dose at this primary tumor site, by exploiting the ability of MR spectroscopy to localize and predict the tumor's Gleason grade [27, 33]. With intensity-modulated radiation therapy, a high dose focusing to that area can indeed be achieved without increasing the risk of complications and while maintaining a sufficient dose to the whole prostate (and seminal vesicles) [36–41].

MR spectroscopy has shown to be a promising tool in the detection of recurrences after failed surgery or nonsurgical treatment.

After external-beam radiation therapy (EBRT), reparative phenomena seem to alter the energy requirements of the involved normal prostate cells and promote their conversion from citrate producing to citrate oxidizing. In addition, their augmented phospholipid cell membrane synthesis and degradation increases the demand for choline compounds. As a result, even nonmalignant irradiated prostate parenchyma will show lower citrate peaks and higher choline peaks [42, 43]. It therefore remains unclear what metabolic criteria should be used to differentiate benign from malignant areas in the irradiated prostate. Pucar et al. used a CC/C ratio threshold of 0.5 or higher as indicative of a recurrence and found an area under the receiver-operating characteristic (ROC) curve of 0.88 for discrimination of benign and malignant prostatic tissue after EBRT [43]. On the other hand, Coakley et al. used an increased C/C ratio or an increased ratio of choline relative to background noise (if creatine was undetectable) and reported an ROC of 0.81 for the detection of recurrent cancer [44]. On the other hand, absence of significant metabolite peaks (also known as "metabolic atrophy," i.e., spectra with peak area-to-noise ratios of less than 5) has been reported to indicate absence of local recurrence [44, 45]. This can be particularly valuable for reassuring patients with rising or repeatedly elevated ("bouncing") posttreatment PSA [45] or to assess local control after brachytherapy [46].

After radical prostatectomy, MR spectroscopy inevitably struggles with some difficulties to reliably detect tumor recurrence, especially when it is still small. A normal metabolic background is obviously lacking when all prostatic tissue has been removed; particularly, citrate should not be measurable after proper removal of the prostate. A CC/C ratio is therefore difficult to calculate in the prostatectomy fossa. Surgical clips in the anastomotic area may further compromise or preclude successful spectroscopic measurements because of field inhomogeneities and susceptibility artifacts [47]. Nevertheless, sensitivity and specificity values up to 88 % have recently been reported, and it was suggested to combine MRS with DCE-MRI to detect or rule out a recurrence in patients with biochemical failure [48].

In other types of focal therapy (cryosurgery, HIFU), the role of MRS currently remains unclear [49–51].

## Diffusion-Weighted Imaging

Diffusion-weighted MR imaging (DWI) is an MR technique that provides information about the amount of thermally induced random movement of water molecules, also called Brownian movements. The degree of motion as measured by DWI relates to the mean path length traveled by water molecules within an observation period, during which the DWI signal decays proportional to the degree of magnetization dephasing caused by this molecular motion [18, 52–56]. In addition, the signal intensity on DWI is influenced by the T2 relaxation of water protons (i.e., T2 shine-through effect) [53]. The extent to which a DWI sequence is sensitive to diffusion rather than to this T2 relaxation is described by its so-called *b*-value [52]. A low *b*-value primarily reflects T2 relaxation, whereas a high *b*-value is optimal for diffusion measurement [53]. In a typical DWI sequence, 4-mm single-shot fat-suppressed spin-echo echo-planar MR images (EPI) are acquired at different *b*-values ranging from 0 to 1,000 or even to 2,000 s/mm$^2$, although there is currently no consensus on the optimal choice of *b*-values to be used in DWI of the prostate [18, 53–57]. To eliminate the T2 shine-through effect and to quantify the DWI information, an apparent diffusion coefficient (ADC) is calculated from two or more DWI images, identical in every aspect other than their *b*-value [52, 53]. The ADC calculation is performed in every pixel of the image and is displayed as a parametric map (ADC map) [18, 53–56]. Longer traveled path lengths of the water

molecules (i.e., more diffusion) are associated with higher ADC values and vice versa [52].

DWI can easily be implemented in a routine clinical practice MRI acquisition protocol due to its relatively short scan time and the availability of standard post-processing tools provided by the manufacturers [53, 54]. The use of an endorectal coil improves image quality as it provides superior signal-to-noise ratio (SNR) although it may lead to reduced patient compliance and more susceptibility artifacts [53]. DWI is likely to perform better with a 3-T MRI system compared with a 1.5 T system since it provides higher SNR as well as greater spatial and temporal resolution [53, 55, 58]. The higher spatial resolution improves zonal and tumor delineation on DWI and allows more accurate correlation or registration of the ADC map with T2W images. Additionally, 3-T MRI may offer sufficient DWI image quality to perform the examination without application of an endorectal coil [58].

Water diffusion in biologic tissues is dependent on tissue cellularity and integrity of cell membranes [18, 52, 53, 59]. Water molecules are very mobile in glandular tissue, such as healthy prostate parenchyma, and are restricted in their movements in tissues with a high cellular density and intact cell membranes, such as tumor tissue [18, 52, 53]. Most prostate cancers have a high cellular density, with multiple inter- and intracellular membranes impeding the movement of water molecules. This results in reduced molecular path lengths and hence lower ADC values compared to benign prostatic tissue [52, 53, 56]. Prostate cancer can thus be detected and localized on the basis of decreased ADC values. deSouza et al. indeed found a sensitivity of 86.7 % and a specificity of 72.2 % using a threshold ADC of 1.6 $\times 10^{-3}$ mm$^2$/s to separate benign from malignant peripheral zone tissue [60]. Nevertheless, a wide interpatient variation and significant overlap of ADC values in cancerous versus noncancerous tissue has been reported, and a threshold that works for one patient may not necessarily work for other patients. It has therefore been recommended to compare relative intrapatient differences of ADC values in different areas of the prostate, rather than using absolute ADC values. Several other factors may further limit the accuracy of DWI in cancer detection and localization. For instance, alternative types of molecular motion can contribute to the ADC values as well, such as blood flow through the capillaries within a voxel. This is called intravoxel incoherent motion, and it influences the mean path length of water molecules measured in the observation period [52, 53]. The elevated vascular flow to a prostate cancer might thus theoretically offset the expected ADC reduction due to increased tumoral cellularity [52]. To eliminate such perfusion artifacts, the ADC calculation should not include a *b*-value of 0 s/mm$^2$ (e.g., *b*-values of 50 and 800 s/mm$^2$ rather than 0 and 800 s/mm$^2$) [53]. Secondly, normal ADC values tend to vary with prostatic anatomy. The normal peripheral zone is primarily composed of fluid-containing glandular tissue (i.e., higher ADCs), whereas the central gland has more compact stroma and longitudinally arranged smooth muscle fibers (i.e., lower ADCs) [53]. Benign prostatic hyperplasia (BPH) can cause inhomogeneous diffusion patterns as it changes the distribution of cellular density. For instance, the increased cellular density and resulting ADC reduction in hyperplastic stromal nodules may be confounded with that of prostate cancer, although the latter reduction is usually more predominant [53, 55, 61]. ADC values may also change with increasing age due to atrophy of the prostate, with reduced cell volume and enlarged glandular ducts [53]. Finally, acute prostatitis may restrict diffusion and mimic prostate cancer, as it is characterized by increased cellular density due to aggregation of lymphocytes, plasma cells, macrophages, and neutrophils in the prostatic stroma and by extracellular edema causing increased interstitial pressure [53, 55].

For primary tumor detection and localization, the combination of T2W and DWI seems to outperform T2W imaging alone, with reported sensitivities of 71–88 % and specificities of 61–84 %, compared to 50–74 % and 54–91 %, respectively [18, 52–55, 60, 62–65]. For prostate cancer staging, DWI does not seem to add any value to the detection of capsular penetration due to its low spatial resolution, but the combination of T2W and DWI has been reported to better predict seminal vesicle invasion than T2W alone [55, 66] (Fig. 41.3).

DWI seems to be a promising tool for noninvasive grading of prostate cancer. Some authors reported a correlation between ADC values and histological Gleason grade, with higher-grade prostate cancers being associated with lower ADC values and vice versa [65, 67]. Yoshimitsu et al. only found significant ADC differences between well and poorly differentiated prostate cancers but not between well and moderately differentiated or between moderately and poorly differentiated prostate cancers [65]. Still other authors suggested that low ADC values merely correspond to dense and compact cellularity, whatever the Gleason grade [68]. From a histopathological perspective, it is true that higher-grade tumors usually contain more densely packed cancer cells, restricting the movement of water molecules and resulting in lower ADC values, whereas in lower-grade tumors, the glandular architecture is more preserved, with a significant volume of fluid-filled luminal spaces and relatively unhindered motion of the water molecules, resulting in higher ADC values [55, 65, 67, 69, 70]. But higher-grade cancers may also diffusely infiltrate within the normal prostatic tissue, resulting in unexpectedly high ADC values [18]. Further research is clearly needed to elucidate these discrepancies.

DWI may be valuable to guide minimally invasive therapies, targeted radiotherapy, or hemi-ablation, in which

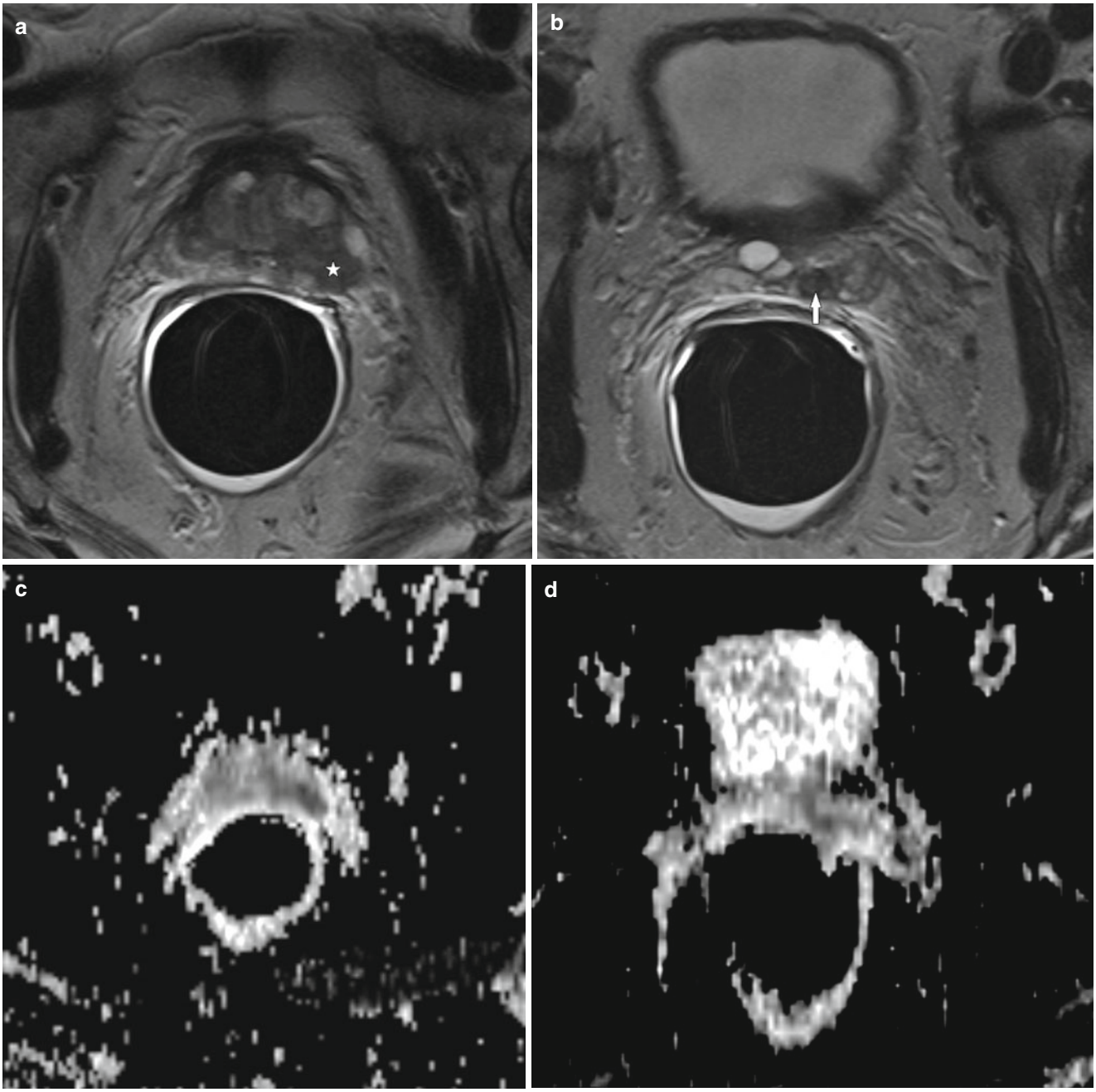


**Fig. 41.3** A 78-year-old patient with biopsy-proven prostate cancer. On a transverse T2W image at level of the prostatic base (**a**), the prostate cancer is demonstrated as a low-signal intensity area on the left side (*white star*). On a transverse T2W image at the level of the seminal vesicles (**b**), invasion of the left seminal vesicles is suspected (*white arrow*). On ADC maps (**c** and **d**, at the same levels as **a** and **b**, respectively), the prostate cancer shows restricted diffusion and consequently low ADC values in the left side of the prostate and in the left seminal vesicles. Despite its low spatial resolution, DWI added to T2W improves assessment of seminal vesicle invasion

accurate assessment of tumor size and localization within the prostate is very important [71]. It is a particularly helpful adjunct to T2W imaging for tumor detection in the central gland because hypointense tumors are usually difficult to differentiate from normal hypointense fibrous stroma and benign nodules on T2W imaging alone [65] (Fig. 41.4). DWI may also be valuable for the evaluation of treatment response. The cellularity in a treated area changes over time, and DWI can easily differentiate highly cellular from acellular regions [60]. In a study in mice, Wang et al. reported an increase of ADC values in prostate cancer after photodynamic therapy and suggested that DWI may provide a noninvasive imaging marker for monitoring early tumor response and predicting therapeutic efficacy [72].

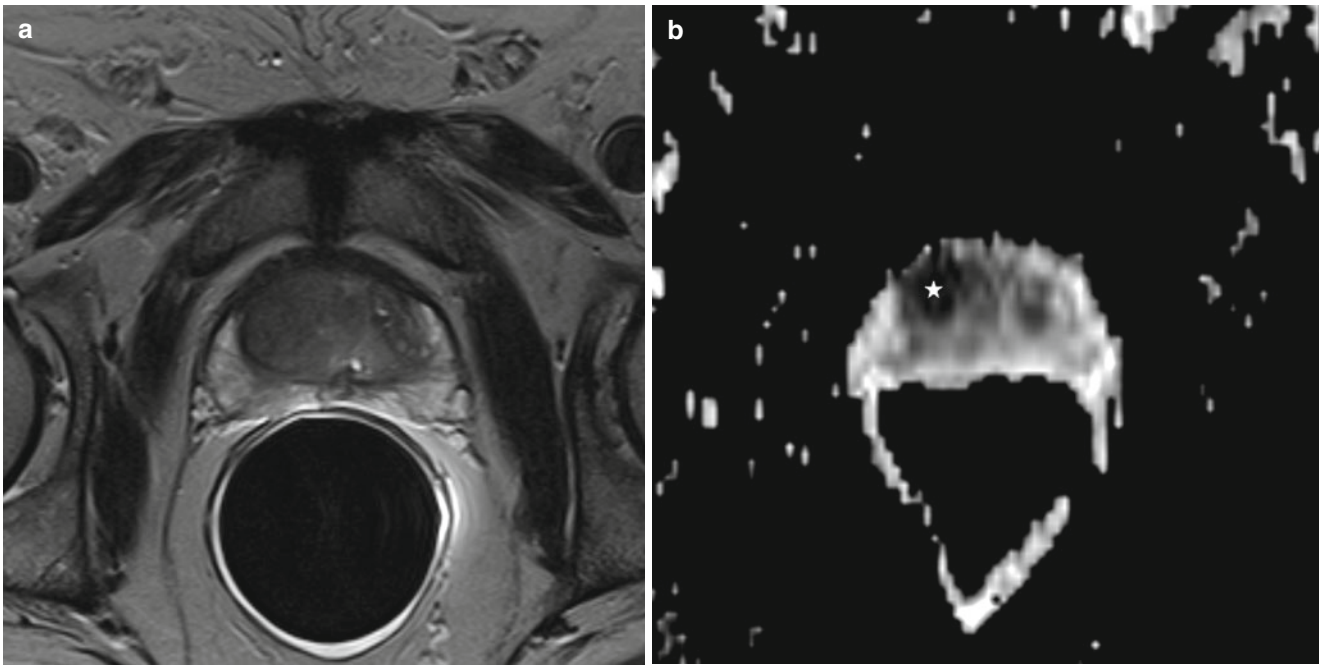


**Fig. 41.4** A 71-year-old patient with prostate cancer in the central gland. On a transverse T2W image, the central gland shows normal diffuse heterogeneously low signal intensity, without suspicious lesions (**a**). On DWI (**b**, at the same level as **a**), strikingly low ADC values are obvious in the right side of the central gland (*white star*), which was confirmed to be prostate cancer. DWI is a particularly helpful adjunct to T2W for tumor detection in the central gland

Hormonotherapy (androgen deprivation) causes the prostatic tissue to become atrophic and diffusely hypointense and nonspecific on T2W imaging, but increasing ADC values due to a reduction in cell density may be an indication of treatment response [73].

The role of DWI in the detection of local recurrence in patients with biochemical failure after treatment for prostate cancer has not been systematically investigated. Yoshimitsu et al. reported a case in which a prostate cancer was relatively clearly depicted on DWI within areas of diffusely decreased signal intensity on T2W, in a patient who had received preoperative hormonal therapy [65]. Only two studies have been published about the value of DWI after external radiation therapy. Kim et al. reported that recurrent prostate cancer had a lower ADC value compared to irradiated benign tissue, predicting recurrence with a sensitivity and specificity of 49 and 93 %, respectively [59]. In a second study, the same authors reported that the use of combined T2W and DWI was significantly more sensitive than T2W imaging alone for the prediction of local recurrence after radiation therapy [74]. After high-intensity focused ultrasound ablation (HIFU), fibrosis, residual benign prostatic hypertrophic nodules, and prostate cancer recurrence may all show low ADC values, compromising the use of DWI [75].

DWI is also being evaluated for the assessment of metastatic lymph nodes. ADC values in benign lymph nodes have been found to be higher than in metastatic nodes, but with a significant overlap [76]. Nevertheless, this approach might perform better than the unsatisfactory size criteria that are routinely used to discriminate benign from malignant lymph nodes [76]. More studies will be needed to validate this new approach.

A variant of DWI is diffusion tensor imaging (DTI). This exciting new concept for the evaluation of prostate cancer has been previously used especially in brain studies. Unhindered water molecules can normally diffuse in any direction of their 3-dimensional environment, but molecules within an anatomical structure (such as cerebral neurons or prostatic ducts) will preferably diffuse in a direction defined by this anatomical constraint. DTI can reconstruct this predominant diffusion direction (or tensor) into a three-dimensional map, yielding a fiber tract (or tractography) of cerebral neurons or prostatic ducts [77]. Tensors in a noncancerous prostate generally show a symmetrical and concentric arrangement, while tensors point at several directions in prostate cancer, hypertrophy, or hematoma-induced deformities [78]. Tractographic analysis allows determining the structural organization of tissue along which diffusion takes place, and it may facilitate assessment of the tumor extension and capsule infiltration [55, 77]. In future, it might be able to discriminate benign tissue from tumors, or it may be useful for predicting therapeutic effects, but more studies are needed to identify the role of DTI in prostate cancer imaging [54, 77, 78].

## Dynamic Contrast-Enhanced MRI

Dynamic contrast-enhanced (DCE) MR imaging provides information about tumoral neoangiogenesis, microvessel density, and vascular permeability, by serial image acquisition before and during the passage of a paramagnetic contrast agent [14, 18, 52–54, 79]. In a typical DCE-MRI examination, an intravenous bolus of a low molecular weight gadolinium contrast agent at a dose of 0.1–0.2 mmol/kg body weight and an injection rate of 3 ml/s is administered, immediately followed by a 20 ml saline flush at the same flow rate [14, 54, 55, 80]. A power injector delivery system is recommended to ensure a constant injection rate [54]. To prevent prostate movement during the serial image acquisition, and to suppress artifacts due to bowel peristalsis, an antiperistaltic agent such as glucagon or butylscopolamine can be administered [53]. The prostate is typically scanned every 2–5 s using a 3-dimensional T1-weighted gradient-echo MR sequence, which is sensitive to the T1 relaxivity of contrast agent in the extracellular extravascular space and reflects microvessel perfusion, permeability, and extracellular leakage. Less frequently, a subsecond T2*-weighted sequence (also called dynamic susceptibility contrast imaging) is used, which is sensitive to the passage of contrast agent in the capillary bed and reflects tissue perfusion and blood volume [18, 54, 55]. When DCE-MRI is part of a multimodality approach (also including morphologic T2-weighted imaging, DWI, and MRS), it is preferably performed at the end of the multimodality sequence, in order not to influence the results of the other modalities [14, 80]. DCE-MRI can also be performed on a 3-T MRI system. This not only provides increased spatial resolution with better visualization of anatomic details but also increased temporal resolution, allowing faster dynamic image acquisition [54, 58, 80]. Some authors have suggested that this can be accomplished even without the use of an endorectal coil [80].

DCE-MRI data evaluation is based on the signal intensity changes following contrast agent administration. To explain the underlying vascular physiology, a two-compartment model is commonly used as theoretical background. The tissue is divided in an intravascular (capillary) portion and an extravascular (interstitial) portion [54]. The contrast agent enters both compartments, and the transfer between the compartments depends on a concentration gradient [53]. The intravenously injected contrast agent is assumed to first diffuse from the intravascular space into the extravascular space and to subsequently leak back into the intravascular space [80]. In a tissue with defective capillary endothelial membranes, such as in cancer neoangiogenesis, the intravascular contrast agent will diffuse faster into the extracellular space but will also leak back faster into the intravascular space. Prostate cancer requires neoangiogenesis for growth beyond a diameter of 2 mm, for invasion of neighboring structures and for successful metastasis to distant sites [53, 55, 81]. It results in chaotic vascular structures, arteriovenous shunts, increased capillary wall permeability, and areas of hemorrhage [18, 53]. The neoplastic interstitial space volume increases and raises a larger gadolinium concentration difference between the intravascular space and the interstitium [18, 53]. This characteristic environment results in a particular enhancement pattern, with early and strong T1-signal increase and rapid de-enhancement (washout) [53]. These phenomena can be visualized using time-signal intensity curves, in which the voxel signal intensity on serial images is plotted over a time scale. Time-signal intensity curves can be analyzed semiquantitatively (using simple curve shape parameters) or quantitatively (using tracer kinetic models with sophisticated perfusion parameters) [53]. Frequently used semiquantitative parameters include peak enhancement (i.e., the maximum signal intensity after contrast injection), time to peak (i.e., the time interval until the signal intensity plateau is reached), initial enhancement slope (i.e., the percentage of initial signal intensity gain, in % base/min), and washout slope (i.e., the percentage of signal intensity loss after the peak has been reached, in % base/min) [54, 82]. Quantitative parameters that have been developed to estimate pharmacokinetic properties include $K^{trans}$, $v_e$, and $k_{ep}$. $K^{trans}$ (transfer constant) describes the diffusion of contrast agent from the intravascular space to the extravascular (interstitial) space. It depends on the flow rate per unit volume, the permeability, and the surface area of the tissue capillaries [54, 81]. $v_e$ is an estimate of the extravascular extracellular volume, also referred to as EES or interstitial space. $k_{ep}$ (rate constant) represents the backleak of contrast from the extravascular space to blood plasma [14, 28, 53–55, 80–82]. Most prostate carcinomas show earlier and higher peak enhancement with initial steep slope of the signal intensity curve, as well as early washout and significantly higher $K^{trans}$, $k_{ep}$, and $v_e$ values than healthy peripheral zone tissue [14, 53, 64, 79–81, 83]. A major challenge for the interpretation of DCE-MRI is the multiplicity of parameters to evaluate, but logistic regression models and computer-aided diagnosis (CAD) systems may be valuable to simplify the interpretation of these data [53, 80, 84]. Combining several pharmacokinetic parameters into a mean pharmacokinetic score (MPKS) for prostate cancer localization indeed seems to perform better than each individual parameter alone [28]. Unfortunately, some overlap in enhancement patterns exists between cancerous versus noncancerous tissue. Neoangiogenesis is not a constant feature of all prostate tumors. Especially small tumors may not exhibit this feature, while angiogenesis can also occur in inflammatory conditions such as prostatitis [53, 80]. Postbiopsy hemorrhage equally tends to enhance abnormally or may even show hyperenhancement, most likely due to reparative granulation tissue [80]. Even benign prostatic hyperplasia may show increased angiogenesis

resulting in early and high initial enhancement pattern, washout slope, high $K_{trans}$, and high $k_{ep}$, mimicking prostate cancer [53, 80, 83].

Sensitivities, specificities, and accuracies of 69–95 %, 80–94 %, and 77–92 %, respectively, have been reported for DCE-MRI in the primary diagnosis of prostate carcinoma, and these figures are significantly better than those of T2W imaging alone [18, 28, 80, 81]. Combining T2W imaging with pharmacokinetic parameters has been shown to primarily increase specificity rather than sensitivity compared with T2W alone [80]. DCE-MRI indeed can more easily attribute a higher malignant potential to rapidly enhancing low T2-signal intensity tumors than to morphologically similar but nonenhancing benign processes [80].

The addition of DCE-MRI to T2W imaging seems to improve the local staging performance only in less experienced readers [14, 28, 55, 85]. Yet Bloch et al. found a higher staging accuracy and better prediction of extracapsular extension for combined T2W and DCE-MRI than for T2W imaging alone, using DCE-MRI with high spatial resolution at the expense of temporal resolution [86].

Studies are ongoing to define whether pharmacokinetic parameters can predict the Gleason grade. Some investigators have suggested that low-grade prostate cancers have higher blood volume and higher vascular permeability than high-grade cancers, but others did not find any strong correlations [82, 87].

Preliminary investigations on the use of pharmacokinetic parameters in treatment follow-up have suggested that DCE-MRI might allow earlier assessment of tumor response than PSA monitoring [82, 88]. Primary radiotherapy seems to be associated with changes of tumor perfusion, and a decrease in tumor vascular permeability has been observed following hormonal treatment [82]. As neovascularization is the histological basis of DCE-MRI, this technique might be the ideal biomarker for treatment monitoring of angiogenesis inhibitors [82].

DCE-MRI has been proven to be of substantial value in the detection of local prostate cancer recurrence in patients with biochemical failure after prostatectomy, radiotherapy, HIFU, or cryosurgery with improvement of patient selection for salvage therapies. After prostatectomy, DCE-MRI can differentiate prostate cancer recurrence from fibrosis in the prostatectomy fossa, from remnants of normal prostatic tissue and from hyperplastic nodules, because tumor recurrence tends to enhance earlier and faster than benign postoperative changes (Fig. 41.5). When used in addition to T2W imaging, DCE-MRI has shown higher sensitivity and specificity as compared to T2W imaging alone (84–88 vs. 48–61 % and 89–100 vs. 52–82 %, respectively) [79, 89]. Various pharmacokinetic parameters have been used to define recurrence on DCE-MRI. Sciarra et al. reported a sensitivity and specificity of 79 and 100 %, respectively, using

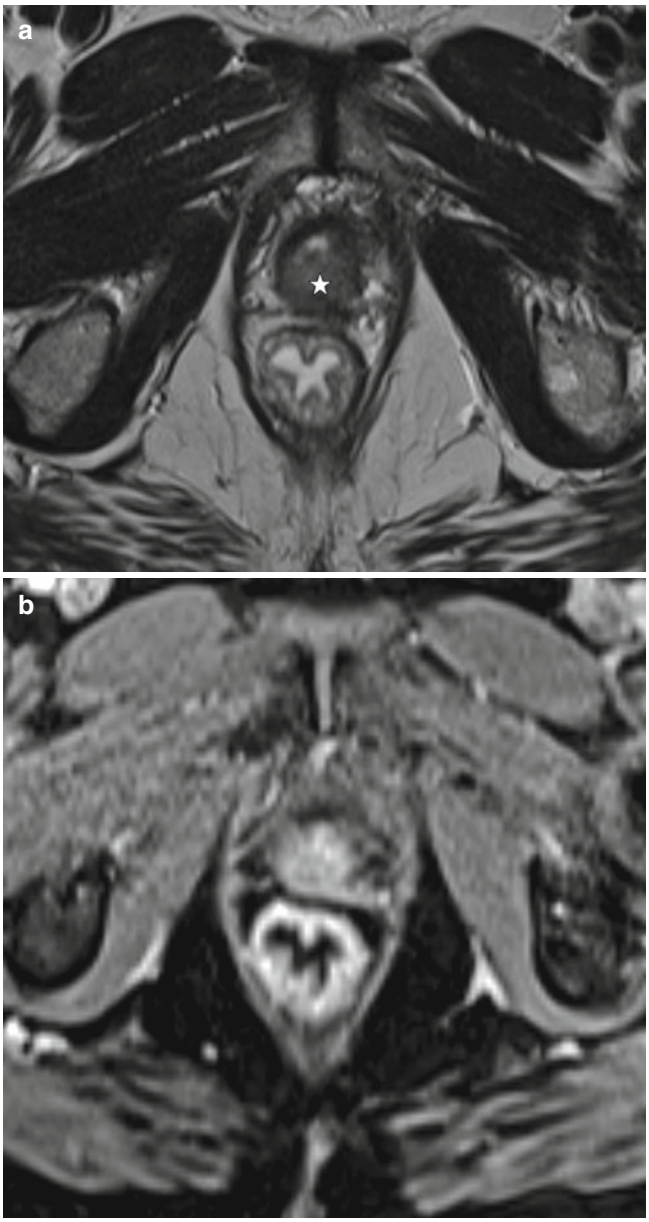


**Fig. 41.5** A 69-year-old patient with prostate cancer recurrence after radical prostatectomy. On a transverse T2W image (**a**), a nodular lesion (*white star*) is demonstrated in the posterior prostatectomy fossa, with higher signal intensity than the vesicourethral anastomosis. On dynamic contrast-enhanced MRI (**b**, at the same level as **a**), the recurrence enhances earlier and faster than postoperative fibrosis. DCE-MRI is valuable in the differentiation of prostate cancer recurrence from benign postoperative changes

onset time, time to peak, peak enhancement, and washout as diagnostic parameters [48]. They combined DCE-MRI with MRS and found a higher diagnostic performance than with either modality alone. After radiation therapy, DCE-MRI is increasingly used in the early detection and localization of local recurrence. Most of the clinically significant tumor recurrences after radiation therapy are located at the site of the primary tumor [34, 90]. They can be recognized as early

enhancing areas that contrast well with the surrounding tissue that enhances less, presumably because of radiation-induced fibrosis and vascular damage [59, 64, 91, 92]. DCE-MRI has been reported to significantly increase the diagnostic sensitivity and specificity as compared to T2W imaging alone for predicting locally recurrent prostate cancer after radiation therapy [59, 64, 82, 91]. After HIFU, the devascularized volume is initially depicted as a nonenhancing area surrounded by an enhancing rim on contrast-enhanced MR images [75, 79]. Consequently, detection of residual cancer foci at that time is limited (even with DCE-MRI) both because of their small size and the difficulty to distinguish them from inflammatory rim enhancement [93]. During the months following HIFU, the devascularized zone and peripheral rim enhancement progressively disappear in a centripetal manner as coagulation necrosis is replaced by fibrous scar tissue [93]. This creates more favorable conditions for distinguishing residual or recurrent cancers using DCE-MRI. Recurrences are usually early enhancing and hypervascular, while post-HIFU fibrosis is rather homogeneous, poorly enhancing, and hypovascular, with the exception of residual benign prostatic hypertrophic nodules, which can also be hypervascular and mimic tumor progression or recurrence [75, 93]. Rouvière et al. suggested that simple visual diagnostic criteria (instead of quantitative parameters) might be sufficient to detect recurrent cancer after HIFU ablation [93]. After cryosurgery, contrast-enhanced MR imaging is not accurate in the prediction of treatment success because nonenhancement is not invariably consistent with complete cell death and enhancement cannot differentiate between residual benign tissue and prostate cancer recurrence [94, 95].

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# Prostate Biopsy

# 42

Paras B. Singh, Caroline M. Moore, and Mark Emberton

## Introduction

Much of the increased diagnosis of prostate cancer in the past two decades is as a result of the widespread use of PSA testing, coupled with the development of transrectal ultrasound for prostate visualization, the spring-loaded biopsy gun, and effective antibiotic prophylaxis regimens [1].

In the pre-PSA era, prostate cancer was diagnosed with digital rectal examination and digitally guided biopsies. Watanabe reported the use of the transrectal probe for prostate visualization in 1968 [2]. It was not, however, until the development of the 7-MHz probe in the mid-1970s that it became more widely used to target the hypoechoic areas in the prostate. In 1989, Hodge and coworkers reported the use of transrectal ultrasound-guided prostate biopsies, in men with a palpably abnormal prostate. They showed that random systematic TRUS-guided biopsies diagnosed additional cancers than biopsy directed to a palpable or ultrasound-detected abnormality alone [3]. This led to the adoption of systematic biopsies and paved the way for modern biopsy techniques. Since that time, the population being studied has become increasingly lower risk than that originally reported, including screening of men with a normal-feeling prostate and increasingly low PSA levels.

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## Prostate Anatomy

Lowsley initially described five lobes of the prostate based on his work on fetal prostates; however, McNeal's later work replaced this concept following evaluation of adult prostates. McNeal recognized the division of the prostate into histologically distinct zones comprising the anterior fibromuscular stroma, central zone (CZ), transitional zone (TZ), periurethral zone, and the peripheral zone (PZ) [4]. The prostatic urethra and the histological architecture delineate these different zones. Nearly 75 % of the normal prostate gland is occupied by the PZ. The TZ makes up approximately 5–10 %. In both zones, the acini are small, round, and smooth walled, while the stroma is more compact in the TZ. The CZ constitutes 25 % of the gland and is located behind the proximal prostatic urethra. The ejaculatory ducts pass through the CZ. The PZ, TZ, and periurethral zones are derived from the urogenital sinus, while the histologically distinct CZ originates from the mesonephric duct. The AFS lacks any glands and extends anteriorly from the bladder neck to the external spincter [4, 5]. The PZ is the commonest site of prostate cancer, while benign prostatic hyperplasia (BPH) occurs in the TZ [6].

## Principles of Ultrasound

An ultrasound machine consists of a transducer, which emits ultrasound waves, and a detector that picks up waves reflected by the body. The ultrasound waves are generated using the piezoelectric effect, with the transducer being located in the probe. The sound waves enter the body and are then differentially reflected or propagated further, depending upon the tissue density. The reflected waves generate vibrations that are detected and then converted to electrical signals within the ultrasound probe. The resulting electrical signals are displayed

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as images. As different tissues have different tissue densities, there is a variation in the amount of ultrasound wave that is reflected back to the probe. This tissue-specific characteristic is called acoustic impedance. The amount of ultrasound wave reflected from the tissue is dependent upon the acoustic impedance, further propagation of the pulse, and any scatter [7, 8].

Higher frequencies of emitted ultrasound give better resolution, at a cost of reduced depth of penetration. Hence, the highest permissible frequency transducer should be used in order to obtain the best possible image. For TRUS purposes, a probe of 6–10 MHz is used [7–9]. This results in sharply focused near-field images of high resolution. Lower frequency is used to properly visualize the anterior aspect of a large prostate, while a smaller prostate is best visualized in its entirety using higher frequencies.

## Optimization of Ultrasound for Transrectal Visualization of the Prostate

Most modern TRUS machines have probes with frequencies between 6 and 10 MHz. The prostate can be viewed in the sagittal and transverse planes with switching between the two done either via the console or the probe handle. Optimal magnification of these images should be utilized for scanning and biopsies. Most machines have predetermined optimal settings for TRUS use.

The scanning probes come in end-fire and side-fire configurations based upon the site of needle exit on the probe. The cancer detection rates with the end-fire probe seem to be significantly higher in patients with PSA between 4 and 10 ng/ml [10, 11].

Once the prostate is visualized, the brightness should be adjusted so that the PZ has a mid-gray tone. This is used as a reference point to which other regions/lesions are compared. Depending upon whether the gray tone of the lesion is similar or darker or brighter than the normal PZ, it is classified as isoechoic, hypoechoic, or hyperechoic, respectively [9].

Measurement of the prostate gland volume is based on the volume of an ellipsoid organ ($\pi/6 \times$ anteroposterior $\times$ transverse $\times$ sagittal diameter). For more accurate volume estimation, planimetry is used where the cross-sectional surface area of the prostate is measured in small (3–5 mm) sections. The sum of the surface areas is multiplied by the sagittal diameter of the prostate to calculate the volume [9].

## Transrectal Ultrasound (TRUS) Appearance of the Prostate

On TRUS, the normal prostatic urethra is visualized in the midline on sagittal sections, and the anatomy of the PZ/CZ and TZ may be seen on transverse sections (Fig. 42.1). The TZ on normal prostate gland may be seen as a small heterogenous signal on both sides of the prostatic urethra. The PZ and CZ have more homogenous appearances and are situated posterior to the PZ. The seminal vesicles are seen as paired structures above the prostate on the posterior surface of the bladder. They lie laterally to the ipsilateral vas deferens (Fig. 42.2). The seminal vesicles appear as convoluted sacs that taper toward the prostate. The ampulla of the vas deferens can be seen joining with the duct of seminal vesicle to form the ejaculatory duct toward the base of the prostate. The ejaculatory ducts enter the prostate and traverse the CZ to empty into the prostatic urethra at the level of the verumontanum.

Depending on the degree of benign prostatic hyperplasia in the TZ, the PZ becomes progressively compressed as the surgical capsule. The convex boundary between the TZ and PZ can be visualized on TRUS. There is often a hyperechoic rim of calcification called corpora amylacea at the junction between the two zones. Progressive BPH gives rise to a heterogenous appearance of the TZ, and BPH nodules in the TZ appear as hypoechoic areas. Additionally, there are multiple anechoic (black), smooth-walled cysts in the TZ seen with BPH.

TRUS findings for carcinoma are variable. It was initially thought that prostate cancer was seen as hypoechoic areas on TRUS. However, it was realized that solely targeting these areas would miss nearly 50 % of the tumors [12].

Certain changes are observed in the prostate after therapy for prostate cancer. After external radiotherapy, prostate decreases in volume and becomes hypoechoic. There is also associated rectal thickening. These changes are seen from 6 months following radiotherapy. Immediately post-brachytherapy, the prostate increases in volume due to interstitial edema; however, the long-term changes are similar to those observed after external radiation, although brachytherapy seeds are seen as hyperechoic areas. Androgen deprivation therapy results in up to 30 % decrease in the volume of the prostate, which is most apparent in larger glands.

## Indications for TRUS-Guided Prostate Biopsy

Abnormal digital rectal examination (DRE) and a raised serum PSA are the usual indications for TRUS-guided prostate biopsy, with the commonest being a raised PSA. While the former indication has remained unchanged, there have been several important recommendations for PSA parameters to increase the detection of prostate cancer. Initially, a value above 4 ng/ml, based on the PSA assay manufacturer's recommendation, was used as a trigger to recommend prostate biopsies. In individuals with serum PSA between 4 and 10 ng/ml, 22 % of the prostate biopsies had prostate cancer, this increased to 67 % when the PSA level was above 10 ng/ml. Performing prostate biopsy based on either an abnormal

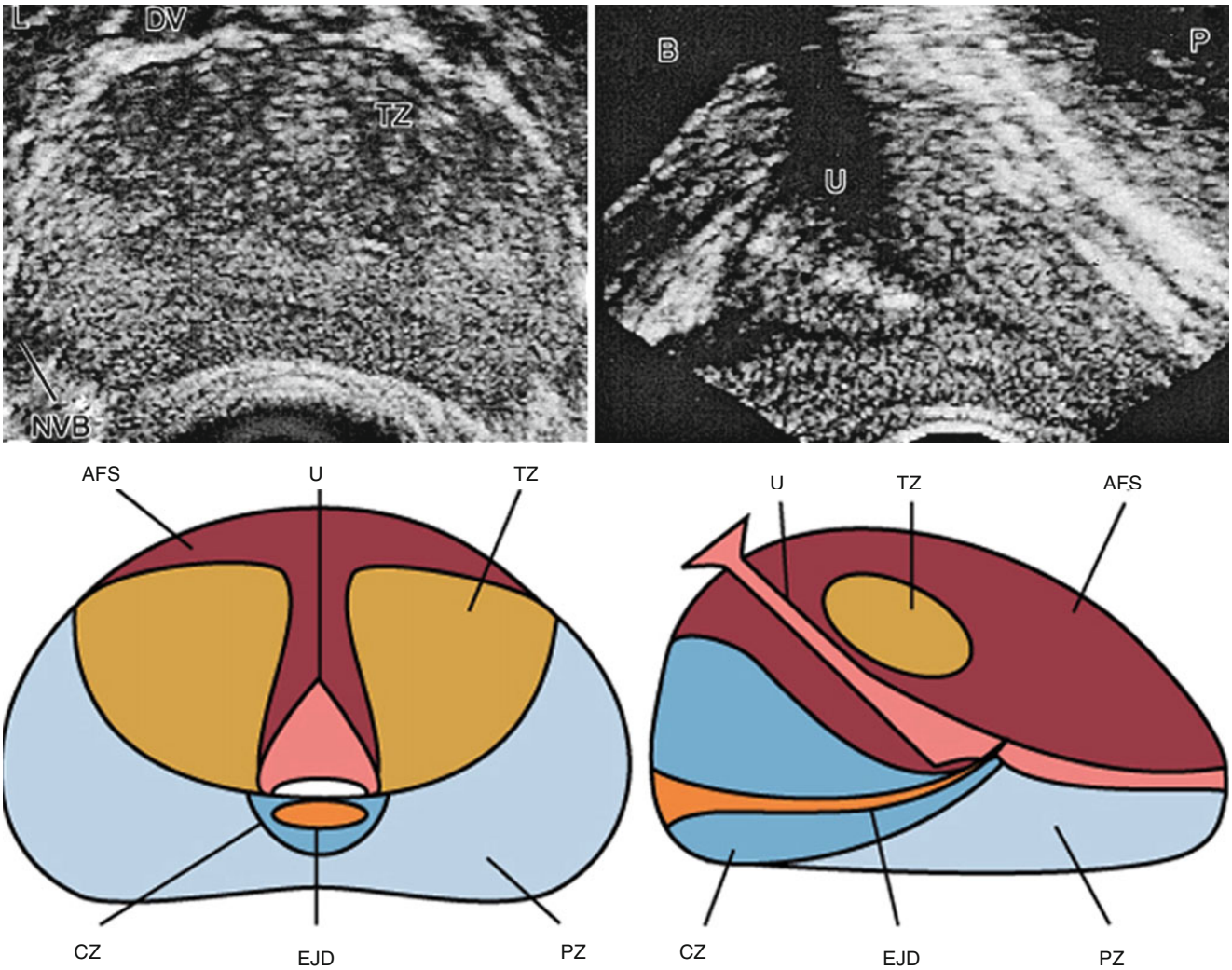


**Fig. 42.1** Normal prostate ultrasound images (*top*) with diagrams (*bottom*) at approximately the level of the verumontanum demonstrating zonal anatomy. (**a**) Transverse view. (**b**) Sagittal view. *AFS* anterior fibromuscular stroma, *CZ* central zone, *DV* dorsal vein complex, *EJD* ejaculatory ducts, *NVB* neurovascular bundle, *L* levator muscles, *PZ* peripheral zone, *TZ* transition zone, *U* urethra (From Ramey et al. [9]. Copyright Saunders, an imprint of Elsevier Inc. Reproduced with permission)

DRE and PSA measurement was deemed the best combination to detect prostate cancer [13]. Data from the screening arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC) also showed that in the presence of an abnormal DRE with an elevated PSA (>3 ng/ml), the positive predictive value to detect prostate cancer was 48.6 % compared to 22.4 % for men with a normal DRE [14].

From its earliest discovery, it was realized that PSA was not specific to prostate cancer [15]. As the level of PSA correlates with patient's advancing age and prostate volume, it was realized that a single cutoff value of 4 μg/ml resulted in missed cancers in younger men and possible unnecessary prostate biopsies in older men. Oesterling recommended using age-adjusted PSA cutoff levels based on his prospective, community-based study of 2,119 healthy men. The recommended reference range for age group 40–49 years was 0–2.5, 50–59 years was 0–3.5, 60–69 years was 0–4.5, and 70–79 years was 0–6.5 ng/ml [16]. A large screening study from Austria demonstrated that using the age-specific PSA ranges would increase tumor detection in younger men by 8 % while reducing unnecessary biopsies in older men (a reduction of 21 % in men over 60 years old). Also, in the older men, it would miss 4 % of organ-confined prostate cancer [17]. On the contrary, the multicenter study by Catalona et al. showed that use of the age-specific, higher PSA ranges in older men would miss a significant proportion of organ-confined, potentially curable prostate cancer [18].

A lower PSA threshold of 2.5 ng/ml has been recommended by some especially in younger men. Catalona et al. initially suggested the threshold to be lowered based on their study that demonstrated a prostate cancer detection rate of 22 % in the PSA range 2.6–4 ng/ml [19]. Among the 2,950

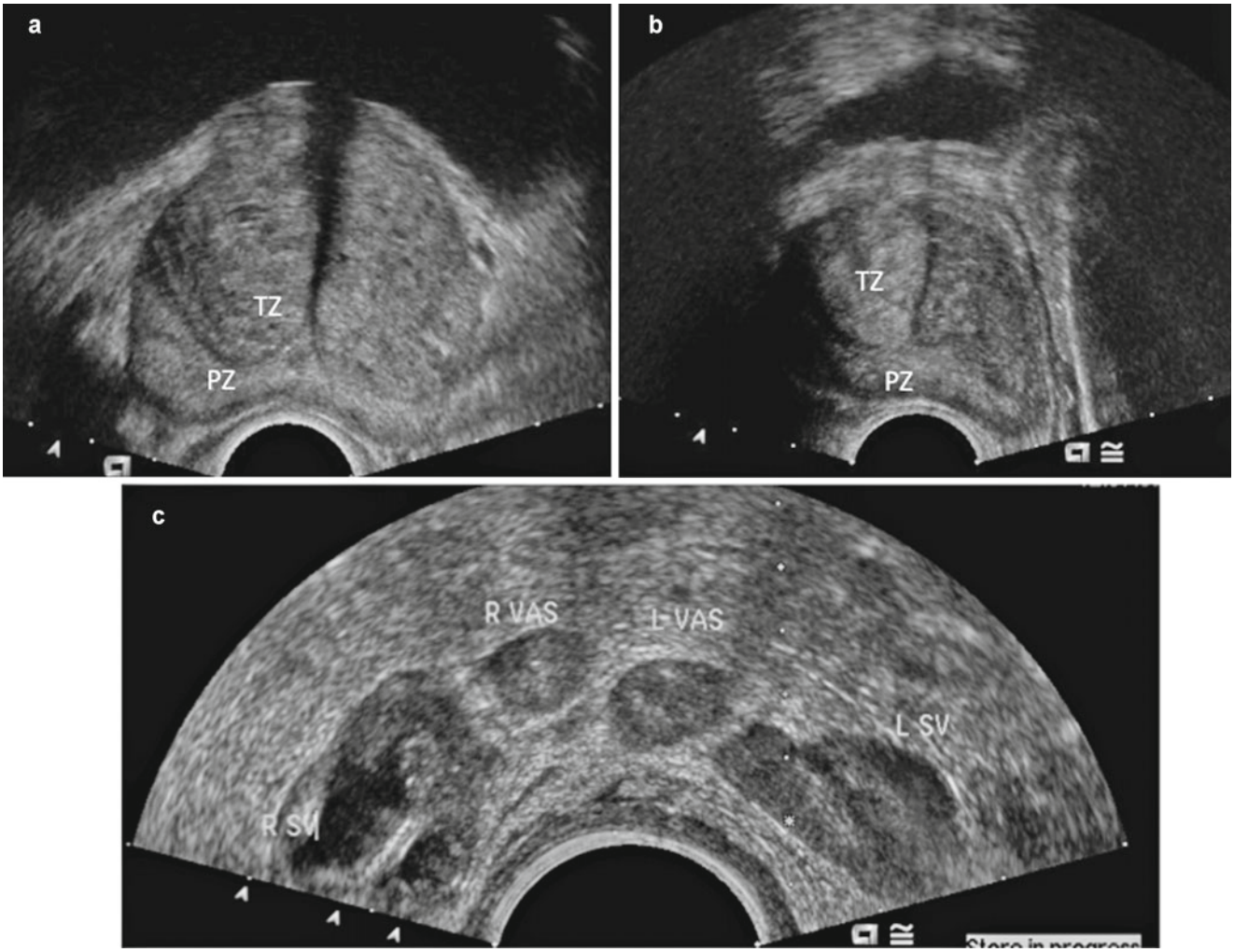


**Fig. 42.2** Transrectal ultrasound images of the prostate. (**a**) Transverse view. (**b**) Sagittal view. (**c**) At the level of the seminal vesicles (*SV*) and vas deferens (*vas*). *TZ* transition zone, *PZ* peripheral zone, *R* right, *L* left

men in the placebo arm of the Prostate Cancer Prevention Trial (PCPT) who never had a PSA level above 4 ng/ml, prostate cancer was diagnosed in 15.2 % of which 14.9 % had Gleason 7 or higher cancers [20].

To increase the sensitivity of PSA for early detection of prostate cancer, several PSA derivatives like free-to-total PSA ratio [21], PSA density, and PSA velocity [22] have been described.

There are various nomograms that give individualized assessment of a patient's risk of having prostate cancer and high-risk prostate cancer. These nomograms, derived from studies on large groups of men, incorporate the PSA along with other patient-specific variables like age, ethnicity, family history, DRE findings, and prostate volume in a statistical model to predict an individual's risk [23, 24]. The nomograms can be validated to the host population, and some of these are predictive models and are flexible enough to allow for newer biomarkers like the PCA3 to be incorporated in the risk calculation.

A subsequent set of TRUS-guided prostate biopsies may be performed in those with persistently elevated or rising PSA with previous negative biopsies. In men with atypia or suspicious foci or atypical small acinar proliferation (ASAP) on their prostate biopsies, a review by a dedicated genitourinary pathologist is recommended before proceeding with repeat biopsies. High-grade prostatic intraepithelial neoplasia (HGPIN) on its own is not an indication for immediate repeat biopsies as the contemporary studies show similar cancer detection rates as performing repeat biopsies after a benign diagnosis [25].

## Contraindications to Prostate Biopsy

Prostate biopsy should be avoided in patients with active urinary tract infection and acute prostatitis and in those on anticoagulation. Antiplatelet agents like clopidogrel and high-dose aspirin should be discontinued for sufficient period

(at least 7 days) prior to the biopsy. Where relevant, the opinion of the cardiologists should be sought prior to advising patients to stop these medications, and a bridging therapy with heparin may be indicated in patients who are at high risk of thrombotic complications. Many clinicians are happy to perform prostate biopsies on patients who are on low-dose aspirin.

## Patient Preparation for Prostate Biopsy

Patients should be counseled regarding the indication, risks, and benefits of the TRUS-guided prostate biopsy. A formal informed consent document should be signed prior to proceeding with the biopsy.

### Antibiotic Prophylaxis

TRUS-guided prostate biopsies cause bacteremia in the majority of patients, which occasionally results in urinary tract infection and, rarely, severe sepsis [26, 27]. There is uniform consensus that antibiotics significantly reduce infective complications following TRUS-guided prostate biopsies. The commonest antibiotic regimens use fluoroquinolones, such as ciprofloxacin, levofloxacin, or ofloxacin, possibly in combination with other agents. However, there appears to be no agreement with regard to the optimal duration of antibiotics after TRUS biopsy, with some using a single-dose prebiopsy and others using a 1–4-day course.

### Cleansing Enema

Prebiopsy enemas significantly decrease bacteremia in the post-biopsy setting; however, there is no evidence to suggest this leads to decrease in urinary tract infection or sepsis [28].

### Patient Positioning

Adequate thought should be given to safeguard patients' dignity and privacy during a prostate biopsy. A clean, well-lit, and warm room is essential and can positively enhance the patient experience in what is an uncomfortable procedure at the very least [29].

The patient is usually positioned in the left lateral decubitus position on the biopsy table. The buttocks should be at the edge of the table with hips and knees bent at right angles. This is especially important for biopsies using end-fire probes, which unlike the side-fire ones, need to be raised or lowered to visualize the lateral borders of the prostate. The probes should be adequately lubricated prior to insertion. A gentle DRE prior to probe insertion and asking patients to breath in and out slowly during probe insertion facilitate sphincter relaxation. Probe insertion should be done in a gentle, controlled fashion [29].

### Analgesia

Initially, sextant prostate biopsies were carried out without any analgesia. However, several studies have shown that TRUS-guided prostate biopsies cause significant patient anxiety, discomfort, and pain [30–33]. This seems to be due to anal stretch during probe insertion and also due to passage of biopsy needle through the prostate capsule and stroma. Periprostatic nerve block (PNB), proposed by Nash in 1996, provides the most superior form of analgesia for prostate biopsies. In this prospective, randomized double-blind study, a 7-in. 22-gauge spinal needle directed under TRUS guidance to the neurovascular bundle just lateral to the junction of the prostate and seminal vesicle was used. Either 5 ml of normal saline or 5 ml of 1 % lidocaine was injected to one side, and sextant biopsies were performed. Significant decrease in pain score on the sides with lidocaine injection was observed [34]. Soloway and Obek described a 3-location technique where 1 % lidocaine was injected; the first injection was at the similar location described by Nash, second injection was at the mid gland level laterally, and the third was at the apex [35]. Equally effective results were observed by periprostatic infiltration of lidocaine at each side of the apex [36, 37]. Several other effective techniques of PNB have been described. Some investigators have suggested the combination of lidocaine and bupivacaine to minimize rebound pain after the effect of short-acting lidocaine [38].

Administration of topical lidocaine gel as a sole method of analgesia for prostate biopsies was shown to be unsatisfactory. Combining intrarectal local anesthetic gel with PNB may give superior results by lessening the discomfort of the probe insertion [39, 40].

Apical biopsies are particularly painful, thought to be due to the stimulation of anal pain fibers below the dentate line. Advancing the probe by a few millimeters and angling the probe to ensure the needle entry above the dentate line lessen this pain [41].

## TRUS-Guided Transrectal Biopsy Techniques

Prostate biopsies are undertaken using a spring-loaded 18-G biopsy gun. It was initially recommended to withdraw the tip of the gun needle by 0.5 cm to properly sample the capsule in the specimen [42]. Recent work suggests placing the biopsy gun needle adjacent to the capsule results in adequate sampling [43].

## Initial Biopsy Strategies

The sextant systematic biopsy approach initially described by Hodge in 1989 included biopsies from the base, mid, and apical parasagittal regions (halfway between the midline and the lateral borders of the prostate) on the right and left side. Stamey, following evaluation of cancer location from radical prostatectomy specimens, later suggested shifting the biopsy needle more laterally to increase cancer detection rates. This paved the way for extended biopsy schemes [44]. It was found that increasing the biopsy cores increased cancer detection, with sextant biopsies missing a significant proportion of cancers [45, 46]. Levine performed two consecutive sets of sextant biopsies during the same session with increased cancer detection rate of 30 % on the second set of sextant biopsies [47]. Eskew reported a five-region technique where zones 2 and 4 were the traditional parasagittal sextant regions, zones 1 and 5 were the lateral aspects of the gland, and zone 3 was from the midline. The biopsies from zones 1, 3, and 5 detected 35 % additional cancers compared to the sextant biopsies (zones 2 and 4). The lowest detection yield was noted from the midline (zone 3) with increase risk of hematuria; hence, it was recommended to omit this zone in extended biopsies [48]. Other series comparing the extended biopsy techniques (8–12 cores) to the standard sextant cores have also shown improved cancer detection with the additional lateral cores. Depending upon the number of additional laterally directed cores, the increased cancer detection ranged from 15 to 30 % in these studies [49–53].

A systematic review by Eichler and colleagues, comparing studies with the sextant biopsy scheme with extended biopsy methods, showed an increased detection rate with the extended biopsy schemes. Schemes with the 12 cores showed increased detection by 31 % [54].

The issue of whether increasing number of biopsy cores risks detection of insignificant prostate cancer was addressed by Chen and colleagues. They found that with increasing sampling of the prostate, there is no rise in the detection of potentially insignificant prostate cancer. Moreover, they observed that the increasing core numbers (9–12 vs. 8 or less) seem to detect cancer at an earlier stage of the disease [55]. Increasing the number of cores beyond 12 cores adds little additional cancer detection information in the first set of prostate biopsies [56, 57]. Additionally, increasing the cores beyond 18 cores seems to contribute to poor side effect profile [54].

Though McNeal initially showed that 24 % of prostate cancer originates in the TZ [6]; the rate of detection of solely TZ cancers on initial biopsies on several studies is low – in the order of 2–3 % [58–61]. Similar findings were also seen on cancer mapping of radical prostatectomy specimens [62, 63]. Hence, biopsy of the TZ is not recommended in the initial set of prostate biopsies.

## Repeat Biopsy Strategies

Indications for repeat prostate biopsies in patients, who have undergone prior negative TRUS-guided prostate biopsies, may be: adverse trend in the PSA or its derivatives, suspicious histology or ASAP on the initial biopsy, or a strong family history of prostate cancer.

The cancer detection rate on repeat biopsy varies depending upon the extent of the initial biopsy. In individuals with sextant biopsies, the detection rate on subsequent extended biopsy scheme was around 40 %, compared to 17–28 % in those with initial extended biopsies [64–66]. Prostate gland volume also impacts negatively on the cancer detection rate on initial biopsies [47, 67]. Levine performed two consecutive sets of sextant biopsies during the same session and found lower detection rates in larger prostates on the first set of biopsies. On immediate re-biopsy, higher rates of cancer detection were observed in larger prostates (15 % vs. 9 %) [47]. Sampling of the TZ still has low yield in the first repeat biopsy setting.

In a cohort of 1,051 men, the cancer detection rate on 1st, 2nd, 3rd, and 4th set of prostate biopsies was 22, 10, 5, and 4 %. The biopsy scheme consisted of sextant plus two TZ biopsies. The characteristics of the cancer detected on the first two sets of biopsies were similar with the cancers on the 3rd and the 4th set of prostate biopsies having lower grade, stage, and volume. Higher complication rates were also observed in the 3rd and the 4th biopsies compared to the initial two biopsies [68]. Other investigators have also confirmed diminishing returns on further biopsies after the 2nd set prostate biopsies with 91 % of cancers being diagnosed on the first two sets of biopsies [69].

Recommendations based on repeat biopsies and/or cancer mapping of radical prostatectomy studies suggest extended biopsy schemes incorporating the anterior horn (posterolateral) and apical aspects of PZ [63, 65, 70]. If sampling the TZ, the biopsy needle should be advanced near the midline, close to the urethra till the inner aspect of the PZ, before firing the needle. For larger glands, the needle should be in the TZ to sample the anterior region of the TZ [71].

To reduce the number of repeat biopsies and to increase the yield in the first set of prostate biopsies, Remzi and colleagues validated the Vienna nomogram between the PSA range 2 and 10 ng/ml. This nomogram predicts the minimum number of cores (6–18) needed to detect prostate cancer according to prostate volume and patient's age [72].

## Saturation Prostate Biopsies

Even in men who have undergone repeat biopsies, increasing the number of biopsy cores detected cancer in up to a third of men. Barboroglu initially described the technique where the

peripheral zone on each side was sampled as three sagittal regions and additional biopsies were taken from the TZ with total core numbers ranging from 15 to 31 (mean 22.5 cores), in men who had previously undergone 1–4 negative sextant biopsies. They found cancer in 30 % of these men [73]. Stewart described a similar saturation biopsy technique in 224 men with 1–7 previous negative biopsies with a detection rate of 34 % [74]. Both these studies were performed under intravenous sedation or anesthesia.

Jones and colleagues showed that saturation biopsies could be performed safely and successfully under periprostatic nerve block using local anesthesia [75]. They also observed a high detection rate of 29 % with a saturation biopsy scheme in men who had previously undergone one or more negative standard prostate biopsies. In this cohort of 116 men, only 22 % had undergone prior sextant biopsies, while the rest had extended core initial negative biopsies. In the prior single negative sextant biopsy cohort, a detection rate of 64 % on the saturation biopsy scheme was noted [76]. On the contrary, Fleshner and Klotz found the detection rate of aggressive saturation biopsies, performed under anesthesia, to be only 13.5 % in a small cohort of 37 patients that had prior 3–6 sets of prior negative biopsies. Their saturation biopsy scheme consisted of 24 peripheral zone cores, 6–12 TZ cores, and two lateral lobe transurethral samples. There were no isolated TZ cancers in this series [77].

Saturation biopsies as an initial biopsy strategy have been shown to have similar detection rate as an initial 10–12 core prostate biopsies, with the detection rate of 42–45 % [56, 78]. Similarly, repeat saturation biopsy in 59 men, after the first set of negative saturation biopsy, was seen to detect prostate cancer in 24 % after a median follow-up of 3.2 years. Based on the cancer mapping of individual zones, saturation biopsy technique comprising 20 laterally based cores mainly focusing on the apex and anterior horn has been recommended in the repeat biopsy setting [79].

In the systematic review by Eichler et al. a significant improvement in cancer detection was observed by shifting from sextant biopsy to 12-core biopsy scheme. However, there was no benefit in increasing the number of cores beyond 12 cores [54].

## Transperineal Biopsy Techniques

Biopsies of the prostate through the transperineal route have been performed since the pre-PSA era [80]. Initially, this was under digital guidance and later under TRUS guidance. From the earliest time, the main benefit of this route was seen in terms of lower rate of infective complications [26, 81]. It is also a possible route in men in whom the rectum has been surgically removed. In these men, a perineal or abdominal probe provides a limited view of the prostate.

Two types of transperineal biopsy techniques have been described. The first is the fan technique with a common entry site for sampling the prostate on each side. This procedure can be performed under local anesthesia. The patient is positioned in the dorsal lithotomy position with sterile prepping of the perineum. The scrotum is held away from the biopsy field. A TRUS probe is inserted in the rectum. A 22-G spinal needle is inserted 1.5 cm lateral and 45° above the anal verge. After skin infiltration, the needle is advanced to the prostate apex where local anesthetic is injected. The needle is further pushed to the base of the prostate up to the insertion of the seminal vesicle. Further local anesthetic is injected as the needle is gently retracted. This procedure is repeated on the contralateral side. An 18-G biopsy needle is inserted through the initial puncture site, and six cores with a fan technique are obtained from each lobe [82]. In the original study by Emiliozzi and colleagues describing this fan technique, detection rates of 51 and 45 % were seen in men with PSA level above 4 ng/ml and between 4 and 10 ng/ml, respectively [83]. In a separate cohort of 143 men with one or more previous negative TRUS-guided transrectal biopsies, cancer was detected in 26 % after a 24-core transperineal biopsy. A significant association with prostate volume was seen, with detection rates of 47, 25.5, and 14 % for prostate volumes of <40 ml, 40–60 ml, and ≥60 ml, respectively [84].

The second technique uses a more extensive three-dimensional transperineal template-guided approach, with a brachytherapy-type grid and stepping system for the transrectal probe (Fig. 42.3). This is most commonly performed under general or spinal anesthesia. It is more often used in men with previous negative transrectal biopsies, for risk stratification prior to active surveillance, or for lesion characterization prior to focal therapy, although some use it as an initial diagnostic approach. The brachytherapy grid allows systematic sampling at 5 or 10 mm intervals, with accurate labeling of the biopsy cores based on the grid of origin. Occasionally, each core will be labeled with a grid reference, although it is more common to divide the prostate into 20–32 zones, with a pot per zone [85].

The initial study of this technique was performed in men with previous negative transrectal biopsies. The majority of these 85 men had at least 2 sets of negative biopsies. The prostate was sampled in 4 coronal planes: 2 lateral peripheral zones, mid peripheral zone, and the TZ. In big glands, separate anterior and posterior cores were taken to sample the whole length of the gland. The mean number of cores were 17 with the detection rate of 43 % [86]. More recently described TPM techniques retrieve very high number of cores (50 or more). A contemporary series describing 373 men who underwent TPM biopsies as an initial biopsy ($n=79$) or in the context of previous negative TRUS-guided transrectal biopsies found cancer in 75.9 % of men in initial biopsy setting. In the repeat biopsy setting, the overall detection

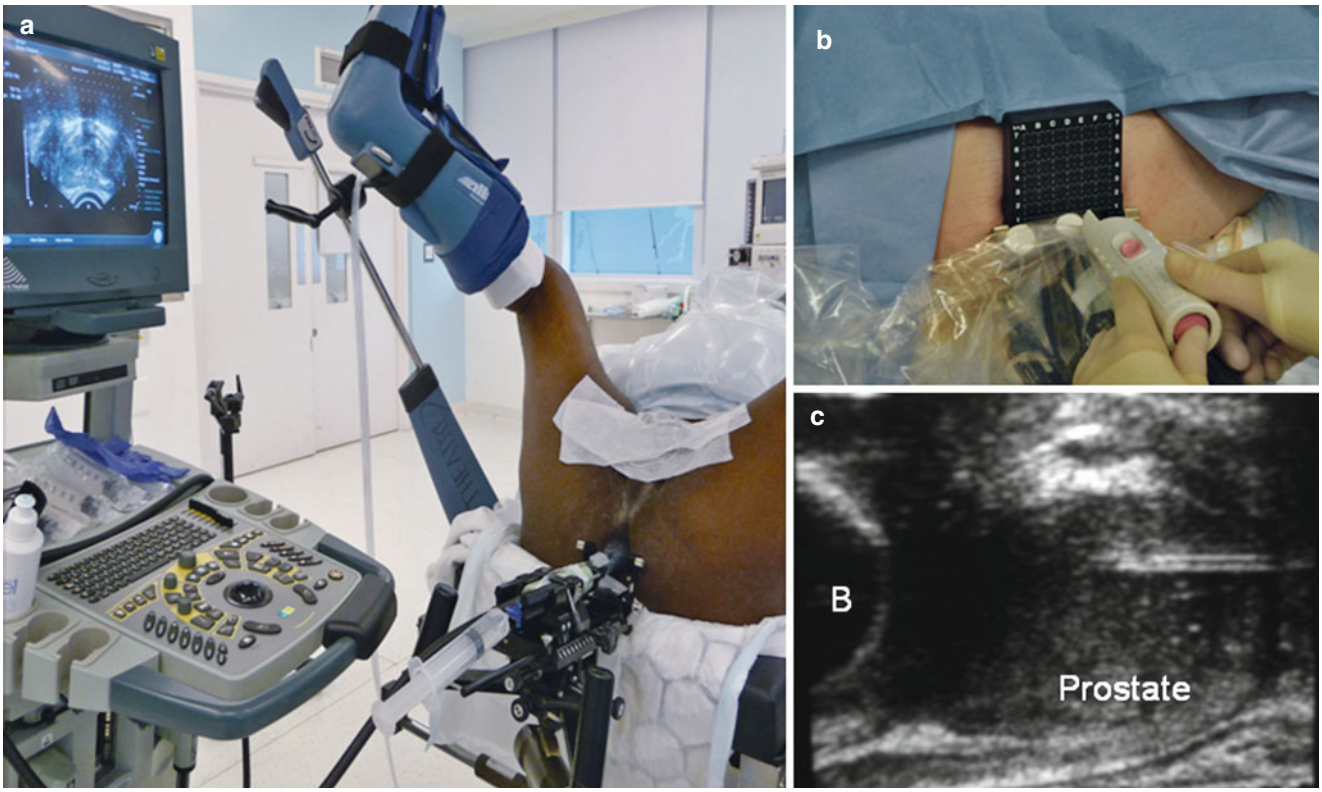


**Fig. 42.3** Three-dimensional transperineal prostate mapping biopsies, using brachytherapy grid and frame. (**a**) Patient position. (**b**) Biopsy being performed using the grid. (**c**) TRUS image of a biopsy being taken. *B* catheter balloon

rate for cancer was 47 %; with 55.5, 41.7, and 34.4 % detection rates in men with 1, 2, and ≥3 prior negative biopsies, respectively. Overall, only 11.1 % of the detected cancers were deemed potentially insignificant [87].

## Risk Stratification Using Transperineal Template-Guided Biopsies

Standard TRUS-guided prostate biopsies miss up to a third of prostate cancers [88, 89], and when compared to radical prostatectomy histology, TRUS-guided biopsies show poor accuracy in terms of disease burden [90]. Computer simulation and mathematical models predict 95 % accuracy for detection of all cancer foci using a 5-mm interval on the brachytherapy grid [91, 92].

Initial reports of transperineal template-guided biopsy in men with one or more negative TRUS-guided biopsies and a persistently elevated PSA showed a high proportion of transitional zone cancers. In addition, nearly a third to half the biopsied men had cancers that were Gleason score 7 or greater [87, 93, 94].

The use of template-guided transperineal biopsies has also been described for characterization of disease in men with cancer diagnosed on transrectal biopsy, who wish to pursue a tissue-preserving approach, using either active surveillance or focal therapy. Onik et al. performed TPM biopsies in 180 men who were found to have unilateral cancer on TRUS biopsies. In 61 % of these men, TPM biopsies revealed bilateral cancers, and Gleason upgrading to ≥7 was observed in 26 % [95]. Another study showed a Gleason upgrading of 16 %, and only 29 % of the patient who were initially referred for focal therapy based on TRUS biopsy findings were actually suitable for such treatment after reassessment with TPM biopsies [85]. As TPM biopsies provide a detailed pathological map of individual prostate cancer locations, some now deem such biopsies an essential component for selecting patients for focal therapy [96].

## Complications of Prostate Biopsies

TRUS-guided transrectal prostate biopsies have acceptably low morbidity for use in men at risk of prostate cancer. However, bleeding, infective complications, and urinary retention can occur. In a recent large population-based study by Nam, an overall 30-day hospital admission rate of 1.9 % was reported in 41,682 men who underwent prostate biopsies. In the same study, the 30-day mortality was 0.09 % [97].

## Bleeding

Bleeding is frequently seen after prostate biopsies. In a pooled analysis of 36 studies, minor, self-limiting hematuria was reported in up to 80 % of patients after extended core biopsies. The reported rates of minor rectal bleeding and hematospermia were up to 33.8 and 75 %, respectively [54]. Raaijmakers observed hematuria lasting longer than 3 days in 22.6 % men [98]. Severe bleeding complications are rare ranging from 0 0.7 % [54, 98]. Hematospermia, though self-limiting, can last for 4–6 weeks, and for patients it can be a cause of significant concern especially if they are not informed about the possibility of this [98].

## Infection

Prostate biopsies result in significant bacteriuria and bacteremia [26]. In some men, this will result in clinically apparent infection, despite antibiotic prophylaxis. The overall infective complications in contemporary large series, in terms of symptomatic urinary tract infections (UTI) and febrile episodes, are low, ranging from 0.1 to 3.5 % where antibiotic prophylaxis is used. Major sepsis is rare and has been reported in up to 0.1 % of cases [27, 54, 98–100].

Nam found a rising trend in the hospital admissions due to infective complications in their population study from 0.6 % in 1996 to 3.6 % in 2005 [97]. Some recent studies have highlighted the rise in UTI and sepsis from fluoroquinolone-resistant Escherichia coli strains following prostate biopsy [101, 102]. This risk seems more prominent in healthcare workers and in men with a prior history of fluoroquinolone use in the 8 months prior to the biopsy [101, 103].

## Urinary Retention

In the pooled analysis of extended core biopsies by Eichler, voiding difficulties were reported in up to 7.2 % of patients [54]. Urinary retention post-biopsy has been reported in 0.2–0.9 % of cohorts in some large series [27, 98, 99].

The morbidity following transperineal biopsy is comparable to transrectal biopsy, except for a higher observed incidence of urinary retention – reported in up to 15 %. Use of alpha-blockers seems to reduce this risk. Risk of hematuria requiring urethral catheterization is less than 2 % [85, 94, 95]. One significant observed difference to transrectal biopsies is the lack of any reported case of urinary sepsis, presumably due to avoidance of contaminated rectal mucosa in the needle tract.

## Other Ultrasound-Based Applications

A number of ultrasound-based applications have been evaluated as a way of visualizing areas of the prostate with a greater likelihood of prostate cancer, in order to improve the sampling of the transrectal approach. These include color and power Doppler ultrasound, contrast-enhanced ultrasound, elastography, and tissue characterization protocols such as HistoScanning.

There is increased vascularity in prostate cancer compared to benign tissue, and Doppler ultrasound techniques can be used to detect this phenomenon. Power Doppler exploits the cancer characteristics of neovascularization and increased blood flow without considering the directionality of the blood flow. Hence, power Doppler helps to localize smaller and lower-flow vessels which can be detected in the tumor microenvironment. Remzi et al. showed an increased cancer detection rate and high negative predictive value using power Doppler TRUS biopsies when compared to grayscale TRUS [104]. Contrast-enhanced ultrasound uses microbubble contrast agents which are more reflective than blood and their own vibrations generate higher harmonics compared to the surrounding tissues, thus improving the signal-to-noise ratio. Several small studies have shown a modest increase in cancer detection with contrast-enhanced targeted biopsy compared to systematic prostate biopsies [105].

Prostate cancer tissue is more rigid than normal tissue. This altered tissue elasticity of cancer tissue produces a characteristic sonographic pattern when the tissue is subjected to compression and decompression compared to the neighboring areas [105]. Konig et al. performed systematic sextant biopsies in 404 men in conjunction with elastography. In 127 (84.1 %) of 151 cases with prostate cancer, elastography indicated the pathological process [106]. In another study, compared with systematic biopsies, elastography targeted prostate biopsies were 2.9-fold more likely to detect prostate cancer [107].

The TargetScan transrectal ultrasound and prostatic biopsy system (Envisioneering Medical Technologies, St. Louis, MO) uses a transrectal probe that remains stationary throughout the procedure. The transrectal probe has an ultrasound transducer which moves within the probe to provide, within 1–2 min, a scan of the prostate created in 1-mm increments. The acquired 3-dimensional and simultaneous biplanar ultrasound imaging is used to target prostate biopsies. The precise location of each biopsy specimen is defined by the distance from the apex of the prostate and degree of rotation [108]. A 18-G Nitinol biopsy needle is used to sample the prostate along the biopsy guide under imaging. In a retrospective review of a cohort of 140 men who had TargetScan transrectal biopsies, an overall prostate cancer detection rate of 35.7 % was observed. In 39 of these men with no prior biopsies, cancer was found in 47.6 %. Also it was noted that

in those who underwent radical prostatectomy, majority (87 %) had significant disease [109].

Ultrasound radio-frequency (RF) echo can characterize tissue and has been used in in vitro and in vivo models for distinguishing cancerous and noncancerous prostate tissue. At the present moment, these methods require standardization, further testing for generating baseline data, and validation for repeatability of techniques in different subsets of prostate cancer patients. As manufactures incorporate RF acquiring hardware as standard in ultrasound machines, the tissue-characterizing capability by this technique is likely to improve in future [110].

HistoScanning is a computer-aided ultrasound-based technique that exploits the differential texture and density seen in cancer, by extracting and quantifying statistical features from backscattered ultrasonography data. In a small study, it showed great promise in localizing prostate cancer foci >0.5 cc with sensitivity of 100 % and specificity of 82 % [111].

Despite the novel US-based applications showing great promise in small studies, larger studies are required to define their role in targeted prostate biopsies.

## Magnetic Resonance Imaging (MRI) and Prostate Biopsies

MRI has shown increasing success with cancer detection and localization. Studies have looked at various sequences such as T2-weighted (T2W) images, dynamic contrast enhancement (DCE), diffusion weighting (DW), and spectroscopy (MRSI), either in isolation or in combination, for their predictive accuracy in prostate cancer localization. T2W sequences can accurately predict 37–96 % of peripheral zone tumors. This rate is much lower for the anteriorly placed transitional zone tumors [112].

DCE-MRI utilizes the differential handling of the low molecular weight paramagnetic contrast agent gadolinium by normal and tumor tissues. DCE-MRI shows a superior accuracy for prostate cancer localization and local staging when compared to T2W MRI. It also provides accurate information for treatment planning and in assessment and follow-up of treatment response [113].

DW exploits the fact that prostate cancer has high cellular density and abundant stroma which results in restrictions in free water diffusion compared to normal tissue. This gives rise to a decreased apparent diffusion coefficient (ADC) value for cancer when compared to the normal prostate tissue [114]. MRSI for prostate cancer utilizes the fact that there is lower citrate and increased choline and creatine content in prostate cancer. MRSI may be up to 85 % accurate in localizing prostate cancer [112].

Currently, the best accuracy seems to be from multiparametric prostate imaging by combining two or more of the MR sequences. T2W and DCE-MR combination has a sensitivity and negative predictive value of 90–95 % for cancer foci >0.5 ml [115]. However, the performance characteristics of MRI for prostate cancer do not yet allow us to dispense with needle biopsies and histological verification.

## MRI Targeted Biopsies

Multiparametric MRI sequences can localize suspicious areas which can then be targeted by TRUS-guided biopsies. Thus, MRI sequences are used to localize suspicious areas, whereas the TRUS-guided biopsies are employed to target these lesions. This is especially relevant in the context of persistent suspicion despite a negative first set of biopsies. Sciarra performed a randomized study on 180 men with one set of prior negative biopsies. A higher cancer detection rate of 45.5 % was observed in men who underwent systematic and multiparametric MRI targeted biopsies, as opposed to the 24.4 % detection rate in men that underwent systematic biopsies alone [116]. In a review by Lawrentschuk and Fleshner of six prospective studies in men undergoing MRI and prostate biopsies after prior negative biopsies, 54 % of cancers were detected due to MRI targeted cores alone [117].

Ahmed et al. have suggested MRI before prostate biopsy as a triage tool for selecting men for biopsy. Additionally, as multiparametric MRI shows high accuracy for detecting significant prostate cancer, if validated, it could be used to counsel men before a biopsy and may avoid unnecessary biopsies, thus avoiding treatment of men with insignificant tumor burden. Prebiopsy MRI information could also be used to target biopsies or to choose the type of prostate biopsy (transrectal or transperineal), depending on the location and accessibility of the MR-defined lesion. In those subsequently diagnosed with cancer, a prebiopsy MRI allows more accurate local staging, with review of images unaffected by post-biopsy hemorrhage [118]. Availability of imaging facilities, radiological expertise, and cost may be the limiting factors for universal application of such an approach.

MR-TRUS fusion techniques have also been developed where the images of the two modalities are registered and fused with the aim of accurate targeting of lesions. Initially, simple rigid fusion of prior obtained MR images to the TRUS images during the procedure was used [119]. This approach, though simple, does not compensate for gland deformation and movement during these procedures. More sophisticated deformable registration methods have been described which take into consideration the three-dimensional shape, movement, and deformation of the prostate and thus allow elastic fusion. Both manual and automated registration techniques have been described [120, 121]. Their precise validation holds great promise in lesion-directed biopsies.

## In-Magnet Biopsies

MR-guided biopsies taken within the magnet are currently in the stage of initial development as these require special MR-compatible equipment. Currently, there are no large studies examining these methods. Studies using MR-compatible biopsy guides have shown feasibility of such techniques in small cohorts of men [122–124]. In a recent study by Hambrock, using a 3-T MR scanner in 68 men with a median of previous 3 negative TRUS biopsies showed a cancer detection rate of 59 %. They used only directed cores (median number of biopsy cores 3–4) in this cohort of men. Of the 20 men who underwent radical prostatectomy, all harbored clinically significant disease [125].

### Conclusion

Extended core transrectally directed prostate biopsies are currently the accepted standard for diagnosing prostate cancer. Transperineal template-guided biopsies offer greater certainty in accurate diagnosis and risk stratification, although the healthcare burden and cost may be prohibitive. Additionally, this is a more time-consuming procedure for both the patient and the pathologist. Newer US- and MRI-based applications for prostate biopsies hold great promise for the future, although they require validation in larger studies before lesion-directed biopsies become standard.

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# The Staging of Prostate Cancer

# 43

Benjamin J. Challacombe and Giles Rottenberg

## Introduction

In order to effectively treat prostate cancer and to make the most appropriate decision in terms of treatment modality, it is vital to reliably and rapidly gain good information on the staging of the disease. As patients with prostate cancer are presenting at an increasingly early point in the disease pathway, the ability of clinicians to stage their disease in a highly accurate and reliable manner is crucial. Initially, some information can be gained from clinical examination of the prostate by digital rectal examination, but a variety of imaging modalities have been developed to perform this role.

The TNM staging system (American Joint Committee on Cancer, 6th edition, 2002) is the most commonly used method for classification [1]. These staging criteria are designed to serve several purposes: helping to predict a patient's prognosis, assisting in the planning of treatment strategies, and providing a common language for practitioners to report the extent of disease. Previously, the Whitmore-Jewett staging system was employed, but this is only useful currently when reviewing older literature in this field.

**Evaluation of the (primary) tumor ("T")**

TX: cannot evaluate the primary tumor
T0: no evidence of tumor
T1: tumor present but not detectable clinically or with imaging
T1a: tumor was incidentally found in less than 5 % of prostate tissue resected (for other reasons)
T1b: tumor was incidentally found in greater than 5 % of prostate tissue resected
T1c: tumor was found in a needle biopsy performed due to an elevated serum PSA
T2: the tumor can be felt (palpated) on examination but has not spread outside the prostate
T2a: the tumor is in half or less than half of one of the prostate gland's two lobes
T2b: the tumor is in more than half of one lobe but not both
T2c: the tumor is in both lobes
T3: the tumor has spread through the prostatic capsule (if it is only partway through, it is still T2)
T3a: the tumor has spread through the capsule on one or both sides
T3b: the tumor has invaded one or both seminal vesicles
T4: the tumor has invaded other nearby structures (rectum, pelvic side wall)

**Evaluation of the regional lymph nodes ("N")**

NX: cannot evaluate the regional lymph nodes
N0: there has been no spread to the regional lymph nodes
N1: there has been spread to the regional lymph nodes

**Evaluation of distant metastasis ("M")**

MX: cannot evaluate distant metastasis
M0: there is no distant metastasis
M1: there is distant metastasis
M1a: the cancer has spread to lymph nodes beyond the regional ones
M1b: the cancer has spread to bone
M1c: the cancer has spread to other sites (regardless of bone involvement)

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**The Whitmore-Jewett System**

Roman numerals are sometimes used instead of Latin letters for the overall stages (e.g., stage I for stage A, stage II for stage B, and so on)

A: tumor is present but not detectable clinically; found incidentally

A1: tissue resembles normal cells; found in a few chips from one lobe

A2: more extensive involvement

B: the tumor can be felt on physical examination but has not spread outside the prostatic capsule

BIN: the tumor can be felt, it does not occupy a whole lobe, and is surrounded by normal tissue

B1: the tumor can be felt, and it does not occupy a whole lobe

B2: the tumor can be felt, and it occupies a whole lobe or both lobes

C: the tumor has extended through the capsule

C1: the tumor has extended through the capsule but does not involve the seminal vesicles

C2: the tumor involves the seminal vesicles

D: the tumor has spread to other organs

Prostate cancer staging can be divided into three main areas: evaluation of the primary tumor, evaluation of regional lymphadenopathy, and evaluation of metastatic disease. Following initial diagnosis, MRI forms the cornerstone imaging modality for determining the extent of the primary prostate cancer including key prognostic variables of evaluating extracapsular extension and seminal vesicle involvement.

## Evaluation of the Primary Tumor

### Clinical Staging

The primary tumor is initially assessed in the office or clinic setting by a combination of digital rectal examination and transrectal ultrasound (TRUS). The ability of the surgeon's finger to differentiate between T2 and T3 disease is unreliable due to significant interobserver variability [2]. This results from differing interpretations of the staging system as well as huge variations clinical skills, patient anatomy, and prostate size. It has been suggested that clinical T stage is not independently associated with biochemical recurrence of localized prostate cancer after radical prostatectomy [3]. Some feel that current clinical staging techniques may lack the sensitivity to reliably determine tumor extent and should not be used as a primary element of prostate cancer assessment.

The ability of the doctor to accurately clinically stage prostate cancer has always been regarded as a vital component of the patient assessment. This allows treatment planning, prognosis evaluation, and allows clinicians to speak the same language. The clinical stage is also included as a component of several frequently cited multivariable prognostic instruments such as the Kattan [4] and Memorial Sloane-Kettering nomograms [5].

### Transrectal Ultrasound (TRUS)

The transrectal ultrasound probe was introduced by Watanabe and colleagues in 1968 [6], and the initial reports and development of the diagnostic procedure were led by first Holm and Gammelgard in 1981 [7]. These advances have significantly contributed to the early diagnosis of prostate cancer. Besides having a major role in positioning the needle trajectory for both transrectal and increasingly trans-perineal biopsy, TRUS enables visualization of focal lesions suspected to be prostate cancer. It is usually performed prior to diagnosis of cancer, and staging information prior to biopsy is very operator dependent. An experienced observer can readily assess locally advanced (T3) disease, and there is a correlation between the ultrasound images and the volume and grade of tumor.

TRUS has previously been thought to add significant prognostic value in the assessment of the majority of men presenting with localized prostate cancer. Although high Gleason grade disease is more readily visualized on US as large focal areas of reduced echogenicity, low grade disease and small volume disease is frequently undetectable. These hypoechoic lesions are more likely to be due to adenocarcinoma than BPH, and it has been shown that TRUS has the ability to predict prostate cancer outcomes in some high volume specialist centers [8], but many feel that it is inconsistent regarding interobserver reproducibility, sensitivity and specificity, and overall utility in defining tumor size and disease extent. There have been developments in probe design over the past years, and the use of a high-frequency probe provides higher resolution images that better demonstrate the difference between normal and abnormal prostatic tissue (Fig. 43.1).

Color Doppler US (CDU) and Power Doppler have been available for over 20 years and are a useful adjunct to the diagnosis and staging of disease [9]. CDU may demonstrate areas of abnormal color flow in otherwise normal gray scale appearances although there is a limited practical use to this technique at present, as there is limited sensitivity for small tumors. Small tumors tend not to have sufficient angiogenesis to cause a significant change in color or Power Doppler trace.

There has been constant interest in the use of contrast US and microbubbles to improve the sensitivity of color Doppler and the detection of tumors. Although the ease of use of

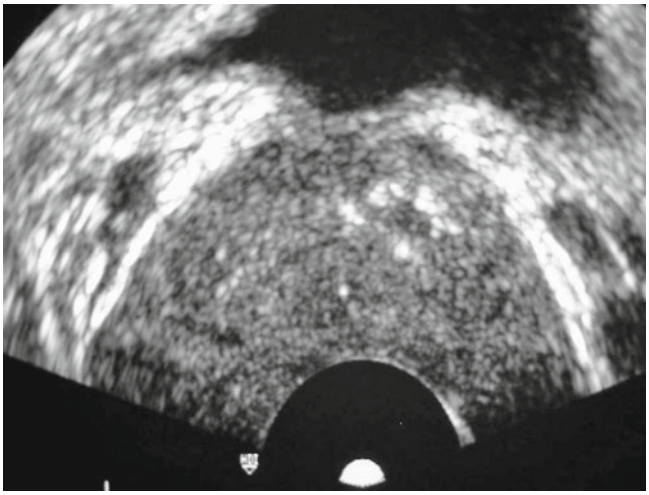

**Fig. 43.1** Axial transrectal US of the prostate demonstrates normal homogenous appearances of the peripheral zones

microbubbles has improved over the past few years, there has been a limited uptake in the technique partially due to increased cost, complexity, and time involved. A recent study has reported a statistically significant increase in detection of cancer detection using contrast-enhanced ultrasound-guided biopsy compared to systematic biopsy – 31 % of 559 men had cancer detected with contrast-assisted US, compared to 23 % with systematic biopsy despite the use of fewer cores in the contrast group (5 vs. 10) [10]. The rate of cancer detection per core was twice as high with the contrast-assisted technique.

TRUS- and US-guided biopsy still play the major part in the diagnosis of prostate cancer, although increasingly imaging can be used performed prior to biopsy to locate tumor and direct or target biopsy or to obtain staging information before the prostate gland has been affected by post biopsy changes which can make subsequent assessment difficult. It is generally felt that biopsy data should not be included in assigning clinical stage. Although clinical staging of malignancy is fundamental to medical practice, we should bear in mind that it offered no independent prognostic information when predicting biochemical recurrence in patients with organ-confined prostate cancer after controlling for other clinical variables [11].

## Magnetic Resonance Imaging (MRI) for Staging Prostate Cancer

### Introduction

MRI is currently the best noninvasive method for the detection and staging of localized prostate cancer. MRI allows excellent anatomical demonstration of the prostate. The soft tissue resolution exceeds that of other imaging modalities, which allows information to be obtained for both the detection and staging of prostate cancer. The signal-to-noise ratio is dependent on many parameters but the key factors are the strength of the magnet and the design of the coil. Most clinical scanners are 1.5 T machines, although 3 T machines are increasingly becoming available for routine practice rather than purely research tools.

An important development in MRI for prostate imaging was the introduction of phased array body coils, which produce higher signal-to-noise ratio and improve resolution of the image and acquisition time. Conventional protocols used for staging prostate cancer include T1-, and T2-weighted sequences. The parameters used will depend upon the manufacturer of machine and the strength of the magnet. T1 imaging is usually obtained in the axial plane and covers the whole of the pelvis from the aortic bifurcation down to the symphysis pubis. T1 imaging provides information on the presence of enlarged lymph nodes in the pelvis, as well as demonstrating the presence of bone disease in the pelvis.

The T1 images are also useful for demonstrating the presence of hemorrhage within the prostate following biopsy, which is seen as foci of high signal within the prostate. The presence of extensive hemorrhage can make detection or staging of cancer more difficult, although there is significant variation to what degree the hemorrhage degrades the T2 images. Historically, a period of at least 3 weeks (21 days) has been suggested between the prostate biopsy and a staging MRI to allow hemorrhage to subside [12] and to reduce the overestimation of tumor presence and extracapsular extension. More recently, up to 8 weeks has been recommended [13], although the desires of the patient, clinician, or hospital targets may force staging investigations to be performed earlier. Other papers have returned to the view that a delay of only 3 weeks is sufficient to allow significant hemorrhagic changes to resolve [14].

In patients who have a high suspicion of cancer prior to the prostate biopsy (e.g., a palpable nodule, or significantly raised PSA), and who may be suitable for radical treatment, it can be very helpful to perform MRI before the biopsy [15]. This has the benefit of providing information from the MRI to guide the location of biopsy but also eliminates the post biopsy changes, which can make accurate staging difficult or impossible. The additional cost of this approach is not very great, as the incidence of cancer in these patients is high, and it can be time- and cost-effective to be able to consider treatment options immediately following the biopsy results if staging investigations have already been performed.

T2 imaging sequences are the most important for demonstrating disease in the prostate and for staging tumor. It is important to obtain T2 sequences in the axial, sagittal, and coronal planes. It is not necessary to angle the plane of the images to the axis of the prostate, and in some cases this can make evaluation of the seminal vesicles more difficult. The T2 images demonstrate the internal architecture of the

prostate well and allow differentiation of the central gland from the peripheral zones. The "true" capsule of the gland can usually be well seen as a focus of low signal surrounding the peripheral zones. The peripheral zones are usually seen as homogenously high signal areas, while the central gland, which comprises the central and transition zones, is of a more heterogeneous and low signal appearance. The normal seminal vesicles (SV) are of high signal intensity (white), while the vas deferens is of low signal intensity. The neurovascular bundles are important structures that can be identified on high-resolution MRI and are seen as paired structures at 5 and 7 o'clock posterolaterally to the prostatic capsule (Fig. 43.2).

Tumor is usually found in the peripheral zones and is seen as either well- or ill-defined foci of low signal. Unfortunately, these appearances are not specific for cancer and may be seen in prostatitis, hemorrhage, and following prior treatment (e.g., radiotherapy). The presence of tumor in the central gland is more difficult to demonstrate and may be better demonstrated with other supplementary MR techniques (see below). Seminal vesicle invasion is clearly demonstrated on T2 imaging with asymmetrical signal intensity from the lumen in the absence of hemorrhage or thickening of the wall of the seminal vesicle (Figs. 43.3 and 43.4).

Staging depends upon the accurate demonstration of the prostatic capsule, and the periprostatic tissues. The presence of soft tissue extending through the capsule in the absence of significant hemorrhage on T1 images is reliable in confirming the presence of T3a disease with a high specificity. Unfortunately, microscopic disease is not visible on MR, and therefore the sensitivity for small volume T3a disease is low. Secondary signs of extra prostatic disease include irregular capsular margins, capsular retraction, loss of the recto prostatic angle, and asymmetry of the neurovascular bundles. MRI may also show additional pathology of direct relevance to the clinical situation, e.g., a large prostatic middle lobe or bladder tumor (Figs. 43.5, 43.6, and 43.7).

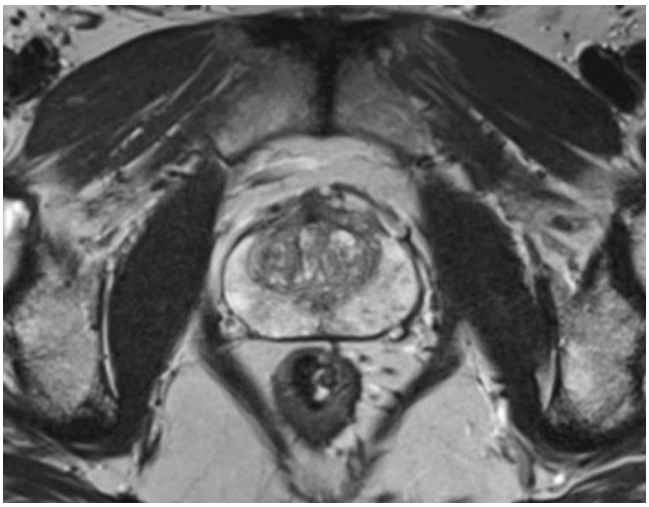

**Fig. 43.2** Axial T2 images with a small field of view demonstrate homogenous T2 signal in the peripheral zones of the prostate with no evidence of tumor

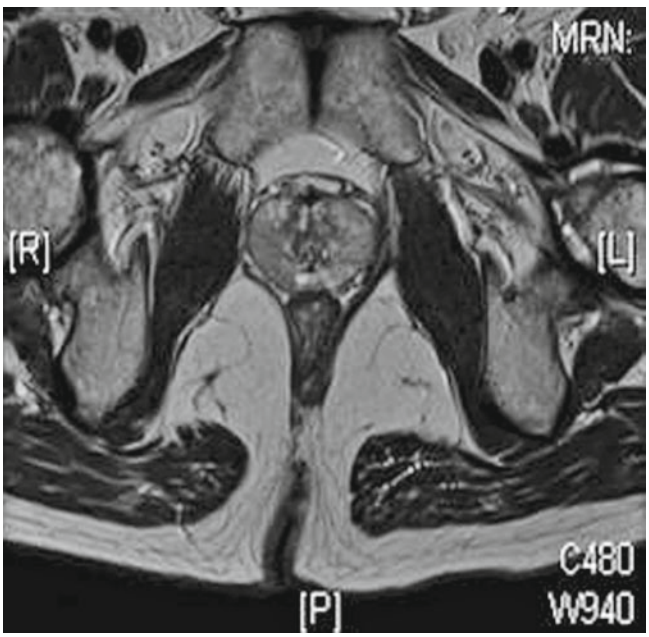


**Fig. 43.3** Axial T2 MRI demonstrates focal tumor in the right peripheral zone of the prostate with no evidence of extracapsular extension

## Accuracy of MRI for Staging of Prostate Cancer

There are wide varying reports of the ability of MRI to accurately stage prostate cancer. Sensitivities of between 22 and 85 % and specificities of between 50 and 99 % have been reported [16]. This huge variation in reported results is multifactorial and may be due to patient selection, equipment, radiological experience, and accurate correlation with post-surgical pathology. The diagnostic criteria used to define T3 disease can significantly affect either the sensitivity of specificity obtained. The playing field is changing rapidly with new innovations in MRI, and published series more than a few years old should now probably be viewed as historical due to technology upgrades.

## Endorectal MRI

MRI can be used in conjunction with a coil placed into the rectum in order to obtain high-quality images of the surrounding area. The coil consists of a probe with an inflatable balloon which helps maintain appropriate positioning during the 45-min examination. The use of endorectal coil significantly improves signal quality and allows thinner slices with increased resolution. It has been demonstrated that the addition of endorectal MRI and spectroscopic information can produce a significant incremental value to staging

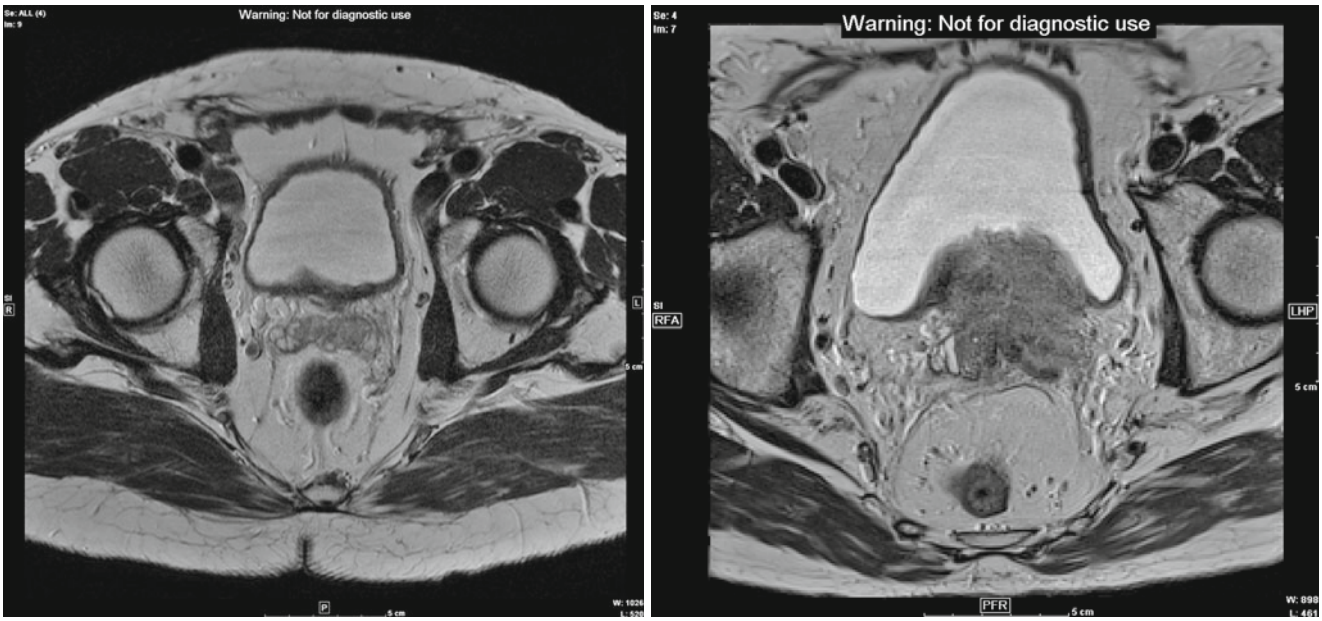


**Fig. 43.4** T2 MRI demonstrates invasion of the seminal vesicles in keeping with T3B carcinoma of the prostate in both images

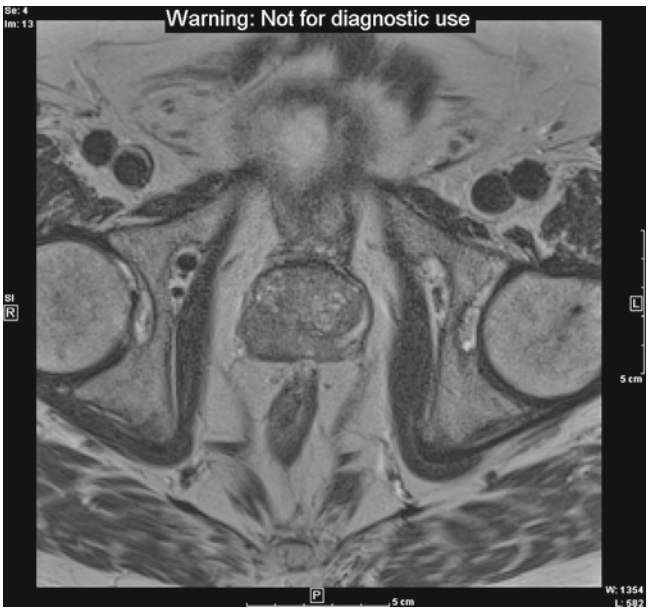


**Fig. 43.5** Axial T2 MRI of the prostate demonstrate focal disease in the right peripheral zone of the prostate with convincing tumor passing through the capsule of the gland consistent with T3a disease

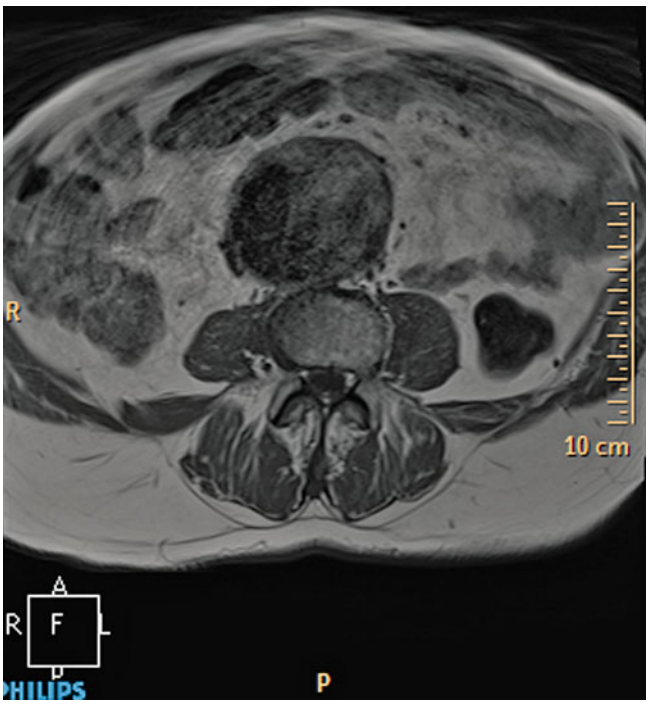


**Fig. 43.6** Axial T1 scans through the pelvis demonstrate an incidental aortic aneurysm. Review of the T1 scans is important to exclude bone metastases and incidental pelvic masses in adjacent organs such as the bladder or rectum

nomograms in predicting organ-confined prostate cancer [17, 18]. It can also act as a guide for neurovascular bundle preservation [19] and prove sensitive (83 %) but not specific (62 %) in the clinical setting of patients with a persistently elevated PSA level and one or more prior negative TRUS-guided biopsies.

When using a 3 T MRI, endorectal techniques have been shown to outperform body coils [20] providing significantly improved image quality and localization compared with body-array coil imaging in the hands of experienced radiologists. The recent dissemination of 3 T body coil MRI has generally produced images with increased spatial resolution that equal that of 1.5 T endorectal coil MRI without the cost, inconvenience, and discomfort of endorectal MR.

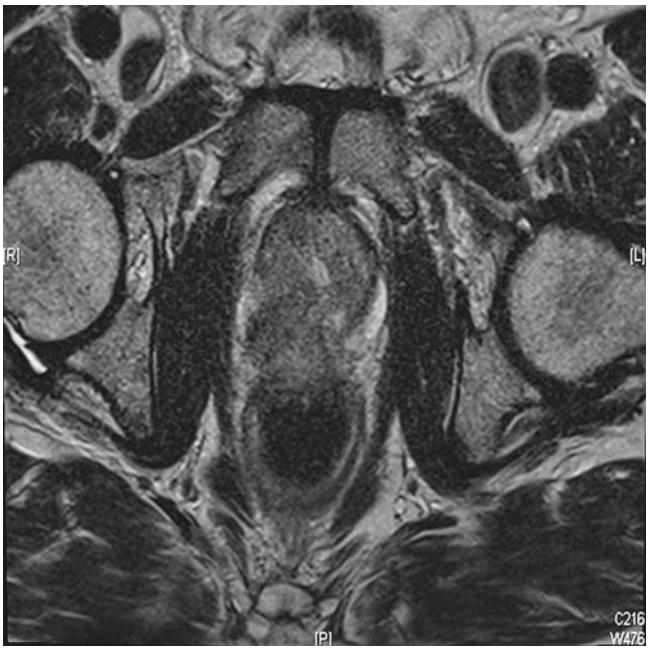


**Fig. 43.7** Axial T2 MRI of the prostate demonstrates a bulky tumor passing through the prostate into the rectum in keeping with T4 disease

## Dynamic Contrast-Enhanced MRI

Dynamic contrast-enhanced MRI (DCMRI) demonstrates the vascularity and vascular permeability of tissues over time. Tumors tend to have permeable vessels that leak contrast after injection and also demonstrate early rapid enhancement.

Dynamic MRI is not routinely used in staging prostate cancer, although there are specific uses for the technique. It can be used in the detection of tumor in patients with an elevated PSA as a prelude to biopsy. The presence of abnormal areas of enhancement may influence the decision to biopsy or the location of biopsy. It is unusual in most institutions to perform DCMRI routinely prior to biopsy, although there can be times when this information can be useful, e.g., high-risk biopsies. DCMRI can be more usefully utilized in patients who have had a set of negative biopsies but in whom there is a high index of suspicion for cancer [21]. Dynamic scans may demonstrate tumor in the anterior gland that can be specifically targeted although our current practice is to proceed directly to trans-perineal template biopsy in these cases.

A recent study looking at the use of DCMRI prior to repeat prostate biopsy [21] demonstrated an 83 % sensitivity of DCMRI compared to standard T2 imaging. Unfortunately, the specificity of DCMRI was only 20 % on a patient-based analysis compared to 44 % for T2 imaging. When evaluated on a more stringent sector analysis, the sensitivity of DCMRI was 52 % compared to 32 % for T2 imaging. Combining both modalities on a sector by sector analysis produced an improved specificity of 92 % but a sensitivity of only 31 %. The group from Lille has compared the diagnostic performance of DCMRI with whole-mount radical prostatectomy specimens. In their initial report in 2006 on pre-biopsy pelvic-phased DCMRI, the sensitivity and specificity for cancer detection were 90 and 88 % for foci greater than 0.5 cc [22]. In the updated study, DCMRI had a sensitivity and specificity of 86 and 94 %, respectively, for the identification of cancer foci >0.5 mls with an area the under the ROC curve of 0.874 showing good concordance and a negative predictive value of 95 %. They conclude that DCE-MRI can accurately identify intraprostatic cancer foci [23].

## CT/MRI Detection of Lymph Node Disease

The detection of lymph node metastases using standard MRI or CT is based entirely on size criteria. An arbitrary measurement of 1.0 cm is chosen as the upper limit for normal lymph nodes. Early lymph node metastasis is more commonly seen in sub centimeter lymph nodes and is therefore frequently missed with CT and MRI. In addition, benignly enlarged lymph nodes are common and may be falsely diagnosed as malignant. Benign nodes generally have a smooth, well-defined border with a homogeneous density or signal intensity.

Pelvic lymph node dissection has been used to more accurately stage lymph node status. Despite histological evidence, the surgical resection often fails to correctly identify all positive lymph nodes due to incomplete dissection or the presence of metastatic lymph nodes in the upper pelvic or abdominal lymph nodes. A meta-analysis of 24 studies evaluating accuracy of CT and MRI for lymph node metastases in prostate cancer demonstrated a pooled sensitivity of 0.42 and specificity of 0.82 for CT and sensitivity of 0.39 and specificity of 0.82 for MRI [24]. These results suggest that both CT and MRI have an equally poor performance in the detection of lymph node metastases. Improved accuracy may be better with the use of lymph node specific agents – see below (Fig. 43.8).

## Whole Body MRI for Metastases

Whole body MRI relies on the use of T1 and short T1 inversion recovery (STIR) images of the whole spine and ribs to detect early bone metastases with a greater sensitivity and specificity than an isotope bone scan. Whole body MRI has been compared to bone scintigraphy and has found to be superior for the detection of small bone metastases. Ketelsen et al. found that 96 % of the metastases found on isotope scan were detected at MRI, while only 59 % of the metastases depicted at MRI could be detected on the isotope scan [25]. MRI performed better with sub centimeter lesions as well as

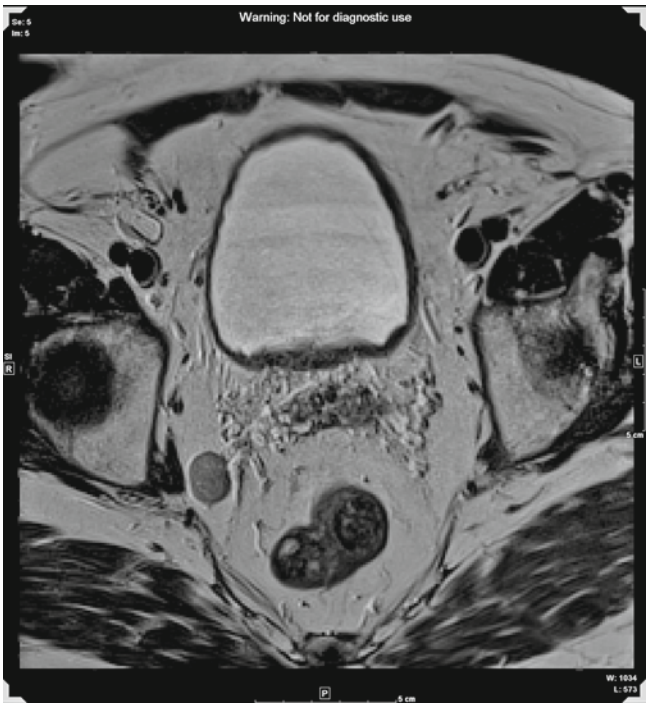


**Fig. 43.8** MRI demonstrates enlarged right obturator nodes in keeping with nodal metastatic disease (N1)

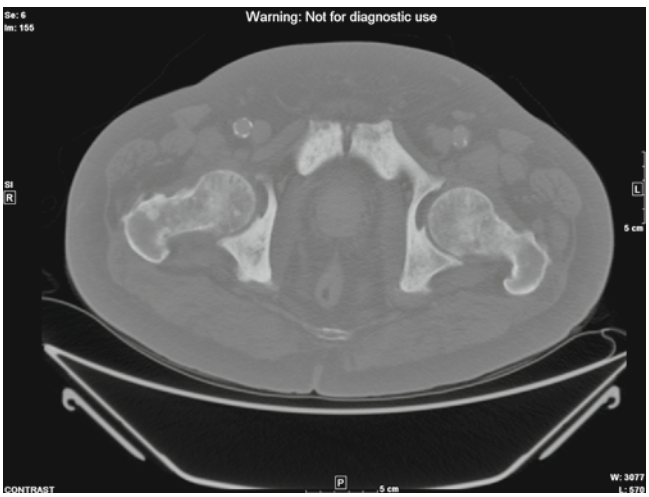


**Fig. 43.9** Non-enhanced axial CT through the pelvis on bone windows demonstrates extensive sclerotic metastases throughout the pelvis

providing additional information about extra osseous tumor (Fig. 43.9).

## Diffusion-Weighted Imaging (DWI)

Diffusion refers to the random motion of molecules along a concentration gradient and relies upon endogenous contrast using the motion of spin reduced signal changes. The signal produced depends on the degree of diffusion and the strength and timing of the gradient. The time of the gradient is expressed by the gradient factor or B factor. The diffusion property is determined by the distribution of water molecules between cell spaces. B factors can be acquired with different values therefore enabling a value for the apparent diffusion coefficient (ADC calculated).

Originally developed for imaging the brain, DWI has been used for solid organ tumors to improve sensitivity and specificity of disease detection. DWI can be used in addition to standard MRI for both identification and localization of prostate cancer. Prostate cancer demonstrates reduced diffusion due to edema and abnormal cell density resulting in high signal intensity for prostate cancer compared to normal prostatic tissue. Prostate cancer is displayed as areas of reduced signal on the ADC map. Unfortunately, benign prostatic hyperplasia (BPH) can also alter cellular density and can produce an abnormal diffusion pattern mimicking prostatic malignancy. Similar false positives can be seen in prostatitis [26].

DWI has been reported to produce an increase in sensitivity and specificity when combined with standard T2-weighted imaging. Limb reported increased sensitivity from 74 to 88 % with a corresponding increase in specificity from 79 to 88 % and an overall increase in accuracy from 77 to 88 % [27]. It has also been reported that diffusion-weighted imaging can improve accuracy for staging and in particular for assessment of seminal vesicle disease [27]. DWI does not require intravenous contrast unlike dynamic enhancement and is simpler to process. The time for acquisition is significantly less than spectroscopy.

DWI imaging can easily be combined with standard imaging protocols with very little increased time of scanning. Recent studies [28] have suggested that there is a reduction in the ADC value with increased Gleason grade of tumor as well as the percentage of tumor on core biopsies. This study suggested that DWI may help differentiate between the low-risk Gleason 6 tumors and the intermediate and high-risk tumors (7–10). It also opens the door for MRI-guided focal therapy treatments for isolated lesions (Fig. 43.10).

## MRI Spectroscopy

MRI spectroscopy (MRS) is a new technique for displaying metabolic information which relies on the differences in frequency for chemical shifts that exist due to different chemical environments. MRI spectroscopy information once obtained is represented in the form of a spectrum, which provides the biochemical information contained with a selected voxel (volume) of tissue. It can be used to detect the absence or presence of certain compounds and can assist in differential diagnosis when standard clinical imaging fails. MRS can be used for tumor localization [29], characterization planning,

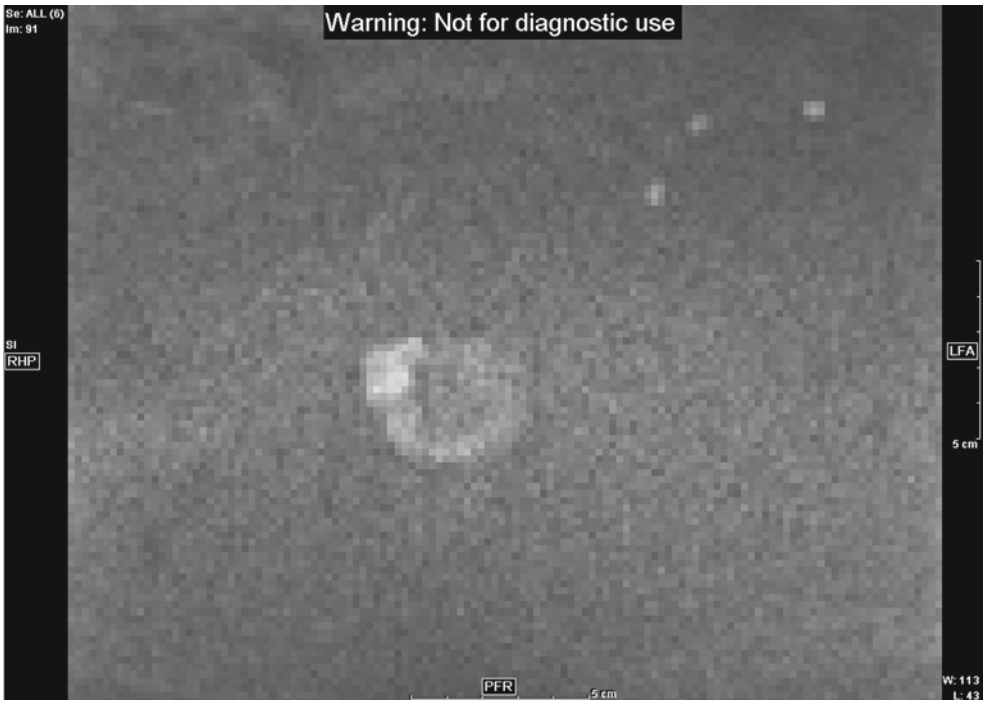


**Fig. 43.10** MRI demonstrates an area of abnormal high signal seen in the right anterior prostate on diffusion imaging in a patient with previous negative TRUS biopsy and elevated PSA. Repeat anterior-guided biopsy confirmed carcinoma of the prostate

and therapy evaluation [30]. Three metabolites are measured, citrate, choline, and creatine. A reduced level of citrate and increased level of choline is suggestive of prostatic cancer. These changes can be mapped onto T2 images to localize disease.

## 3 T (Tesla) MRI

High field strength MRI scanners have become increasingly more available in both research and clinical settings. There is an increase in signal-to-noise ratio at the high magnetic field which allows potential reduction in acquisition time and increased special resolution. These improvements may result in an improved local staging and localization of organ confined carcinoma of the prostate.

With increasing field strength of the magnet there is a linear increase of the signal-to-noise ratio with little reduction in the noise. Kitajima and colleagues found a sensitivity and specificity of 81 and 96 % (area under ROC 0.89), respectively, when using a 3 T MRI with a combination of T2WI, DWI, DCEI in patients with elevated PSA levels [31].

Additional benefits of higher field strength magnets would be in the use of dynamic contrast MRI at the increased signal to noise can lead to improved temporal resolution of the dynamic measurements. There are some potential drawbacks of high field strength imaging with an increase in artifacts, which can be corrected.

## MRI and Lymph Node Specific Agents

Super paramagnetic particles contain nanoparticles which when administered intravenously have taken up by macrophages and transported to healthy node lymph tissues. The presence of the iron causes changes in the magnetic characteristics of the tissue resulting in reduced signal on MRI imaging. Lymph nodes with metastases demonstrate absence of macrophages and therefore these lymph nodes are not of reduced signal and appear white rather than black. The use of MRI suggests this is a more reliable method of excluding or confirming lymph node metastases than surgical staging which is limited by the number of lymph nodes removed and adequate access to all lymph nodes regions.

Harisinghani reported the use of lymphotropic super magnetic nanoparticles in the detection of micrometastases in prostatic cancer [32]. The study found a significantly increased sensitivity of MRI with contrast agents on a node by node basis with a 90.5 % sensitivity compared to 35 % sensitivity with conventional MRI. The specificity increased from 90 to 98 %. The use of paramagnetic particles is associated with an increase cost of the contrast agent in addition to the duplication of scans required, as MRI is required before and after injection of the nanoparticles. However, a negative MRI lymphangiogram may obviate the need for lymph node dissection in staging of prostate cancer.

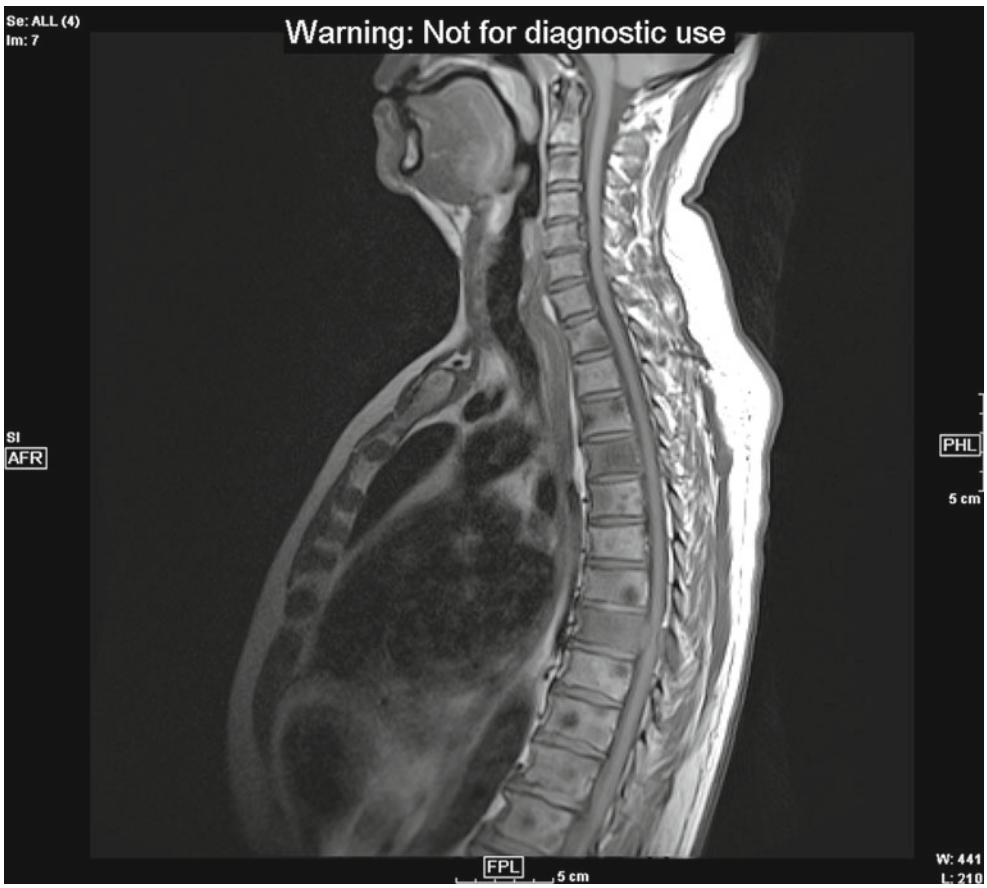


**Fig. 43.11** Sagittal MRI of the spine demonstrates metastatic disease in the vertebral body causing cord compression

## Computerized Tomography (CT) for Staging Prostate Cancer

There have been significant advances in CT technology over the past decade, but it still plays a relatively minor role in the staging of prostate cancer in most large centers. This is due to the limited soft tissue resolution of CT when compared to MRI, and its inability to differentiate the prostatic capsule from the surrounding structures rendering it of very little use in local staging.

CT can be used to stage patients with locally advanced or advanced prostate cancer who may be suitable for hormonal manipulation, pelvic radiotherapy, or chemotherapy. It will demonstrate nodal disease in the abdomen and pelvis, as well as the presence of visceral or lung disease. If a patient has a pacemaker, they will need to have CT staging rather than MRI. Unfortunately, CT depends solely upon the size of lymph nodes to determine if they are involved, and micrometastases can readily be missed, or benign enlarged nodes can be incorrectly called as metastatic. Other techniques such as PET or MR lymphangiography may be far more reliable in resolving the presence of lymph node disease if it is clinically important.

CT can also be useful to evaluate bone lesions in patients with an abnormal but non-diagnostic bone scan although increasingly MRI will be used for imaging of metastases in the spine and pelvis. CT can be used to locate and guide biopsy of solitary bone lesions to confirm the presence of metastatic disease in patients who are otherwise suitable for radical local therapy. Recently, dynamic contrast-enhanced (DCE)-CT has been proposed as a useful tool for localization of prostate tumors and the quantification of therapeutic responses in prostate cancer. It may be that a combination of DCE-CT with CT or 11C-choline PET/CT may be a useful alternative to MRI, offering a combination of quantitative parameters that may correlate with prognosis as well as cancer localization for focal therapies [33] (Fig. 43.11).

## Positron Emission Tomography (PET)

Information on lymph node status is vital when planning appropriate treatment for patients with newly diagnosed prostate cancer. PET is a diagnostic tool using radiotracers to show changes in metabolic activities in tissues. It is combined with CT imaging (PET/CT) to give useful informa-

tion regarding potential metastases in a variety of urological and other malignancies. The integration of both PET and CT imaging techniques overcomes the limitations of the individual techniques and permits precise location of lesions while providing additional functional information. The most widely used radiotracer is fluorodeoxyglucose, a glucose analogue taken up by high-glucose-using cells including cancer cells, where phosphorylation prevents the glucose from being released intact. Fluorine-18 is usually the positron – emitting radioactive isotope used although it has a limited role in prostate cancer primary diagnosis and staging because prostate tumors often lack an increased glucose metabolism in contrast to others. In past years, studies using 11C- or 18F-choline have shown promising results. de Jong et al. [34] reported excellent results with 11C-choline PET on preoperative lymph node staging in newly diagnosed cases (sensitivity, specificity, and accuracy were 80, 96, 93 %, respectively). However, it should be noted that the mean preoperative PSA level of patients with lymph node metastases in this study was 123 ng/mL and did not represent the typical high-risk patient. This group have also recently shown the potential use of PET/CT for the staging of locally advanced prostate cancer prior to radiotherapy [35].

## HistoScanning

Computer-aided ultrasound or HistoScanning (Advanced Medical Diagnostics, Waterloo, Belgium) is an emerging ultrasound-based technology that hopes to better localize and characterize prostate cancer. It is primarily aimed at the detection of the primary tumor in localized disease. It works by detecting specific changes in prostate tissue morphology by extracting and quantifying statistical features from backscattered ultrasonographic data [36]. It is hoped that this might allow differentiation between benign and malignant tissue. It employs characterization via specific tissue characterization algorithms which exploit the physical changes to sound waves that result from the interaction of the ultrasound beam and the cancerous tissue.

The HistoScan test comprises of a standardized three-dimensional (3D) examination of the prostate using motorized TRUS in the sagittal plane. The volume of cancerous lesions can be calculated by summing the sub-volumes present in adjacent locations which were positive by HistoScanning. The distance of the center of any detected lesion from the rectal wall and from the base of the prostate can be measured using known scan parameters and geometry. The spatial (3D) position within the prostate can be established by having a fixed and standardized scan direction (right to left of the patient) with a known fixed angle step(0.2°) between every scanning frame.

Early data has shown that the technique can identify tumor foci as small as 0.5 ml [37]. The attraction is the potential to utilize a platform that is widely available in both hospital and in diagnostic/office settings where most prostate cancers are diagnosed. The technology is not overly expensive, quick (approx. 45 s), noninvasive and simple to use. It spans 179° and typically captures ~800 frames. It could be employed as an adjunct to a standard TRUS examination and potentially reduce the number of unnecessary prostate biopsies while targeting suspect lesions to improve detection rates. It could be used for men who are deemed to be at high risk of prostate cancer as a result of an abnormal PSA level or a positive family history; however, full validation in the target populations and negative predictive ability is yet to be seen (Fig. 43.12).

### Conclusions

With huge advances in our ability to precisely image prostate cancer in the last few years, we are entering an exciting time in the field of prostate cancer staging. Multiparametric MRI with all of its intricacies and nuances seems increasingly able to deliver accurate and specific information to the urologist for interpretation. There has been little change in the diagnostic process in prostate cancer for two decades. Until recently, imaging has not been seen to be part of the diagnostic pathway for localized prostate cancer or the decision to biopsy or target biopsies themselves [15]. It has been predominantly used for staging once diagnosis has been made. There are many described variations in technique and interpretation of images which have contributed to inconsistency in the previously reported performance characteristics of MRI.

Recently, a combined group of uroradiologists have made recommendations on a standardized method for the conduct, interpretation, and reporting of prostate multiparametric MRI for prostate cancer detection and localization [38]. This attempts to standardize specific numbered zones, scoring scales, and a universal electronic presentation to aid reporting. There now seem to be evidence that MRI can actually assess the aggressiveness of prostate cancer as ADC values have been shown to be negatively correlated with Gleason grade [39]. It may also be the best imaging modality to stage the regional lymph nodes if used as MR lymphangiography and has such a good negative predictive value that it may allow surgeons to omit a lymphadenectomy at radical surgery [40].

Combined with substantial recent significant improvements in our ability to detect prostate cancer within the gland from imaging alone, imaging may now become part of the screening, diagnostic, and staging process, influencing all decisions along the patient's journey.

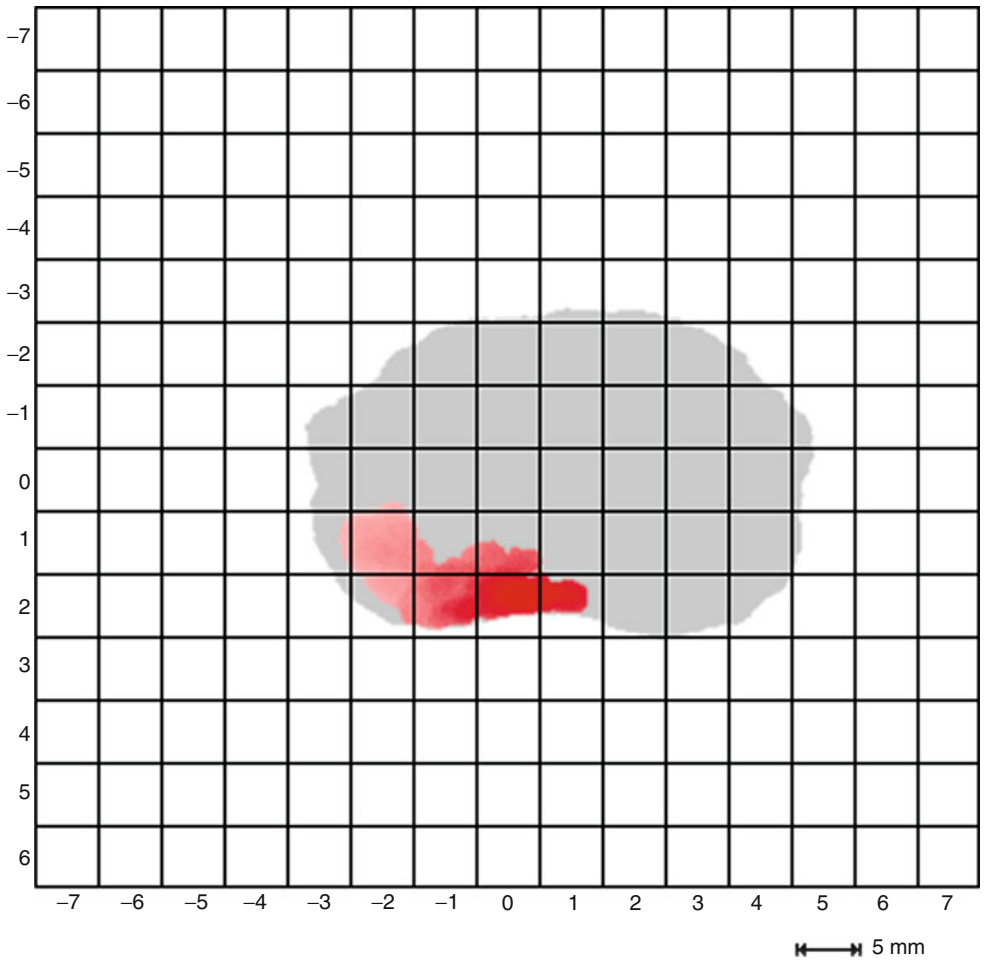


**Fig. 43.12** HistoScan demonstrates abnormality seen in the right peripheral zone of the prostate, later confirmed as Gleason 4+4 carcinoma of the prostate

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# Nuclear Medicine in Prostate Cancer

# 44

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## Introduction

The field of nuclear medicine exploits the properties of unstable, radioactive nuclei. The stability of a nucleus is dependent upon the relative number of protons and neutrons within the nucleus. Nuclei with too many neutrons or protons are unstable and decay to a stable state with the emission of radioactive energy.

The emitted radioactive energy can occur in different forms: auger electrons, alpha particles, beta particles, positrons, or gamma rays. Auger electrons and alpha and beta particles travel only a short distance and are used for the delivery of targeted therapy. A positron is a positive electron, a form of antimatter and is therefore short-lived; it soon collides with an electron with the formation of high-energy gamma rays. Gamma rays are a form of electromagnetic radiation, similar to X-rays, and have a longer range which allows their use in imaging.

The principle of nuclear medicine imaging and therapy involves the administration of trace amounts of radioactive material which is attached to a pharmaceutical designed to localize to the organ of interest, that is, the target organ. As the radioactive nucleus decays, it emits radioactive energy which, in the case of gamma photons, can be detected by a gamma camera. Gamma photons are emitted in all directions from the patient; however, those that are detected by the scintillation crystal of the gamma camera are localized using a lead grid, known as a collimator, allowing the formation of an image which reflects the distribution of the radioactive nuclei within the body.

The resulting image is of lower resolution than other imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) but has the advantage of reflecting functional processes, that is, what is happening at a cellular level. The functional aspect of nuclear medicine imaging allows the detection of pathological processes at an earlier stage than with those modalities that rely on changes in size or shape of an organ to determine pathology.

The following chapter discusses the applications of nuclear medicine in the management of prostate cancer including the role of bone scintigraphy, the current and future applications of positron emission tomography (PET) imaging, and the therapeutic applications.

## Radionuclide Bone Scanning

Metastatic spread of prostate cancer is most common to lymph nodes and bone, with bone metastases evident in 90 % of patients dying from this condition [1, 2]. Bone scintigraphy uses the radioisotope technetium-99m, labeled to a diphosphonate, the most commonly used being $^{99m}$Tc-methlyene diphosphonate ($^{99m}$Tc-MDP), and is a quick, cost-effective method of imaging the whole skeleton. It is currently the primary test for the assessment of skeletal metastases in prostate cancer [3].

Newly presenting patients without evidence of metastatic spread may be eligible for curative radical localized treatment, while in contrast, patients with advanced disease with proven metastatic spread may require a change in management [4]. Therefore, bone scintigraphy has a fundamental role in the management of prostate cancer from primary staging of the disease through to assessing treatment response [4].

Bone metastases induce either bone resorption, secondary to increased osteoclastic activity, or bone formation,

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secondary to increased osteoblastic activity. Prostate cancer metastases have shown a predilection for the bone marrow endothelium, the typical site of osteoblastic activity, with a particular affinity for the axial skeleton [5, 6]. The osteoblastic response is further stimulated by prostate specific antigen (PSA) which has been shown to encourage osteoblastic proliferation while at the same time causing apoptosis of the osteoclastic precursors [7, 8]. These factors give rise to the typical appearance of a sclerotic rather than lytic lesion.

Uptake of $^{99m}$Tc-MDP is directly correlated with the degree of calcium within a tissue, with bone having the highest concentration [9]. The exact mechanism of uptake is not clear, but it is postulated that the tracer is chemadsorbed in the hydroxyapatite mineral component of the osseous matrix [10]. Other factors that play a crucial role in the degree of bone uptake include local blood flow and osteoblastic activity [9].

Bone scintigraphy is a sensitive modality for assessing bone involvement, with studies showing sensitivities higher than serum markers and plain radiographs [11]. However, false negatives can occur with slow-growing lesions and some aggressive metastases that cause severe destruction of bone, leading to occult or photopenic defects [7]. Additionally, its specificity is limited as the tracer is not tumor specific and can accumulate in a variety of conditions, such as Paget's disease, degenerative change, recent surgery, and infections leading to false positive results.

When determining the need for bone scintigraphy in the assessment of primary cancers and recurrent disease, variables such as the clinical stage, PSA level, and Gleason score at biopsy have been found to be invaluable tools [12]. They allow categorization of primary cancers into low and high risk [4]. Asymptomatic patients or those with a serum PSA < 10 ng/ml are low risk and unlikely to have metastases [7, 13, 14]. Oesterling et al. showed a negative predictive rate of 99 % with a PSA < 20 ng/ml [15]. Studies have also shown patients with a Gleason score of <7 and >8 were associated with metastatic bone detection rates of 6.4 and 49.5 %, respectively [16, 17].

Bone scintigraphy is commonly used in the initial assessment of high-risk patients (PSA > 20 ng/ml, Gleason score > 8, bone pain or stage T3/T4 disease) and postoperative patients with a rising PSA level [4]; indeed studies have shown the extent of skeletal metastatic deposits is an independent prognostic factor [7, 18].

Bone scintigraphy can also be used to assess response to treatment to determine whether other treatment options should be considered. The accuracy of bone scan interpretation can be improved using a semiquantitative computer algorithm, the bone scan index [7]. This has been found to correlate well with the rapid exponential growth phase of metastasized androgen-independent prostate cancers and can therefore predict their outcome [19, 20].

## Patterns of Uptake

Bone scintigraphic imaging for skeletal metastases is performed in the delayed phase, between 2 and 4 h after injection, in order to optimize the uptake in bone and minimize background activity. A normal bone study shows homogenous uptake throughout the skeleton with excretion via the urinary system.

Increased uptake on a bone scintigraphy study may not, as mentioned earlier, be secondary to metastatic infiltration. By examining the intensity , distribution, and degree of symmetry of uptake, it is sometimes possible to ascertain the diagnoses without the need for further investigation [10].

Non-pathological foci of increased uptake are seen at the ends of ribs, tips of the scapula, and at the manubriosternal junction (Fig. 44.1). These typically show bilateral uniform uptake indicative of their benign nature, but if there is any doubt, further views or correlative imaging can be performed [10].

The typical appearances of diffuse metastatic disease are multiple scattered foci of increased uptake seen throughout the skeleton, in particular the axial skeleton (Fig. 44.2). The foci correspond to areas of increased osteoblastic activity which usually manifest radiographically as sclerotic foci.

Solitary lesions can prove difficult to categorize depending on their location. A single rib lesion is often secondary to benign causes such as trauma (Fig. 44.3) [21], but a lesion extending along the rib is concerning for malignant infiltration (see Fig. 44.4) [10]. A solitary lesion within the long bones is more suggestive of a metastatic deposit and is of concern as there is a risk of pathological fracture (Fig. 44.5).

The majority of bone metastases involve the axial skeleton, particularly the pedicles, many of which remain asymptomatic [7]. Their detection is therefore of paramount importance in determining prognosis, guiding treatment and preventing neurological complications. Planar bone scintigraphy is often of limited diagnostic accuracy in assessing the axial skeleton due to concomitant disease such as degenerative change. This is made particularly difficult when assessing solitary lesions. Plain radiographs are often performed to evaluate areas of abnormal uptake [22]. Studies have shown that a radiographically benign lesion that corresponds to an area of abnormality on the bone study is typically benign [22, 23].

Two characteristic patterns of uptake are sometimes seen with bone scintigraphic imaging. In patients with diffuse disseminated bone metastases, there is markedly increased uniform uptake throughout the bone, with scintigraphic findings resembling a normal bone study. However, in these studies the degree of uptake within the kidneys is faint or absent [24]. This study, termed a "superscan" (Fig. 44.6), is seen in disseminated disease.

Another typical pattern of bone scintigraphic uptake can occur in patients who have just completed, or are having, cyclical

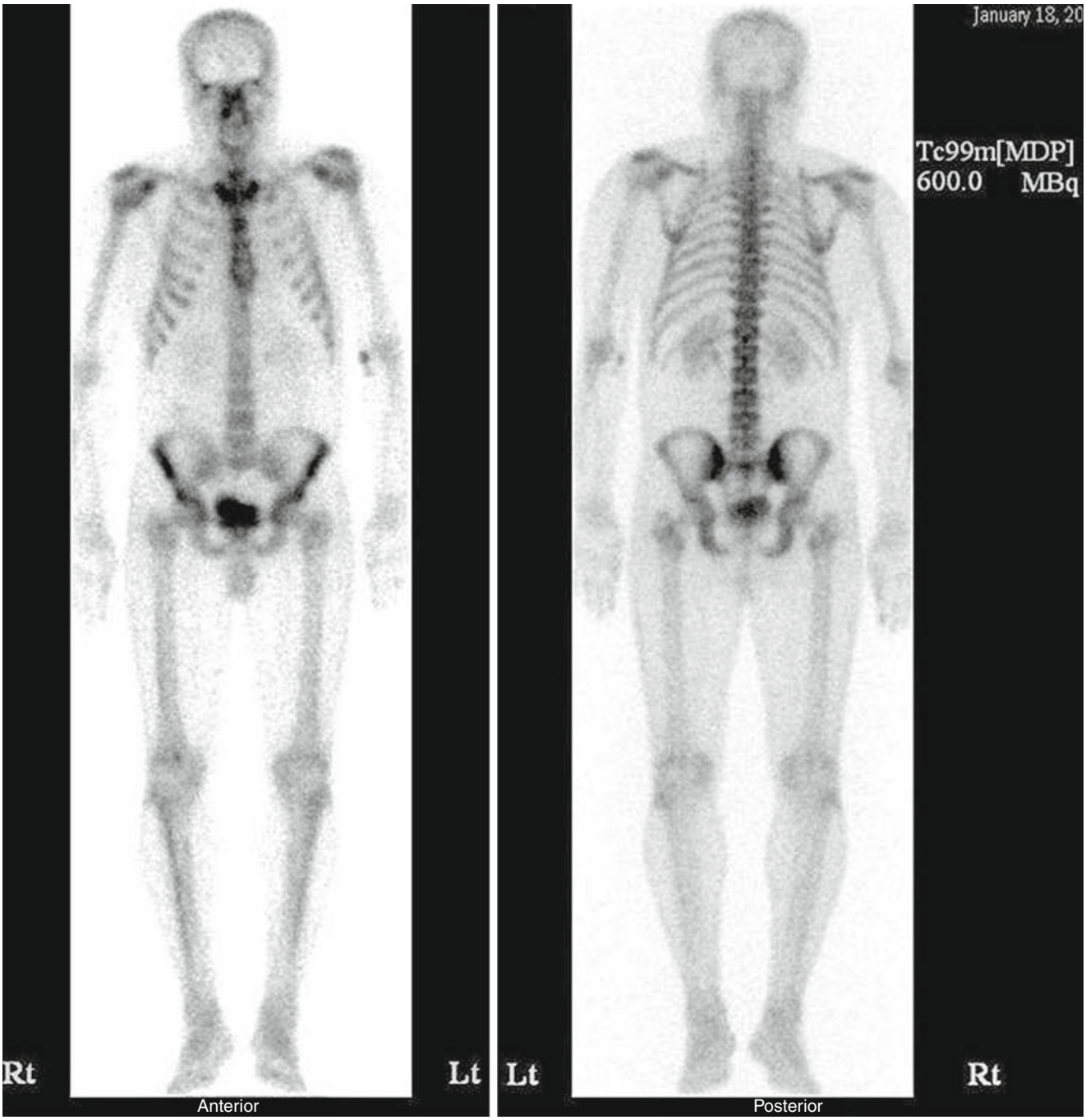



**Fig. 44.1** Normal $^{99m}$Tc-MDP bone study shows diffuse homogenous uptake throughout the skeleton and urinary system. Minor symmetrical physiological areas of increased uptake are seen at the tips of scapulae, shoulder joints, and within the mandible

chemotherapy, particularly when imaging is performed too early. The "flare phenomenon" (Fig. 44.7) may show a worsening of the bone scintigraphy images despite a good response to treatment. This is due to increased sclerosis which corresponds to osteoblastic activity, occurring in the bone surrounding the bone lesion as it heals. The response usually lasts 3–6 months after therapy and is associated with a good prognosis [7, 25].

## Single Photon Emission Computed Tomography (SPECT) Imaging

Planar imaging is two-dimensional, with activity from overlying structures superimposed on the final image. SPECT imaging allows the formation of 3D images by acquiring multiple projections over a 360° arc around the patient.

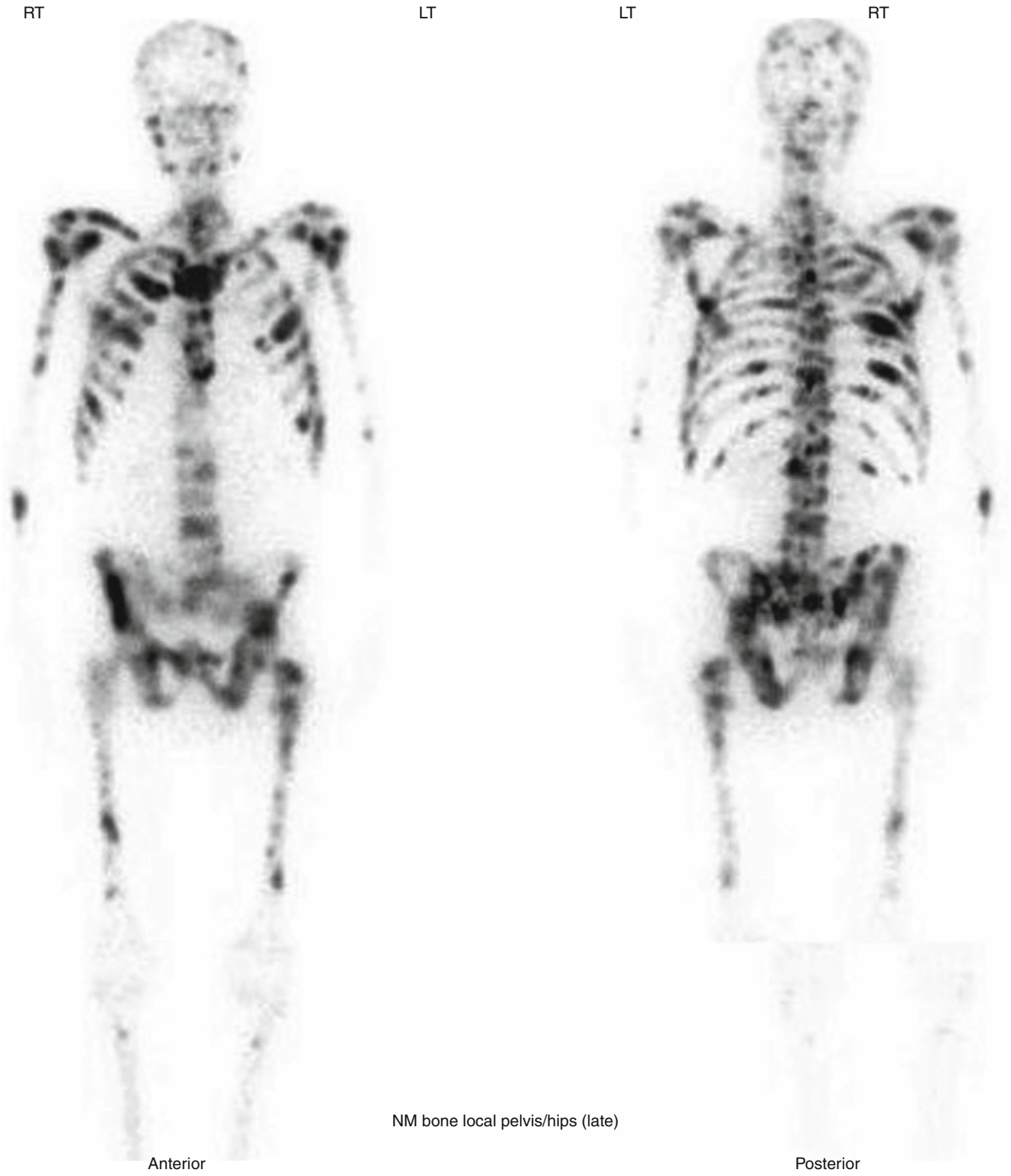



**Fig. 44.2** Multiple scattered foci of increased osteoblastic activity consistent with metastatic disease

When combined with CT or MRI, this hybrid imaging allows correlation of anatomical data with functional SPECT data, with a concomitant improvement in specificity and diagnostic accuracy [26, 27]. Reported sensitivities and specificities of bone SPECT data are 87 and 90 %, respectively [28–30]. A recent study has shown improved sensitivity rates of 92 % compared to 69 % using multi field of view (FOV) SPECT [4].

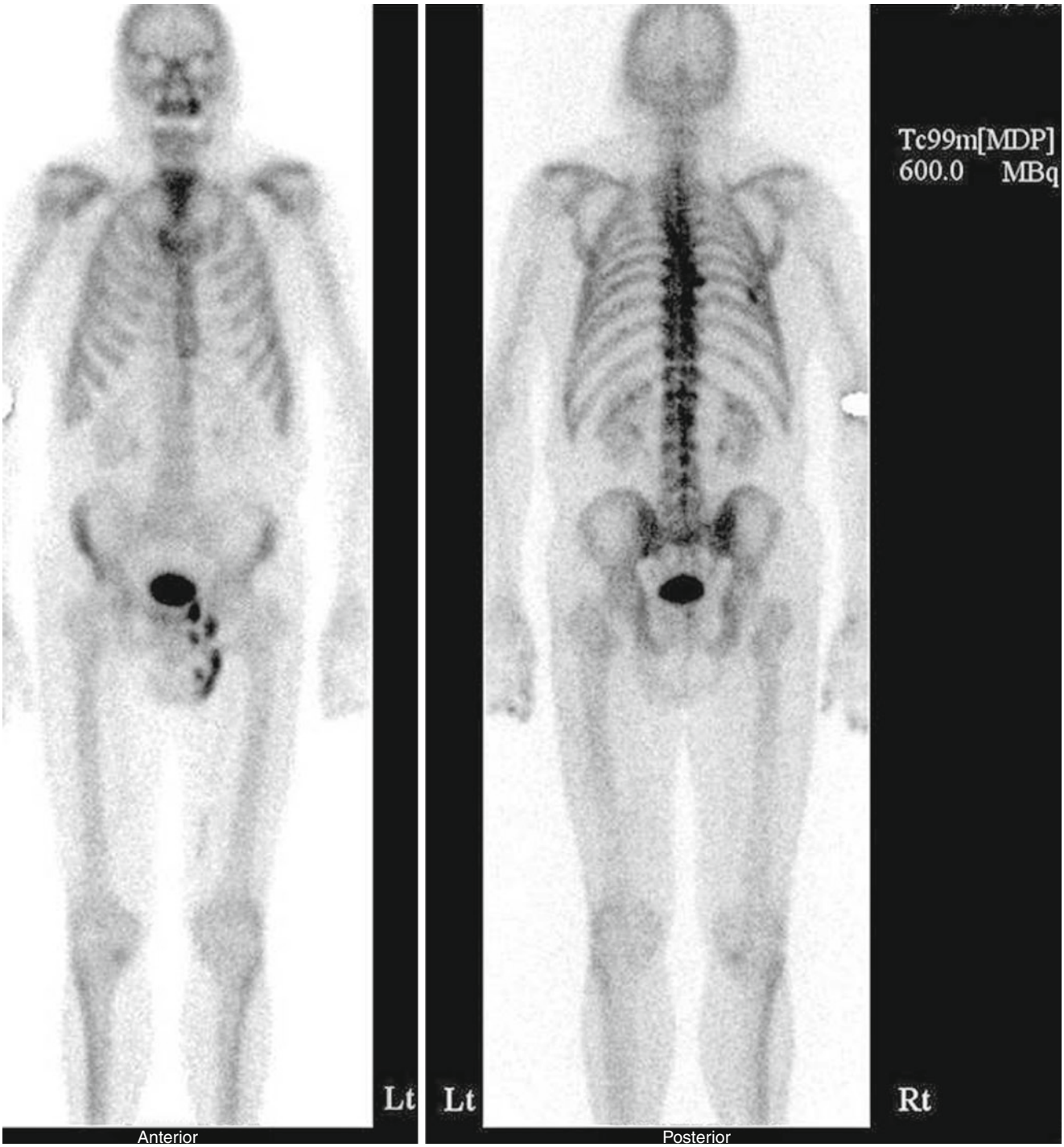



**Fig. 44.3** $^{99m}$Tc-MDP bone study shows solitary uptake within the right posterior 8th rib that was confirmed on CXR to be due to a rib fracture secondary to trauma

## Indium-111

Radioimmunotargeting using capromab pendetide (ProstaScint) labeled with indium-111 is useful in the detection of prostate cancer cells showing sensitivities and specificities of 60 and 70 %, respectively [7, 31, 32]. However, due to its limited availability and cost, it is not currently used in the preoperative assessment of patients. This is discussed in greater detail in an earlier chapter.

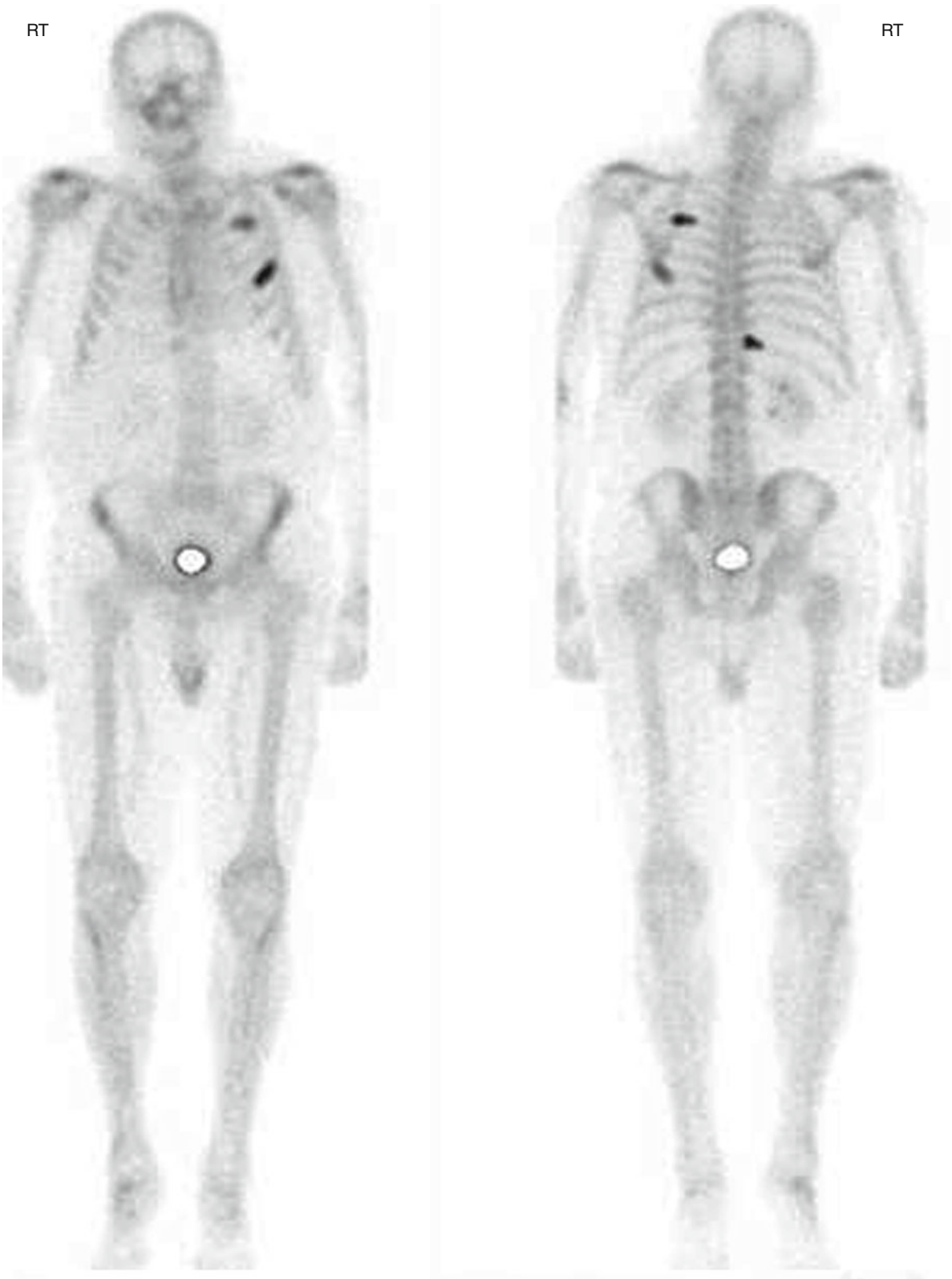



**Fig. 44.4** Increased activity extending along the length of the left anterior 4th rib indicative of metastatic disease

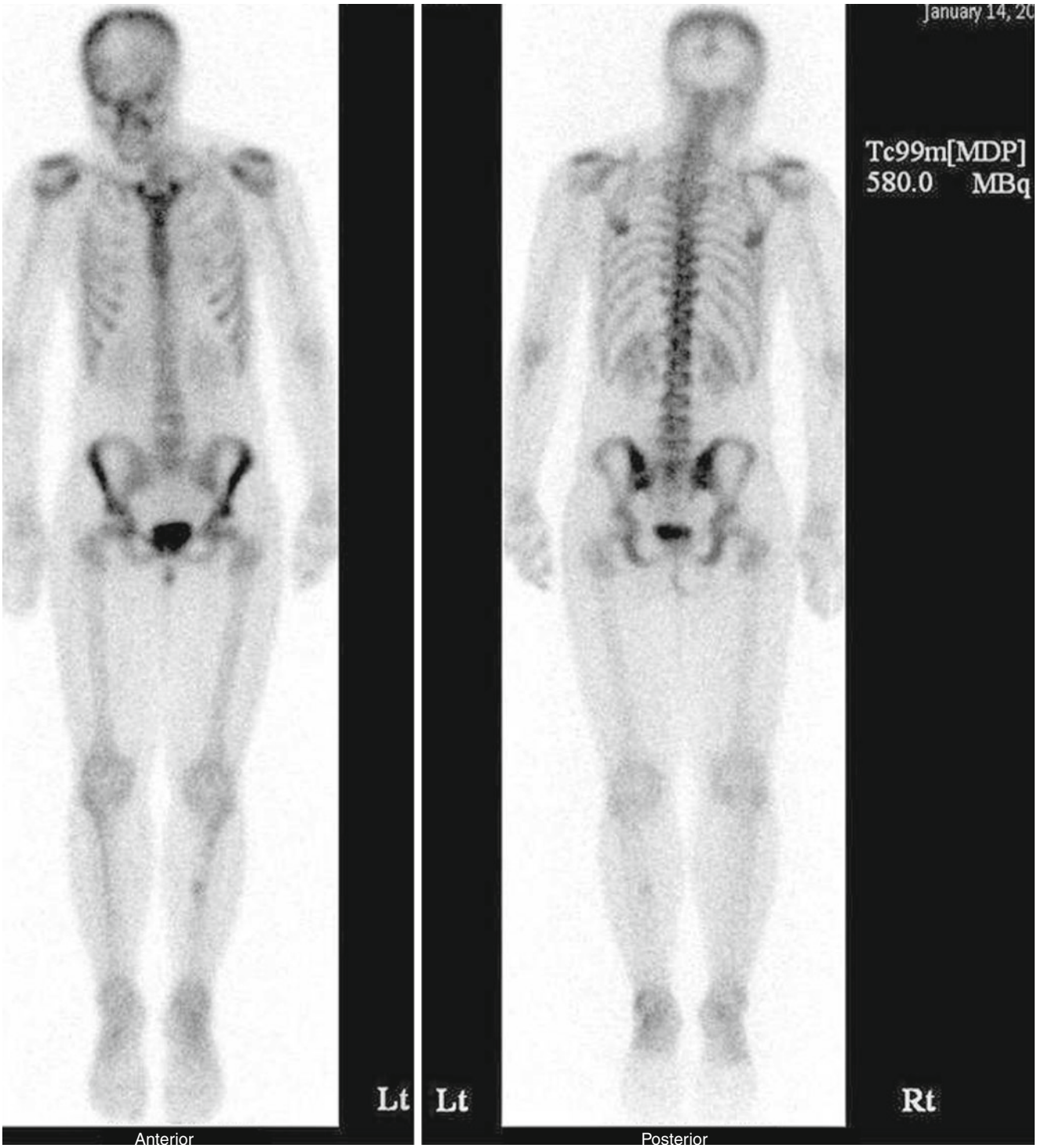



**Fig. 44.5** $^{99m}$Tc-MDP bone study shows a focus of increased uptake within the left tibia that was confirmed on plain radiography to represent a metastatic deposit. This is at risk of pathological fracture

## Positron Emission Tomography (PET)

### The Principles of Positron Emission Imaging

One of the ways nuclei with a relative proton excess can attempt to achieve stability is by the decay of a proton into a neutron with the emission of a positron (positively charged beta particle) and a neutrino.

$$\text{Proton } (\text{p}) \rightarrow \text{ neutron } (\text{n}) + \text{ neutrino } + \text{ positron } (\beta^+)$$

The emitted positron has a characteristic energy particular to the emitting radionuclide. The positron will travel a short

distance depending on its initial energy and, when it is of low enough energy, it will collide with an electron resulting in the formation of two 511 keV (kiloelectron volt) gamma photons. This is known as an "annihilation event" (Fig. 44.8a).

The two gamma photons created by an annihilation event are emitted at almost 180° to each other (179.5–180.5°) and can be detected by the scintillation crystals in a PET camera. Opposing gamma photons that arrive within nanoseconds of each other, that is, within the coincidence window, are attrib-

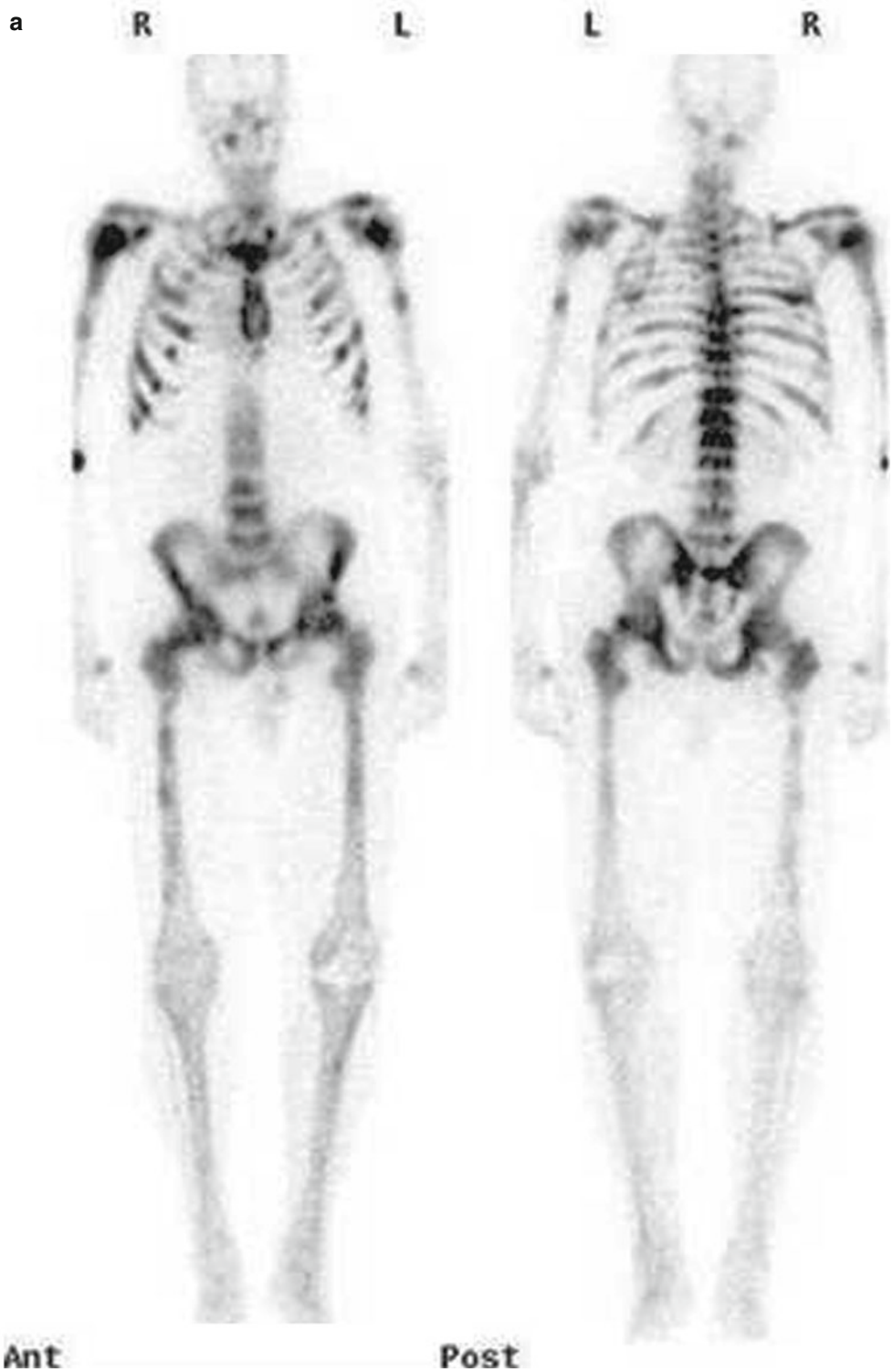



**Fig. 44.6** A "Superscan." (**a**) The bone scan demonstrates diffuse uptake throughout the axial skeleton, proximal humeri and femora consistent with metastatic disease. Note that the kidneys are not visible. (**b**, **c**) The plain radiograph and CT of the pelvis confirm sclerotic metastases

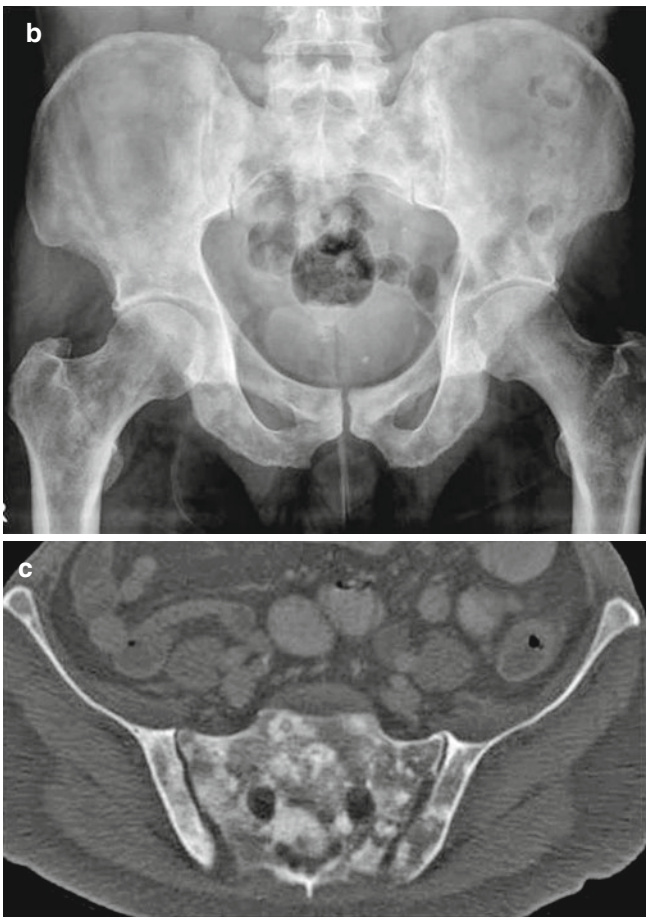



**Fig. 44.6** (continued)

uted to the same annihilation event and are presumed to occur along a "line of response" between the two detecting scintillation crystals (Fig. 44.8b). Multiple annihilation events, and their subsequent detection, allow the formation of an image which reflects the distribution of the radioactive tracer within the body.

The high-energy gamma photons will be attenuated by structures within the body prior to reaching the scintillation crystals of the PET camera. For this reason, a form of attenuation correction needs to be applied to improve localization of the radioactive tracer. All modern day PET scanners are combined with computed tomography (CT) as this enables both attenuation corrections of the PET data and has the added advantage of providing anatomical data for more accurate localization of the sites of disease.

## Positron Emitting Radioisotopes

Naturally occurring positron emitting nuclei are very rare; most are artificially produced within a cyclotron or by nuclear reactions. A cyclotron is a type of particle accelerator which enables the formation of a beam of charged particles which are then rapidly accelerated in an ever enlarging spiral circuit towards the target material, with the subsequent formation of a positron emitting isotope [33]. Table 44.1 lists a few of the available positron-emitting isotopes, their half lives, and positron energy.

Use of the more short-lived radioisotopes of Carbon-11, Nitrogen-13, and Oxygen-15 has required the presence of an on-site cyclotron and therefore limited their availability. The relatively longer half-life of luorine-18 ($^{18}$F) enables its transportation and has therefore allowed its more widespread use and availability.

## Quantitation of Uptake

Exact quantitation of tracer distribution within the body is not possible due to a number of factors, including patient weight, percentage body fat, injected activity, radioactive decay of the isotope, excretion by the body as well as attenuation.

Subjective assessment of the level of uptake can be made using internal comparisons with hepatic, mediastinal, or background metabolic activity. Alternatively, a quantitative method for analyzing the level of tracer uptake within an area is by calculation of the standard uptake value (SUV) which takes into consideration a number of these variables and is calculated using the following formula:

$$\mathrm{SUV} = \frac{\text{Activity in the region of interest } (\mathrm{MBq}) / \text{ volume in region of interest } (\mathrm{ml})}{\text{Injected activity } (\mathrm{MBq}) / \text{ patient weight } (\mathrm{g})}$$

## Fluorine-18 2-Fluoro-2-Deoxy-D-Glucose ($^{18}$F FDG)

$^{18}$F-FDG combines the relatively long-lived positron-emitting radioisotope fluorine-18 with a glucose analog and has allowed imaging of glucose metabolism within the body. In commonality with glucose, FDG (2-fluoro-2-deoxy-D-glucose) is transported by glucose transporters into the cell and undergoes phosphorylation by hexokinase. However, unlike glucose, it cannot undergo further metabolism to glycogen and becomes effectively trapped within the cell [34], thus reflecting the distribution of glucose utilization within the body.

Apart from the brain, most cells in the fasting state use free fatty acids for energy production. Malignant cells however, due to their rapid division and often anaerobic metabolism,

have increased glucose requirements and favor glucose metabolism [33, 35]. To facilitate this they have increased cell surface expression of glucose transporters [33]. Therefore, $^{18}$F-FDG imaging performed in the fasting state allows the higher glucose uptake and utilization by tumor cells to be more evident when compared against a background of free fatty acid metabolism by the majority of normal cells.

$^{18}$F-FDG has gained rapid and widespread acceptance for the evaluation of numerous malignancies. However, its role in the evaluation of prostate cancer is limited for a number of

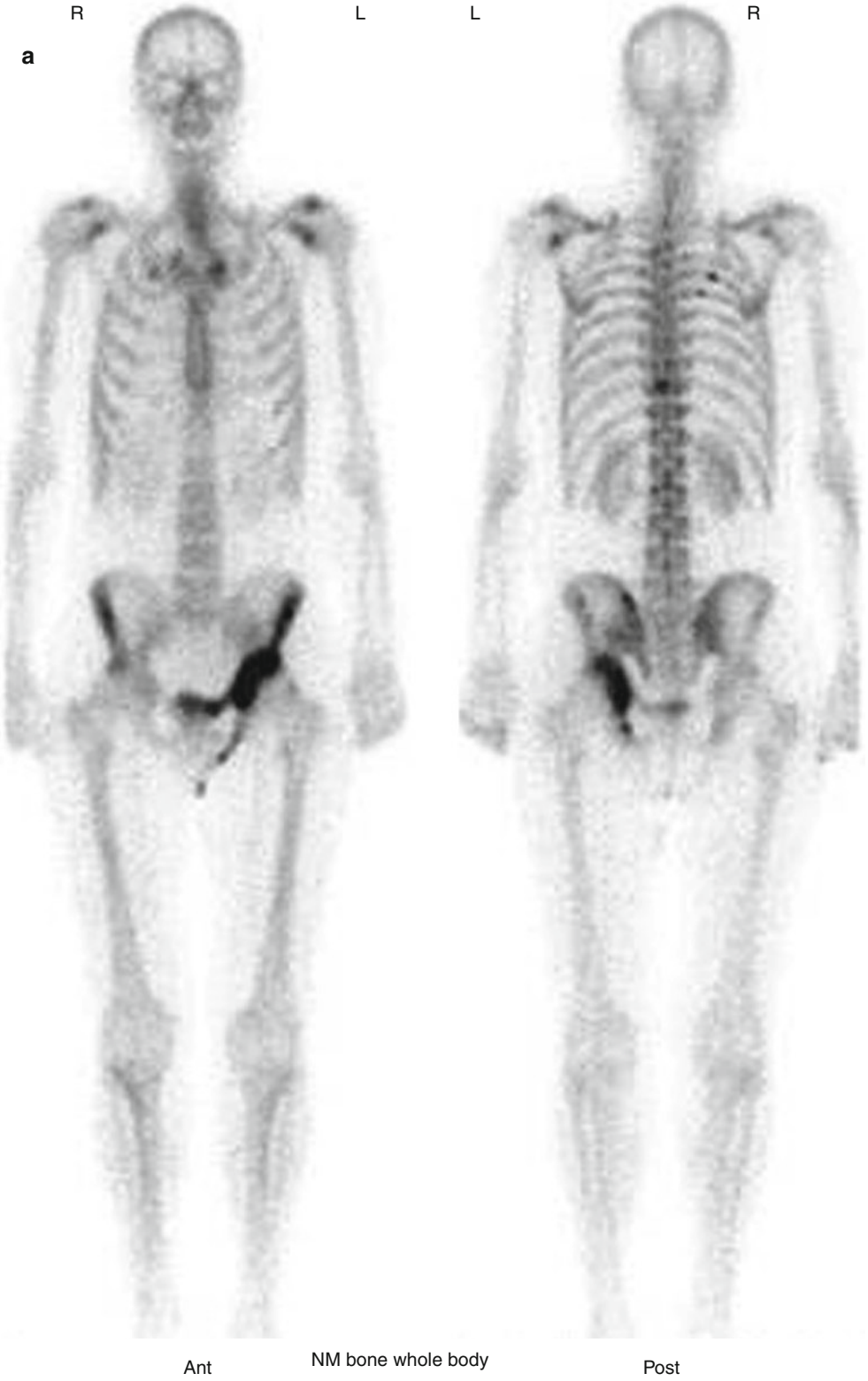
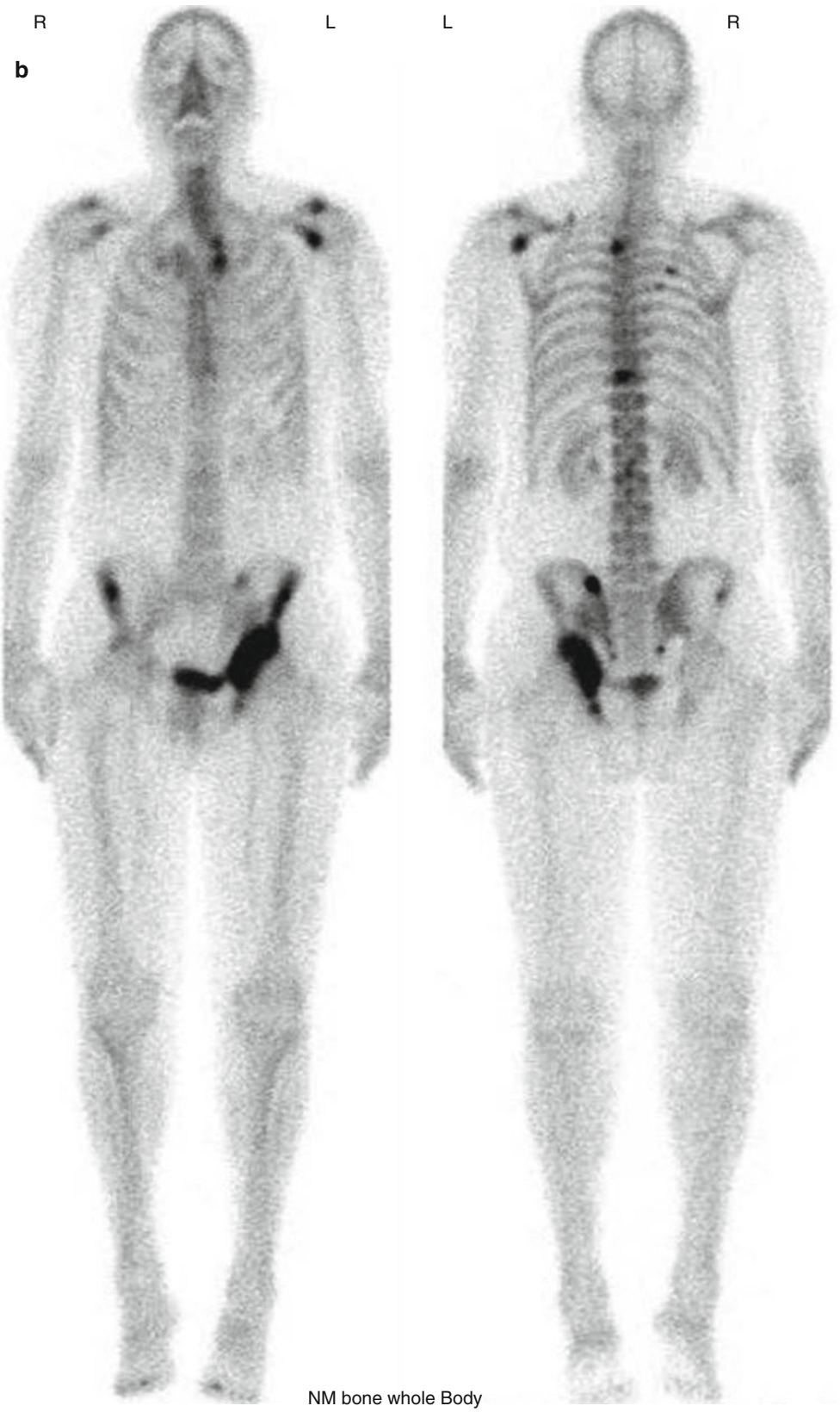



**Fig. 44.7** Flare phenomenon. Bone scans performed (**a**) before and (**b**) 3 months after chemotherapy. On the second scan, the foci of activity in the left iliac bone, left scapula, and thoracic spine are more intense. Apparently new foci of activity within the right iliac bone and sacrum are much more evident

**Fig. 44.7** (continued)



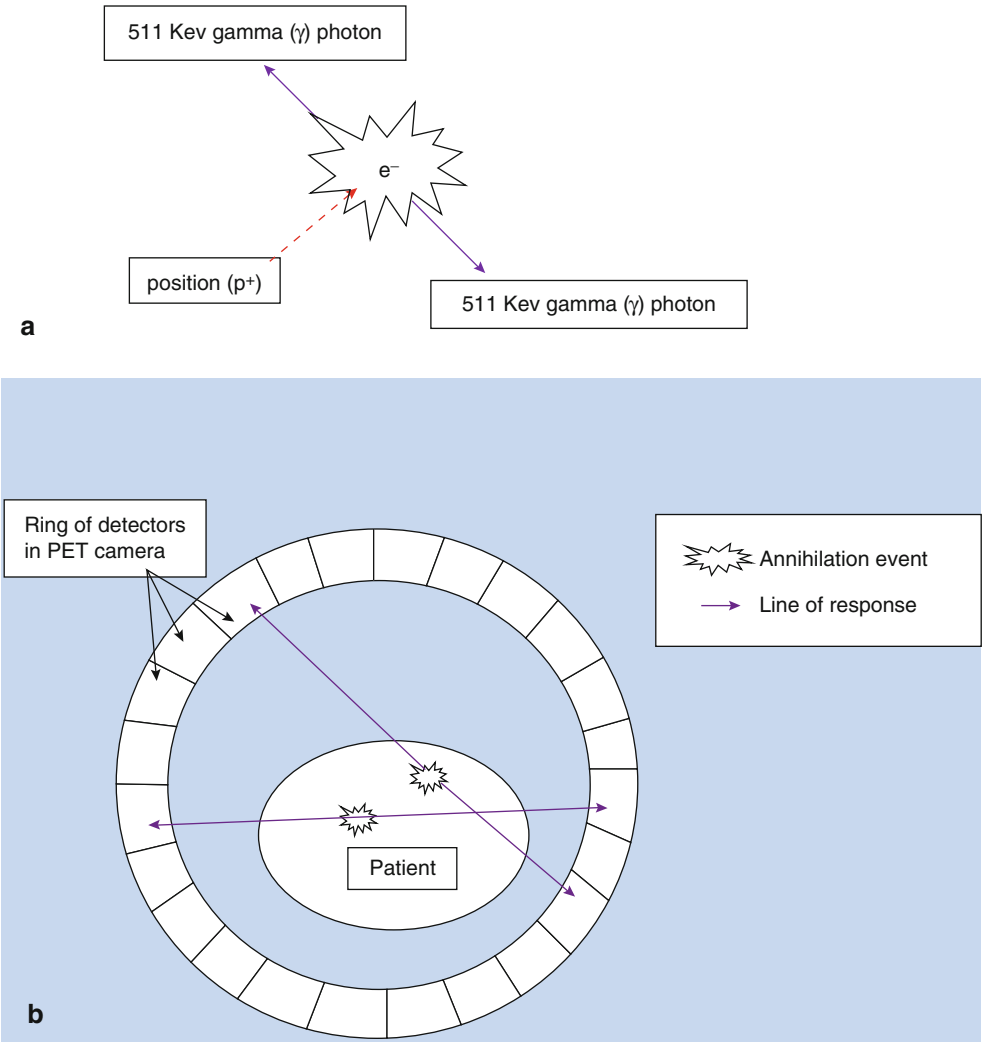



**Fig. 44.8** (**a**) Annihilation event. (**b**) Positron annihilation and detection by a PET scanner

reasons: it is not tumor specific and elevated levels can be seen in infection and inflammation [36]; evaluation of the prostate and pelvic lymph nodes is problematic because of normal renal excretion of $^{18}$F-FDG into the ureters and urinary bladder, as well as physiological bowel activity [23, 37, 38]. Additionally, the low glycolytic rate of prostatic malignancies [39] means that $^{18}$F-FDG uptake is relatively low [40], and the level of uptake overlaps that seen in benign prostatic hyperplasia [35], in the normal gland [41] and in the postoperative scar [42].

**Table 44.1** Positron-emitting radioisotopes

| Isotope | Half-life (min) | Positron energy (MeV) |
|---|---|---|
| Carbon-11 ($^{11}$C) | 20 | 0.385 |
| Nitrogen-13 ($^{13}$N) | 10 | 0.492 |
| Oxygen-15 ($^{15}$O) | 2 | 0.735 |
| Fluorine-18 ($^{18}$F) | 110 | 0.250 |

Aadapted from [33]

$^{18}$F-FDG is therefore not used for the routine evaluation of prostate cancer. However, focal peripheral uptake indicating, in some cases, a prostatic malignancy [43] as an incidental finding on PET studies performed for the evaluation of other malignancies has been described (Fig. 44.9) [44, 45]. This effect is likely attributable to the higher $^{18}$F-FDG uptake seen in androgen-independent tumors [34, 46] which may indicate a poorer prognosis [47, 48]. Studies have shown that the level of $^{18}$F-FDG uptake correlates with higher PSA levels, higher Gleason grade, and more advanced clinical disease [47, 49, 50] and can indicate more aggressive tumors [38] and a poorer prognosis [23, 51].

Although bone scintigraphy demonstrates more bony metastases than $^{18}$F-FDG PET/CT [52], recent studies suggest a potentially complimentary role of these two imaging agents in the initial evaluation of disease, as $^{18}$F-FDG can demonstrate additional distant soft tissue metastases as well as bone marrow lesions [53, 54]. $^{18}$F-FDG activity is also useful in differentiating active osseous metastases from quiescent disease [55].

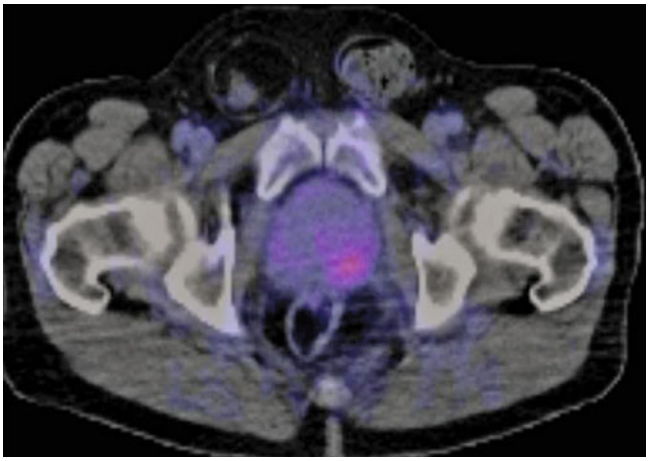


**Fig. 44.9** Peripheral FDG uptake within the prostate. Subsequent PSA and biopsy were indicative of prostate cancer

## Fluorine-18 Fluoride

The radiotracer $^{18}$F fluoride was initially used in the assessment of skeletal metastases, but due to its short half-life and the limited availability of cyclotron generators, it was replaced by the longer lived $^{99m}$technetium isotope. With the increased availability of cyclotron generators and the improvement in PET scanner resolution, $^{18}$F fluoride is again finding a role in the imaging and management of high-risk prostatic cancer. The increased regional blood flow and higher bone turnover around metastatic bone lesions leads to the increased $^{18}$F fluoride uptake.

Comparative studies evaluating the sensitivity and specificity for detection of skeletal metastases have reported sensitivities and specificities of 70 and 57 % for planar $^{99m}$Tc-MDP bone scintigraphy, 92 and 82 % for $^{99m}$Tc-MDP bone SPECT, 100 and 62 % for $^{18}$F fluoride PET imaging, and 100 and 100 % for $^{18}$F fluoride PET/CT [4]. This can provide additional diagnostic confidence when evaluating equivocal lesions; however, it must be noted that densely sclerotic metastatic lesions can sometimes be $^{18}$F fluoride PET negative. With its increased sensitivity and the increasing availability of PET scanners, $^{18}$F fluoride may one day replace $^{99m}$Tc-MDP as the primary radiotracer of choice for the assessment of skeletal metastases.

## Choline

Choline and its metabolites are critical components for many fat-containing compounds found within cell membranes. Phosphorylcholine and sphingomyelin are examples of such compounds. In the setting of prostate cancers, magnetic resonance spectroscopy has revealed an increased level of choline uptake [56, 57] and an accumulation of choline, using carbon-11 ($^{11}$C)-labeled choline, has also been shown in prostate cancer [58]. There are two possible mechanisms that may account for this finding. Firstly, it is thought that cancer cells, in general, have increased cell turnover and proliferation. Choline, an important constituent of many basement membrane compounds, is thought to correspondingly increase in concentration [59, 60]. A second possible mechanism lies with the upregulation of choline kinase in cancer cells and an over expression in prostate cancer cells [61]. $^{11}$C and $^{18}$F compounds labeled to choline are the two main agents available for use as PET tracers. $^{11}$C choline shows a rapid blood clearance and early tumor uptake with high tumor to background ratios occurring within 3–5 min [58]. Several authors have shown preferential $^{11}$C choline uptake in prostate cancers, nodal disease, and metastases [62–64]. The relationship between tracer uptake to PSA [65, 66], Gleason sum score, and tumor stage [60, 66] remains uncertain. The role of $^{11}$C choline in the detection of recurrent disease, like many other imaging modalities, improves with increasing PSA levels [67]. A PSA range of between 1.4 and 2.5 ng/mL has been advocated by some authors as potential triggering levels for accurate detection of recurrent disease [68–70]. It appears that the goad of detection of early recurrence remains limited with $^{11}$C choline-labeled analogs due to the inability to detect microscopic disease [71].

The short physical half-life of $^{11}$C compounds has led to the development of $^{18}$F-labeled choline analogs such as fluorocholine (FCH) and fluoroethylcholine (FECh). These compounds utilize the longer half-life of $^{18}$F (110 min) making these tracers potentially suitable for a wider geographical distribution by allowing off-site production and distribution of these compounds. Like $^{11}$C choline analogs, both FCH and FECh have demonstrated increased uptake in prostate cancer [72, 73]. Like $^{11}$C-labeled choline, inflammatory prostate disease can complicate image interpretation and reduces the potential strength of $^{18}$F-labeled choline in staging cancers [74]. The use of $^{18}$F choline derivatives in detection of recurrent disease remains limited in early recurrence, and the detection rate remains dependent on the PSA level and increased accuracy seen in more advanced cases [75, 76]. Although $^{18}$F compounds have an improved half-life profile, $^{18}$F-FCH has high urinary excretion which may limit its usefulness in urological imaging [72]. In addition, there is now growing recognition that treatment with androgen therapy can reduce uptake of choline-labeled compounds [73, 77].

## Acetate

Acetate is a key component of cholesterol and fatty acid synthesis. The proliferation of cell turnover in cancers, and thus increased lipid synthesis [78], underpins imaging with acetate-labeled compounds. With regard to prostate cancers, an accumulation of $^{11}$C-labeled acetate has been successfully shown in prostate cancer cells [79, 80].

The role of acetate imaging in primary staging remains uncertain with an overlap of tracer accumulation in normal prostate tissue, prostatic hyperplasia, and malignant disease [81]. $^{11}$C acetate has however been shown to be useful in imaging patients with suspected recurrent disease following radical radiotherapy or prostatectomies [82, 83]. As with many other imaging modalities, the success rate of detecting recurrent disease using acetate-labeled compounds appears dependent on the PSA level [84]. The possibility of $^{18}$F acetate, with its better half-life profile, is now being investigated and may be of use in prostate cancers [85].

To date, both choline and acetate-based compounds appear equally effective in prostate cancers, but the data comparing the two groups of tracers are limited. The use of $^{11}$C-choline and $^{18}$F-choline tracers is gaining popularity for patients with suspected recurrent and metastatic disease, but its use in primary staging, and differentiating malignant from benign prostatic disease, is perhaps limited. The effects of androgen therapy and its effects on both choline and acetate-based compounds are uncertain and reveal mixed findings.

### Other PET Tracers

There has been a recent focus on the use of tracers that can act as other markers of malignant prostate cancer cell proliferation from DNA synthesis, testosterone metabolism, and so on. Below are examples of some of these tracers currently being examined. Although there are many studies using the agents described below, their use, efficacy, and clinical impact have not been fully examined.

Anti-1-amino-3-1$^{18}$F-flurocyclobutane-1-caboxylic acid is a synthetic L-leucine analog that has been shown to have in vitro uptake in prostate malignancy [86] possibly via the sodium-independent L large neutral amino acid transport system [87]. Initial results have shown increase uptake in primary and recurrent prostate cancer cases [88].

These has been some success in showing an increase in $^{11}$C-methionine compounds [89]. This has been attributed to an increase in amino acid transport and metabolism [90].

The role of testosterone in prostate cancer is now well established. An accumulation of $^{18}$F-fluourodihydrotestosterone (FDHT), an androgen analog, has been shown in normal prostate glands [91] and preferential tracer uptake in prostate cancer compared to normal tissue [92].

## Therapy

Unlike gamma rays which have a long range, alpha and beta particles, as well as Auger electrons, have a short range and therefore deposit their energy locally. The range of a *beta particle* depends on its energy, which is related to the emitting radionuclide, but is usually a few millimeters. *Alpha particles* have a range of a few cell diameters and are slow, heavy particles with a high linear energy transfer, that is, they deposit a large amount of energy over their range and therefore cause greater cell damage than particles of lower linear energy transfer like gamma photons. *Auger electrons* are electrons emitted from the outer shell of the atom with a range of <1 μm and therefore have an effect on the cell nucleus [93].

The principle of radionuclide therapy for oncological disease requires the internal delivery of an alpha or beta particle or auger electron-emitting radionuclide to the tumor site, a process known as internal targeting. The radionuclide can be delivered by ingestion, intravenous injection, or by direct or intra-arterial placement [93]. If delivered remotely, the chosen radionuclide will localize by virtue of its pharmacokinetics to the tumor site, for example, iodine-131 is administered orally but once absorbed in the stomach, it rapidly localizes in the thyroid for treatment of thyroid disease. Other key considerations in the choice of radiopharmaceutical include the half-life of the radioisotope as well as the energy and range of the emitted alpha or beta particles.

## Radionuclide Therapy for Bone Disease

A primary cause of morbidity from prostate cancer is pain from bone metastases. Palliation of this pain can be achieved by a combination of treatment methods, for example, analgesics, bisphosphonates, hormonal therapy, chemotherapy, or external beam radiotherapy [94]. In patients with widespread bony metastases that are refractory to other treatments, systemic therapy can be administered using bone-seeking radiopharmaceuticals which localize to sites of increased osteoblastic activity, corresponding to the bone metastases. Table 44.2 lists some of the radiopharmaceuticals that can be used for palliation of bone pain.

Strontium acts in a similar way to phosphate and is taken up at sites of remineralization [93]. Samarium-153 and rhenium-186 are attached to a phosphate-based complex (EDTMP-ethylene diamine tetraline tetramethyline phosphonic acid or HEDP-1-1-hydroethylidene diphosphate [93]) allowing their uptake in bone.

The emitted beta particle deposits its energy over a few millimeters into the adjacent cells thus targeting the tumor and limiting, but not preventing, damage to normal cells. Its localization in bone results in a degree of myelotoxicity, the main side effect; however, this is usually mild and transient [95–98]. As the radiopharmaceutical is primarily renally excreted, renal impairment will reduce its clearance, prolong the biological half-life, and hence increase toxicity. Therefore, patients with severely reduced renal function are not eligible for this treatment [94].

**Table 44.2** Radiopharmaceuticals used for refractory metastatic bone pain

| Radionuclide | Radiopharmaceutical | Emitted particle | Maximum energy (MeV) | Range in soft tissue (mm) | Physical half-life (days) |
|---|---|---|---|---|---|
| Strontium-89 | $^{89}SrCl_2$ | Beta (β)[a] | 1.46 | 2.4 | 50.5 |
| Samarium-153 | $^{153}$Sm EDTMP | Beta (β)[a] | 0.81 | 0.6 | 1.9 |
| Rhenium-186 | $^{186}$Re HEDP | Beta (β)[a] | 1.07 | 1.1 | 3.7 |

[a]Abundant gamma emissions also [95]

The choice of radiopharmaceutical is therefore determined by a combination of factors which include the extent of metastatic disease and available bone marrow reserve [94].

Radionuclide therapy is an effective treatment in refractory bone pain [96, 97, 99–102]; however, following treatment a percentage of patients may describe an initial increase in bone pain, often termed a "flare response," and patients should be advised of this possibility [93]. Repeat treatments are possible after a minimum interval of 3 months [99] dependent on renal function and hematological indices.

Newer approaches to treatment include the use of combination therapies. A number of studies have demonstrated an additive effect when bone-seeking radiopharmaceuticals are combined with conventional therapies for the treatment of bone metastases [103, 104].

Radium-223 chloride ($^{223}RaCl_2$) is a newer radiopharmaceutical that emits alpha particles which are high-energy, short-range particles. Early clinical trials have confirmed similar efficacy to the beta particle emitters with lower myelotoxicity [105, 106].

## Radioimmunotherapy in Prostate Cancer

Radioimmunotherapy is the process by which an antibody specific to the tumor cell is labeled with a therapeutic isotope and administered to the patient, enabling delivery of targeted therapy [93]. Prostate-specific membrane antigen is expressed on prostate cells, with increased expression on prostatic cancer cells, and is a suitable in vivo target for this type of therapy [40]. This is discussed in much greater depth in an earlier chapter.

### Conclusion

Nuclear medicine imaging provides a fundamental role in the assessment of high-risk prostate cancers, as determined by clinical variables. The imaging mainly focuses on the detection of skeletal and lymph node metastases, but some tracers have also been used to indentify cancer cells within the prostate itself. The mainstay of imaging the skeletal system remains the radiopharmaceutical $^{99m}$Tc-MDP due to its low cost, wealth of research, and wide availability. Detection rates can be further improved with the use of SPECT imaging, particularly when assessing the axial skeleton.

PET tracers, including $^{18}$F FDG, have been considered but their main use is still currently in research. With the increasing availability of cyclotron generators and the increasing resolution of PET scanners, they may one day become the primary imaging modality of choice.

Nuclear medicine radiopharmaceuticals have also found a role in therapy, due to the effect of their emitted alpha and beta particles, particularly when treating bone metastases.

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# Nanotechnology and Prostate Cancer

# 45

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## Introduction

Prostate cancer (PCa) is the second leading cause of cancer-related death. Despite its high incidence, many uncertainties related to PCa diagnosis and management remains. Current treatment including surgery, radiation therapy, and chemotherapy are mostly ineffective against advanced-stage PCa [1]. PCa can be largely asymptomatic in the "early" stages. Thus, in some countries, men above the age of 50 are screened regularly by digital rectal examination (DRE) or for elevated serum prostate-specific antigen (PSA) levels. Patients with abnormal test results are recommended for prostatic biopsy, which can confirm a diagnosis of PCa. Despite the use of an advanced protocol, sampling error still can occur in some patients, especially those with large prostate glands. Thus, novel approaches are needed to overcome the limitations of the present methods. At the same time, identification of molecular signatures corresponding to histological subtypes is an essential step toward understanding of the molecular basis of tumor development. There is mounting evidence that a substantial proportion of men with screen-detected PCa would otherwise have not known about the disease during their life in the absence of screening. In these men, cancer treatment may not be beneficial. Thus, it is critically important to establish ways to perform accurate and meaningful assessments of men with a potential to develop the disease.

Although modern biology has provided us with a greater understanding of the molecular events implicated in prostatic disease, both benign prostatic hyperplasia (BPH) and PCa

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continue to pose a significant healthcare problem. Our understanding of the mechanisms that contribute to the pathogenesis of these diseases is still rudimentary. While traditional in vitro approaches may be helpful to elucidate some of these mechanisms, microsystems create new opportunities for design of microenvironments that more closely mimic the in vivo situation, with higher sensitivity and throughput. Nanomedicine and integrated microchips can recapitulate the spatial and temporal control of cell proliferation and cell-cell/matrix communication by combining surfaces that mimic the complex biochemistries and geometries of the extracellular matrix. It is expected that new technological platforms will show great promise for basic biomedical and pathological research and insight for true biological mechanisms at play. Nanotechnology is the science, engineering, and technology conducted at the nanoscale. A nanometer is $10^{-9}$ of a meter. The National Nanotechnology Initiative (NNI) defines nanotechnology in dimensions of roughly 1–100 nm [2]. Some groups anticipate this range to extend up to 1,000 nm. The concept of nanoscience was introduced in a talk entitled "There's Plenty of Room at the Bottom" at the California Institute of Technology (CalTech) on December 29, 1959, by physicist Richard Feynman. He described the concept in which one could manipulate and control individual atoms and molecules. Later, Professor Norio Taniguchi coined the term nanotechnology. In 1981, with the development of the scanning tunneling microscope (STM) and later with the advent of the atomic force microscope (AFM), modern nanotechnology began. Recent advances in nanotechnology have resulted in the manufacture of numerous nanoparticles with distinct characteristics including size, shape, surface modifications properties and core physiological and biochemical characteristics that are being investigated for potential medical applications. From a biomedical point of view, particle size skews toward that of a DNA doublestrand, a ribosome or the smallest bacteria and significantly smaller than a standard eukaryotic cell (7-μm diameter of a small red blood cell). Thus, the potential exists for systemically administered nanoparticles to extravasate across the vascular endothelium such that they can interact with biomolecules at both cellular and molecular levels. Currently, in terms of nanoparticle platforms studied for biomedical applications, most work has focused on particle delivery with diagnostic and therapeutic intent. The particles include liposomes and uni- or multi-lamellar vesicles (organic biolipid layers that encapsulate specific payloads), dendrimers (branched chain polymeric structures), carbon nanotubes (allotropes of carbon with a cylindrical nanostructure), paramagnetic nanoparticles (iron oxide fixed particles), gold nanoparticles (produced as shells, rods, spheres, or cages), and quantum dots (semiconductors with electronic characteristics that exist as metallic core-shell nanoparticles with the ability to fluoresce at targeted wavelengths). Nanotechnology platforms could have potential applications in the management of PCa including PSA-based nano diagnostic methods, Nanocarriers to deliver drugs, and therapeutic effect of such nanodrugs [3].

## Diagnostic Role of Nanotechnology in Prostate Cancer

Measurement of prostate-specific antigen (PSA) in blood is a relatively reliable approach toward monitoring PCa recurrence following current "intent to cure" treatment options. Approximately one-third of men who undergo radical prostatectomy for PCa will develop a detectable prostate-specific antigen (PSA) level within 10 years. Biochemical recurrence of disease is currently defined as a rising PSA level in the absence of clinical or radiographic evidence of disease. The PSA detection at extremely low concentration levels may be important for the detection of relapses of PCa after definitive treatment. In an effort to increase the sensitivity of PSA detection at much lower levels than is currently utilized, there is a drive toward nanotechnological applications. A Northwestern University research group has developed a bio-barcode protocol that has significantly improved the PSA detection capability. The method uses magnetic microparticles functionalized with anti-PSA antibody that will capture PSA molecules from serum samples. A probe gold nanoparticle that carries a barcode like DNA and secondary anti-PSA antibody will bind to the magnetic particle and form a sandwich structure. Magnetic separation will be able to collect PSA and DNA-gold nanoparticle. Upon releasing the DNA strands from the collected sample, an amplification of thousands of times is expected and the read of PSA is replaced by reading the DNA barcode strand. The method is proved to measure PSA level as low as 5 pg/mL (Fig. 45.1) [4]. Lee et al. reported two types of signal enhancement strategies derived from the origin of mechanical response, surface stress and mass, of the dynamic mode microcantilever for the detection of PSA at low picogram scales (low femtomolar concentration). PSA polyclonal antibody (PSA pAb) as an additional surface stress inducer and PSA polyclonal antibody-conjugated silica nanoparticles (pAb-SiNPs) as a mass inducer were applied to the PSA-captured microcantilevers resulting in improved sensitivity (two approximately four times enhanced at the same concentrations), enough to detect PSA at low picogram levels (LOD of 1 pg/mL or below) [5].

Liu et al. demonstrated a hybrid optical probe by incorporating nanocrescent particle and peptides with artificial tag molecules and performed a proof-of-concept study using prostate-specific antigen (PSA). They stated that the high reaction specificity of the peptides on individual nanoparticles minimized the false detection of other serine proteases

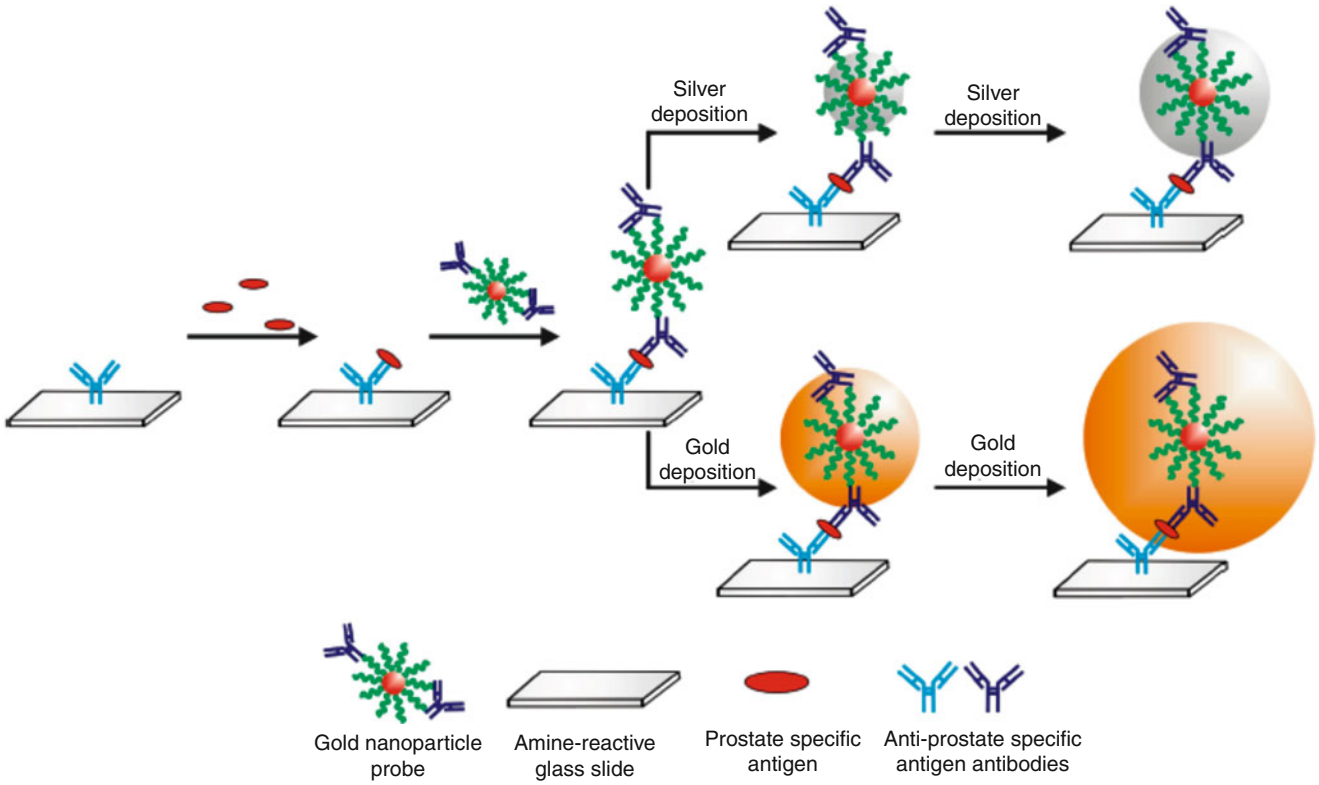



**Fig. 45.1** Scheme of bio-barcode PSA assay (Image Courtesy: Kim and Han [119])

and background signals which resulted in a high-fidelity and high-signal-to-noise-ratio cancer nanoprobe that could potentially be incorporated into nano/microfluidic devices [6]. Magnetic beads have served as a conventional bioassay platform in biotechnology. Matsunaga et al. performed a fully automated immunoassay using novel nano- and microbead composites constructed by assembling nano-magnetic beads onto polystyrene microbeads, designated "Beads on Beads." Nano-sized bacterial magnetic particles (BacMPs) displaying the immunoglobulin G (IgG)-binding domain of protein A (ZZ domain) were used for the construction of "Beads on Beads" via the interaction of biotin-streptavidin. These were magnetized and separated from the suspension. A fully automated detection of PSA was performed with the detection limit of 1.48 ng/mL. They concluded that "Beads on Beads" could be a powerful tool in the development of high-throughput, fully automated multiplexed bioassays [7]. Gokarna et al. demonstrated the manufacture of cancer protein biochips consisting of micro- and nanoarrays whereby pegylated quantum dots (QDs) conjugated to antibodies (Abs) of PSA were used for the detection of PSA. PSA tends to show an interaction with QDs. This fact was utilized to show that nanoarrays of QD-conjugated PSA Abs having a spot size of nearly 900 nm can be made hence introducing the potential offered by QDs in in vitro analysis of Pca biomarker imaging [8]. Cao et al. reported on another alternative sensing platform for the detection of protein biomarker (PSA-ACT complex) based on homogenous growth of Au nanocrystals in solution phase. The immuno-recognition event was translated into the gold nanoparticle growth signal, which can be intuitively recognized by an unaided eye, or quantitatively measured by a UV–vis spectrophotometric analysis. The PSA-ACT complex was determined to be 10 fm. They concluded that this approach using gold nanoparticles was a sensitive, robust, simple, and economically efficient strategy for the detection of PSA and potentially other biomarkers [9]. Kong et al. introduced a nano-nucleic acid barcode dot detection technology to determine ultramicro concentrations of protein. Magnetic probe (IgG-M) and dual-labeled gold nanoparticle bio-probe (IgG-Au-DNA) were prepared. Protein was captured and separated magnetically. The DNA barcode was released with dithiothreitol (DTT) and detected directly without the requirement for polymerase chain reaction (PCR). They applied this technique to 135 patients and results compared with enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA). They found that the sensitivity of nano-nucleic acid barcode dot detection technology could allow detection of 1 fg/mL. However, they found no significant differences in serum PSA from 135 patients when comparing the three methods. They concluded that the nucleic acid barcode dot method does not require special equipment or complex procedures but that its detection limit is 2–3 orders of magnitude lower than ELISA [10].

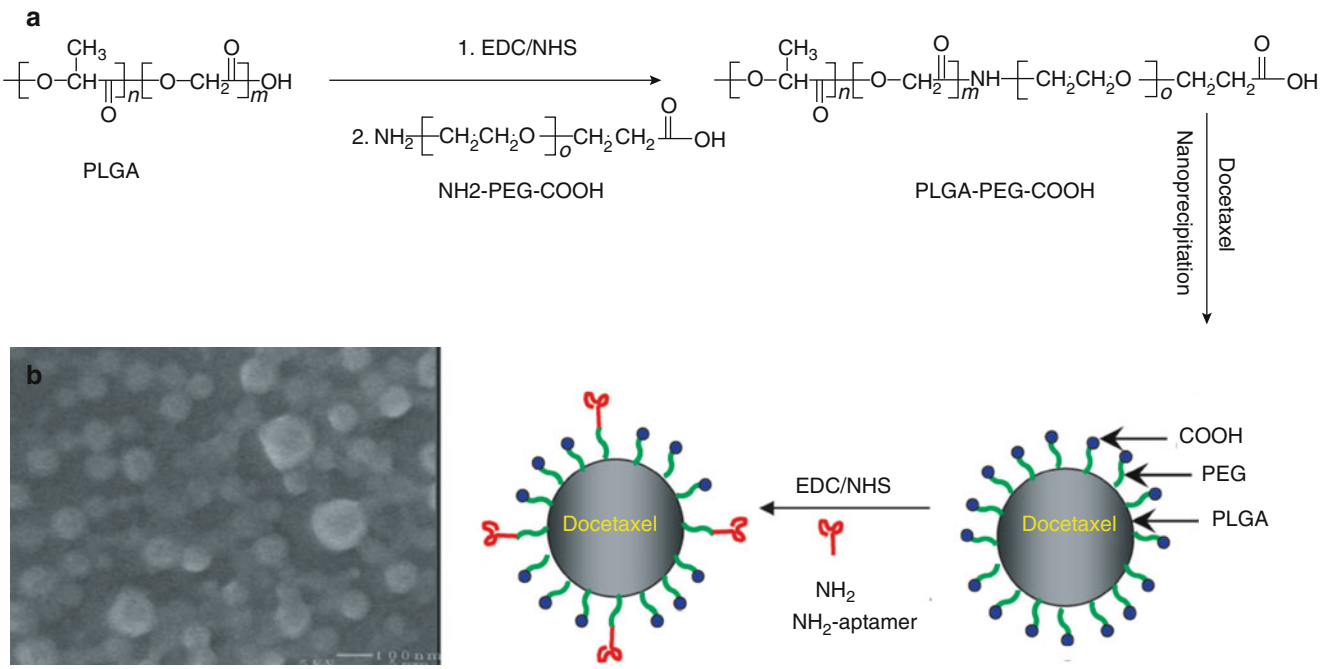



**Fig. 45.2** Scheme of the development of Dtxl-encapsulated pegylated PLGA NP-Apt bioconjugates. (**a**) Synthesis of PLGA-PEG-COOH copolymer and design of encapsulation of Dtxl. (**b**) A representative SEM image of Dtxl-encapsulated NPs (Image Courtesy: Farokhzad et al. [20])

## Nanoparticle Delivery Systems in Prostate Cancer Treatment: Principles and Challenges

### Nanoparticle Characteristics and Challenges of Delivery

Besides diagnostics, delivery of tumor therapeutic reagents, and controlled release of such agents are areas of great interest especially for the treatment of early-stage cancer. In PCa, brachytherapy represents an attractive therapeutic option for low- and intermediate-risk prostate cancer (PCa) patients [11] with increasing use of 4 % in 1993–1995 to 22 % in 1999–2001 [12]. Despite the proven efficacy of this treatment modality, complications including erectile dysfunction (33–53 %) [13], urinary retention (15–32 %) [14, 15], and severe radiation-induced bowel injury (1 %) [16] still occur. Also, recurrent disease can occur [17]. Nanotechnological approaches where chemotherapy is delivered directly to cancer cells over an extended period may result in alternative and/or supplementary therapeutic options for early-stage PCa. The challenge is to develop nanoparticles that are specifically and differentially taken up by the targeted cells. The particles then have to release their payload over an extended and optimal period to achieve a desired clinical response [18, 19]. Using the PCa model, researchers aimed to develop NPs using biodegradable and biocompatible components that were previously approved by the Food and Drug Administration (FDA) for a clinical use. They developed docetaxel (Dtxl)-encapsulated nanoparticles formulated with biocompatible and biodegradable poly (D, L-lactic-*co*-glycolic acid)-*block*-poly (ethylene glycol) (PLGA-*b*-PEG) copolymer. The particle surface was functionalized with the A10 2-fluoropyrimidine RNA aptamers that recognizes the extracellular domain of the prostate-specific membrane antigen (PSMA). These Dtxl-encapsulated nanoparticle aptamer bioconjugates (Dtxl-NP-Apt) were found to bind to the PSMA protein expressed on the surface of LNCaP prostate epithelial cells and taken up by these cells resulting in significantly enhanced in vitro cellular toxicity as compared with nontargeted nanoparticles that lack the PSMA aptamer (Dtxl-NP) ($P<0.0004$) (Fig. 45.2) [20].

For an efficient delivery of drug, Dhar et al. developed a nanocarrier protocol that delivers cisplatin to PCa cells by aptamer functionalized Pt (IV) prodrug-PLGA-PEG nanoparticles. Cisplatin's therapeutic effect is quite limited to a few types of cancer including prostate due to its dose-limiting toxicities and intrinsic and acquired resistance. One of the reasons for this limitation is the poor targeting of tumor sites and the development of resistance. To overcome these drawbacks, the group devised a strategy based on mechanisms that target critical molecular pathways of PCa and that employ chemical functionalized carriers to deliver such drugs. The nanoparticles to deliver cisplatin were designed based on poly (D, L-lactic-*co*-glycolic acid) (PLGA), a biocompatible polymer material, as the controlled release vehicle. Pt (IV)-prodrug was encapsulated into pegylated PLGA nanoparticle bioconjugates that bind to the PSMA protein on the surface of PCa cells for targeted delivery of the Pt (IV) prodrug that led to release of cisplatin upon intracellular reduction. The particles were designed to target PSMA, which is overexpressed in PCa, by functionalizing the surface of the particles with the

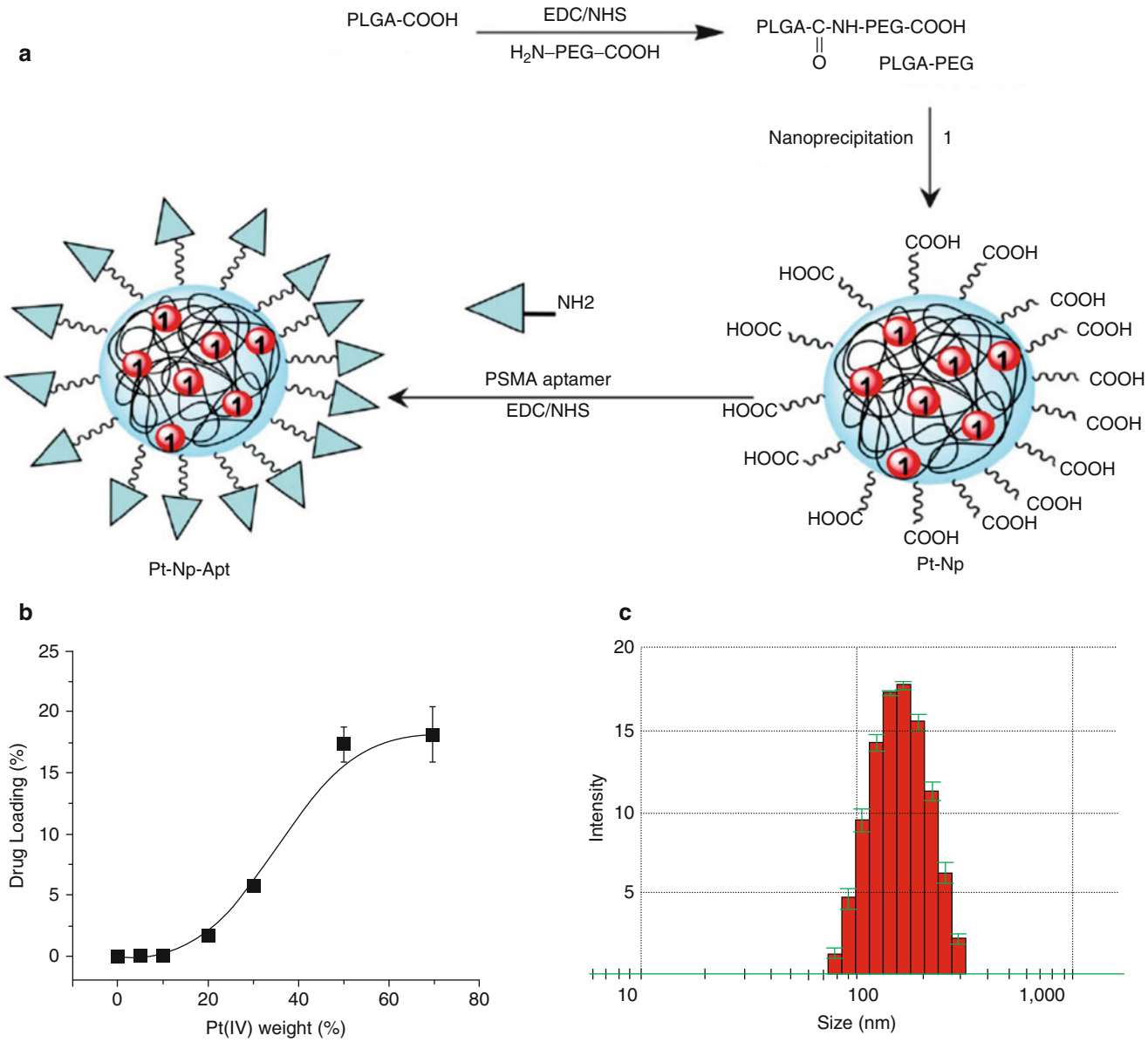



**Fig. 45.3** Design of aptamer-functionalized Pt(IV) nanoparticles. (**a**) Synthesis route of Pt(IV)-encapsulated PLGA-*b*-PEG-COOH nanoparticles by nanoprecipitation and conjugation of PSMA aptamer to NP. (**b**) Loading of *1* in the PLGA-*b*-PEG-COOH nanoparticles. (**c**) Size of the Pt(IV)-encapsulated nanoparticles (Image courtesy: Dhar et al. [21])

A10 aptamer that specifically binds to the extracellular domain of PSMA. This aptamer-derivatized Pt (IV)- encapsulated nanoparticles have been demonstrated to be significantly superior to cisplatin or nontargeted nanoparticles against the LNCaP cells because of the delicate design of the nano delivery scheme (Fig. 45.3) [21].

Intravascularly injected nanoparticles have been studied for early detection, imaging, and treatment of diseases and promise accelerated diagnosis, more precise biomedical imaging, and improved therapeutic delivery [22]. Such particles range in size from a few tens of nanometers (i.e., dendrimers, micelles, gold, and iron oxide particles) [23] up to hundreds of nanometers (polymeric spheres, liposomes, and nanoshells) [24] and even microns (such as polymeric, lipid, and silica-based microspheres and microemulsions) [25–29]. Spherical, discoidal, hemispherical, cylindrical, and conical shapes have been explored [30, 31]. Surface properties such as electrostatic charge and functional molecule conjugations exist [32, 33]. Regulatory approval of injected nanoparticle delivery systems will require standardized manufacturing processes that demand an understanding of the effects of size, and shape of artificial vectors impact biodistribution, efficacy, and toxicity. In the case of spherical beads, the number of particles accumulating in the non-RES organs is inversely proportional to the particle diameter. However, discoidal particles have been observed to accumulate more than others in most of the organs but the liver, where cylindrical particles are deposited at a larger extent. A large

number of combinations of the aforementioned particle characteristics are possible, defining a parameter space that affords engineering of nanoparticles precisely to specific cancers. The hyperpermeability of the tumor vasculature enhances the permeation and retention effect (EPR), whereby small particles (~500 nm) can passively extravasate and accumulate in tumor parenchyma [34, 35]. This strategy generated the first examples of "nanomedicines," such as doxorubicin and antifungal agents within liposomes. EPR is currently being used for tumor-associated localization of many families of therapeutic and imaging contrast nanoparticles. A second strategy actively targets tumors using various affinity moieties and biomolecules as ligands to the core nanoparticles.

The ultimate goal of engineered nanoparticles for therapeutic delivery is to mimic monoclonocal antibodies (with sizes in the 5–10 nm range) in targeting specificity. No such technology has made it to market. Part of the problem may be the fact that surface decoration with targeting moieties frequently renders more difficult physical transport across biological barriers such as vascular endothelium, thus reducing or completely reversing the intended beneficial effect of the targeting molecules. A difficulty is that the targeting ligands on the surface of the particles can sometimes reduce transport across biological barriers, such as the vascular endothelium, thus circumventing the intended effect. This is due to differences in expression level and types of specific receptors from normal to abnormal vasculature, leading to the development of strategies to target vascular receptors [36, 37]. Sakamoto et al. pioneered a comprehensive approach, utilizing all three targeting approaches, called Multistage Delivery Systems [38], which provide for sequential circumvention of biological barriers en route to delivery of therapeutics to tumors. For example, a first-stage particle might target the diseased vasculature, while a second stage would target extravascular diseased cells. Recently, siRNA delivery was accomplished with such a system: the first-stage targeted "biological depots," such as the sinusoids of the liver and the spleen, and from these, a second stage was released over time that targeted the diseased microenvironment [39]. Although still at an early stage of development, several trends are evident regarding the behavior of particles within the parameter space described above. With respect to size, systemically injected particles are transported throughout the vasculature and accumulate in various organs through a variety of mechanisms. Slack et al. studied the acute hemodynamic effects and blood pool kinetics polystyrene microspheres of three different diameters (3.4, 7.4, and 11.6 μm) following intravenous administration. The later two were filtered by the pulmonary capillary network, the majority during the first pass. Intravenous administration of 3.4-μm diameter microspheres produced significant dose-dependent systemic hypotension and depression of myocardial performance. Although elimination of the smaller spheres from the blood during the first 6–8 min was rapid,10 (3.4) spheres/g of blood were present in the circulation for greater than 1 h. They concluded that size of microspheres, as a drug delivery system to target organs, should be studied further [40].

Litzinger et al. found that particles as large as 4–5 μm were engulfed by phagocytic cells in the organs of the reticuloendothelial system (RES) [41, 42]. Particles smaller than 500 nm accumulate in the extravascular space of the fenestrated discontinuous endothelium on account of EPR [43] as well as for permeable tumor vessels [44, 45]. Dendrimers, QDots, gold colloids, ultrashort carbon nanotubes, and other nanoparticles (<30 nm) can cross-tight endothelial junctions (10–20 nm) but are rapidly excreted through the glomeruli of the kidneys [46, 47]. Regarding surface modification and functionality, it is well established that poly (ethylene glycol) (PEG) chains help particles evade RES uptake and prolong circulation (whereas un-PEGylated particles accumulate in the liver and spleen) [48, 49]. With respect to particle shape, mathematical models and in vitro microfluidic experiments have demonstrated that discoidal particles can partition toward the vascular wall [50] and exhibit relatively stronger adhesion to removal by fluid forces [51, 52] than spherical and quasi-hemispherical particles. In vitro experiments have also confirmed the model prediction that oblong particles have advantages over spherical ones in evading capture by different cell types [53–55]. These results could justify the observation of lower accumulation for discoidal particles in the liver, where the main mechanism of accumulation is believed to be sequestration by the Kupffer cells [49]. Simultaneously, the enhanced margination of elongated particles to the vascular wall could explain their relatively higher sequestration in the other organs. Conversely, spherical, quasi-hemispherical, and cylindrical particles, with approximately unity aspect ratio, are more easily captured—a performance difference recently confirmed in vivo using anti-ICAM-coated polymer microparticles [56].

Although our growing understanding of the behavior of systemically injected microparticles evokes some confidence in our ability to engineer delivery vectors that can circumvent the arsenal of biological barriers that the body wields to defend against foreign agents, the key question is that of the delivery of therapies to the tumor. In this regard, several factors have to be considered. Ideally, an optimum concentration of the specific therapeutic agent must be delivered to tumor sites, while minimizing the side effects caused in the patient. To the extent that engineered nano- and microcarriers can achieve these ends is the basis for regulatory scrutiny and approval, as evidenced by the first clinically deployed nanovectored anticancer agent, liposomally encapsulated doxorubicin [57]. In 2010, Decuzzi et al. [58] demonstrated that liposomally encapsulated siRNA could be delivered using nanoporous hemispherical silicon carriers (Fig. 45.4). This approach yielded high therapeutic efficacy in orthotopic murine models of ovarian cancer, silencing the target gene for 6 weeks with a single injection. This level of performance

was not obviously caused by enhanced accumulation of the multistage particles in the tumor. On the contrary, higher concentrations were found in the liver and spleen, possibly forming "depots" in the sinusoids that time-release the liposomally encapsulated siRNA. In light of this example, the definition of a "good" delivery system becomes somewhat subjective and dependent on the specifics of the performance versus the disease. Nothing suggests that increased accumulation of carriers in the tumor sites would improve therapeutic efficacy in this case; indeed, the exposure of the particles to the nuclease-rich tumor tissue and phagocytes might incur faster degradation and reduced effect. Thus, elucidation of the performance of nanoengineered delivery systems versus design variables is continuing in order to realize the ultimate goal of identifying the optimum features for specific therapeutic agents, cancer models, modes of action, and treatment objectives.

Mesoporous silicon is biocompatible [59, 60] and has received Food and Drug Administration approval for use in brachytherapy and drug delivery from implants [61]. The

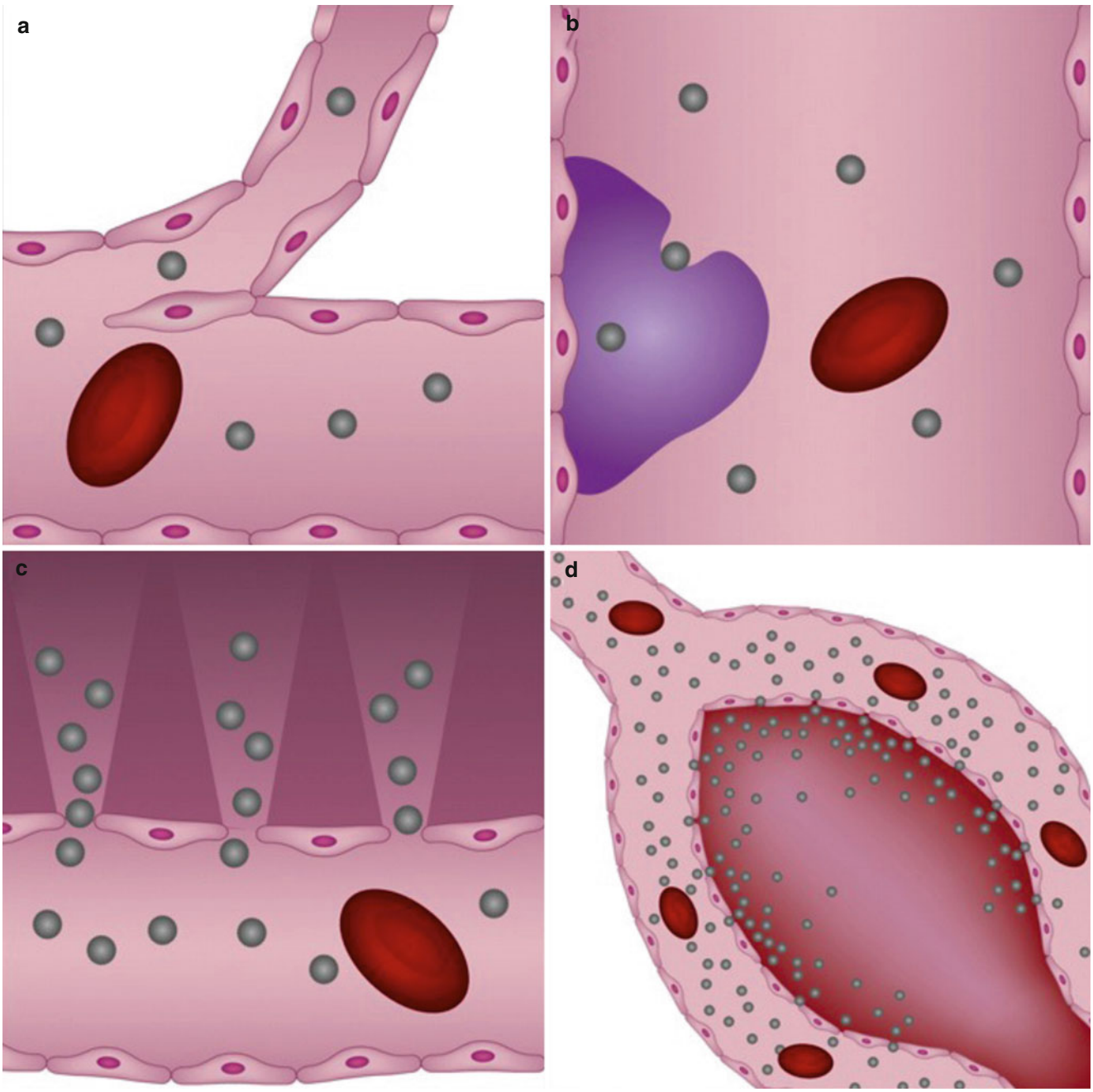
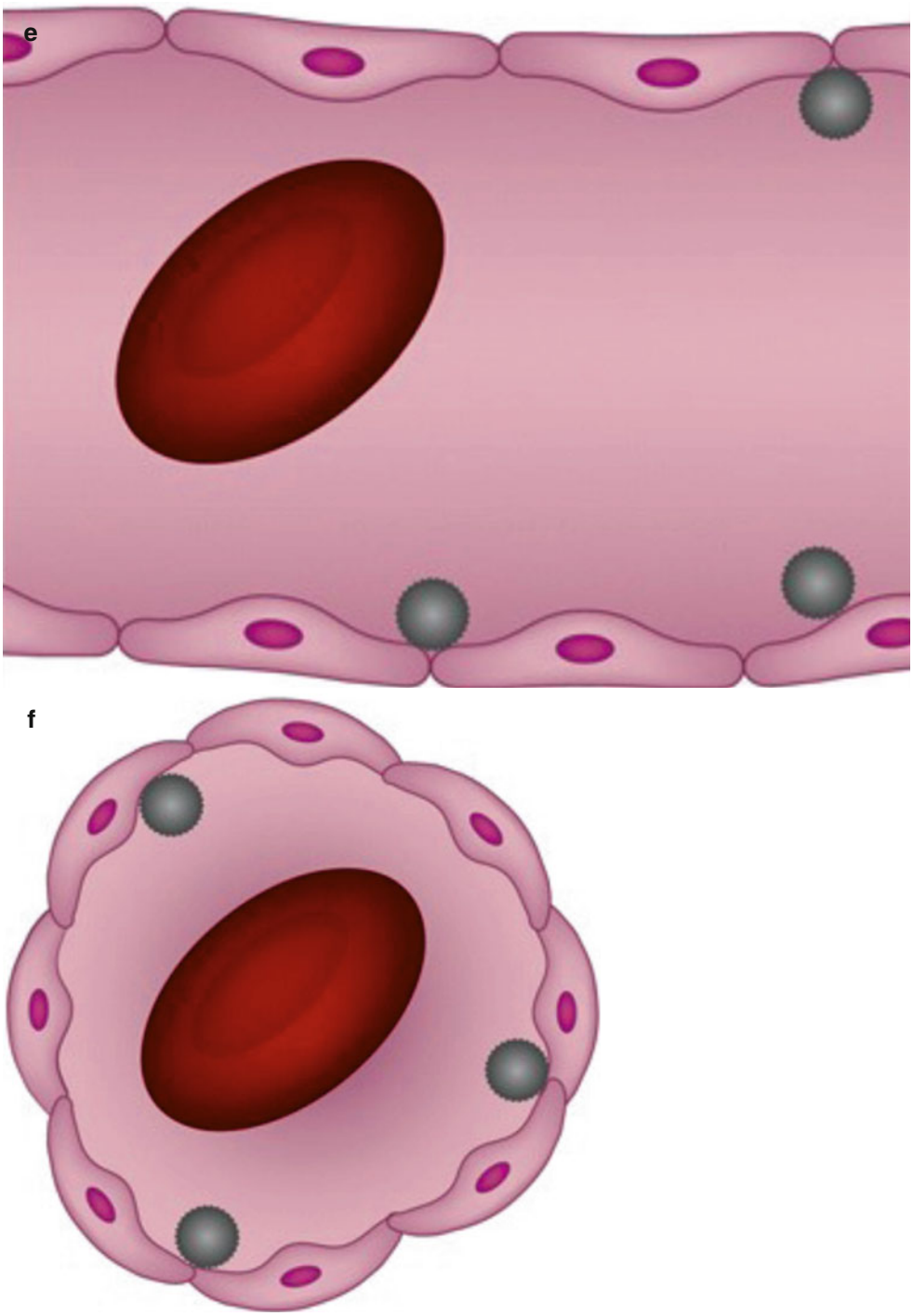



**Fig. 45.4** Mechanisms of particle sequestration from the circulation after intravenous injection: (**a**) entrapment in small capillaries; (**b**) engulfment by phagocytic cells; (**c**) extravasation through fenestrated endothelium; (**d**) excretion through the kidneys glomeruli; (**e**, **f**) adhesion to the blood vessel walls (Image courtesy: Decuzzi et al. [58])

**Fig. 45.4** (continued)




surface chemistry of porous silicon nanocarriers determines the loading and release kinetics of any payload [62]. Tanaka et al. used positively charged (amine-functionalized) S1MP for enhanced entrapment of the negatively charged (−2.9 mV) DOPC-siRNA [63]. The electrostatic interactions between the carrier and payload are likely to contribute to the sustained release of the liposomes from the porous structure as the S1MP degrades. The materials for the two delivery stages in this study, mesoporous silicon and DOPC neutral liposome, are biodegradable, biocompatible, and yield-sustained delivery of therapy with no liver or renal toxicity at a dose of 25 μg of mesoporous silicon with no inducement of pro-inflammatory cytokines A separate study indicated safe dosing up to 250 μg of silicon carriers under both intraperitoneal and intravenous administration in mice [64]. The antitumor effect was due to gene silencing of EphA2 payload of the DOPC liposomes.

The sustained release of liposomal siRNA delivery is likely the result of two characteristics of the S1MP: biodegradation and biodistribution. The rate of biodegradation is

controllable by the particle porosity and pore size, which can be precisely tuned during fabrication. The biodistribution of the particles is controlled by their size, shape, and exterior surface properties [65, 66]. Possible mechanisms involved in the geometry-dependent organ sequestration of particles are capillary size, capillary architecture, hemodynamics, and endocytosis. Considering the differences in microenvironment found in different organs, both accumulation and biodegradation of the particles could vary, leading to predictable release kinetics of encapsulated payloads.

The key results of the study by Tanaka et al. [63] (Figs. 45.5 and 45.6) are that a single injection of multistage delivery system comprised of mesoporous silicon particles loaded with nanoliposomal siRNA against oncogene, EphA2, resulted in: (1) sustained gene silencing for up to at least 3 weeks in ovarian tumor; (2) substantial reduction of tumor burden; (3) substantial decrease of angiogenesis and cellular proliferation; (4) no production of ascites; and (5) no detected toxicity associated with the S1MP vectors, the neutral nanoliposomes, or the therapeutic siRNA. This was purported to be the first study to achieve these collective goals in vivo and, in particular, in two orthotopic models of ovarian cancer. These finding encourage the development of a "library" of targets and drugs that can be further tailored toward specific genetic abnormalities in cancer. In the broader context of cancer, many oncoproteins have been identified in the past two decades, although many of them are "undrugable" with traditional approaches due to lack of detailed structural knowledge. The same group then targeted oncoprotein EphA2 (a tyrosine kinase receptor in the ephrin family), which plays roles in angiogenesis [67] and cell proliferation [68]. EphA2 is absent in the normal tissue but is overexpressed in different types of tumor including prostate [69], ovarian [70], breast [71], lung [72], and melanoma [73] with strong association with poor survival, advanced-stage, or high-metastatic potential [74]. Although not optimized, from this example it follows that as other cancer targets are discovered, our multistage targeting strategy might have similar advantages especially PCa.

A third generation of nanovectors have been recently developed by our group. These multistage agents incorporate engineered features that enable programmatic action following a certain time or site-determined "logic" event [75]. In these constructs, each component is responsible for a different task from among the following: bio-recognition, degradation control, toxicity reduction, overcoming biobarriers, and efficient intracellular delivery. Encoding is achieved via the material and particle parameters, as described above. Each stage performs a function along the path to the target site, with a cumulative effect that enhances selectivity. Additionally, systems may incorporate imaging and therapeutic components in the same vehicle to enable external control of release. Alternatively, embedded "logic" is being developed that would cause the nanoengineered particle to respond to in situ stimuli without external control. This would enable an appropriate therapeutic dose to be delivered even while the genotypic and phenotypic evolution of the cancer cells progresses. The Ferrari group has recently designed the latest multistage technology platform, which incorporates these fundamental components and are called logic embedded vectors (LEVs) [76] based on nanoporous silicon microparticles (Stage I) that utilize unique size, shape, and other physical characteristics along with active biological targeting (Stage II) to efficiently deliver payloads of therapeutic nanoparticle constructs (Stage III) to the disease loci.

As described previously, the optimal mathematical design of first-stage vector particles with respect to margination [77, 78], firm cellular adhesion [79, 80], internalization [53, 81] was determined from biodistribution studies correlating the model design with the in vivo data. Through using the appropriate photolithographic techniques and bioconjugation methods, a large number of particle configurations can be created rapidly by modifying the size and shape of "first-stage" particles and choosing specific surface characteristics, to meet the criteria selected from the design maps (Fig. 45.2). These first-stage particles enable efficient transport and margination in blood vessels as well as recognition of the diseased vasculature. Within the biodegradable nanoporous structure is contained various payloads—the second stage nanovectors—which share similar design elements as the above-mentioned first- or second-generation vectors [76, 82]. The release profiles of the second stage vector from the multistage particle can be finely tuned to take place at different times and through different mechanisms, and these particles can be internalized by cells [83] to deliver their payloads to different subcellular structures. The versatility of the LEV platform allows for a vast variety of applications. The delivery of targeted therapeutics in the management of PCa will depend on our increasing understanding of these platforms, and our knowledge of these is increasing gradually.

## Challenges of Nanoparticle-Controlled Release of Therapies

While the multistage particles and logic embedded vectors described above aim to deliver drugs to the "right" place, temporal control of delivery is also a key component of personalized therapies. As nanotechnologies and other supporting technologies have advanced, the ability to miniaturize the necessary components of control into implantable drug delivery systems has been realized. This has evoked new strategies that promise to provide higher efficacy to anticancer therapies by manipulation of dose level, delivery rate, and release profile using wireless control and embedded sensors for feedback. Continuous, metronomic (i.e., "pulsed"), and "on-demand" dosing are being explored for specific drug

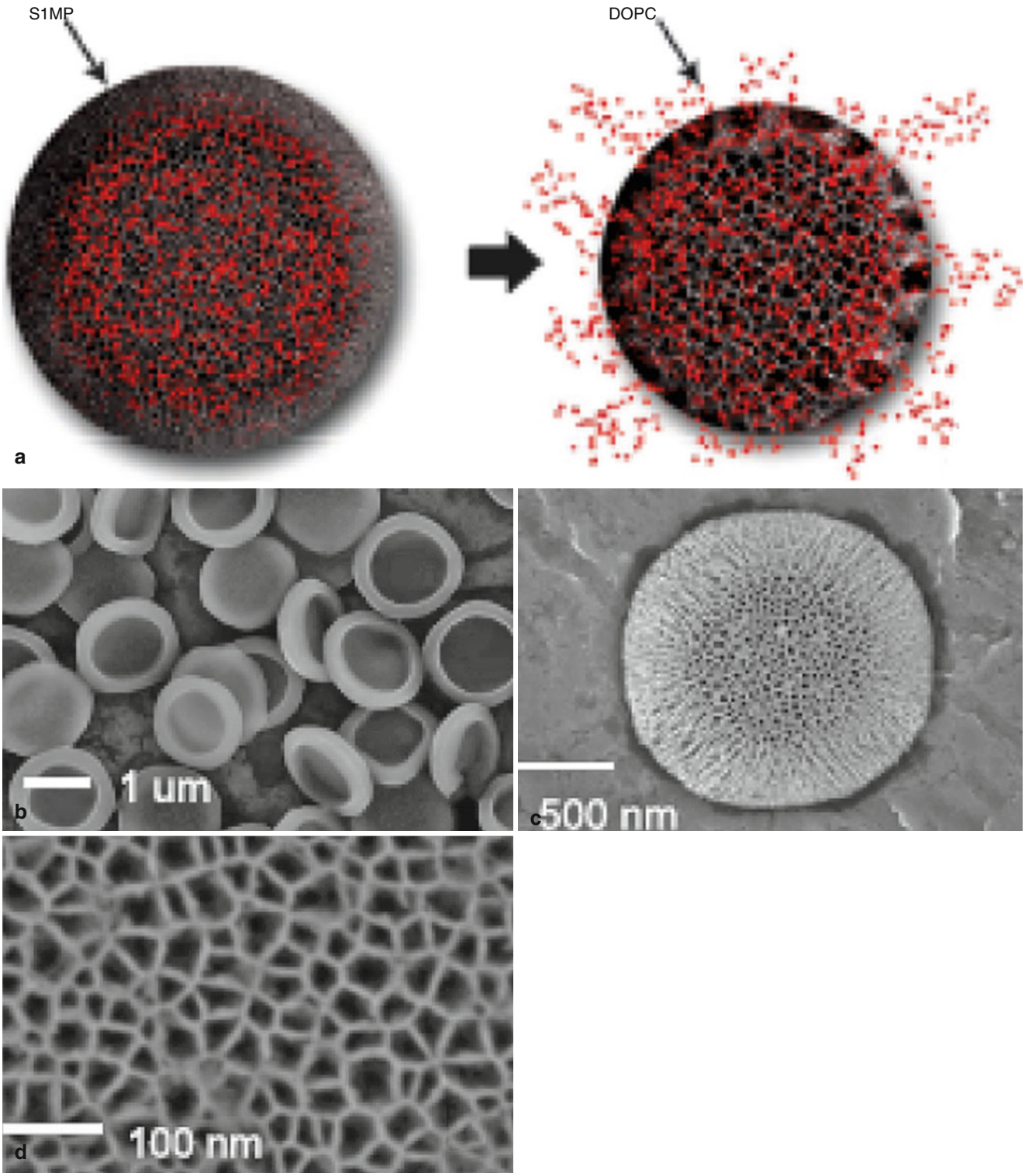



**Fig. 45.5** Assembly of S1MP-siRNA-DOPC. (**a**) Concept of multi-stage delivery system. (**b**–**d**) Scanning electron microscopic images of S1MP at different magnifications. (**e**) Loading of Alexa555-siRNA-DOPC to the S1MP. After the loading, fluorescence from unincorporated Alexa555-siRNA-DOPC was measured to assess the loading efficacy. S1MP loaded with Alexa555-siRNA-DOPC were dissolved in 0.25 % tetramethylammonium hydroxide and the loaded siRNA were separated by gel electrophoresis and visualized with SYBR Gold. (**f**) Release kinetics of Alexa555-siRNA-DOPC from the S1MP. The Alexa555-siRNA-DOPC–loaded S1MP were incubated in 10 % FBS and the supernatant was separated to measure fluorescent intensity at Ex544/Em590 at different time points (Image courtesy: Tanaka et al. [63])

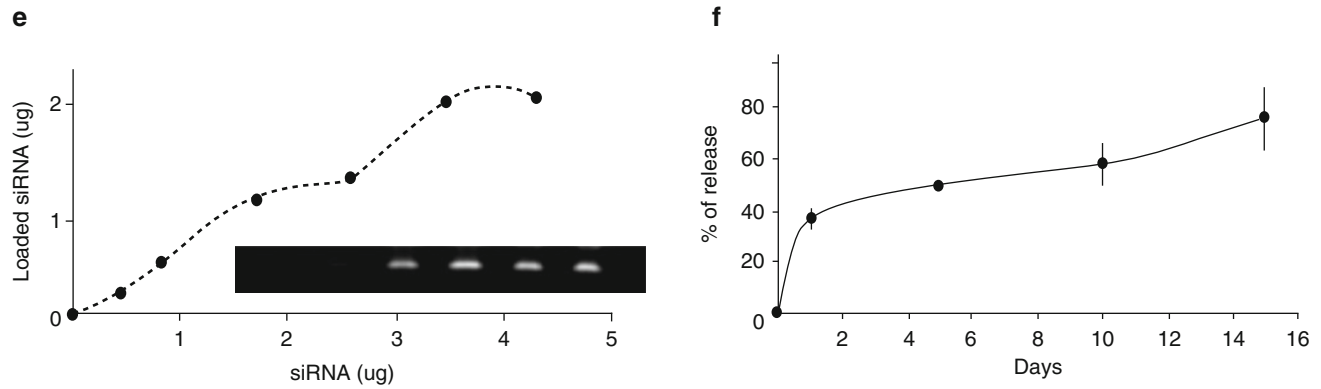



**Fig. 44.5** (continued)

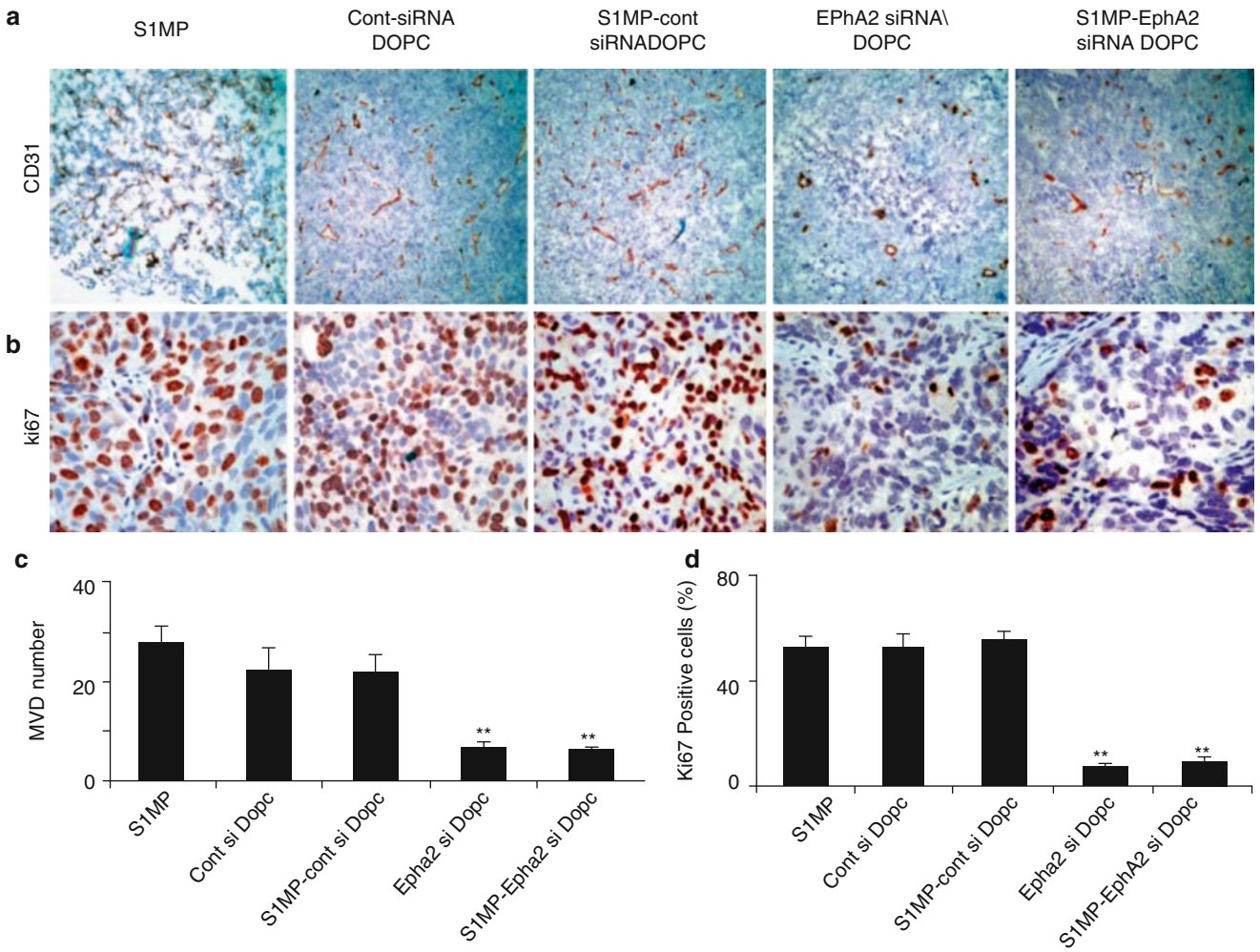



**Fig. 45.6** Effect of sustained siRNA delivery on angiogenesis and cell proliferation. Tumors from animals with the SKOV3ip1 ovarian tumor were examined for microvessel density (CD31) and cell proliferation (Ki67). Representative sections from each treatment group are shown (final magnification, ×100 for CD31 and ×400 for Ki67), with mean number of vessels per field or mean % of proliferative cells, summarized in the graph at the bottom. Five different fields per slides, at least three individual tumors per treatment group were examined. Both microvessel density (MVD; **a**, **c**) and cell proliferation (**b**, **d**) were significantly reduced in tumor when treated with repeated administration of EphA2-siRNA-DOPC and a single administration of the S1MP-EphA2-siRNA-DOPC (overall ANOVA: ** $P<0.001$) (Image courtesy: Tanaka et al. [63])

candidates and malignancies as having advantages over traditional administration methods. Aside from the benefits of more precise control over therapeutic delivery are the anticipated enhancements to patient compliance, especially with long-term regimens.

Most current therapies are based upon the systemic administration of drug, via oral, intravenous, transdermal, subcutaneous, rectal, ocular, intramuscular, or inhaled administration. Choice of method is determined based on the disease locus/loci, the pharmacological properties of the therapeutic (here to include chemical composition, solubility, ADME characteristics (adsorption, distribution, metabolism, excretion, toxicity, and mechanism of action), and clinical aspects (patient convenience, comfort, and compliance). In all cases, however, dosing typically follows a rapid increase in therapeutic blood concentration (even exceeding the optimal therapeutic range) followed by a rate of decline that varies due to the metabolic idiosyncrasies of the patient. Many drugs have a narrow range of concentration for optimal efficacy, and doses above or below this range indicate toxicity or nonresponse. Therapeutic regimens lasting for months or longer can exacerbate these effects, leading to deleterious side effects, poor patient compliance, and reduced effectiveness. The motivation for nanotechnology-based controlled delivery is to resolve these issues. Hepatitis and various forms of cancer are thought to be best treated with a relatively constant, sustained concentration of drug over a sustained time frame. This is difficult to achieve using traditional "dissolve and diffuse" administration (i.e., injections or tablets) that result in a declining concentration over time. However, nanoengineered implantable devices have been developed that afford active pumping of therapeutic agents from enclosed reservoirs through nano- or microfluidic membranes using electrokinetic or mechanical mechanisms. Tuning of device parameters, such as the dimensions of the fluidic channels, interior and exterior surface charges [84–88], pore wall hydrophobicity [89], and generated pressure profiles [90] are important considerations.

It has recently been established that the natural metabolic rhythm (i.e., circadian cycles) can have a profound effect on therapeutic efficacy [91, 92]. Consequently, recent investigations have sought to understand the ideal times for therapeutic administration; this has driven development of "chronotherapy" strategies for cancer [93–96]. This includes both metronomic (i.e., repetitive uniform doses) and time-varying delivery schemes and devices utilizing preprogrammed, on-demand, or feedback-driven operation [97–102]. Remote control over drug release can be achieved using radio frequency (RF) [103], magnetic field [104], light [105–108], or combinations of these, such as temperature/magnetic field [109]. The selection of materials can determine or be determined by the aforementioned design and operational choices. Many different materials have been used to generate nanochannels and nanopores, including silicon, [110–113], silica [114], alumina [115], silicon nitride [116], carbon [117], titanium dioxide [118], polydimethylsiloxane [119], SU-8 [120], and gold [121] along with an array of techniques for their manufacturing [122]. An exciting possibility for nanoengineered drug delivery implants is that of autonomous action driven by in situ measurement of biological signals, resulting in the release, cessation, or calibration of drug release from the device. One such device operated as an artificial pancreas, measuring blood glucose levels through integrated microsensors and delivering insulin as needed [123].

Another approach leveraged chemically responsive polymers or hydrogels [124] to release siRNA [125]. For cancer and other diseases, autonomous control promises a more rapid response than externally controlled systems, enabling more precise management of acute conditions. To date, however, reliable devices have not advanced to clinical use. Keller and Ferrari have focused on developing silicon nanochannel membranes for controlled diffusive transport [126]. By constraining the flow of the mobile phase and drug within nanoscale (<20 nm) fluidic *vias*, the diffusion-driven transport becomes independent of the concentration gradient across the membrane (i.e., become zero-order). Modification of the channel wall surfaces can provide for sustained (weeks) constant release of biomolecules, as demonstrated for bovine serum albumin, interferon-alpha, lysozyme, fluorescein isothiocyanate-conjugated dextran (FITC-dextran), and glucose [84–87].

## Nanotechnology and Proteomics Chips

Personalized cancer therapies not only demand advances in therapeutic targeting and delivery, but will also require molecular diagnostic technologies that will enable prediction of efficacy and disease-state monitoring for individual patients. This is not only a question of detection platforms capable of rapid point of care use but also the development of validated biomarkers for cancer at different stages of progression [127, 128]. Biomarkers in this context include mutated genes, altered genetic expression levels (i.e., RNA), as well as proteins, enzymes, metabolites, and their post-translational modifications. As cancers progress, however, their rapid genomic and proteomic evolution can result in alteration of the specific biomarkers and thresholds for detection. Coupled with the heterogeneity of cell types within a tumor, this factor makes biomarker discovery and validation an arduous task. The complexity of differentiating tumors at different points of growth has promoted multi-biomarker over single analyte strategies. Current strategies raise exciting opportunities of using multiparametric analysis of "-omic" technology constituents (e.g., genome, transcriptome, proteome, and metabalome) for a diagnosis based on

the molecular profiles of individual patients. In the post-genomic era, proteomics has demonstrated an increasing interest in biomarker research. Proteins are the products of the genes and represent the functional picture of the pathological state of patients [129–131]. Thousands of studies have shown the potential use of proteins as a promising source of biomarkers [132, 133]. Developments in mass spectrometry technology have allowed the analysis of complex proteomes from minimally or noninvasive methods such as serum, plasma, and other body fluids, offering opportunities for reliable early detection approaches [134, 135]. In spite of the optimism brought by proteomics, the lack of sensitivity of those techniques remains a major limitation for the identification of clinically relevant protein biomarkers [136–138]. The major challenge yet to be addressed is the sensitive and selective detection of circulating biomarkers to improve diagnosis, assess treatment efficacy, and design personalized therapies with limited invasiveness. The low molecular weight (LMW) region of the blood proteome provides an unprecedented opportunity for clinical diagnosis or prognosis, and for monitoring response to therapy [90, 97]. Proteins and peptide are degraded by proteases in the tumor stromal environment and shed into the circulation from leaky vessels; therefore, LMW peptidome presents an attractive opportunity to capture pathological changes occurring in the tumor [139]. However, despite such promise, successful translation of this technology to routine clinical application is limited due to: (1) the large dynamic range of blood proteins limiting the detection of low abundance biomarkers and (2) the rapid enzymatic degradation by endogenous and exogenous proteases [136]. To overcome the vast complexity and the relative instability of serum samples, a high throughput and reproducible fractionation system based on nanoporous silica chips (NSC) is currently being developed [140] (Fig. 45.7). The NSC effectively depletes most of the abundant high molecular weight (HMW) proteins and allows the enrichment and stabilization of LMW species present in the human circulating proteome [141]. The NSC are designed and engineered with defined nano-pore size and physicochemical properties allowing substantial control over the molecular cutoff and the specific harvesting and stabilization of proteins and peptides [142]. Figure 45.8 illustrates the advantages that the NSC demonstrates in harvesting low molecular weight peptides selectively from serum samples. This NSC technology in combination with mass spectrometry will provide a fast, efficient, and reliable fractionation system for high-throughput enrichment, stabilization, and detection of LMW biomarkers present in the human circulating proteome. Another approach presented by Luchini et al. demonstrated the use of smart hydrogel particles for the harvesting and protection of circulating LMW biomarkers [143]. The hydrogel particles are fabricated with a defined porosity and contained an affinity moiety for a rapid one-step sequestration and concentration of the LMW fraction of serum molecules. The captured peptides and proteins are then protected from further enzymatic degradation. The ability to structurally design the nanoporous sieve and the chemical functionalization increases the selectivity of peptides enrichment. The combination of these enrichment methods with current proteomics technologies such as mass spectrometry profiling can provide enormous enhancement of low abundant disease marker discovery.

## Nanoparticle Therapeutic Applications in Prostate Cancer Treatment: Evolving Trends

The use of nanoparticles by means of using heat energy for tumor treatment is emerging as a novel approach. Several potential particles for delivery of heat such as silver, lanthanum, and zinc nanoparticles are available [144]. However, the thermal activation properties of gold nanoparticles, magnetic nanoparticles, and carbon nanotubes have been extensively characterized preclinically. They are platforms that are furthest in development in potential translation to clinical applicaton. Several studies illustrate the feasibility and efficacy of tumor-specific targeting by means of gold nanoparticles for photothermal therapy [145–152]. Gold nanoshells were shown to produce mild hyperthermia in murine tumor models and enhance the therapeutic efficacy of RT. In vitro studies of gold nanoshell-mediated photothermal ablation of PC-3 and C4-2 PCa cells demonstrated a total loss of cell viability while maintaining cellular morphology [153]. A subsequent in vivo study on a murine subcutaneous PCa model compared the therapeutic efficacy of two different doses of gold nanoshells and showed enhanced therapeutic efficacy with the high concentration of gold nanoshells [154]. Targeted thermal therapy of PC-3 PCa cell lines using prostate-specific EphrinA1-conjugated gold nanoshells showed localized thermal damage to cells bound to conjugates [155]. PCa cell-specific uptake and toxicity studies of different nanoparticles (gold nanoshells and gold nanorods) have showed size-specific uptake with minimal toxicity [156]. Thermotherapy with the use of magnetic nanoparticles involves coupling of an external magnetic field to tumor-laden magnetic particles that generate high-energy photons through a magnetic field. This occurs near the nanoparticle resulting in magnetic hyperthermia effect by the Neel's relaxation process [157]. The first in vivo evaluation of a PCa rat model demonstrated successful intraprostatic nanoparticle infiltration and stable steady-state thermoablative intratumoral temperatures [157]. Subsequent studies of magnetic nanoparticle-mediated hyperthermia in combination with RT (20 Gy) in a PCa rat model demonstrated a therapeutic efficacy equivalent to a single radiation of 60 Gy [158]. Carbon nanotubes (CNT) are another class of nano-

particles that have potential for biomedical applications including extrinsically activated hyperthermia. Several in vitro studies have demonstrated the use of targeted and nontargeted CNTs for photothermal ablation of tumor cells [159–164]. However, preliminary results raised concerns about toxicity based on its structural profile [165–168]. Furthermore, the route of administration is thought to contribute to potential toxicity. The role of nanoparticle-mediated tumor ablation continues to be explored. Recently, Schwartz et al. reported nanoparticle-directed photothermal treatment of prostate disease by using normal canine prostate in vivo. Canine prostates were directly injected with suspensions of nanoparticles (nanoshells) and irradiated by a NIR laser source delivered percutaneously by an optical fiber catheter and isotropic diffuser during laparotomy of the live canine model. The photothermal lesions were permitted to resolve for several days, following which the euthanized animal's prostate was excised and evaluated histopathologically. They found that the addition of nanoshells to native tissue, combined with a marginally ablative laser dose, could generate ablative thermal lesions with reasonable precision [169].

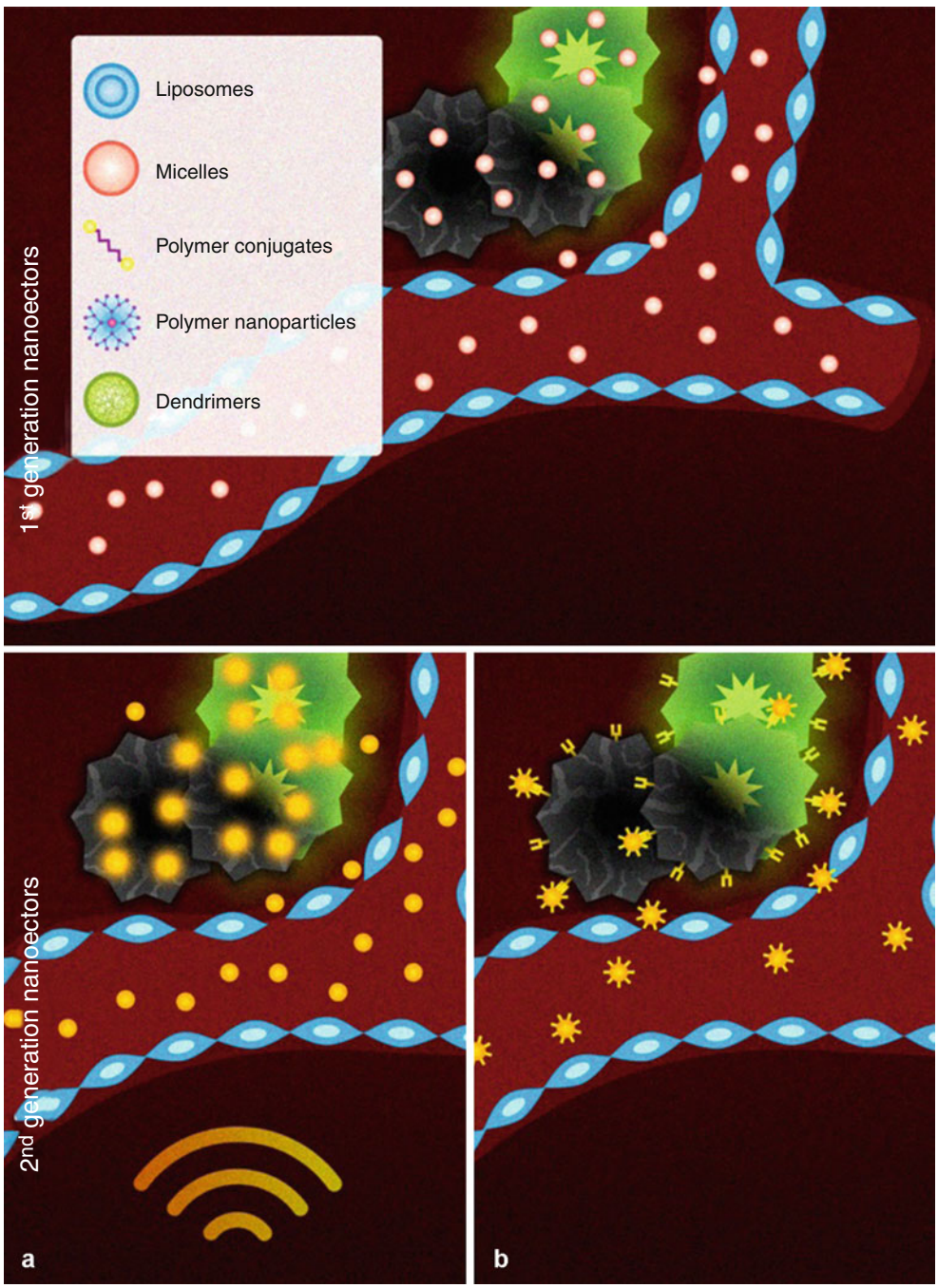
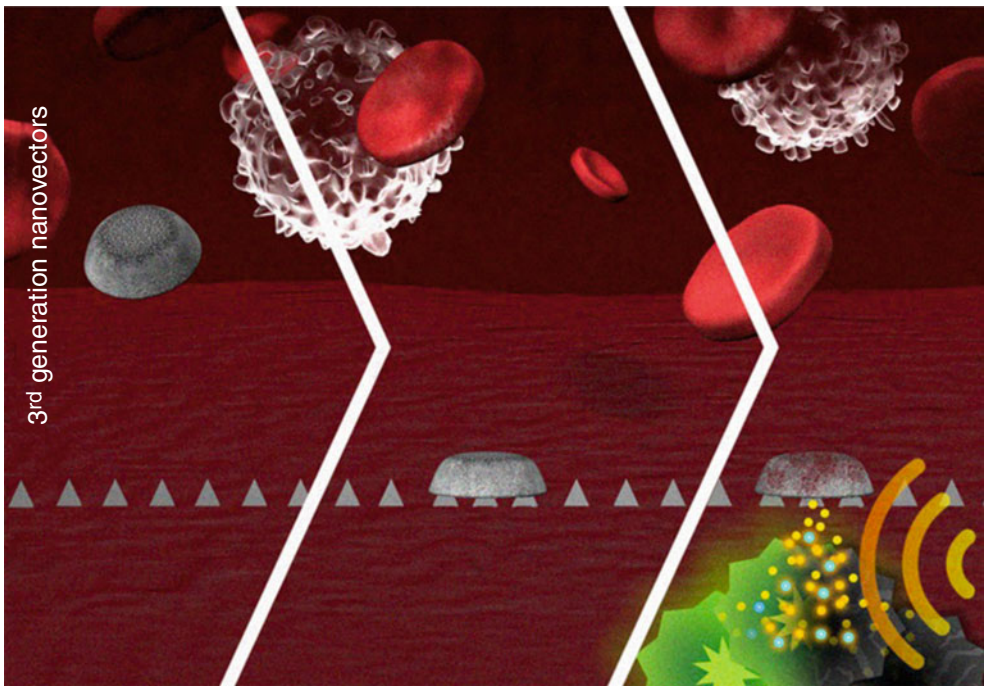



**Fig. 45.7** Schematic presentation of three generations of therapeutic nanovectors. First generation: nanoparticles localizing in tumor through the EPR passive mechanism; second generation: nanovectors possessing additional level of complexity such as (**a**) remote activation by means of radio frequency (RF) or near-infrared (NIR) energy or (**b**) active targeting through specific ligands overexpressed on tumor cells; third generation: logic embedded vectors, LEV comprised of different nano-components which act through a time-sequence of synergistic and logic-driven events (Image courtesy of: Sakamoto et al. [140])

**Fig. 45.7** (continued)



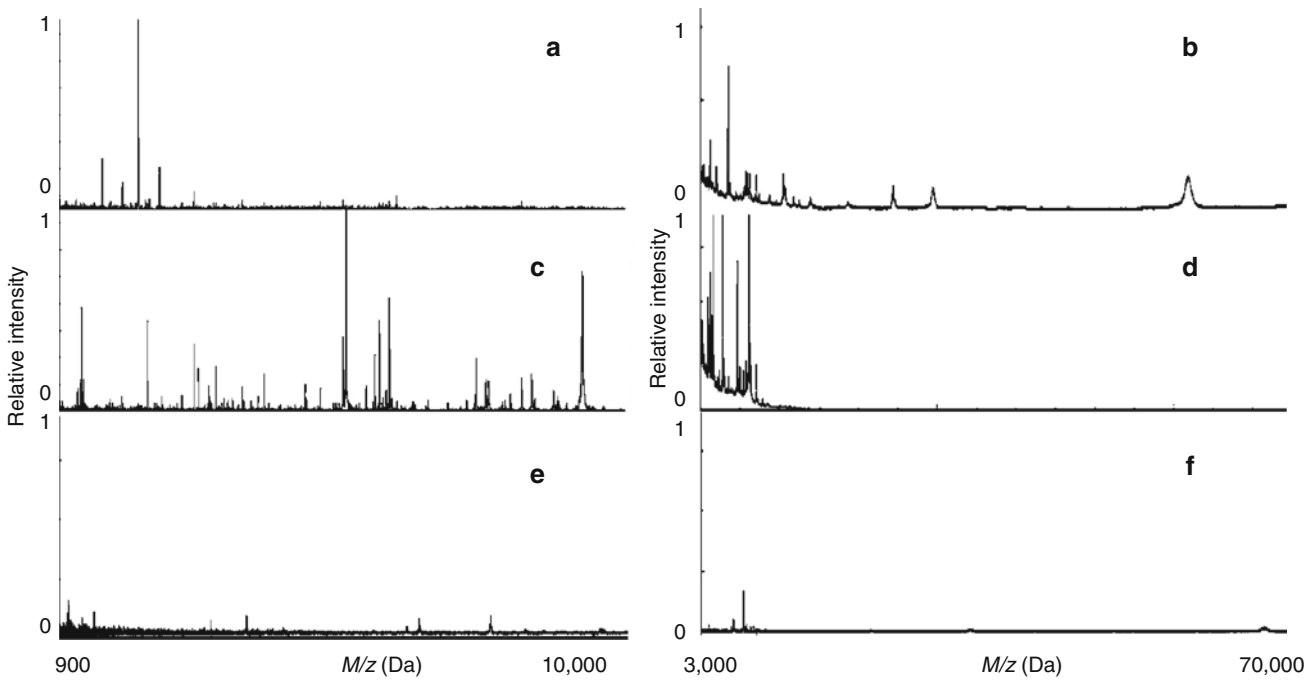




**Fig. 45.8** Peptide enrichment using the mesoporous silica thin film chips. MALDI MS profiles in both the low mass range (900–10,000 Da) and the high mass range (3,000–70,000 Da) before (**a**, **b**) and after (**c**, **d**) serum processing on the mesoporous silica thin films. The molecular recovery is significantly reduced when using blank nonporous silica surfaces (**e**, **f**) (Image courtesy: Kustandi et al. [115])

Within the realms of utilizing nanotechnology in managing advanced or metastatic PCa, there are interesting developments. Ling et al. worked on the premise that supressing, or at least immobilizing the cancer stem cell (CSC) in a nano-self-assembling material might help prevent PCa progression or metastasis. CSCs were plated in different concentrations of self-assembled peptide (SAP). Their findings seemed to suggest that SAP could completely inhibit a prostate CSC from self-renewal while preserving its viability and CSC property. They concluded that SAP might be an effec-

tive nanomaterial for inhibiting cancer progression and metastasis [170].

More recently, several groups are working on the concept that the lymphatic system aids metastatic spread of most human cancers including PCa and that eradication of those metastatic cancer cells from the lymphatic system could control spread. Thus, many groups are working toward developing novel, efficient lymphatic targeting drug delivery systems. Molecular targeting of liposomes to the lymphatic system could potentially enhance therapeutic efficacy by enhancing the initial lymphatic uptake and the lymph nodes' retention of liposomes [171].

Nanotechnology and its role in the management of PCa continue to evolve. The development of nanorobots may provide remarkable advances for surgery and treatment of urological tumors. By utilizing chemical sensors, nanorobots can be programmed to sense specific levels of E-cadherin and beta-catenin and help surgeons with surgical navigation during laparoscopic surgery. Nanorobots could act as useful supplementary tools in biomedical instrumentation isolation and precise mapping of cancer tissues thus potentially aiding with tumor extirpation [172].

## Summary and Future Perspectives

Nanotechnology has the potential to enhance the monitoring of the therapeutic efficacy, permitting the development of novel means of detecting and profiling early PCa. It is envisaged that it would enable surgeons to delineate, with precision, tumor margins and lymph nodes. The advent of numerous nanomaterials and nanotechnology platforms could aid with detection of PCa biomarkers with more precision and sensitivity than is currently availabe.

There is an exponential increase in the number of studies geared at developing sensing mechanisms to aid optimal detection of PCa. Furthermore, novel biomarkers can be discovered and verified with sensitive tools. The simultaneous coupling of nanotechnology with proteomic platforms is expected to aid with biomarker discovery. In the near future, there is cautious optimism that nanotechnology will enhance early detection of PCa and permit monitoring of disease progression with greater precision. It is also anticipated that targeted drug and energy delivery would add to our armamentarium against PCa.

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# Part IV

# Risk Assessment and Decision-Making Strategies for Localized Prostate Cancer

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# Disease Risk Stratification

# 46

Alastair Henderson

## Prostate Cancer Risk Stratification

Disease risk stratification is performed daily in every prostate cancer or urology clinic where men receive care for their disease. It is the use of clinical variables to predict cancer-specific outcomes such as biochemical recurrence or progression, clinical progression such as metastasis or prostate cancer-specific mortality (PCSM). The subsequent chapter covers clinical risk stratification, which includes other factors important in clinical decision making such as the presence of lower urinary tract symptoms, erectile function, and other comorbidities. As large data sets relating presenting features of disease and subsequent treatment to outcome have become more widely available, the estimates that clinicians have always used to decide on whether to treat patients and what treatment to apply have become more complex but also potentially more useful and accurate.

Risk stratification has been applied to a number of areas including the pre-biopsy/rebiopsy stratification in terms of risk of a positive diagnosis and subsequently to level of risk of future disease events for men with a positive prostate biopsy. Risk stratification at its simplest level involves clinicopathological staging of disease into organ-confined disease, locally advanced disease, or disease that has spread to regional lymph nodes or distant sites. Staging systems including the Jewlett-Whitmore and TNM systems are described in detail in Chap. 38. While the process of clinicopathological staging involves the collation of data from a number of clinical observations, serological tests (PSA/Kallakreins/growth factors), and radiological tests such as bone, computed tomography, or MRI scanning, and attempts to order the stages of disease in a logical manner based on previous prognostic reports of outcome, they do not attempt to risk adjust for the combined impact of each of these details on outcome for an individual.

The most usual aim of risk stratification for individuals is to predict whether the patient will develop a rising PSA (biochemical failure) after potentially curative treatment. This may be helpful for treatment planning for younger, fitter patients, but it may be more important to predict metastasis or prostate cancer-specific mortality (PCSM) for patients. A recent review identified more than 40 risk classifications relating to prostate cancer and the risk of subsequent clinical outcomes such as biochemical failure, metastasis, and PCSM [1].

Though the protocols to decide which patients are eligible for inclusion in clinical trials have in the past been based on risk stratification, it is likely that future studies will more overtly stratify risk. They may also help to identify patient at higher risk of failing their primary treatment who might benefit from adjuvant treatment trials such as hormonal or chemotherapy manipulations, or for salvage treatment.

## Individual Factors to Predict Risk

### Serum PSA

In patient populations where screening of high levels of case finding activity occurs, the majority of men present with impalpable disease. Serum PSA is the most important predictor of biochemical progression-free survival (BPFS) in men who have biopsy-proven cancer and undergo treatment [2]. D'Amico demonstrated that in impalpable (TNM T1C) prostate cancer, PSA values of <10, 10.1–20, and >20.1 ng/ml separated men into low-, intermediate-, and high-risk disease categories [3] for risk of posttreatment biochemical recurrence.

### PSA Kinetics

PSA doubling time [4] and velocity of PSA increase [5, 6] have been established to impact on BPFS after radical surgery

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**Table 46.1** Early prostate cancer: risk group classification systems for biochemical PSA recurrence fee survival after radical treatment for prostate cancer

| Group | Low risk | Intermediate risk | High risk |
|---|---|---|---|
| D'Amico et al. [3] (Harvard MS) | PSA <10 ng/ml<br>Gleason score 2–6<br>Stage T1–T2a | PSA 10.1–20 ng/ml<br>Gleason score 7<br>Stage T2b | PSA >20 ng/ml and/or Gleason score 8–10 and/or Stage ≥ T2c |
| Zelefsky et al. [11] (Memorial Sloan-Kettering, NY classification) | PSA ≤10 ng/ml<br>Gleason score 2–6<br>Stage T1–T2b | PSA >10 ng/ml<br>Gleason score ≥7<br>Stage >T2b | Two or three of the intermediate-risk factors |
| Stock, Stone [12] (Mount Sinai, NY) | PSA <10 ng/ml<br>Gleason score 2–6<br>Stage T1–T2a | PSA 10.1–20 ng/ml<br>Gleason score 7<br>Stage T2b | Two or three of the intermediate-risk factors and/or PSA >20 ng/ml and/or Gleason score 8–10 and/or Stage ≥ T2c |

and radiotherapy, and have been suggested as predictors of lower-risk disease with PSA velocity perhaps more suitable for use as a criteria for stratifying risk in active monitoring programs as it correlates with future biopsy upgrades [7].

## Pathological Outcome of Prostate Biopsy

While there have been changes in how prostate biopsies have been performed and how pathology specimens have been processed and interpreted over time [8], Gleason score remains a powerful predictor of outcome with common groupings, stratifying Gleason scores as <7 = low risk, 7 = intermediate risk, and >7 = high risk [3]. This is based on the ability of Gleason biopsy score to predict biochemical recurrence after treatment for prostate cancer. The number of positive cores for cancer and the percentage of each core involved with cancer also impact on final pathological stage accuracy [9, 10].

## Risk Stratification Before Treatment in Organ-Confined Prostate Cancer

While individual prognostic factors may be found to impact on BRFS, the overall impact of a particular factor is difficult to interpret. Most of the systems which purport to describe risk stages actually describe relatively small variation in risk of metastasis or death within a broader group, most usually organ-confined prostate cancer which is to undergo a treatment or monitoring intervention

The most commonly used classification relates to disease which has been staged as organ-confined on clinicopathological grounds. The widely used D'Amico risk grouping [3] is outlined in Table 46.1. Other risk stratifications that have been described are those of Zelefsky et al. [11] and Stock and Stone [12]. These three similar classifications all relate risk of biochemical recurrence-free survival after radical treatment to a number of preoperative characteristics. Although only the D'Amico group has been validated in both radiotherapy and surgical treatment groups, the broadly similar risk groupings are likely to produce broadly similar results given the commonality of their criteria. D'Amico grouping has also been validated in predicting local and systemic recurrence and PCSM [13] in men treated with radical prostatectomy. The other advantages of these risk groupings is that they are fast and straightforward to use and therefore easily applied to everyday clinical practice.

## Relative Value of Different Predictors in High-Risk Organ-Confined Disease

It has been shown that of these factors, presenting PSA is the most important predictor of biochemical progression-free survival (in risk stratifications which were designed for stratification of organ-confined disease), although not the most important predictor of cancer death after radiotherapy or surgical treatment [2]. Factors more likely to predict cancer death are the presence of T3 disease or Gleason Stage 8–10 at diagnosis [13]. It is clear that patients defined as high risk of biochemical relapse after radical radiotherapy for organ-confined disease may survive 10–15 years after biochemical relapse [2, 14]. It is therefore important that we are clear to patients what our calculations are estimating a risk of and to be clear that even patients at high risk of biochemical progression may have a good period of disease control with treatment.

## Nomograms

The further evolution of risk stratifications to allow risk adjustment for individuals is the development of nomograms. Nomograms are mathematical graphic-calculating scales which are developed and then outputted as an algorithm (which have been adapted into more simple to use web-based

calculators [15, 16]). These recognize that simple risk stratification groups while broadly representative will not always appropriately weigh the impact of clinical variables of an individual. The classic work in this area is by Michael Kattan currently of the Cleveland Clinic who coauthored the majority of papers in the recent prostate cancer nomogram literature.

The first nomograms were based on the work of Partin et al. [17] who produced tables to allow clinicians to predict rick of extra capsular-extension, seminal vesicle invasion, or lymph node invasion after radical prostatectomy. While these were helpful and significant first steps, subsequent nomograms offered more clinically useful information including the side of potential extracapsular disease with the ability to influence operative decision making [18]

A series of nomograms to predict the probability of outcomes for a variety of clinical scenarios including preoperative risk of biochemical failure depending on whether treatment with radical prostatectomy, brachytherapy, or external beam radiotherapy [19–21] have also been devised. These have effectively been used to risk stratify patients and therefore by clinicians to recommend types of treatment to patients. It has been demonstrated that nomograms are no worse than experienced clinicians in predicting PCSM [1] after different treatment options. Nomograms have also been shown to be superior to other methods of estimating risk of clinical events such as neural networks [22].

The Kattan nomograms are derived from data collected mainly from institutions associated with Memorial Sloan-Kettering hospital which is an elite academic and clinical institution in New York, USA, with the original nomogram detailing outcomes from the practice of a single highly experienced open radical prostatectomy surgeon [19]. The Kattan nomogram has since been validated in patients who come from a variety of different D'Amico risk groups [23], and it has been shown to perform well in other datasets. If nomograms were used only to stratify risk of outcomes such as biochemical failure after a specific treatment, then they would have been a relatively uncontroversial development.

There are however some problems with the interpretation of this data which mainly relate to whether it is appropriate to use the data from what are highly selected patient populations to stratify risk of outcomes in other populations. For instance, if the patient population from which the data is derived selects out patients who are unsuitable for a particular radical treatment based on PSA or clinical extent of disease, then the remaining "high-risk" patients may be more favorable than those encountered in the general population. Further confounding may occur if the population being assessed differs significantly in terms of ethnicity, age, or genetic make-up. In addition for complex interventions such as brachytherapy or radical prostatectomy, a significant learning curve exists [24]. Therefore, less experienced clinicians might not achieve the relative distribution of results outlined in these large series.

Elements of bias in the selection process of treatment choice which these patients underwent may affect that the results suggested from these nomograms. These results might not be reproduced in populations where treatment selection was a truly random event (for example, in nomograms produced by randomized controlled trial datasets).

However, it has been suggested that with the current state of the art, practicing clinicians might choose to recommend any of the following options for predicting outcome [25]:

1. Deny the ability to accurately predict at the individual level
2. Predict the outcome based on clinical judgment and experience
3. Predict the outcome for the general group or class that the patient lies in (such as D'Amico)
4. Assess risk and apply an algorithm or nomogram.

## The Future for Risk Stratification

Risk stratification is necessarily an estimate of future outcomes based on experience of patients previously treated. As treatments and outcomes progress, nomograms will need to be updated to reflect current practice. It is also likely that novel diagnostic techniques including imaging data will need to be incorporated particularly as imaging biopsy and serological tests give greater insight into the metabolic and genetic activity of tumors. Whether the healthcare systems of the world will be able to afford the routine application of the full technological gamut of these interventions is as yet unknown.

### Conclusion

Risk stratifications remain an essential part of prostate cancer care. The state of the art is to incorporate multiple clinical variables to give patients as much information as possible on their future outcome though many centers will prefer the simplicity of risk groupings.

In the absence of randomized controlled trial data available to answer many clinical questions, nomograms based on case series seem to offer good evidence with which to inform patients of their future risk of various clinical outcomes allowing for multiple independent variables which may impact on outcome. The development and validation of these nomograms may allow a wider application in clinical practice.

Risk stratification should be a part of clinical trial design and routine clinical practice, but patients must be clearly informed of what clinical outcome they are "at risk" of

since even patients at high risk of biochemical progression may survive for periods of years without metastasis of PCSM.

## Summary

Disease risk stratification is the use of clinical variables to predict cancer-specific outcomes such as biochemical recurrence or progression, clinical progression such as metastasis or prostate cancer-specific mortality (PCSM). Individual factors such as pretreatment PSA, prostate biopsy Gleason sum, and rectal examination or imaging-based clinical stage have been found to be predictive of prostate cancer outcome particularly in the most-studied area of potentially organ-confined prostate cancer. These have been combined into simple systems such as those described by D'Amico to describe risk of biochemical relapse-free survival (BRFS). More complex systems include nomograms and neural networks. Nomograms have been demonstrated to be at least as accurate at expert clinicians in predicting BRFS for individual patients. In the future, simplified and increasingly accurate nomograms are likely to be used in counseling patients and will be likely to incorporate novel information from imaging, serological, and pathological variables (including potentially genomic, proteinomic, or metabolic information). Patients at high risk of biochemical recurrence may choose to consider clinical trials of adjuvant chemotherapy, radiotherapy, or hormonal treatment. It is important to maintain clarity that patients at high risk of biochemical progression after primary treatment may have years of disease control after biochemical failure or be effectively treated by salvage therapy and do not universally progress to prostate cancer death.

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# Nomograms in Prostate Cancer

47

Carvell T. Nguyen and Michael W. Kattan

## Introduction

Researchers have made significant advances in the understanding and treatment of prostate cancer over the last several decades, ranging from the development of PSA testing to the identification of the neurovascular bundles and advent of nerve-sparing prostatectomy. These and other breakthroughs have imparted both diagnostic and therapeutic benefits and changed the very epidemiology of prostate cancer. For example, the widespread use of PSA testing has led to increased detection of prostate cancer at lower stages, which has been associated with a greater rate of cure with definitive treatment and a lower risk of mortality [1, 2].

However, many questions about the management of prostate cancer remain unanswered and controversies abound. For example, the increased detection of prostate cancer has resulted in a significant rise in the number of men who undergo treatment with surgery or radiation. While this may appear to be a beneficial phenomenon, recent data suggest that some men (i.e., those with clinically insignificant disease) derive little therapeutic benefit from intervention and are being exposed to unnecessary morbidity and healthcare costs [2–5].

This stems from our inability to predict the natural history or tumor biology of a given patient's disease. Because not all prostate cancers are created equal with regard to biological aggressiveness and lethality, a shotgun approach to management, whereby all men with localized prostate cancer are treated in an identical fashion, is inherently flawed. Moreover, the optimal therapy for men who warrant intervention remains undefined, largely due to the lack of data from randomized trials comparing alternative treatment modalities. Therefore, the ability to accurately predict clinical outcomes is integral to all facets of prostate cancer management, from screening and diagnosis to treatment selection and follow-up.

## Rationale for Formalized Prediction of Clinical Outcomes

Adequate counseling of patients diagnosed with prostate cancer requires knowledge of many clinically relevant outcomes, such as the probability of long-term survival, the risk of treatment failure, and the likelihood of complications. Armed with such data, patients can then make informed treatment decisions that are less likely to be regretted in the future [6]. Ideally, risk assessment would be based upon conclusive data from randomized controlled trials that compare the efficacy and morbidity of alternative prostate cancer treatment modalities. Unfortunately, due to ethical and logistical concerns, such trials are often unfeasible, and physicians and patients have had to rely on surrogate means of estimating the probabilities of relevant clinical outcomes.

In the past, individual physicians utilized their own experience and judgment to provide patients with outcomes predictions. In recommending a particular treatment strategy to a patient, a clinician presumably believes that outcomes for that modality are superior to available alternatives, but such an assumption is not always supported by the data. Personal judgment is subject to several kinds of bias and can lead to inaccurate predictions [7–9]. First, physicians do not recall all cases equally; certain cases can stand out and exert a disproportionate impact on the prediction process. Second, when predictions are actually made, clinicians tend to predict their preferred outcome rather than the outcome with the highest probability [10]. Related to this is the observation that physicians often recommend the treatment modality that they perform themselves. For example, urologists are more likely to favor radical prostatectomy over radiation therapy in treating prostate cancer [11, 12].

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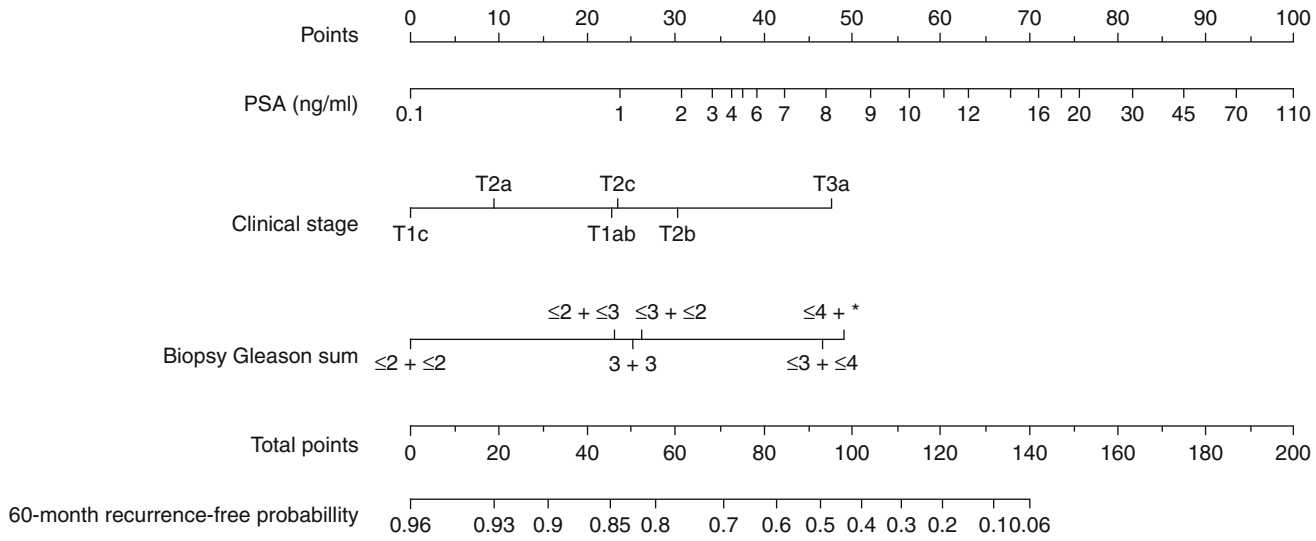


**Fig. 47.1** Nomogram for predicting 5-year recurrence-free probability following radical prostatectomy [55]

Finally, a given clinical outcome is generally influenced by multiple variables that can interact in a complex fashion. For example, numerous prognostic variables for prostate cancer progression have been identified including serum PSA, clinical stage, and biopsy Gleason score. Likewise, the likelihood of potency after radical prostatectomy is influenced by preoperative erectile function, patient age, comorbid medical conditions, preservation of the neurovascular bundle, and individual surgeon technique [13]. As such, an unaided physician will likely have difficulty weighing the relative importance of each of these variables and may simply fall back on heuristics in order to formulate a prediction [14].

## The Evolution of Prostate Cancer Prediction Models

Risk estimation that is based solely on personal judgment or single clinical factors, such as PSA or Gleason score, is destined to be inaccurate given the complexity and heterogeneity of prostate cancer. As such, formal decision aids that can generate uniform and accurate predictions have been created to mitigate the inherent bias of these traditional methods. These prediction tools, including risk groupings, probability tables, or nomograms, typically incorporate multiple prognostic factors using a mathematical model and generally predict outcomes more accurately than physicians can [9].

Risk grouping schema, such as those based on the NCCN and D'Amico classifications, determine prognosis by assigning patients into risk categories based on the presence or absence of particular clinical variables (e.g., PSA, stage, Gleason grade) and have enjoyed widespread popularity because of their simplicity. The resulting patient groups are presumed to have similar characteristics and, therefore, should experience similar clinical outcomes. For example, D'Amico et al. developed a model that predicts cancer control for patients treated with radical prostatectomy, external beam radiotherapy, or brachytherapy by placing patients into mutually exclusive risk groups based on clinical stage, biopsy Gleason score, and pretreatment PSA level [15].

Another popular method is the prognostic index. These models are often based on a Cox or logistic regression model, and a numerical score is assigned to each parameter in the model based on its parameter estimate or hazard ratio. A total score is calculated by summing each of the scores for the individual parameters. The Cancer of the Prostate Risk Assessment (CAPRA) score is an example of a prognostic index [16]. Patients are assigned a CAPRA score between 0 and 10 based on the points assigned for PSA (0–4), biopsy Gleason score (0–3), clinical stage (0–1), percentage of positive biopsy cores (0–1), and age (0–1). Each point on the CAPRA score corresponds with an estimated 5-year recurrence-free probability after radical prostatectomy.

In recent years, the field of prediction modeling has turned to the development of continuous multivariable models called nomograms. A nomogram is a graphic representation of a mathematical formula or algorithm that incorporates several predictors modeled as continuous variables to predict a particular endpoint (Fig. 47.1). Nomograms consist of sets of axes; each variable is represented by a scale, with each value of that variable corresponding to a specific number of points according to its prognostic significance. By using scales, nomograms calculate the continuous probability of a particular outcome.

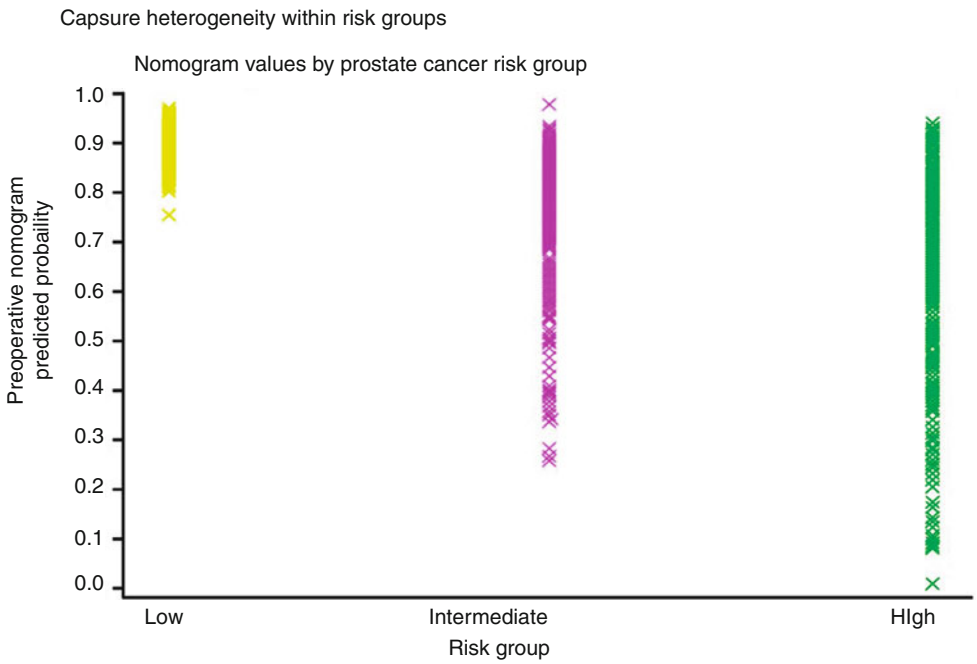


**Fig. 47.2** Demonstration of the heterogeneity within risk groups when compared against the outcomes predicted by a preoperative nomogram for prostate cancer [26]

## The Superiority of Nomograms in Outcomes Prediction

With all of these different classes of prediction tools and over 100 published models for use in prostate cancer alone [17], a clinician can be faced with the dilemma of deciding which is the best prediction tool to use for patient counseling.

Knowledge of the criteria that are critical to the design and evaluation of a prediction tool can be helpful in establishing the best tool to use in patient counseling. The key factors that measure accuracy and quality include discrimination (the ability to predict which patients will or will not demonstrate the outcome of interest), calibration (generating risk estimates that closely approximate actual outcomes), and validation (providing consistent results when applied to external patient cohorts). Utilizing these criteria, comparative studies suggest that nomograms predict outcomes more accurately than any other method of risk estimation, including physician judgment, risk groupings, neural networks, or probability tables [18–25].

There are several reasons that may account for the greater accuracy displayed by nomograms. First, they incorporate patient-specific values and generate risk estimates that are tailored to the individual. In contrast, other types of prediction models, such as risk groupings, often depend on average values derived from heterogeneous populations that may not be representative of a given patient. The predictive capacity of risk groupings is based on the assumption that all patients within a given risk group are equal, when, in fact, such groups can be quite dissimilar. This prognostic disparity is especially evident when analyzing outcomes generated by a preoperative nomogram for prostate cancer patients initially stratified by a risk grouping (Fig. 47.2) [26].

Such incongruity within risk groups is likely due to variable inclusion criteria. It would be reasonable to conclude that inclusion into a high-risk category on the basis of multiple adverse factors (e.g., PSA >20, T2b, and Gleason 8) represents a worse prognosis than that based on just a single factor. Such heterogeneity blunts the predictive value of risk assignments and likely explains why risk groupings predict less accurately than nomograms [21, 25]. Furthermore, the method of counting risk factors assumes that each variable exerts an equal prognostic weight on the outcome, which is unlikely to represent the true relationship between variables and prognosis [27].

Second, nomograms are based upon comprehensive statistical models (e.g., a multiple regression equation) that analyze multiple variables simultaneously, allowing a greater number of predictors to be included. Models with more prognostic factors are more likely to reflect the complexity of a disease like prostate cancer and, therefore, predict outcomes more accurately. Moreover, continuous variables can be kept continuous in a nomogram, whereas other prediction models, like risk groupings or probability tables, require creation of cut points that are often arbitrary with little prognostic basis. Categorizing a continuous variable, such as PSA level, blunts its prognostic value and lowers the overall accuracy of the model [22].

Finally, the complex statistical model behind a nomogram is presented in a simple graphical format that avoids

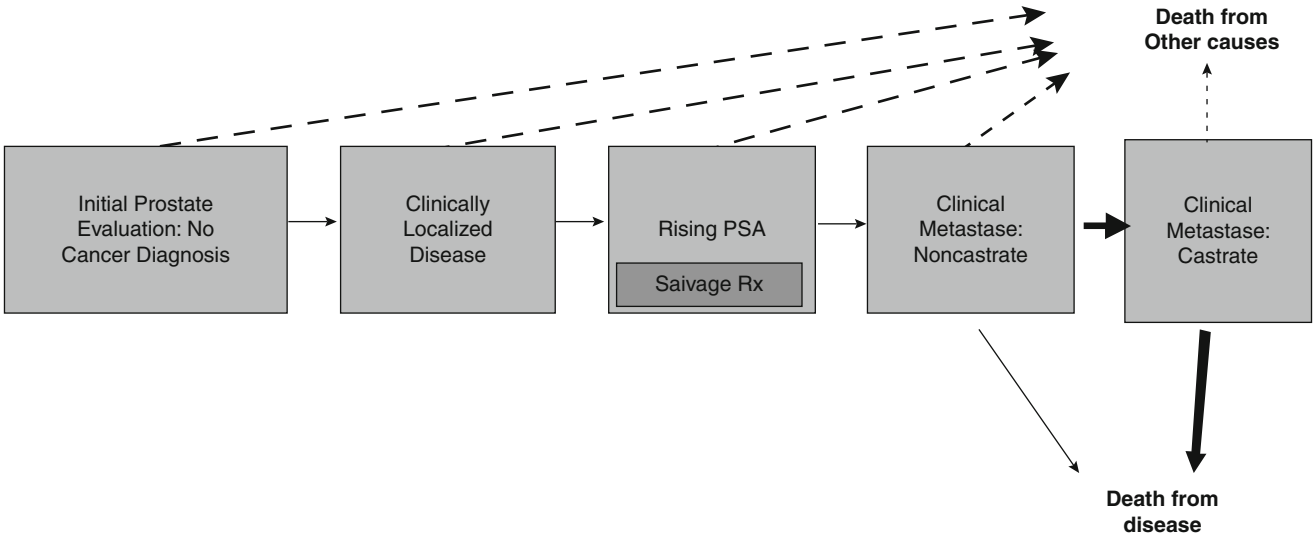


**Fig. 47.3** Clinical states model of prostate cancer progression [28]. *Dashed line arrows* indicate pathways from a clinical state to a non-prostate cancer-related mortality; *solid line arrows* indicate pathways from a clinical state to a prostate cancer-related mortality

complex calculations (Fig. 47.1). Without need of a calculator, nomograms are easy to use and interpret by physicians and patients alike. Currently, many nomograms are now available as online software presented in a "fill-in-the-blank" format that further facilitates everyday use. These online tools utilize the same statistical models that underlie the original nomograms, and examples, organized by prostate cancer clinical state, are available at www.nomograms.org and rcalc.ccf.org.

Considered together, these advantages explain why nomograms have become widespread in general medical practice and have been adopted with particular enthusiasm by the urologic oncology community. A number of nomograms have been developed and validated for use in various prostate cancer clinical states.

## Clinical States of Prostate Cancer and Their Corresponding Nomograms

The natural history of prostate cancer can be divided into a series of clinical states from diagnosis to death from prostate cancer or from competing causes (Fig. 47.3) [28]. Conceptualization of prostate cancer in this way allows organization of current nomograms and also allows researchers to determine where additional novel nomograms would be most useful. At each clinical state along the prostate cancer continuum, a man is faced with different prognoses in terms of the risk of progressing to the next clinical state (and ultimately dying from his disease) versus dying from competing causes and different treatment decisions about the need of further therapy and the nature, risks, and benefits of those treatment alternatives.

Appropriate treatment of the patient within each of these clinical states (and informed decision-making) requires accurate estimates of oncological efficacy and the risk of morbidity. There are a substantial number of validated nomograms that have been developed for use in risk estimation for some of the clinically relevant endpoints at each clinical state. Some of the prediction models that are available for each of these clinical states will be reviewed, with an emphasis on those for localized prostate cancer.

## Screening and Diagnosis

Despite better understanding of its biology and development of more effective treatment modalities, prostate cancer can still be associated with significant morbidity and mortality, particularly if found at an advanced stage. As such, the contemporary approach to prostate cancer emphasizes early detection of disease. This presumably catches tumors in a state of favorable biology (i.e., organ-confined) and increases the chances of cure with definitive treatment. Indeed, since the advent of PSA testing several decades ago, a significant downward stage migration has been observed with the majority of men today diagnosed with organ-confined prostate cancer [1].

Despite vastly improving cancer detection, PSA screening alone actually achieves a relatively low accuracy for predicting disease, ranging from 52 to 60 % [29–32]. Multivariable tools such as the Prostate Cancer Prevention Trial risk calculator consider PSA, age, ethnicity, family history, and DRE findings but have demonstrated only slightly greater predictive accuracy (57–70 %) [30–32]. Because suboptimal accuracy in predicting cancer can either result in

unnecessary prostate biopsies or miss disease altogether, there is an obvious need to validate and refine current models as well as develop new tools.

A number of nomograms have been developed to predict the probability of cancer prior to actual diagnosis and have consistently demonstrated greater accuracy than other methods of estimation [33–38]. Such nomograms can limit unnecessary biopsies and their attendant morbidity, as well as help formulate active surveillance protocols. For example, using data from the European Randomised Study of Screening for Prostate Cancer, Roobol and colleagues developed a nomogram that predicts the chances of a positive initial biopsy by incorporating PSA, prostate volume, DRE, and transrectal ultrasound findings [35]. Compared to PSA alone, this nomogram increased the accuracy of cancer detection and decreased the number of unnecessary prostate biopsies by a third. A nomogram developed by the group at Memorial Sloan-Kettering Cancer Center predicts the chances of a positive repeat biopsy after previous negative biopsies, demonstrating a concordance index of 0.71 on external validation [38]. Additional comparative studies will be needed to validate these screening nomograms and confirm that they are more accurate than PSA alone for cancer detection. However, they do represent the first step toward a more discriminating, responsible, and cost-effective approach to screening.

## Pretreatment Counseling

After a patient has been diagnosed with cancer, the most important decisions in disease management still remain to be made. Appropriate counseling of patients during the pretreatment phase of disease management depends upon our best estimates of relevant clinical outcomes, including the natural history of a patient's cancer, estimation of life expectancy, or what might occur after receiving a given primary treatment. A man with localized prostate cancer is interested in knowing the risk of developing symptoms and/or dying from his disease, with or without definitive local therapy, the likelihood of treatment success with radical therapy, and the short- and long-term complications of therapy. Nomograms have tried to fill this void by providing individualized predictions of relevant clinical outcomes that can be used by patients to make informed decisions regarding their own optimal management strategy. Many nomograms exist for prostate cancer recurrence after definitive local therapy [17]. Currently, similar nomograms that estimate the likelihood of treatment-related morbidity (e.g., urinary incontinence, sexual dysfunction, bowel dysfunction, hormonal symptoms) are lacking.

The first, and perhaps most important, decision that must be reached is whether or not a given patient's cancer merits treatment at all. The rational application of therapy has profound ethical and economic implications and is particularly important now because of the growing concern over the overdiagnosis and overtreatment of prostate cancer that has been attributed to PSA screening. Using SEER data, Welch and colleagues recently reported that PSA testing has resulted in the additional diagnosis and treatment of more than a million cases of prostate cancer [5]. Because the majority of detected cancers are organ-confined and unlikely to progress [39], many men are undergoing unnecessary treatment, placing them at risk for treatment-related complications (such as impotence or incontinence) as well as incurring significant healthcare costs.

As such, the ability to accurately predict clinically significant tumors (i.e., those that progress and merit treatment) can facilitate appropriate patient selection for active surveillance. There are several pretreatment nomograms that have been designed to predict the probability that a patient harbors indolent disease (Table 47.1) [40, 41]. For example, Kattan and colleagues developed a nomogram to predict the probability of indolent prostate cancer, defined as a tumor volume <0.5 cc, pathological Gleason score ≤6, and confined to the prostate [41]. The nomogram incorporated PSA, Gleason grade, ultrasound volume, and percentage of tissue cores positive for cancer and predicted indolent cancer with a concordance index of 0.79 [41].

Assessment of life expectancy is another critical factor in determining whether or not treatment will ultimately be beneficial. Patients with a long life expectancy (i.e., ≥10 years) have a greater risk of suffering morbidity or mortality from prostate cancer, while those with a shorter life expectancy may die from other comorbidities before their disease ever progresses. To this end, Walz et al. published a nomogram that predicts 10-year life expectancy for patients treated with either RP or EBRT [42]. Their nomogram demonstrated an accuracy of 84 % in identifying men who did not survive beyond 10 years, a group of patients for whom definitive therapy may not be warranted. Kattan et al. developed another nomogram that predicts prostate cancer-specific survival at 10 years among men who did not undergo definitive local therapy [43]. The dataset consisted of 1,911 patients identified from six cancer registries in England between 1990 and 1996 who did not receive any form of local therapy within 6 months of diagnosis. The model incorporated PSA, biopsy Gleason score, clinical stage, method of diagnosis (biopsy vs. TURP), percentage of cancer, age, and the use of androgen deprivation therapy within 6 months of diagnosis and demonstrated a c-index of 0.73. Use of these pretreatment nomograms may help reduce the aforementioned overtreatment of prostate cancer along with its attendant morbidity and healthcare costs.

**Table 47.1** Prostate cancer nomograms for use in pre-treatment counseling

| Nomogram | Outcome predicted | CI | Variables |
|---|---|---|---|
| Kattan et al. [21] | 5 year PFP after EBRT | NA | Clinical stage, biopsy Gleason score, pretreatment PSA, neoadjuvant ADT, and radiation dose |
| Kattan et al. [10] | 5 year PFP after brachytherapy | 0.61–0.64 | clinical stage, biopsy Gleason sum, pretreatment prostate-specific antigen (PSA) value, and administration of external beam radiation |
| Koh et al. [50] | Probability of seminal vesicle invasion | 0.88 | PSA, clinical stage, Gleason grade, % cancer at base |
| Cagiannos et al. [45] | Probability of LN involvement | 0.76 | Clinical stage, Gleason sum and PSA |
| Kattan et al. [22] | Probability of indolent cancer | 0.79 | Serum PSA, clinical stage, biopsy Gleason grade, TRUS volume, % of biopsy cores involved with cancer and high grade cancer, total length of biopsy cores involved |
| Kattan et al. [22] | 5 year probability of metastasis after conformal RT | 0.81 | Pretreatment PSA level, clinical stage, and biopsy Gleason sum |
| Ohori et al. [51] | Probability of ECE | 0.81 | Pretreatment PSA, clinical stage, biopsy Gleason sum, % positive cores, % cancer in cores |
| Chun et al. [46] | Probability of Gleason score upgrading at RP | 0.8 | PSA, clinical stage, primary and secondary Gleason patterns |
| Stephenson et al. [52] | 5 and 10 year PFP after RP | 0.79 | Clinical stage, PSA, biopsy Gleason grade, year of surgery, # of positive and negative biopsy cores |
| Wang et al. [53] | Organ confined cancer | 0.81–0.90 | PSA, biopsy Gleason grade, clinical stage, MRI findings |
| Zelefsky et al. [54] | 10 year PFP after conformal RT | 0.72 | pretreatment PSA level, Gleason score, radiation dose, use of neoadjuvant androgen deprivation, and clinical stage |
| Briganti et al. [44] | Probability of LN involvement | 0.81 | PSA, clinical stage, Gleason sum |
| Chun et al. [40] | Probability of indolent cancer | 0.9 | PSA, clinical stage, primary and secondary Gleason grades, % tissue involved with cancer, % positive cores |
| Walz et al. [37] | Probability of 10 year life expectancy for candidates of RP or RT | NA | Charlson comorbidities, age at treatment |

*PFP* progression-free probability, *EBRT* external beam radiotherapy, *LN* lymph node, *RT* radiation therapy, *ECE* extracapsular extension, *RP* radical prostatectomy, *ADT* androgen deprivation therapy

## Selection of Optimal Therapy

Traditionally, definitive treatment of men with clinically localized disease has been accomplished with radical prostatectomy (RP) or radiation therapy (RT). The optimal therapy of the modern prostate cancer patient with organ-confined disease remains nebulous due to a combination of factors. The contemporary approach to prostate cancer now includes a greater number of options including minimally invasive surgery (standard and robotic-assisted laparoscopy), interstitial brachytherapy, and novel energy ablative modalities (e.g., cryoablation and HIFU). Due to a lack of randomized trials comparing these treatment alternatives in a head-to-head fashion, there is no consensus on the ideal treatment (i.e., demonstrating greatest oncological efficacy and/or least morbidity) that can be applied to all patients diagnosed with prostate cancer.

Various pretreatment nomograms have tried to fill this void in the literature by providing individualized predictions of relevant clinical outcomes that can be used by patients to make informed decisions regarding their own optimal management strategy.

Endpoints that can be utilized for treatment selection include the likelihood of organ-confined prostate cancer as well as the probability of not recurring or progressing following various forms of primary treatment (Table 47.1) [21, 37, 44–54]. Nomograms that predict the former can be used to determine eligibility for definitive local monotherapy as patients with locally advanced disease may benefit from more aggressive, multimodal therapy. Estimation of primary treatment outcomes, such as short- and long-term probabilities of PSA recurrence, can help patients decide their preferred mode of definitive treatment.

For example, Kattan et al. developed a pretreatment nomogram incorporating clinical stage, biopsy Gleason score, and pretreatment PSA level that predicts the 5-year progression-free probability (PFP) for patients who choose RP [55]. The dataset included 983 patients with clinically localized prostate cancer treated by a single surgeon, with an overall 5-year PFP of 73 %. The nomogram demonstrated c-indices of 0.75 when applied to an international external validation cohort [56] and 0.74 when validated in the African-American population [57].

However, the 5-year endpoint may not be sufficient to predict the long-term likelihood of cure after RP as a substantial number of patients are at risk for disease progression beyond 5 years [58, 59]. Using 10-year PFP may allow more accurate predictions of long-term survival and cure given the

low risk of recurrence after 10 years following RP [52]. To this end, Stephenson and colleagues updated their original nomogram by extending the predictions to 10 years [52]. Year of treatment was added as a predictor to adjust for the downward stage migration due to PSA screening, and systematic prostate biopsy data were included as well. The updated model was based on 1,978 patients treated by two high-volume surgeons and externally validated on 1,545 patients treated at a separate institution, demonstrating a c-index of 0.78.

Another preoperative nomogram developed by the group from Memorial Sloan Kettering Cancer Center (MSKCC) predicts 15-year prostate cancer-specific mortality (PCSM) after RP using PSA, clinical stage, biopsy Gleason score, and year of treatment [60]. The internal dataset consisted of 6,398 patients treated between 1987 and 2005 by surgeons at MSKCC, while the external validation cohort included 6,279 patients treated at the Cleveland Clinic and University of Michigan during the same period. The overall 15-year PCSM was low (12 %) and was less than 20 % for those with a risk of biochemical recurrence greater than 50 %. The c-index of the model was 0.84, and the statistically significant predictors in the model were biopsy primary and secondary Gleason grade, PSA, and year of treatment.

Similarly, there are nomograms that predict oncological outcomes following radiation as primary therapy. Examples include models that predict the probability of biochemical recurrence at 5 years after EBRT or brachytherapy with concordance indices ranging from 0.61 to 0.81 [21, 47]. Because biochemical recurrence may not truly correlate with disease aggressiveness or treatment failure, investigators have developed nomograms that evaluate more meaningful endpoints, such as the probability of metastasis after EBRT [49].

Moreover, pretreatment prediction of disease extent and pathologic features can assist surgical planning for patients undergoing RP. Estimation of the risks of extracapsular extension [51, 53] or seminal vesicle invasion [50] can dictate the extent of local resection, for example, whether or not to spare the neurovascular bundles. Investigators from MSKCC published a validated nomogram based on PSA, Gleason sum, and clinical stage that predicts lymph node metastases with greater accuracy than the Partin probability tables [45]. Accurate prediction of nodal status can determine the necessity of a pelvic lymphadenectomy, which can be associated with significant cost and morbidity.

## Posttreatment Counseling and Selection for Clinical Trials

Several nomograms incorporate posttreatment clinical variables, including pathological stage and surgical findings, to determine follow-up protocols or identify patients who may benefit from adjuvant therapy (Table 47.2) [55, 61–68]. Models designed for use in patients who have failed primary therapy (i.e., those at high risk for adverse outcomes) can facilitate selection for adjuvant and/or experimental treatment regimens. For example, Dotan and colleagues created a nomogram that predicts the likelihood of bony metastases in men with rising PSA after RP [61]. Other investigators have developed tools that predict overall survival in patients with progressive, hormone-refractory prostate cancer [62, 63].

Risk estimation by posttreatment nomograms can also facilitate the design, powering, and interpretation of clinical trials. By calculating individualized outcomes and avoiding the heterogeneity inherent to risk groupings, nomograms ensure that recruited patients are truly and homogeneously high risk and, therefore, more likely to benefit from an investigational therapy. Moreover, exclusion of low-risk patients reduces sample size, improves statistical power, and avoids exposing patients to aggressive therapy that is more likely to harm than help.

Lastly, it has been suggested that nomograms can be used to apply results from clinical trials to individual patients by providing tailored estimates of treatment benefit [69]. Critical data from trials, such as the observed response rates to the novel treatment regimen being evaluated, are generally reported as group-level estimates. This method of reporting averaged results ignores individual patient factors and incorrectly assumes homogeneity within study cohorts as well as similarity between a given patient and those studied in the trial. Indeed, the individual patient being evaluated may differ from trial patients with regard to key prognostic factors, such as tumor stage, grade, or PSA. By using nomogram-generated predictions, one may find that a given patient's risk is quite different from the group-level results reported in a trial. As a result, clinicians can better discriminate between effective and ineffective treatment alternatives, allowing more effective patient counseling.

## Limitations of Nomograms

Although nomograms currently represent the best option for predicting outcomes, certain limitations should be kept in mind when determining their utility in clinical practice. Despite their widespread use, there are no data demonstrating that use of nomograms in clinical decision-making improves patient outcomes in prostate cancer. In truth, the effect of prediction tools in general upon medical decision-making and subsequent outcomes may never be elucidated. Unfortunately, a randomized controlled trial assessing the efficacy of nomograms on patient outcomes may never be undertaken given the ethical dilemma of withholding nomogram-generated predictions from patients in any control group. Clinicians should also be aware that current

**Table 47.2** Nomograms for post-treatment counseling

| Nomogram | Outcome predicted | CI | Variables |
|---|---|---|---|
| Kattan et al. [55] | Probability of disease recurrence after RP | 0.68–0.75 | Pretreatment PSA, pathological Gleason sum, prostatic capsular invasion, surgical margin status, SV invasion, and LN status |
| Smaletz et al. [63] | Overall survival in hormone refractory disease | 0.67 | Age, Karnofsky performance status, hemoglobin, PSA, lactate dehydrogenase, alkaline phosphatase, and albumin |
| Halabi et al. [62] | Overall survival in HR disease | 0.68 | Lactate dehydrogenase, PSA, alkaline phosphatase, Gleason sum, Eastern Cooperative Oncology Group performance status, hemoglobin, and the presence of visceral disease |
| Stephenson et al. [65] | 10 year probability of recurrence after RP | 0.79 | PSA, primary and secondary Gleason grade, ECE, positive surgical margins, SV invasion, lymph node involvement, treatment year, and adjuvant RT |
| Dotan et al. [61] | Probability of positive bone scan in patients with rising PSA after RP | 0.93 | Pretreatment and present PSA levels, surgical margin status, SV invasion, pathologic Gleason sum, ECE, PSA slope, and PSA velocity |
| Svatek et al. [68] | Probability of mortality in HR disease | 0.81 | PSA at ADT initiation, PSA DT, nadir PSA during ADT, months from ADT to HR disease |
| Stephenson et al. [66] | Progression-free probability after salvage RT for post-RP recurrence | 0.69 | PSA, Gleason score, SV invasion, ECE, surgical margins, LN involvement, elevated post-RP PSA, pre-RT PSA, PDA DT, neoadjuvant ADT, radiation dose |
| Porter et al. [77] | Prostate cancer-specific survival after post-RP recurrence | 0.66 | Stage pT3, Gleason 8–10, positive surgical margins, age at hormone therapy, recurrence type |
| Porter et al. [78] | Probability of distant metastases after RP | 0.76–0.80 | Pathologic stage, pathologic Gleason sum, comorbidity index, adjuvant RT |
| Suardi et al. [67] | Long term PSA recurrence-free probability after RP | 0.77–0.86 | Clinical stage, surgical margins, pathologic Gleason sum, nodal dissection status, adjuvant RT |
| Stephenson et al. [64] | Prostate cancer-specific mortality after RP | 0.82 | Primary and secondary Gleason grades, PSA, clinical stage |

*HR* hormone refractory, *RP* radical prostatectomy, *PSA* prostate specific antigen, *ADT* androgen deprivation therapy, *DT* doubling time, *SV* seminal vesicle, *ECE* extra-capsular extension, *RT* radiation therapy, *LN* lymph node

nomograms are not perfect and may not be applicable to all patients diagnosed with prostate cancer. In general, nomograms are constructed and validated using patients treated at academic centers, whose outcomes may differ considerably from outcomes of patients treated at community health centers, since the quality and availability of treatments can vary with the location and experience level of the treating physician [70, 71]. As such, nomogram predictions should not be the sole determinant of medical decision-making and should be coordinated with published data, physician judgment and experience, as well as patient preference.

The explosion in the field of nomograms over the last decade has posed another problem. As aforementioned, there are over 100 published prediction tools (nearly half of which are nomograms) that have been developed for use in various clinical states of prostate cancer [17]. Although there are substantial data suggesting that nomograms are more accurate than any other class of prediction model, there is a distinct lack of head-to-head studies analyzing the quality and utility of nomograms that predict the same endpoints. Without such guidance from the literature, a physician may have difficulty deciding which nomogram to use for a given clinical state. A novel prediction tool, dubbed the "metagram," has been proposed that may obviate physicians from having to make these complex decisions [72]. Designed for use in clinically localized prostate cancer, the metagram considers a number of relevant clinical outcomes (related to oncological efficacy and morbidity) organized by various treatment modalities (Fig. 47.4). Using published criteria to determine the accuracy and quality of alternative nomograms for each clinical state [73], each cell of the metagram is populated by the preferred model for a given treatment-outcome combination. This metagram could be incorporated into a software program that allows simultaneous prediction of clinically relevant outcomes for all available treatment modalities that are tailored to the individual patient, allowing him to make a management decision that is best suited for him. For example, the patient who is mainly concerned with surviving cancer-free may select a different treatment strategy from one who wants to avoid a negative impact on quality of life, such as incontinence or impotence.

Another potential criticism of using nomograms in clinical practice concerns whether the average patient has the literacy or numeracy required to comprehend data presented by nomograms. Fortunately, nomograms are presented in a simple graphical format that eschews unwieldy calculations and does not require the patient to see or understand the "black box" of complex mathematical equations that govern them. Indeed, there are data to suggest that the majority of people,

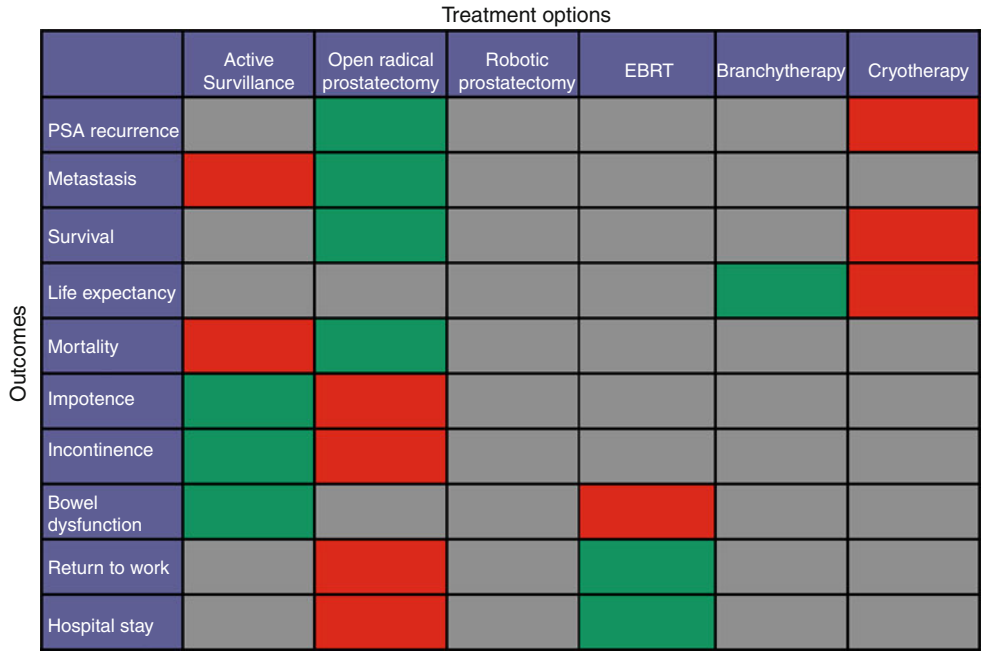


**Fig. 47.4** Hypothetical example of a prostate cancer metagram incorporating various clinical outcomes for an array of treatment modalities. Each cell is populated by the nomogram that predicts most accurately for that particular treatment/outcome endpoint. After entering patient-specific variables, a software program would then generate predictions for each cell that can be visually interpreted. Green cells correspond to the best value for a given outcome, red cells represent the worst outcome, and gray cells represent intermediate outcomes. For example, looking at impotence, active surveillance is associated with the lowest risk of this complication, while open RP is associated with the highest risk

regardless of educational level, are able to understand and interpret tabular data for comparative purposes [74].

## Future Directions

No currently available nomogram predicts with perfect accuracy, and knowledge of the reasons can provide opportunities for improvement. A nomogram that is based on a dataset that has insufficient sample size is missing significant information, or incorporates too few, or the wrong predictors will demonstrate reduced accuracy and applicability to external patient populations [75]. The generalizability of a particular nomogram to different patient cohorts can also be influenced by variability in clinical practice between different institutions and physicians.

If not already performed, existing prostate cancer nomograms should be subject to external validation using large patient cohorts from other institutions. This can adjust for bias due to small sample size of the internal dataset as well as that due to temporal changes in practice patterns. Identification and incorporation of additional predictive markers can also improve accuracy in predicting an endpoint. For example, novel biomarkers that correlate with the presence of prostate cancer, such as PCA3, may increase the accuracy of nomograms that predict disease prior to biopsy [76].

Attention should also be directed to developing novel nomograms that consider other clinical states not currently available in the literature. For instance, nomograms that directly predict metastatic progression or mortality are more useful in assessing the actual curative potential of a treatment option than those that use PSA recurrence as a surrogate for the aforementioned outcomes. Nomograms that consider newer treatment modalities, like robotic prostatectomy or cryoablation, or quality of life outcomes, such as risk of impotence or length of convalescence, will allow patients to consider all available treatment options and their impact on all facets of their lives.

### Conclusions

Patients with prostate cancer require our best estimates of clinical outcomes in order to make informed and appropriate decisions at all stages of disease. Nomograms have become the prediction tools of choice for many physicians because of their ease of use, high accuracy, and generation of risk estimates tailored to the individual patient. With accurate estimates of treatment success or the risk of morbidity, patients can make an informed, appropriate treatment decision and are less likely to experience regret in the future. However, it should be emphasized that nomogram predictions are not infallible and may not be generalizable to every man with prostate cancer.

Nomograms do not make treatment recommendations or act as a surrogate for physician-patient interactions. Furthermore, not all nomograms demonstrate equivalent quality or utility, and clinicians must be aware of their limitations and be willing to contribute to their refinement. Therefore, the role of current nomograms is to provide patients with the best estimates of relevant outcomes, which, combined with clinician expertise and patient preference, can then form the basis for truly informed decision-making.

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# Comparative Effectiveness of Treatment Alternatives for Localized Prostate Cancer

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## Introduction: Why Comparative Effectiveness Research for Prostate Cancer?

A patient newly diagnosed with prostate cancer in 2013 faces a potentially bewildering menu of treatment options. Alternatives endorsed by the American Urological Association (AUA)'s 2007 practice guideline for localized prostate cancer [1], for example, include active surveillance, radical prostatectomy, interstitial radiation (brachytherapy), or external beam radiation therapy (EBRT). However, the detailed list of options becomes longer, including among surgical options open radical retropubic prostatectomy (ORRP), radical perineal prostatectomy (RPP), "straight" laparoscopic radical prostatectomy (LRP), and robot-assisted radical prostatectomy (RARP), within brachytherapy, permanent (low-dose rate) seed implantation or temporary (high-dose rate [HDR]) via catheters, and within EBRT, "conventional" 3-D conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), or proton beam therapy, possibly combined with brachytherapy and/or with androgen deprivation therapy (ADT). Other options not necessarily endorsed by the guideline but frequently used in practice include primary ADT (PADT) monotherapy and cryotherapy; those traveling outside the United States also have the option of high-intensity focused ultrasound (HIFU).

There are major differences in the costs and short-term risk profiles of these alternatives and potentially significant differences in long-term health-related quality of life (HRQOL) and oncologic outcomes as well [2, 3]. Indeed, men are increasingly diagnosed years or decades before they face potential morbidity or mortality from the cancer itself, but may experience HRQOL effects for years. Moreover, clinicians and patients deciding among options for localized prostate cancer treatment do so in the setting of a relative dearth of high-quality data comparing outcomes following the various alternatives. A large, systematic review commissioned by the Agency for Healthcare Research and Quality in fact concluded that insufficient evidence exists to construe greater benefit for any given treatment approach over another [4]. The AUA guideline likewise makes no recommendations with respect to the superiority or inferiority of any of the endorsed alternatives.

In the vacuum of evidence regarding optimal management, wide and excessive local and regional variation has developed in the utilization of various interventions for localized disease [5–7]. Indeed, treatment of prostate cancer has been typical of what has been termed *preference-sensitive* health care: care driven by patient or clinician preferences, beliefs, or values in the absence of strong scientific evidence. In some cases, prostate cancer care may also be *supply-sensitive*, with utilization guided more by availability of and reimbursement for services than evidence that use of those services yields improved outcomes [8]. Indeed, high utilization of services has been associated in some settings with *worse* mortality outcomes and no improvement in satisfaction compared to more efficient utilization [9]. Given this uncertainty and variation in management of a disease with high public health significance for an aging population, a recent Institute of Medicine (IOM) report recently included treatment for localized prostate cancer among the 25 most important topics for comparative effectiveness research (CER) [10].

Even defining CER is not without controversy. The IOM report summarized six extant definitions from such diverse bodies as the Congressional Budget Office and the American College of Physicians. The report further accepted that ambiguity exists in defining CER depending on "what is 'compared,' how one defines 'effectiveness,' and what constitutes 'research'" [10]. Indeed, as available funding for CER has rapidly expanded in recent years, particularly through the 2009 American Recovery and Reinvestment Act (ARRA), a somewhat cynical viewpoint might see "rebranding" of exist-

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ing efforts in outcomes research and other domains in order to gain access to these funds. The IOM report itself defined CER as "a strategy that focuses on the practical comparison of two or more health interventions to discern what works best for which patients and populations" [10]. This definition clearly remains broad, but emphasizes direct comparison, assessment of "real-world" impact of competing interventions, and emphasis on population—rather than patient-level outcomes—that is, *effectiveness* rather than *efficacy*.

## Randomized Trials in Localized Prostate Cancer

Randomized controlled trials (RCTs) for men with localized prostate cancer remain the gold standard for determination of efficacy. However, they are difficult to fund and accrue given the high costs associated with long follow-up, as well as patient and/or clinician biases a priori in favor of one approach or another. While many RCTs have been completed within modalities—particularly EBRT (e.g., high- vs. low-dose, short- vs. long-term neoadjuvant ADT)—summarizing the total history of RCTs comparing *different* treatment modalities for localized prostate cancer is unfortunately easy, as few such trials have been completed successfully.

A small, older study randomizing men between ORRP and watchful waiting reported median overall survival of 10.6 years for surgery patients vs. 8 years for watchful waiting [11]. The larger Scandinavian Prostate Cancer Group-4 (SPCG-4) trial, which also randomized men between ORRP and watchful waiting, was recently updated. The relative risk for cancer-specific mortality (CSM) at 10 years was 0.62 (95 % CI 0.44–0.87, $p=0.01$) for surgery vs. watchful waiting. Accrual was completed in the 1990s; most men had clinically detected tumors and would be considered intermediate risk by contemporary standards. The bulk of the benefit was seen for men under 65 years of age at diagnosis [12]. The study was prescient for its era in including prospective HRQOL assessment; perhaps not surprisingly, urinary incontinence and erectile dysfunction were more common after surgery, whereas obstructive urinary symptoms were worse on watchful waiting—though there was little difference in overall well-being between the two arms [13].

Two recent trials randomized patients to PADT monotherapy with or without EBRT. The first randomized patients with cT3N0M0 disease to flutamide with or without radiation therapy. The study found a strong benefit for the combination treatment arm [14], though flutamide monotherapy would generally be considered inadequate therapy by contemporary standards, particularly for locally advanced disease. The other found that with 6 years follow-up, CSM was nearly twice as high among men receiving PADT (medical or surgical castration) compared to those receiving ADT with EBRT [15].

Radical prostatectomy and radiation therapy are the most commonly employed local treatments for prostate cancer. To date, however, the only completed randomized trial comparing these modalities was a small ($n=106$) study reported over 25 years ago, which found a higher rate of clinical progression at 5 years following EBRT compared to ORRP (39 % vs. 14 %, $p=0.04$) [16]. This result clearly would not be considered sufficient to inform contemporary practice. Other trials have been attempted. The Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT), for example, inaugurated in 2002, intended to randomize men to ORRP vs. brachytherapy. Despite a standardized 90-min multidisciplinary patient educational session intended to facilitate accrual, however, only 56 patients accrued at 31 centers over 2 years, and the study was closed early [17].

Three major randomized trials in localized prostate cancer are ongoing. The Prostate cancer Intervention Versus Observation Trial (PIVOT) study randomized men between ORRP and watchful waiting. Though successfully accrued, the study still exemplified the difficulties in localized prostate cancer trials: the investigators screened 13,022 men at 52 sites over 7 years to identify 5,023 eligible men, of whom 731 (14.5 % of eligible patients, 5.6 % of those screened) agreed to participate, for an average of two patients per site per year. Accrued men were older, more likely to be African-American, and had lower-grade disease compared with those eligible but declining participation [18]. Preliminary results presented at the 2011 American Urological Association meeting found equivalent survival for men with low-risk disease and a strong survival benefit for surgery for men with high-risk disease.

The Surveillance Therapy Against Radical Treatment (START) trial, sponsored jointly by the National Cancer Institute of Canada and four US cooperative oncology groups, is currently randomizing patients to surveillance vs. the patient's choice of surgery or radiation. Finally, the Prostate testing for cancer and Treatment (ProtecT) study is the only ongoing randomized trial including both surgery and radiation arms. The study has randomized men in the United Kingdom to prostatectomy, EBRT, or watchful waiting, with notably greater success in accrual attributed to a complex intervention aimed to increase patient acceptance of randomization [19]. Results will require years, however, to reach maturity. No prior or ongoing randomized trials have compared PADT to radical prostatectomy or EBRT monotherapy, nor either radiation or PADT to active surveillance.

The barriers, then, to RCT accrual and completion for localized prostate cancer are clearly substantial and unlikely to abate. Moreover, even when RCTs are completed successfully, questions of external applicability—as with the SPIRIT—may remain. Thus, as noted above, RCTs assess *efficacy* of an intervention in a controlled setting but not necessarily *effectiveness* in real-world practice [10]. With RCTs

thus unlikely to settle the question of optimal treatment for localized prostate cancer—at least not in the short-term—useful results may be gained from CER studies based on retrospective study of prospectively accrued registries and other high-quality sources of data. Although there are unique challenges specific to prostate cancer CER, recent analyses are beginning to provide insight and, at least preliminarily, answers.

## Challenges for Prostate Cancer CER

### Biochemical Recurrence

Given the prolonged natural history of prostate cancer, relatively few studies report distal clinical endpoints such as metastasis, CSM, and all-cause mortality (ACM). Most instead rely on surrogate endpoints based on biochemical failure—that is, PSA-defined recurrence. While these endpoints are frequently useful for comparing short-term outcomes among cohorts undergoing the same treatment, they cannot be used to compare different modalities. The first problem with biochemical endpoints is the multiplicity of definitions: as of the mid-2000s, there were 53 different definitions of biochemical failure following prostatectomy, and 99 definitions of failure following radiation therapy [20]. Another problem is variability of natural history after progression: in one surgical series, for example, among men failing after surgery by the definition of a single PSA >0.2 ng/ml, the likelihood of cancer-specific mortality 10 years later ranged from 2 to 99 %, depending in this case on the Gleason score, time to recurrence, and PSA doubling time [21].

Perhaps most importantly, from the standpoint of CER research, however, are substantial variation in the biological impact of various treatments, the expected time course of the PSA response, and the intent of the definitions of failure. With prostatectomy, the prostate is removed—presumably in its entirety—and the PSA should be undetectable within 6–8 weeks postoperatively and never rise. Surgical definitions, usually based on absolute PSA thresholds (most commonly between 0.2 and 0.4 ng/ml), are meant to detect any sign of recurrence and in many cases to identify men early for potential salvage therapy. Radiation, on the other hand, may be administered over a period of months and exerts its biological effect over further months and years; the PSA may take years to reach its nadir. The commonly used radiation definitions (e.g., the American Society for Therapeutic Radiation and Oncology [ASTRO] definition of three consecutive rises above the nadir, back-dated to the midpoint of the nadir and first rise [22]; and the "Phoenix" definition of a rise of 2 ng/ml above the nadir with no backdating [23]) reflect this biology. The Phoenix definition in particular was intended to predict subsequent mortality with the greatest accuracy, not to identify all persistent disease as is the intent of the surgical definitions.

By nature of the intent and structure of these definitions, it is much "harder" to fail by a postradiation definition than by a postsurgical definition, so survival curves following radiation will tend to be artifactually right-shifted compared to those for surgical patients. The radiation definitions, by requiring more follow-up time and PSA values, are also more prone to right censoring. This phenomenon was well characterized in a pair of studies which applied the radiation definitions to a surgical cohort. Applying the original ASTRO definition to a surgical cohort rather than the >0.2 ng/ml threshold definition increased the 10- and 15-year recurrence-free survival (RFS) rate from 76 and 68 %, respectively, to 88 and 87 % [24]. In the second study, applying the Phoenix definition rather than the >0.2 ng/ml threshold increased the 10- and 15-year RFS rates from 81 and 78 % to 89 and 84 % and moreover shifted the median time to recurrence from 2.8 to 7.9 years [25].

### Risk Adjustment

In light of the tremendous prognostic heterogeneity of prostate cancer, any meaningful CER efforts must account for differences in disease-risk characteristics across treatment modalities [7]. Prostate cancer risk assessment has been covered in detail in the preceding chapters of this book. A few points particularly relevant to CER merit emphasis here. First, over 100 nomograms and other risk instruments have been published for prostate cancer [26]. Most of these intended for use with localized disease have been shown only to predict biochemical recurrence which, as noted above, is not necessarily useful for CER between modalities. There are a few notable exceptions which have been shown to predict metastasis and mortality [27–30]. Of these, only the D'Amico risk groups and the UCSF Cancer of the Prostate Risk Assessment (CAPRA) have been validated across multiple treatment modalities [28, 29]. Overall, instruments based on multivariable regression models, such as nomograms and the CAPRA score, have greater discriminatory accuracy than risk groups.

Furthermore, most risk instruments have not been even internally validated, and relatively few have been externally validated [26]. Some nomograms which perform well in an academic setting have good discriminatory accuracy but poor calibration when applied in broader community settings [31]. Finally, application of nomograms or other tools must recognize the potential impact of secular changes in risk assessment variables such as stage and grade. The clinical staging system for prostate cancer, for example, has varied over the years in terms of how much detail is reported on digital rectal exam and/or local imaging findings. It is relatively easy to

recode men from one staging system to the next, with the primary exception that T2a patients in the 1997 system could be T2a or T2b in the 1992 or 2002 systems. In any case, clinical stage is not a major driver of outcomes with adjustment for other risk variables [32].

Of potentially greater concern is variation in the Gleason grading system. Grading standards have evolved with time [33], with the primary result that Gleason patterns 1 and 2 are rarely assigned in modern practice, and many cases graded in the 1990s would be upgraded if regraded to contemporary standards [34]. This concern is particularly relevant to mortality studies, since in general those men at risk of prostate cancer mortality are those diagnosed years ago, and most research groups do not have the resources to systematically reread hundreds or thousands of pathology cases.

## HRQOL Definitions

The complexity of HRQOL assessment in prostate cancer is discussed in depth in Part VII more particularly Chap. 84 of this book. Again, a few points germane to CER bear emphasis here. Apparent HRQOL outcomes may vary tremendously based on methods of assessment: reported by whom, using what standards, how long after treatment, controlled for which baseline characteristics, etc. Thus, reported rates of incontinence after surgery, for example, vary from 2.5 to 87 % [35]. Likewise, reported rates of erectile dysfunction range from 14 to 98 % after radiation and from 18 to 86 % after surgery [36]. There is strong evidence, at least, that HRQOL outcomes must be patient-reported, rather than clinician-reported or derived from administrative coding data [37, 38].

Moreover, HRQOL should be assessed with standardized, validated questionnaires specifically intended to capture the impact of different modalities [39]. General HRQOL (i.e., overall physical and mental functioning) tends not to vary substantially across local treatment modalities, especially with adjustment for baseline characteristics [40]. ADT, however, may affect these domains, as well as overall vitality; a specific "hormonal function" domain is incorporated into some questionnaires [39]. Other disease-specific HRQOL domains—for example, urinary, sexual, and bowel function—will clearly vary by treatment. However, different questionnaires may give a different impression of HRQOL. Urinary function, for example, is affected differently by different modalities, so assessing only stress incontinence, for example, would underestimate the impact of radiation therapy. Indeed, urinary urge incontinence has been shown to affect overall perception of urinary HRQOL to a greater extent than stress incontinence per se [41]. Finally, translating varying decrements in HRQOL domains consistently to health state utilities for formal cost-effectiveness studies is far from straightforward, and while some investigators have published such conversions [42], there has been little formal validation of these, and no consensus as to their application yet exists.

Adjusting for baseline function is critical—older men more likely to receive EBRT are more likely to have erectile dysfunction before treatment, for example. Longitudinal assessment is also important: surgery tends to cause HRQOL impairment followed by recovery, whereas radiation may be more likely associated with delayed decrements in function [2, 37]. Thus, an analysis at 6 months posttreatment might favor EBRT, and follow-up at 5 years may favor surgery. Neither alone is adequate; while long-term outcomes are most important, substantial short-term impairment is likewise an important consideration. Finally, multimodal therapy—adding ADT to radiation, or EBRT to surgery, for example—does entail additional HRQOL risk [40]. Thus, an analysis of HRQOL outcomes, for example, of EBRT for high-risk disease, in which neoadjuvant ADT is clearly indicated, cannot discount the HRQOL impact of the ADT.

## Sources of Data

Important analyses of outcomes across treatments—particularly focusing on treatment vs. conservative management and on in the impact of PADT—have been gained from research based on large data sources such as Surveillance, Epidemiology, and End Results (SEER) and Medicare [43, 44]. However, Medicare includes minimal clinical detail, and until recently SEER included clinical stage and 3-level tumor grade, but not the more informative Gleason grade, pretreatment PSA, or treatment details. SEER and Medicare data are both valid population-based samples, but Medicare is by definition restricted to men over 65, and SEER is not fully representative of the USA geographically. These same limitations—together with the fact that much prostate cancer treatment is administered in the outpatient setting—have restricted the relevance to prostate cancer CER of other administrative databases such as the Nationwide Inpatient Sample.

An important extension from SEER was the Prostate Cancer Outcomes Study (PCOS), which prospectively followed 5,672 men identified from the SEER registries in 1994–1995, including patient-reported HRQOL assessment [45]. This was a population-based sample followed longitudinally, though the cohort itself is by now somewhat dated as treatments have evolved in the subsequent 15 years. A similar registry-based study has been undertaken in New South Wales, Australia, and recently reported [46].

Many academic departments accrue their treated patients to local registries, some of which include thousands of men. Only in the minority of such departments, however, do these registries extend far enough into the past to analyze

long-term outcomes, and in very few cases do institutions track large numbers of men with prostate cancer uniformly and with good follow-up across urology, radiation oncology, and medical oncology practices. Multi-institutional disease-specific registries are therefore emerging as an increasingly valuable source of CER data [47]. The Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROSTQA) consortium, for example, enrolled 1,201 men undergoing RP, EBRT, or brachytherapy at nine US academic medical centers between 2003 and 2006 and to date has focused on comparative HRQOL outcomes across treatments [2]. The Spanish Multicentric Study of Clinically Localized Prostate Cancer is a similar consortium of ten hospitals in Spain which enrolled 435 men undergoing the same three treatments between 2003 and 2005 [3].

The Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE™) is a national disease registry accruing men urology practices, primarily community-based, across the USA. Participating urologists recruit men consecutively at diagnosis, regardless of treatment selection. Patients are treated per their clinicians' usual practices and are followed until death or withdrawal from the study. Clinicians report clinical data and follow-up, and patients directly report their HRQOL outcomes and health care resource utilization. Nearly 14,000 men have enrolled since 1995, and accrual continues [48]. Each of these data sources has its strengths and limitations; however, they are frequently complementary, and in aggregate they form the core of a growing body of high-quality prostate cancer CER research.

## Outcomes

### Surgical Modalities

As RARP gains an ever-increasing share of prostatectomy procedures in the United States and worldwide [49], the efficacy of this procedure relative to ORRP has become an increasingly important question. A large, recent systematic review identified 37 studies comparing ORRP, LRP, and RARP. These studies included one RCT of ORRP vs. LRP but none including RARP. The review authors found few differences among the approaches to prostatectomy in terms of oncologic or HRQOL outcomes, concluding, perhaps charitably, that the quality of existing comparative studies is "not excellent" [50].

A recent single-center study compared intermediate-term HRQOL outcomes, regret, and satisfaction between ORRP and RARP patients. There were no statistically significant differences between the two approaches for any HRQOL domain. However, RARP was associated with significantly greater decisional regret and lower satisfaction than ORRP even with adjustment for HRQOL scores [51]. This phenomenon presumably reflects higher expectations among those men electing RARP, which in turn may be driven by multiple factors including the inherent appeal of novel technology, insufficient clinician counseling, and/or direct-to-consumer advertising by the robot manufacturer and other sources of media buildup.

One paper published in 2009 in *JAMA* gained a great deal of lay press attention. This study aimed to compare short-term complications, intermediate-term HRQOL outcomes, and oncologic outcomes between ORRP and LRP/RARP using the SEER-Medicare database [52]. Because Medicare does not distinguish LRP from RARP, these modalities were combined in the analysis. The authors reported a >4-fold increase in use of LRP/RARP from 2003 to 2007. In general, the LRP/RARP patients were slightly more likely than ORRP to be Caucasian and much more likely to be well-educated and high-income earners. The analysis confirmed shorter length of stay and lower transfusion rates among the LRP/RARP patients, as well as fewer respiratory complications and anastomotic strictures. Rates of "other" genitourinary complications (including, e.g., cystitis, pyelonephritis, and bladder/ureteral injuries) were higher for LRP/RARP patients, but there was no detailed description of complications within the category.

Tumor recurrence—defined only by application of secondary radiation and/or hormonal therapy—was not significantly different between LRP/RARP and ORRP, though follow-up was quite short for most cases in the cohort. The paper drew the controversial conclusion that men undergoing LRP/RARP had more incontinence and erectile dysfunction than those undergoing ORRP. In fact, there was no statistically significant difference in subsequent procedures for either domain. LRP/RARP was associated with higher encounter form *coding* rates for incontinence (OR 1.3, 95 % CI 1.1–1.6) and impotence (OR 1.4, 95 % CI 1.1–1.7) compared to ORRP. However, as noted above, HRQOL assessment for prostate cancer is complex and must be multidimensional and patient-centric.

Litwin et al. demonstrated a decade earlier that physician report inadequately captures HRQOL outcomes after prostate cancer treatment [53]. A more recent study confirmed that in contemporary practice, direct patient report is no less critical [38]. Multiple biases bear heavily coding practices for HRQOL. Fewer than half of new prostate cancer diagnoses are associated with documentation of baseline sexual function in the chart [54]; the proportion with baseline erectile dysfunction whose billing forms include a secondary ICD-9 code to indicate this is presumably much lower. In follow-up, moreover, the decision to code "incontinence" or "impotence" may reflect only the loudness of a patient's dissatisfaction with the outcome rather than the actual degree of impairment (as per the regret study noted above [51]).

Much of the literature to date has compared surgeons' early experience with RARP to established outcomes following ORRP. Multiple papers have examined the impact of surgical volume [55] and learning curve [56] on outcomes of prostatectomy. One recent study suggested that the learning curve may be steeper for LRP than for ORRP [57], but none has compared curves for RARP to other surgical modalities. Indirectly addressing this question, a recent literature review restricted only to reports of high-volume ($N \geq 250$) cohorts found better surgical margin, continence, and potency rates for RARP compared to LRP or ORRP [58]. Ultimately, longer follow-up and prospective comparison studies in cohorts established among surgeons experienced in both approaches will be required to quantify precisely what the benefit of robot assistance may be for prostatectomy care. Indeed, in addition to listing localized treatment for prostate cancer among the top 25 priority areas for future research, the IOM CER report specifically listed ORRP vs. RARP again on a list of 100 research priorities [10]. An ongoing collaborative project between CaPSURE and PROSTQA is funded to explore HRQOL outcomes and cost-effectiveness between open and robot-assisted surgery.

It should be noted that multiple contemporary studies of RPP have suggested outcomes at least comparable to ORRP or RARP [59–61]. However, these have focused on perioperative variables and short-term complications; data comparing RPP to other approaches in terms of long-term oncologic and HRQOL outcomes are very sparse, reflecting the relatively small number of surgeons performing RPP in contemporary practice. Indeed, the market share of RPP has fallen further from already-low levels with the advent of robot-as sisted approaches to less than 4 % of cases by 2005 in a large private insurance database [49] and less than 2 % in SEER-Medicare by 2007 [62].

## Radiation Modalities

Contemporary photon-based EBRT is administered as 3DCRT or IMRT; non-CT guided planning is no longer considered standard of care for prostate cancer [63]. As of 2001, only 5.4 % of cases were planned without CT [54], and presumably this number has fallen further in the subsequent decade. In general, higher doses of radiation have been associated with improvement in recurrence-free survival [64, 65], but have not been demonstrated to improve likelihood of CSM or ACM, even at nearly 9 years median follow-up [4, 65]. A recent meta-analysis identified seven RCTs reporting a total of 2,812 men randomized to high-dose vs. conventional-dose EBRT, again finding improved biochemical recurrence rates for high-dose treatment, but no differences in CSM or ACM. This study found higher rates of gastrointestinal toxicity among the high-dose therapy group. Biochemical benefits were seen across risk strata and appeared to associate linearly with radiation dose [66].

With specific regard to the question of 3DCRT vs. IMRT, a recent systematic review identified only eight published studies comparing the two modalities, six of which addressed localized disease [67]. Only two of these reported contemporary patients treated at the same hospital [68, 69]. In general, IMRT was associated with reduced gastrointestinal toxicity than 3DCRT. To the extent that IMRT facilitates dose escalation, it was associated with reduced biochemical recurrence, possibly at the price of increased urinary toxicity. Neither improved recurrence rates nor increased toxicity was noted consistently across studies. The magnitude of recurrence benefit was highly dependent on definition of recurrence (ASTRO vs. Phoenix) [67].

Fewer studies have compared brachytherapy to EBRT. In some, brachytherapy has been shown to yield superior outcomes compared to dose-escalated EBRT in terms of biochemical recurrence, with higher late urinary toxicity but lower late bowel toxicity [70–72]. Another study showed equivalent or better outcomes at over 5 years follow-up, depending on definition of biochemical recurrence, for brachytherapy patients compared to those undergoing either photon- or proton-based EBRT [73]. Others have demonstrated dosimetric and metabolic benefits for brachytherapy over IMRT [74, 75]. Many men are in fact treated with combination EBRT+ brachytherapy; a systematic review found a survival benefit for this combination over EBRT alone [76]. Combination therapy has a greater impact on HRQOL, especially when combined with ADT [40, 77]. Conventional (low-dose rate) and HDR brachytherapy are often considered interchangeably in the literature, but in fact there exist minimal data comparing the two modalities directly [78].

The literature is replete with articles arguing the benefits of proton-beam therapy over photon-based radiation based on radiation physics, anticipated dosimetry, and related endpoints. No paper yet published, however, has shown any benefit in terms of either HRQOL or cancer recurrence. Moreover, even based on an extrapolated benefit based on theoretical increases in dose, proton-beam treatment has been shown not to be cost-effective [79].

Additional detailed reviews of both surgical and radiation treatment modality outcomes will be presented in section "Surgery versus radiation".

## Surgery Versus Radiation

Several studies have compared HRQOL outcomes across various modalities. In a variety of clinical settings and cohorts, findings have been relatively consistent. Surgery is consistently associated with greater likelihood of stress urinary incontinence, but less irritative and obstructive

symptoms, than other modalities. Radiation, in turn, tends to cause more irritative symptoms, particularly in men with concomitant symptomatic benign prostatic hyperplasia [2, 3, 37, 46, 80, 81]. Bowel symptoms are essentially unique to patients treated with radiation, while those who receive neoadjuvant and/or adjuvant ADT face additional side effects and HRQOL impact [2, 3, 40, 46, 81].

Erectile function is generally impaired after surgery followed by a period of recovery lasting up to 2 years or longer. There is less initial impact following radiation therapy, but function may decline over time; with longer follow-up, differences in sexual function by treatment selection tend to attenuate [3, 37, 46, 80, 81]. Adding ADT to radiation further impacts sexual function, though this impact tends to be temporary [77]. It is important to recognize that sexual HRQOL is multidimensional, and sub-domains beyond erectile function per se should be considered. For example, ADT has a pronounced effect on libido, and prostatectomy will permanently eliminate ejaculation in all men. Brachytherapy may also impact ejaculatory and orgasm function, though usually to a lesser extent than surgery [82]. A point worth emphasis is that general—rather than disease-specific—HRQOL, reflecting overall physical and mental function, if often of greatest importance to patients, and tends to differ little across local treatment options [40, 83].

As described above, differences in definitions of recurrence for surgical and radiation patients do not allow meaningful comparisons to be made among the modalities based on biochemical definitions of recurrence. However, as a number of cohorts are accruing prolonged follow-up, sufficient numbers of men are starting to reach metastasis and mortality endpoints to allow CER studies between surgery and radiation using these endpoints.

A recent analysis from CaPSURE compared mortality outcomes for men undergoing ORRP ($N=5{,}066$), EBRT ($N=1{,}143$), or PADT ($N=1{,}329$). At mean 6.8 years follow-up, 1,293 men (17.2 %) died, a minority of whom (226, 3.0 %) died of prostate cancer. With adjustment for age, year of treatment, and disease risk using a well-validated preoperative nomogram [84, 85], the hazard ratio (HR) for CSM relative to ORRP was 2.2 (95 % CI 1.5–3.2) for EBRT and 3.2 (95 % CI 2.2–4.8) for PADT. Adjusting via CAPRA score [29, 86] yielded very similar results, as did analysis via competing risks analysis rather than adjusted Cox regression. The HR for ACM relative to ORRP was 1.6 (95 % CI 1.3–1.9) for EBRT and 2.3 (95 % CI 1.9–2.7) for PADT [87].

A key finding from this study was that the CSM differences across treatments were minimal for men with low-risk disease—very few of them died of prostate cancer regardless of treatment decision. On the other hand, as disease risk increased, the difference across treatments rose progressively and substantially. Reflecting a breadth of community practice, there was variation among the CaPSURE EBRT patients in radiation dose and technique and in application of secondary and salvage therapy. Use of neoadjuvant ADT associated tightly with disease risk; with increasing risk, likelihood of ADT use rose consistently. As such, ADT use did not independently predict outcomes.

A large study from Memorial-Sloan Kettering Cancer Center (MSKCC) also compared outcomes between ORRP ($N=1{,}318$) and EBRT ($N=1{,}062$). In this study, all EBRT was given as IMRT with a dose of at least 81 Gy. In this study, 56 % of men undergoing EBRT received neoadjuvant ADT, and as in the CaPSURE study, there was some variability in use of salvage therapies. On multivariable analysis, again controlling for disease risk, age, and year of treatment, the HR for CSM for EBRT relative to ORRP was 3.1 (95 % CI 1.2–8.3). The effect was again persistent across multiple risk-adjustment approaches [88]. As in the CaPSURE study, use of ADT with EBRT did not significantly affect the outcomes, nor did use of salvage therapy. Of note, longer-term neoadjuvant ADT that was given in either the CaPSURE for MSKCC cohorts has been associated with improved survival, but the increment is modest, seen only for high-risk disease, and not validated in all trials [89, 90]. Also as in the CaPSURE study, the differences in the MSKCC study in outcomes for men with low-risk were minimal, but rose progressively with increasing disease risk [88].

A reflexive critique of both these analyses is that despite best efforts at careful risk adjustment, unmeasured variation in disease risk between surgery and radiation patients may explain the results. Therefore, as a means of quantifying the degree of unmeasured confounding which would have to be assumed to invalidate the results, the CaPSURE study also included a sensitivity analysis in which the nomogram scores for ORRP patients were artificially increased by successive five-point increments until the mortality difference between ORRP and EBRT was no longer statistically significant. Scores for ORRP had to be increased by 20 points before the difference lost statistically significance; thus, a patient undergoing EBRT, for example, with a Gleason 3+3, PSA 4.1 ng/ml, stage T1c tumor would have to have the same true risk as a surgical patient with Gleason 3+4, PSA 9.2 ng/ml, stage T2a tumor. Given the extensive validation the prediction models have undergone previously, such a substantial and consistent misclassification seems very unlikely. Of note, the direction of survival benefit for ORRP vs. EBRT did not actually flip until the nomogram scores for ORRP patients were raised by 30 points [7]. While there may be unmeasured confounding in any retrospective analysis, the likelihood of such pervasive and severe confounding across both large, complementary studies is very unlikely.

Neither the CaPSURE study nor the MSKCC study included a brachytherapy arm. A final study recently presented but not yet published, reporting data from Cleveland

Clinic and Barnes-Jewish Hospital, is the first to include brachytherapy ($N=1,719$) alongside surgery ($N=6,493$) and EBRT ($N=2,260$). With propensity score-based adjustment for disease risk, age, and comorbidity, this study found increased ACM on competing risks analysis relative to ORRP for EBRT (HR 1.6, 95 % CI 1.4–1.9) and brachytherapy (HR 1.7, 95 % CI 1.4–2.1). CSM was higher relative to ORRP for EBRT (HR 1.6, 95 % CI 1.0–2.6) but not brachytherapy (HR 1.1, 95 % CI 0.5–2.6) [91].

## Active Surveillance

Though active surveillance remains an option used in a small minority of men with prostate cancer [7, 92], it is supported by a growing number of mature academic cohorts, and the preponderance of evidence supports its safety for many men with low-risk tumors [93–96] and even carefully selected men with intermediate-risk disease [97]. The SPCG-4 study referenced above [98], as well as a large SEER-Medicare study examining PADT vs. expectant management [43], among others, supports expectant management for older men. Another SEER-Medicare, conversely, found that even older men receiving surgery or radiation had better survival than those not treated [44]. However, these studies—as well as the forthcoming PIVOT study described above [18]—were all more reflective of an older concept of watchful waiting rather than contemporary active surveillance. The latter term includes careful serial assessments of PSA levels, repeat biopsies, and other tests intended to identify early signs of progression and implies treatment with intent to cure at first sign of progression.

A recent comparative study based on a Markov model comparing ORRP, IMRT, brachytherapy, and active surveillance for men with low-risk disease, surveillance was associated with the greatest quality-adjusted life expectancy [99]. Sensitivity analyses demonstrated, however, that the outcomes were highly dependent on health state utilities, which, as noted above, have not been well-validated. While active surveillance will doubtless play a greater role in the management of low-risk prostate cancer in the future, ongoing prospective studies will help determine which patients are ideal candidates for this approach and must compare it directly to immediate treatment in terms of both oncologic and HRQOL outcomes.

## Practice Patterns

Absent clear guidance regarding ideal treatment, management for localized prostate cancer has varied substantially over time and across regions and practice sites. The Dartmouth Atlas of Health Care investigators, for example, analyzed the mid-1990s Medicare data on the ten most commonly performed surgical procedures in the USA, including ORRP. Among the ten procedures, ORRP was characterized by the greatest local variation: over 12-fold greater than the procedure (hip fracture repair) with the least variation and over 8-fold greater than colectomy for colon cancer. With adjustment for disease prevalence, the absolute rates of ORRP varied by a factor of nearly ten, from 0.5 to 4.7 per 1,000 Medicare enrollees [100].

A recent study from CaPSURE documented updated trends in community-based prostate cancer management across 30 practice sites. Treatment varied with disease risk: low-risk men were most likely to receive prostatectomy; with increasing risk, use of prostatectomy fell, EBRT increased, and PADT increased substantially. Over time, use of active surveillance first fell then began rising in the 2000s, though still accounted for only 8.5 % of men with low-risk disease in 2004–2007. Use of brachytherapy peaked in the early 2000s then fell. Use of PADT among men with intermediate- and high-risk disease increased over the past 15 years [7]. What is striking is how dissonant these findings are with the emerging CER studies described above, which would support a greater role for surveillance for lower-risk disease and surgery or combined modality therapy for higher-risk disease.

These patterns may in part reflect an age bias in treatment. Men diagnosed with high-risk disease are more likely to be older than those with low-risk disease. Multiple studies have found that older men are less likely to receive potentially curative treatments with surgery or radiotherapy, regardless of disease risk and comorbidity/life expectancy [101–105]. Men under 60 years of age are 25 times more likely to receive surgery than those over 70 [106, 107]. A substantial proportion of men over 75 with high-risk disease are undertreated, and a majority in fact never receive curative therapy for their prostate cancer [104, 108, 109]. The clinical impact of such age bias is substantial: within 5–10 years of follow-up for men over 75 with high-grade disease who are not treated with local therapy, cancer-specific mortality reaches 20 % [104, 110].

The CaPSURE treatment patterns study found substantial variation across clinical practice sites for all treatments. Use of prostatectomy varied from 11 to 82 % [7], nearly as great a range as the tenfold variation observed in the Dartmouth Atlas study [100]. The proportion of variation attributable to practice site alone after control for patient and disease characteristics ranged from 13 % for PADT to 74 % for cryotherapy [7]. Another recent study focused on the use of ADT using the 1990s data from the SEER-Medicare. The investigators performed analyses for "evidence-based" ADT—that is, therapy given together with EBRT for high-risk disease—and "uncertain-benefit" therapy, including all other uses. For the evidence-based setting, they found that

disease characteristics accounted for 6.6 % of variation, other patient characteristics explained 7.3 %, and the treating urologist accounted for 25.4 %. For the uncertain benefit setting, the corresponding proportions were 5.3, 5.0, and 22.7 %. Over time, the proportion of variation attributable to the urologist appeared to be increasing [6].

Another recent study explored pretreatment consultation patterns as another source of variance [105]. In a SEER-Medicare study building on prior work from a smaller physician-based sample [111], the authors found substantial variation in likelihood of a visit with a radiation oncologist and/or medical oncologist prior to treatment. Offering referral to a radiation oncologist is a candidate indicator of high-quality prostate cancer care [63]; in this study, just under half the men did in fact see a radiation oncologist. An important but unanswerable question is the proportion of men who were *offered* referral but declined. The factors associated with referral to a radiation oncologist notably did not include higher-risk disease features. Among men who saw only a urologist, 34 % received prostatectomy, 34 % watchful waiting/active surveillance, 27 % PADT, and 5 % radiation therapy. Among those seeing a radiation oncologist as well as a urologist, the likelihood of receiving radiation rose to 83 %. Additional consultation with a medical oncologist shifted the distribution only slightly.

Of course, most men receiving radiation therapy will see a radiation oncologist first, so these data do not indicate a causal relationship between consultation and treatment. Particularly notable is the fact that use of surveillance even among men in their 80s or older fell from 45.3 % among those seeing a urologist only to 8.2 % among those also seeing a radiation oncologist. Given that most men in SEER have low-risk disease characteristics [112], this trend confirms pervasive overtreatment, worsened in particular by consultation with radiation oncologists. Conversely, while relatively few men saw primary care providers between diagnosis and treatment, those that did were much more likely to be followed expectantly, less likely to receive prostatectomy, and much less likely to receive radiation therapy [105]. In addition to referral patterns, of course, multiple nonclinical concerns—financial, legal, logistical, psychological, and others—weigh on decision-making and contribute to both treatment uncertainty and resulting variation in care.

## Cost-Effectiveness

Even while the comparative efficacy of treatment options for prostate cancer remains controversial, there is no argument that there are profound differences among treatments in terms of costs of care [113, 114]. One study using 2002–2004 costs estimated total costs over the first 5 years of treatment to be $32,135 for watchful waiting, $35,143 for brachytherapy, $36,888 for ORRP, $43,108 for cryotherapy, $59,455 for EBRT, and $69,244 for PADT [114]. The data for this study were collected before RARP and IMRT gained popularity and before Medicare substantially reduced reimbursements for PADT in 2005.

It is important to acknowledge important differences in the economic implications of new technologies as they are adopted. In the USA, the increased costs of laparoscopic and robot-assisted surgery, in particular, are absorbed by hospitals and are not reimbursed at higher rates than open surgery. IMRT and proton-beam therapy, on the other hand, are very highly reimbursed by Medicare and other payors.

One group estimated median hospital direct costs for prostatectomy to vary from $4,437 for ORRP to $5,687 for LRP and $6,752 for RARP [115]. An interesting follow-up study found that for obese men, the costs for ORRP and LRP rose substantially but those for RARP did not [116]. These figures do not reflect the $1.5M purchase price and annual maintenance contract costs for the robot itself; these would add $2,698 per case assuming 126 cases per year and 7-year amortization [115]. Clearly, with higher annual hospitals volumes and longer service life, this figure would fall—but conversely, for hospitals which purchase a robot but use it infrequently, the per-case cost will be very high. Other estimates of gross costs have ranged from $5,554 to $10,704 for ORRP and $7,280 to $10,047 for RARP [117].

Direct treatment costs for 3DCRT and IMRT are estimated to range from $10,900 to $27,357 and $33,837 to $52,170, respectively [67]. Another analysis calculated total costs over 15 years of $36,808–$39,355 for IMRT and $63,511–$64,989 for proton-beam therapy. Capital costs for advanced EBRT facilities dwarf those of surgical robotic systems: by one recent estimate €23.4M (US$31.8M) for a new photon facility and €94.9M (US$129.0M) for a new proton facility [118]. The financial considerations may vary greatly across different health-care systems. A recent Japanese study, for example, found that ORRP and LRP yielded a net hospital profit, respectively, of ¥61,001 (US$732) and ¥75,672 (US$902) per patient. For 3DCRT, the profit was ¥168,727 (US$2,024), whereas for brachytherapy, low-dose-rate and high-dose therapy resulted in profit of ¥199 (US$2) and *loss* of ¥654,016 (US$7,848), respectively [119].

Formal cost-effectiveness comparisons in prostate cancer are challenging due both to the complexities of defining and measuring oncologic and HRQOL outcomes for prostate cancer, as discussed above, and to weak associations among costs, charges, and collections for prostate cancer care. Several efforts in this area are ongoing, however, using both literature-based estimates of costs and outcomes and direct analyses of data from large registries, with important findings expected in the coming years. However, regardless of published analyses, current financial structures in health-care

delivery offer little to no motivation for providers to pursue cost-effective care. Indeed, payment incentives often reward overutilization of interventions or, as is clear from the discussion above, heavily favor one modality over another in the absence of evidence of differences in outcomes.

A recent study, for example, demonstrated that hypofractionating EBRT to 20 treatments over 5 weeks rather than the typical 40 treatments over 8 weeks yielded *improved* biochemical outcomes and no difference in late toxicity [120]. This protocol, if validated, would improve both outcomes and convenience for patients—but as long as payment is organized on a per-fraction rather that per-patient basis, providers will have a continued incentive to maximize the number of fractions. Likewise, despite outcomes for brachytherapy which appear to be consistently as good or better than EBRT for low- and intermediate-risk disease, the lower reimbursement for brachytherapy compared to IMRT will continue to drive utilization of the latter. For another example, as noted above, RPP might in fact be a more cost-effective approach to prostatectomy than other modalities for some men, yet it is rarely used in practice [62].

## Conclusions

The challenges to high-quality CER for prostate cancer detailed in this chapter are clearly substantial. Indeed, prostate cancer is likely one of the most difficult areas in health care for this type of research—which only highlights the importance of ongoing efforts. A broad consensus on management strategies for this disease is not likely to be reached in the short-term. However, emerging evidence supports a few general conclusions:

- Prostate cancer is extremely heterogeneous in its likelihood of progression to clinical symptoms or to mortality. Underappreciation of this heterogeneity and/or inconsistency in application of risk stratification strategies has led to widespread overtreatment of low-risk disease and—less commonly but not less importantly—undertreatment of high-risk disease, particularly among older men.
- Randomized trials between surgery and radiation are lacking. However, emerging studies in multiple clinical contexts—employing rigorously risk-adjusted analyses of prospectively collected data—have found consistently that there is minimal difference in oncologic outcomes for men with low-risk disease, but for those with higher-risk disease, surgery appears to confer better prostate cancer-specific and overall survival than EBRT with or without neoadjuvant ADT. The impact of brachytherapy, alone or together with EBRT, compared to EBRT alone or to surgery, has been studied to a limited extent to date.
- Various treatments affect HRQOL differently. Surgery causes a short-term drop in urinary and sexual HRQOL, followed by a recovery period; radiation has little immediate effect, but the impact may grow over time. Assessing the urinary and bowel effects of surgery (urinary incontinence) vs. those of radiation (urinary and/or bowel irritation) on overall HRQOL is not straightforward and will require additional careful health state utility studies.
- Costs for different treatments diverge substantially. Emerging technologies such as robot-assisted surgery and, in particular, advanced EBRT techniques entail large additional costs. How these costs are distributed to hospitals, payors, and patients in terms of time costs varies across modalities and should be considered in future cost-effectiveness analyses.

Additional RCTs for men with high-risk disease in particular are essential, and these must include surgical arms. In the interim, emerging data appears to support a greater role for surgery—in many cases as part of multimodal therapy also including EBRT and/or ADT—for high-risk disease. Increasingly rigorous cost-effectiveness studies currently underway will help shed further light on the question of optimal management strategies across the risk spectrum. Better collection and dissemination to patients of unbiased, risk-adjusted prostate cancer outcomes data will ultimately facilitate better decision-making, greater satisfaction, less practice variation, and more efficient and effective care.

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# Part V

# Management of Localized Disease

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# Radical Treatment for Localized Disease: An Overview of Options and Strategies for Decision Making

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Joseph A. Smith Jr

It is a daunting task for a man diagnosed with apparently localized carcinoma of the prostate to become sufficiently educated that he can make an informed decision about the best management approach. Although there are numerous sources of information including books, internet web sites, and support groups, patients often rely to a great extent upon the advice of their physician. It is incumbent upon the physician, then, to provide information which is sufficiently comprehensive that patients can adequately weigh all options yet is devoid of personal agendas or biases. However, this is not easy, even for professionals who devote their careers to the study and treatment of prostate cancer. The remarkable disparity of opinions and recommendations among clinicians with access to the same information and, often, the same treatments contributes to the controversies about prostate cancer management.

This chapter will review some of the considerations which must be addressed in deciding upon a treatment recommendation for a man with clinically localized carcinoma of the prostate. Parameters which can help select appropriate therapy are discussed. Treatment of prostate cancer is the ultimate example of "personalized" medicine. Matching the right treatment with the right individual is paramount, and attention must be addressed toward balancing of cancer cure versus quality of life. Given the same clinical setting and the same options, not all men make the same choice. The clinician's role is to help the patient make a personalized choice.

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## To Treat or Not to Treat?

The concept that not all men with prostate cancer need treatment is certainly not novel. For over half a century, the literature has been replete with discussions of which men need therapy and which ones do not. The tremendous increase in diagnosis of prostate cancer which occurred with the advent of widespread PSA testing, though, has increased the importance of the treatment versus surveillance debate. Further, early detection programs have been successful in permitting a stage migration wherein most cancers detected in contemporary series are localized and of relatively low grade. In prior decades, the primary consideration was not that cancers were being found too early but, often, too late. The lay public is now becoming much more aware of and accepting of an option for surveillance rather than active treatment.

A general benchmark that has been used is that observation alone is appropriate for a man with a low-grade cancer who has an anticipated life expectancy of less than ten or, perhaps, 15 years. Typically, then, men over the age of 70 or 75 years are at low risk to die from a localized and low-grade prostate cancer [1]. Although there is some calculated risk in withholding therapy, this is the preferred management approach for most men with relatively limited life expectancy.

The concept of initial nontreatment has been further expanded to encompass "active surveillance," even in men with a long life expectancy [2]. The implications of active surveillance are different than what had previously been termed "watchful waiting." It is assumed that some men who pursue active surveillance will ultimately require treatment. The underlying premise is that treatment can be deferred until there is evidence of disease progression with minimal risk that the cancer will progress from a curable to an incurable state [3].

This presents multiple, not easily addressed issues. First, many men psychologically have difficulty accepting nontreatment for their cancer and end up pursuing therapy which may prove to be curative but for a cancer which was likely

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not life-threatening to them. Further, the most useful information for men on active surveillance comes from repeat prostate biopsies. An increasing risk of infection or sepsis from transrectal ultrasound-directed prostate biopsies is being recognized along with a possible decrease in erectile function from biopsy needle damage to the cavernous nerves. Finally, there is disagreement in published studies about the impact of a delay in therapy on the pathologic parameters of prostate cancer [4–6].

## Defining Prognosis and Who Needs Treatment

It has been axiomatic for decades that a prognostic marker which identifies men who will benefit from aggressive early treatment is needed. Although genetic, pathologic, and biochemical markers to help identify prostate cancers at risk of progression are being evaluated, none have emerged with sufficient accuracy to segregate with confidence patients who require immediate treatment from those in whom deferred therapy is appropriate. However, there are a number of parameters in widespread clinical use which are of utility.

### Prostate-Specific Antigen

The merits of prostate-specific antigen (PSA) as a marker for either diagnosis or prognosis of prostate cancer remain a subject of intense debate and controversy [7]. What is not arguable, though, is that PSA testing has produced a substantial stage migration. The considerable majority of men with newly diagnosed prostate cancer in contemporary series have localized disease, a finding directly attributable to PSA screening. Arguments that men should not undergo PSA screening ignore the concept that treatment choices can be made once a diagnosis is established but that an informed decision cannot be made in the absence of knowledge about the presence of prostate cancer.

Beyond screening and early detection, PSA has a role in predicting prognosis and selecting therapy. It is now recognized that there is no "normal" serum PSA level and that there is a continuum of risk wherein there is no level below which a man can be declared to have no risk of prostate cancer and none above which a diagnosis can be made simply on biochemical parameters [8]. Other than the absolute PSA level, various methodologies can be used to improve the performance of serum PSA. As the antigen is made by both the benign and malignant aspects of the prostate, PSA levels generally are higher in men with a larger prostate. Therefore, PSA density (the amount of PSA relative to the prostate volume) has both diagnostic and prognostic value. Segregation of PSA into its free and bound components can be useful in deciding which men may need a biopsy for diagnostic purposes but does not yield substantial prognostic information.

Changes in PSA, though, are important. An increase in serum PSA of 2 or more ng/ml within 1 year of diagnosis has been associated in some studies with a worse prognosis. PSA doubling time is important – the longer the better [9–11].

### Digital Rectal Examination

Most prostate adenocarcinomas arise from the peripheral zone of the prostate, making them amenable to palpation by digital rectal examination once they attain a sufficient size. Digital rectal examination is, then, complementary to serum PSA in diagnosing prostate cancer. Some 20 % of prostate cancers are diagnosed because of a biopsy prompted by an abnormal examination rather than a change in PSA value.

Despite inaccuracies, digital rectal examination remains an important staging maneuver. In fact, comparative studies have not demonstrated definitively the ability of any imaging test to more accurately stage prostate cancer compared to digital rectal examination. Although patients in most contemporary series do not have any palpable abnormalities of the prostate (Stage T1c), physical examination findings can help distinguish palpable tumors localized to the prostate (Stage T2) from those which extend into the extraprostatic tissues (Stage T3).

### Gleason Grade

Without question, one of the most powerful independent prognostic parameters for the behavior of prostate cancer is tumor grade. The Gleason system is commonly used worldwide and, although modified over the years, strongly correlates with prognosis. A Gleason sum of less than 6 has become, for all practical purposes, a clinical nonentity, and the most common grade at presentation is 3 + 3. The category of Gleason 7 cancers incorporates both 3 + 4 and 4 + 3 lesions even though the dominant pattern 4 involvement of the latter clearly distinguishes it from the lower grade tumors. Gleason 8, 9, and 10 cancers are commonly accepted as aggressive and, unfortunately, may be beyond the confines of the prostate even at the time of diagnosis.

Multiple studies have shown disparity between Gleason grade obtained by biopsy specimens and that found at radical prostatectomy. The first is based upon a biopsy sampling of <1 % of the prostate tissue while, of course, a radical prostatectomy specimen has the entire prostate available for review. Up to 30 or 40 % of patients will have an increased Gleason grade on radical prostatectomy pathology compared to that of the biopsy. Most of this upgrading is from a Gleason 3 + 3 to a 3 + 4 cancer, a change of somewhat

dubious clinical significance. However, in other circumstances, the change in grade may be more substantial. Clinicians, then, have only the biopsy grade upon which to rely but must recognize the inherent limitations which come from the sampling error associated with prostate biopsy.

### Other Pathologic Characteristics

Beyond tumor grade, other aspects of the pathology are important in determining prognosis as well as the likelihood of a cancer being confined within the prostate. The number of biopsy cores involved and the percentage involvement of each core both correlate with tumor volume. Biopsies segregated by site can help establish the multifocality of the tumor. Patients with perineural invasion are somewhat more likely to have extraprostatic disease in most studies. Various staining techniques can be used to help establish a diagnosis of prostate cancer but are not predictive of tumor aggressiveness independent of Gleason grade.

### Prostate Imaging

Transrectal ultrasonography of the prostate (TRUS) typically is used to direct prostate biopsies. Often, the prostate gland has no specific echo abnormalities when a biopsy is prompted by a mild or moderate increase in PSA. However, there are some characteristic findings which correlate with prostate cancer, in particular hypoechoic changes in the peripheral zone. Bulging of the prostate or irregularity in the outline are suggestive of extraprostatic extension, but TRUS has not been shown to be superior to digital rectal examination in diagnosing extraprostatic extension.

The role of magnetic resonance imaging (MRI) remains controversial. Without doubt, MRI is able to visualize some prostate cancers. In particular, MRI may be useful for anterior tumors which are harder to visualize with ultrasound and may not be amenable to palpation. The specificity of MRI in identifying extraprostatic extension remains suspect, though.

### Risk Stratification

A number of different parameters to help determine tumor aggressiveness and the need for treatment are discussed above. Some have independent prognostic ability in multivariable analyses. Even more powerful, though, are combinations of different, known prognostic parameters.

Prognostic grouping systems have been in common use. Often, they combine PSA, digital rectal examination findings, and Gleason grade to segregate patients into low, intermediate, and high risk for disease outside the prostate. Multiple nomograms have been constructed and shown to have utility.

In the end, though, although nomograms and prognostic groupings can provide some probability information, they fall short on an individual basis. Clinicians and patients are reluctant to forego potentially curative therapy in some circumstances despite unfavorable calculations from nomograms. Nonetheless, this information is key in helping patients make informed decisions about treatment strategy.

### Focal Therapy

An emerging concept is that of focal therapy for carcinoma of the prostate [12]. Often, an analogy with "lumpectomy" for breast cancer is made. However, this is of questionable validity as lumpectomy for breast cancer is virtually always followed by radiation treatment to the breast. Moreover, almost 80 % of prostate cancers are multifocal. Arguments are made that the index cancer is the most threatening and the one most likely to be associated with a higher Gleason grade or extraprostatic extension.

Beyond tumor multifocality, focal therapy is hindered by the inability to localize accurately prostate cancer. Imaging studies such as MRI can be helpful but fall short of the accuracy needed for confidence in performing focal therapy. Template biopsies may be used in an effort to determine tumor location but require an anesthetic and performance of multiple punctures of the prostate. Their accuracy in localizing cancers is still argued.

Although focal therapy will undoubtedly continue to garner attention and investigation, it is very difficult to assess its benefit. While PSA can be an accurate posttreatment monitor for whole prostate ablative therapies, it loses both sensitivity and specificity with focal treatments. Interpretation of posttreatment biopsies may be problematic.

## Radical Treatment Strategies for Localized Prostate Cancer

In this chapter, the term "radical" is used to denote treatments which seek to remove or ablate all prostate tissue. A successful ablative therapy obviates the considerations of tumor multifocality and also improves the ability to monitor treatment success. The problem, though, is that there are multiple methodologies which can be used in an effort to achieve this goal. All ablative therapies have as a requirement the need to destroy all prostate cells while limiting damage to surrounding structures. Since adenocarcinoma of the prostate often extends very close to the peripheral portion of the prostate, there is a fine line between a treatment which

successfully eliminates the cancer and one which damages adjacent nerves, muscles, or blood vessels.

## Radiation Therapy

Radiation therapy can clearly not be considered a single treatment modality as the term encompasses external beam sources, brachytherapy with various isotopes, proton beam therapy, and focused radiosurgery approaches. In addition, combinations of radiation treatment can be used.

Intensity-modulated radiation therapy (IMRT) has the distinct advantage that anesthesia is not required. IMRT methodology allows precise focus of the radiation on the target organ. However, the prostate gland moves. Fiducial markers are sometimes placed to help localize the prostate, but the target organ can move even during a relatively short treatment session.

Brachytherapy can be performed with a number of different isotopes, although Iodine-125 is used most commonly. A good spatial distribution of the seeds is required to provide uniform radiation to the prostate. The relatively limited tissue penetration of Iodine-125 can help provide sufficient intraprostatic radiation doses which taper quickly beyond the margin of the prostate.

Proton beam therapy has been strongly advocated by the centers which have the available equipment [13]. Proton facilities are extremely expensive and must rely upon men with prostate cancer to maintain sufficient volume for economic feasibility. The available data would suggest that proton beam therapy is equivalent to IMRT and/or brachytherapy both for tumor control and in avoiding side effects. However, there is no convincing data to show superiority for proton beam therapy for either of these parameters.

## Radical Prostatectomy

Radical prostatectomy has maintained a cardinal role in the management of localized prostate cancer for over a century. It remains the most proven and successful treatment for cancers histologically confined within the prostate. Without question, refinements in understanding of the periprostatic anatomy and technologic developments which alter the surgical approach have virtually revolutionized the performance of radical prostatectomy and lessened its overall impact on patients. Nonetheless, it remains a surgical procedure with the potential for perioperative morbidity or quality of life compromises.

There has been significant debate on the merits of various surgical approaches for radical prostatectomy. Radical perineal prostatectomy is associated with relatively limited bleeding, minimal postoperative pain, and pathologic results comparable to alternative approaches. The methodology for preservation of the cavernous nerves for avoidance of erectile function is not as well developed with radical perineal prostatectomy. Further, there are limited numbers of practitioners currently who are skilled at radical perineal prostatectomy.

The retropubic approach became dominant over the last 20 or 30 years. Initially, this was partly fueled by the ability to perform simultaneous pelvic lymph node dissection. It remains the most common open approach for radical prostatectomy.

While a pure laparoscopic approach for radical prostatectomy remains dominant in some portions of Europe and other countries, robotic-assisted laparoscopic prostatectomy (RALP) is the most common surgical approach for radical prostatectomy in the USA. Virtually all new trainees entering practice from either residency or fellowship adopt RALP, and it is estimated that 75–80 % of radical prostatectomies performed in the USA are performed via a robotic-assisted laparoscopic approach currently. The advantages sometimes become exaggerated through hospital and physician practice marketing efforts. Nonetheless, it is commonly accepted that blood loss is significantly less with robotic prostatectomy, postoperative pain is minimal, and length of stay is typically only 1 day. Bladder neck contractures occur in fewer than 1 % of patients. Although reports in the literature are variable, there seems to be sufficient evidence to consider RALP at least equivalent to open surgical approaches for tumor control and avoidance of incontinence and erectile dysfunction [14].

A distinct advantage of radical prostatectomy in treating carcinoma of the prostate is the degree of knowledge which comes from having the entire prostate available for histologic examination. Pathology can confirm the intraprostatic location of a tumor and presence of negative surgical margins. Further, the PSA should fall to undetectable levels within a month of surgery. Thus, patients with a good prognosis can be reassured with a high degree of confidence after surgery.

On the other hand, the presence of residual malignant elements can be recognized early. Postoperative radiation, either in an adjuvant or early salvage setting, improves tumor-free survival in the presence of extraprostatic disease or positive margins [15]. The best PSA kinetics for a favorable outcome are values which initially are undetectable and then have a delayed, slow increase. Results of salvage radiation are improved when treatment is initiated early (with a PSA value of <0.5 ng/ml) as opposed to delayed therapy.

## Cryotherapy

Freezing of the prostate is not a new treatment. Cryotherapy has been a treatment option for over 50 years. More recently, though, the cryotherapy probes are vastly improved,

and freezing can be used as an ablative therapy. Most reports show that the extent of the ice ball can be monitored with some precision using ultrasound. However, it is difficult to achieve complete prostate necrosis without damage to the cavernous nerves. Urethral warming devices are used to avoid damage to the urethra.

Without long-term follow-up, treatment results have been difficult to monitor [16]. A relatively limited number of patients have undergone routine post-cryotherapy biopsies. Presumably, when the treatment is used in an ablative effort, PSA levels should become undetectable. This is rarely the case, though. Many reports have used the "Phoenix criteria" which were specifically developed for external beam radiation of the prostate and defined as a PSA nadir plus 2. Whether this is a valid response definition for cryotherapy is highly debatable.

## High-Intensity Focused Ultrasound

Just as freezing can destroy prostate cancer cells, heating via focused ultrasound is a potential treatment option. High-intensity focused ultrasound (HIFU) is sometimes used as an energy source for focal therapy as discussed above, but it also can be considered for whole gland ablation. HIFU is not FDA approved for treatment in the USA, and some practitioners have taken patients out of the country to deliver therapy. Reports of whole gland HIFU have included relatively small numbers of patients with short-term follow-up and inconsistent biopsy data [17].

## Androgen Deprivation Therapy (ADT)

Hormonal therapy designed to deprive the cancer cells of androgens has been a mainstay of treatment for carcinoma of the prostate since the early 1940s. The effects of androgen deprivation on prostate cancer cells are rapid and profound. Tumor volume and serum PSA levels decline precipitously after ADT is instituted.

Generally, though, androgen deprivation is not considered primary therapy for localized carcinoma of the prostate. Eventually, castration-resistant cells emerge so ADT is not curative. Further, there are recognized short- and long-term consequences of ADT. Decreased libido, loss of muscle mass, weight gain, vasomotor hot flushes, and development of the metabolic syndrome all may occur with ADT.

ADT has been proven to be useful for adjuvant therapy with external beam radiation. For men with intermediate or high-risk tumors, adjuvant androgen deprivation therapy improves long-term tumor-free survival with radiation treatment. Its role in neoadjuvant or adjuvant therapy with radical prostatectomy is less defined.

## Treatment-Related Morbidity

Since most men with localized carcinoma of the prostate have no symptoms, treatment-related side effects can decrease quality of life. Radiation treatment methods can cause radiation cystitis or proctitis as well as urethral stricture and, sometimes, incontinence. Rectourethral fistulas occur rarely. There is at least some concern about secondary tumor development either in the bladder or rectum.

Surgery carries with it the attendant risks of anesthesia as well as the potential for intraoperative bleeding or postoperative infection. Significant incontinence is relatively unusual and can be addressed with secondary procedures, but up to 10 % of men will require a protective pad because of some degree of leakage [18, 19].

Virtually all of the treatments for localized carcinoma of the prostate are associated with a risk of erectile dysfunction [20]. The cavernous nerves which help control blood flow in and out of the penis are intimately associated with the prostate. These nerves can be damaged during surgical efforts to separate them from the prostate or by radiation freezing or heating methods at ablative therapy. With all treatment approaches, results correlate with patient age and preoperative erectile function.

## How Does a Man Choose?

Discussed above are multiple treatment options, each with its own merits and some with their own unique risks. Virtually all, though, have some applicability. Although some circumstances may make one treatment strongly preferable over another, many patients are eligible for multiple different treatment options.

The first decision a man must make is whether or not to pursue definitive therapy. The prognostic parameters discussed above, coupled with the patient's health status and age, can help predict the probability of tumor progression within a man's anticipated lifetime. Patients can often understand that, just as life insurance companies use a set of parameters to predict overall survival for a group, some factors can be used to predict the probability of tumor progression. However, even though the statistics may be valid for a group, they do not necessarily apply to an individual person or to an individual tumor. In the end, each man must decide his risk tolerance in deciding whether to pursue a less aggressive management strategy.

A man who wants to pursue potentially curative therapy must weigh the pros and cons of multiple different treatment options. A strong consideration is the risk of treatment-related side effects. For some men, avoiding quality of life compromises is paramount while others are more focused on eliminating any threat from cancer. Virtually all men want to avoid

treatment-related voiding dysfunction such as radiation cystitis or surgically related incontinence. Probably the greatest variability, though, comes with regard to erectile function. Many men in a prostate cancer age group may already be having some difficulty with erectile function such that it is no longer a priority in their life. Others, though, greatly fear the potential compromise which would come from treatment-related erectile dysfunction. The best available information would suggest that the risk of posttreatment erectile dysfunction is almost the same for surgery or one of the radiation treatment methods.

Some men choose surgery because of its more definitive nature and the information that comes from the availability of the surgical specimen. The rapid decrease in PSA to undetectable levels which should occur if all of the cancer has been removed can be a great source of reassurance. Further, they may be comforted by the knowledge that additional treatments can be employed with the sequence of surgery followed by radiation if necessary.

Clinicians have an essential role in advising patients. They should not be hesitant to make recommendations while at the same time exploring various treatment options and listening to the patient's wishes. Patients will often elicit the physician's opinion by asking, "What would you do if it were you, doctor?" This is both a valid and a fair question, but the answer may not necessarily be relevant. Each individual has different risk tolerance and weighs quality of life issues versus cancer control in a different manner [21]. In the end, management of prostate cancer is the ultimate in "personalized medicine."

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# Quality of Life and Management of Localized Disease

50

Andreas E. Nilsson, Gunnar Steineck, and N. Peter Wiklund

## Introduction

Quality of life for the prostate cancer survivor has evoked an increasing amount of interest during the last decade [1, 2]. Attention has mainly been directed toward the documentation of quality of life and symptoms after radical therapy for localized disease since none of the common treatment modalities – radical prostatectomy, external beam radiation, or brachytherapy – has been found to be superior regarding long-term survival, so the choice between them has often been based on future quality of life issues. It has been reported that after curative treatment for prostate cancer (prostatectomy, brachytherapy, or external beam radiation), survivors have on the average 5.1 new symptoms caused by the therapy [3]. The importance of quality of life issues after radical therapy for prostate cancer is highlighted due to the high number of patients that must be treated to prevent one death from prostate cancer [4] and because of the possible negative consequences on basic functions such as sexual, urinary, and bowel functions resulting from treatment [1, 2]. There exist no randomized studies comparing outcomes between radical prostatectomy and radiation therapy, so comparison concerning symptoms and self-assessed quality of life between these treatment modalities is based on observational data.

Possible negative consequences of a radical prostatectomy include perioperative death, short- and long-term complications of anesthesia and analgesia during operation, inguinal hernia, urethral stricture, urinary incontinence, decreased erectile rigidity, difficulties to maintain erection during intercourse, climacturia (involuntary loss of urine at orgasm), decreased volume of the ejaculate, or decreased orgasmic pleasure [5–8]. Possible negative consequences of radiotherapy (external or given as brachytherapy) are the same (but at lower risks) as for radical prostatectomy. In addition, a man who has undergone radiotherapy has an excess risk of symptoms originating from a disturbed anal sphincter or large bowel function [6, 9]. Such disturbances may result in fecal leakage, painful defecation, defecation urgency, uncontrolled flatulence, frequent defecation, loose stools, or abdominal pain. Castration by medical or surgical means, as well as antiandrogens (but to a smaller degree), can result in fatigue, apathy or depression, motor weakness, hot flushes, decreased libido, decreased erectile rigidity, decreased maintenance during intercourse, or altered orgasmic function [10].

A man who contracts localized prostate cancer can find a full smorgasbord of alternative treatments and management recommendations for his disease, and choosing between them can often be frustrating. Many men seek second, third, and even fourth opinions, and some encounter contradictory recommendations. However, the extent of this frustration, its determinants, and methods to relieve it are poorly documented scientifically [11].

Health-related quality of life research for prostate cancer survivors is complicated by numerous factors such as response

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shift, declining function with increasing age of the affected functions (sexual, urinary, and bowel), and dichotomization between normal and pathological (empirically or arbitrarily), and commonly used quality of life instruments provide summarized scores and therefore are lacking in detail for refining therapy. A man's ability to adapt to and accept most of life's burdens, response shift, is well documented regarding prostate cancer [12]. But nevertheless, the medical literature amply documents the side effects of treatment and their potential for impairing quality of life after radical treatment (surgery or radiation). Side effects after curative treatment, such as erectile dysfunction, can induce psychological symptoms such as anxiety and depression which will influence self-assessment regarding quality of life.

## Measurement of Health-Related Quality of Life

Questionnaires assessing health-related quality of life (HRQOL) are often referred to as "instruments." These "instruments" are standardized and validated questionnaires providing an objective assessment of nonspecific and disease-specific functions. For quality of life research on prostate cancer survivors, three questionnaires are commonly used. The University of California Los Angeles Prostate Cancer Index (UCLA-PCI) combines prostate-specific domains regarding function and bother from sexual, bowel, and urinary domains with a general HRQOL adapted from Medical Outcomes Study Short Form (SF-36) [13]. The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) is a general questionnaire assessing HRQOL for cancer survivors. This is paired with 25 variables specific for prostate cancer survivors (EORTC QLQ-C30 PR25) [14]. The Expanded Prostate Cancer Index Composite (EPIC) is a modified version of UCLA-PCI also assessing additional symptoms induced by the treatment [15].

These questionnaires provide summarized scores for each investigated domain and have been validated in numerous cultural settings. Validation of a questionnaire ensuring that the participants understand the questions and interpret them correctly as intended is crucial, and in a study by Kilbridge et al. this phenomenon was highlighted by the finding that many prostate cancer survivors do not understand terms such as "incontinence" [16]. Summarizing different domains into scores makes them user friendly (from an investigator perspective), but there is an inevitable risk of oversimplifying and thereby losing information about important details regarding different symptoms. For example, an "unknown" symptom after treatment such as climacturia (involuntary loss of urine during sexual climax) is a symptom that is seldom discussed after radical prostatectomy even though it seems to affect about 20 % of patients after surgery [17]. This symptom is not assessed in the commonly used instruments; if one is interested in evaluating specific issues such as the eventual effect of climacturia on sexual life and HRQOL, then one has to construct a study-specific questionnaire. Study-specific questionnaires usually asses quality of life by utilizing visual or digital scales. These scales are often anchored with categories such as no quality of life or best possible quality of life.

## Prostate Cancer Treatment and HRQOL

### Active Surveillance and Watchful Waiting

Considering the number of patients that must be treated in order to prevent one prostate cancer death, a reasonable approach for low-risk tumors is to employ active surveillance, an approach that thereby delays definite treatment or avoids it altogether [18]. It is still uncertain to what extent active surveillance has a negative effect on survival, and little is known about the effect of delayed interventions on HRQOL. There are data indicating that a high PSA or an abnormal digital rectal examination in a screening setting is enough to raise anxiety in a subgroup (10 %) of men [19, 20]. Ercole et al. concluded that one of the two main reasons for abandoning active monitoring was anxiety (the other was PSA progression) [21]. In a study evaluating psychological morbidity in an active monitoring program, 16 % had anxiety and 6 % had depression, but the authors conclude that these frequencies were comparable to those in a nonclinical population [22]. In a smaller qualitative study comparing men from the USA and Ireland, cultural differences were seen where men in the USA displayed a higher degree of uncertainty in a monitoring program compared to Irish men [23]. It seems that a smaller subset of patients with a "neurotic" personality has higher depression scores during surveillance and therefore is unsuited for this treatment modality [24].

In a Scandinavian study (SPCG-4) randomizing between radical prostatectomy and watchful waiting, the side effects of surgery were balanced by an increase in local symptoms from tumor progression in the watchful waiting arm, and the mean effect on self-assessed quality was similar in the groups [1]. This study started recruitment of patients before the PSA era, and there was a high prevalence of locally advanced tumors. Therefore, few patients were nerve spared which led to erectile dysfunction in approximately 90 % of the patients in the surgical arm. Surprisingly, the mean effect on self-assessed quality of life was similar in both groups 4 years after randomization. Even though erectile dysfunction was more frequent among the surgical patients, with time, this symptom was also seen among the watchful waiting patients. Obstructive urinary tract symptoms and anxiety were more common in watchful waiting patients. It seems that local

symptoms from an untreated prostate cancer will eventually, with time, evoke similar symptoms to those that one can expect after radical treatment. This finding is confirmed by a US study demonstrating that men in watchful waiting had lower scores in sexual and physical domains than expected from the aging process alone ($p<0.001$) [25].

## Radical Prostatectomy

Unwanted side effects of radical surgery for prostate cancer include both urinary incontinence and erectile dysfunction, but obstructive symptoms may also occur. However, in patients with obstructive symptoms before radical prostatectomy, the symptoms are often reduced after surgery [1]. Urinary incontinence is at its worst during the first months after surgery and then improves continuously during the first 2 years. In a prospective longitudinal study, 7 % reported moderate or severe urinary problems 2 years after radical prostatectomy compared to 11 % at baseline [2]. At baseline, the symptoms reported were weak stream in 11 %, increased frequency in 17 %, and urinary leakage 4 %. After 2 years, the symptoms reported were weak stream in 4 %, increased frequency in 10 %, and urinary leakage 14 %. In the same study, 43 % reported moderate or severe problems with sexual function at the 2-year follow-up compared to 12 % at baseline. Sixty-four percent of patients reported poor erections that were not firm, and 51 % reported erections that were not reliable at 2-year follow-up, which was an increase from the reported 17 and 10 % at baseline. If the patients' erectile nerves were spared, fewer patients reported problems with sexual function.

Other known side effects after radical prostatectomy are an increased risk of inguinal hernia, penile shortening, anorgasmia, dysorgasmia, and climacturia (involuntary release of urine during sexual climax) [17, 26, 27]. Little is reported in the literature about the effect of these symptoms on HRQOL.

Observational data suggest an increased risk of inguinal hernia formation 2–3 years after radical prostatectomy. A prospective study demonstrated at the 4-year follow-up a 12 % cumulative risk of inguinal hernia formation after open radical prostatectomy and 6 % cumulative risk after robot-assisted laparoscopic prostatectomy, which was a statistically significant difference [27].

Penile shortening has been reported to occur in approximately 70 % of men after radical prostatectomy [28–30], but in a selected group of nerve-spared men with good postoperative erectile function, no objective length loss could be evaluated [31] indicating that nerve function is a key factor in penile shortening after radical prostatectomy.

Climacturia is reported to occur in approximately 20 % of men after radical prostatectomy, and in men who are still sexually active after surgery, the prevalence is 40 % [17, 32]. In a small study concerning orgasmic function after radical prostatectomy, 36 % of men experiencing climacturia reported that the symptom was sufficient reason to avoid any sexual contact with their partner [33]. Among men experiencing climacturia, many are continent when not engaged in sexual activity indicating that the two symptoms have different underlying mechanisms [17, 32]. During orgasm, the external urethral sphincter relaxes to admit antegrade ejaculation. Normally, an inner-sphincter function protects from urinary leakage, keeping the urine from leaving the bladder. After a radical prostatectomy, the inner-sphincter function becomes dysfunctional, providing a mechanism for climacturia when the outer sphincter relaxes. An alternative theory is an imbalance between parasympatic autonomic nerve function since climacturia has been associated with penile shortening and erectile dysfunction, supporting the belief that the loss of parasympatic autonomic function may be related to orgasm-associated incontinence [17].

## Radiation Therapy

An American study investigating complications after brachytherapy in 5,621 men reported that 54.5 % had a complication within 2 years after therapy. The most common side effects were urinary 33.8 % followed by bowel 21 % and erectile morbidity 16.7 %. Of these, 10.3 % had an invasive procedure due to urinary morbidity [34].

In a small German study comparing external beam radiation (74 Gy) with high-dose-rate (HDR) brachytherapy (2×9 Gy) following external beam radiation (46 Gy), 86 % of patients receiving HDR brachytherapy reported severe erectile problems compared to 34 % of the patients who received external beam radiation [35].

In a longitudinal study by Sanda et al. urinary symptoms were resolved during the first year after external beam radiation but after brachytherapy survivors reported significant detriments regarding incontinence, urinary irritation, or obstruction compared to baseline. Urinary incontinence was reported by 6 % of survivors 2 years after brachytherapy, and at the 2-year follow-up, 18 % of men after brachytherapy and 11 % after external radiation reported moderate or severe distress from overall urinary symptoms [2].

Fecal incontinence was reported by 5 % of men after brachytherapy and 2 % of men after external radiotherapy at the 2-year follow-up. Other bowel symptoms reported after radiotherapy were increased frequency, 10 %, and urgency, 16 %, which was reported after external radiotherapy and in 7 and 9 % after brachytherapy. Overall bowel problems increased fourfold compared to baseline irrespective of whether external beam radiation or brachytherapy was given [2].

Sexual function decreased after both external radiotherapy and brachytherapy with 37 and 30 % respectively characterizing sexual function as a moderate or big problem after 2-year follow-up [2].

**Table 50.1** Different treatment modalities for localized prostate cancer and associated side effects

| Radical prostatectomy | Radiation therapy | Active surveillance/ watchful waiting |
|---|---|---|
| Urinary incontinence | Urinary incontinence | Anxiety |
| Erectile dysfunction | Urgency | Obstructive symptoms |
| Climacturia | Fecal incontinence | Erectile dysfunction |
| Inguinal hernia | Erectile dysfunction | |
| | Proctitis | |
| | Chronic diarrhea | |
| | Hematuria | |

**Table 50.2** Symptoms associated with androgen deprivation therapy

| |
|---|
| Erectile dysfunction |
| Loss of libido |
| Gynecomastia |
| Weight gain |
| Muscle wasting |
| Hot flushes |
| Gastrointestinal symptoms |
| Osteoporosis |
| Deteriorated cognitive function |

## Hormonal Therapy

Use of hormonal therapy is seldom indicated as a primary treatment for localized prostate cancer but can be used as a neoadjuvant, concomitant, or adjuvant treatment together with radiation therapy for intermediate- and high-risk patients. After radical prostatectomy, adjuvant hormonal therapy is recommended in lymph node-positive disease in case of rising PSA (Table 50.1).

Adverse effects of hormonal therapy are numerous and well known (Table 50.2) – loss of sexual desire and erectile function, weight gain, hot flushes, muscle wasting, osteoporosis, and gynecomastia [36]. A recently published study by Alibhai and coworkers demonstrated that endurance and strength are affected within 3 months of starting androgen deprivation therapy [37].

There is increasing evidence indicating that androgen deprivation therapy has a negative effect on cognitive function [38]. A small randomized longitudinal trial by Green and coworkers demonstrated a decline in cognitive function during androgen deprivation therapy; at 1-year follow-up, men on hormonal treatment had significantly more difficulty recalling words compared to men allocated to watchful waiting ($P=0.014$) a difference which was not seen at baseline [39].

### Conclusions

In many cases, the choice between different curative treatment options for a man who has been diagnosed with a localized prostate cancer is governed by "what symptoms do I not wish to contract?" Each treatment modality has its own pattern of risk of acquiring symptoms which has the potential to influence HRQOL. Even when omitting treatment as in active monitoring, anxiety and worry can influence HRQOL, and in the long term, local symptoms evolve due to tumor progression.

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# Active Surveillance for Favorable-Risk Prostate Cancer

51

Nathan Lawrentschuk and Laurence Klotz

## Abbreviations

| | |
|---|---|
| AS | Active surveillance |
| PSA | Prostate-specific antigen |

## Introduction

Over the past two decades, a dramatic paradigm shift has occurred in the diagnosis and treatment of prostate cancer (PCa), as a result of the aging population and the widespread use of serum PSA testing. Alongside an increase in the prevalence and incidence of PCa over the past decade, disease-specific mortality has declined, which is most probably related to earlier diagnosis and improved treatment [1–6]. However, many cases of the low-risk PCa represent biologically indolent disease, and such patients are not likely to die from their cancer, particularly when competing comorbidities exist [7]. Not surprisingly clinicians have questioned whether all early diagnosed low-risk PCa (those diagnosed in most cases decades before symptoms would arise of which many will not be life threatening) should be treated radically, if at all. This led to the alternative option of active surveillance (AS), described by Klotz in 2002 [8]. AS consists of careful monitoring of men with low-risk PCa having deferred radical treatment only when and if required [9].

Active surveillance has now become an accepted treatment strategy for men with low-risk PCa who were previously received radical whole gland treatment (surgery, external-beam radiation, or brachytherapy). The concept of AS evolved from watchful waiting which meant no treatment until progression to metastatic or locally advanced disease, followed by androgen ablation therapy [10]. The concept is to cure clinically significant PCa rather than wait for the development of metastatic disease. For low-risk PCa, AS and radical treatment both have merits and disadvantages. AS has minimal morbidity with the inherent risk of progression associated with expectant management; radical therapies have an impact on erectile function and continence but provide definitive treatment [11, 12]. Somewhere between AS and radical treatment lies focal therapy. Focal therapy has been limited to small cohorts with no extensive follow-up and cannot be recommended outside study protocols [13]. The impact of focal therapy on the natural history of favorable-risk disease remains uncertain. Most men and their physicians with favorable-risk PCa will choose between AS and radical therapy.

In this chapter, we will focus upon the rationale, patient selection, method of follow-up, triggers for intervention, and recent results of this approach.

## Rationale and Advantages of Active Surveillance

Active surveillance for favorable-risk PCa has emerged as a credible management strategy within populations where PCa screening is widespread. This is due to the observation that PCa screening using digital rectal exam (DRE), prostate-specific antigen (PSA), and biopsy results in the detection of disease that is not clinically significant in many patients (i.e., untreated, the cancer would not pose a threat to health or cause death). Furthermore, by treating men

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with favorable-risk PCa, we risk morbidity and even mortality when the disease, due to its long natural history, may never have been destined to have any clinical manifestations during their lifetime. Hence, AS is a solution to the widely acknowledged problems of overdiagnosis and overtreatment of clinically insignificant disease which accompanies early detection of PCa [14].

AS is flexible in that it allows for initial assessment of disease prior to deciding on it as a course of management. This is possible by incorporating a period of initial observation into patient management with the belief that if appropriate triggers for intervention are followed, then the patient will still have a favorable outcome when undergoing radical therapy. This approach helps manage the subset of patients with initially apparent favorable-risk PCa who actually are at risk, due to either higher-risk disease undetected at diagnosis or progression to a more aggressive phenotype of PCa over the period of surveillance. AS relies on defined triggers to detect and predict higher-risk disease while on such a program. Tools utilized in the published surveillance series include serial PSAs, DREs, and repeat prostate biopsies. Magnetic resonance imaging (MRI) and biomarkers have an emerging role. These will be discussed later in greater detail.

The approach of AS has been summarized [14] as that which (1) identifies patients who have a low likelihood of disease progression during their lifetime based on clinical and pathologic features of the disease and patient age and comorbidity, (2) adherence to close monitoring over time, (3) reasonable criteria or triggers for intervention that will both identify more aggressive disease in a timely fashion and also not result in excessive treatment, and (4) improves communication to reduce the psychological burden of living with an untreated cancer.

## Potential Disadvantages of Active Surveillance

The obvious disadvantage of AS where selective delayed therapy is relied upon is that the "window of opportunity" for cure may be missed. Individual risk of disease progression is difficult to assign so of concern is a small but real possibility of progression to death in the AS population because of the loss of opportunity for cure during the surveillance period. PCa has an exceptionally long natural history, characterized typically by initiation in the 30s, clinical diagnosis in the 50s–60s, and death from disease in the 80s. This represents a 50-year time course. Thus, most believe that a treatment delay of 1 or 2 years in patients who are reclassified as higher risk and treated is unlikely to significantly alter cancer mortality. Further, although AS may appear to have little morbidity, several studies have shown deterioration of quality of life (QOL) [15–17] and sexual function [18, 19]. Alternately, the QOL is likely to deteriorate if all men with low-risk disease are offered radical treatments with the known impacts on sexual function and continence, the very reasons why AS was established as a strategy.

Finally, a small attrition rate can be expected because of men who are unable or unwilling to tolerate surveillance, and this must be accepted from the outset for any individual [20].

## Uptake of Active Surveillance

Although AS has gained popularity, it is still infrequently utilized in some regions. Patients and/or their physicians appear to want to treat the PCa once diagnosed. For example, in the USA, only approximately 10 % of eligible men are put on AS protocols [21], and even in countries where AS is largely accepted as a treatment strategy, only 30 % of eligible men are on AS [22]. It must be noted that the discussion and acceptance of AS in guidelines and recommendations by learned bodies have been far greater [23, 24].

## Selection Criteria for Active Surveillance

A genuine concern is that patients thought to have clinically insignificant PCa might actually harbor cancer with unfavorable pathological features [25]. However, in any individual patient, it may be difficult to perfectly differentiate between clinically insignificant and life-threatening PCa [24]. This requires selection for AS patients to be stringent. Prospective studies outlining the ideal selection married with adequate follow-up and intervention data are lacking. No randomized trials comparing selection criteria exist, and data is likely to be obtained from larger prospective cohorts. At present, an array of selection criteria to define the favorable or even low-risk or clinically insignificant cancer confronts a urologist (Table 51.1). Most of the data for selecting patients works backward from the concept of an insignificant tumor found at radical prostatectomy, which in itself may be a flawed concept. This is because given the different theories regarding the relevance of PCa as multifocal and the idea of a dominant or index lesion being responsible for progression and/or metastases, prospective data is likely to be more enlightening but is not yet available.

Outcomes in men outside the more accepted selection criteria (e.g., Gleason 6) for AS are lacking. In selected patients with screen-detected Gleason 3+4=7 prostate cancer, AS might be an option, especially in those with comorbidity and/or a short life expectancy [31]. Interestingly, the original Toronto cohort of AS men included men with Gleason 7 disease who were over 70, but the protocol was amended to only accept men with Gleason 6 [32].

**Table 51.1** Selection criteria for active surveillance based on different protocols currently used worldwide

| Author and institution | Clinical stage | PSA level, ng/mL | Biopsy Gleason score | PSA density, ng/mL | No. of positive cores |
|---|---|---|---|---|---|
| Klotz et al. [32] (*First series from Toronto, Canada*)[a] | T1c/T2a | ≤10.0 | ≤3+3=6 | NI | NI |
| Carter et al. [42]; Johns Hopkins, USA | T1c | NI | ≤3+3=6 | ≤0.15 | 2[b] |
| van den Bergh et al. [31]; Multicentre, Europe | T1c/T2 | ≤10.0 | ≤3+3=6 | <0.2 | 2 |
| Kakehi [41]; Multicentre, Japan | T1c[c] | ≤20.0 | ≤3+3=6 | NI | 2[b] |

Adapted from Lawrentschuk and Klotz [26]
*NI* not included
[a]For patients over age 70, these criteria were relaxed to include Gleason ≥ 7 (3+4) and/or ≤ PSA 15 ng/mL
[b]And <50 % of cancer in any core
[c]Age 50–80 years

## Imaging of Prostate Cancer for Active Surveillance

The key problem in the diagnosis and management of PCa is our "blindness," in terms of whether a given patient has or does not have prostate cancer, where precisely the cancer is located, its stage in terms of extracapsular extension, and whether or not the true grade of the cancer is represented at biopsy [27]. When compared with digital rectal examination (DRE) and transrectal ultrasonography-guided (TRUS) prostate biopsy, MRI is certainly superior at locating PCa [21]. Tumor localization is possible owing to advances in MRI hardware, software, and sequence development (referring to the sequence of radiofrequency pulses and magnetic gradients used to generate a magnetic resonance image e.g., T1- or T2-weighted sequence), with multiparametric approaches now available at 1.5 and 3 T [28, 29]. The use of MRI for tumor localization was critical for the development of focal therapy for men with low-risk prostate cancer [13] and is likely to benefit other patient subgroups, particularly men wishing to commence or remain on active surveillance (AS) and those patients with repeat negative prostate biopsies despite having features suggesting cancer, such as a persistently elevated PSA with a family history of prostate cancer. Ultimately, if patients are selected appropriately and undergo MRI for cancer localization, there is an opportunity to prevent morbidity and ultimately reduce costs to the health-care system by identifying patients not suitable for AS and facilitating guided biopsies. This will be discussed further.

## MRI in Patients on Active Surveillance

Two specific subgroups of patients undergoing AS might benefit from MRI: those with borderline features who wish to proceed with AS and those on AS who experience a PSA rise but still wish to remain on surveillance. Patients from both groups might undergo repeat biopsy or radical treatment, in which case MRI could assist in directing biopsies or revealing cancers in difficult to biopsy zones, such as the anterior prostate, which might be more clinically relevant [30]. Ultimately, MRI might detect prostate cancers that require radical treatment and thereby reduce harm.

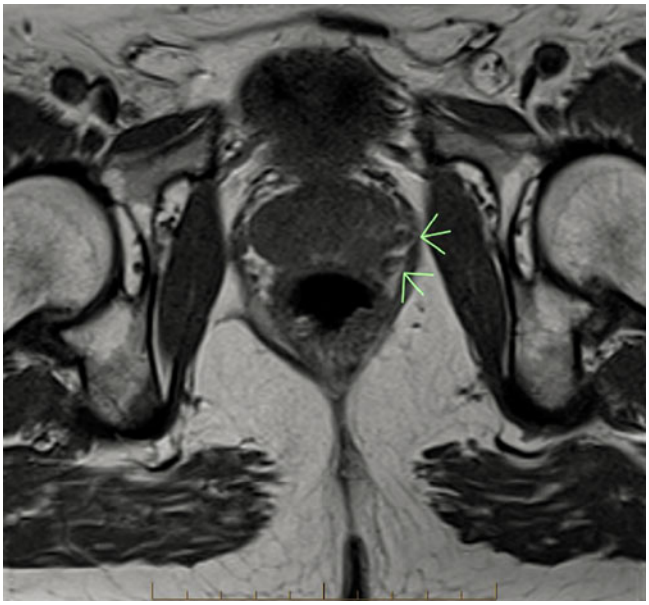

**Fig. 51.1** MRI demonstrating potential extracapsular extension in PCa nodules (*arrows*) of a patient with only 2/14 cores positive with PCa who may now not be suitable for active surveillance despite clinically having organ-confined disease (Image courtesy of Dr. George Koulouris, Melbourne Radiology Clinic, Australia)

AS relies on the accurate staging of PCa at the time of diagnosis and during follow-up [33]. This is currently undertaken with PSA testing, DRE, and repeat biopsy, the latter of which is invasive, carries risks, and might not sample areas of the gland harboring significant disease [30]. Thus, the focus of studies of MRI in PCa has shifted from the identification of advanced disease to its utility as an adjunct to the diagnosis of low volume disease (Fig. 51.1) with precise location and guidance of biopsies, or even for innovative treatments such as the focal therapy [13].

Three studies of MRI as diagnostic tool in the follow-up of AS patients are summarized in Table 51.2. In 2008, Cabrera et al. [35] performed a retrospective study of 92 men with

**Table 51.2** Studies evaluating MRI as a diagnostic tool in the follow-up of men with PCa undergoing active surveillance

| Study | *n* | Study type and patient characteristics | Imaging sequences | Follow-up (months) | Results |
|---|---|---|---|---|---|
| Van As et al. [34] | 86 | Prospective patients eligible for repeat biopsies as part of the AS protocol | 1.5 T whole body MRI with endorectal coil | 29 (median) | Low ADC is associated with adverse histology on repeat biopsy ($P<0.0001$) and shorter time to deferred radical treatment ($P<0.0001$) |
| Cabrera et al. [35] | 92 | Retrospective *patients eligible for AS* | 1.5 T whole body MRI with endorectal coil plus MRS | 56 (mean) | No association between the baseline tumor characteristics and biochemical outcome ($P > 0.05$) |
| de Souza et al. [36] | 44 | Prospective study of patients with localized prostate cancer referred for routine clinical evaluation | DW-MRI and T2W MRI | N/A | ADC significantly different in patients with low-risk ($n=26$) disease, compared to those with intermediate- or high-risk disease ($n=18$) |

Adapted from Raz et al. [27]

biopsy-proven PCa who had undergone baseline endorectal MRI and MRS and who had selected AS for management. In multivariate analysis, no significant association was found between clinical stage, Gleason score, serum PSA level or the presence of apparent tumor on endorectal MRI and MRS imaging at baseline (time of diagnosis), and the biochemical outcome ($P<0.05$ for all) [35]. In 2009, Van As et al. [66] analyzed the ADC generated from DW-MRI with respect to repeat biopsy findings and time to radical treatment in 86 patients. They demonstrated that a low ADC is associated with adverse histology on repeat biopsy and shorter time to deferred radical treatment. Tumor ADC was highly significantly cor related with maximum core involvement, percentage of positive cores, and free-to-total PSA ratio. It was also significantly correlated with initial PSA level, but not with PSA velocity [34]. de Souza et al. [36] assessed 44 consecutive patients with clinically localized PCa by performing DW-MRI in addition to their standard T2W MRI. They demonstrated that the slow and fast components of water diffusion within prostate cancers are significantly different in patients with low risk compared ($n=26$) with those with intermediate- or high-risk disease ($n=18$). ADC values thus offer potential for differentiating indolent from aggressive prostate cancer. This study reveals the potential for DW-MRI to be a valuable tool in the diagnosis and follow-up of patients in undergoing AS, as it confirms that cellular and structural differences exist between low-risk and high-risk lesions [36].

Overall, MRI may become a useful adjunct to current selection criteria and follow-up of men on AS. The key features of MRI are that it is noninvasive, may differentiate low-grade and high-grade PCa, and has much more sensitivity for large volume, clinically significant cancers [37]. Many candidates for AS will have tumor volumes well below 0.5 cc. A "negative" MRI in a patient whose biopsy shows minimal disease therefore increases the likelihood that the patient does not harbor a significant volume of disease. MRI will have an increasing a role in selecting patients for AS and as a trigger for re-biopsy and/or intervention during surveillance. A particular group that may benefit are those who exhibit adverse PSA kinetics in the absence of BPH or inflammation, with minimal disease on repeat biopsy.

Finally, recent data indicates that current biopsy schemes often miss large volume anterior tumors. This has been termed the prostatic evasive anterior tumor syndrome or "PEATS" [30]. MRI may help uncover such patients and direct further biopsies. A current challenge is to better understand MRI images in men considering or being managed with AS. This requires the pooling of data from individual patients' tumors with the combination of different sequences, use of diffusion-weighted MRI (DW-MRI), magnetic resonance spectroscopy, and other contrast manipulations combined with biopsy data [38]. The idea that men on AS could have their cancer volume progression and tumor grade documented with MRI is enticing [27].

## Outcomes of Active Surveillance

A pooled analysis by Chodak et al. [39] of the original data from 828 patients treated by the more traditional watchful waiting with intervention with metastatic disease as described earlier was the catalyst for current AS strategies. The pooled data is based on patients from six non-randomized studies where cancer-specific survival and metastasis-free survival were reported with up to 10 years of follow-up. Low-grade tumors did better than high-grade tumors with the prospect of metastasis development at 10 years approximately twice as great in the high-grade groups. This also translated into poorer survival for the higher-risk tumors.

The largest prospective series of modern AS from Toronto pioneered by Klotz et al. [32] has recently reported the outcome of AS with selective delayed intervention by using clinical prostate-specific antigen (PSA) or histologic progression as treatment indications for clinically localized prostate cancer (Table 51.3). With a median follow-up of around 8 years (range 1–15 years), the total of 453 men represents

**Table 51.3** Outcomes of active surveillance in large prospective series

| Author; location | Year published | Patients | Median follow-up (month) | % treated; treatment-free (%) | Overall/disease-specific survival (%) | % BCR post-deferred treatment |
|---|---|---|---|---|---|---|
| Klotz et al. [32]; University of Toronto, Canada | 2009 | 450 | 80 | 30; 72 at 5 years | 79/97 at 10 years | 50 % (13 % overall) |
| Van den Bergh et al. [22]; Multicentre, Europe | 2009 | 616 | 47 | 32; 43 at 10 years | 77/100 at 10 years | 20 %[a] |
| Dall'Era et al. [40]; University of California San Francisco (UCSF), USA | 2008 | 328 | 43 | 24; 67 at 5 years | 100/100 at 5 years | NR |
| Kakehi et al. [41]; Multicentre, Japan | 2008 | 118 | 36 | 51; 49 at 3 years | NR | NR |
| Carter et al. [42]; Johns Hopkins, USA | 2007 | 407 | NR | 36; NR | NR | NR [50 % "incurable" based on pathology postsurgery] |
| Roemeling et al. [43];Rotterdam Netherlands | 2007 | 273 | 41 | 29; 71 at 5 years | 89/100 at 5 years | NR [31 % of 13 RP-positive margins] |
| Soloway et al. [44]; Miami, USA | 2007 | 99 | 35 | 8; 85 at 5 years | NR | NR |
| Hardie et al. [45]; Royal Marsden, UK | 2005 | 80 | 42 | 14; 79 at 5 years | NR | 0 % |
| Patel et al. [46]; Memorial Sloan Kettering, USA | 2004[b] | 88 | 35 | 35; 58 at 5 years | NR | NR |

Adapted from Lawrentschuk and Klotz [47]

[a]Includes 8 % who had no adjuvant hormones while remainder had adjuvant hormones (so true BCR unknown)

[b]Prospectively collected data but retrospectively reviewed (so called retro-pro study) including Gleason 7 candidates

the largest AS cohort in a prospective, single-arm, cohort study. Definitive intervention was offered to those patients with a PSA doubling time of less than 3 years, Gleason score progression (≥4+3), or unequivocal clinical progression. Overall survival was 79 %. The 10-year PCa actuarial survival was 97 %. Among the 30 % of patients ($n=117$) who were reclassified as higher risk and who were treated, PSA failure was relatively common at 50 % (13 % of the total cohort). Interestingly, data from the Swedish section of the European Randomized Study of Screening for Prostate Cancer [48] did not find differences in intermediate outcomes between immediate RP and delayed RP. There were limited patient numbers available for analysis, and of course the delayed RP group may have been subject to a selection bias. Overall, more prospective data is required to resolve this issue.

Notably in the Klotz series [32], a PSA doubling time of 3 years or less was associated with an 8.5-times higher risk of biochemical failure after definitive treatment compared with a doubling time of >3 years. However, this must be bal anced against an observed low rate of PCa mortality because other-cause mortality accounted for almost all of the deaths. Certainly, the conclusion that additional studies are warranted to improve the identification of patients who harbor more aggressive disease despite favorable clinical parameters at diagnosis remains valid. Other robust sized AS cohorts lead by Carter et al. [42], at Johns Hopkins and Dall'Era [40] University of California at San Francisco, both in the USA are not mature enough yet but in the future may provide the supportive data necessary to help refine selection and interventional criteria.

## Triggers or Criteria for Intervention in Men Undergoing Active Surveillance

Again, as with selection criteria for AS, the triggers for leaving surveillance and having radial therapy are not well defined. Klotz has focused on PSA kinetics [32] whereby a doubling time of >3 years of concern – although this is only likely to happen in around a quarter of men in a large series. Others have elected to follow more regular biopsies while others still believe that the very criteria that patients were entered upon should be deemed exit points even after multiple biopsies [40, 42]. What most agree on at this stage is that a combination of regular DRE, PSA, and biopsies at least between 1 and 3 yearly should all be factored into the decision to progress to radical therapy in the hope of obtaining a cure in men who were initially believed to have low-risk disease. Increasingly, dynamic contrast-enhanced and diffusion-weighted MRI is being incorporated into the algorithm to enhance the identification of men with large volume, usually anterior disease. This is particularly useful in patients with minimal Gleason 6 on biopsy and adverse PSA kinetics.

## Biomarkers in Active Surveillance

Many biomarkers disease are currently being evaluated. These include multiparametric tissue-based assays using a systems pathology approach (i.e., the Aureon test), mitochondrial deletion assays (Mitomics), somatic cell SNP analysis, and the PCa antigen 3 (PCA3) urine-based assay. The PCA3 test may allow pre-biopsy risk stratification. PCA3-based nomograms have been applied and validated in a large, external, European cohort of men at risk of PCa [8] which adds data to the already published in the USA [49]. A biomarker assay which accurately predicts tumor aggressivity (or benignity) would enhance patient selection, PCA3 follow-up, timing, and need for biopsies in AS protocols. While the conventional PSA and biopsy-based approach to surveillance is associated with an extremely low PCa mortality rate, approximately one third of patients have eventually been subject to radical therapy. The benefit of the imaging and biomarker-enhanced approach would be to lower the proportion of patients on surveillance requiring definitive intervention and generating an earlier signal for intervention in the small remaining minority who are reclassified as higher risk. Ultimately biomarkers and imaging may be combined together to create individualized and tailored "biological signatures."

## Mortality from Active Surveillance

Currently, there is little data regarding mortality from AS. The reported data for patients dying while on active surveillance is best addressed by the University of Toronto cohort. Klotz and colleagues [50] reported that out of a series of around 450 patients on AS, five died of PCa. All of them had a PSA doubling time of 1.6 years or less triggering a recommendation of radical therapy. Radical intervention was performed in three of the five patients. Two received radiation and one underwent radical prostatectomy. Of the two patients who did not receive definitive treatment, one was lost to follow up and was treated conservatively by his family doctor while the other elected androgen deprivation therapy rather than radical treatment. Overall, there was a low cacer- specific mortality in this providing support for an AS approach to favorable-risk PCa. This is notable as only one of the 453 patients presented with favorable disease and had a time course of disease progression which left open the possibility that he might have suffered a preventable death. This analysis reinforces the importance of close monitoring and of definitive treatment for those in whom disease is reclassified as higher risk over time.

## 5 Alpha Reductase Inhibitors (5 ARIs) in the Active Surveillance Setting

Another major development may be data supporting the use of 5 alpha reductase inhibitors (5 ARIs) in the AS setting. Two large trials, PCPT [51] and REDUCE [38, 52], have reported that the rate of PCa diagnosis is decreased by 30 % with 5 ARIs. Many men in these studies harbored undiagnosed PCa at entry. Thus, it is a reasonable inference that these drugs act to stabilize and or reduce the volume of existing PCa; indeed, that may be their main mode of action as prevention agents. One study testing this hypothesis in surveillance patients, the REDEEM study [53], has been completed but has not yet reported. It is possible that for many men with favorable-risk PCa, a 5 ARI represents a low-cost, minimal intervention that is sufficient to further reduce their risk of progression to exceedingly low levels. At this point, however, there is no direct evidence to support this hypothesis. While placing men on surveillance on 5 ARIs is appealing, particularly if they have other indications for the drug (i.e., BPH symptoms), it should not be considered a definitive therapy. Such patients still require close monitoring and periodic biopsies. The PSA kinetics in men on 5 ARIs are simply recalibrated from the new baseline nadir.

## The Future of Active Surveillance

AS is increasingly popular as a strategy for selected men in Europe, Canada, and Australia with the USA tentatively following. A suggested eligibility, follow-up schedule, and triggers for intervention are summarized based on current knowledge (Table 51.4). However, the future of AS and uptake as a modality to manage low-risk PCa will depend upon better patient selection and improved identification of when the disease process has altered such that radical intervention is required prior to local advancement or metastases. On the first point, the two most likely candidates for achieving this are imaging, particularly with MRI.

Regarding the ability to better identify those at risk of progression while on AS, the tools available are PSA and PSA velocity, DRE, repeat biopsy, and serial imaging. Most of these tools are currently employed in AS protocols. Imaging has been utilized where discordance between PSA and other biopsy finding exists with anteriorly placed tumors using MRI [30]. Biomarkers for this indication are in development

An area that will potentially expand is focal therapy which is an emerging competitor for AS. Because focal therapy still requires close follow-up and serial biopsies [54], it could be construed as a form of "Surveillance Plus." A likely future scenario is that both approaches will have a role, with AS for those patients whose MRI shows no significant lesion and whose biomarkers are favorable, focal therapy for those with a unifocal index lesion on MRI with favorable biopsy findings, and radical treatment for those with adverse pathology [47].

**Table 51.4** Active surveillance: suggested algorithm for eligibility and follow-up

| |
|---|
| Eligibility |
| PSA ≤ 10 ng/mL |
| Gleason ≤ 6 |
| T1c–T2a |
| Depending on age and comorbidity: <3 cores involved, <50 % of any one core |
| Follow-up schedule |
| PSA, digital rectal examination every 3 months for 2 years, then every 6 months assuming PSA is stable |
| 10–12-core biopsy at 1 year and then every 3 years until age 80 |
| Optional: transrectal ultrasound on alternate visits |
| Triggers for intervention |
| For PSA doubling time of <3 years (in most cases, based on at least eight determinations; about 20 % of patients) |
| For grade progression to Gleason 7 (4 + 3) or higher (about 5 % of patients) |

Adapted from Klotz and Nam [10]
These are guidelines and should be modified according to patient age and comorbidity

In summary, AS represents a new treatment paradigm of minimal morbidity while preventing harm, provided a life-threatening PCa is treated before extraprostatic extension or metastasis develops. Selection criteria for AS are by no means standardized [55]. Currently, selection is based on clinical grounds, biopsy results, and PSA. Imaging is not currently considered in any published protocols of which the PRIAS is the largest study registry gathered to date. Despite the appeal of AS, it has not been universally accepted by clinicians or patients owing to the possibility of understaging or progression leading to unnecessary morbidity from additional treatments or even a preventable death in some instances that may not have been occurred if radical treatment was used upfront to cure the patient [21]. Cohort studies and prospective, randomized trials comparing AS with standard interventions [are] underway to help delineate its true role, for example, the surveillance therapy against radical treatment (START) trial and the prospective validation of active surveillance in prostate cancer (PRIAS) study [56–58]. Until then, eligibility, follow-up schedules, and triggers for intervention will continue to evolve.

Overall, AS is an appealing option for men with favorable-risk prostate cancer, particularly those whose extent of disease appears minimal. It has been demonstrated to be safe in the intermediate time frame. The quality of life benefits are indisputable. The controversy in this field is now related to optimal patient selection and the ideal triggers for intervention with clinicians and patients weighing up the risk and benefits (Table 51.5) in each individual.

**Table 51.5** Risks and benefits of active surveillance

| Risks | Rationale |
|---|---|
| Anxiety | Progression of disease, missing "window of opportunity," " living with cancer" |
| Progression (and ultimately mortality) | Loss of the "window of opportunity for cure" leading ultimately to poorer oncological outcomes and need for adjuvant treatment that may not have been required initially |
| Erectile dysfunction | Secondary to multiple biopsies; concern about "living with cancer" |
| *Benefits* | |
| Morbidity | Reduced morbidity and improved quality of life compared to radical treatments. Avoidance of overtreatment, making early detection efforts for high risk disease more appealing |
| Psychological | Less anxiety (tumor does not require treatment so not life threatening) |
| Costs/resources | More resources focused on life-threatening cancers translating to reduced burden of prostate cancer on the heath systems |

Adapted from Lawrentschuk and Klotz [47]

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# Anesthesia for Robotic-Assisted Prostatectomy

52

Vinod Malhotra and Peter M. Fleischut

## Introduction

This chapter will help the perioperative team acknowledge and address the potential issues associated with robot-assisted laparoscopic surgery. Topics to be discussed will include the physiological effects of pneumoperitoneum with carbon dioxide and its attendant change of increased abdominal pressure and hypercapnia along with the complex changes of steep head down tilt (SHDT) on the respiratory, cardiac, neurologic, and other organ systems. The physical effects of robot-assisted laparoscopic surgery, along with considerations for high-risk patients, logistics, and planning, will also be discussed. Recognition of these factors will help improve the safety for the patients and the quality of perioperative outcomes. Furthermore, interdisciplinary communication is essential in ensuring the delivery of high-quality care to these patients.

Robot-assisted laparoscopic surgery has been proven to have many advantages over open surgery for prostate cancer. Some of the benefits are cosmetic while other benefits include reductions in blood loss, decreased postoperative pain, prevention of ileus, shorter hospital stay, and potential lower cost. A reduced number of postoperative respiratory complications and wound complications have also been reported following robot-assisted laparoscopic surgery [1, 2]. Given the advantages of this procedure, an increasing number of these operations are being performed.

While there are proven surgical benefits, there are many physiologic and anesthetic changes that challenge the anesthetist when performing these procedures. In addition, this type of surgery is associated with a long learning curve, narrowed visual field, need for general anesthesia, longer duration, higher fixed costs, and physical space required to accommodate the equipment in the operating rooms. The recognition of these factors dictates attention to anesthetic problems and the need for teamwork.

Although relative contraindications for robot-assisted laparoscopic surgery have been identified, there are no absolute contraindications. The contraindications may include coagulopathy, diaphragmatic hernia, severe cardiovascular and pulmonary disease, increased intracranial pressure, retinal detachment, renal failure, history of extensive abdominal operations, sickle cell disease, peritonitis, large intra-abdominal mass, tumor of the abdominal wall, or hypovolemic shock [3, 4]. Knowledge of the physiologic changes of the procedure can facilitate preparation for surgery and allow practitioners to address such concerns.

Anesthetic concerns are primarily related to (1) SHDT and its physical and physiologic effects on multiple organ systems and (2) pneumothorax using carbon dioxide ($CO_2$) with attendant effects of increased intra-abdominal pressure and hypercapnia.

## Physiologic Changes due to Pneumoperitoneum

There are many physiologic effects of pneumoperitoneum that can affect various organ systems, most notably the respiratory, cardiac, and neurologic systems. These are mainly due to hypercapnia and increased intra-abdominal pressure.

### Effects of Hypercapnia

The properties of carbon dioxide, that it is nonflammable, readily diffuse across membranes, rapidly removed from the lungs, and highly soluble make it ideal for abdominal insufflation. Carbon dioxide levels can be measured intraoperatively, and

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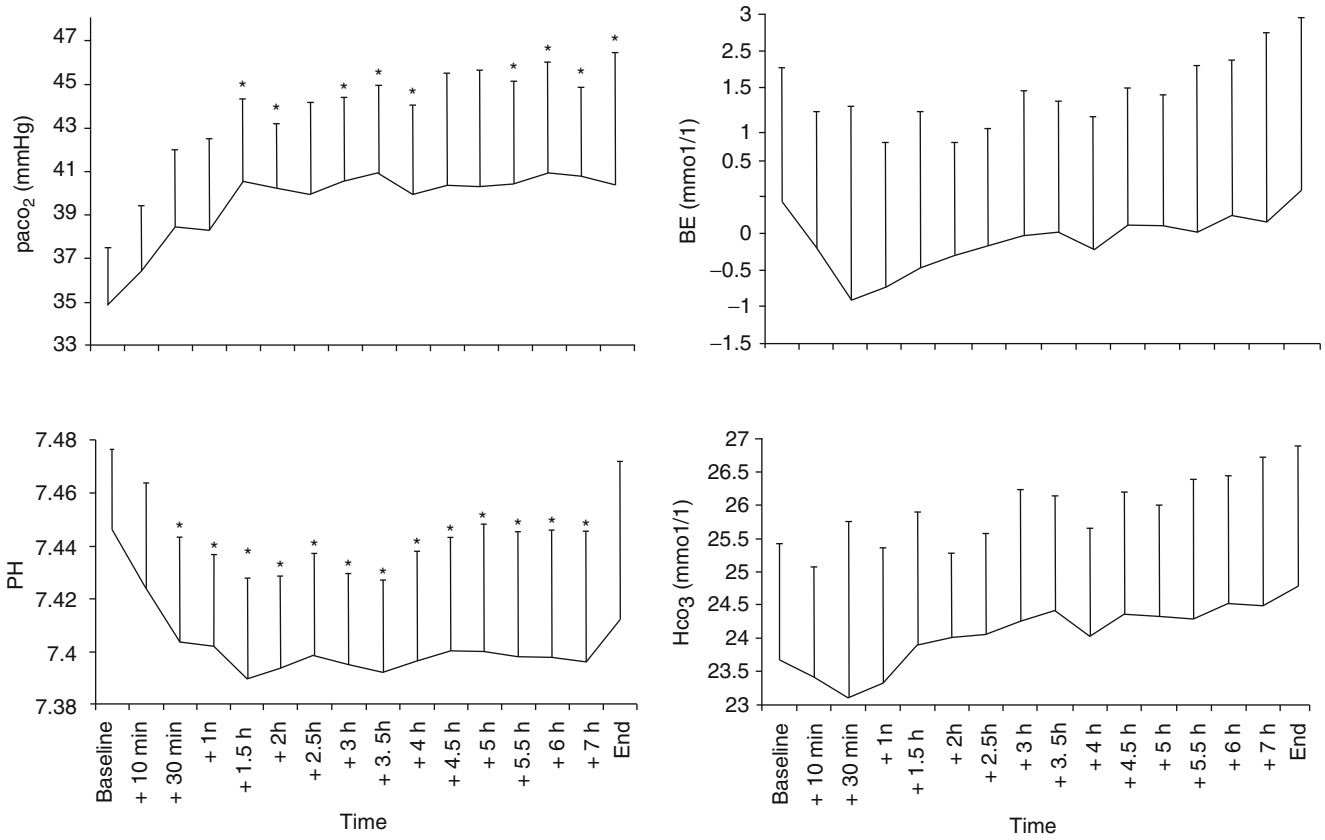


**Fig. 52.1** Changes in $PaCO_2$, pH, base excess, and $HCO_3$ from pneumoperitoneum (Meininger et al. [12], Figure 3)

ventilation can be increased to facilitate removal. While this works effectively in most healthy patients, the end-tidal $CO_2$ and arterial $PCO_2$ may continue to rise in some patients who are extremely obese or have COPD. It has been shown that in most patients, the end-tidal $CO_2$ and arterial $CO_2$ increase within 15–30 min of $CO_2$ insufflation of the peritoneum. This is accompanied by a corresponding decrease in pH. As stated earlier, an increase in ventilation will rectify this in most patients. Proper monitoring and recognition of the consequences of carbon dioxide levels are extremely important as abnormal levels can result in deleterious effects if not addressed [5, 6].

Carbon dioxide is not only the gas that is used for insufflation, it serves as a major end product of metabolism. The average adult produces approximately 200 mL of $CO_2$ per minute. The majority of carbon dioxide is stored in the body tissue, and the amount stored in different tissues depends on the perfusion to various organs. The greater the perfusion, the more that tissue can equilibrate. Tissues that are not as perfused, such as bone and fat, have a larger storing capacity. In the setting of increased carbon dioxide levels with insufflation, these storage sites maintain the carbon dioxide levels until the ventilation is increased. There are many factors that affect the ability of carbon dioxide to move from the peritoneal cavity to the lungs for excretion, such as the diffusion properties of carbon dioxide, the rate of insufflation, the surface area of the cavity, and the partial pressure difference across the membranes, as well as the perfusion and level of hemoglobin. Carbon dioxide has low water and plasma solubility, which would result in its inadequate removal from the peritoneal cavity and create a potential for a $CO_2$ embolism. However, the presence of carbonic anhydrase in red blood cells accelerates the kinetics of $CO_2$ dissolution in water 7,500 times ($CO_2 + H_2O = H_2CO_3 = H^+ + HCO_3^-$) which allows for rapid transfer of $CO_2$ to blood and finally to the lungs for excretion [7–11].

## Respiratory

Carbon dioxide absorption causes hypercapnia and respiratory acidosis that occurs as a result of the increased carbon dioxide stores as seen in Fig. 52.1 and Table 52.1 [12, 13]. In addition to the acidosis, any residual intraperitoneal carbon dioxide can cause peritoneal irritation and pain following laparoscopy. This pain although significantly lower than compared to the amount of pain a patient would experience if he were to undergo an open procedure can still be bothersome in the postoperative period and may lead to shallow breathing, hypoventilation, and further hypercapnia.

**Table 52.1** Changes in respiratory and hemodynamic variables before and after $CO_2$ insufflation

| | | $CO_2$ insufflation | | After $CO_2$ exsufflation | | | | |
|---|---|---|---|---|---|---|---|---|
| | Before anesthesia | 30 min | 80 min | 15 min | 40 min | 60 min | 90 min | 120 min |
| Mode | Spontaneous | PCV | PCV | PCV | PCV | PCV | PCV | Spontaneous |
| PIP (mmHg) | – | 18 | 22 | 22 | 22 | 22 | 18 | – |
| Rate (per min) | – | 14 | 32 | 32 | 28 | 28 | 10 | – |
| I:E | – | 1:2 | 1:1 | 1:1 | 1:1 | 1:1 | 1:4 | – |
| VE (L) | – | 4.5 | 4.5 | 11.0 | 11.0 | 10.6 | 8.0 | – |
| $FIO_2$ | 0.2 | 0.6 | 1.0 | 1.0 | 1.0 | 0.6 | 0.6 | 1.0 |
| pH | 7.44 | 7.20 | 6.94 | 7.10 | 7.22 | 7.31 | 7.31 | 7.27 |
| $PaCO_2$ (mmHg) | 36 | 71 | 137 | 91 | 64 | 50 | 51 | 56 |
| $ETCO_2$ (mmHg) | – | 37 | 63 | 36 | 26 | 21 | 31 | 48 |
| $VD_{phys}$ (%) | – | 48 | 54 | 60 | 59 | 58 | 39 | 14 |
| $PaO_2$ (mmHg) | 65 | 92 | 183 | 189 | 148 | 112 | 133 | 373 |
| $SpO_2$ (%) | 93 | 95 | 97 | 99 | 98 | 98 | 100 | 100 |
| HR (bpm) | 80 | 70 | 105 | 85 | 70 | 65 | 65 | 80 |
| SBP (mmHg) | 130 | 120 | 140 | 80 | 95 | 95 | 125 | 130 |
| DBP (mmHg) | 95 | 70 | 80 | 50 | 55 | 50 | 70 | 75 |
| CVP (mmHg) | – | 9 | 18 | 9 | 8 | 7 | 4 | 5 |

Yoshida et al. [13], Table 1

*Mode* respiration mode, *spontaneous* spontaneous respiration, *PCV* pressure controlled ventilation, *PIP* peak inspiratory airway pressure, *Rate* respiratory rate, *I:E* inspiration:expiration time ratio, $V_E$ minute ventilation, $FIO_2$ fractional inspired concentration of oxygen, *pH* arterial blood pH, $PaCO_2$ partial pressure of arterial carbon dioxide, $ETCO_2$ end-tidal carbon dioxide concentration, $VD_{phys}$ physiological dead space volume, calculated using the modified Bohr equation 1 – $ETCO_2/PaCO_2$, $PaO_2$ partial pressure of arterial oxygen, $SpO_2$ arterial oxygen saturation measured using a pulse oximeter, *HR* heart rate, *SBP* systolic arterial blood pressure, *DBP* diastolic arterial blood pressure, *CVP* central venous pressure

### Cardiac

Hypercapnia can cause multiple cardiac effects such as tachycardia, arrhythmias, vasodilation of vascular beds like cerebral vessels and vasoconstriction of other vasculature such as splanchnic and pulmonary circulation, increased pulmonary artery pressure, increased epinephrine release, and increased norepinephrine release. Lastly, hypercapnia decreases oxygen's affinity to hemoglobin. As can be seen from Fig. 52.1 and Table 52.1, these effects start to occur within approximately 15 min after insufflation and would continue to rise unabated if no intervention is done [12, 13]. Of note is the caution that end-tidal $CO_2$, commonly used as representative of arterial $CO_2$ in these patients who do not have indwelling arterial catheters, may not reflect the arterial $CO_2$ accurately if the patients has pulmonary disease (especially COPD). Then, arterial $CO_2$ can increase to dangerous levels in those patients as evidenced in a case reported by Yoshida et al. citing a robot-assisted laparoscopic cystectomy in a patient with COPD where $paCO_2$ increased to 137 Torr while the end-tidal $CO_2$ was 63 Torr and pH was 6.34. This resulted in a flat electroencephalogram due to the narcotic properties of $CO_2$ [13].

### Neurologic

Hypercapnia causes increased cerebral blood flow and increased intracranial pressure. Narcotic effects of $CO_2$ have been documented in the literature, and in some cases, the hypercapnia can be so significant that it causes a flat electroencephalogram, a marked reduction in the bispectral index (BIS) with an increased burst suppression ratio (SR) [13].

## Effects of Increased Abdominal Pressure

### Respiratory

Pneumoperitoneum causes significant changes to the ventilation and respiratory system. The compliance of the respiratory system is decreased by approximate 30–50 %, leading to increased airway pressures. In addition, a ventilation perfusion increases mismatch. These changes predispose the patient to hypoventilation and hypoxemia [14–18]. Adjustments to ventilation such as changes in tidal volumes, respiratory rates, maximum inspiratory pressure, and positive end expiratory pressure can help the anesthesiologist maximize ventilation and oxygenation. Since the patient has elevated abdominal pressure, employing pressure-controlled ventilation allows us to achieve higher tidal volumes with a lower maximum pressure. In our experience, pressure-controlled ventilation allows the practitioner to set a pressure, and every breath, the patient receives the set pressure for the duration of the breath. This results in a patient requiring less pressure to achieve an adequate tidal volume. Pressure-controlled ventilation has been more effective than volume-controlled ventilation on most occasions in our difficult to ventilate patients. In comparison, volume-controlled ventilation achieves a set tidal volume regardless

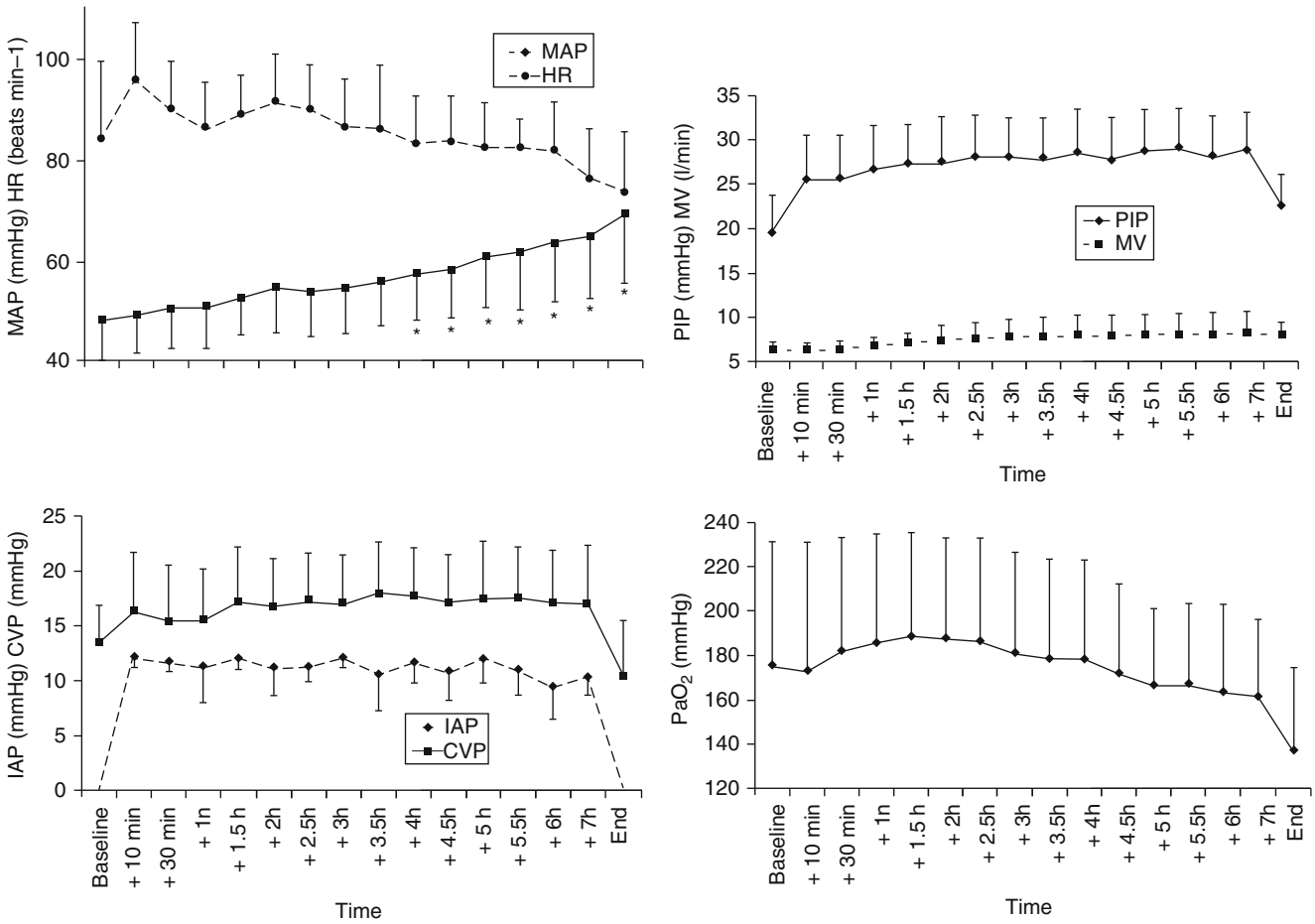


**Fig. 52.2** Changes in MAP, IAP, PIP, and $PaO_2$ from pneumoperitoneum (Meininger et al. [12], Figure 1)

of the pressure required to achieve the set volume. Once the volume is achieved, the pressure decreases. This results in a patient experiencing a rapid, high peak pressure from the ventilator. In this setting, there is a higher potential for barotrauma, inefficient ventilation, and oxygenation. If pressure ventilation is employed, several considerations need to be acknowledged. The anesthesiologist and surgeon should be in constant communication. When the surgeon decreases the pneumoperitoneum, the patient will still be receiving the same driving pressure ventilation. This may lead to much higher tidal volumes than originally set.

## Cardiac

There are many cardiac changes that can occur as a result of increased abdominal pressure. The increase in intra- abdomi nal pressure affects venous return, systemic vascular resistance, and possibly inotropism. Venous return is decreased by caval compression and increased venous resistance. The increased abdominal pressure also increases intrathoracic pressure and possibly stimulates peritoneal receptors causing bradycardia. These factors cause the release of neurohormonal factors such as vasopressin and catecholamines. Lastly, the increased intra-abdominal pressure increases vascular resistance of intra-abdominal organs. The increased vascular resistance and release of neurohormonal factors lead to an increase in systemic vascular resistance. The increase in systemic vascular resistance eventually can increase arterial pressure. The patient's arterial pressure may be elevated while the cardiac output is decreased due to decreased venous return. Changes in heart rate, mean arterial blood pressure, and central venous pressure during carbon dioxide insufflation are shown in Fig. 52.2 [12].

During robotic prostatectomy, intra-abdominal pressure is commonly greater than 12–15 mmHg. Intra-abdominal pressures greater than 10 mmHg have been shown to decrease cardiac output by approximately 10–30 %. These findings have been confirmed via pulmonary artery catheter measurements, thoracic electrical bioimpedance, esophageal echo-Doppler, and transesophageal echocardiography. These changes although significant seem to be very well tolerated in healthy patients. Cardiac filling pressures rise due to

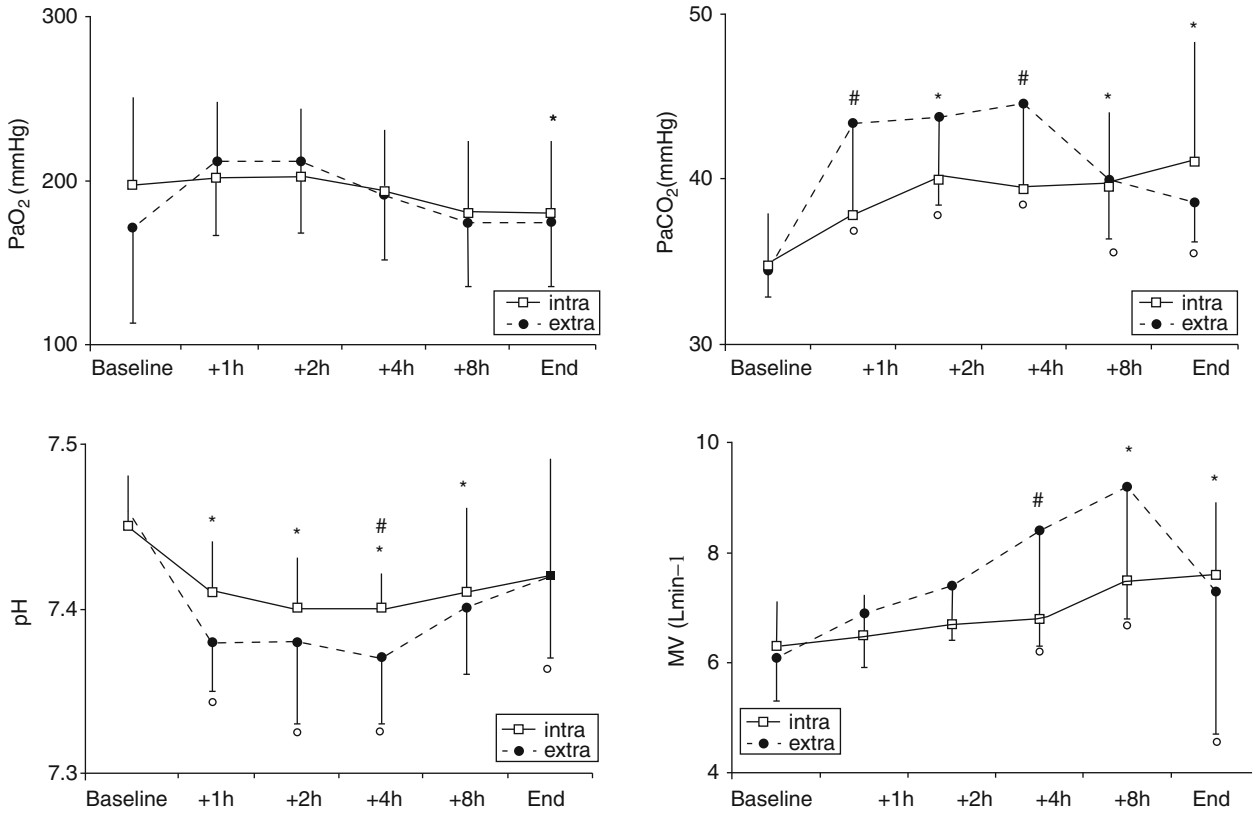


**Fig. 52.3** Respiratory effects of intraperitoneal versus extraperitoneal insufflation (Meininger et al. [19], Figure 2)

increased intrathoracic pressures. The patient's atrial natriotic peptide remains low, indicating decreased venous return. Central venous pressure and pulmonary artery occlusion pressure therefore are falsely high and are not reliable indices of cardiac filling in these patients. Intravascular volume loading prior to abdominal insufflation has been shown to attenuate these changes.

### Neurologic

As mentioned with hypercapnia, increased abdominal pressure with a resultant increase in intrathoracic pressure has an effect like a Valsalva maneuver and thus can contribute to increased intracranial pressure. Most patients without cerebrovascular disease tolerate this well. Special attention should be paid when taking care of a patient with cerebrovascular disease.

## Comparison of Extra- to Intraperitoneal Insufflation

An alternative to intraperitoneal insufflation is insufflating the extraperitoneal space with carbon dioxide. This has been studied as an alternative method to reduce the various physiologic effects. Review of the research literature reveals that there are significant hemodynamic alterations but that these are relatively insignificant from a clinical standpoint. It has been shown that carbon dioxide absorption is more pronounced with the extraperitoneal approach as shown on Figs. 52.3 and 52.4 [19].

## Effects of SHDT

During robotic prostatectomy, SHDT positioning is used to facilitate the surgical exposure. This position has significant physiologic effects that must be considered throughout the operation.

## Physiologic Changes

### Cardiac

There are many hemodynamic changes that are related to the SHDT positioning. Perfusion pressure to the lower extremities decreases while the mean arterial pressure at the Circle of Willis increases. Mean arterial pressure changes 2 mmHg for every inch of vertical height. In SHDT, the head may be 12–15 in. lower in vertical height from the blood pressure cuff on the arm, hence the normal mean arterial

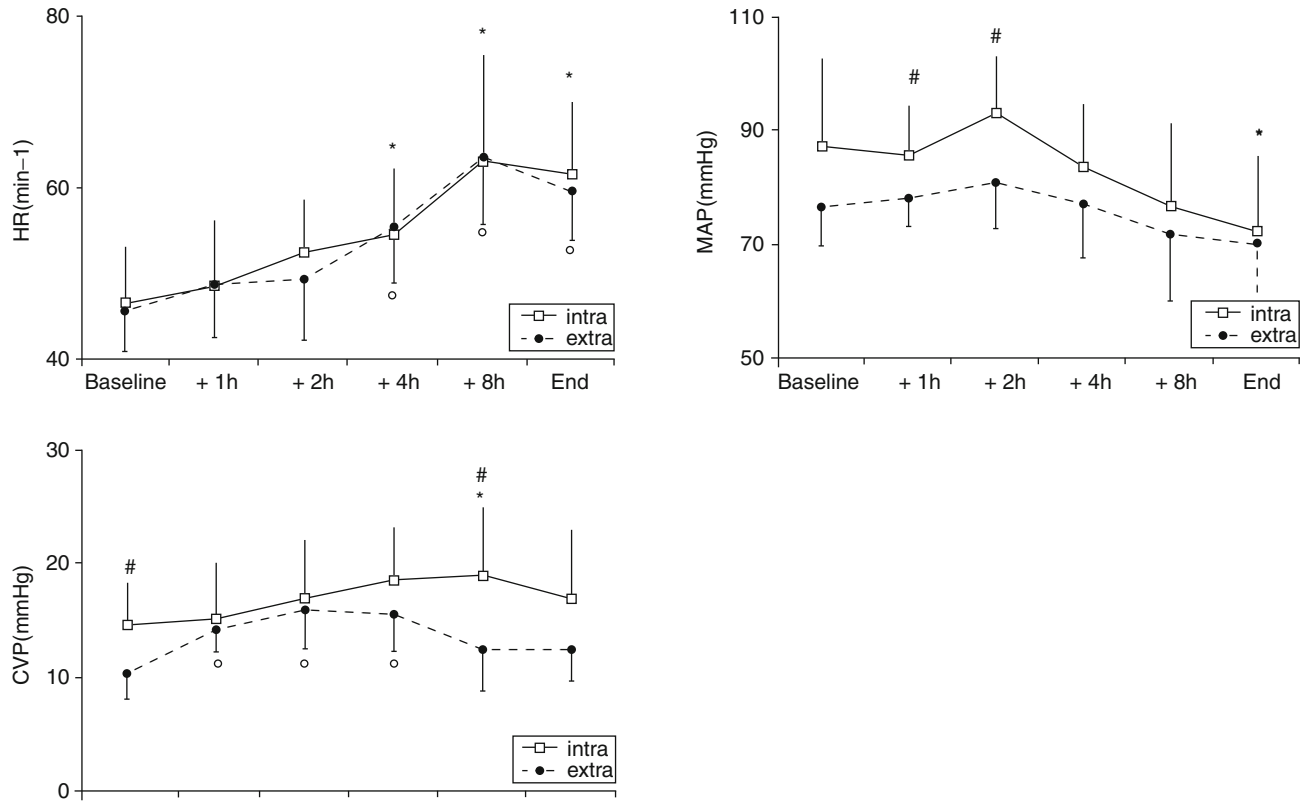


**Fig. 52.4** Hemodynamic effects of intraperitoneal versus extraperitoneal insufflation (Meininger et al. [19], Figure 1)

pressure at the arm may equate to a MAP of 120 mmHg at the head resulting in intracranial hypertension. Further, there is venous engorgement in the head, and we have recorded venous pressures of up to 33 mmHg with the transducer at the level of the ear.

On the other hand, the legs are elevated, and depending on the elevation, we have recorded mean arterial pressures as low as 27 at the ankle with concomitant with the MAP of 90 at the arm as shown in Fig. 52.5 [21]. Commonly used intermittent serial compression stockings for deep venous thrombosis prophylaxis produce 45 mmHg proximal and 52 mmHg distal pressures. It is conceivable that prolonged use of these stockings in this position can produce calf ischemia and compartment syndrome [22–24]. In a patient that is normovolemic, the patient's central blood volume is increased, cardiac output is decreased, and there is reduced perfusion to vital organs such as the brain, heart, and kidneys. These effects can be more severe and deleterious in patients with cardiac disease, therefore the patient can benefit from the use of invasive monitoring.

## Respiratory

SHDT positioning can also physically affect the respiratory system. The diaphragm is pushed up with decreased compliance and vital capacity. In addition, the functional reserve capacity is decreased, and overall there is a 20 % decrease in lung volume. Additive to the effects of pneumoperitoneum, there is a ventilation perfusion mismatch. In some patients, pulmonary edema may result from this type of positioning for a prolonged period of time. Special considerations should be taken with patients who have preexisting pulmonary dysfunction. It is also important to assess the patient for the presence of a hiatal hernia, ascertained from the medical history, physical examination, and review of chest x-ray. A large hiatal hernia may cause severe restrictive disease when the patient is placed in SHDT position [25].

## Neurologic

A triad of increased intracranial arterial pressure, increased intracranial venous pressure (both as a result of SHDT and pneumoperitoneum), and cerebral vasodilation due to hypercapnia will increase intracranial pressure in these patients. Cerebral oximetry has demonstrated increase in brain water and some degree of cerebal edema in some patients. This would certainly be poorly tolerated if any intracranial disease exists.

## Ophthalmologic

Ophthalmologic injuries that result from robotic prostatectomies have been reported frequently [26, 27]. As shown in Fig. 52.6, intraocular pressure increases during this

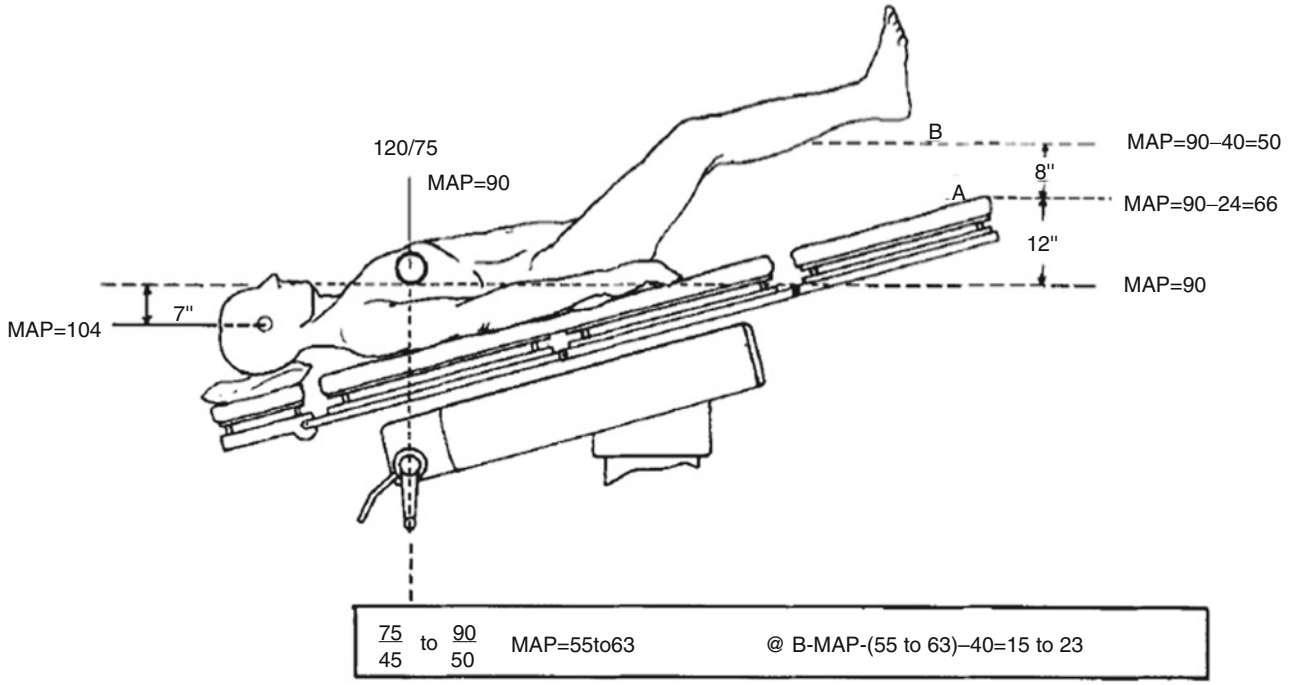


**Fig. 52.5** Blood pressure changes in the head and legs in SHDT with the legs elevated (Martin [20], Figure 4)

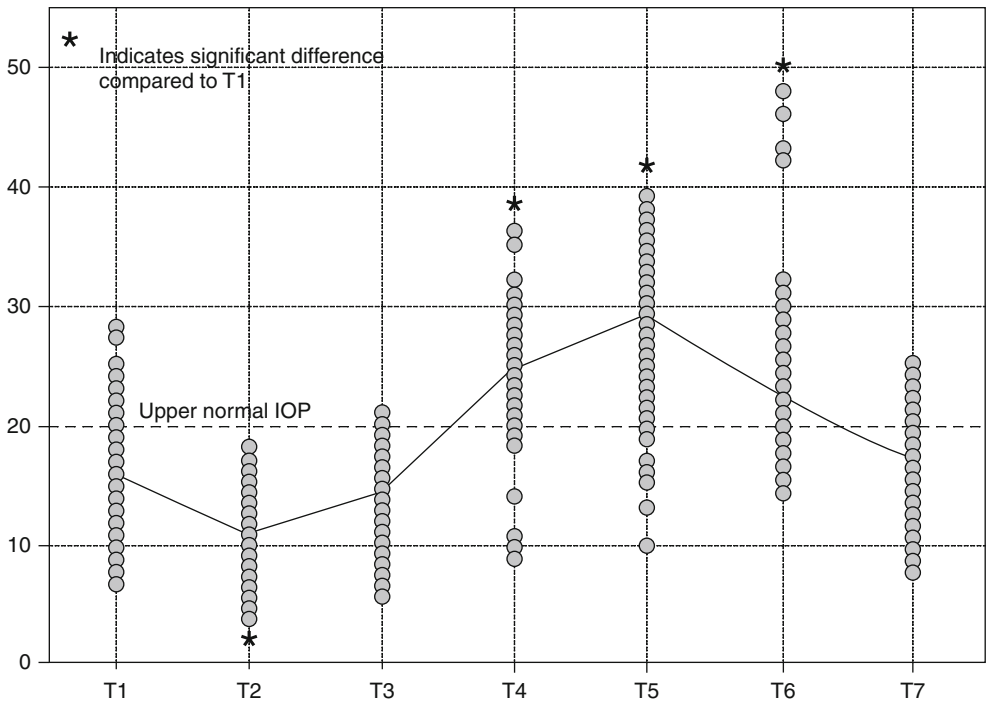


**Fig. 52.6** Effects of pneumoperitoneum and SHDT on intraocular pressure (Awad et al. [28], Figure 1)

procedure [28]. Some have postulated that the injuries are as a result of increased venous pressure, which can lead to corneal thickening, possibly causing these patients to become more susceptible to corneal injury. The visual loss registry of the American Society of Anesthesiologists has 6 reported cases of visual loss following radical prostatectomy [29]. Of these three patients underwent robot-assisted radical prostatectomy. The lesion was identified as posterior ischemic optic neuropathy, occurred in cases lasting longer than 7 h, and was usually discovered within 24 h. It has been attributed to prolonged, severe venous congestion of the head.

## Physical Effects

Other than the systemic effects, patients are also at an increased risk of developing brachial plexopathy, arthralgias, and finger injuries due to positioning. The steep Trendelenburg positioning can also increase gastroesophageal regurgitation.

Special consideration needs to be given to prevent any injury to the patient's face from the robotic arms. We have successfully used a foam headrest placed upside down over the patient's face to accomplish this. The patient's arms must have all pressure points padded to reduce any injuries of the extremity. Intravenous access must be established after securing arms to ensure patency. The patient's chest should be padded for protection and to secure the patient on the table. While securing the patient's chest with padding and tape, one must assess the peak inspiratory pressures to ensure that the patient's thoracic compliance has not been affected.

## Respiratory Complications of Laparoscopy

Many potential complications may occur with laparoscopy. The anesthesiologist must ensure the patient does not have an endobronchial intubation as a result of positioning and pneumoperitoneum as the tracheobronchial tree can ride up as sleeve over the secured ET tube. These patients are also at risk of developing subcutaneous emphysema, capnothorax, pneumothorax, pneumomediastinum, and pneumopericardium. It is essential for the entire operative team, including surgeon, nurse, and anesthesiologist, to communicate effectively to avoid these potentially life-threatening complications. If a patient develops capnothorax, insufflation should be stopped immediately and intra-abdominal pressure should be decreased. PEEP can be applied and the ventilator settings should be adjusted by increasing the respiratory rate and tidal volume to reduce the patient's carbon dioxide level. A thoracocentesis should be avoided unless absolutely necessary.

## Identifying High-Risk Patients

Since there are so many consequences of patients undergoing laparoscopic surgery in SHDT positioning, it is essential to identify patients that are potentially at high risk. These risks include patients with cardiac disease (EF <30 %), severe respiratory illness, morbid obesity, intracranial pathology, acute narrow angle glaucoma, and severe peripheral vascular disease. If a patient has one or more of these conditions, the perioperative team may consider more invasive monitoring to assess the patient pre-, intra-, and postoperatively. An in-depth understanding of the physiologic changes that occur due to laparoscopy and SHDT positioning can potentially reduce the risk and complications in this type of surgery. The patient's medical history and physical examination prior to surgery should be carefully evaluated before proceeding with robotic prostatectomy.

In patients with coronary stents, stent thrombosis is a serious risk and must be weighed against the risk of surgical bleeding. In most cases, it is advisable to continue aspirin if other antiplatelet drugs are discontinued [30, 31].

## Anesthetic Technique

Requirement of controlled ventilation precludes regional anesthesia as an option, and general anesthesia is indicated. Choice of anesthesia is not as important as meeting the goals of rapid smooth induction and quick recovery from the anesthetic, combined with generous muscle relaxation to allow adequate abdominal distention for a wide, quiet operating field. Ventilation requires frequent readjustment to maintain normocapnia and adequate oxygenation. The head should be elevated as much as possible during SHDT to reduce venous congestion of the head. The legs in stirrups should be lowered as much as possible to increase MAP in the lower extremities. Adequate hydration is a must to prevent acute kidney injury. It is not very uncommon for the postoperative BUN and serum creatinine to rise transiently. These patients undergo a bowel preparation with laxatives and may be dehydrated. Some surgeons favor intraoperative fluid restriction to ensure a better operative field. This, however, has not been established to be true beyond doubt and predisposes the patient to acute kidney injury. In the author's experience, bolus of at least 500 mL of fluid prior to pneumoperitoneum and an additional 500 mL of fluid before the prostate is out followed by an additional 1–2 L before the end of the case is optimal provided there are no contraindications to generous fluid therapy.

Laparoscopic procedures are associated with higher incidence of postoperative nausea; hence, nausea and vomiting prophylaxis are necessary. Pain is usually mild to moderate in these patients. A preemptive analgesic dose of ketorolac given toward the end of surgery and maintained for the first 48 h with rescue narcotic analgesics (patient-controlled analgesia) is effective. In our study of 100 consecutive cases, the average pain scores were 1–3 at 1 h postop and in the first 24 h [32]. Blood loss is minimal and transfusions are rarely required.

## Logistics and Planning

As with most new procedures, it is essential for all members of the perioperative team to carefully and appropriately plan for robotic prostatectomies. One primary consideration is the need for adequate space. The equipment includes a sur geon

console positioned away from the patient and robotic-assisted arms, positioned to provide laparoscopic entry into the patient. Because the equipment is large, it can consume most of the space in the operating room, so it is essential that all members of the team determine the best location for the robot. Team building and communication exercises are essential for the team to reduce complications and ensure that quality of care is provided to the patient. Emergency drills provide the opportunity to reenact potential complications and educate all of the staff members in their roles during an emergency. The entire team must ensure patient safety while adapting to these new advances in surgery.

### Conclusion

The robotic prostatectomy procedure has lead to many advantages for the patient.

Blood loss and transfusions and complications thereof have been reduced. Early ambulation and discharge with faster return to normal function have improved outcomes. However, new challenges for the anesthesiologist have been introduced. Recognition and treatment of these effects can help ensure a high quality and safe experience for patients. Above all, it is essential for all members of the perioperative team (surgeon, nursing, and anesthesiologist) to be in close communication to determine what is best for the patient. This will lead to a high-quality outcome with minimal complications.

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# Retropubic Radical Prostatectomy: The Technique

53

Hendrik Van Poppel and Steven Joniau

## Historical Data

The first radical perineal removal of the prostate was performed over a century ago by the French surgeon Proust in 1901. However, most historical reviews will mention Young to be the first to describe the procedure at the Johns Hopkins University. The retropubic approach to radical prostatectomy (RP) was introduced by Millin [1] and adopted by Memmelaar in the 1940s [2], while retrograde radical retropubic prostatectomy (RRP) was described in detail by Chute [3] and later by Campbell in the 1950s [4]. The procedure remained unpopular because of its high associated morbidity, for example, significant bleeding, urinary incontinence, and impotence. Reiner and Walsh described the anatomy of the DVC and presented a technique for ligating this complex in 1977, which reduced bleeding and improved surgical exposure [5]. Walsh et al. later defined the anatomy of the neurovascular bundles (NVBs) and reported the technique for anatomic nerve-sparing RP in 1983 [6, 7]. Since the initial report of anatomic RP by Walsh et al. in 1998 [8] and refinements in the understanding of the surgical anatomy of the prostate, open RRP techniques have been modified and continue to evolve. Together with the widespread application of PSA testing, RP became more popular and is still in many countries the old and gold standard surgical procedure attempting to control localized and locally advanced prostate cancer.

## Preoperative Measures

In the vast majority of centers, RP is advocated for men with a life expectancy of at least 10 years. These are only guidelines for selecting men for whom the benefits of surgery outweigh the potential risks. In order to determine which treatment is appropriate, general health status, comorbidities, and assessment of the individual's life expectancy are of paramount importance.

Before proceeding to RRP, it is best to wait 6–8 weeks after transrectal ultrasound (TRUS)-guided biopsy and at least 12 weeks after transurethral resection of the prostate (TURP). Both procedures cause inflammation, possible hematoma, and periprostatic fibrosis, which could render the identification of the correct anatomical planes during operation difficult and thus increase the risk of surgical complications such as rectal injury. They also complicate the assessment of possible extraprostatic extension or the preservation of the NVB. The time interval between TRUS biopsy and RP enables inflammatory adhesions or hematoma to resolve and allows time for further staging of the tumor, assessment of the surgical risk, and patient counseling. The decision whether or not to perform a nerve-sparing RP should be taken preoperatively taking into account the localization, grade and extent of the tumor, and the findings of the digital rectal examination (DRE), TRUS, and/or magnetic resonance imaging (MRI). Prior to RRP, a clean and empty colon is important both for surgical access and in case of a rectal injury. Rectal injury is a potential complication of RRP and increases the risk of massive contamination of the surgical field. In some cases, a colostomy may be required, but most rectal injuries can be managed by primary closure. The exact substance used for colon preparation can depend on the center. The evening before surgery, our patients receive Fleet oral 45 ml for 1 l of water to be ingested twice. On the day of surgery, they receive subcutaneous low molecular weight heparin before going to the operating room.

Nowadays, most centers prefer a combined spinal-epidural anesthesia. General anesthesia is done in patients who do not want to be awake during surgery and in those who have a history of back surgery or extensive arthrosis. The advantages of epidural anesthesia are a reduction of the intraoperative blood loss [9, 10], a faster recovery, and a reduction in the use of opioid analgesics [11]. There is also a lower incidence of pulmonary embolism

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and deep venous thrombosis. Another advantage is optimal pain management through the epidural catheter, which may stay in place and be used for patient-controlled analgesia for the first 24–48 h postoperatively.

The best case scenario for RRP is a slim patient with a moderately enlarged prostate who had no previous prostate surgery. The worst case scenario might be a very obese patient who had an inguinal hernia repair with a synthetic mesh or who has significant periprostatic fibrosis after a recent TURP.

## Surgical Technique

Unlike radical perineal prostatectomy, RRP requires few special surgical tools. For good visualization of the anatomy of the small pelvis, either a "light on the tip" aspirator or a headlamp is essential. Surgical loop magnification (2.5–4.5 power) may be useful for adequate dissection of the NVBs and ligation of small perforating vessels. Hemoclips and new surgical devices such as LigaSure, UltraCision, SonoSurg, and Sonotone may be used and are time-saving alternatives for the classical ligatures. However, they are better avoided in nerve-sparing dissection in order to avoid heat-induced trauma of the NVBs. The patient is placed in supine position with the chest slightly hyperextended and the table placed in some 15° Trendelenburg position for good exposure of the surgical field. The skin is prepared and draped in the usual way. A latex Foley catheter, at least 20 Fr, is placed.

## Incision and Exposure of the Small Pelvis

An 8–10-cm, midline, extraperitoneal, lower abdominal incision between the umbilicus and the pubis is performed. A Pfannenstiel incision can be helpful for simultaneous repair of an inguinal hernia but is more difficult to reach the deep pelvis. Prolongation of the midline incision caudally toward the base of the penis may further improve the view into the small pelvis. The preperitoneal space of Retzius is opened. The peritoneum is mobilized from the Retzius space laterally up to the bifurcation of the common iliac artery. Gentle cephalad retraction of the bladder and sweeping of fatty tissue provide optimal exposure of the anterior aspect of the prostate and the endopelvic fascia bilaterally. In case of a more extensive lymph node dissection, division of the vas deferens is necessary. This allows retraction of the peritoneum up to the crossing of the ureter with the common iliac artery and even up to the aortic bifurcation. When no lymph node dissection is needed or when lymph node dissection is restricted to the area below the iliac bifurcation, division of the vas deferens is not necessary.

## Pelvic Lymph Node Dissection

When a lymph node dissection (LND) is performed, it is carried out before the RP. In PCa, multiple variations of LND are described including the minimal, the standard, and the extended variant. With a minimal variant, only the lymph nodes in the obturator fossa are removed. A standard LND includes the removal of the lymph nodes in the obturator fossa and the external iliac artery. During the extended variant, a complete LND is performed along the obturator fossa and the external, internal, and common iliac vessels up to the iliac crossing of the ureter [12]. Further details on lymph node dissection are discussed in another chapter of this book.

## Incision of the Endopelvic Fascia and Lateral Dissection (Fig. 53.1)

Following lymph node dissection, all fatty tissue covering the prostate and lateral pelvic side wall is carefully dissected away to expose the endopelvic fascia, the puboprostatic ligaments, and superficial branch of the dorsal vein. The endopelvic fascia must be completely freed (Fig. 53.1a), and every single small bleeding is managed with the electrocautery. First, the right endopelvic fascia is exposed by retracting the prostate medially. The endopelvic fascia is incised over the levator ani muscle laterally taking meticulous care not to damage the DVC (or Santorini's plexus). The small incision in the right endopelvic fascia is then carefully extended posteriorly with curved scissors (Fig. 53.1b) again avoiding entering the periprostatic veins. Then, the dissection is extended laterally and posteriorly which results in exposure of the perirectal fat. Dissection should be done under meticulous hemostasis.

Before starting the same maneuver on the left side, the lateral dissection is accomplished. The levator muscle is carefully dissected off the lateral prostate with the aid of a peanut dissector (Fig. 53.1c). This allows full exposure of the NVBs dorsolaterally to the prostate and anteriorly to the rectum. The endopelvic fascia is then further incised anteriorly until the puboprostatic ligaments are reached and the apex of the prostate can precisely be identified and the apicourethral angle can be clearly recognized.

## Division of the Puboprostatic Ligaments (Fig. 53.2)

At this stage, the prostate is already completely mobilized in its lateral aspect but is still fixed to the pubis by the puboprostatic ligaments. In between these ligaments lies the superficial DVC. When the prostate is adequately pushed in anteroposterior direction, the stretched puboprostatic ligaments are

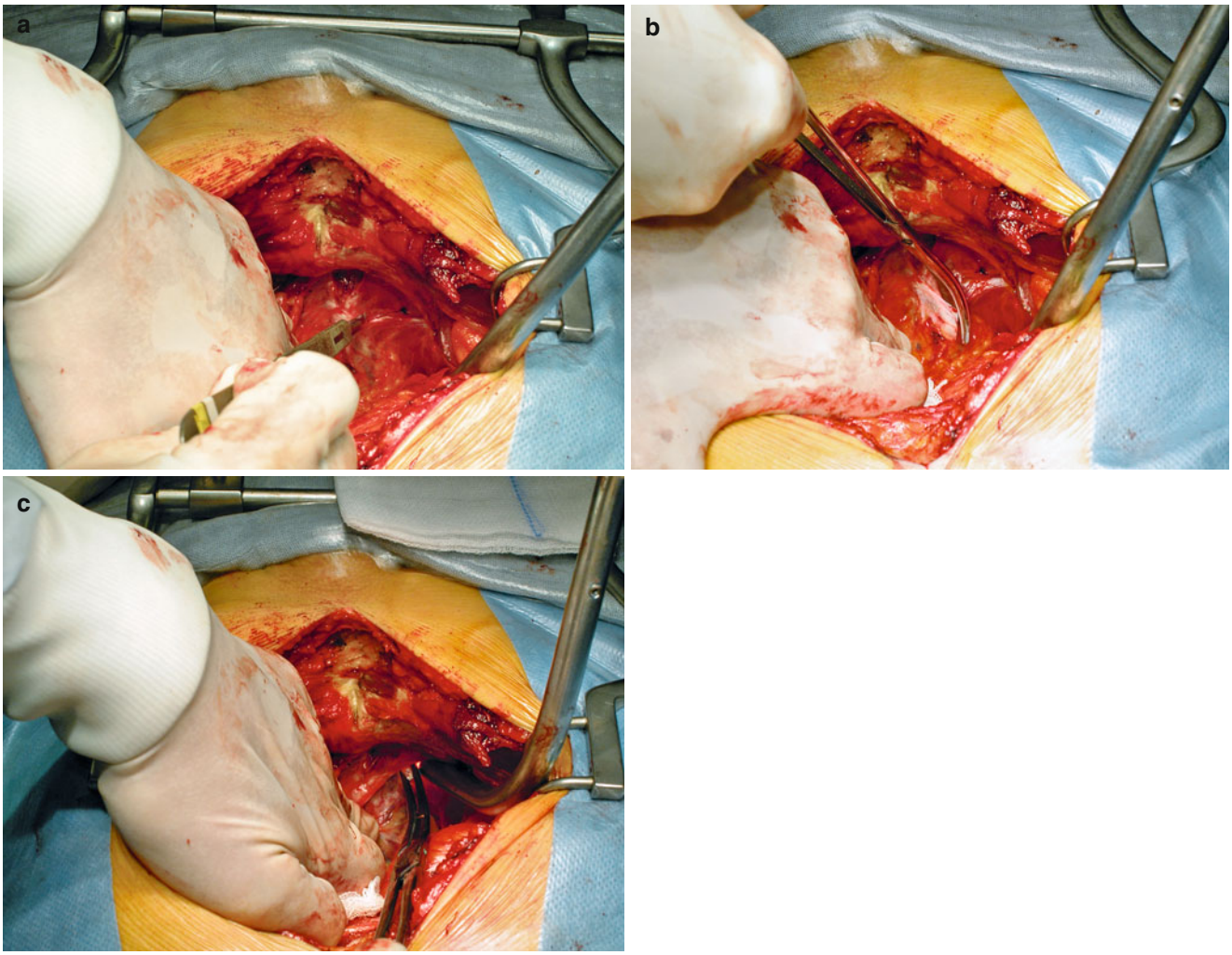


**Fig. 53.1** (**a**) The fully exposed endopelvic fascia. (**b**) Sharp incision of the endopelvic fascia. (**c**) Exposure of the lateral aspect of the prostate

exposed and can be incised, taking care not to damage the veins of the adjacent DVC (Fig. 53.2a). Proper division of the puboprostatic ligaments is necessary in order to get access to the apex of the prostate and the overlying DVC. In order to avoid damage to the pubourethral suspension, isolation of the puboprostatic ligament by a right-angled clamp is advised before sectioning. This can be done without damaging the DVC, avoiding significant blood loss during this step of the operation. We divide the puboprostatic ligaments with electrocautery (Fig. 53.2b), but it can also be done with a cold knife or scissors since they are avascular.

## Control of the Dorsal Venous Complex (Fig. 53.3)

An important step in RRP is to divide the DVC with minimal blood loss and as such providing a bloodless surgical field in which the remainder of the procedure can be performed with improved visualization. Control of blood loss reduces the risk of surgery-related mortality and decreases patient morbidity.

The only way to properly control the DVC allowing at the same time the visualization of the anterior aspect of the prostate-urethral area is by passing a blunt right-angled clamp underneath it, just anterior to the urethra. The maneuver is prepared by palpation of the DVC with the thumb and the index finger of the left hand. This allows further dissection of the DVC from the urethra and allows passage of the right-angled clamp in the correct position, just distal to the prostatic apex. To make this maneuver possible, a big-sized Foley catheter, at least 20 Charrière, is inserted. The right-angled clamp grasps a 1/0 ligature while the first assistant is pushing the prostate posteriorly, enabling the knot to be tied as far caudally as possible (Fig. 53.3a). To avoid backbleeding from the transected DVC, a 2-0 backbleeding stitch is placed through the anterior commissure of the prostate (Fig. 53.3b). Transection of the DVC is then performed using electrocautery (Fig. 53.3c). In cancers

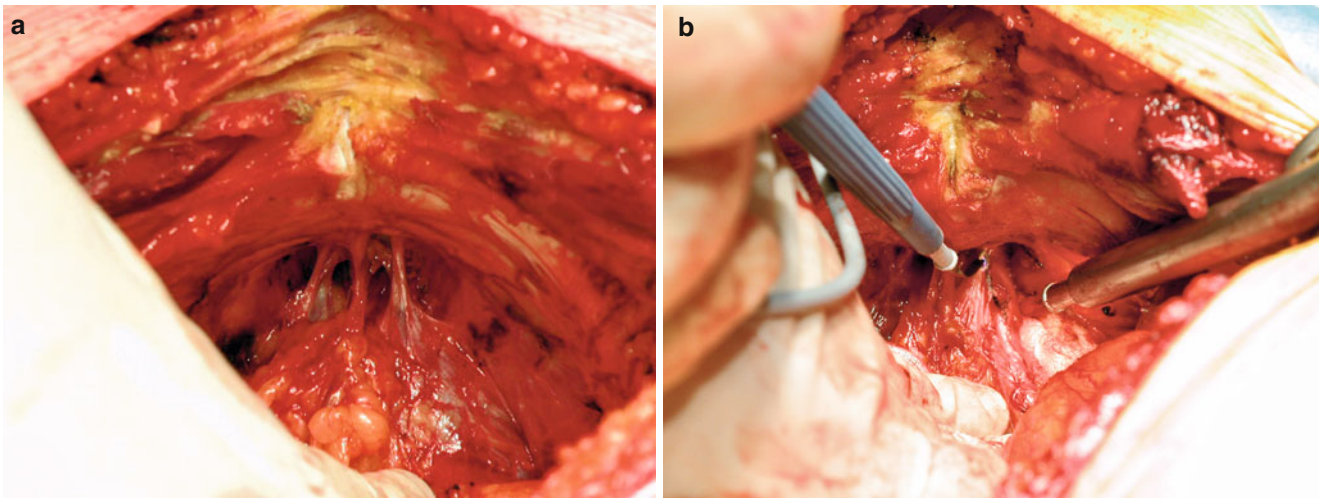


**Fig. 53.2** (**a**) Exposure of the puboprostatic ligaments. (**b**) Section of the puboprostatic ligament with the electrocautery

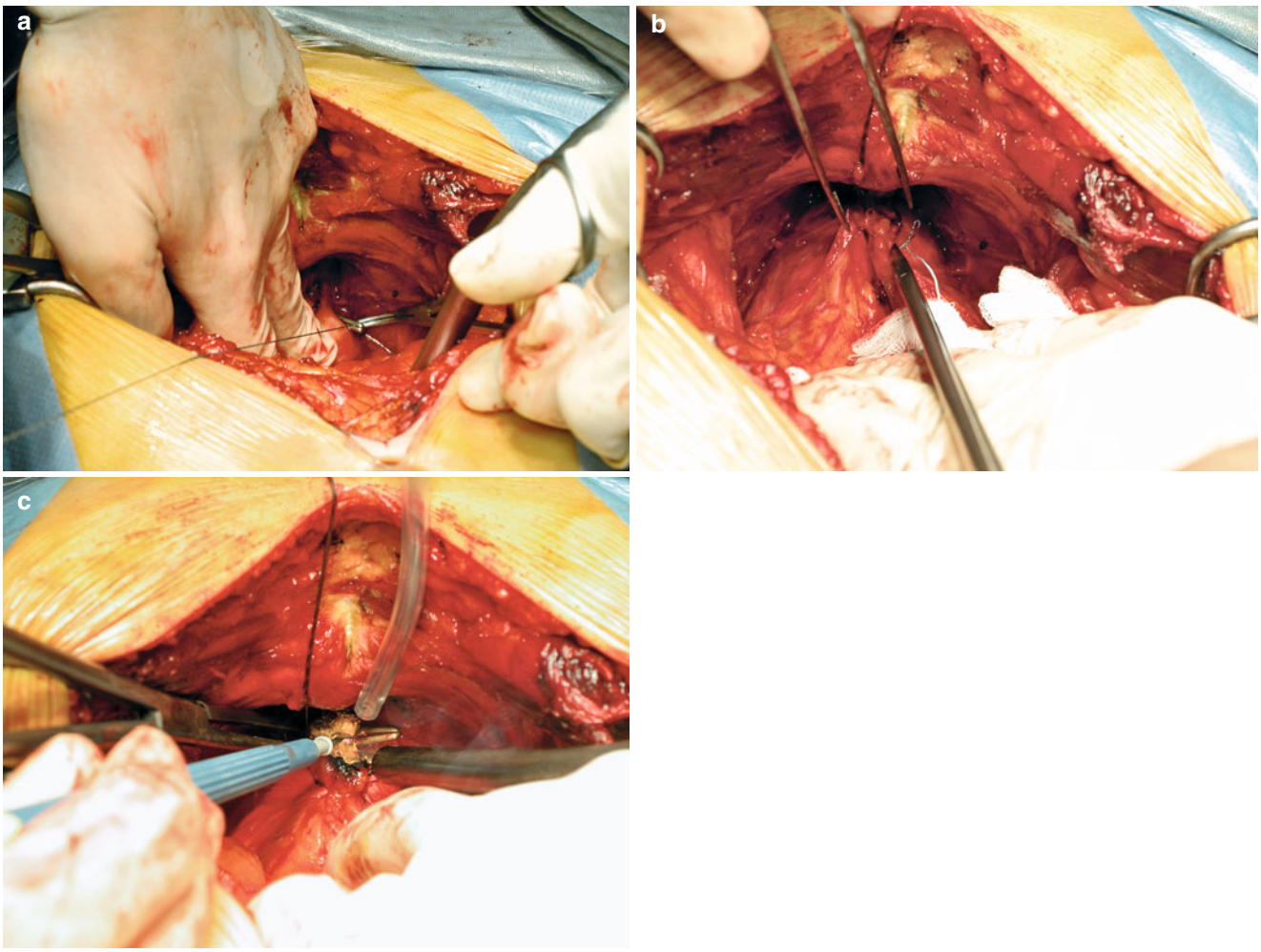


**Fig. 53.3** (**a**) Ligation of the dorsal vein complex caudally. (**b**) Placement of a backbleeding stitch cranially on the dorsal vein complex. (**c**) Section of the dorsal vein complex

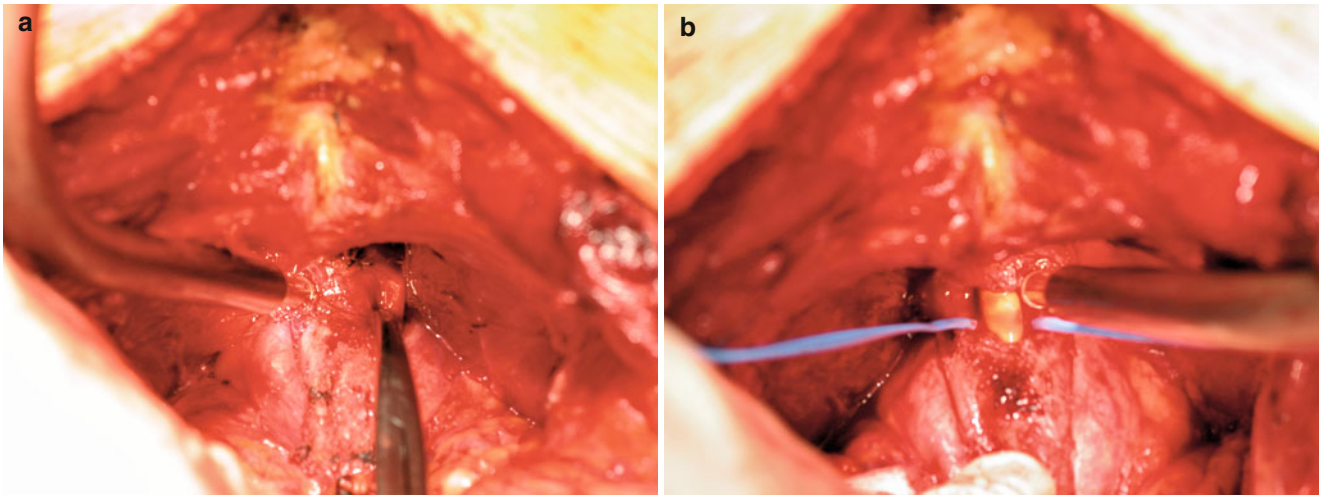


**Fig. 53.4** (**a**) Apical dissection in the nonnerve-sparing procedure. (**b**) Section of the urethra on the bladder catheter

extending to the anterior commissure of the prostate, it is important to transect as far away from the prostate as possible in order to avoid a positive anterior surgical margin. Absolute control of venous bleeding from the DVC is mandatory and may require another transfixion stitch. At this stage of the operation, no more blood loss than just a few milliliters has been allowed. The urethra is now in complete view in its anterior aspect. Cephalad traction on the prostate results in the visualization of the infraprostatic part of the urethra at the apex of the prostate. One should avoid pulling the urethra out of the pelvic floor since this might compromise the recovery of complete urinary continence by shortening of the functional intrasphincteric urethra. Therefore, traction on the urethra during this maneuver should be careful.

## The Urethra

### Nonnerve-Sparing Procedure (Fig. 53.4)

In patients who have apical tumors or clinical T3 prostate cancer, the NVB at the side of the tumor cannot be spared, and in most cases, a bilateral nonnerve-sparing RP needs to be performed. Guided by the left thumb and index finger, a right-angled clamp is passed underneath the urethra just anterior to the rectum, and a vessel loop is placed behind the urethra, allowing accurate dissection of the prostatic apex before transection of the urethra. The frequent presence of cancer in the apex of the prostate makes successful apical dissection the greatest challenge in performing RRP. Injury of the striated sphincter and inadvertent incision into the apex of the prostate, the most common site for positive margins, must be avoided. Complete sphincter preservation during apical dissection substantially decreases the risk of urinary incontinence [13]. To maximally reduce the incidence of positive surgical margins at the level of the apex, the following maneuvers are advised. On the left side, the left index finger is placed behind the urethra at the level of the prostatic apex. The dissection is now proceeded between the tissue laterally to the urethra and the urethra by inserting straight scissors close to the prostate-urethral angle and bringing them out on the top of the index finger (Fig. 53.4a). Clipping and dividing this paraurethral tissue (consisting of the portion of endopelvic fascia overlying the DVS and the external sphincter muscle fascia), including the NVB, result in a complete mobilization and visualization of the left side of the prostatic apex. On the right side, the same maneuver is performed by putting the left middle finger behind the urethra just anterior to the rectum. The prostate is pushed posteriorly with the left thumb, and scissors can be inserted close to the urethra as is described for the left side. Clipping and transection of the NVB result in a complete mobilization of the apex and provide excellent exposure of the prostatic apex and the membranous urethra.

At this point of the procedure, the urethra can be transected while the 20-Ch Foley catheter is left in place (Fig. 53.4b), and the bistouri can continue to transect the complete urethra. Removing the catheter early after transection of the anterior part of the urethra may result in upward traction on the Foley catheter that may displace the posterior apex anteriorly. This increases the risk that the posterior apex becomes inadvertently incised resulting in a positive apical margin. To avoid this, the catheter will be removed only after the urethra has been entirely transected with the knife. At this point of the procedure, some urologists place one or more stitches to facilitate finding the urethral stump at the time of anastomosis. Actually, it is not necessary, although sometimes when the urethral stump is rather short, it may give the impression to retract within the pelvic floor musculature.

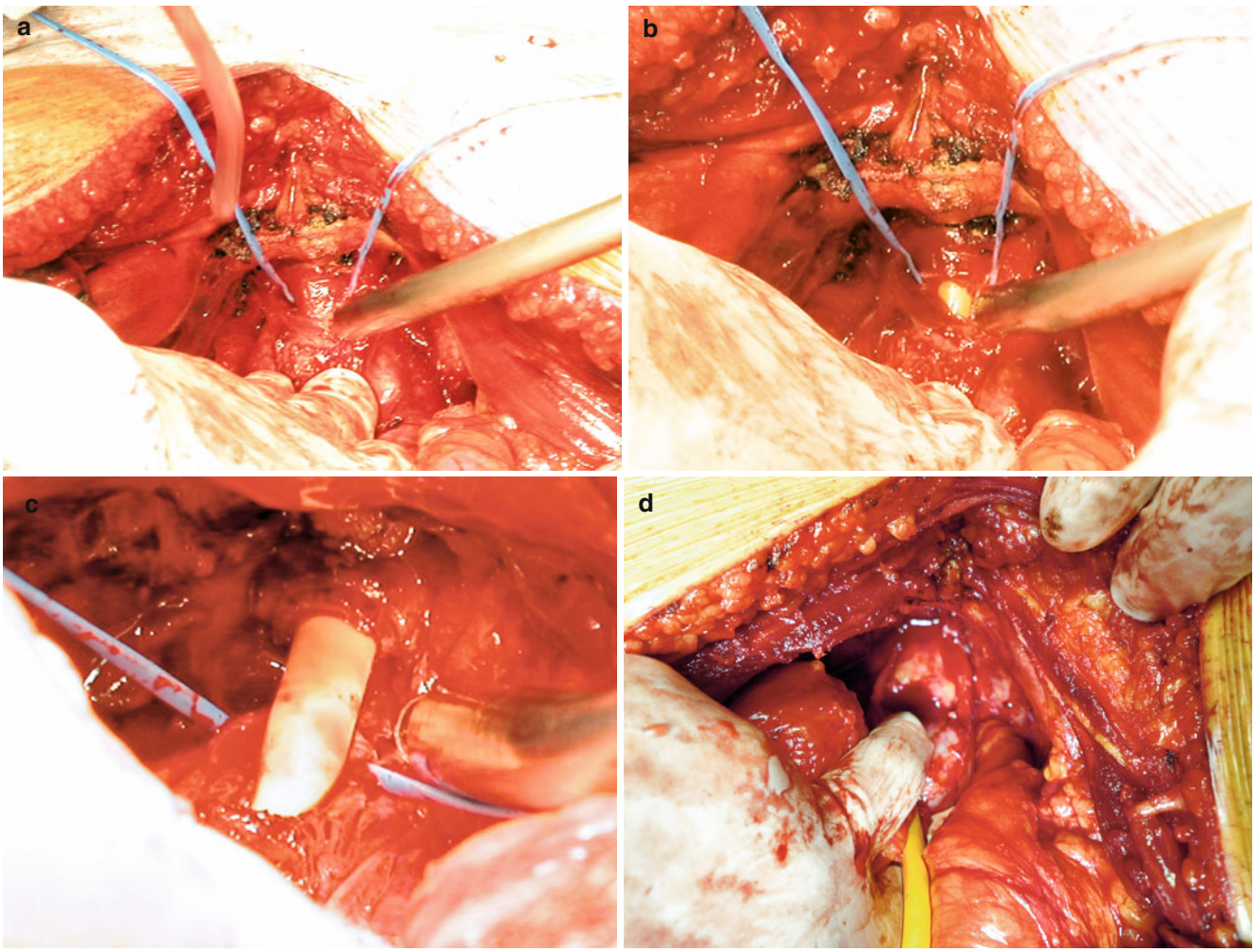


**Fig. 53.5** (**a**) Encircling the urethra at the prostate apex, leaving the NVBs laterally. (**b**) Transection of the urethra with the NVB left intact posteriorly. (**c**) Completed urethral transection and exposure of the entire prostatic apex. (**d**) Blunt enucleation of the prostate out of the two NVBs

As soon as transection of the urethra is completed, one of the most variable steps of the RRP starts. Among different patients, the rectourethralis muscle is very variable in thickness and strength. In some patients, there are no muscle fibers present. In other patients, the muscle is a real plate that is located just anterior to and sometimes adherent to the rectum. In patients with no or nearly no rectourethralis muscle (often in older patients), the index finger will easily identify the correct plane between prostate and rectum following the Denonvilliers' fascia. Blunt posterior dissection on the midline is then simply performed with the index finger up to the base of the seminal vesicles. However, when the patient has a well-developed rectourethralis muscle, it can be difficult for the surgeon to distinguish it from the rectal muscular layer. In such case, the rectourethralis muscle needs to be sharply divided with curved scissors. Then the correct cleavage plane between rectum and prostate is identified with a peanut dissector followed by the right index finger.

## Nerve-Sparing Procedure (Fig. 53.5)

Nerve-sparing surgery has a significant impact on sexual function and urinary continence and should be performed in all patients provided that excision of all tumor is not compromised. Preservation of the NVBs is one of the more delicate and important stages of RRP for men with clinically localized PCa. Today, it is safe to preserve both NVBs in most men who are candidates for RRP, and it is rarely necessary to excise both of them [14].

There are several ways to accomplish nerve preservation during RRP, of which the following are the most popular: the "apical approach" first described by Walsh [6, 8, 15] and the so-called lateral approach, a simplified alternative method described by Ruckle and Zincke [16]. In the "apical or anatomical technique," the nerve dissection is initiated at the apical level after isolation and transection of the urethra. In the "lateral approach," the dissection of the NVBs precedes the apical dissection and the urethral transection [17]. Based

on the current literature, it is challenging to establish whether one approach is superior to the other. There are currently no prospective randomized studies comparing these approaches [18]. At present, nerve-sparing surgery is routinely performed worldwide. When used in properly selected patients, it does not increase the probability of positive surgical margins or biochemical recurrence after RP [19].

Our technique to adequately prepare the NVBs at the apex of the prostate is by encircling the urethra. The safest way to do this is by putting a vessel loop behind the urethra in front of the NVBs. Depending on whether one aims to perform a uni- or bilateral nerve-sparing procedure, one can dissect between the urethra and NVBs on one or both sides. This should be done just after division and oversewing of the DVC, when the urethra and paraurethral tissues are completely visualized. This dissection can be carried out with straight scissors just lateral to the urethra. Then a right-angled clamp can be passed around the urethra while the NVB is left intact posterolaterally into the small pelvis (Fig. 53.5a). In a next step, a U- or V-shaped incision in the intraprostatic urethra anteriorly is made until visualization of the transurethral catheter (Fig. 53.5b). At this stage, the catheter is not transected, but the bistouri is placed just medially to the vessel loop and then turned with its cutting edge toward the urethra in order to section the urethra laterally and posteriorly. By following these steps, even in a nerve-sparing procedure, it is feasible to perform a complete section distal to the verumontanum without removing the catheter. In some cases, this can be difficult. One can then grasp the catheter, pull it out, and cut it. Following this, the sectioning of the posterior aspect of the urethra, clearly distal to the verumontanum, can be carried out with straight scissors. It should be noted that this maneuver augments the risk of a posterior apical positive margin. As soon as the transection of the urethra is completed (Fig. 53.5c), the rectourethralis muscle can be recognized and divided as previously described. The exact cleavage plane between prostate and urethra is identified with a peanut followed by the index finger. Rather than cutting into the ventral aspect of the prostatic fascia and dissecting off the bundles from the anterolateral surface of the prostate, we simply enucleate the apex of the prostate out of the NVBs (Fig. 53.5d). Pulling too hard on the bundles should be avoided as much as possible. This is very important as the latter will result in elongation of the NVB causing neurotmesis and temporary erectile dysfunction mostly for about 9 months. It is crucial not to use electrocoagulation on the NVB and its branches because this will lead to nerve damage. Only small tangentially placed hemostatic clips are used with the right-angled clipping forceps. Figure 53.6a shows a prostatectomy specimen where one NVB is resected while the other was preserved. Figure 53.6b shows the bilaterally spared NVB with the rectum bulging in between both.

## Dissection of the Pedicles

The next step is the transection of the prostatic pedicles. This can be done by passing a 135° angled clamp behind the pedicles, clipping them with large clips, and transecting them with curved scissors. In the nonnerve-sparing procedure, the NVBs are completely resected, and clips are placed close to the rectum. In the nerve-sparing procedure, bleeding from small vessels should be controlled with carefully placed small clips. Electrocautery is not used at the nerve-sparing site to avoid injury to the nerve fibers. As some bleeding is allowed, hemostatic sponges may be useful at this stage. The dissection is continued until the lateral aspects of the seminal vesicles are reached. At this point, the lateral aspect of the bladder neck can also be dissected already.

## Resection of the Seminal Vesicles

Dissection of the seminal vesicles must be carried out very carefully in order to avoid injury to the pelvic plexus and represents a critical point for a successful nerve-sparing technique. The Denonvilliers' fascia is divided sharply between both vasa deferentia reaching the posterior bladder wall. The index finger is inserted at the midline, and a curved dissection clamp is passed under direct vision from outside in behind the seminal vesicles and the vas deferens. Now, the index finger can be placed behind the ejaculatory complex. The top of the seminal vesicle is reached by peanut dissection, and the vessels at the apex of the seminal vesicles are clipped and divided. In a nonnerve-sparing procedure, it can be done by larger clips, while in a nerve-sparing procedure, a carefully placed small clip will suffice in order to avoid damage to the NVB. The same procedure is then repeated at the contralateral side. At this point, the prostate is completely mobilized posteriorly and laterally up to the bladder neck. The prostate is freed from any lateral adherences between prostate and bladder base.

The specimen is inspected carefully for capsular incision. If an incision is found, an extra resection can be performed at the corresponding location. If there is concern about the margin on the posterolateral surface of the prostate, the NVB on that side should be excised [15]. Graefen et al. [20] recommend intraoperative frozen section when there is suspicion about extracapsular tumor growth during a nerve-sparing procedure. A slice from the lateral surface of the removed prostate should be taken from the apex to the base. Then the area of the prostate capsule that was adjacent to the NVB should be inked. Excision of the NVB is recommended when cancer reaches the inked surface [20].

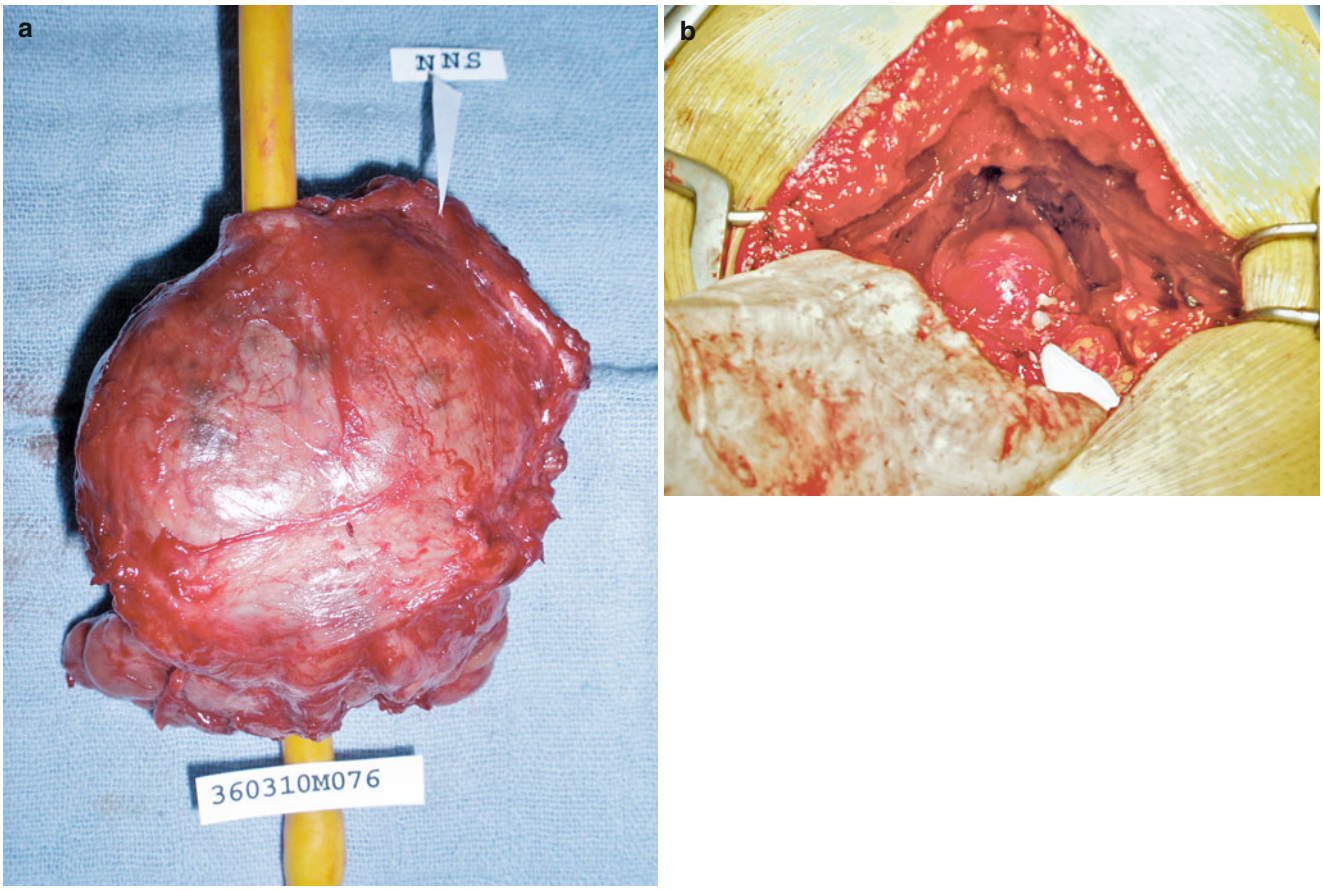


**Fig. 53.6** (**a**) Specimen of a unilateral nonnerve-sparing radical prostatectomy. (**b**) View after prostate removal with the preserved NVBs and the anterior rectal wall bulging in between them

## The Bladder Neck Dissection

The bladder neck can either be spared or resected. The so-called bladder-neck-preserving RP is actually more of an intraprostatic-urethral-preserving resection enabling the reconstruction of a neobladder neck (Fig. 53.7a). At this point, the prostate boundary can be followed with a curved dissector between the detrusor muscle and the prostate gland (Fig. 53.7b). Section of the interface between both can be performed with the electrocautery until the mucosal layer of the intraprostatic urethra is reached. Without opening the bladder, the DVC can be individualized and once more transected with the electrocautery. The intraprostatic urethra will then be circumferentially completely freed (Fig. 53.7c). After deflating the Foley catheter balloon, the intraprostatic urethral dissection is performed as far distal as possible into the prostate gland (Fig. 53.7d). This part of the urethral mucosa will later be everted over the neobladder neck. The urethral mucosa is circumferentially cut with the cold knife (Fig. 53.7e). Lateromedial stitches reinforce the trigone and narrow the bladder neck. Eight to ten everting stitches 3/0 are employed in order to evert the mucosa (Fig. 53.7f). Surgical forceps must easily pass into the neobladder neck, and this size (±18 Fr) is accepted to ensure a patent anastomosis (Fig. 53.7g). Sometimes the bladder neck reconstruction will show to be continent, which is not truly relevant for later urinary continence.

In patients with extracapsular T3 tumors and in those who previously underwent a TURP (Fig. 53.8a), it is often better to widely resect the bladder neck starting anteriorly, as classically described. The bladder is opened, and the Foley catheter balloon is taken out of the bladder, and the two ends of the catheter are clamped together anteriorly in order to provide traction on the prostate-vesicular complex. The posterior part of the bladder can be divided safely taking care not to damage the ureteral orifices. Whenever needed, two small-bore feeding tubes can be inserted into the ureteral orifices to be sure not to damage them or to include them in the sutures of the bladder neck reconstruction (Fig. 53.8b). A "tennis racket" reconstruction of the bladder neck with eversion of the bladder mucosa is performed. By integrating the mucosa in the closure of the bladder neck, hematuria can be avoided. It also facilitates a mucosa-to-mucosa urethrovesical anastomosis. The bladder

neck is narrowed to approximately the diameter of the urethra (Fig. 53.8c). Some surgeons have proposed a bladder neck intussusception with buttressing sutures lateral and posterior to the reconstructed bladder neck to improve continence that would prevent the bladder neck from pulling open as the bladder fills [21].

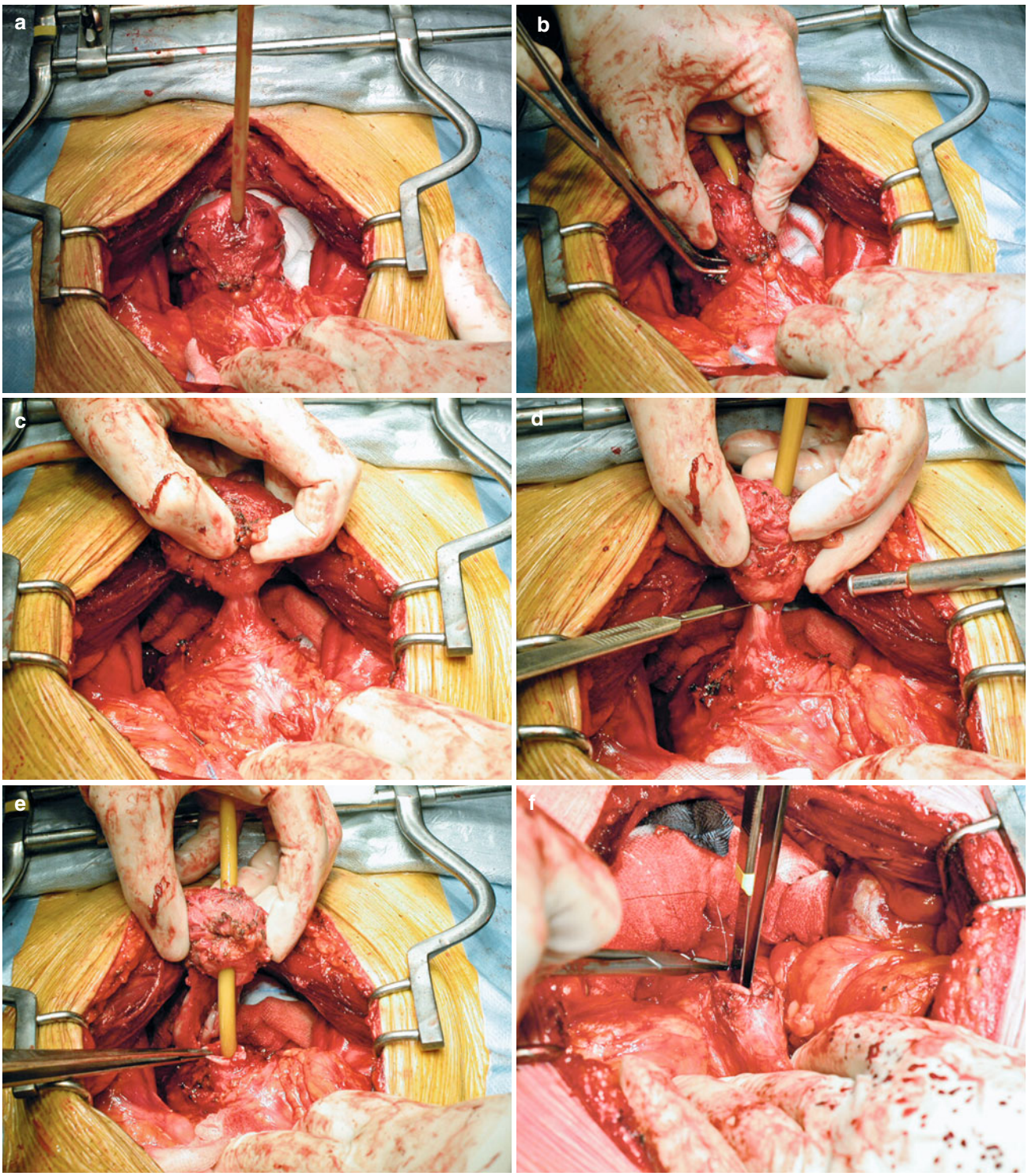


**Fig. 53.7** (**a**) Exposure of the retrogradely dissected prostate. (**b**) Dissection of the prostate from the bladder neck. (**c**) Bladder neck and intraprostatic urethra preservation. (**d**) Section of the intraprostatic urethra. (**e**) Exposure of the preserved bladder neck. (**f**) Eversion of the mucosa on the preserved bladder neck. (**g**) Final view of a continent neobladder neck after bladder neck preservation and eversion of the urethral mucosa

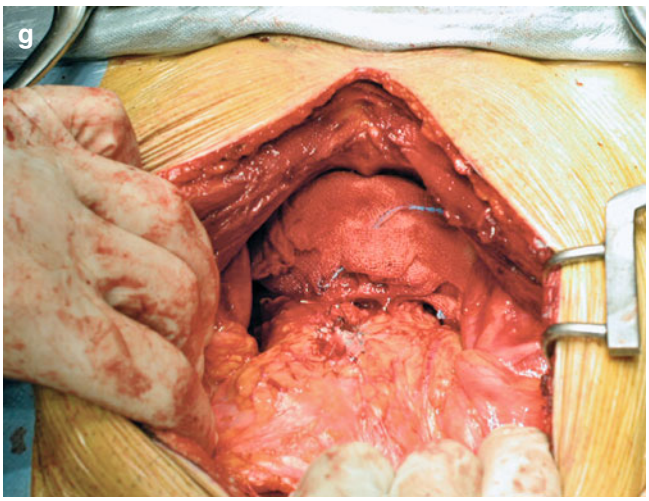


**Fig.53.7** (continued)

An intravenous diuretic may be given to help identify the ureteral orifices. Once the bladder neck has been reconstructed, the ureteral catheters are removed just before completing the vesicourethral anastomosis.

## Anastomosis

The hemostasis is checked before making the anastomosis between neobladder neck and urethra. When bleeding occurs in the nonnerve-sparing procedure, it can be controlled by electrocautery or by placing large-sized clips. When bleeding occurs at the nerve-sparing site, more meticulous hemostasis will be done with small tangentially placed clips or hemostatic sponges. During the nerve-sparing procedure, no electrocautery is used because this could definitely damage the NVBs. Even at the end, some oozing can be allowed, and some hemostatic agents (TachoSil®, FloSeal®, etc.) can be left behind before making the anastomosis. Avoidance of electrocautery or clips just behind the urethral stump is important since it can damage the recurrent branches of the pudendal nerve that innervate the urethral sphincter and consequently may result in sphincter insufficiency.

The quality of the vesicourethral anastomosis is responsible for preventing urinary leakage and stricture formation and for preservation of continence. The basic principle is to obtain a perfect adaptation of the urethra with the reconstructed bladder neck, without compromising the integrity of the external sphincter [22]. A 14–16-Ch Foley (silicon)

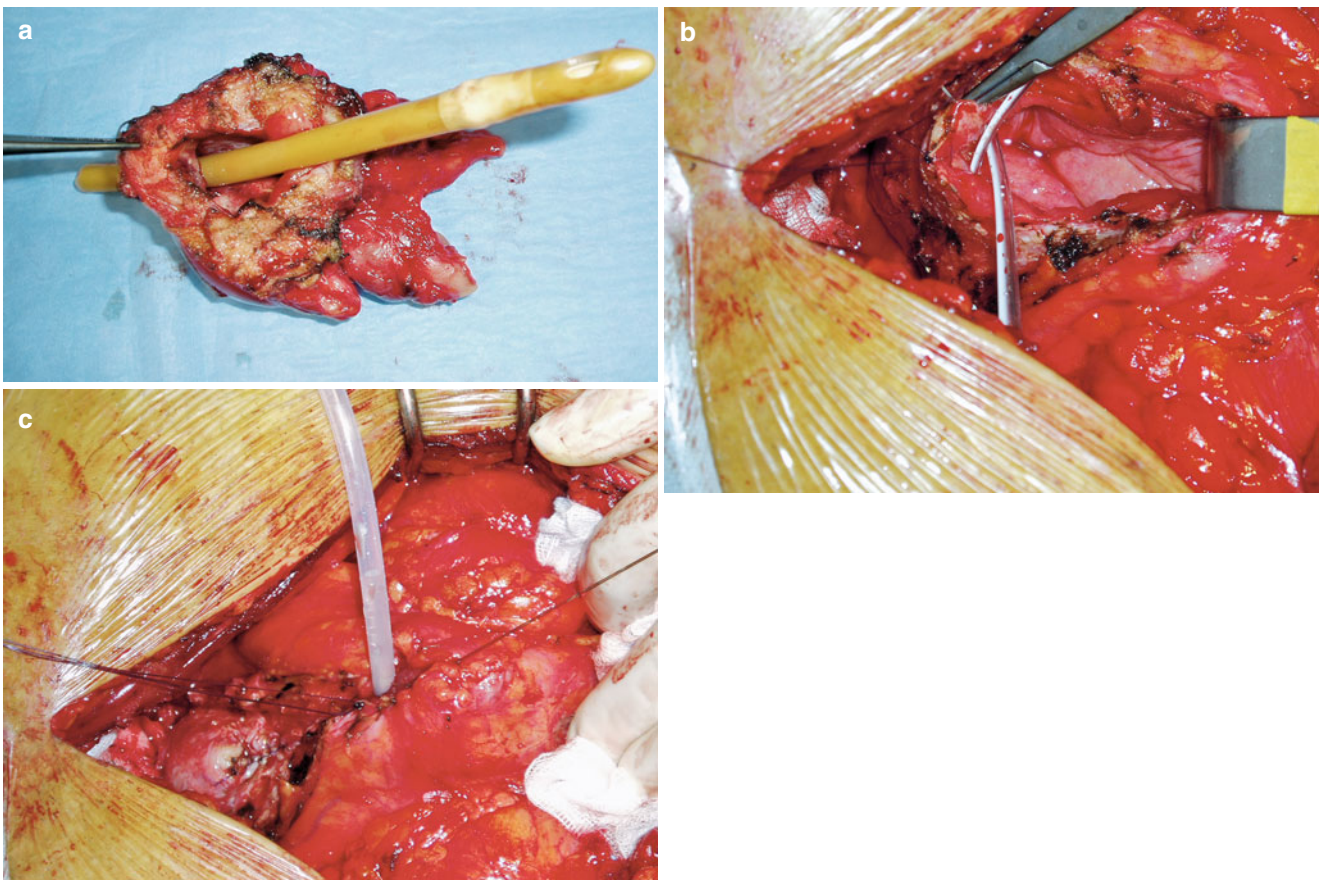


**Fig. 53.8** (**a**) Radical prostatectomy specimen after TURP, with bladder neck resection. (**b**) After bladder neck resection, with both intubated ureters. (**c**) Racket closed neobladder neck with 16-Charrière catheter

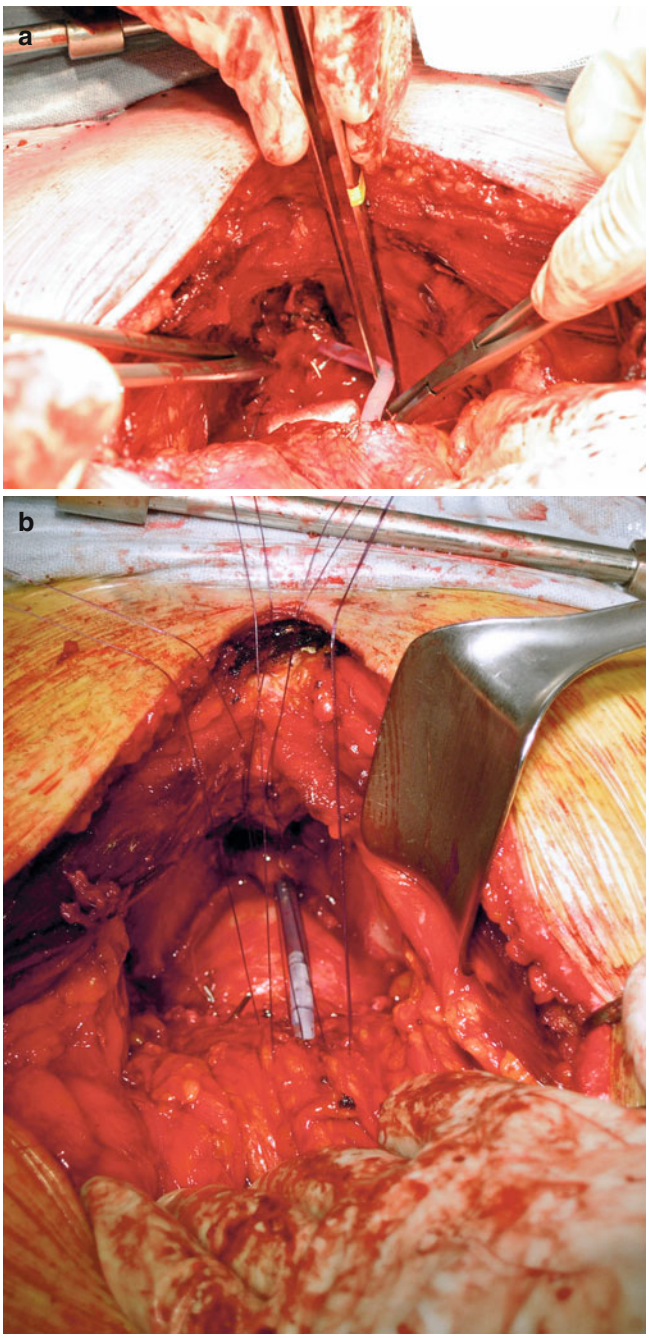


**Fig. 53.9** (**a**) First anastomotic stitch going from outside in at the urethral stump. (**b**) Placement of four stitches for vesicourethral anastomosis

catheter is brought into the new bladder neck; the balloon is not inflated in order to avoid inadvertent damage during the anastomosis. A swab on a stick is placed just posteriorly to the urethra, pushing the rectum downward. The vesicourethral anastomosis is accomplished by placing four anastomotic sutures at 2, 5, 7, and 11 o'clock. The first suture is placed at the 7 o'clock position, outside in at the urethra, guided by the catheter, and inside out at the bladder neck (Fig. 53.9a). The second suture is started outside in at the bladder neck at the 5 o'clock position and inside out at the urethra. The third and the fourth sutures are placed at the 2 and 11 o'clock position in the same way as the second (Fig. 53.9b). At this point, the balloon is inflated. Careful traction on the inflated balloon catheter brings the bladder neck down to the urethral stump. The four anastomotic sutures are then tied, and the bladder can be rinsed to check the anastomosis for leakage. Diuretics can be given to dilute any hematuria. Subsequently, two suction drains are placed in the pelvis, both keeping the Retzius space dry, in order to avoid hematoma or urinoma formation.

## Postoperative Care

After RP, there is no need for intensive care hospitalization. Pain control is perfectly managed with a patient-controlled analgesia (PCA) pump, for the first 48 h after surgery. Postoperatively, attention should be given to general status, wound control, drain volume, and bowel movements. The patient is offered a regular diet on the second postoperative day provided that peristalsis is restored. Drains are removed when daily drainage is less than 10 ml. To prevent thromboembolism, low molecular weight heparin that has already started the day before surgery is continued up to 1 month after the operation. It is given according to the patient's weight and risk factors. The patients are discharged from the hospital on day 5 or 6 with a Foley catheter in place. They return 10–14 days after the operation for removal of the catheter. A cystogram before removal of the catheter is only performed if any postoperative problem occurred that might have caused leakage. Immediately after withdrawal of the Foley catheter, pelvic floor physiotherapy is started, to improve incontinence.

## Surgical Training

Surgical training of young urologists is extremely important. Also practicing urologists that experience too many complications in their patients during or after RP must realize that even short retraining in expert centers can have a positive impact on their surgical quality. It is clear that even when using a standardized technique for the nerve-sparing procedure, a learning curve exists, giving better functional results to the more experienced surgeon.

## Complications

### Intraoperative Complications

Intraoperative complications are hemorrhage, rectal injury, and ureteral injury.

The most common intraoperative complication is *hemorrhage* that can occur because of a blunt lateral dissection of the lateral aspect of the prostate, because of inadequate control of the DVC, because of the presence of veins that perforate the pelvic floor, or because of the sparing of the NVBs. The main source of bleeding is the DVC which can already start bleeding by minimal manipulation. With sufficient understanding of the anatomy of the DVC, the bleeding is usually adequately controlled once the dorsal vein has been divided and ligated [15]. Blood loss will only rarely exceed 1,000 ml. However, the surgeon should always be prepared by having adequate blood available for transfusion. Less common intraoperative complications are rectal injury and ureteral injury. *Rectal laceration* is an infrequent (once in every 100–300 patients) but serious complication. It occurs during apical dissection while attempting to develop the plane between rectum and the rectourethralis muscle or the Denonvilliers' fascia. It can be mandatory to do an omentoplasty and anal dilatation. *Ureteral injury* occurs during transection of the bladder neck with intravesical injury of the ureteral meatus. Therefore, the ureteral catheters should be carefully inserted in case of a bladder neck resection before doing the tennis racket closure of the bladder neck. When the ureteral meatus is too close to the suture line, it can be incised, and a double J catheter can be left behind for a couple of weeks.

## Postoperative Complications

General postoperative complications after RP are deep venous thrombosis and pulmonary embolism that should be prevented by low molecular weight heparin started the day before surgery and continued up to 1 month after the operation. Myocardial infarction and even death should be avoided by an appropriate preoperative anesthesiologic consultation.

Early postoperative complications include anastomotic leak, prolonged lymphatic drainage, premature accidental catheter withdrawal, and rectourethral fistula. *Prolonged lymphatic drainage* occurs because some surgeons will not drain the pelvic cavity after surgery because of one of the following reasons: pain associated with this procedure, the risk of an epigastric vessel injury, the rare event of the inability of removing the drain (because of stitch up), or the risk of breaking the drain on removal. These complications can be avoided in all cases. The suction drains must be inserted far lateral to the epigastric vessels and must be left in place till they drain less than 10 ml per 24 h. Ideally, they should not be taken out before the patient is again walking around. In some patients, certainly when an extensive lymph node dissection has been performed, prolonged drainage can be a problem. When the surgeon is reassured that there is no urine leak (creatinine determination on fluid), he can after 1 week finish active suction that results in about all cases in a sudden stop of the drainage. However, the suction drain should not be removed till daily production is less than 10 ml. This implies that in some patients the suction drain is still in place when they leave the hospital. The occurrence of *urinary fistula* that is clinically meaningful is extremely rare in open RRP. In open RRP, we almost always place four stitches only, and some patients can indeed have a temporary urine leak in the suction drains, but when the catheter is correctly placed in the bladder, this will spontaneously stop in all cases. This means again that the suction drains need to be left in place till dry. When there is any concern about the position of the catheter, a cystogram should be performed. When the catheter is dislocated, it must be reinserted after flexible cystoscopy and introduction of a guide wire through the anastomosis into the bladder. Urinary fistula can occur as a result of catheter blockage (e.g., in case of hemorrhage that must be avoided by proper bladder neck reconstruction and eversion of the bladder neck mucosa). A ureteral damage can be causing a urine leak. Accidental early catheter withdrawal can also induce a problem, but most often the cause of this rare complication is insufficient immediate postoperative suction drainage. *Rectourethral fistula* is rare and in fact only occurs when rectal injury has not been recognized during operation. When however a rectourethral fistula occurs, immediate colostomy is mandatory.

The late complications of RP are anastomotic strictures, urinary incontinence, and erectile dysfunction. *Anastomotic strictures* need to be avoided by a good bladder neck reconstruction with eversion of the mucosa and avoiding to make a too narrow bladder neck. Strictures, mostly in patients who had a previous TURP, excessive bleeding, or an anastomotic leak, can often be managed with a urethral dilatation. Incision of the stricture must be avoided as this may result in incontinence.

Urinary incontinence and erectile function are among the major concerns that men have with regard to outcomes of RRP. *Urinary incontinence* is very difficult to predict. The reason is invariably damage to the urethral sphincter or its innervation. The surgeon must avoid an incorrect apical dissection before urethral division as well as injury of the recurrent branch of the pudendal nerve that runs posterior through the urethra. Why in less than 5 % of patients there is more incontinence immediately after catheter withdrawal and also permanent long-standing incontinence in some patients is not clear. A randomized clinical trial showed that pelvic floor muscle training, before and after RP, may result in earlier recovery of urinary continence. Pharmacologic treatment will only be beneficial in patients with a preexistent overactive bladder. Male slings are a valid option for postprostatectomy incontinence and do offer several advantages over the more invasive artificial urinary sphincter. Long-term data and multicenter series are needed in order to compare them

directly with the artificial urinary sphincter. *Erectile dysfunction* is correlated with age, preoperative erectile function, and the oncologic necessary extent of resection of one or two NVBs. Recovery of erectile function also depends on the correct selection of patients and the competence of the surgeon to perform nerve-sparing operations. The result of an open RP in most patients will be a temporary reduced erectile function. CaverMap designed to aid the surgeon in identifying and preserving the cavernous nerves and looking at erections during electrostimulation is not very helpful in predicting the recovery of sexual function. Controversy exists regarding the true benefit of interposition sural nerve grafting during RP. Many patients that have some penile tumescence or rigidity during sexual stimulation have an improvement in erectile function recovery with early institution of phosphodiesterase-5 inhibitors in the highest dose, maybe by a continuous intake of these drugs, for example, every other day. Men who fail phosphodiesterase-5-inhibitor treatment for their postradical retropubic prostatectomy erectile dysfunction are excellent candidates for intracavernous injection therapy. The need for penile implants in RP patients is very limited. Complications of RRP and management of complications will be further discussed in other chapters in this book.

## Surgical Modifications to Standard Anatomic RP

Refinements in the understanding of the surgical anatomy of the prostate enabled several important modifications in the RRP techniques during the last decades. Surgical modifications to improve early return of urinary continence, erectile function, or both have been concentrated on the role of the bladder neck in urinary control, dissection around the seminal vesicles, and placement of interposition nerve grafts when resection of the NVBs is required [15].

Bladder neck preservation may aid in an early return of continence although its role in recovering urinary continence after RRP is controversial [23–35]. Although in many studies bladder neck preservation was associated with earlier continence [23, 26, 27, 29, 31, 33–35], the randomized study of Srougi [30] found no difference in urinary continence rates in patients with bladder neck reconstruction compared to patients with bladder neck preservation [30].

Few men presenting with localized PCa have disease that has already spread to the seminal vesicle. Some investigators suggest that removal of the seminal vesicle in its entirety is not necessary when the dissection is difficult and propose to spare the seminal vesicle as a modification to the classical RRP. This might eliminate the potential damaging to other adjacent structures such as the pelvic nerves in order to maintain urinary continence during RRP [36]. Other investigators found that complete excision of the seminal vesicle during RRP is essential for cancer control [37]. A double-blind randomized study is needed to find out whether sparing the seminal vesicle is advocated.

Furthermore, investigators have evaluated interposition of sural nerve grafts after unilateral and bilateral NVB resection during RRP [14, 38–47]. Studies have reported a recovery of erectile function in men who underwent bilateral nerve graft placement during RRP when both cavernous nerves were deliberately resected [38–40]. However, the role of bilateral sural nerve grafting still remains to be proved in the randomized setting. The benefits of the more common unilateral graft are difficult to document, since some men recover erectile function when a single nerve is preserved. A randomized phase II trial was conducted to evaluate the erectile function after attempted unilateral cavernous nerve-sparing RRP with versus without unilateral sural nerve grafting for clinically localized PCa. The authors concluded that the addition of sural nerve grafting to a unilateral nerve-sparing RRP did not improve erectile function at 2 years following surgery [46]. Singh et al. [43] investigated the return of urinary control with respect to unilateral sural nerve grafting and suggested that the cavernous nerves may play a role in return of continence [43].

**Conclusion**

Contemporary nerve-sparing open RRP is an ideal and most commonly performed treatment for patients with localized PCa who can be cured and who have at least a 10-year life expectancy. The increasing experience of surgeons together with better knowledge of the periprostatic anatomy and the refinements in nerve-sparing techniques allows excellent cancer control and has resulted in greater chance of success in preventing positive margins, significantly reduced operative complications while improving outcomes related to quality of life.

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# Retropubic Radical Prostatectomy: The Results

54

Wolfgang Horninger and Jasmin Bektic

The increase in prostate-specific antigen (PSA) screening, combined with a reduction in the threshold of indications for prostate biopsy and the greater number of samples taken, has contributed to an increase in the diagnosis of prostate cancer. This has led to earlier detection, to downstaging of the disease, and to an increase in the number of patients presenting with clinically organ-confined disease. This, in turn, has led to an increase in the number of candidates for radical prostatectomy (RP). RP is the standard treatment for patients with an organ-confined prostate cancer and a life expectancy of more than 10 years who accept treatment-related complications [1].

Retropubic radical prostatectomy (RRP) was first reported by Millin in 1945 [2]. Since the standardization of the anatomic RRP with better understanding of the prostate anatomy, specifically the dorsal vein complex and neurovascular bundle (NVB), as described by Walsh and Donker in 1982 [3], many authors have provided important contributions to the optimization of the surgical technique, with the purposes of reducing short-term and long-term complications and of improving functional results both in terms of urinary continence [4–8] and of erectile function [9, 10]. These results were associated with better functional outcomes without compromising oncologic principles.

## Operative Outcomes

The most current reports about outcomes of RRP are comparative studies comparing RRP with laparoscopic (LRP) and robot-assisted prostatectomy (RARP) as so-called minimally invasive radical prostatectomy (MIRP). However, there are some clear problems with comparing these three surgical procedures including lack of randomized studies with standardized definitions used to describe positive surgical margins (PSM), biochemical recurrence (BCR), urinary continence, and erectile function. Centers where one of these techniques is performed are usually focused only in this approach, limiting their practice with other procedures. Consequently, comparative randomized studies that evaluate the three approaches in the same institution are rarity and/or include small number of patients representing the surgeons' learning curve.

## Blood Loss

Because of the rich venous blood supply to the prostate, radical prostatectomy is an operation associated with the potential for significant bleeding. Even when bleeding is not sufficient to require transfusion, it can often be enough to obscure the operative field making visualization of the prostatic apex and/or neurovascular bundle difficult. Moreover, intraoperative bleeding may affect not only perioperative morbidity and transfusion requirements but also other important outcome measures [11]. In a critical review of radical prostatectomy outcomes reported by high-volume centers [12], the mean estimated blood loss (EBL) for RRP was 951 ml and was higher compared to LRP (291.5 ml) and RARP (164.2 ml). Consequently, the mean intraoperative and postoperative transfusion rates were significantly higher for RRP (20.1 %, compared with 3.5 and 1.4 % for LRP and RARP, respectively). Farnham et al. compared intraoperative blood loss and transfusion requirements in 279 patients undergoing RRP versus RARP by a single surgeon [13]. They found that RARP is associated with significant decrease in intraoperative bleeding and greater serum hematocrit at hospital discharge compared with RRP, but there was no statistically significant difference in the perioperative transfusion rate. Kordan et al. reported similar results, but in this study, RRP was associated with the increased need for blood

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transfusion [14]. However, the tamponade effect created by pneumoperitoneum and early identification as well as precise ligation of blood vessels during LRP and RARP seems to be responsible for the limitation of blood loss. There are several studies reporting pharmacologic and/or surgical strategies to decrease the amount of operative blood loss during RRP. The intraoperative administration of activated factor VII [15], preoperative erythropoietin and acute normovolemic hemodilution [16], and delayed intraoperative hydration [17] are some of pharmacologic approaches. Using prophylactic periprostatic sutures before the mobilization of the prostate, as described by Catalona group, it is possible to reduce blood loss and transfusion need in RRP [18]. Furthermore, radical prostatectomies done by surgeons with the high surgical experience decreased the risk of any transfusion [19]. Even after adjustment done by these strategies, the mean EBL during MIRP is lower when compared with RRP, but the clinical significance of this fact has yet to be shown.

## Operative Time

The variations in reporting operative time in the current literature (time for setup, pelvic lymph node dissection or not) make comparison to other surgical techniques sometimes difficult. However, the most reported operative times of RRP vary between 100 and 200 min (Table 54.1), and regarding comparison between different techniques, the authors are unanimous: the mean operative times for RRP and RARP are similar, and one of the main critiques against LRP is the longer operative time. Ficarra et al. suggested that RARP is more time consuming than RRP only in the earlier phase of the learning curve and such differences disappeared with increased surgical experience [28].

## Hospital Stay

Reported differences in terms of in-hospital stay after RRP and other techniques in the current literature are reflecting probably the differences in the location where the studies were performed and not the differences between the surgical approaches. Whereas in Europe the patients often stay in the hospital until the urinary catheter is removed, in the United States they are usually discharged quickly from the hospital after surgery. However, the length of stay decreased for both RRP and minimally invasive techniques over the time, but men undergoing RRP spent significantly more time in hospital compared with those undergoing minimally invasive surgery [29] (Table 54.2). But again, reduced hospital stay for LRP and RARP is uncertain as other local factors may determine patient discharge.

**Table 54.1** Mean operative time for RRP

| Authors | Year of publication | Patients (*n*) | Operative time (min) |
|---|---|---|---|
| Lepor et al. [20] | 2001 | 1,000 | 131 |
| Touijer et al. [21] | 2008 | 818 | 188 |
| Krambeck et al. [22] | 2009 | 588 | 204 |
| Chan et al. [23] | 2008 | 340 | 141 |
| Salomon et al. [24] | 2002 | 219 | 197 |
| Rassweiler et al. [25] | 2003 | 219 | 196 |
| Guilloneau | 2001 | 100 | 135 |
| Artibani et al. [26] | 2003 | 50 | 105 |
| Hsu et al. [27] | 2003 | 1,024 | 131 |

**Table 54.2** Hospital length of stay for RRP

| Authors | Year of publication | Patients (*n*) | In-hospital stay (days) |
|---|---|---|---|
| Zincke et al. [30] | 1994 | 1,143 | 6 |
| Catalona et al. [31] | 1999 | 1,870 | 2.4 |
| Lepor et al. [20] | 2001 | 1,000 | 2.3 |
| Nelson et al. [32] | 2007 | 374 | 1.23 |
| Chan et al. [23] | 2008 | 340 | 1.4 |
| Touijer et al. [21] | 2008 | 818 | 3.3 |
| Hsu et al. [27] | 2003 | 1,024 | 3 |

## Medical and Surgical Complications

The absence of standardized classification systems to report surgical complications makes accurate comparisons across institutions and across different surgical approaches difficult. Martin et al. proposed ten criteria that should be met when reporting complications following surgery [33], but urological publications that met these criteria are rare [34]. Clavien et al. proposed in 1992 a classification system for surgical complications [35] that was recently tested and confirmed to be valid [36] (available at: www.surgicalcomplication.info). Currently, this system was used in a few publications in regard to RRP [37–39]. Rabbani et al. investigated retrospectively the incidence, severity, and timing of onset of medical and surgical complications in 4,592 patients who underwent RRP or LRP between January 1999 and June 2007 [38]. In this comprehensive standardized report, the medical and surgical complications were present in 8.8 and 18.7 % of RRP patients, respectively, and in 14.5 and 24.5 % of LRP patients, respectively. Compared to RRP, LRP was associated with a higher incidence of any grade medical and surgical complications but a lower incidence of major surgical complications. The overall complication rate of 2,893 patients undergoing RRP in a recent study reported by Loeppenberg et al. was 27.7 % [39]. Of these, 63.2 % were grade I, 19.5 % grade II, 15.1 % grade III, and 1.8 % grade IV. Grade V complication (the mortality rate) was 0.1 %. These results are comparable with the results obtained by Constantinides et al. [37].

Most available series that compare RRP and minimally invasive surgical approaches have reported similar complication rates between these techniques. Krambeck et al. recently reported comparable overall perioperative complication rates between RARP and RRP (8.0 % vs. 4.8 %, $P=0.064$) [22]. Similarly, Nelson et al. showed equivalent rates of unscheduled visits (RRP = 10 %, RARP = 10 %, $P=0.95$) and readmissions (RRP = 5 %, RARP = 7 %, $P=0.12$) because of postoperative complications between these two surgical approaches [32]. The weighted mean postoperative complication rates for RRP, RLP, and RARP in high-volume centers, reported by Coehlo et al., were 10.3 % (range of means 4.8–26.9 %), 10.98 % (range of means 8.9–27.7 %), and 10.3 % (range of means 4.3–15.7 %), respectively [12].

## Oncologic Outcomes

The primary goal of any cancer surgery is to provide satisfactory oncologic outcomes. In case of prostate cancer, positive surgical margins (PSM) and biochemical recurrence (BCR) are the two commonly used indices to assess oncologic outcomes following radical prostatectomy. The ideal measures in determining long-term oncologic control are overall and cancer-specific survival rates.

In the current literature, there are several definitions of a PSM after RP. However, most define it as a presence of tumor at the inked margin of the surgically removed specimen [40]. However, severe crush artifacts of the surgical specimens, which usually occur at the apex of the prostate, can make the assignment of the surgical margin status impossible [41]. Positive surgical margins at RP can be associated with extraprostatic extension (EPE) of cancer or can result from areas of intraprostatic incision where the surgeon inadvertently cut into the prostatic parenchyma. Encouragingly, studies indicate that a higher risk of progression after RP is not usually associated with positive surgical margins arising from capsular incisions [42–45]. The incidence of positive margins in RRP specimens reported in the literature varies widely, from 4 % to greater than 40 % [46–51], with an overall positive surgical margin rate of 21–28 % (Table 54.3).

There are several reasons for this discrepancy including the era in which patients underwent surgery, cancer characteristics of the patients investigated, the technique of pathologic review, surgical experience, etc. Over time, there was a striking decrease in the incidence of positive margins due to better understanding of periprostatic anatomy, improved patient selection, and surgical techniques as well as marked stage migration of prostate cancer at diagnosis in the early 1990s, with 75 % of men in the USA presenting with clinical stage T1c disease [58]. In a recent study, Vickers et al. demonstrated high correlation of positive surgical margins and the 5-year probability of tumor recurrence with surgeon experience in a study of more than 7,000 prostate cancer patients treated with RRP at four major academic medical centers [59]. In this study, they showed that surgeon performing less than 50 RRPs had a positive surgical margin rate of 42 % and a 27 % 5-year probability of recurrence. In the hands of a surgeon performing 250 or more, positive surgical margin rate and 5-year probability of cancer recurrence were significantly lower (21 and 16 %).

**Table 54.3** Incidence of positive surgical margins in patients undergoing RRP

| Author | Number of patients | Positive surgical margins (%) |
|---|---|---|
| Blute et al. [52] | 2,518 | 39 |
| Grossfeld et al. [53] | 1,383 | 34 |
| Swindle et al. [54] | 1,389 | 12.9 |
| Catalona et al. [55] | 1,778 | 20.9 |
| Hsu et al. [27] | 1,024 | 21 |
| Hull et al. [56] | 1,000 | 12.8 |
| Chun et al. [57] | 2,708 | 21.5 |

Surgical margin status is an independent risk factor for biochemical recurrence. Various PSA thresholds have been used to define BCR after RP. Definitions in the literature include single or multiple PSA values between 0.1 and 0.5 ng/ml [2–5]. The most commonly cited limit for PSA after RP is ≥0.2 ng/ml, and two sequential PSA values ≥0.2 ng/ml are accepted by the EAU as the basis for treatment initiation [7].

Although RRP provides excellent cancer control in most men with clinically localized disease, approximately 35 % of patients will develop a PSA recurrence within 10 years after surgery [56, 60–62]. The most comprehensive study of the natural history of BCR was performed in a cohort of 1,997 men who underwent RP between 1982 and 1997 at Johns Hopkins [63]. BCR occurred in 15 % of these men, and time from RP to BCR averaged 3.5 years. In patients who underwent at the Mayo Clinic 3-year and 5-year PSA, progression-free survival estimated rates of 99 and 98 %, respectively, were reported [64]. Bianco et al. examined the natural history of BCR in a cohort of 1,746 men who underwent RP over a 20-year period beginning in 1983 [65]. Of these men, 17 % experienced BCR, and prostate cancer-specific mortality (PCSM) at 5, 10, and 15 years was 1, 5, and 11 %, respectively.

## Functional Outcomes

The best way to analyze functional outcome and to be able to compare different surgical techniques is undoubtedly the use of validated questionnaires. Unfortunately, many differences exist between definitions of urinary continence and erectile function and the way that this information is obtained. There are only a few studies performed using validated question-

**Table 54.4** Continence rates after RRP

| Author | (*n*) | Mean age (years) | Method of assessment | Definition of incontinence (pads) | Time of assessment (months) | Continence rate (%) |
|---|---|---|---|---|---|---|
| Leandri et al. [72] | 620 | 68.0 | P | 0–1 | 12 | 95.0 |
| Geary et al. [73] | 456 | 64.1 | P | 0 | >18 | 80.1 |
| Davidson et al. [74] | 170 | 63.0 | Q | 0–1 | 12 | 85.9 |
| Feneley et al. [75] | 177 | 63.0 | P | 0–1 | 12 | 97.0 |
| Catalona | 1,325 | 63.0 | P | 0–1 | 50 | 92.0 |
| Steiner et al. [5] | 593 | 34–76 | P | 0 | 12 | 94.5 |
| Stanford et al. [71] | 1,291 | 62.9 | Q | 0 | >18 | 91.6 |
| Goluboff et al. [76] | 615 | 62.6 | Q | 0 | 39.6 | 91.8 |
| Eastham et al. [70] | 581 | 63.0 | P,Q | 0 | 24 | 95.0 |
| Catalona et al. [31] | 1,870 | 63.0 | P,Q | 0 | >18 | 96.0 |
| Kundu et al. [77] | 3,477 | 61.0 | Q | 0 | 18 | 93.0 |
| Bianco et al. [65] | 1,746 | – | P | 0–1[a] | 12 | 91.0 |
| Loeb et al. [78] | 4,265 | 61.0 | Q | 0 | 18 | 94.0 |
| Hsu et al. [27] | 1,024 | 60.9 | Q | 0–1 | 12 | 91.0 |
| Penson et al. [79] | 1,213 | – | Q | 0–1[b] | 24 | 90.0 |
| | | | Q | 0–1[b] | 60 | 86.0 |

*P* physician, *Q* questionary
[a]Occasional use of pad for moderate exercise activities
[b]Occasional leakage

naires in the current literature. Many authors used nonvalidated institutional questionnaires; others assessed the functional outcome just by an interview.

## Urinary Continence

A wide experience of urinary continence following RRP exists in the current literature [5, 31, 66–71] (Table 54.4). However, reported urinary incontinence rates after RRP vary widely, and reported continence rates may differ because of the use of different definition of incontinence [68] and who is reporting incontinence, patient or physician [67]. Identified preoperative risk factors affecting continence include surgical technique (Eastham 1996), membranous urethral length [80], patient age [68, 70], obesity [81], history of transurethral resection of the prostate (TURP), anastomotic stricture [73, 82], and the experience of the surgeon [70, 83]. Whereas Foley et al. reported that prostate size at RRP does not affect the risk of incontinence afterward [84], Oefelein identified prostate volume and prostatic urethral length as additional important values which predict time to pad-free urinary continence [85]. The most comprehensive cumulative analysis of studies comparing RRP with MIRP was done by Ficarra and coworkers [86]. Regarding urinary continence, the authors suggest that the continence recovery after RRP and MIRP was similar. Roumeguere and coworkers showed slight but not significant difference in 1-year continence rates for RRP versus LRP (83.9 % vs. 80.7 %) [87]. Similar results were obtained by Rassweiler et al. [25]. Touijer et al. reported in 2008 in a nonrandomized, prospective study statistically significant difference with twofold higher risk of urinary incontinence following LRP [21]. However, no comparative study showed a statistically significant difference in favor of LRP. Comparing RRP with RARP, Tewari et al. suggested faster recovery of continence in those patients who underwent RARP [88], but the available studies comparing functional outcome of RRP versus RARP are still rarity. Taken together, currently available data suggest similar continence recovery following RRP and MIRP.

## Erectile Function

As the prostate cancer is being detected in an increasingly young population of men, the preservation of erectile function is one of the major factors to men facing treatment of localized prostate cancer. The variability of terminology used to describe erectile function and differences in evaluation methods makes the comparison of outcomes between different studies and surgical approaches difficult. Burnett et al. (American Urological Association (AUA) prostate cancer guideline panel) analyzed 100 articles on erectile function following treatment for clinically localized prostate cancer [89]. Using data from 31 articles, with at least 50 patients, rates for complete erectile dysfunction, partial erectile function, and intact erectile function were 26–100 %, 16–48 %, and 9–86 % following radical prostatectomy. The authors underline the importance of use of scientifically rigorous methodology and standard outcome measures in future studies. One of important studies concerning this issue was done by Schroeck et al. [90]. Comparing a number of

**Table 54.5** Potency rates following RRP

| Author | (*n*) | Time of assessment (months) | Potency rate (%) |
|---|---|---|---|
| Catalona et al. [31] | 798 | 18 | 68 |
| Walsh et al. [95] | 64 | 12 | 73 |
| | | 18 | 86 |
| Kundu et al. [77] | 3,477 | 18 | 76 |
| Bianco et al. [65] | 1,963 | 18 | 63 |
| | | 24 | 70 |
| Loeb et al. [78] | 4,265 | 18 | 74 |
| Graefen et al. [10] | 542 | 12 | 90 |
| | | 12 | 56 (no PDE5-I)[a] |
| Eastham et al. [96] | 97 | 6 | 72 |

[a]PDE5-I: phosphodiesterase type 5 inhibitor

definitions for erectile dysfunction, the authors found that an expanded prostate cancer index composite (EPIC) score more than 60 and an international index on erectile function (IIEF) score more than 20 correlate highly with sexual function and suggest that these scores should be used to define erectile dysfunction. Marien et al. identified multiple factors important for the maintenance of potency after RRP [91]. However, using multivariate analysis, the authors suggest that only age at the operation, absence of diabetes mellitus, and nerve sparing were independent predictors of the preservation of potency. However, RRP results in an estimated 60–85 % recovery of erectile function in men with normal preoperative potency [65, 92–94] (Table 54.5). Despite the supposed benefits of magnification during LRP or RARP helping to preserve the neurovascular bundles and thus potency and continence, no clinical improvement has been demonstrated.

## The "Trifecta" Outcome

Excellent long-term oncologic outcomes in several RRP series have lead to increased focus on the recovery of continence and erectile function. The likelihood of each of these three outcomes (oncologic control, continence, and erectile function) has been well documented, but many patients request their likelihood of achieving an optimal outcome, meaning cancer-free and full functional recovery (trifecta). Salomon and coworkers designed a concept of the combined reporting of cancer control and functional outcomes after RP using a 0–7-point scale to assess outcomes [97]. Analyzing the data of 205 patients undergoing RRP, optimal cancer control with no functional disorders (score 7) was found in 20 % of patients. Saranchuk et al. investigated outcomes of 647 patients and found a consecutive increase in the rate of patient with trifecta outcome over the time being 30 % after 12 months and increase to 53 % after 48 months [98]. An update of this study and a presentation of a nomogram estimating the likelihood of an individual achieving of trifecta outcome were done 2 years later [99]. In this study, trifecta outcome was achieved in 62 % of patients. Recently, similar results were obtained analyzing the results of LRP [100] and RARP [101].

## Costs

One of the main factors institutions take into consideration when acquiring new technology are costs. The analysis of the costs of a surgical technique depends on many factors including characteristics of the hospital, surgeon's ability and experience, the use of non- or disposable instruments, or even geographic difference [102]. For example, the economics of RP are different in the USA and Europe, because the patients usually stay in the hospital until the urinary catheter is removed. Due to reduced hospitalization, Rassweiler et al. reported a cost saving of $1,237 using LRP as compared with RRP [25]. Though, most available studies comparing LPR with RRP suggest that LPR is more expensive than RRP [103–105]. In the publication of Anderson et al., the total cost of the procedure for LPR versus RRP was $6,760 versus $5,253 mostly due to the higher surgical supply and operating room costs [105]. The authors estimated that using non-disposable instruments, completing LPR in 3.4 h, and discharging the patients on second postoperative day, the cost equivalence could be achieved. In regard to RARP, the cost difference to the RRP is mainly based on the price of da Vinci system (1.2 million dollar) and high maintenance costs ($100,000 per year). Lotan et al. reported cost reduction of $1,726 using RRP compared to RARP [104]. Scales et al. suggested that the costs of RARP are volume dependent and that the cost equivalence with RRP is, to date, possible only at higher volume centers [106].

### Conclusion

With wider availability of the minimally invasive radical prostatectomy techniques (MIRP), there is a debate regarding what the standard treatment will be for the management of localized prostate cancer in the near future. However, to date, the RRP is still the gold standard and serves as the reference by which other therapy modalities must be compared. At the moment, there is no reason for experienced surgeon with excellent oncologic and functional outcomes to change to another surgical technique. The tactile sensation allowing assessment of the extent of local tumor and proven long-term oncologic outcomes are just some of advantages of RRP. Others include an extensive lymphadenectomy, which is more easily done with the open technique and may be important in staging and possibly curing patients at a high risk for prostate cancer, surgery of obese patients, those with

a history of extensive prior surgical procedures, or patients with extremely large prostates which all may experience advantages with the open technique. The current literature lacks large randomized trials which compare different surgical approaches in the therapy of prostate cancer. Before concluding the superiority of RRP or MIRP, more comparative effectiveness studies are needed.

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# Radical Perineal Prostatectomy

# 55

Rolf Gillitzer and Joachim W. Thüroff

Historically, perineal prostatectomy was the primary type of surgery for prostate cancer, performed for the first time by Billroth in 1867 mostly without visual control. However, Hugh Hampton Young received credit for the first perineal prostatectomy after reporting in 1905 his experience with a mostly visually controlled operation and new special instruments [1]. Different perineal routes of access to the prostate have been described, but the most commonly used route is Young's suprasphincteric approach ventral to the external and internal sphincter ani. It was the mainstay of surgical treatment until by the mid of last century pelvic lymph node dissection became part of the procedure. Radical retropubic prostatectomy began to take over since it allowed simultaneous pelvic lymph node dissection through the same incision. By the early 1980s, introduction of anatomic radical retropubic prostatectomy [2] left only a limited number of centers worldwide practicing and teaching perineal prostatectomy. Renewed interest in perineal prostatectomy ensued with introduction of laparoscopic pelvic lymph node dissection. In addition, with the widespread use of prostate specific antigen (PSA) in the 1980s, a shift toward lower clinical stages and localized disease took place, and implementation of various nomograms allowed preoperatively to predict the probability of lymph node involvement. The trend toward less invasive surgery and technical refinements in perineal prostatectomy has finally thrust perineal prostatectomy again to the forefront as a less invasive surgical treatment option for some types of prostate cancer.

With the turn of the millennium, the introduction of robotic-assisted laparoscopic prostatectomy (RALP) as minimally invasive form of treatment with a relatively short learning curve has started to displace other surgical options for prostate cancer and became by now the most widely used surgical treatment in the USA. Its associated high investment and running costs are still prohibitive to become accepted worldwide. However, radical perineal prostatectomy can still be considered the first "minimally invasive" surgical treatment of localized disease, since its associated morbidity is not different from that of RALP. Its simplicity, relatively short learning curve [3], outcomes, and cost efficiency make it an established option of surgical treatment for prostate cancer that has stood the test of time.

## Indications

Radical perineal prostatectomy is an option for surgical treatment of patients with clinically organ-confined prostate cancer (≤T2) and a life expectancy of minimum 10 years.

Indications for radical perineal prostatectomy without lymph node dissection are clinical stages ≤T2, total PSA ≤10 ng/ml, Gleason score <7, and the patient's choice for the perineal approach. Although it has been demonstrated by some groups that lymph node dissection can be performed through the same perineal incision [4, 5], it is not to be expected that this technique will find its way into a widely accepted clinical practice. If indicated, lymphadenectomy can be done laparoscopically. In general, patients eligible for retropubic prostatectomy are also candidates for perineal prostatectomy. Perineal prostatectomy may have an advantage over retropubic prostatectomy in some specific cases such as morbid obesity, previous retropubic/pelvic surgery (i.e., laparoscopic herniotomy with mesh placement, deep rectum resection, renal transplantation, pelvic vascular surgery), and in the elderly.

Perianal pathology (third degree hemorrhoids, previous anal fissures, or perianal abscess) is usually not a contraindication for the perineal approach.

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## Contraindications

- Impossibility of patient positioning in the exaggerated lithotomy position (i.e., ankylosis of the hip, severe coxarthrosis, unstable artificial hip, complex vertebral column disorders).
- Compromised respiratory function that requires high intraoperative ventilatory pressures.
- Prostate gland size >100–120 cc is a relative contraindication, because visibility and working space is greatly reduced in the limited operative field.

## Planning and Preparation

Preoperative patient preparation is identical with retropubic or laparoscopic radical prostatectomy. Preoperatively, anticoagulants should be stopped or switched to lowmolecular weight heparin. Complete bowel preparation is not obligatory, but a fleet enema is administered the night before surgery. "Type and screen" blood group is recommended. Thrombotic prophylaxis is performed with tight and high antithrombotic stockings and perioperative low molecular weight subcutaneous heparin (although the thrombosis risk is extremely low due to excellent venous drainage provided by the specific patient positioning). Antibiotic prophylaxis is performed with intravenous third-generation cephalosporin which is begun intraoperatively and continued until the patient is taking oral nutrition (except cases with intraoperative rectal lesion which also require a 5-day course of antibiotics covering gram negative bacteria, i.e., metronidazole).

## Specific Instruments and Suture Material

- Curved and straight Lowsley retractors
- Notched Young bulbar retractor
- Long right-angle clamps with short branches

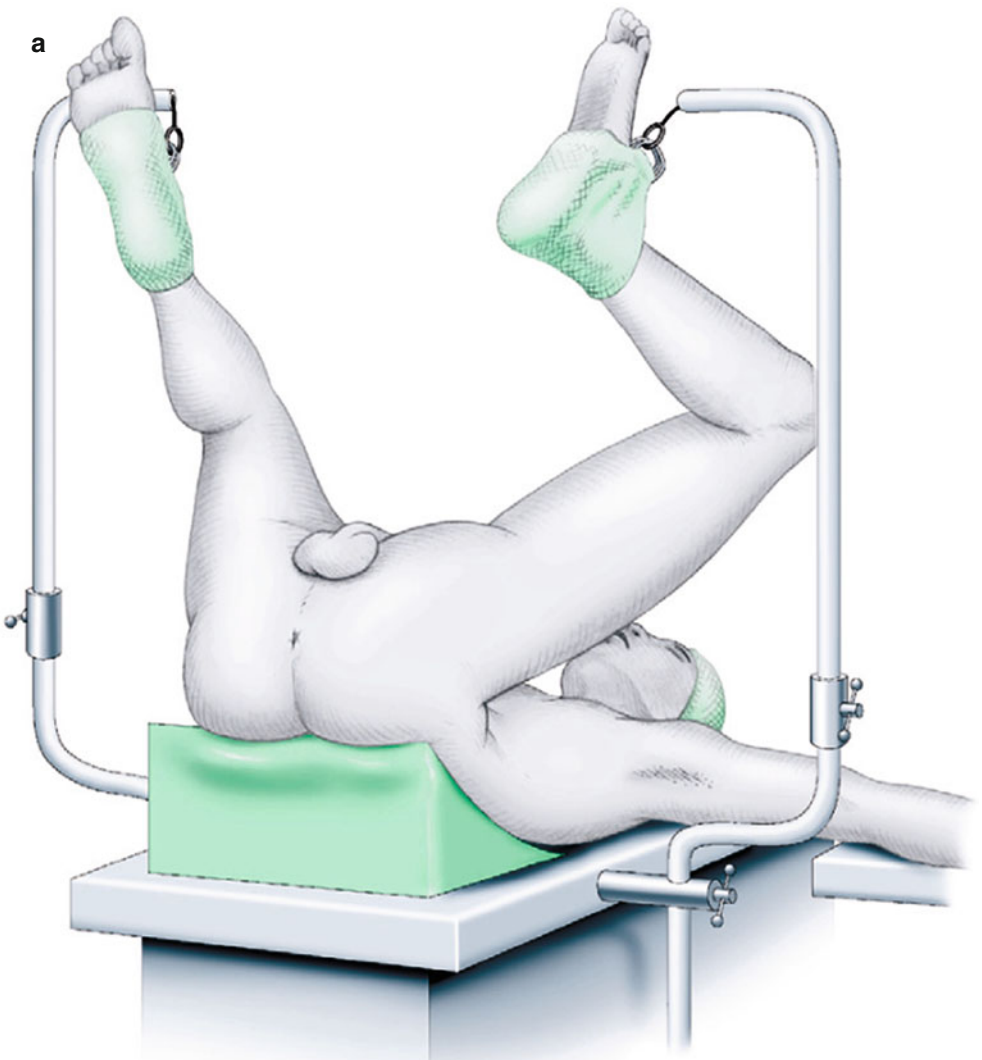


**Fig. 55.1** (**a**) Patient in the exaggerated dorsal lithotomy position (**b**) Transurethral insertion of the curved Lowsley retractor into the bladder and opening of the blades

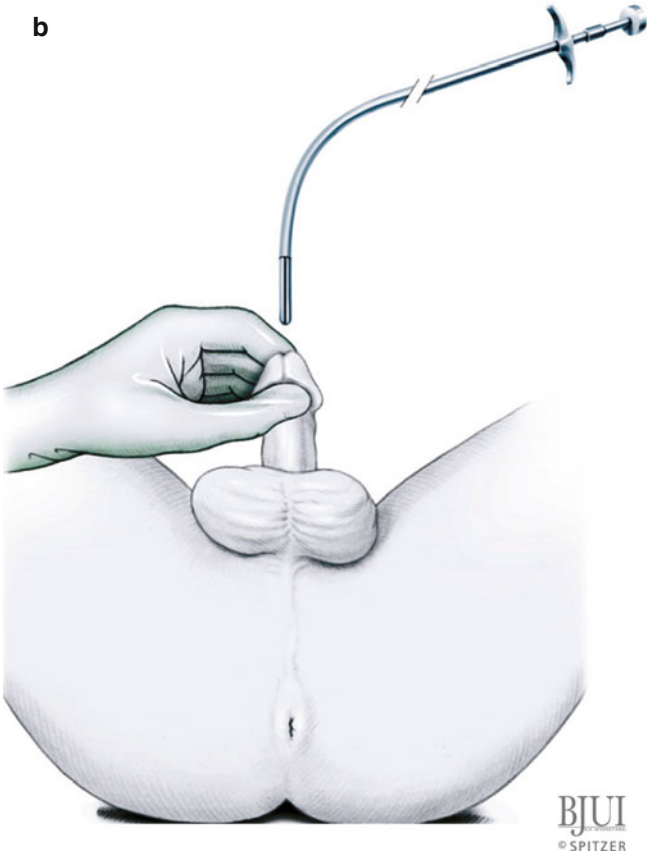


**Fig. 55.1** (continued)

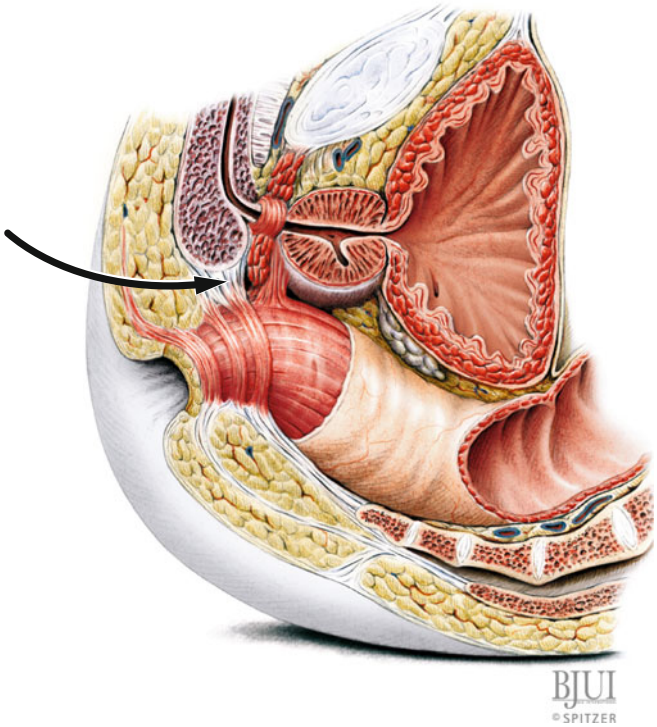


**Fig. 55.2** Young's suprasphincteric approach (*arrow*), which follows a plane through the central tendon below the bulbocavernosus muscle of the urethra and above the sphincter ani externus muscle

- Curved scissors (Satinsky)
- Headlight
- Self-retaining retractor system is optional (Bookwalter®; Omni-Tract®)
- Harmonic scalpel (optional)
- Suture material: 4/0 glycolide (Monosyn®), double-armed 5/8 needles

## Surgical Technique

The patient is placed in the exaggerated dorsal lithotomy position, which brings the perineum into a 45° plane from horizontal, with the buttocks just off the table edge. The legs are supported by cushioned restraints at the ankles, with the calves hanging free to avoid developing compartment syndrome (Fig. 55.1). Patient draping includes a rectal shield to allow for digital rectal guidance during the procedure and checking for a rectal lesion.

Transurethral insertion of the curved Lowsley retractor into the bladder and opening of the blades. This retractor increases maneuverability of the prostate in the operative field (Fig. 55.1).

We prefer Young's "suprasphincteric" route (Fig. 55.2, arrow), which follows a plane through the central tendon below the bulbocavernous muscle of the urethra and above the sphincter ani externus muscle. Another widely used route elevates the sphincter ani externus muscle ("subsphincteric") and uses the anterior rectal surface as a landmark to reach the prostate ("highway to the prostate" of Paulson).

Semicircular incision above the anus, medial from one ischial tuberosity to the other (Fig. 55.3a). Section of the subcutaneous fatty tissue with electrocautery (Fig. 55.3b).

Placement of a traction suture on the skin flap at the level of the perineal raphe. Traction on this suture will exert tension on the tissues, specifically the central tendon, and accentuate its course, making identification easier.

Further sectioning of the subcutaneous fatty tissue, in the midline, muscular fibers of the subcutaneous portion of the external anal sphincter may be encountered and should be transected with electrocautery.

The central tendon connects the bulbospongiosus muscle with the middle and deep portions of the external anal sphincter (Fig. 55.4).

Transect the central tendon. Sometimes the bulbospongiosus muscle and the external anal sphincter will be clearly separated by this tendinous structure. Deaver retractors sweep the superficial transverse perineal muscles from the operative field, but this is usually not required. Note that

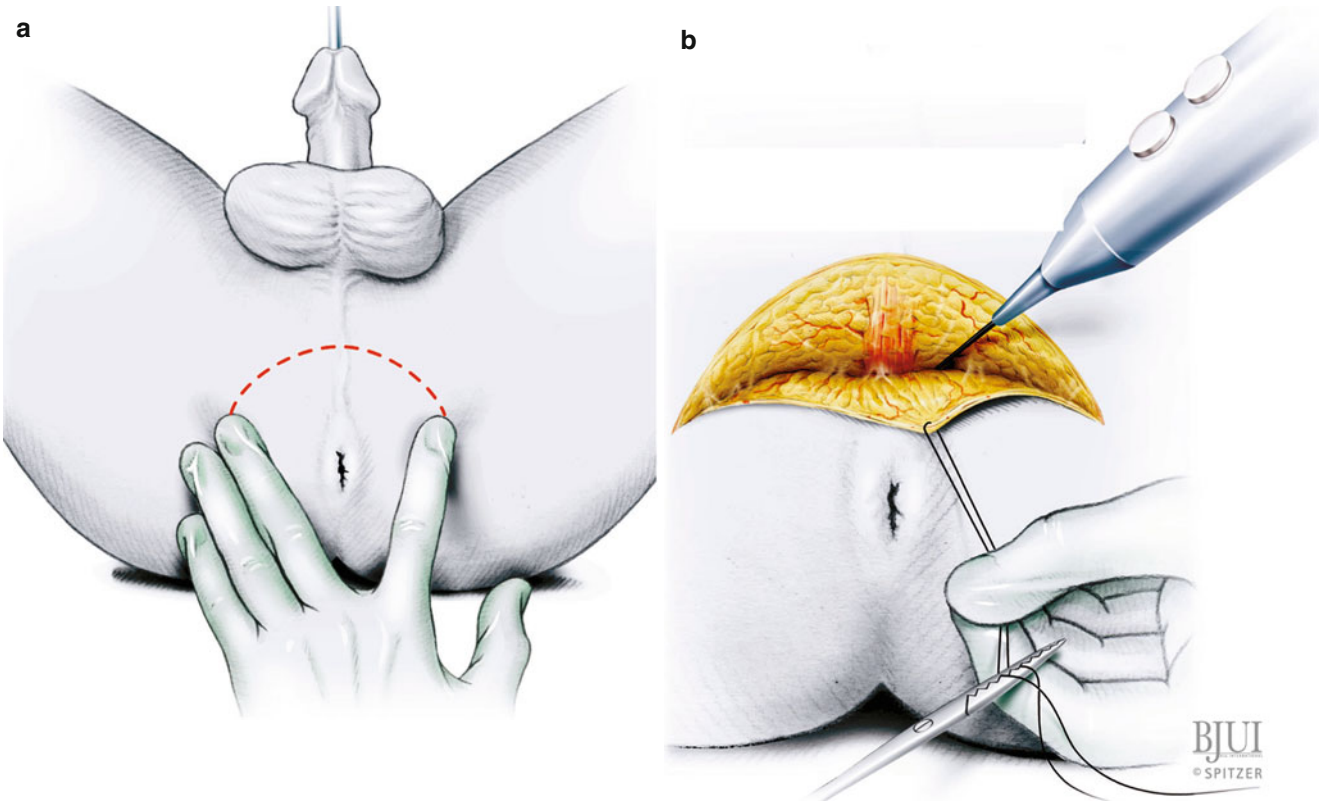


**Fig. 55.3** (**a**) Semicircular incision above the anus, medial from one ischial tuberosity to the other (**b**) Section of the subcutaneous fatty tissue with electrocautery

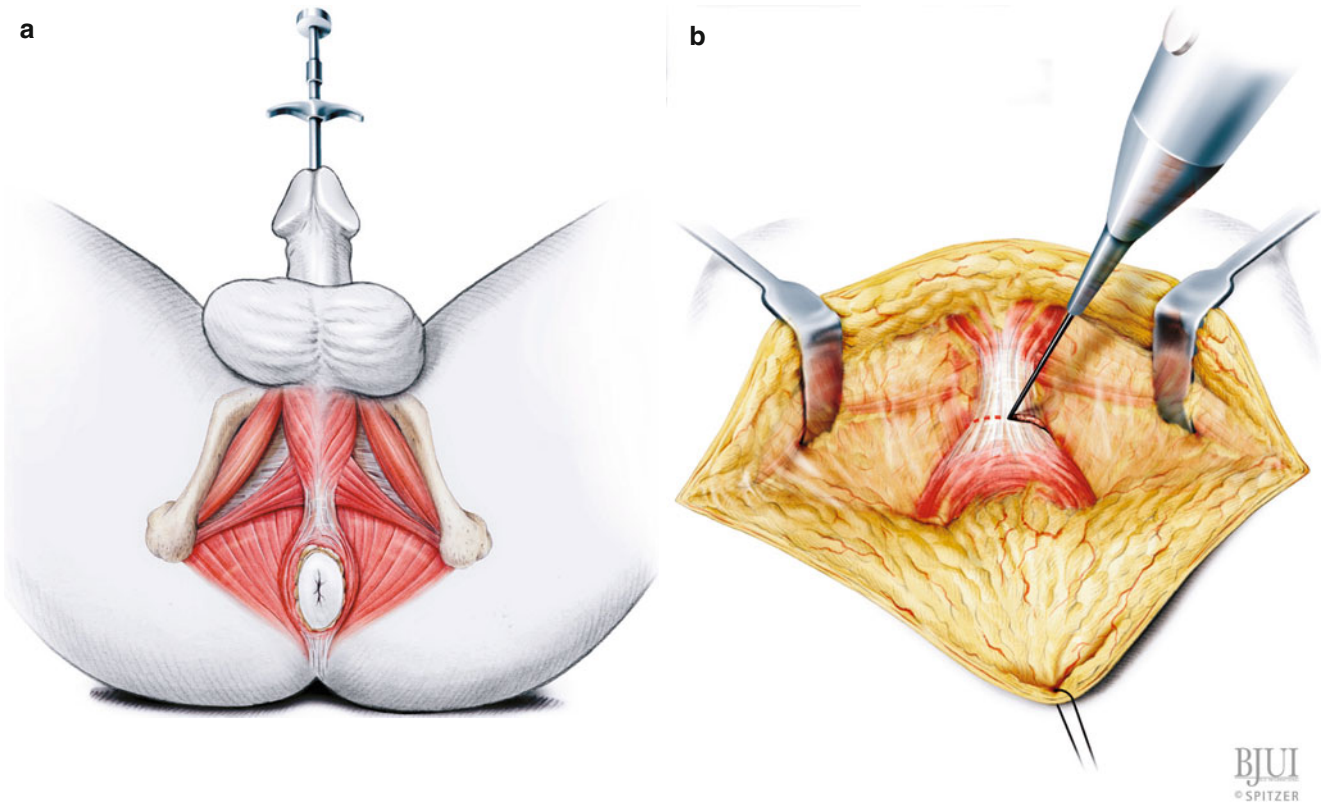


**Fig. 55.4** (**a**) Schematic view of the relevant muscular structures in perineal prostatectomy. The central tendon connects the bulbospongiosus muscle with the middle and deep portions of the external anal sphincter (**b**) Transection of the central tendon. Continuous traction is exerted on the skin flap to better define the anatomical structures

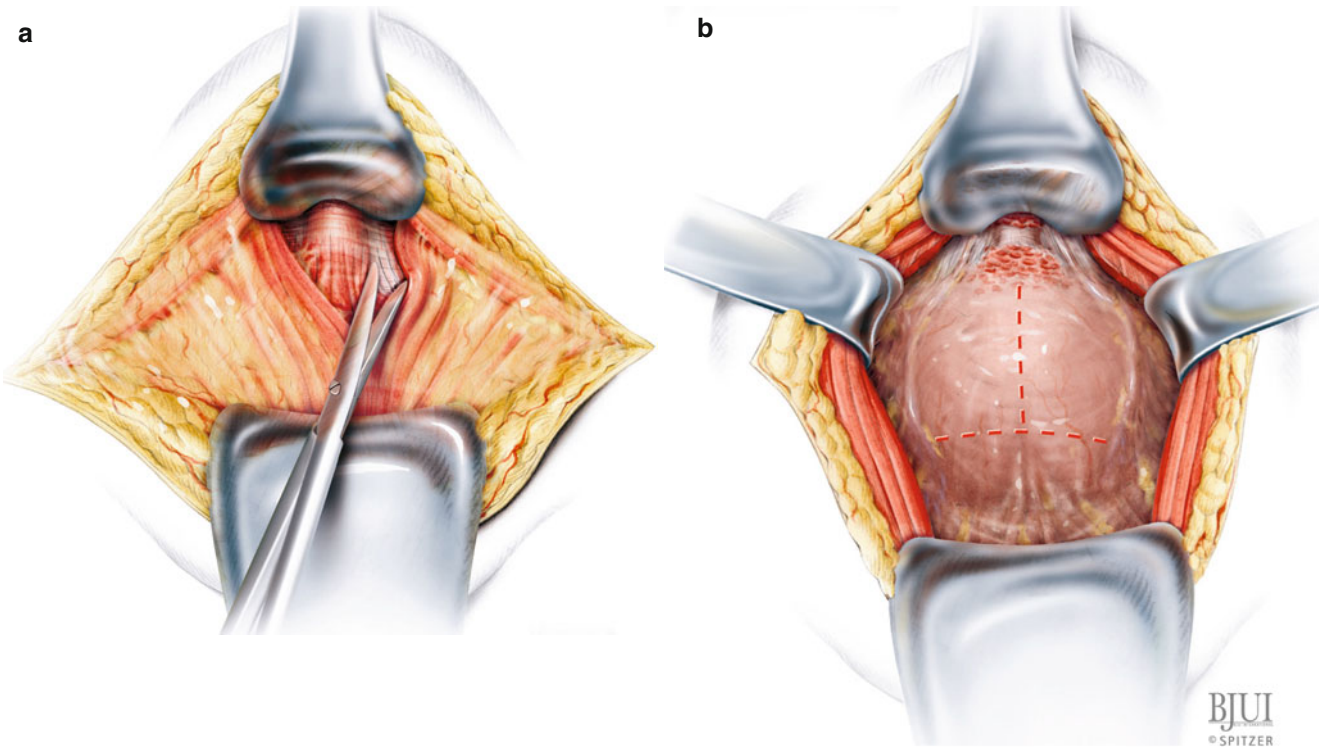


**Fig. 55.5** (**a**) Transection of the rectourethralis muscle (**b**) Incision of Denonvillier's fascia along the dotted line in nerve-sparing perineal radical prostatectomy

continuous traction is exerted on the skin flap to better define the anatomical structures.

Placing the Young retractor on the bulbospongiosus muscle is important to delineate the fibers of the rectum. Caudal traction can be accomplished by pulling on the skin flap suture or with a speculum. Dissect the levator ani muscles laterally off the apex of the prostate by advancing and opening the branches of Metzenbaum scissors immediately lateral on either side of the prostatic apex (Fig. 55.5a). The rectourethralis is the last attachment of the rectum to the prostatourethral junction. Once the ischiorectal fossa is open, the attachment of the rectum to the rectourethralis muscle will be apparent. The rectum is fixed to the distal end of Denonvilliers' fascia by the rectourethralis muscle, so that – in this position – it assumes the configuration of a tent and may be easily injured if dissection is carried on in a caudal manner. The combination of sharp and blunt dissection and digital guidance through the rectal shield allow to define the correct plane of dissection, and the rectourethralis muscle is incised in little increments as dissection progresses. Once the rectourethralis muscle has been divided, the rectum can be swept off the prostate, and the prostatic dorsal surface with Denonvilliers' fascia covering it as a whitish membrane will be visualized.

(As an alternative, the ischiorectal fossa on both sides of the prostate may be developed by incising the superficial perineal fascia and inserting the index and the middle fingers of the left hand, respectively, medial to each ischial tuberosity and parallel to the prostate. Caudal traction on both sides will delineate the plane of attachment of the rectum by the rectourethralis muscle to the prostatic apex and facilitate dissection.)

The rectourethralis muscle has been divided. The levator ani muscles on both sides are held laterally with retractors. The surgeon views the prostatic dorsal face with Denonvilliers' fascia.

The self-retaining retractor may be installed at this time.

If *nerve-sparing prostatectomy* is attempted, Denonvilliers' fascia is incised in the midline with a knife along the dotted line (Fig. 55.5b). At the level of the base of the prostate, Denonvilliers' fascia is then incised perpendicular, but exercise caution not to advance the incision too laterally toward the posterolateral course of the neurovascular bundles.

In *nerve-sparing prostatectomy*, the posterior layer of Denonvilliers' fascia can be dissected laterally off the prostate to include the neurovascular bundles. Small vessels tethering the neurovascular bundles to the prostatic gland can be controlled with the use of small clips (Fig. 55.6).

Dissection of the neurovascular bundles is continued cranially toward the apex and caudally to the seminal vesicles. Minimal manipulation of the neurovascular bundles will prevent stretching injury, grasping the fascial margin only. A vessel loop on the left side has been placed for better depiction of the illustration (Fig. 55.6b). Any form of traction on these delicate structures should be avoided. The neurovascular bundles must be completely dissected from the prostatic surface. Dissection is carried past the prostatic apex and a few millimeters past the prostatourethral junction separating

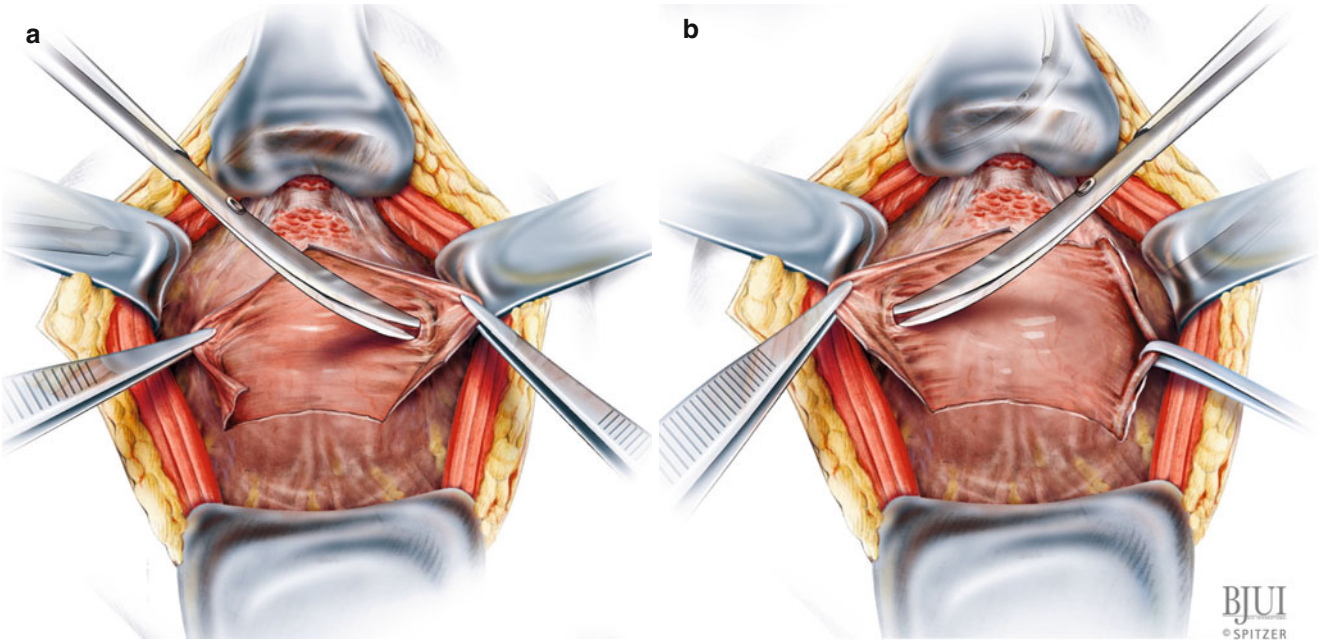


**Fig. 55.6** (**a**) Dissection of the posterior layer of Denonvillier's fascia including the neurovascular bundles in nerve-sparing perineal radical prostatectomy (**b**) Dissection of the neurovascular bundle on the right side. A vessel loop isolates the neurovascular bundle on the left side

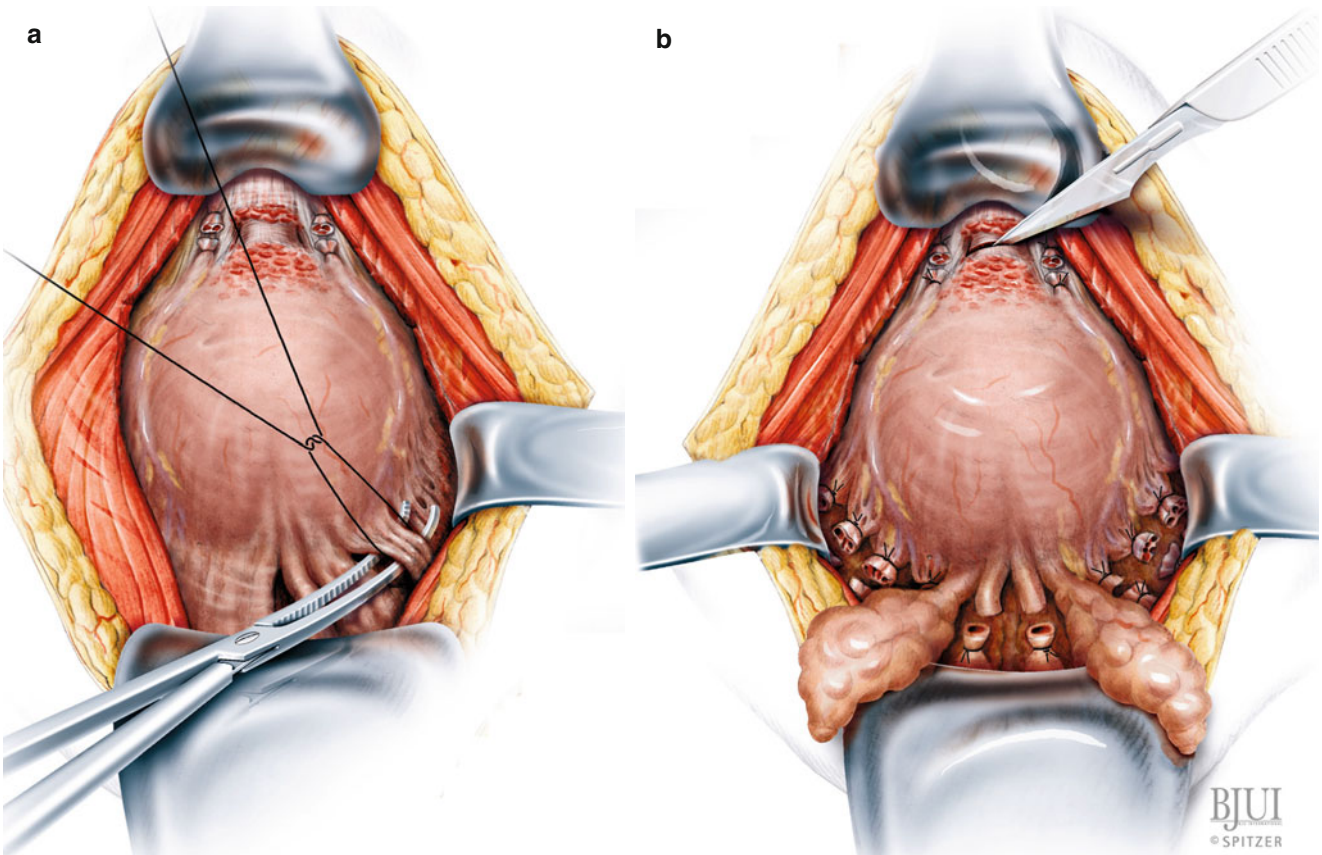


**Fig. 55.7** (**a**) Ligation of the prostatic pedicles (**b**) Knife incision of the dorsal circumference of the urethra

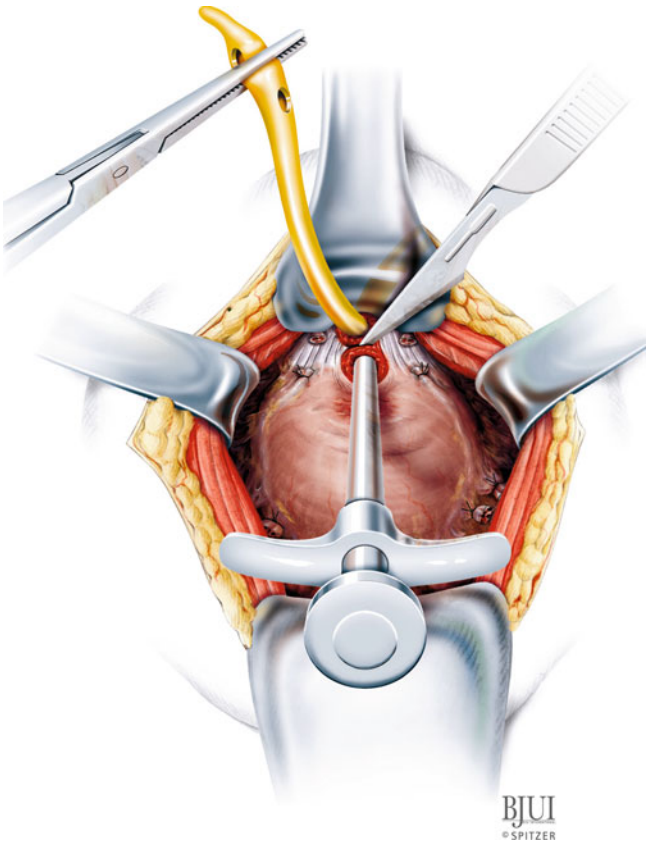


**Fig. 55.8** Knife incision of the ventral circumference of the urethra

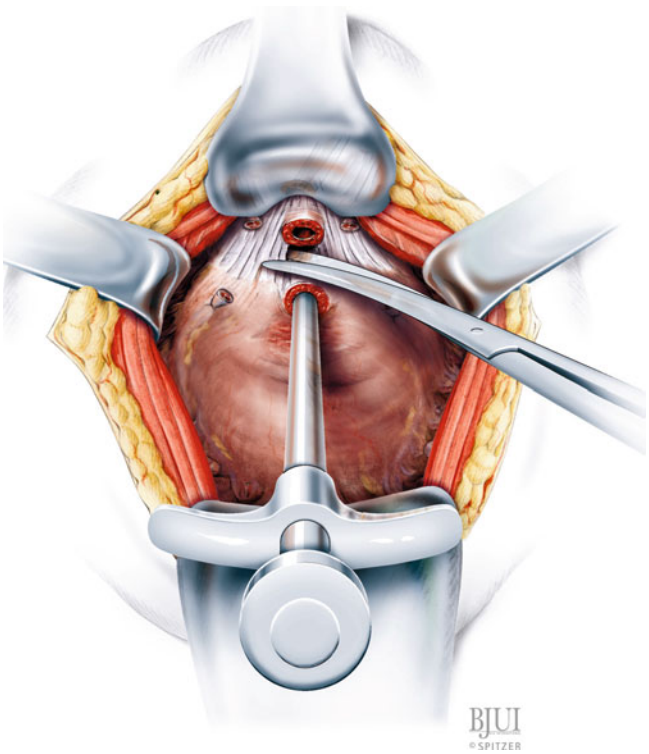


**Fig. 55.9** Division of the puboprostatic ligaments

the neurovascular bundle from the urethral margin to avoid damage while placing the anastomotic sutures. Proximally, the neurovascular bundle has to be dissected off the tips of the seminal vesicles. Denonvilliers' fascia covering the seminal vesicle tips should be stripped off from the seminal vesicles and left as a protecting shield on the neurovascular bundles.

The neurovascular bundles have been ligated and divided on both sides at the apex. Denonvilliers' posterior layer is covering the neurovascular bundles when nerve-sparing surgery is not indicated (Fig. 55.7). The assistant exerts traction on the curved Lowsley retractor to elevate the prostate and define the neurovascular bundles at the level of the seminal vesicles. Using right-angle clamps, these structures can be controlled (Fig. 55.7a). After sectioning the neurovascular bundles, the vas deferens and the seminal vesicles are identified and dissected free with blunt and sharp dissection on either side (not shown). The vas deferens is divided and ligated. Traction on the divided distal vas deferens in the contralateral direction will aid in identifying the corresponding seminal vesicle which should be dissected carefully to avoid tearing. Atraumatic traction to the seminal vesicle may be applied by using a Babcock clamp. Once the seminal vesicle body has been readily dissected, the seminal vesicle artery can be controlled at its tip under vision. Caution should be taken in *nerve-sparing prostatectomy* to avoid damaging the nerve plexus by dissecting lateral to the tips of the seminal vesicles. Once the vas and seminal vesicle have been dissected free on either side, by pulling them in a contralateral and cranial direction, the prostatic pedicles will become evident and can be transected between right-angle clamps. Thereafter, by pulling both seminal vesicles and vas stumps cranially, retroprostatic dissection of the bladder neck can be carried on with curved scissors or using the harmonic scalpel (not shown). Dissection will begin in the midline and follow laterally on both sides to control remnant perivesical tissue with right-angle clamps or with the harmonic scalpel. Once dissection of the vesical neck has been completed, the seminal vesicles can be pushed back and dissection of the apex and urethra may begin.

The dorsal circumference of the urethra is mobilized by blunt dissection off the prostatic apex with a peanut dissector and incised with a knife adapting to the apical shape of the prostate (Fig. 55.7b). To visualize a long urethral stump, the surgeon can push down the prostatic apex with a strong forceps or a peanut clamp.

After sectioning the dorsal circumference of the urethra, the curved Lowsley retractor is replaced by a straight Lowsley retractor, which is used to push the prostate downward. An endotracheal suction catheter is placed transurethrally, exteriorized through the incision and pulled upward to improve visualization of the prostatourethral junction. Under tension, the ventral circumference of the urethra can be sectioned with a knife or curved Satinsky scissors (Fig. 55.8).

Once the urethra has been transected, the puboprostatic ligaments are identified by blunt dissection of the midline with the finger or a peanut dissector, sweeping off the dorsal vein complex ventrally and working against the bladder neck

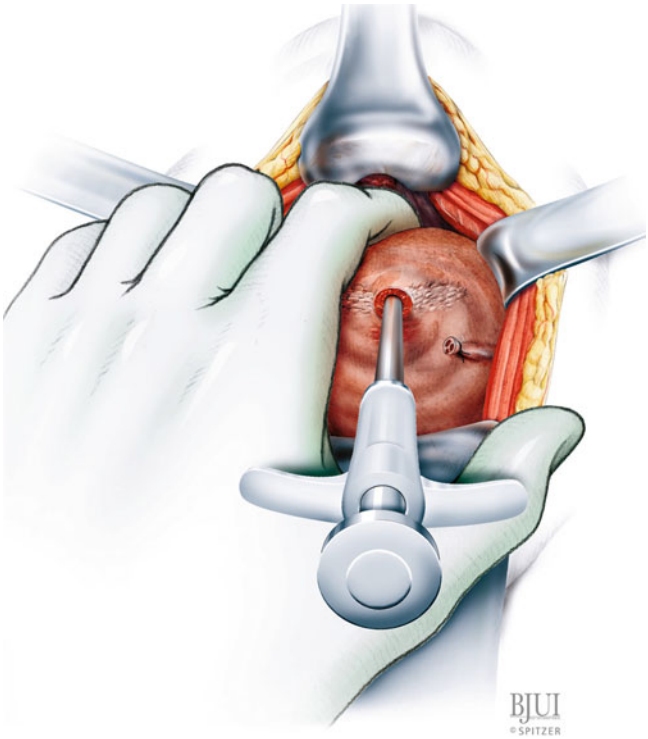


**Fig. 55.10** Identification of the anterior prostatovesical junction by palpating the open branch of the straight Lowsley retractor in the bladder

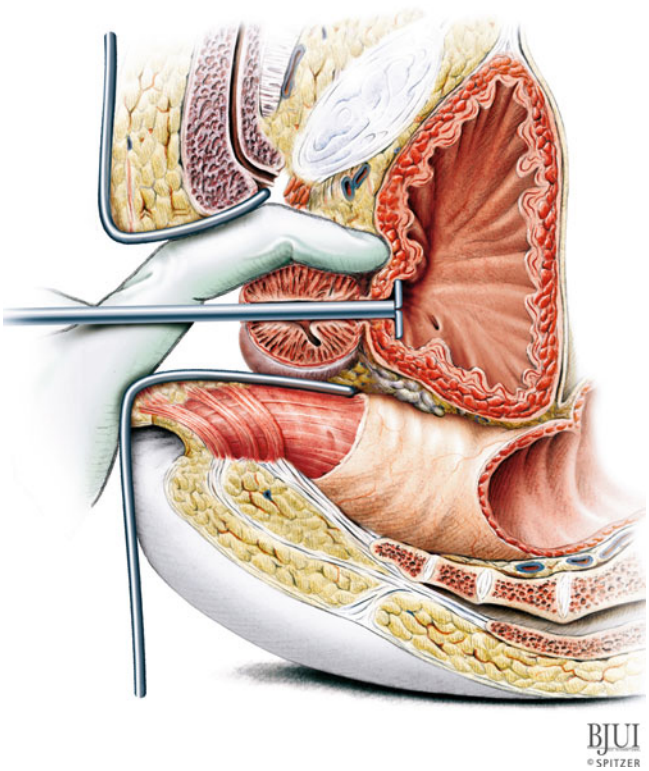


**Fig. 55.11** Schematic view during identification of the anterior prostatovesical junction

dorsally, and are divided (Fig. 55.9). Identification of the bladder neck is helped by 90° turning of the straight Lowsley retractor so that one of its blades can be palpated in the 12 o'clock position of the bladder neck (Figs. 55.10 and 55.11).

The prostate is dissected off the anterior bladder neck with curved scissors or the harmonic scalpel.

Once the prostatovesical junction has been dissected free, the bladder neck is incised (Fig. 55.12a). The straight Lowsley retractor is removed and an endotracheal suction catheter passed through the prostatic urethra for traction (Fig. 55.12b).

A bladder catheter is inserted through the bladder neck incision into the bladder and blocked with 20–30 ml and the remaining bladder neck circumference incised. At this point, bladder neck frozen section biopsies can be excised (Fig. 55.13a).

Before cutting the dorsal circumference of the bladder neck, the ureteral orifices can be identified and may even be intubated by stents, if a large prostate or a middle lobe have developed intravesically.

After sectioning the remaining attachments of the prostate to the bladder, the specimen is removed (Fig. 55.13b).

A full eversion of the bladder neck mucosa may be performed to ensure exact mucosal apposition with the urethra (4/0 monofilament tie), but often is unnecessary due to the excellent visualization of the bladder neck during anastomosis with the urethra. Bladder neck reconstruction in a tennis racket fashion is performed to tailor an opening of 22–24 Charr (Fig. 55.14).

We use eight anastomotic sutures (4/0 double-armed Monosyn®) for anastomosing the urethra to the reconstructed bladder neck. The ventral urethrovesical circumference is reconstructed by placing four separate sutures in sequence at the 10, 11, 1, and 2 o'clock positions (Fig. 55.15a). Be certain to take only the urethral wall and full bladder wall with the suture. After transurethral insertion of a silicone Foley catheter (20 Charr.) and intravesical positioning, the dorsal circumference is accomplished by placing sutures in sequence at the 4, 8, 5, and 7 o'clock positions (Fig. 55.15b). All sutures are tied immediately with exception of the 5 and 7 o'clock sutures. These sutures can be anchored at the remnant tissue of the rectourethralis. After completing the anastomosis, water tightness can be controlled by filling the bladder with 200–300 ml of saline, and the bladder catheter balloon is inflated with 30 cc fluid.

After visual-digital inspection of the integrity of the rectum and placement of a drain, the pelvic floor is reconstructed by readapting the levator ani muscles in the midline (Fig. 55.15c).

## Surgical Tricks

– The self-retaining Bookwalter retractor obviates the need for a second assistant.

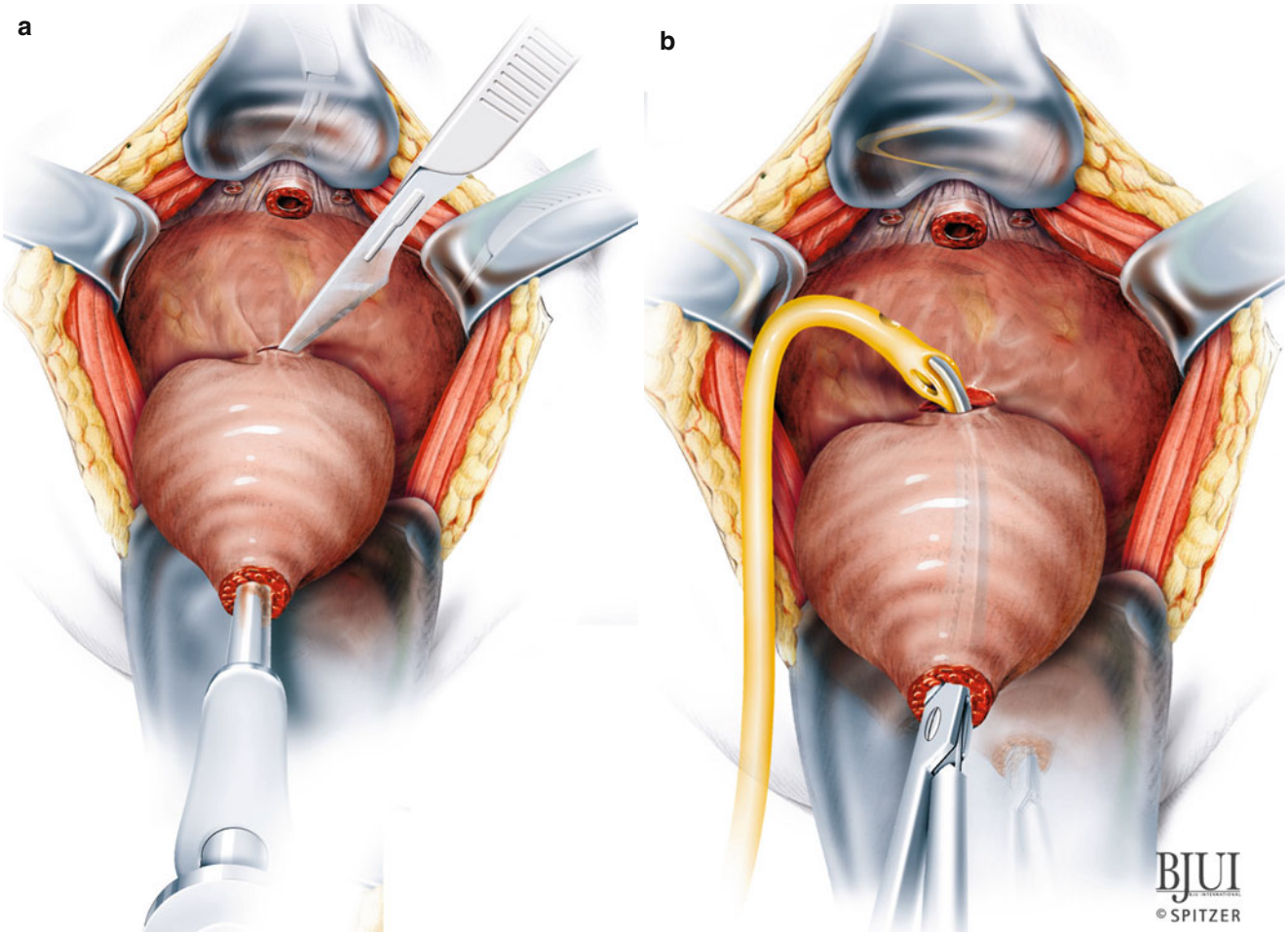


**Fig. 55.12** (**a**) Incision of the anterior bladder neck (**b**) Passage of an endotracheal suction tube trough the incised anterior prostatovesical junction for traction

- Improve visualization of the operative field by tilting the table in a Trendelenburg or anti-Trendelenburg position as needed.
- Use long instruments with small working tips.
- Apply traction to the skin flap tag suture to improve identification of the different layers. Transanal digital guidance may help to identify the position of the rectal wall with respect to the prostatic apex.
- Always place a moist sponge between the rectum and the caudal retractor blade to avoid injury to the rectum.
- Perineal nerve-sparing prostatectomy is not recommended for large prostates because the prostate has to be removed between the neurovascular bundles, and this may cause damage by pressure or traction.
- The vas deferens should be isolated 1–2 cm toward the retrovesical space; otherwise, the ligature will bunch the periductal tissue, including the tissue surrounding the seminal vesicles, and later dissection of the seminal vesicles may become difficult.
- To dissect the seminal vesicles use a Babcock clamp to grasp them. This atraumatic clamp will not traumatize them as easily as would an Allis clamp. Dissection is easier with intact seminal vesicles.
- A Duval clamp or atraumatic lung clamp can be used to grasp both seminal vesicles and vasa together, and pull them in a cranial direction to dissect the retroprostatic bladder neck.
- If the bladder neck has been reconstructed in a tennis racket fashion, leave the end of the suture at the neobladder neck long, to be able to pull on it in cephalad while tying the dorsal circumference anastomotic sutures, thus releasing tension on the sutures.
- 5/8 double-armed needles improve maneuverability and allow for an inside-to-outside suture with no need for a French-eye needle.

## Trouble-Shooting

- We recommend to preoperatively perform retrograde urethrography or cystourethroscopy to exclude a concomitant urethral stricture. If the curved Lowsley retrac-

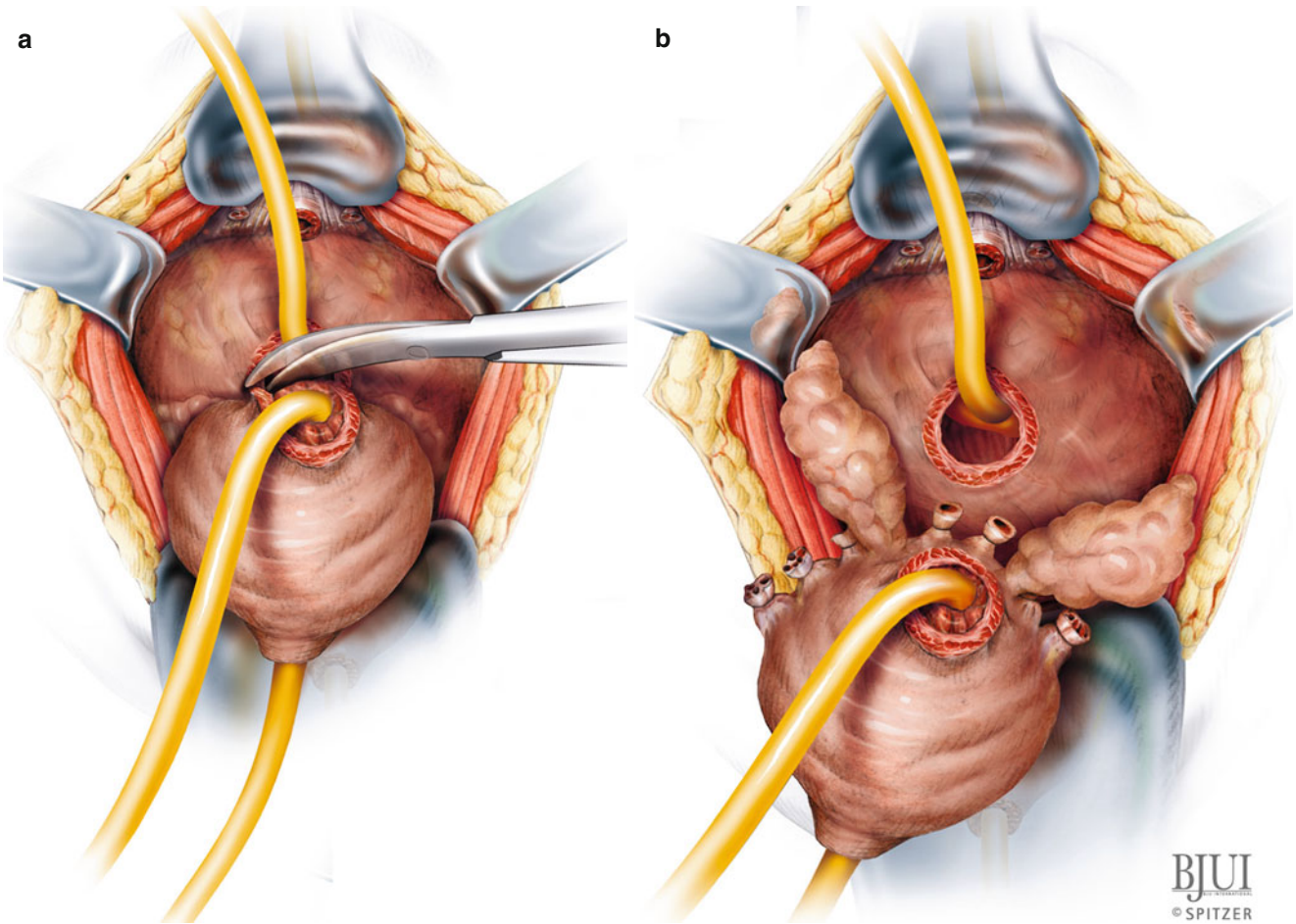


**Fig. 55.13** (**a**) Transection of the posterior bladder neck (**b**) The specimen is removed

tor cannot be introduced, returning the hips to a more stretched position will reduce the sharp entry angle into the bladder. Transrectal digital guidance may also be of help. If the retractor can still not be introduced and urethroscopy has excluded a urethral stricture, we perform the procedure with a transurethral Foley catheter instead of the curved Lowsley retractor. A concomitant urethral stricture can be managed with optical internal urethrotomy in a single session before perineal prostatectomy.

- If the bladder neck was transected close to the ureteric orifices, we recommend temporary insertion of ureteric stents, which can be removed 7 days after surgery.
- Bleeding from Santorini's plexus is rarely encountered and can be controlled with clips or with a figure-of-eight 3/0 absorbable sutures on a 5/8 circle needle.
- If there is a rectal lesion, it should be immediately closed in a transverse fashion in two layers of inverting sutures. Intraoperative application of 500-mg metronidazole should be continued twice daily for 5 days. A rectal tube should be placed and left until the first bowel movement occurs. Parenteral feeding should continue for 5 days.

## Postoperative Care

The patient receives only liquids on the day of surgery. A laxative is administered on the night of surgery; a regular diet is initiated on the first postoperative day. The patient is encouraged to ambulate on the first day. The analgesic requirement is usually adequately covered with intravenous or peroral metamizol.

The drain is removed 1–2 days after surgery, a control cystogram taken after 5–7 days, and the catheter removed on the same day if no extravasation is evident. Pelvic floor training is initiated at 3–4 days after surgery.

## Results

A lower number of centers worldwide have performed and reported their experience on perineal prostatectomy as the primary surgical treatment option for prostate cancer as compared to retropubic prostatectomy. Nevertheless, extractable results compare with those of retropubic prostatectomy in oncological and functional aspects, while showing a reduced

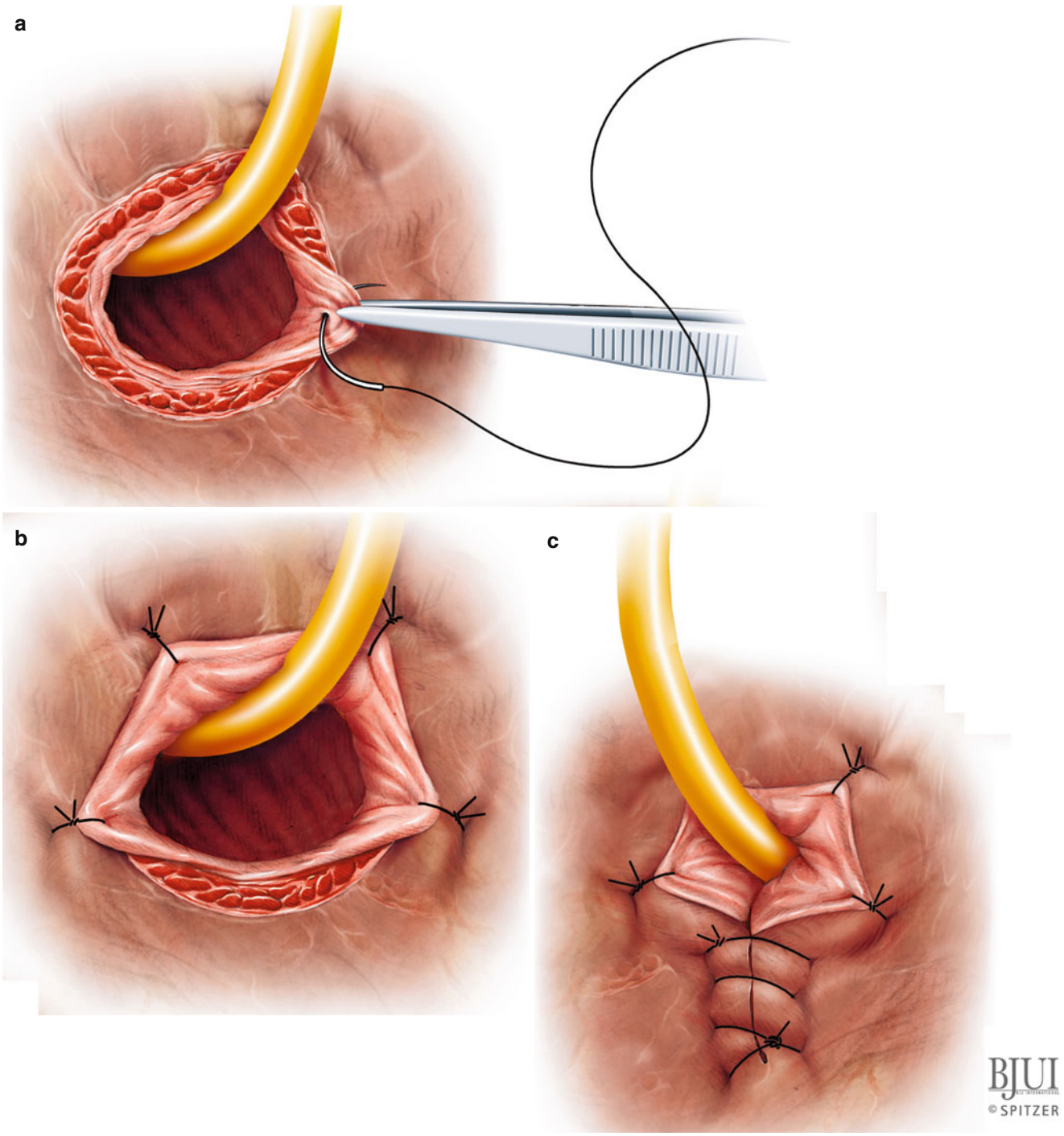


**Fig. 55.14** (**a**–**c**) Bladder neck mucosa eversion and reconstruction in a "tennis racket" fashion

overall morbidity of the procedure. This has been corroborated in direct and randomized comparative studies [6–20].

## Oncological Results

Several publications have shown that overall cancer control with the perineal approach is similar to that achieved with the retropubic approach [6, 18, 20–24]. Nowadays, organ-confined disease is found in about 2/3 of cases due to the stage shift to the left. The reported overall rate of positive margins in the pre-PSA era was about 23 %, but has dropped in later series to 12–18 % [23–27]. Positive margin rates for organ-confined disease range between 0 and 18 % [18, 20, 25, 28, 29]. Actual 5-year PSA-free survival is 94.5, 80.0, and 81.5 % for organ-confined, specimen-confined, and margin-positive disease [23].

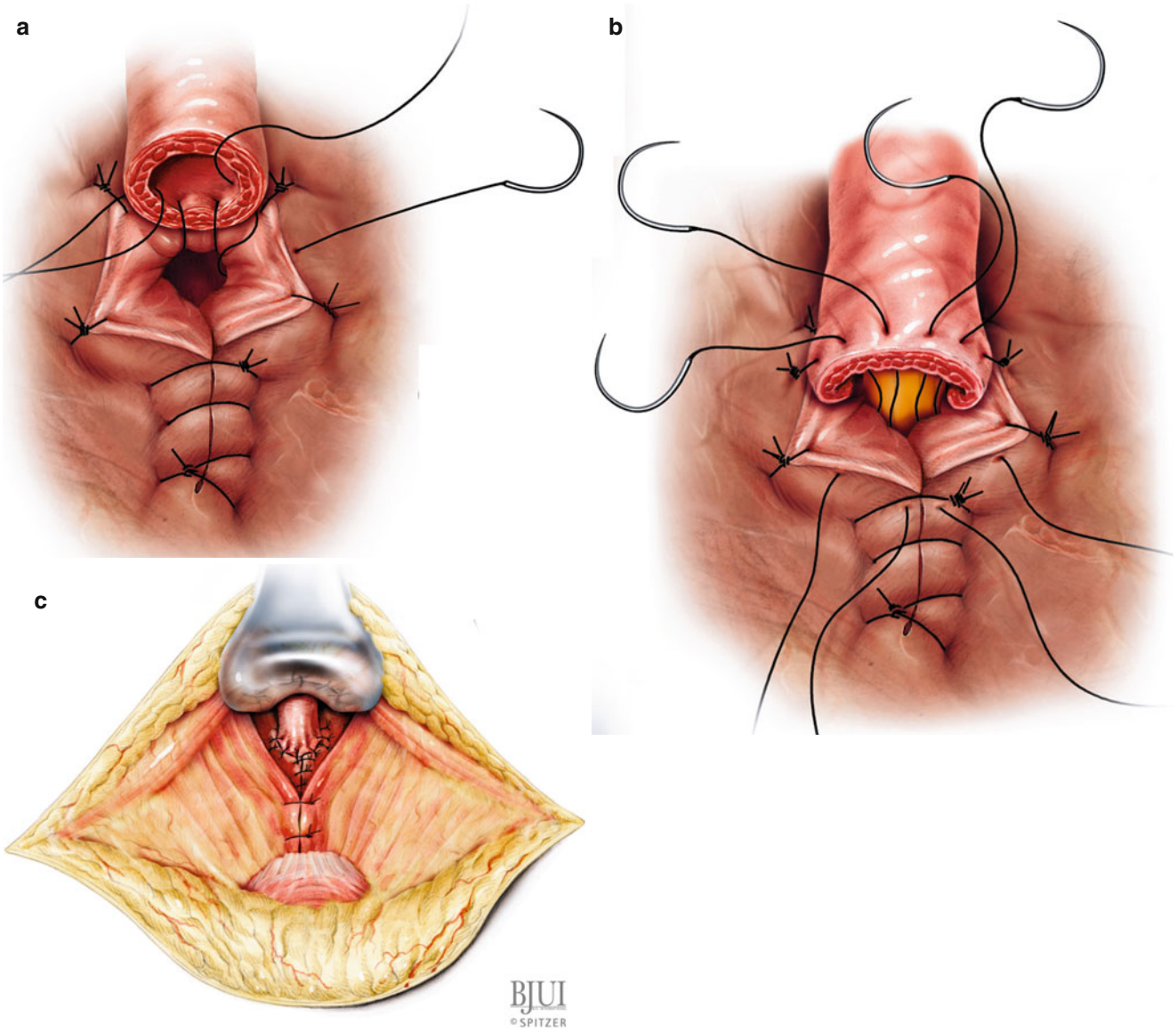


**Fig. 55.15** (**a**–**c**) Anastomotic suture placement with double armed sutures. Pelvic floor muscle readaptation in the midline after completion of the vesicourethral anastomosis

Long-term results of perineal prostatectomy in a small group of 52 patients with clinically organ-confined disease, no adjuvant therapy, and a minimum follow-up of 15 years reveal an overall survival of 64 % and a cause-specific survival of 90 % [30]. Other high-volume centers have reported a long-term disease-free survival probability at 15 years of 86 % for organ-confined and 74 % for specimen-confined cancer, respectively. The cancer-associated median survival time for patients with positive margins is 12.7 years [31, 32]. In our experience with 878 cases of perineal prostatectomy without lymphadenectomy and a median follow-up of 97 months, the observed 5- and 10-year biochemical progression-free survival is 82.2 and 68.7 %, cancer-specific survival is 99.6 and 97.9 %, and overall survival is 95.3 and 89.8 %, respectively (unpublished data).

## Functional Results

### Urinary Continence

Rates of urinary continence vary considerably mostly due to differences in definition and methodology of reporting incontinence. In general, continence rates after radical prostatectomy are mainly age and time dependent. However, improved results can be seen consistently in modern series, probably as a result of the stage shift toward lower stages of disease, of increased surgical experience, and of refinements in surgical technique in respect to newer anatomical and physiological observations. In 1997, Weldon reported a 3-month postoperative continence of 56 % [33]. Ten years later, Harris reported a 3-month postoperative continence rate of 71 % [23]. Early continence rates (4 weeks postop-

erative) range between 41 and 71 % [20, 23]. As demonstrated by a validated patient self-assessment instrument, a nerve-sparing procedure is associated with an earlier recovery of urinary continence and urinary bother scores [34, 35]. Urinary function returns to the preoperative baseline level by 6 months postoperatively. Preoperative quality of life status is generally regained within 3–6 months [36]. Improved continence rates have been reported for a seminal vesicle-sparing technique as compared to standard perineal prostatectomy after 4 weeks (59.3 % vs. 41.0 %) and 12 months (95.7 % vs. 86.4 %), respectively [20]. Urinary continence seems not to be significantly affected from previous prostate surgery for benign prostatic hyperplasia and may even be superior for the perineal route as compared to the retropubic route [37].

Approximately 95 % of men are free from using pads at 1 year [23, 24, 33], and a 96 % complete continence rate (no pads) has been reported at 24 months [18]. Large series with over 100 consecutive patients report total incontinence rates of 1–8 % [6, 33, 38, 39]. Persistent total incontinence requiring placement of an artificial urinary sphincter occurs in less than 1 % [20].

### Potency

V.E. Weldon adapted in 1988 the nerve-sparing technique of retropubic prostatectomy to the perineal approach [40]. As for retropubic prostatectomy, reported potency rates also vary considerably for the perineal approach. Contemporary results after nerve-sparing perineal prostatectomy reveal potency rates (capable of completing unassisted intercourse) after one or more years between 30 and 80 % [18, 20, 23, 24, 33, 35]. However, it has to be considered that a comparison may be biased by the heterogeneity in reporting and generally low case numbers. The return of potency is higher for bilateral than for unilateral nerve-sparing, as is also the case for retropubic or laparoscopic prostatectomy [29].

## Morbidity and Complications

The reported perioperative morbidity of perineal prostatectomy confirms the true minimally invasive character of the procedure. Surgical time is relatively short (90–120 min) [19, 20, 41], intraoperative blood loss is usually 400–600 ml, and the need for blood transfusions is approximately 0–9 % [6, 18–20, 23, 24, 28, 33, 42]. The intraoperative and perioperative mortality rate in contemporary series is close to 0 % [33]. Postoperative pain management requires only short periods of intravenous or epidural analgesics. Generally, oral analgesics are already given on the first or second postoperative day [39, 43–45]. Hospitalization time in the USA, where patients are discharged as early as on the second postoperative day, tends to be shorter than in European countries [32, 33, 45]. A recent report emphasizes the high degree of safety and patient satisfaction of perineal prostatectomy even when performed on an outpatient basis with less than 24 h of hospitalization. In this study, 91 % of patients were home within 23 h of the operation, and 13 % were home the same day of their radical prostatectomy [39].

The transurethral catheter can be removed on the 7th postoperative day in over 90 % of the cases [18, 28]. Prolonged urinary extravasation for 11–21 days in 2 % of the cases usually resolves spontaneously [33]. Urinary leakage through the perineal incision is observed in about 3 % and resolves in most instances by leaving the catheter for about 2 weeks [28, 46].

Reduced morbidity, operation time, and blood loss favor the perineal approach for elderly patients and those with a higher anesthetic risk. Obese patients, as defined by a BMI of $\geq 30$ kg/m$^2$ may especially benefit from perineal prostatectomy as compared to the retropubic approach [47, 48].

### Intraoperative Complications

Rectal lesions are reported in approximately 1–3 % of cases; however, they occur in up to 11 % of cases during the early learning curve [7, 24, 28, 33, 39, 42, 49]. Specially, young surgeons should be aware of this possible complication, as it occurs most frequently during transection of the rectourethralis muscle and mobilization of the rectum as initial steps in perineal prostatectomy to gain access to the prostate. It can easily be repaired primarily with a two-layer closure, but requires perioperative antibiotic treatment covering anaerobic bacteria and rectal drainage (rectal tube) and usually does not have any sequelae. The need for a primary colostomy after rectal injury is rare [7]. However, if a rectal lesion remains undetected intraoperatively and if urinary leakage or perineal hematoma are complicating factors, it can result in perineal abscess and fistula formation [28, 50].

A ureteric lesion requiring reimplantation has been reported occasionally [29, 51].

### Postoperative Complications

Radical perineal prostatectomy is associated with an overall low complication rate. Short-term and long-term complications have been reported at 4 and 12 %, respectively [6]. However, complications can be severe and difficult to manage, and therefore early symptom assessment, detection, and treatment are warranted.

### Acute Urinary Retention

An early complication of perineal prostatectomy is acute urinary retention after catheter removal, which occurs in up to

8.0 % of cases [19]. Immediate acute urinary retention after catheter removal is highly associated with anastomotic stricture formation [52]. Our data has also revealed an association between the modality used to treat acute urinary retention and the development of an anastomotic stricture. In our series, 33.3 % of patients treated with a suprapubic cystostomy catheter for acute urinary retention subsequently developed an anastomotic stricture, whereas only one patient (4.2 %) treated with reinsertion of the transurethral Foley developed an anastomotic stricture [52]. If acute urinary retention develops after catheter removal, the presence of concomitant sub- or retrovesical hematoma should be evaluated sonographically, since an expanding hematoma can also disrupt the anastomosis [28].

## Anastomotic Stricture

Vesicourethral anastomotic strictures occur in about 2–5 % after radical perineal prostatectomy [6, 25, 28, 33, 39, 53]. In retropubic prostatectomy, mucosal eversion did not help to reduce the rate of anastomotic stricture but increased the rate of urinary extravasation in a prospective controlled trial, and therefore probably can also be omitted in perineal prostatectomy [54].

Most of the anastomotic strictures develop within 6 months after the operation and respond well to the established endoscopic treatments. Local recurrence of PCa seems to be a negligible cause of anastomotic obstruction in the early postoperative period [52].

## Rectourethral Fistula

Rectourethral fistula is a rare but severe complication of radical perineal prostatectomy [20, 25, 28]. In our series, over 50 % of the patients who developed a rectourethral fistula had actually experienced an overt intraoperative rectal injury. Accidental rectal injury is a major risk factor for development of a rectourethral fistula. Patients who develop a rectourethral fistula have a prolonged clinical course, often requiring several surgical procedures. Rectourethral fistulae mostly develop 2–3 weeks after radical prostatectomy. Clinical symptoms such as anal urinary discharge, pneumaturia, or fecaluria are pathognomonic. Conservative treatment by transurethral or suprapubic urinary diversion for at least 4 weeks in combination with fully absorbable diet is usually the first attempt in patients without signs of sepsis and fecaluria. In cases with fecaluria and/or signs of systemic infection, the initial step should be colostomy and urinary diversion by transurethral or suprapubic catheter drainage. This may allow healing and spontaneous fistula closure in about 1/3 of cases. The remainder require surgical fistula closure. Surgical fistula closure is highly successful but requires protective colostomy in all cases. Unfortunately, this translates in a prolonged clinical course and reduced continence rates from radical prostatectomy, despite successful fistula closure [55].

## Fecal Incontinence

Bishoff was the first to raise awareness on the possibility of fecal incontinence after perineal prostatectomy by reporting a de novo fecal incontinence rate of 18 % using a validated questionnaire telephone survey to evaluate 127 perineal prostatectomy patients [56]. Interestingly, less than 50 % of the patients with fecal incontinence had told the attending physician about the problem. In our retrospective study of 335 patients with a follow-up >12 months, 9 % reported de novo changes in stool habits after perineal prostatectomy, including 6.6 % stool soiling (underwear staining only) and 2.1 % of patients requiring a protective pad or toilette paper [28]. In a prospective study, Kirschner-Hermanns found a 5 % rate of newly developed fecal incontinence symptoms including reduced sensibility, reduced discrimination, urgency, or stool smearing related to perineal prostatectomy in 116 evaluable patients 12 months postoperatively [57]. Patients presenting with at least one of these symptoms preoperatively had an almost fourfold increased risk of postoperatively developing at least two symptoms of fecal incontinence. The prevalence of preoperative involuntary stool leakage and rectal urgency were reported in 11.5 and 19.2 % of 78 prospectively followed patients [58]. In this study, rectal urgency was the most persistent symptom postoperatively, but it normalized in more than 90 % of patients within a year.

## Neurapraxia

Neurapraxia of the nerves of the lower extremity due to the exaggerated lithotomy position occurs very rarely, but may be underreported due to the low morbidity character in most instances [25, 28, 42]. The sciatic as well as the common peroneal nerve or its cutaneous branches can be affected, resulting in both motor and sensory deficits. Symptoms are usually mild and transient with complete remission within a couple of weeks. The most common complaints include lower extremity anesthesia, paresthesia, decreased proprioception, and muscular weakness. The most important factors influencing the occurrence of neurapraxia are correct patient positioning and limiting the time of exaggerated lithotomy position. Previous vertebral surgery or a history of chronic lower back pain are not predisposing [42].

## Acute Epididymitis

This is a rare complication that develops in about 2 % of the cases, occurs within 1 month after prostatectomy, and may require orchiectomy [28].

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# Laparoscopic Radical Prostatectomy: The Technique

56

Christopher Eden and Anthony Hutton

## Introduction

Radical prostatectomy (RP) is the most effective treatment for localized prostate cancer and the treatment recommended by the majority of urologists to their patients [1]. The retropubic route is most commonly used as the anatomy is more familiar and it allows synchronous pelvic lymphadenectomy and always permits removal of a large prostate intact. In contrast with perineal prostatectomy, the retropubic approach is not associated with an incidence of postoperative fecal incontinence. The motivation behind developing laparoscopic RP (LRP) lay in the wish to expand the number of patients who might benefit from the claimed generic advantages of laparoscopic surgery, namely, less postoperative pain and a shorter convalescence. LRP also appeared to greatly reduce intraoperative blood loss and provided the surgeon with a consistently evenly illuminated and magnified view of the pelvic anatomy and suggested the possibility of superior results through superior vision. Subsequent publications have quashed this hope [2] and have demonstrated a clear link between surgical volume and patient outcomes but no advantage of LRP or robot-assisted LRP in terms of oncological or functional superiority.

## Historical Perspective

Increasing experience with laparoscopic renal surgery more than a decade ago made it inevitable that attempts would eventually be made to replicate RP laparoscopically. Schuessler's initial series of LRP failed to inspire other surgeons to follow his example, chiefly because of the very long operating time (mean = 564 min), and led him to incorrectly conclude that a laparoscopic approach for radical prostatectomy conferred no advantage over open surgery, despite good oncological and early functional results [3]. The seminal paper published in 2000 by Vallancien and Guillonneau demonstrated for the first time that LRP could be performed in an operating time similar to that of open surgery with significantly less blood loss compared to open RP (ORP), good oncological and early functional results, and all the generic advantages of laparoscopic surgery [4]. The Montsouris series inspired a number of urologists to begin their own program of LRP, but some of the initial results served only a reminder that poor surgery produces poor outcomes [5] and others, since updated, that even well-prepared surgeons face a steep learning curve when embarking on a new program of complex surgery [6, 7]. LRP has undergone a great deal of development since the initial cases, and although certain technical details are common between contemporary series, alternative options exist for a number of steps, depending on surgeon preference.

## Patient Positioning

Procedures are typically carried out using a five-port open access laparoscopic approach with exaggerated Trendelenburg tilt. The patient's legs are abducted to allow access to the rectum and are held in leg supports which allow the knees to be flexed by 90° to minimize the risk of lower limb ischemia. Patient's arms are secured by their sides with the elbows and hands protected by padding. An orogastric tube is used to empty the stomach, and the eyes are taped shut for protection. Two assistants stand opposite the surgeon with the scrub nurse standing on the same (left) side as the surgeon. The camera stack is placed between the patient's legs, although the author places the stack on the right side of the patient and a multimedia projector between the legs for projection of the laparoscopic view onto a large screen. Little acuity is lost but the resulting significantly

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enlarged image allows the operative team's eyes to focus at infinity, rather than at 3 ft, which is less tiring. After preparing the patient's skin and draping, the bladder is emptied using a 16F Foley catheter.

## Transperitoneal Versus Extraperitoneal Access

The choice of surgical route of access depends chiefly on surgeon preference, but other factors will determine the final choice, so familiarity with both approaches is preferable. Transperitoneal LRP offers the appeal of an abundance of anatomical landmarks and a larger workspace within which to operate. It also allows access to the internal iliac artery for extended pelvic lymphadenectomy (PLND) and by virtue of its greater bladder mobilization reduces anastomotic tension during reconstruction. Lymphocele formation is also less frequent using this approach. Disadvantages of the transperitoneal route include a less direct approach, mandating dissection of the bladder from the anterior abdominal wall in order to access the prostate, the need to lyse adhesions from previous transperitoneal surgery, the greater risk of intestinal injury during dissection (1.8 % of complications in a series reported by Guillonneau were attributed to the adoption of the transperitoneal route [8]) and access in some previously operated patients, and the lack of containment of blood and urine offered by extraperitoneal LRP. The advantages of extraperitoneal access are the familiarity of this approach to open surgeons and the disadvantages of transperitoneal LRP. The disadvantages of this approach are the inability to perform an adequate extended PLND and greater anastomotic tension. Lack of workspace is not a disadvantage in practice. Both approaches are equally difficult but feasible in patients who have had laparoscopic mesh hernia repair.

## Transperitoneal Access

The use of a Veress needle to create a pneumoperitoneum is associated with a risk of visceral injury of 1/1,000. This, together with the prospect of occasional insufflation of the omentum or abdominal wall and the ease and rapidity of open surgical access (especially in previously operated abdomens), tips the balance firmly in the direction of the latter technique. It may also become difficult to defend the adverse consequences of using a Veress needle medicolegally, if this is not already the case. Once the primary port has been placed just below the umbilicus, it is connected to the $CO_2$ supply, and the abdomen is inflated to 15 mmHg pressure. Subsequent ports are placed under direct vision according to Fig. 56.1. If an extended PLND is indicated, as is the author's practice for patients in the intermediate- and high-risk groups, it is performed at this stage.

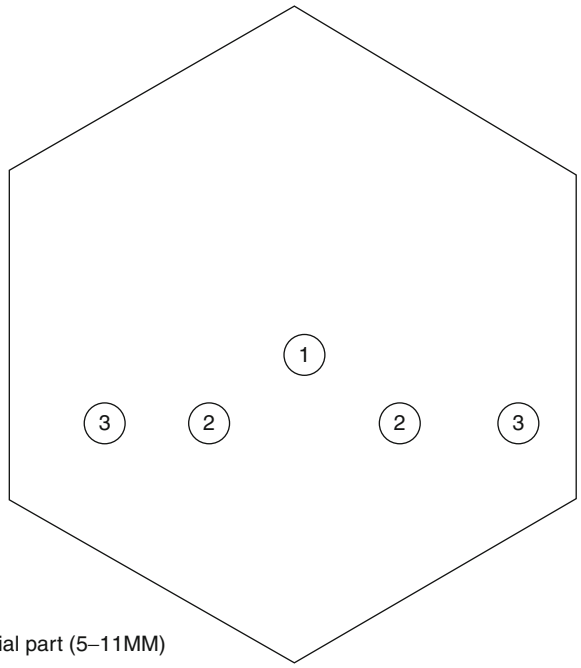


**Fig. 56.1** Port placement

### Extended PLND

The congenital adhesions attaching the sigmoid colon to the left pelvic sidewall are divided to expose the pelvic vasculature and ureter. The peritoneum is incised in a "V" shape with apex starting where the ureter passes over the common artery and extending anteriorly to just medial to the internal inguinal ring, with the lower limb of the "V" passing just anterior to the ureter over 5 cm. The cut peritoneal edge is retracted medially by an assistant's forceps as the tissue overlying the midpoint of the external iliac artery is dissected medially toward the free edge of the external iliac vein. This dissection is continued anteriorly up to Cloquet's node, which forms the superior extent of the lymphadenectomy. This tissue is clipped at this point and divided. The nodal packet is then retracted posteriorly, exposing the back of the pubis and, further posteriorly still, the obturator vessels and nerve. The lymphatic packet is dissected carefully off these structures, clipping vessels and lymphatics where encountered. The nodal packet is next swept laterally off the medial-cut peritoneal edge to expose the medial umbilical ligament (which leads to the proximal internal iliac artery). While the assistant retracts the ureter medially with a sucker to protect it, the lymphatic packet is separated from the anterior aspect of the internal iliac artery from its commencement, past the origin of the medial umbilical ligament and forward until the previous dissection in the obturator fossa is encountered. The obturator nerve is once again identified at its proximal limit in the obturator fossa, medial to the external iliac vein.

The packet is placed anterior to the rectum, and the field inspected for the completeness of the dissection and hemostasis. All nodal tissues are entrapped in a sac and retained for later removal. The left side is differentiated from the right-sided specimen by tying a loop in its string ("L" as in loop and left). Before the same procedure is performed on the right side of the pelvis, a 2/0 nylon suture is inserted through the abdominal wall under vision, passed twice through an appendix epiploicae on the right side of the rectum, and then back through the abdominal wall to be clipped on the outside. This significantly improves access for the right extended PLND.

### Dissection of the Bladder

The bladder is dissected off the back of the anterior abdominal wall using hook diathermy, as the assistant uses the sucker for countertraction of the tissues. The dissection of the peritoneum is started in the midline and extended laterally toward the already exposed pubic bone before the bladder is swept off the abdominal wall.

## Extraperitoneal Access

The initial incision is made just below the umbilicus and is deepened to expose the anterior rectus sheath. This is incised longitudinally to the left of the midline, exposing the left rectus muscle. An oval balloon dilator (Tyco, Mansfield, USA) is introduced under the free medial edge of the left rectus muscle and advanced in the midline. It is inflated to dissect a preperitoneal workspace. A structural balloon trocar (Tyco, Mansfield, USA) is then exchanged for the balloon dilator, the foam collar cinched onto the skin to create a gas-tight seal, and the extraperitoneal workspace then distended with $CO_2$. The four secondary ports are then inserted, as in Fig. 56.1. If the surgeon wishes to perform a standard (external iliac and obturator) PLND, this is done next.

## Common Steps of LRP

The connective tissue on either side of the prostate is gently, bluntly dissected with the sucker to fully expose the back of the pubis, the fat overlying the prostate and the endopelvic fascia on either side. The fat is dissected off the front of the prostate with hook diathermy, dividing it laterally where it intersects the endopelvic fascia, over the bladder neck and anteriorly after coagulating the superficial dorsal vein. The fat is then removed. If either neurovascular bundle (NVB) is to be sacrificed, the endopelvic fascia on that side may be incised and the levator ani fibers swept off the side of the prostate to serve as a marker.

### Bladder Neck Management

The Foley catheter is removed and an 18/22F curved sound is inserted into the urethra. The anterior bladder neck is incised with hook diathermy at the vesicoprostatic junction, which is recognized by the following: (1) the point at which fat is adherent, (2) where a triangle of detrusor muscle fibers is seen, and (3) where the Foley catheter balloon stopped when pulled inferiorly. Once the anterior bladder neck has been incised to reveal the bladder mucosa, the sound is used to elevate the prostate (a cut Foley catheter with the balloon still inflated can be used as an alternative). Posterior countertraction of the anterior bladder neck with a sucker exposes the posterior bladder neck, which is also incised with hook diathermy. It is important to maintain the same thickness of (posterior bladder neck) tissue being dissected to prevent either inadvertent entry into the prostate (indicated by the emergence of white prostatic sections) or buttonholing or thinning the posterior bladder neck. Arrival at the anterior layer of Denonvillier's fascia is indicated by a loss of resistance to the sucker, which is used to retract the bladder neck posteriorly, exposing the vasa in the midline. In nerve-preserving cases, the vessels overlying the vas are controlled with bipolar diathermy and the seminal vesicle arteries with clips. If nerve preservation is not envisaged on that side, the vasa and seminal vesicles are dissected using hook diathermy.

Bladder neck preservation can be achieved by alternating diathermy and blunt dissection of the bladder base off the prostate base, working on either side from a lateral to a medial direction, until a tube of prostatic urethra is encountered at the prostate base, which can then be divided. It has the appeal of obviating the need for bladder neck reconstruction but risks a positive base margin, is difficult to achieve if a median lobe is present, and does not contribute toward postoperative continence [9].

### NVB Management

The decision as to whether to nerve preserve on both, one, or neither sides needs to be taken in the light of the patient's age, potency, expectations, priorities, PSA, Gleason grade, number and percentage of positive biopsy cores involved, preoperative imaging, and clinical stage. The decision is an important one as it may affect cancer control, continence, and potency. A number of nomograms are available to aid this decision-making process. The surgeon and his patient initially need to decide whether to nerve preserve (in low- and intermediate- risk potent patients), nerve damage (in intermediate-risk impotent patients), or widely excise a NVB (in patients with high-risk, especially T3, tumors) on each side. The process of nerve preservation can be further classified by the plane in which the body of the NVB is separated from the prostate: between the prostate capsule and the lateral prostatic fascia (intrafascial), between the layers of the lateral prostatic fascia (interfascial), or leaving a rim of

variable thickness of NVB on the prostate (partial nerve preservation). However, the nerve sparing is done, no energy must be applied to the pelvic plexus or NVB, the NVB should be pushed off the prostate rather than pulled off it, and accessory pudendal arteries on either side of the prostate must be preserved. Nerve preservation is usually performed in an antegrade direction as that is the direction in which the laparoscope, and therefore the surgeon, looks. Retrograde NVB dissection, as described by Rassweiler, has failed to gain popularity, possibly because of the greater blood loss with which it is associated [10].

Nerve preservation starts with high incision (just lateral to the dorsal vein complex) of the lateral prostatic fascia, which allows appreciation of the lateral contour of the prostate. Once Denonvillier's fascia has been incised, the medial aspect of the prostate can also be seen, allowing the structures posterolateral to the prostate (at this stage: the remaining fibers of detrusor, the lateral pedicle of the prostate, and the NVB itself) to be separated from it at precisely the level at which they abut each other. These first two structures are divided between clips before the NVB is reached. In patients with higher-risk prostate cancer, the lateral prostatic fascia may be incised just above the NVB to leave more tissue covering the antero- and posterolateral aspects of the prostate. Clips are used to secure vessels passing from the NVB toward the prostate with minimal retraction of the NVB. Once the correct intrafascial plane has been reached between the prostate and the NVB, the latter structure can be pushed off the prostate with blunt dissection. In contrast, interfascial and partial nerve-preserving techniques mandate the use of sharp dissection along the length of the prostate. The curve of the prostate prevents easy access to the terminal 1 cm of NVB from below, and this is best performed after division of the urethra.

The author's practice is to dissect the right-sided posterior structures (vas, seminal vesicle, and NVB), followed by the left-sided posterior structures, and then to separate the prerectal fat and rectum from the posterior surface of the prostate as far forward as is possible. Other surgeons prefer to incise Denonvillier's fascia and separate the rectum from the prostate in the midline before either NVB is dissected. Both approaches achieve the same aim.

If wide excision of a NVB is deemed to be necessary, the lateral pedicle of the prostate is first divided using LigaSure (Covidien, Mansfield, USA) or ENSEAL (Ethicon, USA). The anterolateral aspect of the rectum is then laid bare, by separating the adjacent prostate and NVB from it using the chosen energy source proximally and metal clips further anteriorly where the rectum and prostate lie in contact with one another to prevent thermal rectal injury. The end result is a rectum which is naked anterolaterally with exposed ischiorectal fat lateral to it. A nerve-damaging technique, rarely used by the author, involves liberation of the prostate from its posterolateral attachments in a more anterior plane and is easier to perform as less soft tissue is left on the gland.

At this stage, only the DVC, urethra, and terminal 1–2 cm of NVB on each side remain attached.

## Dissection of the Apex of the Prostate

An 18/22F sound is placed in the urethra, and the $CO_2$ pressure is increased to 20 mmHg. The DVC is divided with scissors, using the sound to easily identify the urethra. Little bleeding is usually encountered: arterial bleeding is controlled by bipolar diathermy and venous bleeding by the Trendelenburg tilt, pneumoperitoneum, and by avoiding using the sucker while the veins of the DVC are open. The DVC is oversewn using 3/0 POLYSORB on a 5/8 needle (Covidien, Mansfield, USA). The author prefers this technique to the "blind" placement of a large needle posterior to the DVC to ligate because of the concern regarding tethering of the anterior aspect of the urethra by such a suture and because of the frequency of ligature slippage when the DVC is wide.

Once the DVC has been sutured, the $CO_2$ pressure is decreased to 15 mmHg to check for hemostasis. Additional sutures are placed if needed. The urethra is divided at this stage, until the rectourethralis muscle can be seen posteriorly, to prevent traction injury of the external sphincter, which may occur during manipulation of the prostate during the apical dissection.

The prostate is displaced medially and upward on each side using tissue forceps applied to the ipsilateral seminal vesicle to allow a clear view of the terminal NVB and its relationship with the prostate apex and the pelvic floor. The NVB is pushed off the prostate apex with blunt and sharp dissection, as appropriate, using clips to control the apical branches of the NVB.

## Specimen Retrieval and Examination

Once the prostate is free, it is entrapped in a small impermeable retrieval bag. If NVB preservation has been carried out on either side, the prostate (and lymph node specimens, if present) may be removed at this stage through the subumbilical incision for visual and tactile inspection. If concern exists regarding the surgical margin, further tissue (in practice, usually the ipsilateral NVB) can be excised. The author does not use frozen section analysis to determine involved surgical margins because of its frequently poor correlation with paraffin section histology.

## Reconstruction

Eversion of the bladder neck mucosa [11] reduces the incidence of bladder neck stenosis, facilitates insertion of the catheter, and aids construction of the bladder neck by allowing easy identification of its proximal margin. The authors routinely reconstruct the bladder neck posteriorly, in

"racket-handle" fashion, with interrupted sutures as this moves the ureteric orifices further away from the anastomosis. In cases of a widely open bladder neck, especially while using an extraperitoneal laparoscopic approach, it might be preferable to close the bladder neck (at least partly) anteriorly to avoid excessive anastomotic tension. Steps that are useful in reducing anastomotic tension include reducing the degree of Trendelenburg tilt, transverse incision of the connective tissue anterior to the bladder (extraperitoneal approach), and the use of a continuous monofilament for at least the posterior aspect of the urethrovesical anastomosis which acts as a winch, evenly distributing tension between tissue bites and reducing the likelihood of them cutting through the tissues.

Either a continuous or an interrupted anastomotic technique can be employed, according to personal preference. The former technique, popularized by Van Velthoven et al. [12], employs two cut sutures which are tied together and are run from the posterior midline around the clockface to the 12 o'clock position before being tied together again. The theoretical disadvantage of this is ischemia. The authors use an interrupted technique with five or six 3/0 POLYSORB sutures carried on a 27 mm 5/8 circle needle. Laterally, the prostate "pillars" are reconstructed, and anteriorly the DVC is incorporated, both to provide some support to the underlying stump. A 16F catheter is placed using a catheter introducer to facilitate direction of its tip into the bladder once the posterior sutures have been placed. When the anastomosis is complete, 120 ml saline is instilled using a catheter-tip syringe via the catheter to check integrity of the reconstruction. An Endo Close (Covidien, Mansfield, USA) device is used to close 10-mm port sites after transperitoneal LRP before a 20F drain is inserted through the right iliac fossa 10-mm port. Wounds are closed in layers and are infiltrated with local anesthetic.

Antibiotic prophylaxis is continued for 48 h and DVT prophylaxis (subcutaneous low molecular weight heparin, thromboembolic deterrent stockings, and encouraging ambulation) until discharge. Oral fluids and diet are introduced as tolerated. The drain is removed when drainage was <100 ml/24 h. Patients are discharged home when comfortable. Timing of catheter removal is influenced as much by patient expectations, logistics, and habit as by sound reasoning. Although the catheter can be removed in 3 days, this is associated with the unacceptably high rate of recatheterization of 50 %. Conversely, 2 weeks after surgery, the risk of needing to reinsert the catheter is 1–2 %. Cystography prior to catheter removal is not necessary except following salvage prostatectomy.

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# Laparoscopic Radical Prostatectomy: The Results

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Laparoscopic radical prostatectomy (LRP) is already a well-established, feasible, and safe alternative to the open approach for more than 10 years. Despite its steep learning curve and the dexterity needed on behalf of the surgeon, LRP evolved greatly over the last decade, taking advantage of the recent advances in laparoscopic and robotic equipment (especially the DaVinci System). During the course of time, the extraperitoneal approach to LRP gained more ground among laparoscopic surgeons, establishing the procedure as a viable, long-lasting, and constantly refined technique. The initial problems of insufficient long-term randomized prospective trials were surpassed over the last years, giving a boost to the technique, which was initially described as a "European virus with global potentials" [1, 2]. The results of LRP, presented in this chapter, are primarily divided in two categories: functional results, including postoperative continence and potency, and oncological results.

As with any surgical procedure, LRP has its own specific complications. The constant evolution of the technique, the evolving laparoscopic and robotic equipment, as well as the presentation of long-term prospective results would probably render LRP as the mainstay in urologic laparoscopic surgery for years to come.

## Continence

Since the preliminary evaluations of the procedure and the short-term follow-up, as shown by Guilloneau et al. [3, 4], the postoperative continence results of LRP were more than encouraging. In a preliminary study of 28 cases, continence was assessed in 20 patients after 6 months and 18 patients had already been continent. In a later study, involving a larger number of patients, a continence rate of 73.3 % was reported in a 6-month follow-up period [5]. In that study, continence was evaluated more objectively, using the ICS questionnaire. Several other groups confirmed these encouraging preliminary results, reporting continence rates up to 84 % of the patients at 1 month after the procedure [6, 7].

Prospective studies showed that continence rates greater than 93 % could be achieved even if the catheter was to be removed as early as to 2–4 days after LRP. Nevertheless, urinary retention made recatheterization necessary in 10 % of the patients as Nadu et al. reported [8]. The group of Olsson et al. was the first to conduct a large prospective study regarding their urinary continence in patients who underwent LRP using questionnaires 1, 3, 6, and 12 months after the procedure. Totally, 56.8 % of the patients reported to be continent (described not only as the absence of need for pads but as the absence of any leakage at all). In addition, there was not a single patient out of the 228 patients of the study that was using more than one pad daily at 6 months after the procedure [9]. This was later confirmed by other groups, such as Link et al. reporting a continence rate of 93.4 % (using 0–1 pads daily) in a 12-month follow-up period utilizing the EPIC questionnaire, in an attempt to make the results more objective and less "interview dependent" [10]. Recently, it was proven by Milhoua et al. that the large prostate size (an objective factor) can be responsible for the delay of postoperative continence [11]. In addition, a surprising finding was that no factor pertaining to prostate cancer seems to be a predictor for postoperative continence. In that study, patient age and Charlson comorbidity index were the most important predicting factors [12].

When the Heilbronn technique was introduced by Rassweiler et al. [13–15], the first results were more than encouraging: out of 180 patients, 33 % were continent on discharge from the hospital, 74 % on the first 6 months, and 97 % after 12 months. Nevertheless, the steep learning curve

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of this technique was a major drawback preventing less experienced centers from employing it.

Reports from three investigating groups confirmed the positive results on continence, not only in a preliminary stage but also in significantly longer follow-up periods [16–18]. Salomon et al. reported continence rates of up to 97 % in the first year of follow-up, while Goeman et al. reported 91 % over a 2-year follow-up period. Functional results of LRP after transurethral resection of the prostate (TURP) were examined in the study by Menard et al. [17], and the functional results were compared to a group of patients undergoing LRP without previous TURP. Continence rates in the first group (the patients who underwent TURP before LRP) were approximately 10 % lower than the second group (86.9 % vs. 95.8 %) in a 2-year follow-up period, thus providing sufficient long-term evidence that LRP could achieve high continence rates in patients with previous prostatic surgery.

Endoscopic extraperitoneal radical prostatectomy (EERPE) is a viable and feasible alternative to the traditional transperitoneal laparoscopic technique and is associated with encouraging results regarding continence [19–21]. The introduction of intrafascial nerve-sparing EERPE technique by Stolzenburg et al. showed that 71.7 % of the patients were continent already in the first trimester after the procedure. Moreover, the same group reported their experience with 2,400 EERPE cases and reported that 94.7 % of the patients were continent in the first year. Rozet et al. [22] demonstrated similar results, reporting a rate of 84 % continence (described as the complete lack of pad usage) and a 7 % rate of 1-pad usage daily during the first year of follow-up.

Several refinements of the LRP technique have been proposed in an attempt to improve early postoperative continence at catheter removal and at 3 months postoperatively. These modifications include bladder neck preservation, bladder neck suspension, and preservation of puboprostatic ligaments [23–25] and have been associated with controversial results among investigators. In general, continence results in LRP have associated with significant biases among investigators due to the lack of a uniformly accepted evaluation methods which would render the results of different techniques and investigators directly comparable.

## Erection and Potency Results

The preservation of potency, described as the potential to have sufficient erectile function to achieve sexual intercourse, is a major factor regarding the quality of life of the patient undergoing LRP, especially in younger and more sexually active patients. The recovery of potency and the time in which it occurs after LRP depends on many factors, including age and preoperative potency despite the predominant factor of the preservation of neurovascular bundles (NVBs) of the prostate during the procedure [10, 26, 27]. Guilloneau et al. and Matin et al. recently proved that preservation of accessory pudendal arteries also helps recovery of spontaneous erections [28, 29].

The anatomy of the NVBs, especially their relation to the lateral pelvic fascia and Denonvilliers' fascia, was mapped and described after continuous investigation in cadaveric models [30]. The anatomic relation between the pelvic plexus ganglions and the seminal vesicles was also described in detail in the same study offering a "map" for the laparoscopic surgeon to understand the sensitivity of these ganglions to injury occurring during the dissection of the seminal vesicles. The improved visualization and magnification of the operative field offered by the laparoscopic camera in comparison to open prostatectomy is an important factor influencing the capability of the surgeon to perform nerve-sparing technique, thus increasing the potential for postoperative erections, especially in younger patients [30]. Also, a high incision or a "curtain dissection" of the lateral prostatic fascia may help visualize these elements better and is proved to improve the early postoperative potency rates [31]. In fact, it has been proven that the lateral prostatic fascias include nerve fibers which result in cavernosal vasoconstriction when stimulated [32]. However, the surgeon should take under consideration that during bilateral NVB preservation, the oncological outcome may be affected. Tumor sites may avoid detection, even though a meticulous observation may take place. Thus, some investigators recommend the preservation of the NVB contralateral to the tumor [21], while others report that NVB preservation does not affect the risk of positive surgical margins [33].

Preliminary results indicated that the preservation of one of the prostatic NVBs raised the potency rates while the preservation of both NVBs further improves the potency outcome. Early reports showed that non-nerve-sparing LRP (Pic 1) had potency rates up to 41 % which was comparable if not better when compared to the open approach (in the same study 30 %) [34]. When NVB preservation was considered (Pic 2), the potency rates improve even more. In the same study by Anastasiadis et al. potency rates were 44 and 53 % for unilateral and bilateral preservation, respectively (Figs. 57.1 and 57.2). When the age was taken into account, the rates were 72 and 81 % for unilateral and bilateral NVB preservation in patients younger than 60 years of age, respectively. Roumeguere et al. also reported that patients undergoing LRP had more spontaneous erections than those of the open approach [35].

Goeman et al. reported potency rates of 64 % (both NVBs preserved) at 2-year follow-up while 78.6 % of the patients younger than 60 years were potent [16]. Mariano et al. reported similar rates (61 %) in patients undergoing the bilat-

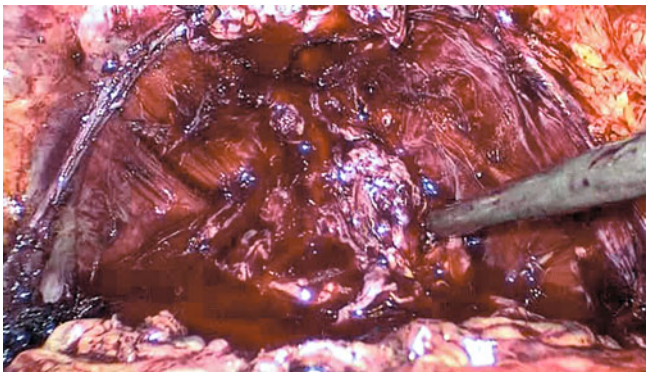

**Fig. 57.1** Non-nerve-sparing technique has been used. The prostate has been removed, and there are no neurovascular bundles. The next step of the procedure is the performance of the vesicourethral anastomosis

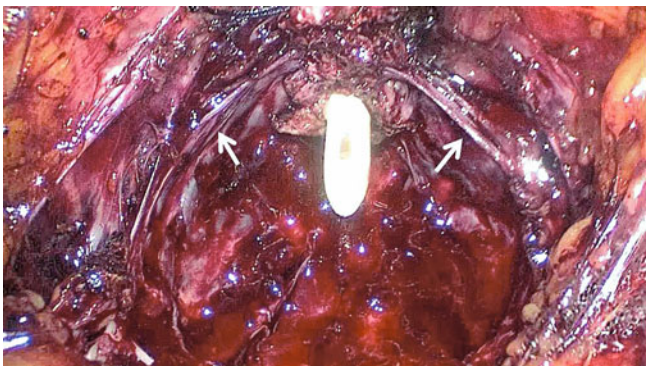

**Fig. 57.2** Bilateral preservation of the neurovascular bundles has been performed (the prostate is removed). The *arrows* show the preserved neurovascular bundles

eral nerve-sparing LRP when their experience over a period of 10 years of performing LRP was evaluated [36]. Robotic-assisted LRP was reported to have similar potency rates: 62 % in the bilateral nerve-sparing approach at 12 months postoperatively [37]. In the extraperitoneal approach, the results were comparable: overall potency rates reported were 44 % in the unilateral nerve-sparing approach, while in bilateral NVB preservation, the rates were significantly higher reaching 72 % at 12 months after the procedure. In patients younger than 55 years of age, the respective rates reported were 50 and 84.9 % [21].

The dissection technique of the NVBs has been related to different outcomes. NVB preservation techniques include the excision of the prostate with its surrounding fascias without involving the NVBs (interfascial dissection) and the excision of only the prostate with preservation of the NVBs and surrounding prostate fascias (intrafascial dissection). The latter dissection method has been associated with improved erectile function as well as early postoperative continence in comparison to interfascial NVB dissection [38].

Erectile function is important for the quality of life of the patients undergoing radical prostatectomy [39]. The performance of bilateral intrafascial NVB preservation seems to be the most efficient in providing sufficient postoperative erectile function in preoperatively potent patients [38, 40]. The lack of a widely accepted approach in the evaluation of erectile function results in confusion and limited potential to compare results among different series.

## Oncological Results

The main endpoint of oncological efficacy of LRP is the presence or absence of positive surgical margins. Other factors that should be taken into account in the evaluation are the postoperative PSA recurrence (described in literature as PSA > 0.2 ng/mL and confirmed by a second increase), the clinical progression, and progression-free survival [32, 41]. Even though prostate size, especially larger than 75 g, is a factor associated with fewer positive surgical margins, the latter observation should not interfere with patient selection for LRP. On the contrary, prostate sizes smaller than 30 g are associated with a higher rate of positive surgical margins. Considering the above, further studies with longer follow-up periods should be conducted in an attempt to draw positive conclusions [42, 43]. Preservation of the accessory pudendal arteries can be performed without compromising the oncological aspect, as it does not affect the risk for positive surgical margins [44]. On the contrary, techniques of nerve reconstruction, such as sural nerve grafting, increase the risk [45]. Finally, previous training in open or laparoscopic techniques does not seem to interfere with the oncological results of LRP [46].

Martorana et al. proved that oncological results of LRP were similar to those of the open approach despite the limited experience of the group in LRP and the small number of patients (50 consecutive patients for each approach). It was also shown that the positive surgical margins were found in the same locations in both specimen groups [47]. These findings were confirmed later by Rassweiler et al. [15].

Salomon et al. reported positive surgical margins and 3-year progression-free survival rates to be 20.6 and 86.2 % in pT2 cases after LRP, respectively. These results were compared to the open approach in patients with PSA < 10 ng/mL. No significant differences were observed on the above comparison [48]. This was also confirmed later by Roumeguere et al. [35]. Ruiz et al. reported their results in 330 consecutive patients, who underwent either transperitoneal LRP ($n=165$) or extraperitoneal LRP ($n=165$). The overall surgical margins were 23 and 29.7 % ($p=0.8$), respectively. The respective figures were 13.0 and 17.0 % ($p=0.42$) in pT2 tumors and 43.6 and 44.7 % ($p=0.99$) in pT3 tumors. Nevertheless, an advantage of shorter operative time for the

extraperitoneal group was noted [49]. The same comparison was conducted by Erdogru et al. using match-pair analysis techniques, reporting similar overall rates: 22.6 % for the extraperitoneal group versus 20.7 % for the transperitoneal, approach [50].

Guilloneau et al. conducted a prospective study in 1,000 patients, reporting that 94 % of the patients with negative surgical margins and 80 % with positive surgical margins (overall rate 90.5 %) had progression-free survival for 3 years postoperative. Of these patients, stage pT2aN0/Nx (20.3 %) had a positive surgical margin rate of 6.9 %, whereas stages pT2bN0/Nx (57.2 %), pT3aN0/Nx (14.2 %), and pT3bN0/Nx (7.7 %) had rates of 18.6, 30, and 34 %, respectively. Main factors affecting the positive margin rate were Gleason score, clinical stage (TNM), pathological stage, and preoperative PSA [32]. Nevertheless, other investigators claim only Gleason score and pathological stage are of importance regarding biochemical progression [51].

Similar rates were reported by Rozet et al.: overall positive margin rate was 17.7%, 14.6 % for pT2 and 25.6 % for pT3 tumors [22]. The same group compared directly the "conventional" LRP with the robotic-assisted approach, reporting overall positive surgical margins rates of 15.8 % versus 19.5 %, respectively. Goeman et al. reported a 5-year progression-free survival rate of 78.8 %, with positive surgical margin rates of 17.9 % for pT2, 44.8 % for pT3, and 71.4 % for pT4a tumors using only the extraperitoneal approach [16]. The oncological outcome was improved over time in a larger recent study by Stolzenburg et al. [21]: overall rates for positive surgical margins were 16.4 %, 8 % for pT2 stage and 35.6 % for pT3 stage. Pavlovich et al. reported also positive surgical margin rates directly increasing alongside pathological stage: 8.2 % in pT2 and 39.3 % in pT3 cases. Biochemical progression-free survival rate in a 3-year follow-up period was 98.2 % for pT2 and 78.7 % for pT3 disease, and 94.5 % overall (PSA > 0.2 ng/mL confirmed by a second measurement is defined as biochemical progression/recurrence in the study).

In robotic-assisted LRP, Sharma et al. proved that even though the positive margin rates are similar to the "traditional" LRP technique, the learning curve can be longer than expected: in a prospective study for 500 patients who were operated by two surgeons, the overall positive surgical margin rate was 24.0 %, and the stage specific rates were 16.1, 30.4, 55.0, and 100.0 % for pT2, pT3a, pT3b, and pT4 pathological stages, respectively. Nevertheless, the last 50 patients for each surgeon were associated with improved oncological results. The positive surgical margin rates were 8.0 and 19.1 % (surgeon 1) and 12.9 and 23.5 % (surgeon 2) for pT2 and pT3a pathological stages, respectively [52]. In summary, the oncological outcome of LRP is directly comparable to all available radical prostatectomy methods. Experience seems to be important in the reduction of the positive surgical margins [52, 53].

## Complications

Guilloneau et al. demonstrated that vascular complications, including vessel injury, bleeding, and the formation of hematomas, represent a substantial percentage of the perioperative complications of LRP, namely, 89.4 % of all complications [54], with an incidence up to 6 % [55–60]. Hemorrhage from the inferior epigastric vessels the Santorini plexus, or the external iliac vein is a common intraoperative complication. It is commonly caused during trocar insertion, especially when done either without direct visual control or without carefully inspection of the abdominal wall before trocar insertion. Hemorrhage can be controlled, if not avoided, by using bipolar coagulation and/or clipping (if the vessel is damaged), suturing and "encaging" of the vessel in the abdomen wall (in the case of inferior epigastric vessel bleeding) or even direct tamponade of the vessel using the pneumoperitoneum gas pressure [55–60]. In the postoperative period, hematomas are also common: they can arise from the neurovascular bundles or epigastric vessels. Meticulous hemostasis prevents the latter complication.

Rectal and intestinal injury is another relatively common and very severe complication, which can be life-treating if not recognized immediately. Symptoms include vomiting, distension, fecaluria, and persistent abdominal pain. If not treated in time, intestinal injury can lead to leukocytosis and eventual septic shock. The surgeon must be alert that every patient presenting with persistent abdominal pain during the first few days or weeks after LRP or EERPE must be carefully examined to exclude an undetected intestinal injury. Its incidence is reported up to 9 % of the cases [55–60]. The way this complication can be avoided is not definite. Groups have reported the use of special devices such as intrarectal insufflation device enabling the surgeon to visualize the rectum during crucial stages of LRP [14]. Careful suturing of the site of injury and parenteric feeding for the next 3 days is the treatment of choice. Injury to the bladder is a complication mainly of EEPRE, due to the extraperitoneal nature of the technique. If detected intraoperatively, it can be corrected in single layer suturing [55].

Ureteral injuries, anastomotic leakage, or acute urinary retention can also be present. In these cases, if placing a mono-J catheter is not enough, the anastomosis can be strengthened with more sutures or revised with an endoscopic neoanastomosis, if not controlled properly. However, controlling intraoperatively whether the anastomosis is functional and watertight is of crucial importance. In some cases, early removal of the catheter can cause acute urinary

retention due to anastomotic stricture. In these cases, further catheterization can lead to a solution [54].

Concomitant pelvic lymphadenectomy is related to the formation of lymphoceles. The presenting symptoms vary from pelvic pain, to leg edema, hydronephrosis, deep venous thrombosis, and infection. Laparoscopic fenestration, sclerotherapy, or percutaneous drainage can be performed to manage this common complication. The incidence of the complication is approximately 4 % [55, 56, 58–60]. Other not so common complications may include gas embolism, obturator nerve injury and subsequent paralysis, catheter blockage, deep venous thrombosis, pulmonary edema, pulmonary embolism, perineal pain, pubic osteitis, and prolonged ileus (due to presence of urine in the peritoneum).

Most of these complications should ideally be prevented in the hands of an experienced surgeon. In addition, prompt recognition of the complication (especially intraoperatively) is important for the successful management of the incident. Delayed management of LRP complications may pose a serious threat to a trouble-free recuperation of a patient undergoing an otherwise minimally invasive surgical procedure or even may result in life-threatening conditions [55, 56, 58–60].

### Conclusion

Laparoscopic radical prostatectomy has become a mainstay in the arsenal of the endoscopic/laparoscopic urologic surgeon. Its minimally invasive nature, combined with its potential to yield similar, if not better results when compared to the open approach, represents a significant advantage. Taking into account the constant refinements made in the technique by many groups of experienced surgeons around the world, the constant progress and development in the existing equipment, as well as the recent "invasion" of robotic assistance in the field, lead to the conclusion that the results of LRP will be constantly improved in the long run, making it a mainstream surgical procedure for years to come.

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# Robotic-Assisted Radical Prostatectomy: The Technique

58

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## Introduction

Robotic-assisted radical prostatectomy (RARP) using the da Vinci® surgical platform has become very popular in recent years, accounting for over 70 % of all radical prostatectomies performed in the United States in 2008 [1, 2]. Its postulated advantages over the conventional open approach include better intraoperative dexterity and visualization of periprostatic tissue architecture with up to 12-fold optical magnification for the surgeon, while patients experience less intraoperative blood loss, less painful recovery, and shorter hospital stays [3]. However, despite innovations in surgical techniques, surgeons are still faced with the daily dilemma of balancing complete cancer clearance while striving for potency preservation during surgery. In several series, 20–50 % of patients still remain impotent at 1 year following nerve-sparing radical prostatectomy (RP) [4–6].

Over the past few years, our group has made several advances in mapping out a trizonal approach to the complex periprostatic neural architecture through cadaveric and real-time operative dissections. Our subsequent appreciation of the course of the trizonal lattice of nerves around the prostate in different fascial planes enveloping the prostatic capsule led us to adopt a risk-stratified approach to nerve preservation while maintaining adequate clearance of cancer [7]. Herein, we describe our current technique of athermal nerve-sparing robotic prostatectomy and also discuss published results associated with RARP.

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## Technique of Trizonal Athermal Robotic Prostatectomy

### Anterior Dissection and Dropping the Bladder

After port placement, we develop the extraperitoneal space to expose the space of Retzius until the prostate and the prostatovesical junction are seen.

### Incising Endopelvic Fascia

After clearing the fat, the endopelvic fascia is exposed and incised with scissors just medial to the white line sparing its most distal part, which is in continuity with the puboprostatic ligaments. The arcus tendineus is dissected out on both sides and preserved. These structures collectively form what we term the "puboprostatic collar," which serves as a fibrotendinous scaffold for subsequent anterior reconstruction of the bladder neck after the prostate is removed.

### Bladder Neck Dissection

The "bimanual robotic pinch," together with simultaneous retraction of the indwelling catheter balloon against the bladder neck, helps the surgeon accurately identify the prostatovesical junction. The anterior bladder neck is then incised, and the incision extended posteriorly taking care not to injure the ureteral orifices. This allows entry into the retrotrigonal

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fibromuscular layer, a musculofascial plane behind the posterior wall of the bladder neck. Dividing the retrotrigonal layer exposes the vasa deferentia (VD) and the seminal vesicles (SVs). Electrocautery is avoided from this point onward.

## Dissection of the VD and SVs

The VD and SVs are identified behind the retrotrigonal layer. Each SV has its own compartment, and most of the blood supply enters near its tip and anterolateral aspect. Lateral to this compartment and near the tip lies the proximal neurovascular plate. This spatial relationship has profound implications for our nerve-sparing technique because the crucial neural tissue can be damaged (or avulsed) by heat, crushing, and the torque of pulling during seminal vesicle dissection. We then mobilize the VD and clip the proximal end behind the trigone. Since most of the medial wall of a seminal vesicle lies adjacent to a nearly avascular space, this medial avascular plane serves as a safe starting point for lateral dissection of the seminal vesicles.

## Posterior Dissection

Since cross-communicating nerve fibers have been demonstrated in the layers of the Denonvilliers' fascia, in appropriate cases with low-risk cancer, we develop a plane just outside the prostatic capsule, leaving some layers of Denonvilliers' fascia in the patient. If there are concerns about oncologic safety, we go deeper and excise the fascia with the specimen. Keeping the undersurface of the prostate capsule under vision, the dissection proceeds laterally and a plane is developed that is either interfascial or intrafascial. At this point, tenting vessels entering the prostate base near the attachment of the SVs are controlled bilaterally with small clips. The transected distal ends of the VD are grasped by the left side assistant (or the fourth robotic arm) and pulled anteriorly, tenting the Denonvilliers' fascia occupying the retroprostatic space. This fascia is incised in the midline, and the opening is enlarged laterally toward the medial edge of the pedicles. A cave-like space is created behind the prostate, and dissection is deliberately extended distally to release the apex and the urethra from deeper tissue.

## Lateral Pedicle Control

Upward traction is exerted on the VD and SVs by the left side assistant and the pedicles are easily differentiated from the predominant neurovascular bundle. Selective clipping or ligation of the prostatic vessels is performed. The pedicles are controlled close to the base. Electrocautery and mass ligature are avoided, with small clips to control individual pedicles being preferred.

## Release of Neurovascular Bundles

Next, we release the neurovascular tissue using both our trizonal-neural-hammock-release technique and our athermal approach. We employ sharp athermal dissection of the prostatic pedicles, controlling arteries and veins with Hem-O-Lok® clips (Teleflex Medical Inc, Research Triangle Park, NC) as they enter the prostatic base. The lack of use of cautery results in preservation of natural tissue texture, and the predominant neurovascular bundle can often be identified and differentiated from the vascular pedicle. Depending on the preoperative decision about the extent of cancer, we develop a plane very close (just on the prostatic capsule: more aggressive nerve sparing/intrafascial/grade 1 nerve sparing) or close (outside the prostatic fascia – moderate nerve sparing: most commonly performed/interfascial/grade 2 nerve sparing) or farther (leaving a few medial layers of lateral pelvic fascia on the specimen: partial/incremental nerve sparing/grade 4 nerve sparing). In appropriate cases, we also preserve the retroapical nerve plexus by leaving a distal layer of superficial Denonvilliers' fascia. In our practice, the predominant neurovascular bundles are usually released in an antegrade fashion; that is, dissection continues from the bladder neck to the prostate apex.

## Retroapical Dissection

This portion of the robotic prostatectomy poses several challenges to the surgeon, its execution having a significant impact on the primary outcomes of margin positivity, continence, and sexual function. These challenges include significant variations in the size and shape of the prostate gland and its relationship to the functional rhabdosphincter complex, nerves, and urethra. In our experience, the prostatic apex either tapers like a spin top or forms a ledge over the membranous urethra. To overcome this difficulty, we have developed an anatomic retroapical technique. Using this approach, our positive apical margin rates have dropped fourfold. The prostate is completely freed posterolaterally on either side. At this point, it is quite mobile and is lifted anteriorly toward the anterior abdominal wall and pubic symphysis. This action opens up the space behind the urethra and apex and torques and angles the DVC, thus temporarily occluding it. The camera lens is changed to 30° upward-facing for a retroapical approach to the apical-urethral junction. Once positioned at the perfect vantage point, the glistening white surface of apex can be differentiated from the membranous urethra. The transition from prostatic

apex into urethra is further appreciated by manipulating the 20 Fr Foley catheter in and out of the apical-urethral junction. The prostate has a few layers of Denonvilliers' fascia covering its posterior surface, and the membranous urethra is posteriorly supported by the rectourethralis muscle. Using sharp, curved scissors, we dissect the superficial layers of the Denonvilliers' fascia and expose the precise prostatourethral junction. Next, the posterior hemicircumference of the urethra is sharply incised 1 mm distal to the apex. The Foley catheter is exposed and positioned with its tip at the distal urethral opening. This permits appreciation of the anterior urethral hemicircumference, with urethral mucosa and muscular wall being seen clearly. Using blunt and sharp dissections, the urethra is divided circumferentially. At this point, all the muscle fibers are transected, and the DVC is left attached to the anterior surface of the prostate.

### DVC Control and Transection

Management of the DVC now depends upon the width and thickness of the anterior tissue. If the remaining tissue is thin, we increase the pneumoperitoneum to 20 cm water column pressure and inflate the Foley catheter balloon to 30 cc behind the prostate. The Foley balloon is placed on caudal traction, resulting in partial occlusion of the DVC and developing the space behind the prostate. The lens is now changed to 0°, and the prostatic apical dissection is continued anteriorly. The prostate is retracted cephalad by the left assistant grasping the SVs and distal ends of the transected VD. Employing robotic Maryland dissectors on the left arm, the anterior tissue is grasped between its two jaws to ensure that only venous tissue and some parts of the ligaments are grabbed. We sharply cut distally to the grip and can see the sharp scissors cutting through the venous sinuses. Bleeding is minimal due to the inflated Foley balloon placed under traction or suture used. The prostate is freed with a 1 mm hood of ligaments and venous tissue still on the prostatic apex. Care is taken in preserving the puboprostatic ligaments and arcus tendineus for later reconstruction. If the remaining tissue is broad and thick, we ligate the DVC using a CT-1 needle and an O-Polyglactin suture using a slipknot. Once the prostate is freed, we perform lymph node dissection, limited/standard or extended depending on the D'Amico risk grouping of the patient, and place the specimen in a laparoscopic entrapment bag.

### Total Anatomic Reconstruction

We routinely reconstruct the posterior bladder neck as well as the Denonvilliers' musculofascial plate before performing the vesicourethral anastomosis. This technical modification serves to relieve tension on the anastomosis and provide suspensory support for the posteriorly deficient Ω-shaped rhabdosphincter to contract effectively against.

We complete the bladder neck reconstruction anteriorly by taking partial thickness sutures of the anterior bladder neck to the preserved arcus tendineus and puboprostatic ligaments for all round suspensory support.

## Results

Urologists increasingly prefer RARP as the treatment of choice for excision of a cancerous prostate. In 2007, this surgical method constituted about 10 % of the total volume of radical prostatectomies carried out by American urologists; however, by 2008–2009, it has increased to more than 60 % [8]. This method is selected as it provides many advantages that both the surgeon and patient appreciate: decreased bleeding, decreased transfusion rates, reduced hospital stay, earlier return to daily activities, decreased analgesic requirements, and improved cosmetics [9, 10]. In addition to these benefits, RARP also provides success for the patient in achieving improved trifecta rates, which denotes the likelihood of the postoperative patient achieving urinary continence, potency, and biochemical recurrence [11].

Recently, two new models for reporting the outcomes of RARP have been created. In 2011, Patel et al. introduced a more comprehensive method for reporting the outcomes after radical prostatectomy: pentafecta [12]. This model has added complications and positive surgical margin rates to the current trifecta model. In 2012, Ficarra et al. created a more generalized system that can be used to report the most relevant intermediate- and long-term outcomes after radical prostatectomy for all patients undergoing radical prostatectomy [13]. However, there has been much research conducted to determine the trifecta rates of RARP.

### Trifecta Outcomes

Many studies have been conducted that depict trifecta outcomes following radical prostatectomy. Of the studies, 12 will be discussed [7, 11, 12, 14–22]. The number of cases that were evaluated for the trifecta outcomes ranged from 28 to 62 % of the total patients treated within the study. This was due to the varying patient selection criteria in the studies. In addition, it was unable to determine the percentage for two of the studies because the total number of patients treated was not available [14, 18]. Patients were excluded from trifecta analysis because they were either incontinent or impotent preoperatively, patients did not receive a bilateral nerve-sparing surgical procedure to cancer characteristics, patients were lost to follow-up, and/or patients received

adjuvant therapies. These are some of the more common problems experienced by scientists who conduct these type of studies. The most common reason in one study for why patients were unable to achieve trifecta was erectile dysfunction, followed by biochemical recurrence, and finally urinary incontinence [12].

Of the analysis of trifecta studies, one study analyzed the cases independently of the surgical approach [14], four studies evaluated patients who received retropubic radical prostatectomy [11, 15–17], one study evaluated patients who received extraperitoneal laparoscopic radical prostatectomy [18], five studies evaluated patients who received transperitoneal robotic-assisted radical prostatectomy [7, 12, 19–21], and the final study included patients who underwent extraperitoneal robotic-assisted radical prostatectomy [22]. No studies were found that analyzed the different surgical approaches for treatment.

The trifecta outcome was reached in a range of 20–89 % of the patients in the studies with a mean value of 61 %. This wide distribution is due to the difference of patient characteristics, each respective study's definition of potency and continence, methods used to evaluate functional outcomes, and the duration of patient follow-up.

Four of the studies included only patients that received bilateral nerve-sparing radical prostatectomy [12, 19–21]. Seven of the studies also considered patients who received a monolateral nerve-sparing approach and a small amount of patients who did not receive a nerve-sparing approach [7, 11, 15–18, 22]. Of these seven studies, the percentage of patients who received bilateral nerve-sparing radical prostatectomy ranged from 62 to 92.5 % of cases.

To determine each patient's functional outcome, self-administered validated questionnaires were evaluated in five of the studies [7, 12, 20–22], self-administered institutional questionnaires were administered in two studies [14, 18], and four studies utilized a patient-physician interview [11, 15–17]. In the last study, Shikanov's group compared the trifecta outcomes using two different methods [19]. The study had a 76 % trifecta rate when the functional outcome was evaluated by a patient-physician interview, and then 44 % when it used self-administered, validated questionnaires.

Most studies defined continence as "no pad" [12, 14, 16, 19, 20]. Two of the studies defined continence as "no leak" [21, 22]. Five studies accepted using a safety pad as achieving continence [7, 11, 15, 17, 18].

The majority of the studies defined potency as an erection that was sufficient for intercourse with or without the use of a phosphodiesterase type 5 inhibitor [11, 12, 14, 15, 17–20, 22]. One study defined patients as potent as those patients with an International Index of Erectile Function-6 score of ≤18 [21]. The other two studies defined patients achieving potency as the ability to achieve a full erection with or without the use of a phosphodiesterase type 5 inhibitor or patients with a Sexual Health Inventory for Men greater than 21 [7, 16]. It was unable to determine if these definitions of potency were used for both preoperative and postoperative.

The majority of studies defined free of biochemical recurrence as PSA < 0.2 ng/ml except for the Bianco et al. and Shikanov et al. studies which viewed it as PSA < 0.4 and PSA < 0.5 ng/ml, respectively [15, 19].

The follow-up duration for the patients varied as well for the studies. Five studies had a follow-up period of 12 months for the evaluation of trifecta outcomes [7, 12, 14, 17, 21], 18 months in one study [20], 24 months in five studies [15, 16, 18, 19, 22], and 48 months in the final study [11]. Table 58.1 summarizes the data reported from each study [13].

From the studies, those with the highest trifecta rate were found in those studies that utilized robotic-assisted radical prostatectomy. These six studies that utilized RARP achieved a trifecta % rate that ranged from 44 to 91 %. The 44 % was low and may perhaps be attributed to the difference in the collection of the patient's functional outcome, as that was from Shikanov et al. who utilized two methods; the other collection method in that study had a 76 % trifecta rate [19].

## The Pentafecta Concept

Patel et al. in 2011 created a new method for reporting the outcomes of radical prostatectomy. This method was coined "Pentafecta." This was created in order to provide a more comprehensive method of reporting. Because of prostate-specific antigen screening, more, younger, and healthier men are being diagnosed with prostate cancer. Patients have higher demands and expectations from surgical treatment for prostate cancer, and it cannot be addressed appropriately from trifecta outcomes alone [23]. Patient satisfaction is also determined by perioperative complications and by the presence of positive surgical margin (PSM) rates [24]. The Pentafecta method incorporates the traditional trifecta components, potency, continence, and biochemical recurrence-free survival, and it also includes complications and surgical margin status. From the study, while the trifecta rate at 12 months was found to be 83.1 % (276/332), the pentafecta rate at 12 months was 70.8 % (235/332) [12]. In the study, 22 of the 332 patients experienced either perioperative or postoperative complications (6.6 %). The most common perioperative complication was ileus (18.18 %), and the most common postoperative complication was anastomotic leakage (31.82 %) [12]. The overall PSM rate was 9.3 %. The most common reasons for patients not reaching the pentafecta were erectile dysfunction (35.0 %) and positive surgical margins (31.9 %) [12].

Pentafecta rates are believed to demonstrate postoperative patient satisfaction more accurately. Even though some tri-

**Table 58.1** Characteristics, methods, and trifecta outcomes reported in included studies

| Author | Trifecta/total cases | Follow-up, months | Questionnaires | Definition of continence | Continence rate, % | Definition of potency | Potency rate, % | Definition of bDFS ng/ml | bDFS, % | Trifecta rate, % |
|---|---|---|---|---|---|---|---|---|---|---|
| Eastham et al. [11] | 1,577/2,906 = 54 % | 48 | Physicians | No pad | 94 | ESI | 67 | >0.2 | 91 | 62 |
| Tewari et al. [7] | 1,263/2,317 = 54.5 % | 12 | Self-administered, validated | No pad/safety | 97 | SHIM >21 | 90.9 | >0.2 | 95.9 | 89 |
| Patel et al. [12] | 332/1,111 = 30 % | 12 | Self-administered, validated | No pad | 96.4 | ESI | 89.8 | >0.2 | 96.4 | 83.1 |
| Salomon et al. [14] | 205/NA | 12 | Self-administered, institutional | No pad | 65.8 | ESI | 32.7 | >0.2 | 85.4 | 20 |
| Bianco et al. [15] | 758/1,726 = 44 % | 24 | Physicians | No pad/safety | 95 | ESI | 70 | >0.4 or 0.2 | 88 | 60 |
| Saranchuk et al. [16] | 647/1,133 = 57 % | 24 | Physicians | No pad | 93 | Full erection | 62 | >0.2 | 88 | 42 |
| Pierorazio et al. [17] | 314/503 = 62 % | 12 | Physicians | No pad/safety | 93.8 (L), 94.4 (I), 93.3(H) | ESI | 81.3 (L), 67.7 (I), 69.6 (H) | >0.2 | 96.4 (L), 90.3 (I), 78.7 (H) | 72.6 (L), 56.2 (I), 40 (H) |
| Ploussard et al. [18] | 911/NA | 24 | Self-administered, institutional | No pad/safety | 97.4 | ESI | 64.6 | >0.2 | 87.7 | 54.4 |
| Shikanov et al. [19] | 380/1,362 = 28 % | 24 | Physicians | No pad/safety | 98 | ESI | 93 | >0.05 | 91 | 76 |
| | | | Self-administered, validated | No pad | 80 | ESI | 69 | >0.05 | | 44 |
| Patel et al. [20] | 404/1,100 = 37 % | 18 | Self-administered, validated | No pad | 97.9 | ESI | 96.6 | >0.2 | 91.4 | 91 |
| Novara et al. [21] | 242/415 = 58 % | 12 | Self-administered, validated | No leak | 89 | IIEF-6 ≥18 | 60 | >0.2 | 98 | 57 |
| Xylinas et al. [22] | 500/540 = 92.5 % | 24 | Self-administered, validated | No leak | 88 | ESI | 63 | >0.2 | 88 | 53 |

*bDFS* biochemical disease-free survival, E*SI* erection sufficient for intercourse, *L* low-risk group, *I* intermediate-risk group, *H* high-risk group, *IIEF-6* International Index of Erectile Function-6, *SHIM* Sexual Health Inventory for Men

fecta rates may be encouraging, one of the studies reports overall PSM rates as high as 19.5 %, which may not represent patient satisfaction accurately [19]. Patel et al. have demonstrated that there is a 13.2 % difference between the trifecta and pentafecta rates from their study and attribute it to a subset of patients who had a suboptimal conclusion from their surgery and are potentially not entirely satisfied with their surgical treatment [12]. This provides a more comprehensive patient evaluation that while some trifecta rates may report success, further follow-up and criteria need to be investigated to determine whether postoperative patients are indeed fully satisfied with their mode of care.

## The Survival, Continence, and Potency Classification

It was recently reported that Ficarra et al. have created a new system that can be used to report the most relevant intermediate- and long-term outcomes after radical prostatectomy: Survival, Continence, and Potency (SCP) Classification [13]. This new system is viewed as a more generalized method that can be applied to all patients that receive this surgical treatment. It differs from the currently used trifecta system in that it weighs the outcomes of the surgery differently. It allows urologic oncology surgeons to accurately classify all patients who undergo RP according to oncologic and functional outcomes of relevance on an individual basis. With RP, the main objective from the surgery should be to eradicate as much of the oncologic tissue as possible. Functional outcomes, continence and potency, are thus secondary to oncologic results. The problem encountered with the trifecta and pentafecta systems is that they do not place an importance on different outcomes (i.e., biochemical disease-free survival is more important than continence rate and potency rate). The current trifecta system in addition is only applicable to patients who were preoperatively continent and potent and received bilateral nerve-sparing radical prostatectomy. With this new system, it can be applied to all patients that underwent RP postoperatively where oncologic outcomes, survival, are prioritized over functional outcomes, continence and potency [13].

This system provides a more descriptive classification as it has subdivisions for each category (survival, continence, and potency). In addition, it also includes a time factor as the number of months of follow-up is included in its formula [13]. Utilizing all these components of the system allows it to be applied to all patients who undergo radical prostatectomy and thus can be viewed as analogous to the TNM system that is currently being used for cancer staging. The SCP classification has four different clinical outcome scenarios: oncologic and functional success, oncologic success and functional failure, oncologic failure and functional success, and oncologic failure and functional success [13].

The survival, continence, and potency classification system is able to report oncologic and functional results for every patient that underwent RP, thus making more generalizable than other classification systems like trifecta and pentafecta [13]. It allows the identification of patients who were preoperatively incontinent, impotent, those who did not receive a bilateral nerve-sparing procedure, and those patients who received adjuvant therapy after surgery to have a classified oncologic and/or functional outcome relevant to that specific patient. It is postulated that this system could provide a standardized classification method for urologic oncologist surgeons to accurately report the outcome from radical prostatectomy for all patients in all clinical scenarios [13]. In addition, it would allow better comparisons between different surgical approaches and techniques and allow surgeons to better counsel patients preoperatively as opposed to using the trifecta system where it provides the best case scenario.

Robotic-assisted radical prostatectomy is rapidly becoming the gold standard for treatment of prostate cancer. It is a safe and effective technique and is becoming the preferred method of treatment by urologic surgeons and patients as it is less invasive, provides minimal pain, and has a decreased amount of blood loss which all allow for a quicker recovery for the patient. There are many advanced techniques being implemented to ensure improved quality of treatment of patients, both surgically and staging.

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# Lymph Node Dissection in Prostate Cancer Surgery

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## Introduction: Anatomy of Pelvic Lymph Nodes, Defining Limited and Extended Pelvic Lymph Node Dissection

Pelvic lymphadenectomy or pelvic lymph node dissection (PLND) has long been the gold standard for determining if lymph node (LN) metastasis has occurred in patients with prostate cancer. Dissection can include lymph tissue from the obturator fossa as well the common, external, and internal iliac vessels, although other LN areas can also be included (Fig. 59.1).

There is still no agreement on what the anatomical boundaries of the PLND should be or how many nodes should be removed. Weingartner et al. suggested that based on their experience in cadaveric and surgical patients, approximately 20 nodes should be removed in a standard lymph node dissection in order to detect LN invasion (LNI) [1]. Their dissection was limited to the area between the external and internal iliac arteries from the bifurcation of the common iliac vessels to the circumflex iliac vein. Briganti et al. examined the lymph node yield using an extended dissection, with boundaries of the genitofemoral nerve laterally, the obturator fossa medially, the deep circumflex vein distally, and the bifurcation of the common iliac artery proximally [2]. They showed that the number of nodes removed correlates almost linearly with the sensitivity of determining LNI and that removal of 28 nodes provides 90 % sensitivity. This would suggest that removal of as many nodes as possible without compromising patient safety would lead to the most accurate prediction of whether or not LNI is present. However, determining lymph node count in the operating room is difficult if not impossible. There can be significant differences in the amount of lymph nodes from patient to patient. Technical issues can play a role as well since it has been shown that the way lymph node packets are submitted for pathological analysis can affect the number of nodes found [3]. So, rather than focusing on the actual number of lymph nodes removed, more recent emphasis has been on defining the anatomical extent of the dissection based on the areas with the highest likelihood of metastasis [4].

It is commonly accepted that a limited pelvic lymph node dissection (lPLND) must include nodes from the obturator fossa at a very minimum. Most agree, however, with the definition by Studer's group that a lPLND should also include nodes from the bifurcation of the common iliac vessels proximally to the circumflex iliac vessels distally and the external iliac vessels laterally [5]. These same authors define an extended PLND (ePLND) as a dissection that starts proximally at the crossing of the ureter over the iliac vessels and also skeletonizes the internal iliac vessels. Others suggest that the presacral and presciatic nodes should be excised since they are often sites of metastases [6–8].

Mapping studies have provided valuable information about the likely routes of metastatic spread. Mattei et al. injected patients with intraprostatic technetium nanocolloid and then performed SPECT/CT or SPECT/MRI 1 h later. They also used an intraoperative gamma probe to determine positive lymph nodes at the time of surgery. They determined that lPLND covered the sites of spread only 38 % of the time and that by converting to an ePLND, 75 % of LNs that may harbor metastases were successfully removed [9]. Interestingly, they found up to 12 % of primary landing sites were in the paraaortic/caval regions (Fig. 59.2). In another mapping study, Briganti et al. determined that

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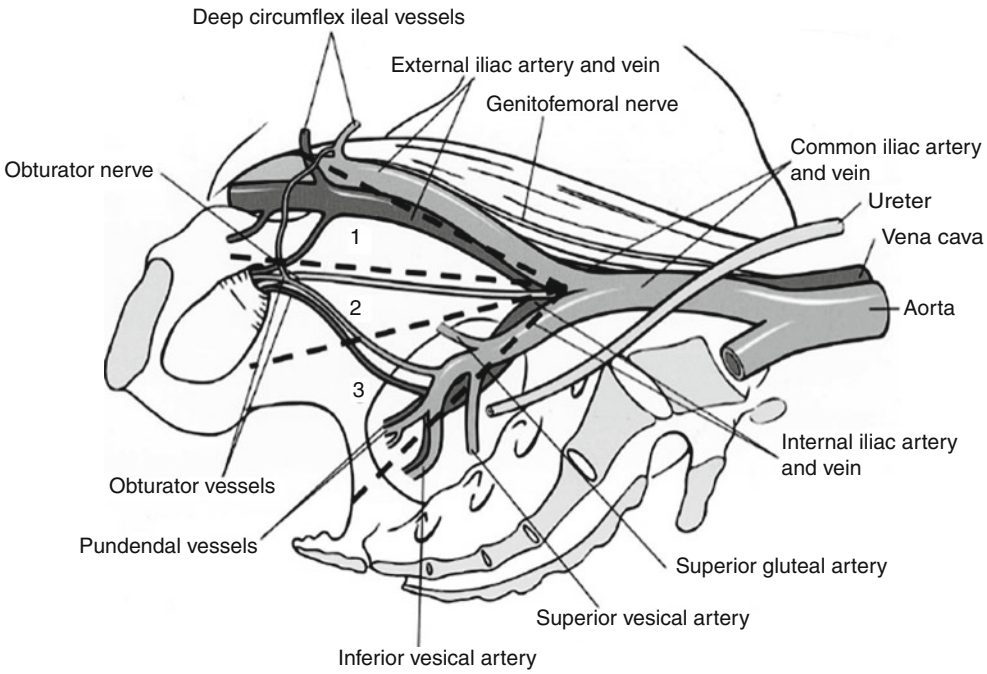


**Fig. 59.1** Diagrammatic depiction of the pelvic sidewall. Areas of anatomic lymph node dissection include the (*1*) external iliac vessels, (*2*) obturator fossa, and (*3*) internal iliac vessels (Reproduced with permission from Bader et al. [36])

high-risk prostate cancer patients (PSA > 20, cT3 disease, and Gleason score ≥ 8) had extremely complex lymphatic drainage, leading to significant variability and difficulty in predicting where LN metastases would occur [10]. In their study, ePLND included removal of the obturator, internal iliac, external iliac, presacral, and common iliac lymph nodes. LNI varied greatly among the patients, with the obturator nodes being most commonly affected (89 % of cases). Seventy-eight percent of patients demonstrated involvement of retroperitoneal nodes, all of whom also had positive common iliac nodes. Therefore, in contradiction to the Mattei study, they proposed that LNI occurs from the pelvis to the retroperitoneum in an orderly fashion through the common iliac nodes and that LNI can be divided into two categories, pelvic or common iliac/retroperitoneal, depending on the extent of invasion. Relatively small numbers limit the generalizability of both of these studies.

Due to these various definitions and findings, several nomograms have been created to determine which, if any, PLND should be performed in prostate cancer patients based on their preoperative risk factors [4, 7, 11–13]. Caution should be used when interpreting these data because they are often derived from relatively limited dissections and are typically not validated on external samples. Nonetheless, these studies suggest that when performing PLND, especially in higher-risk patients, an ePLND would be favored over a standard or limited PLND due to complex lymphatic drainage and unpredictability in the pattern of spread. These findings are more difficult to apply to low- and intermediate-risk patients, who remain at the center of debate and will be discussed later in this chapter.

## The Prevalence of Lymph Node Invasion in Prostate Cancer

The prevalence of LNI varies significantly depending on a patient's risk status, determined preoperatively with PSA, clinical stage, and Gleason score. Patients with low-risk prostate cancer on final pathology have considerably less risk for metastatic disease, originally believed to be less than 1 %, compared to patients with intermediate-or higher-risk cancer originally believed to be less [14–16]. Although this incidence is low, there may be a staging bias since LNI depends not only on whether or not metastatic disease is actually present but also on what type of PLND is performed (Table 59.1).

In the last 10 years, other studies have specifically examined the extent of PLND performed, the patient's risk based on preoperative variables, and the extent of LNI seen after PLND. Most studies show consistently higher rates of LNI in ePLND compared to lPLND (3–7 % vs. <1 %), even in low-risk prostate cancer patients [6, 16–19]. Whether such differences exist in intermediate- or high-risk patients and whether these differences are clinically relevant is not as well explored and is a critical area of research.

Interestingly, not all results have suggested that an extended dissection always leads to higher rates of LNI. Clark et al. looked to determine the difference in results when ePLND was performed versus lPLND [20]. They randomized patients by performing an extended dissection on one side of the pelvis and a limited dissection on the other. They determined that there was no higher rate of LNI in the ePLNDs versus the lPLNDs. It is important to note that most

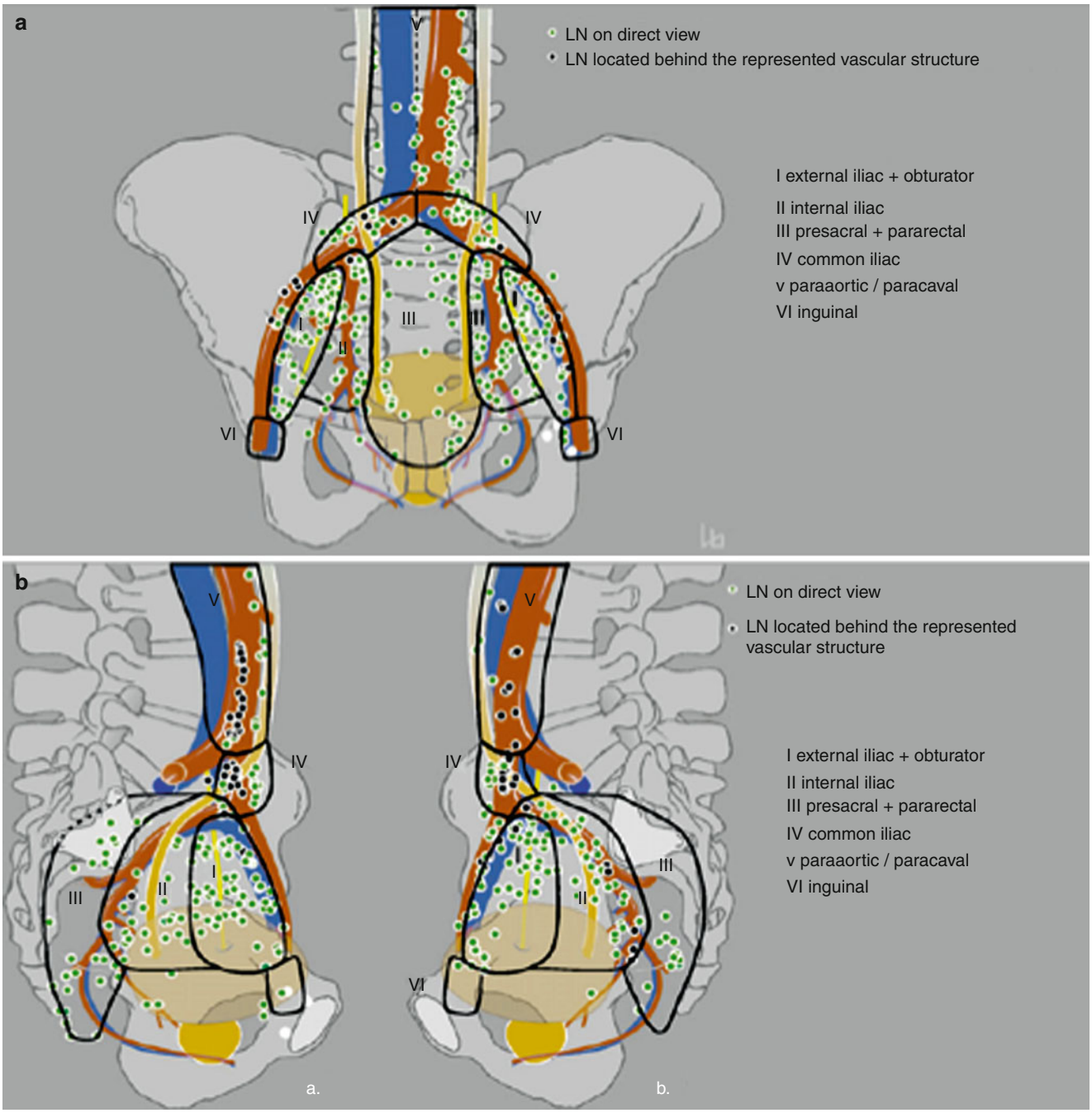


**Fig. 59.2** (**a**) Primary lymphatic sites projected onto a coronal view of the abdomen and pelvis, based on 3-D reconstruction of SPECT/CT/MRI data and confirmed intraoperatively. SPECT imaging was performed 1 h after injection of Tc-99 m nanocolloid into six locations of the prostate. Outlined areas represent different anatomic lymph node packets. (**b**) The same primary landing sites, now projected onto sagittal planes (Reproduced with permission from Mattei et al. [9])

of their patients had low-risk prostate cancer (94 % of patients were either cT1c or cT2a), but this nonetheless suggests that in low-risk prostate cancer, ePLND may not provide any additional information relative to lPLND. Because ePLND requires more extensive surgery and is associated with higher complication rates than lPLND, the appropriate extent of dissection in this population is yet to be determined.

## Imaging of Lymph Nodes in Prostate Cancer

While imaging for prostate cancer is discussed in detail elsewhere, it is worth mentioning its role in the detection of pelvic lymph node metastases. The gold standard for lymph node staging in prostate cancer is undoubtedly PLND, but recent advances in imaging have increased its utility. Initially,

**Table 59.1** Prevalence of nodal metastases according to the extent of PLND and prostate cancer risk

| | PLND extent | Mean number of nodes removed | Low risk (cT1c, PSA < 10, Gleason ≤ 6), % | Intermediate risk (cT2, Gleason 7, PSA 10–20) | High risk (cT3, Gleason 8–10, PSA > 20) |
|---|---|---|---|---|---|
| Bhatta-Dar et al. [14] | Limited | N/A | 0.5 | N/A | N/A |
| Makarov et al. [16] | Limited | 5.5 | 0.5 | N/A | N/A |
| Kawakami et al. [17] | Limited | 5.7 | 0.87 | 2 % | 7 % |
| Heidenreich et [66] | Extended | 21 | 5.8 | 20 % | 55 % |
| Studer et al. [18] | Extended | 20 | 3 | N/A | N/A |
| Briganti et al. [4] | Extended | 17.3 | 1.8 | 8.2 % | 33.7 % |
| Weckermann et al. [19] | Extended | N/A | 7 | N/A | N/A |

the use of computed tomography (CT) and magnetic resonance imaging (MRI) was limited due to low sensitivity (>50 %) and the inability to detect LNs > 1 cm in size [21]. More advanced techniques, such as (11)C-choline positron emission tomography/CT (PET/CT) and MRI with lymphotropic superparamagnetic nanoparticles, have reported increased sensitivity and specificity of over 90 % [4, 22, 23]. However, none of these novel modalities have been proven prospectively to improve the detection of LNI or reduce the need for PLND. So, while promising, additional high-quality studies need to be performed before imaging can select which patients merit a PLND and the extent of that dissection.

As mentioned earlier, sentinel lymphoscintigraphy (SLN), which has been used in LN mapping, is another recent imaging modality that can be used in operative planning of PLND. More recent studies have examined whether this could in fact replace PLND [24–26]. The paradigm follows that for breast cancer and melanoma, where metastases follow a very specific pattern and a negative sentinel node acts as a primary drainage site. If this node is negative for disease, no additional lymph node dissection needs to be performed. Because of the difficulty of specifically locating the tumor in the prostate, the radioactive colloid is injected in different locations throughout the gland, typically in at least three areas on each side. Most investigators then perform planar scintigraphy several hours later to locate the first echelon of drainage. Surgery is performed 24–48 h later, and the sites seen on planar scintigraphy are excised. Additionally, manual gamma probes are typically used to excise additional radioactive tissue at the time of the procedure.

In a relatively small study of patients with intermediate- or high-risk disease who received both a sentinel lymph node dissection (SLND) and an ePLND in the same setting, there were no false-negative results [27]. Six of the sentinel nodes were outside the template for an ePLND, and two of these were positive for metastatic disease, although in only one patient was this node the only positive node. In the largest study published to date, Holl et al. examined over 2,000 patients treated between 1999 and 2008. The first 350 of these patients underwent SLND followed by a lPLND. Subsequently, low- and intermediate-risk patients were treated with an SLND only, although the protocol eventually evolved until all patients with Gleason score of 3+4 or less received only SLND; those with Gleason 4+3 underwent SLND and ePLND, and patients with Gleason sum of eight or greater underwent an ePLND only. These authors ultimately found positive lymph nodes in 16.7 % of patients. Five percent of these patients were found to have positive lymph nodes in areas that would not have been detected with SLND.

All the studies on SLND suffer from significant methodological flaws. Firstly, standardization and optimization studies examining the appropriate administration and subsequent imaging of the radionuclide have not been performed. Because lymph node drainage of the prostate is so variable, injecting nonspecifically into the prostate rather than the areas containing tumor does not necessarily identify primary or secondary nodes. Other technical issues include the fact that planar scintigraphy may understage the presacral and perirectal area due to artifact from the bladder, that sentinel lymph nodes may not be detected due to blockage of the lymphatic channels with tumor, and that intraoperative examination with the gamma probe can be problematic due to background signal. Moreover, the studies themselves do not contain comparative arms, and the majority have not performed ePLND after SLND. This precludes determining the true sensitivity, specificity, and false-negative rates. No studies have examined oncological outcomes in terms of biochemical recurrence or other clinical endpoints. Before coming into widespread acceptance, these limitations need to be addressed, particularly the need to have comparative arms. Nonetheless, SLND may allow a surgeon to know which LNs are most likely to be involved in the spread of cancer to the lymphatics and may decrease the routine use of ePLND in the future, potentially reducing complications.

## Lymph Node Invasion in Prostate Cancer: Outcomes

PLND has been found to influence outcomes for patients with prostate cancer, although the data varies for node-negative versus node-positive patients. In an early analysis of the Mayo Clinic experience, the number of nodes removed did not affect PSA recurrence, systemic progression, or cancer-specific survival [28]. This was a relatively early cohort, from 1987 to 1999, but still had relatively low-stage disease, with a mean PSA of 6.6 ng/ml and 57 % of patients having ≤cT2a disease. The median number of nodes removed was nine. One of the major drawbacks was that PLND was surgeon dependent and did not always include either the external iliac or hypogastric areas. Interestingly, the number of nodes removed significantly decreased with time, from 14 down to 5, suggesting that the trend toward a more limited PLND was occurring even before the advent of minimally invasive surgery. Other studies have not validated these findings.

Masterson et al. showed in a retrospective review that the more nodes removed correlated with a lower rate of biochemical recurrence but only for those patients who were node negative [29]. While multiple surgeons were involved, the PLND was relatively well defined, with a proximal border consisting of the bifurcation of the common iliac arteries. This is further suggested by a population-based SEER study of over 127,000 patients [30]. In patients with organ-confined disease, lack of a PLND conveyed an increased risk of cancer-specific mortality and overall mortality on multivariate analysis. Another population-based study used a case-cohort methodology to examine the same question [31]. Although it did not reach statistical significance, this analysis showed that there may be a 5 % benefit in cancer-specific mortality for each extra lymph node removed. More definitively, another analysis of the SEER database found that removal of at least four lymph nodes improved cancer-specific mortality in patients undergoing a lymphadenectomy compared to those who did not have a PLND [32]. For node-negative patients, the removal of ten or more lymph nodes conveyed a hazard ratio of 0.85 for cancer-specific death compared to those who were pNX.

Although retrospective in nature, these studies suggest a clinical benefit, either by removing micrometastases or by improving staging. Even with just additional immunohistochemistry, occult metastases have been shown to be present in up to 13 % of pN0 patients, and these patients have been shown to have worse outcomes compared to truly node-negative patients [33]. Because some patients with positive nodal disease have prolonged survival, there may be some benefit to removing sites of micrometastases. An alternative explanation of these findings is the so-called Will Rogers phenomenon [34, 35]. This is a form of staging bias, where shifting stages actually improve outcomes across groups without actually benefiting individual patients. In terms of PLND, increased sampling wound find more positive nodes compared to more limited sampling. Presumably, those patients who are restaged by ePLND would have better survival since their metastatic burden is lower to start with compared to those who would have positive nodes with a lPLND. This would improve the survival of the pN+ group. At the same time, you are removing patients from the pN0 group with metastatic disease, improving outcomes in that sample as well. This gives the appearance of a therapeutic benefit of ePLND, although it may not benefit any specific individual. So, while removal of more nodes may decrease biochemical recurrence and improve survival outcomes, more studies are needed to assess to what extent this benefit is therapeutic or due to more accurate staging and in which patient population (low- vs. intermediate- vs. high-risk patients).

The effect of LND on patients with node-positive disease has also been studied. In an early study of patients between 1989 and 1999, up to 25 % of patients had positive nodes with an ePLND [36]. These patients did not receive adjuvant therapy, and subsequent progression correlated with the number of positive lymph nodes. With only one positive lymph node, median time to symptomatic progression was 46 months. Only 8 % died of disease with a median follow-up of 45 months compared to 25 and 36 % for patients with 2 and >2 positive lymph nodes, respectively. Unfortunately, the total number of lymph nodes removed was not analyzed. In an updated description of that institute's experience (again without the routine use of adjuvant therapy), median cancer-specific survival at 10 years was 78.6 % for patients with two or fewer positive lymph nodes versus 33.4 % for patients with three or more positive nodes [37]. A median number of 22 nodes were removed, and on multivariate analysis, the total number of nodes removed and the number of positive nodes removed predicted cancer-specific survival. Further analysis revealed that extranodal extension and a metastatic diameter greater than 10 mm conveyed a worse prognosis [38, 39].

The role of adjuvant therapy for node-positive disease remains controversial. In a randomized controlled trial of immediate androgen deprivation therapy versus observation for patients with positive lymph nodes, Messing et al. found that adjuvant therapy reduced recurrence and improved survival [40]. In a subsequent publication with longer follow-up, those who were randomized to adjuvant therapy achieved improved overall survival (HR 1.84, 95 % CI 1.01–3.35), prostate cancer-specific mortality (HR 4.09, 95 % CI 1.76–9.49), and progression-free survival (HR 3.42, 95 % CI 1.96–5.98) [41]. The extent of the pelvic lymphadenectomy was not defined, but the median number of nodes assessed was 11 and 14 in the two arms. These studies have been criticized because of the small number of patients and the lack of centralized pathology review [42].

Subsequent retrospective analyses have been performed to further risk stratify these patients. In the Mayo Clinic experience over several decades, two or more positive nodes predicted worse cancer-specific survival [43, 44]. Cheng et al. found a nearly identical 5-year survival rate between patients that had no positive nodes and patients that had one positive node after PLND (99.3 % vs. 99 %), and the difference was also very minimal for 10-year survival [43]. Interestingly, the total number of nodes removed did not affect outcome [44]. In a more recent, multi-institutional study of 702 patients, all of whom received adjuvant hormonal therapy, three or more positive lymph nodes led to significantly worse cancer-specific survival [45]. Finally, there is a suggestion that adjuvant hormonal therapy combined with radiation therapy leads to even better outcomes [46]. Two hundred fifty consecutive node-positive patients between 1988 and 2007 with a follow-up of at least 5 years received an ePLND. One hundred twenty-nine of these patients received both radiation and androgen deprivation therapy, and 74 % of these patients received both pelvic and prostate bed irradiation. The median number of lymph nodes removed was 15 with a mean of 2.5 lymph nodes positive. In multivariate analysis, adjuvant radiation and the number of positive nodes predicted biochemical recurrence-free survival and cancer-specific survival. The effect of the total number of nodes removed was not described, but the anatomical boundaries of the dissection were defined, with a proximal boundary at the bifurcation of the common iliacs.

In summary, the outcomes for patients undergoing a pelvic lymph node dissection need to be further evaluated. For node-negative patients, any benefits accrued by increasing lymph node count could be due to excision of micrometastatic disease or because of improved staging. For node-positive disease, the role of adjuvant therapy needs to be further defined, and risk stratification by the number of nodes as well as the size or extranodal extension of these nodes should be considered for future clinical trials. Moreover, the benefits of increasing lymph node yield and wider dissection may be offset by the potential morbidity of the LND.

## Complications of Pelvic Lymph Node Dissection

PLND is not a completely benign procedure and has complications distinct from the prostatectomy itself. Intraoperatively, ureteral, rectal, and pelvic nerve injury (most commonly the obturator), as well as blood loss are the most commonly encountered problems. Postoperatively, complications include deep venous thrombosis, pulmonary embolism, pelvic abscess formation, fever, pelvic hematoma, prolonged lymphorrhea, lymphocele, and rarely lymphedema. The actual rate of complications from PLND is not known because of differences in defining complications, trouble capturing events, and until recently the lack of a standardized system for reporting complications. But, it does seem these rates differ depending on whether a limited or extended dissection was performed. While overall rates tend to be low, a complication rate up to 50 % has been reported in early studies with ePLND [47].

With the exception of one review, which showed complication rates to be equal, most comparisons of lPLND versus ePLND have found consistently higher complication rates in the extended dissections (2–9 % for limited, 8–36 % for extended) [20, 48–50]. While a majority of the complications encountered were not life threatening, the difference in rates is significant. These complications can prolong hospital stay and lead to the need for additional imaging or procedures, such as CT imaging or drainage of fluid collections.

Because of these risks, precautions can be taken to prevent common complications in PLND. Lymphatics should be well dissected and carefully ligated after removal of LNs to decrease the possibility of lymphorrhea after surgery. Many recommend that pelvic drains should be placed after the surgery is completed [51], although Sachedina et al. argue that the placement of drains actually leads to lymphocele formation, especially if negative-pressure suction is employed and that a pelvic drain does not need to be placed when there is appropriate hemostasis and a good vesicourethral anastomosis [52]. If output is persistently high, the fluid can be tested for its creatinine level to determine whether there is drainage of urine from a vesicourethral leak.

There is additional debate about the role of pharmacologic versus mechanical venous thromboembolism (VTE) prophylaxis. In one study of over 1,300 radical prostatectomies where no pharmacologic prophylaxis was given, the rate of clinical VTE was only 0.21 % [53]. Another study did show a decrease in the rate of VTE with heparin, but this came at the cost of increasing hemorrhagic complications [54]. This, combined with a historic concern for an increased rate of lymphoceles after prostatectomy, makes some surgeons question the routine use of pharmacologic VTE prophylaxis, especially in an age where early mobilization and mechanical compression devices have become the norm [54].

## Role of Minimally Invasive Surgery in Pelvic Lymph Node Dissection

With the introduction of robotic surgery, the role of minimally invasive surgery—particularly in patients with prostate cancer—has expanded greatly. Large series have examined the ability to use minimally invasive techniques to reduce complications and compare outcomes between open and minimally invasive surgery [55–57]. There has been significant work to examine PLND in robotic-assisted

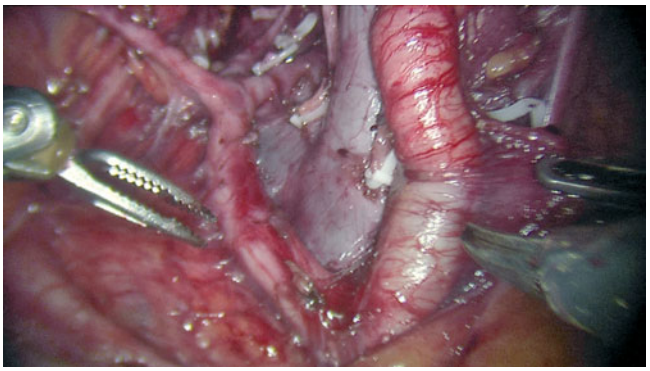

**Fig. 59.3** An intraoperative view of a robotically assisted pelvic lymph node dissection. The external and internal iliac vessels have been skeletonized, and the ureter is clearly seen in the lower left corner of the image

radical prostatectomy (RARP) [58–61], as well as to compare the outcomes, complication, and LNI rates of robotic to open prostatectomy [58].

Lallas et al. suggest that the performance of PLND should be done in any clinically indicated patient regardless of technique and that the outcome of PLND in RARP is comparable to that of open PLND [62]. In contrast to this, Yates et al. suggest that with intermediate- and higher-risk prostate cancer patients, fewer LNs are able to be removed when performing a PLND during RARP, suggesting that open PLND remains the gold standard in higher-risk patients [59]. More recently, Davis et al. performed a robotic PLND that was followed by a second-look open LND on the same patient at the same surgery. The authors showed that the lymph node yield of robotic PLND was 93 % compared to a second-look open LND, suggesting robotic PLNDs can be performed with sufficient accuracy compared to the open approach (Fig. 59.3) [63]. This argues that with appropriate care and time, equivalent node dissections can be performed. No study has specifically examined the time required for a robotic PLND compared to an open PLND nor has any study specifically examined the learning curve for either a minimally invasive or open PLND in prostate cancer.

Feifer et al. recently looked at the trends in performance of PLND in open versus minimally invasive prostatectomy. They found that over time, surgeons are less likely to perform a PLND in minimally invasive prostatectomies and that only elevated PSA and biopsy score, not clinical stage, were predictors for performance of PLND [64]. Since performance of PLND and evaluation for LNI increase positive outcome factors in the treatment of prostate cancer, this suggests that the use of minimally invasive techniques may interfere with the proper staging and treatment of patients after prostatectomy. Special efforts should therefore be made so that the introduction of novel technologies or techniques does not compromise oncologic outcomes.

## Which Patients Should Have a Pelvic Lymph Node Dissection?

Should all patients undergo PLND during prostatectomy, and should they have an extended or limited dissection? Partin et al. suggest that patients with low-risk localized prostate cancer can be operated on without ever doing a PLND because of the very low risk for LNI [13]. Others would suggest that even low-risk patients should have at least an lPLND; still others recommend ePLND regardless of how low risk the patient is. The major urologic associations have established guidelines to help answer these questions.

The American Urologic Association (AUA), European Association of Urology (EAU), and the National Comprehensive Cancer Network (NCCN) have all published guidelines indicating which patients should undergo PLND and the extent of dissection that should be performed [65–67]. As would be expected in an area with so much ambiguity in the literature, there is no consensus among the three groups. The AUA states that PLND should be performed in patients with higher risk of nodal involvement, but they do not differentiate who should undergo an lPLND or an ePLND. The EAU guidelines differ slightly, with their recommendations suggesting that patients with intermediate- or high-risk prostate cancer according to the D'Amico risk grouping should all undergo an ePLND. Finally, the NCCN recommends that a nomogram should be applied and that if the patient is at less than 7 % risk of LNI, there is no need to perform PLND. If the risk is higher than 7 %, they recommend ePLND, suggesting that there is no role for the performance of lPLND [4]. While the use of any of these guidelines would be considered acceptable, the difference in these recommendations shows that there is still no established solution.

Since the answer to when PLND should be performed is not always clear, a variety of predictive nomograms have been created to determine risk for LNI and the need for PLND. One of the largest studies to date by Cagiannos et al. looked at 7,014 patients undergoing prostatectomy with PLND. Their preoperative nomogram based on PSA, stage, and Gleason score was able to accurately predict LNI in 76 % of cases [68]. The limitation of this study was that only lPLND was performed. Other studies have determined similar nomograms with comparable success predicting LNI and thus the need for lPLND [69, 70]. Briganti et al. determined preoperative nomograms based on similar preoperative variables for ePLND, once again with comparable predictive accuracy for detecting LNI (76–83 %) [71, 72].

These nomograms are useful when evaluating preoperative patients and determining if a PLND should be performed. Because PLND is not without complications (as discussed above), strong models for when to perform PLND are clinically useful. With close to 80 % accuracy, there is still room

to improve our predictive capabilities, but in conjunction with preoperative imaging and clinical judgment, they are excellent tools for determining which patients should undergo PLND.

## Conclusions

PLND is a key element in radical prostatectomy, and despite advances in imaging and surgical technology, PLND remains the gold standard to determine the presence of LNI in prostate cancer. While the recommendations for when to perform PLND vary, a large number of studies have shown that the performance of PLND should always be used in intermediate- and high-risk patients, and its role in low-risk patients is still a highly debated topic. Because no single consensus exists, research has focused on the use of medical imaging to help detect the presence of LNI before surgery, as well as the creation of nomograms to predict which patients should undergo PLND during prostatectomy. As advances continue to be made, the understanding of PLND and its use in surgery will continue to be defined.

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# External Beam Radiotherapy for Low-Risk Prostate Cancer

60

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## Definition of Low-Risk Disease

Due to widespread screening with prostate-specific antigen (PSA), prostate cancer is diagnosed at an earlier stage, which has led to the so-called stage migration. Consequently, more diagnosed prostate cancers are low-risk disease [1]. The D'Amico criteria are often used to define "low-risk" patients: typically, they have a PSA level < 10 ng/ml, a biopsy Gleason score ≤ 6, and a clinical T-stage ≤T2a [2]. These criteria are used by the National Comprehensive Cancer Network to create guidelines for the treatment of prostate cancer [3]. Nomograms to predict treatment failure incorporate the same criteria [4, 5]. More recently, the University of California-San Francisco has published and validated the Cancer of the Prostate Risk Assessment (CAPRA) score [1, 6]. The CAPRA score assigns points to different characteristics of the tumor and the patient. PSA level (up to 4 points) and Gleason score (up to 3 points) are considered as the most strong predictors for biochemical recurrence after radical prostatectomy, followed by age, T-stage, and percentage of positive biopsy cores (1 point each). Consequently, the CAPRA score is calculated from 0 to 10 points [1, 7]. Other factors such as PSA doubling time [8], presence of perineural invasion [9–11], and more recently modern imaging such as magnetic resonance imaging (MRI) [12–15], diffusion-weighted MR [16], dynamic contrast-enhanced MR [15], and magnetic resonance spectroscopy (MRS) [16, 17] might further refine the "low-risk" patient group. Interestingly, the recently updated TNM classification recognizes the value of additional imaging in T- staging. On page 243 of the 7th edition, they state the following: "The following are the procedures for assessing T categories: physical examination, imaging, endoscopy, biopsy and biochemical tests." Although it is not clear how biochemical tests can add to the final T-staging, imaging certainly does.

## External Beam Radiotherapy for Low-Risk Disease

For patients with low-risk disease, there are three standard treatment options: active surveillance (certainly for patients with a CAPRA score < 4), radical prostatectomy, and radiotherapy (both external beam radiotherapy and brachytherapy). In the absence of randomized trials that compare the different treatment options, the results of several large institutional series that have compared the different treatment options should serve as the base for decision-making. Analysis of those trials suggests equality of the different treatment options for low-risk prostate cancer [18–22].

External beam radiotherapy (EBRT) is a cornerstone treatment of low-risk prostate cancer. Over the last decade, there has been a substantial progress in the field of EBRT including planning [23] and safe delivery of higher doses [24–26], improvement in daily prostate positioning by means of ultrasound [27, 28], gold markers [29, 30], and/or cone-beam computed tomography [31] and implementation of

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modern imaging such magnetic resonance imaging (MRI) in staging and localization of the tumor [32] and the delivery of a simultaneous boost to the dominant intraprostatic lesion as visualized on MRI [33] or choline PET-CT [34].

## EBRT

In contradiction to the situation after radical prostatectomy, PSA does not have to become undetectable after EBRT. There still is PSA production from the remaining nonmalignant glandular tissue, resulting in a detectable nadir even many years after EBRT. A single PSA rise after EBRT can therefore not be considered as biochemical failure. Therefore, two consensus guidelines have been proposed over time. At first, there was the ASTRO definition of biochemical failure (BF), which involved three *consecutive* rises in PSA [35, 36]. More recently, the Phoenix definition of BF was proposed. This definition defined biochemical failure as a PSA rise ≥2 ng/ml above the nadir post-EBRT [35].

### Some History

Before the so-called conformal radiotherapy had proven to reduce late toxicity, EBRT for prostate cancer typically consisted of a four-field "box." The borders of the treatment fields were based on bony anatomy and plain films. Because of the invisibility of the prostate on plain films, there was substantial uncertainty concerning the exact localization of the prostate, and consequently, large treatment portals were created to cope with this positioning uncertainty. As a consequence, a lot of normal tissue (bladder, small intestine, rectum, sigmoid colon) was included in the treatment fields. In order to minimize the toxicity risk, the dose was limited to 60–66 Gy, and less than 50 % of patients presenting with T1–2 tumors were free from biochemical progression at 10 years [37, 38].

A first and major step toward more precise EBRT was the introduction of computed tomography (CT) in the simulation and treatment planning. CT-based planning allowed the use of the three-dimensional (3D) anatomical information of the patient to generate more individualized treatment plans and beam shapes that were conformal to the shape of the target in beam's eye view [39]. Consequently, less normal tissue was exposed to a high radiation dose. The concept of 3D-conformal radiotherapy (3DCRT) was born, and the combination of better target coverage with less normal tissue exposed to a high dose lead to the hypothesis that 3DCRT could increase the therapeutic benefit in EBRT for prostate cancer. 3DCRT was the first radiation technique that enabled the safe delivery of a higher dose (i.e., >70 Gy) to the prostate. Numerous single-institution studies demonstrated significantly lower acute toxicity rates when compared to conventional techniques at the same dose with reductions of >10 % [40, 41]. In 1996, Pollack et al. demonstrated that increasing the dose from 70 Gy using conventional techniques to 78 Gy using 3DCRT was not accompanied with an increase in acute toxicity [42]. The actuarial risk of grade ≥3 rectal complications at 5 years is generally lower than 5 % [43, 44]. In a randomized trial, Dearnaley et al. compared 2 EBRT regimens. The rate of grade 2+ proctitis and rectal bleeding was significantly reduced in the 3DCRT arm (5 % vs. 15 %) [45].

Also for low-risk prostate cancer patients, the delivery of a higher dose has lead to better biochemical nonevidence of disease (bNED) [19, 40, 41, 46, 47] and a lower rate of distant metastasis [48].

### Target Volume Delineation

The probability that low-risk disease is accompanied by bone or lymph node metastasis at diagnosis is very low. Consequently, a staging with bone scan and CT scan of the abdominopelvic region is not necessary [49, 50]. The guidelines of the American Urological Association [50], the National Comprehensive Cancer Network [51], the American College of Radiology [52] as well as the European Association of Urology [53] advice to perform NO staging imaging in low-risk disease.

The clinical target volume should only encompass the prostate whether or not combined with the seminal vesicles. There is no need to include the pelvic lymph nodes in the treatment fields, because this does not add anything to the treatment efficacy [54].

To calculate the risk of nodal involvement, one can use the Partin tables [55], nomograms [56], and/or mathematical formulas such as the Roach formula [57] and the Yale formula. The latter involves also T-stage, making it more accurate than the older Roach formula [58]. As an example, for a patient with a cT1c disease, a Gleason score of 6, and a PSA of 6, the probability of lymph node involvement would be close to zero independently whether the Partin tables, the nomogram, or the mathematical formulas would be used.

Also the probability of seminal vesicle invasion is generally lower than 5 %. There is no need to include them completely to the end dose [25, 59, 60].

### Evidence from Randomized Trials

Several randomized trials have shown that a higher radiation dose is associated with improved biochemical outcomes in localized prostate cancer. However, the subgroup of patients for whom dose escalation is most beneficial has not been clearly identified. It is still a matter of debate whether higher

doses are necessary to treat low-risk prostate cancer. Opponents argue that the delivery of a higher dose may lead to an unacceptable high rate of late toxicity in this subset of patients who are likely not to die of their disease. And of course, a dose of "0 Gy" is defendable in those low-risk patients [61]. Two questions need to be answered. At first, is the evidence to deny this higher dose to low-risk patients really out there? And secondly, does the delivery of a higher dose unavoidable lead to a higher complication rate?

In 2010, Zietman and colleagues updated the results of the PROG 95-09 trial. This randomized phase III trial randomized 394 patients, equally allocated to conventional-dose (70.2 Gy, $n=197$) or high-dose radiotherapy (79.2 Gy, $n=197$). All patients were treated to the prostate and seminal vesicles to 50.4 Gy using photons, followed by a boost to the prostate only delivered by protons. The boost dose was 19.8 or 28.8 GyE (gray equivalent) depending on the treatment arm. Median follow-up was almost 9 years. Independently of definition of BF, patients in the high-dose group had 15 % less risk of BF at 10 years. The significant advantage of a higher dose was also observed in the low-risk group, which consisted of 227 patients. Of those 227 patients, 111 were treated to 70.2 Gy, and 116 were treated to 79.2 Gy. There was a 21 % lower risk of BF at 10 years in favor of the high-dose group (28 % vs. 7 %, HR: 0.22; $p<0.0001$) [62].

In the MD Anderson trial, 301 patients were randomized to receive conventional-dose radiotherapy to 70 Gy ($n=150$) or high-dose radiotherapy to 78 Gy ($n=151$). With a median follow-up of almost 9 years, there was a significant benefit for the high-dose group concerning BF: 22 % vs. 41 %. Although the initial report of the MD Anderson phase III randomized trial did not show a benefit for a higher radiotherapy dose in the low-risk group the update published in 2008 did show a significant advantage for the 78 Gy. The difference was 25 %, with an 8-years BF rate of 37 % in the 70 Gy arm vs. 12 % in the 78 Gy arm [59].

Other randomized trials did not confirm (yet) this significant benefit for a higher dose in the low-risk population. The MRC RT01 trial randomized 843 patients between 2 radiotherapy schedules. The conventional-dose arm received 64 Gy in 32 fractions, while the high-dose arm was planned to receive 74 Gy in 37 fractions. All patients were treated by means of 3DCRT and neoadjuvant androgen suppression. After a follow-up of 63 months, there was 11 % less BF in the high-dose arm at 5 years (29 % vs. 40 %). This corresponded with a hazard ratio (HR) of 0.67 and a $p$-value of 0.0007. About 23 % of the randomized patients belonged to the low-risk population: 95 in the conventional arm and 99 in the high-dose arm. At 5 years, there was a 6 % BF difference in favor of the high-dose group (85 % vs. 79 %). This difference, however, did not reach significance (HR: 0.78; 0.41–1.48) [63].

The GETUG trial randomized 306 patients between two treatment arms: the conventional arm received 70 Gy, while the study group received 80 Gy. The radiation modality was 3DCRT. Rather surprisingly, IMRT was not allowed as treatment modality. After a median follow-up of 61 months, there was significant lower BF in the 80 Gy group with a benefit of 10 %. The authors stated that the benefit was restricted to the patients with an initial PSA > 15 ng/ml. Indirectly—there was no risk group classification presented in this trial—one can conclude that the GETUG data show no benefit for low-risk patients, not forgetting the relatively short follow-up [64]. More or less the same conclusions were drawn in the recently published update of the Dutch multicenter trial. In this trial, 664 patients were randomized between two treatment groups: the control group was scheduled to receive 68 Gy, and the study group was scheduled to receive 78 Gy. After a median follow-up of almost 7 years, there was a significant drop in BF in favor of the high-dose group with an absolute difference of—again—10 % (odds ratio 0.75, $p=0.04$). The authors stated that there was no benefit for dose escalation in the low-risk group [65].

Should we therefore abandon a higher dose (78 Gy) for low-risk patients? This would at least be based on preliminary conclusions. It is of interest to notice that the first reports of the PROG 95-09 and the MD Anderson trial did not show any benefit for the low-risk group either [66, 67]. This is important when drawing definitive conclusions. Because the natural history of low-risk prostate cancer is long, longer follow-up is necessary to see the benefit of dose escalation appear in the low-risk group in the other randomized trials too. A follow-up of about 9 years seems necessary before firm conclusions concerning the benefit from dose escalation in the low-risk group can be made.

In the PROG 95-09 trial, there was no significant increase in late RTOG intestinal (GI) or urinary (GU) toxicity. Severe toxicity was observed in only 2 % (GU) and 1 % (GI) and did not differ between the two dose regimens. There was a slight but nonsignificant increase in late grade ≥2 toxicity in the high-dose arm [62]. In contradiction, the MRC RT01 trial, the Dutch multicenter trial, and the MD Anderson trial showed a higher incidence of late grade ≥2 GI toxicity for the high-dose group. There was no increase in late ≥2 GU toxicity [59, 63, 65]. In the MRC RT01 trial, the difference remained significant independently of the toxicity score that was used [63]. Compared to the PROG 95-09 trial, there are two important differences: at first, in the MRC RT01 trial and the MD Anderson trial, the seminal vesicles were treated to a higher dose, resulting in more rectal mucosa irradiated to full dose. The Dutch multicenter trial requested a larger margin around the CTV of prostate and seminal vesicles [65]. Secondly, the full dose was delivered using photons compared to a proton boost in the PROG 95-09 trial [59, 62, 63, 65].

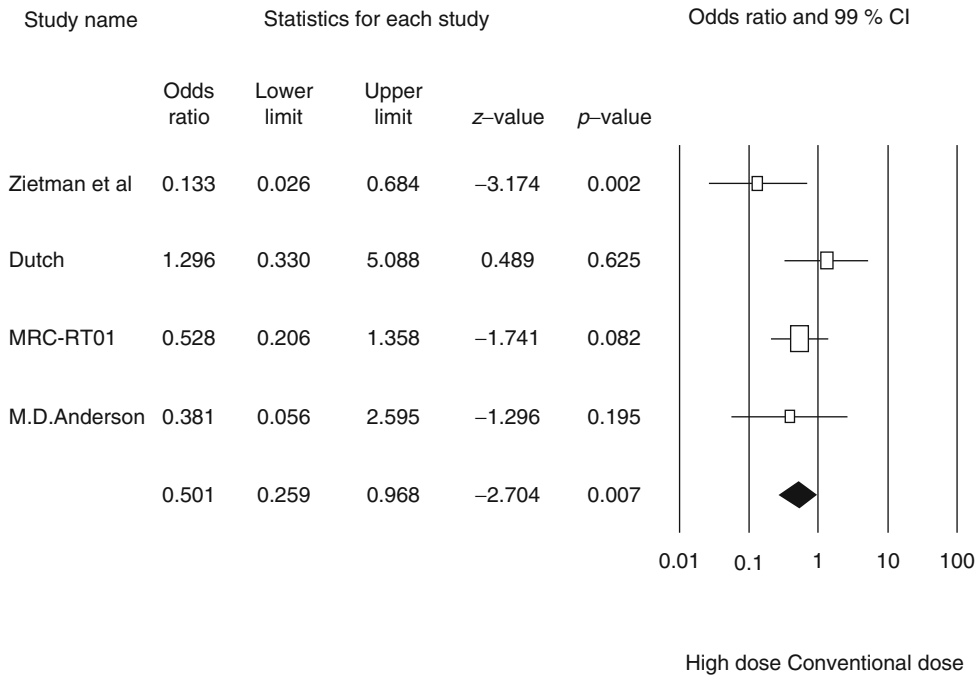


**Fig. 60.1** Meta-analysis regarding biochemical failure for the low-risk group. *CI* confidence interval (Figure printed with permission of the original author Viani et al. [68])

With sufficiently long follow-up, there is solid evidence that also in the low-risk population, higher doses are associated with an improved biochemical outcome. In a recent meta-analysis that was published before the update of the PROG 95-09 trial, Viani and coworkers demonstrated that also in the low-risk group, the BF rate was significantly lower with higher doses of radiotherapy (Fig. 60.1). Consequently they concluded that high-dose radiotherapy should be offered as treatment for all patients, regardless of their risk status [68].

To observe any difference in clinical end points, such as cancer-specific survival or overall survival, longer follow-up and further maturation of the data should be awaited.

## Erectile Dysfunction

Although most research to decrease radiation toxicity has been focused on rectal and urinary toxicity, erectile dysfunction (ED) is a relatively common symptom after EBRT. The reason is mainly anatomical: both the neurovascular bundles and penile bulb are located in close vicinity to the prostate and will consequently receive the full radiation dose in most cases. In case of the penile bulb, a dose relationship has been suggested [69]. Due to the close anatomical relationship of both structures, dose escalation to the prostate might also increase the dose to the penile bulb and consequently increase the rates of ED. Prospective evaluation after EBRT has shown intact potency rates of 40–50 % [70, 71]. These rates were confirmed in a meta-analysis of which showed potency preservation rate of 52 % (95 % CI 48–56 %) [72]. Preliminary reports suggest a benefit of IMRT over conventional and 3DCRT concerning preservation of erectile function [73]. In cases where EBRT induces ED, treatment with phosphodiesterase type 5 inhibitors significantly improves erectile function. This has been shown in randomized trials [74, 75].

## New Technical Evolutions

### Intensity-Modulated Radiotherapy

Apart from statistical comparisons, there are other important findings in the randomized trials. The incidence of late grade 2+ GI toxicity is balanced between 20 and 35 %, depending on the toxicity score that was used and follow-up time [59, 63, 64, 76]. All above mentioned trials used 3DCRT as radiation modality, and conclusions concerning toxicity should only be withheld for this technique. 3DCRT was certainly an important step in reducing radiotherapy-induced toxicity when compared to conventional technology [45]. However, 3DCRT was only a first step of a huge technological improvement that took place in the last 15 years. Intensity-modulated radiotherapy (IMRT) was the second and probably even more important step to combine the benefit from dose escalation with a further reduction of late toxicity. In the 1990s, planning studies already proved the superiority of IMRT when compared to 3DCRT. The largest advantage of IMRT was the significant reduction of rectal volume receiving intermediate doses such as 40, 50, and 60 Gy [23, 77, 78]. An even more innovative tool was the use of the so-called leaf position optimization which could further reduce the rectal volume that

received an intermediate dose [79]. Intermediate doses received by the rectum are nowadays considered to be the strongest inducers of late rectal toxicity [24]. Clinical results on IMRT support the planning-generated hypothesis. After IMRT, the incidence of acute GI toxicity grade ≥2 varied from 4 to 29 %, depending on the toxicity score that was used and on the total dose [26, 80, 81]. Acute grade 3 toxicity has been absent or neglectable, even when a more detailed scoring system than the RTOG toxicity scoring system was used. Moreover, most toxicity was transient [26, 81, 82]. These data compare favorable when compared to 3DCRT radiotherapy techniques [83].

For the low-risk disease group, IMRT has led to excellent disease control. At the Memorial Sloan-Kettering Institute, Zelefsky and coworkers treated 275 low-risk patients to 81 Gy (1.8 Gy per fraction). The 3-year actuarial BF rate was only 8 %. Only 2 % of the patients developed grade 2 rectal bleeding, while 10 % of the patients developed grade 2 urethritis. The 3-year actuarial likelihood of developing grade ≥2 late rectal and urinary toxicities was 4 and 10 %, respectively [26]. Meanwhile, two updates of this patient cohort have been reported. The first one was published in 2006. With a median follow-up of 7 years, the 8-year BF rate was 15 % in the low-risk patient group [84]. Very recently, the 10-year BF rate was reported to be 19 % for a follow-up of more than 8 years [85]. Researchers from the same institution reported in 2008 the feasibility of delivering—what they call "ultra-high dose"—86.4 Gy using IMRT. The 5-year actuarial rate of developing grade ≥2 late rectal and urinary toxicity was 4 and 16 %, respectively. For the 100 low-risk patients who were treated, the 5-year actuarial BF rate was 1 % (ASTRO definition) and 2 % (Houston definition), respectively [80]. Other research groups from the USA confirmed these excellent results. With a follow-up of 53 months, the BF rate at 4 years was 3 % [82].

A European study reported no BF in low-risk patients after a rather short follow-up of 3 years. Treatment was delivered in 2 Gy fractions to a total dose of 74–76 Gy. The 3-year actuarial likelihood of developing grade ≥2 late rectal and urinary toxicity was 11 and 18 %, respectively. The toxicity scoring system that was used was more stringent and complete than the RTOG or SOMA/LENT scoring system [24, 25]. The use of leaf position optimization significantly reduced late rectal toxicity [25, 79].

Recently, others confirmed these low late toxicity rates [82, 86]. IMRT did not impair quality of life either [87]. Compared to brachytherapy with transperineal prostate seed implant, IMRT might have less acute and late toxicity for comparable outcomes [88, 89].

Newer and even more promising technologies have been tested since the worldwide implementation of IMRT. Several authors demonstrated the superiority of volumetric arc therapy (VMAT) over static field IMRT [90–93]. Other technological improvements include helical tomotherapy [94, 95].

## Proton Radiotherapy

Proton beam radiation is another form of EBRT that might be beneficial over photon EBRT. This hypothesized advantage is attributed to the so-called "Bragg peak" which is a unique physical property of a proton beam. This "Bragg peak" means that proton beam can be stopped sharply in tissue positioned posterior from the target, or in other words that no dose is delivered beyond the "Bragg peak." However, caution is needed because of motion of the prostate along the proton beam axis. Consequently, the "Bragg peak" must encompass a larger volume. Until intensity-modulated proton beams are applicable in daily clinical routine, opposed lateral fields are the preferred beam setup because they are perpendicular to the rectum [96, 97]. This situation applies to the prostate-rectum interface. There is, compared to a photon beam, less radiation delivered to any point "beyond the target," meaning that the rectal wall would receive less dose without compromising the dose to the clinical target volume. Slater and coworkers reported the Loma Linda experience of proton therapy in 524 patients. Although there was no stratification into the three classical risk groups, patients with low PSA and low Gleason score had low BF rates at 5 years. The actuarial 5- and 10-year rates of developing grade ≥3 GI and GU toxicity were less than 1 % [97]. Mendenhall and coworkers reported their initial experience with proton therapy in 89 low-risk patients. The delivered dose was 78 cobalt gray equivalent (CGE). No patient developed a BF, but follow-up was short. There seemed to be lower GI and GU toxicity when compared to the randomized trials that used 3DCRT to deliver a higher dose to the prostate. However, indirectly compared to IMRT, toxicity rates resembled closely [98].

In theory, proton therapy might also reduce the risk of secondary malignancies when compared to photon therapy [96, 99].

A major drawback of proton therapy for prostate cancer is its immense cost. Coen and Zietman estimated the installation cost of a proton center to be at least US$ 25 million. They also doubted the cost-effectiveness of proton therapy when compared to IMRT [96].

## Hypofractionation

The $\alpha/\beta$ ratio of prostate cancer is assumed to be low with estimated values between 1.5 and 5 [100, 101]. This makes prostate cancer cells sensitive to a higher fraction dose or in other words to hypofractionation. Clinical reports on

hypofractionation for prostate cancer show promising results. Different fractionation schedules have been reported. Yeoh et al. demonstrated the equivalence of hypofractionation when compared to conventional fractionation in a phase III randomized trial [102]. Leborgne confirmed this equivalence in a nonrandomized study [28, 103]. Kupelian and coworkers treated 262 low-risk patients to 70 Gy at 2.5 Gy per fraction. After a median follow-up of almost 4 years, the BF rate was only 5 %. Acute grade ≥2 GI and GU toxicity was 9 and 19 %, respectively. The actuarial rate of late grade ≥2 GI toxicity was 6 % at 5 years, while the actuarial rate of late grade ≥2 GU toxicity was 7 % [28]. A Canadian group treated 129 patients to 66 Gy to be delivered in 3 Gy per fractions. The 5-year actuarial BF rate was only 2 %, and persistent grade ≥2 late GI and GU toxicity was present in only 1.5 and 2 % of the patients, respectively [104]. Leborgne et al. described equivalent outcomes [103].

## Image-Guided Radiotherapy

In the past decade, radiotherapy delivery itself has become much more precise thanks to the advent of image-guided radiotherapy (IGRT) which is conducted by means of daily transabdominal ultrasound [105], cone-beam CT (CBCT) [31, 106, 107], and the use of implanted radio-opaque gold markers [107, 108].

## Conclusive Remarks

External beam radiotherapy offers excellent biochemical control in low-risk disease prostate cancer. Dose escalation to at least 78 Gy should be the treatment of choice seen the significant biochemical control advantage compared to lower doses when follow-up is sufficient. When 3DCRT is used, dose escalation is accompanied with a higher rate of rectal toxicity, while urinary toxicity remains unchanged.

Modern technologies such as IMRT, tomotherapy, arc therapy, and IGRT and new radiation modalities such as proton therapy are promising in further reduce rectal toxicity. Severe rectal toxicity is neglectable with this technology.

The RTOG toxicity scale should no longer be used to score late toxicity.

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# Prostate Brachytherapy: Low Dose Rate

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Peter Grimm

## History of Low Dose Permanent Seed Prostate Brachytherapy

The concept of prostate brachytherapy began in the early 1900s with Alexander Bell's suggestion that tiny fragments of radium could be sealed in a glass tube, inserted into a cancer and "act on the disease material." Radium needles were used for prostate cancer in 1915 by both Dr Benjamin Barringer (after whom the Barringer Award is named) and Hugh Hampton Young (the pioneer in radical prostatectomy). Dr Young performed over 500 implants in this fashion from 1915 to 1927 with modest results [1].

In 1930, Rubin Flocks reported his results using radioactive gold. He actually was planning to place radon seeds into the prostate, but radon seeds were not available. Instead, he injected 60 mc colloidal radioactive gold in 20 cc throughout the enlarged prostate and demonstrated a dramatic reduction in the size of tumors. Most of his work involved doing combined prostatectomy for localized disease and insertion of the colloidal gold into the cavity. He would ultimately come to use about 2 cc of the colloidal material with a millicurie dose of 100 mc. His local recurrence in the prostatic fossa was 4.5 % [2].

In the 1970s, Willet Whitmore and Basil Hilaris at Memorial Sloan-Kettering Cancer Center, New York, placed I-125 seeds in titanium capsules into the prostate via an open laparotomy approach and a Mick applicator. The approach resulted in some success but was abandoned as surgery and radiation techniques improved [3].

In 1983, Hans Holm, University of Copenhagen, Denmark, was the first physician to perform the transperineal approach, which utilized transrectal ultrasound (TRUS) and direct (ultrasound) visualization of seed placement [4].

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In 1985, Haakon Ragde, John Blasko, and Peter Grimm further modified Holm's transperineal approach in Seattle, Washington [5].

The 1990s demonstrated a dramatic increase in seed implantation as training programs in Seattle and other locations trained thousands of practitioners [6–10].

In the 2000s, significant advances occur in dosimetry, patient selection, and implant technique including stranded and linked technologies [11–14].

## Rationale for Low Dose Rate Permanent Prostate Brachytherapy (PPB): Monotherapy Versus Combined External Beam and Seeds

### Disease Within the Gland

The primary advantage of PPB is the ability to deliver high doses to a confined area of the prostate and the immediate surrounding areas and to deliver continuous radiation in vulnerable phase of the cell cycle. Radiation control of prostate cancer has been well documented both in brachytherapy and external beam series to be dose dependent, with higher doses correlating with better cancer control rates [15]. The radiobiological effective (RBE) dose of permanent seed implantation has been shown to be higher than EBRT approaches, such as three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT). 16 multiple PPB studies have also demonstrated a dose gradient, with doses over 140 Gy being ideal to achieve sufficient control of the cancer with very low local recurrence rates of less than 2 %, even for high-risk disease [16].

### Disease Beyond the Gland

With few exceptions, all prostate cancers have some risk of disease beyond the prostate, regardless of stage or

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grade. It is incumbent, therefore, prior to treatment, to determine the likelihood of disease extent beyond the prostate and the distance that disease extends beyond the gland. The Partin tables and other histologic RP studies have demonstrated that as stage, grade, and PSA increase, so does the risk of lymph node, seminal vesicle, and extraprostatic disease involvement [17]. Percentage of cores involved and perineural invasion are other identified factors which increase the risk of extraprostatic extension (EPE) [19]. Imaging studies cannot accurately image this extraprostatic microscopic disease; therefore, it is necessary to estimate it from predictive tools such as the Partin tables. The rationale for monotherapy versus combined treatment is based on these estimates of EPE, the distance disease has likely spread, and the ability of the implant to cover the potential disease spread adequately.

## Rationale for Monotherapy or Combined Treatment: Histological Extent of Disease

Brachytherapy alone (Monotherapy) is designed to treat the prostate and the immediate surrounding areas of suspected extraprostatic extension (EPE). For low-risk disease, the likelihood of disease beyond 3 mm is less than 2 %, well within a standard implant margin of 5–10 mm [18]. For intermediate-risk disease, the estimated risk of EPE is more varied, and disease extent has not been well characterized [17]. However, monotherapy results suggest that many patients can be treated with local therapy. For example, the BC Cancer Agency Group reported a 95 % 5-year RFS in their intermediate-risk group treated with monotherapy. Many practitioners recommend breaking the intermediate-risk group into low and high intermediate groups, with combined therapy be considered if over 33 % of the biopsies are positive. This split of the intermediate-risk group arose primarily out of RP data that indicated that as the percentage of biopsies increased, the failure rates increased, due to extraprostatic disease [19]. There is also a concern that in some patients, the seminal vesicles may be at higher risk with more disease, particularly at the base and therefore require EBRT.

For high-risk patients, there is little doubt that combination of EBRT and seeds is necessary to cover the EPE beyond the implant volume as well as deliver a high intraprostatic dose. The Partin tables predict for a high risk of EPE in this group and therefore predictably would fail a local treatment. Of note is that to date, there are no identifiable pretreatment factors which will predict for "good" high-risk patient suitable for a prostate only treatment [20]. The results with implant alone have been poor; therefore, these patients universally receive, at minimum, a combined external beam and implant approach.

## Target Volume: Sites of Extraprostatic Disease

In order to adequately implant the EPE, it is necessary to know not only if it has likely occurred, but also where. studies have demonstrated that most significant disease (>2 mm) beyond the prostate is located in the posterior lateral region surrounding the nerves [21]. This nerve bundle is responsible for erection ability, is in close proximity to the gland (<2 mm), and is therefore vulnerable to surgical failure due to positive margins. The posterolateral margins around these nerves are an important primary areas of coverage included in an implant volume.

## Dose

There is no controversy about prostate cancer control and role of radiation dose. More dose, more cancer control [24, 28–30, 51]. Theoretically, as risk group and cancer volume increases, the need for treatment beyond the gland increases. Surgical studies have PSA failure rates of 8–22 % in low–risk disease and higher in intermediate and high risk, supporting the notion that extraprostatic disease plays a large role in surgical failure and must be addressed with the implant [22, 23].

Intraprostatic dose is well recognized as important for ultimate control, especially as the cancers increase in volume or aggressiveness. Efforts with all EBRT techniques (IMRT, stereotactic, protons, etc.) are all attempts to give more dose to the prostate in the expectation that higher dose will result in more cancer control. The primary advantage of PPB is the ability to deliver a higher bioequivalent dose than IMRT to the periphery of the prostate and a higher dose to the tumor bed. The dosimetry of both EBRT and seeds has planned margins to cover the potential EPE microscopic disease with tumoricidal doses (≥45 Gy).

## History/Background/Technical Breakthroughs

The technical advantage of permanent seed brachytherapy is the ability to deliver a very high dose of radiation over a short distance. However, PPB must be done accurately. Misplacement of seeds can result in either hot or cold spots, increasing the risk of complications or failure. Open laparotomy techniques with free seeds in the 1960s–1970s at MSKCC using the Mick applicator demonstrated that poor-quality implants (<120 Gy) had poor results but that good implant (>140 Gy) had results similar to the best surgical series [3].

In 1985, Blasko, Grimm, and Ragde introduced the preplanned, transrectal ultrasound, template-guided transperineal permanent I-125 seed implant in the United States.

Based on dose from the MSKCC experience, the group demonstrated high-quality implants and cancer control rates could consistently be achieved with appropriately staged patients [5, 6]. Technical improvements since the early experience include the development of CT dosimetry, improved imaging and contouring, connected seeds, and more recently connected seeds in smaller gauge needles [168].

## Patient Selection

Patients undergoing permanent seed implantation (PPB) should be initially evaluated and screened pretreatment for contraindications. This would include a determination of the biopsy Gleason score, pretherapy serum PSA as well as establishing a patient's risk group, stage, and preexisting clinical status. Technical factors relevant for planning and performing the procedure require a planning volume study or CT scan of the prostate.

## Absolute Contraindications to TRUS-Guided PPB

Limited life expectancy
Unacceptable operative risks
Distant metastases
Absence of rectum such that TRUS-guidance is precluded
Large TURP defects, which preclude seed placement and acceptable radiation dosimetry
Pubic arch interference despite downsizing
Ataxia telangiectasia

### Limited Life Expectancy or Operative Risk

Because of the long natural history of prostate cancer, patients with a limited life expectancy are considered poor candidates for PPB. PPB requires general or spinal anesthesia, which also may preclude some patients.

### Distant Metastasis

Patients with proven lymph node involvement (N1) or distant metastatic disease (M1) are not likely going to benefit from PPB monotherapy because the active metastatic disease will determine their long-term prognosis. However, patients with a high risk of lymph node involvement should not be excluded from consideration of combined external beam, and PPB extracapsular extension does not exclude a patient from brachytherapy as the treatment includes a margin around the prostate.

### Large TURP

*A Large TURP* is a contraindication to PPB. A large TURP defect may not permit implantation of seeds throughout the entire gland, resulting in unacceptable dosimetry [25–27]. Patients who have undergone prior TURP should be evaluated carefully as their postoperative complication risks are higher, especially with regard to urinary incontinence. .

### Pubic Arch Interference

Pubic arch interference can prevent adequate placement of needles and seeds. Techniques using either CT or ultrasound can identify patients with significant pubic arch interference. Most patients can be converted to an acceptable size (<60 cc) with hormonal downsizing.

### Ataxia Telangiectasia

*Ataxia telangiectasia* is caused by a defect in the gene responsible for recognizing and correcting errors in DNA replication when cells divide and in destroying the cells when the errors cannot be corrected. The protein normally repairs double-stranded DNA breaks, and, thus, its absence results in patients who suffer from extreme sensitivity to ionizing radiation and is not considered candidates for PPB or, typically, other forms or radiotherapy [40].

## Relative Contraindications to TRUS-Guided PPB

Small transurethral resection (TURP) defects
High IPSS score (typically defined as >20)
History of prior pelvic radiotherapy
Gland size >60 cc at time of implantation
Inflammatory bowel disease
Patients with relative contraindications may undergo PPB if appropriately evaluated by an experienced team.

### Small TURP Defects

In the 1980s and 1990s, higher rates of incontinence were noted when TURP patients were treated with a uniform loading pattern of seeds . The uniform loading of seeds, without a compensatory urethral-sparing technique, leads to a significantly higher dose to the urethra, resulting in tissue breakdown and scarring of the urethra, causing obstruction or incontinence. Patients with small TURP defects can undergo PPB, Newer dosimetry approaches intentionally decrease

high doses to the urethral area, and TURP detects and thereby reduces the risk of injury significantly. However, all TURP patients should be advised that they still have a slightly higher risk of incontinence than non-TURP patients [25–27].

### High IPSS Scores

As the IPSS score increases, the likelihood of transient, acute obstruction increases. High IPSS scores do not increase the long-term obstructive issues however. If the IPPS score is above 20, patients need to be evaluated by cystoscopic evaluation to determine the cause of anatomic obstruction, such as a stricture, bladder neck contracture, or prominent obstructing median lobes. If a patient is noted to have obstruction due to bladder neck contraction, a TUIP 6–8 weeks prior to implantation may decrease the risk of retention. A urodynamic study to evaluate the postvoid residual volume, volume voided and peak flow, may also be helpful. Caution and appropriate patient consent are indicated if patient's have a peak flow rate <10 cc/s and postvoid residual volume prior to PPB >100 cc; but these factors by themselves do not preclude PPB as a treatment option. In addition, patients with high IPSS scores can become candidates for implantation if their urinary symptoms respond well to alpha blockers and/or 5 alpha reductase inhibitors. A rare patient may require a TURP or urethrotomy at a later date because of continued retention or obstructive symptoms. A TURP or TUIP preimplant is preferable, as a postimplantation TURP can increase the risk for incontinence.

### Gland Size >60 cc at Time of Implantation

Size of the prostate is an important consideration. There is no minimum size that can be treated, but at most centers, rarely are glands over 60 cc treated. The volume study allows for evaluation of the size and shape of the gland and for determining if there is significant pubic arch interference. A size limit is based on the concern and experience that implants involving large glands will:

1. Require more needles and seeds to achieve adequate dosimetric coverage.
2. Have more intraoperative bleeding and trauma within and around the gland. This bleeding during the procedure can interfere with prostate visualization on ultrasound and therefore negatively impact the quality of the implant.
3. May have more movement during the procedure. Prostate swelling and bleeding into the perineum can also move the prostate further away from the perineum and template, making it difficult with some ultrasound systems to easily image the base position of the prostate.
4. Have more likelihood of pubic arch interference. Significant pubic arch interference (PAI) can prevent proper placement of needles, and therefore seeds, along the periphery of the gland. The technique for assessing this risk is discussed in the ultrasound planning section. Evaluation of the pubic arch in every patient is necessary since occasionally a patient with an average size (30–40 cc) prostate will have significant PAI. If necessary, medical downsizing can be used. Traditionally, a combination of leuprolide depot (LHRH agonist) and bicalutamide (oral antiandrogen) is used. Our experience demonstrated approximate 30–40 % volume downsizing effect after 3 months of total androgen deprivation therapy. Side effects include temporary emotional lability, hot flashes, loss of libido, gynecomastia, fatigue, and weight gain. Merrick et al. demonstrated that bicalutamide and dutasteride can result in an approximate 33 % volume reduction after 3 months of therapy, with less side effects than the leuprolide depot/bicalutamide combination.

### Inflammatory Bowel Disease

Patients with inflammatory bowel disease need to be carefully evaluated. Usual precautions and limitations for pelvic radiation need to be taken. A retrospective study from Mt. Sinai, however, demonstrated that patients with Crohn's disease or ulcerative colitis did not have elevated rectal toxicity. We recommend that patients with inflammatory bowel syndrome undergo a colonoscopy to rule out active disease in the anterior rectum prior to implantation.

### Not a Contraindication to PPB

*Age*, *obesity*, *diabetes*, *small glands*

## Treatment Selection

Patients meeting patient selection criteria of PPB are selected for a treatment regimen based primarily on their risk group and pathological features.

### Low Risk

"Low-risk" prostate cancer group is defined by most definitions as those with Gleason score 2–6, PSA ≤10 ng/ml and stage cT1a–cT2a [40]. Low-risk patients typically may be treated with PPB alone, also known as monotherapy [32–38]. Assuming an optimal dosimetric outcome can be achieved, excellent long-term outcome can be expected

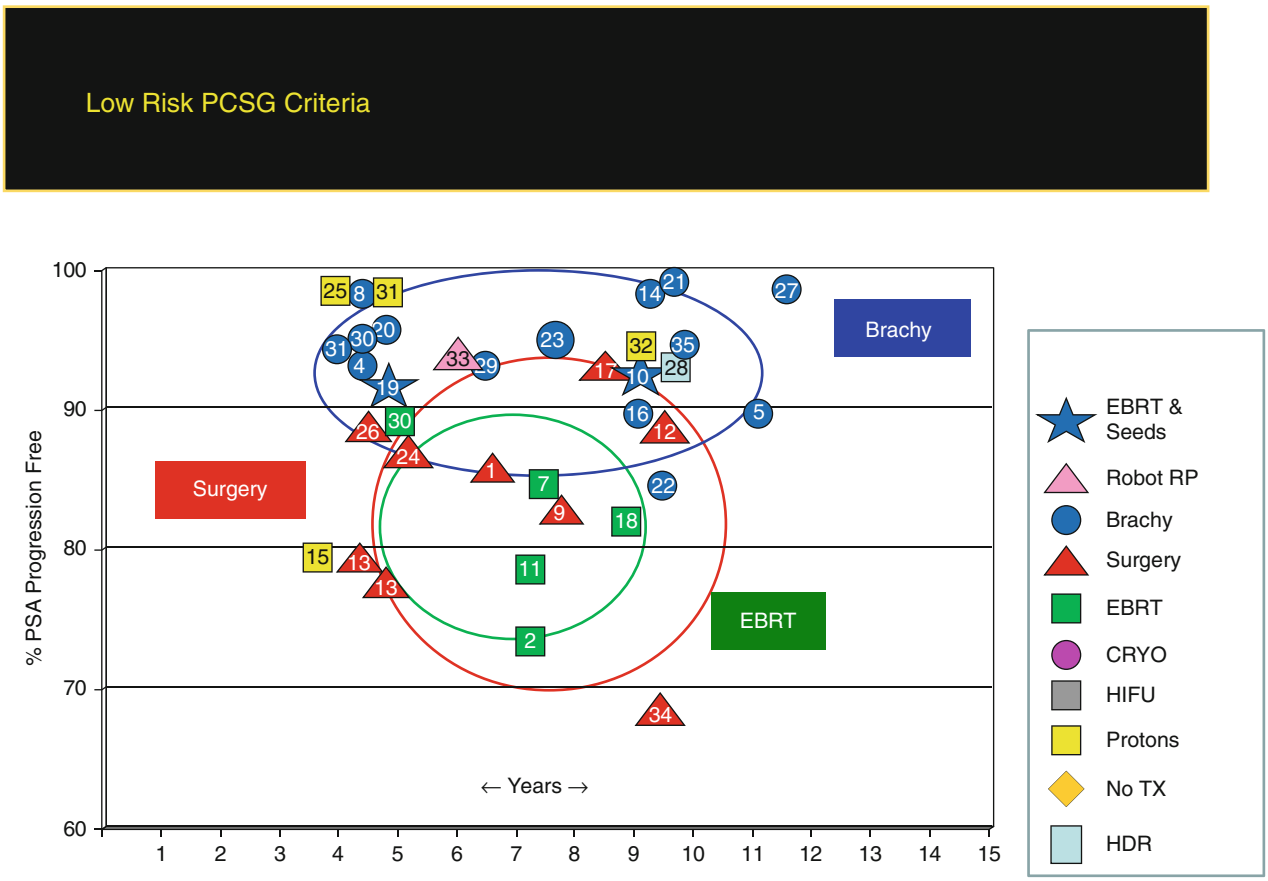


**Fig. 61.1** Prostate cancer results study group: low-risk comparison, which met criteria. Numbers within symbols refer to references

(see Fig. 61.1). PPB combined with EBRT is generally unnecessary in low-risk patients. ADT has not been shown to improve cancer control rates in low-risk disease and is used only for the purpose of prostate downsizing [31].

The rationale for monotherapy in the low-risk group is the pathological findings of a high likelihood of organ-confined disease and disease within a close margin of the gland [17, 18, 39]. An exception to using PPB monotherapy in low-risk patients may involve patients with a high percentage of positive biopsies. D'Amico demonstrated that in low-risk patients undergoing radical prostatectomy, who had a high percentage of positive biopsy cores, there was a significantly higher biochemical failure rate than those with a low percentage of positive biopsy cores, suggesting a greater risk of significant EPE in this group [19]. However, this has not yet been determined as an independent risk factor in PPB.

## Intermediate Risk

Intermediate-risk patients are usually defined using the D'Amico system (Gleason score of 7 *or* PSA of 10–20 or cT2b disease or higher by clinical examination) [40].

The Intermediate risk group is associated with greater risk of extraprostatic extension (EPE), seminal vesicle invasion (SVI) or occult lymph node involvement than the low-risk group and therefore local failure after surgery [17, 50]. However, some intermediate-risk patients may be effectively treated with PPB monotherapy, without supplemental EBRT or ADT [31, 35, 41, 43]. At present, the use of monotherapy or combined EBRT and seeds is a judgment call based on the histological prediction of EPE and the confidence that monotherapy can treat a sufficient treatment volume. The ongoing RTOG clinical trial 0232, which randomizes men with favorable or intermediate-risk disease to PPB monotherapy or PPB combined with EBRT, is attempting to sort out the issue. Most centers differentiate between a low intermediate and a high intermediate risk group based on number of cores involved.

### Histological Rational of Monotherapy Versus Combined for Intermediate-Risk Disease

PPB monotherapy for intermediate-risk disease recognizes that the addition of external beam radiation is adding only a slightly larger volume to the treatment (i.e., the seminal vesicles), which may be of limited value for many intermediate-risk

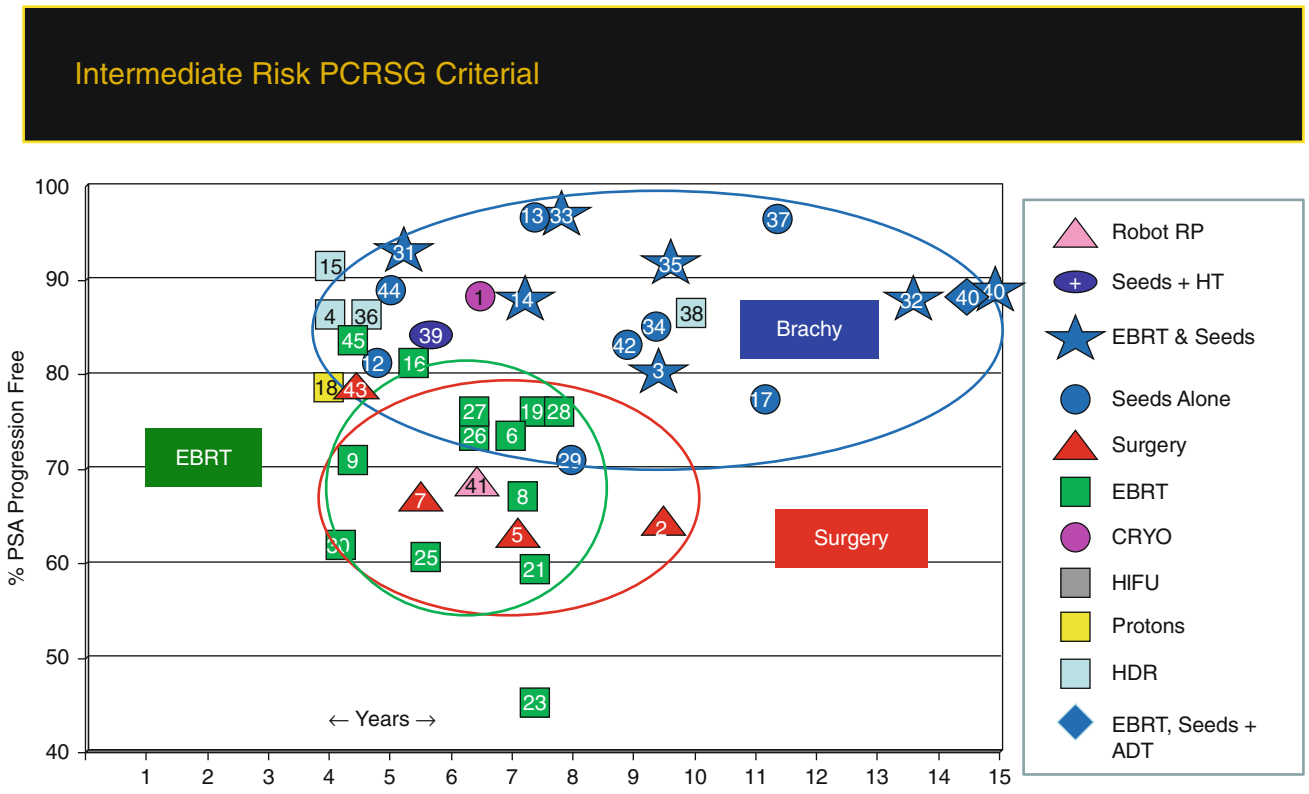


**Fig. 61.2** Prostate cancer results study group: intermediate-risk comparison, which met criteria. Numbers within symbols refer to references

patients. Seminal vesicle involvement is primarily a direct spread issue from the base of the gland. If there is no base involvement or a low percentage of biopsies positive, the likelihood of seminal vesicle involvement is also likely low and therefore will minimize the benefit of EBRT. The radial distance of spread, primarily in the postero lateral region has been measured [21, 39]. Only a small percentage of patients with clinical organ confined CaP manifest microscopic disease beyond 5 mm. Seed implantation, particularly with connected seeds and other techniques can easily cover a margin of 5–10 mm [10]. In addition, the radiation dose beyond the margin of an implant is also likely tumoricidal for an additional distance.

### Clinical Results Rationale for Monotherapy Versus Combined for Intermediate-Risk Disease

Taira, Merrick et al. demonstrated that an excellent 12-year biochemical control rate of 96 % at 12 years could be achieved in intermediate-risk patients with PPB alone [35]. A clear pattern of benefit for EBRT in this group is not apparent (Fig. 61.2). Because of the controversy in deciding for combined treatment in this group, Frank, Grimm et al. conducted a patterns-of-care survey of 18 brachytherapy expert practitioners. This survey demonstrated that percentage cores were a large factor in experts selecting for combined treatment and that patients with percentage cores above 33 % in the intermediate group were more likely to receive a recommendation for combined therapy. [43] (Detailed results of the survey can be requested at peter@grimm.com.) The bottom line is that until long-term follow-up of randomized controlled clinical trials are available, intermediate risk patients should be considered for PPB monotherapy, but as the extent of disease increases, consideration should be given for combined EBRT (prostate and SVs) and seeds.

## High Risk

### Histological and Clinical Evidence for Combined Treatment

Patients with high-risk features (D'Amico: PSA >20, GS ≥8, or stage >T2c) are known to have a substantial risk of EPE, often beyond the range of surgery and likely a PPB implant and therefore would be histologically predicted to have a high likelihood of failure with PPB alone [17, 40–43]. Reported results of PPB monotherapy or prostate only therapies for high-risk disease reveal generally poorer outcomes compared to combined approaches (Fig. 61.3). Several studies have demonstrated an improvement in cancer control rates with the use of ADT in combination with EBRT and Seeds [46, 47]. Merrick et al.

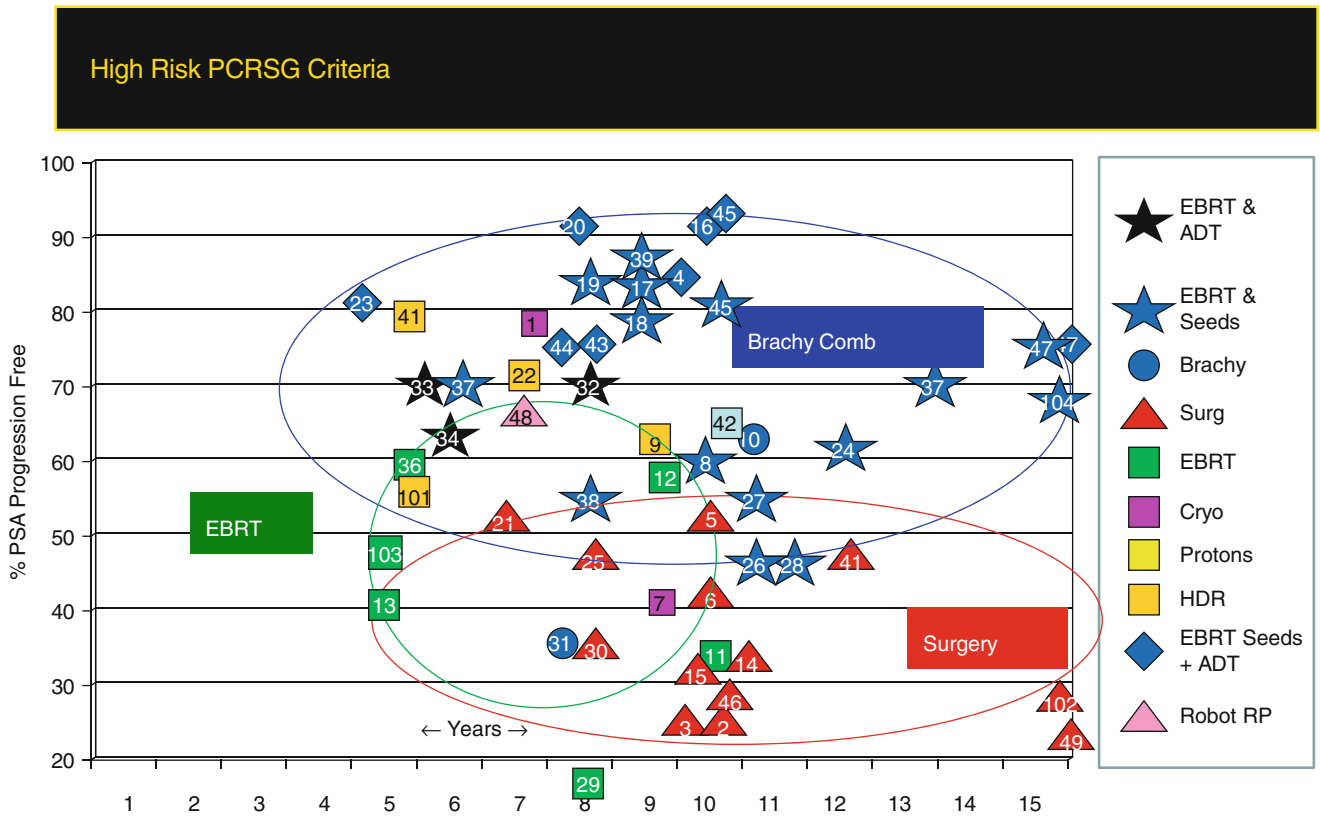


**Fig. 61.3** Prostate cancer results study group: high-risk comparison, which met criteria. Numbers within symbols refer to references

reported no improvement in cause-specific and overall survival with ADT seeds and EBRT for high-risk disease but did show improvement in 10-year biochemical progression-free survival [31]. The increased radiobiological effective dose possible with combination EBRT and seeds may also play an important role. Stone et al. demonstrated improved overall and metastasis free survival for patients with Gleason score 8–10 if a greater biologically effective dose was delivered (Fig. 61.3) [48]. Therefore, it is considered standard that if PPB is considered, it be combined with EBRT plus or minus ADT in high-risk patients.

### Seminal Vesicle Invasion (SVI)

SVI increases with stage grade and PSA and typically involves the proximal portion adjacent to the base of the prostate [17]. This region can be encompassed within the range of a typical PPB implant; however, this can be a technical challenge and difficult to reproduce [10]. The seminal vesicles are included in an EBRT field in high-risk patient, and therefore any value of including them in the implant volume is unknown in this group. Most centers will attempt to include the proximal portion of the SVs in the implant volume to insure sufficiently high doses are received to this region.

## Technique

### Dosimetry

*Isotope Selection*: I-125, Pd-103, Cs-131

I-125 and Pd-103 have been shown to have excellent long-term outcomes. No advantage has been demonstrated for one or the other [52]. Cesium-131 was introduced in 2004 for PPB and is being investigated in multiple clinical trials. The half-life for I-125 (60 days), Pd-103 (17 days), and cesium (9.7 days) may have practical implications for individual situations. Our center has used Pd-103 for higher grade tumors (8–10) and I-125 for moderate grade (5–7).

### Doses and Activity: Seattle

#### Monotherapy

| Isotope | Dose (Gy) | Activity (mCi) |
|---|---|---|
| I-125 | 144 | 0.30–0.40 |
| Palladium-103 | 125 | 1.3–1.5 |
| Cesium-l3l | 115 | 2.78–3.68 |

**Combination**

| Isotope | Dose (Gy) | Activity EBRT |
|---|---|---|
| I-125 | 110–125 | 0.25–0.30, 45–50.4 Gy |
| Palladium-103 | 90 | 1.0–1.2 mCi, 45–50.4 |
| Cesium-l3l | 84 | 2.3 mCi, 45–50.4 Gy |

## Seed Activity and Total Activity

Presently, there is no consensus regarding optimal seed activity, seed number, or total activity. An analysis by Aronowitz et al. of implant activity for PPB among several institutions found that total activity as a function of volume varied by 25 % for large prostates and 40 % for small prostates [53]. Excellent dosimetry can be achieved with varied activities. In the RTOG clinical trials, seed activity has been specified at 0.23–0.43 mCi/seed, for I-125 and 1.0–2.0 mCi/seed for Pd-103 [49]. In an ongoing CALBG trial [54] seed strength for PPB combined with EBRT was similar to the RTOG trials, but 0.8–1.0 mCi for Pd-103. Total activity implanted is a function of prostate size and shape, as well as treatment margin, implant techniques and dosimetry philosophy of the physicians.

## Source Distribution Philosophy

Clinical studies comparing dosimetric philosophies are lacking. Most centers follow a modified uniform (Seattle approach) or modified peripheral loading of seeds [8, 11]. Modified uniform loading or modified peripheral loading philosophies have distinct advantages over pure uniform or pure peripheral loading patterns. These advantages can be summarized as follows:

1. They are technically feasible while still achieving dosimetric goals.
2. High urethral doses are avoided.
3. Provide for placement of extraprostatic seeds.
4. Avoid high rectal doses.

## Preplan Versus Intraoperative Planning

Proponents of either intraoperative and preoperative planning are typically passionate in their belief of their system. Some centers have documented difficulties in achieving excellent postoperative dosimetry with the preplan technique, yet have done well with the real-time technique. Sylvester, Grimm et al. reported on 1,131 consecutive patients using a preplan, preloaded needle approach. Dosimetric outcomes with day 1 dosimetry demonstrated excellent coverage of the prostate in 1,130/1,131 patients with no rectal overdoses (RV 100 > 1.0 cc) [55]. Learning curve effect, quality of the preplanning TRUS volume study or individual physician strengths or weaknesses in performing in the operation room likely affect outcomes more than a true technique effect. Postimplant quality assurance evaluation programs are essential to evaluate technique and planning philosophies. Post-op CT or MRI for postoperative dosimetry are considered mandatory [56]. D90, which is the isodose enclosing 90 % of the prostate, and V100 correlate with biochemical outcome and should be included in the posttreatment analysis [56].

## Sequencing of EBRT and PPB

External beam radiation may be delivered either pre- or postimplant. Delivering PPB first, followed by EBRT, exposes tissue to small amounts of simultaneous radiation but to date has not increased normal tissue toxicity. Performing an initial PPB can also allow assessment of the implant such that the EBRT dose may be adjusted if necessary. In Seattle, sequencing is currently based on the convenience of the patient. A 2–4-week interval between external beam and seed implantation is generally recommended if EBRT is given first followed by either I-125 or Pd-103 implant. If an implant is first performed, Pd-103 is prescribed to insure adequate degradation of dose, and the external beam is started 6–8 weeks later.

## Transrectal Ultrasound Volume Study

A high-quality TRUS at 5 mm transverse images from base to apex is performed either preoperatively or intraoperatively to allow for accurate dosimetric planning. A clear sagittal image that simultaneously shows the base and the apex is obtained in order to measure the midsagittal length of the prostate. This allows for an accurate determination and validation of the correct number of seeds in each centrally placed preloaded needle. The total number of images obtained equals the length of the prostate in centimeters times 2, plus 1. For example, a 4.0-cm-long gland should produce 9 ($4 \times 2 + 1$) transverse images.

### Quality Images

Image distortion can occur with undo probe pressure on the prostate. A gel-filled condom is typically inadequate to fill the rectal cavity as the gel is pushed to the exterior. Several of the commercial, water-filled condoms can provide adequate contact with the rectal surface to obtain good, consistent images without distortion.

## Pubic Arch Evaluation

The angle of the TRUS probe is usually set at 10–15° to insure avoidance of pubic arch interference and also avoid

the posterior row being too close to the rectal wall. Pubic arch interference (PAI) can be evaluated during the TRUS by scanning the best pubic arch image caudal to the apex. The arch can be outlined on the ultrasound monitor (with a dry-erase marker) and compared to the largest midgland image for interference. Alternatively, a hard copy outline of the arch is made and transferred to a clear plastic overlay, which is then superimposed on each transverse image. If significant interference exists, it may sometimes be overcome by altering the ultrasound probe angle to a flatter, lower, angle or if necessary, by shrinking the prostate with short-term hormonal therapy. After the images are obtained, the target volume is drawn by the radiation oncologist for dosimetry planning.

## Target Volumes

Target volumes include the prostate plus a margin. A target volume larger than the prostate at the base and apex is necessary to allow satisfactory dosimetry coverage of those regions as well as for EPE and for slight prostate or seed movement. Extraprostatic extension (EPE) is common and usually <3 mm. Expert centers draw a 5–10-mm postero lateral margin in the area of the neurovascular bundle (NVB) in all patients as radical prostatectomy specimens have demonstrated significant extracapsular extension occurring at or near the NVB [21]. Margins are typically approximately 2 mm posteriorly and 2–5 mm anteriorly at the dorsal venous plexus. At the apex and base, the margins are typically a minimum 5 mm in all directions.

## Preplanning (Seattle Technique)

The dosimetry process involves creating a preplan that is simple and easy to execute in the O.R. Since slight seed movement will occur in every case, we plan to bracket a region which on original plan calls for one seed, with two or more seeds. The plans are typically symmetrical, right and left mirror images. Special loading with a reduced number of seeds in the few periurethral needles helps to avoid overdosage to the urethra. While the rectal dose cannot be accurately determined preoperatively because of the ultrasound, postanalysis of technique and preplan adjustments to future implants is therefore critical.

The combination of planning from an undistorted TRUS, a symmetrical plan that limits the number of needles, an approximately 5-mm PTV (posterolaterally), and higher numbers of lower activity seeds creates a preplan that is easy to reproduce in the O.R and is forgiving for slight seed movement.

This modified uniform planning philosophy is robust enough that minor/moderate adjustments or changes in needle position in the O.R. will not negatively affect the quality of the patient's postimplant CT dosimetry. Of note is that moving the periurethral needles from the preplanned positions of c3 to C3 and d3 to E3 will keep the mean apical urethral dose well under 150 % of prescription dose without lowering the V100 or D90.

## Implant Procedure: Seattle Technique

Anesthesia can be spinal or general. We typically perform light general anesthesia at our Ambulatory Surgical Centers (ASC) in Seattle. Following anesthesia, the patient undergoes a perineal prep and then ~200 cc of sterile water is instilled into the bladder. This expands the bladder and improves the contrast and visualization between the base of the prostate and the bladder. A 16 french red robinson catheter (cut in middle) is attached to a syringe filled with aerated surgical lubrication jelly and then is inserted a short distance into the membranous urethra. This aerated jelly is injected periodically to visualize the urethra.

The transrectal ultrasound probe is inserted into the rectum at the same angle and with the same pressure as during the TRUS volume study. In transverse imaging, the prostate is aligned in the center of the grid and the base and apex identified and the length double-checked and equipment stabilized. The template grid is secured 2–4 cm from the perineum and image position again confirmed from base to apex.

Preloaded needles are inserted into the prostate one row at a time beginning with the anterior coordinates. The row of needles stabilizes the gland and insures correct seed to seed spacing. A transverse image, 1.0 or 1.5 cm from the prostate base, is used for initial targeting during these needle insertions. Insertion at midgland allows easier identification of the needle, avoids bladder trauma, and allows for quick recognition of prostate drift (due to small amounts of swelling and/or bleeding).

The needles are inserted into their preplanned transverse coordinates and confirmed as to depth, using the sagittal image. Needle positions are also verified by measuring a reference length from the template to the hub of the needle. A urethrogram of aerated gel/H20 is used to identify and avoid the urethra. The depth can be determined in the transverse plane by rotating the bevel of the needle creating a "flip sign" at the planned insertion in which the needle tip can be seen to turn. The reference depth can be established (a ruler measurement from the template to the needle hub) and may be used later if the needle tip visualization is difficult.

With the tip visually at the proper depth, the reference depth is verified prior to deploying to seeds, and the distal seed advanced to the bevel of the needle. The stylet needs to be advanced to a length equal to the number of seeds in

centimeters. For example, the stylet hub in a needle with four seeds will extend approximately 4.5 cm from the needle hub and will need to be advanced to approximately 4-cm extension prior to insertion of the seeds to insure that the distal seed is at the bevel at the time of implantation.

With each row, the ultrasound grid position and seed positions are confirmed so that the prostate's position within the grid matches its preplan position and any seed misplacement noted. The linked or stranded seeds orient horizontally and are easily seen on ultrasound imaging.

The periurethral needles are positioned 3–5 mm from the urethra, which is visualized with the aid of aerated surgical lubrication jelly.

### Rectal Prostate Interface

Minimizing high rectal doses requires attention to needle placement at the rectal prostate interface. The needles in the posterior row are placed approximately 2–3 mm within the gland. The posterior needle position can be checked on both transverse and sagittal imaging. If the needle is too close the rectum at the apical region, we insert the needle in a coordinate 0.5 anteriorly to the planned target and direct the needle to its target. This minor needle position change will limit the RV100 to <1.0 cc without any underdoses of the posterior wall of the prostate.

### Seed Position Verification

Evaluation of seed position is done at the end of each row placement and at the completion by a fluoroscopy. A repeat, overall ultrasound survey from base to apex to can help identify any potential "cold" areas. Extra seeds are very rarely required with connected seeds. Cystoscopy is recommended in our opinion as we have found an occasional bladder tumor, stones or large clots.

### Post-op Procedures

Postimplant radiation exposure measurements are taken in the OR. These measurements are of the radiation exposure at the anterior pelvic surface and at 100 cm from the patient's surface. The OR room, including staff, Foley catheter, and drainage bag, is surveyed to avoid loss of radioactive seeds. A 3-way catheter is placed for bladder irrigation and removed in the recovery when the anesthesia is resolved. The catheter is removed prior to discharge from the ASC that day. In Seattle, we perform the post-op dosimetry CT scan the following day. Some centers perform this at day 28.

### Postoperative Dosimetry Evaluation

CT-based postoperative dosimetry is considered minimal QA for all patients regardless of whether the implant is pre- or intraoperatively planned and should be performed within 30 days of the implant [56]. CT scans can overestimate the size of the prostate make contouring the gland difficult. The use of MRI fusion studies to do dosimetry is being done in some centers [57]. A variability in postimplant CT contouring of the prostate can occur even within centers, which results in differences in computed doses to the prostate. Timing of the dosimetry should be consistent as postimplant CT edema will change with time and will produce differing dosimetry results. In Seattle, we match the preoperative TRUS to the CT images and use the ultrasound image to contour the gland on the CT. While this is not completely accurate because of prostate swelling, it can be consistently performed and understood. Serial CT scans show continual shrinkage of the gland over time with 28 days agreed upon as a reasonable time to perform the dosimetry.

### Quality Assurance

Postoperative dosimetry provides important immediate feedback. It should include V100, V150 isodose curves superimposed on the prostate as well as recorded D90, RV100, and urethral doses [56]. Stock et al. [58] documented better bRFS in those patients treated with I-125 monotherapy who received a D90 of greater than 140 Gy, than those with a D90 less than 140 Gy. Potters et al. [59] reported significantly better bRFS in monotherapy PPB (I-125 or Pd-103) patients who achieved a postoperative D90 of greater than 90 %. Grimm and colleagues showed that later technique Seattle $I^{125}$ monotherapy patients treated after 1987 and having sufficient DVH analysis achieved significantly better bRFS than $I^{125}$ monotherapy patients treated at the same institution, by the same physicians, in a earlier group from 1985 to 1987 [60]. Penile bulb doses are also being recorded because of the possible relationship to potency [61, 62]. Significant intraprostatic "cold spots" can be addressed with supplemental EBRT, HDR, or further strategically placed seeds at a second PPB procedure. QA should involve periodic evaluation of potential trends in either dosimetry planning or technique, which may affect cancer control or complications.

## Dosimetric Goals

### Cancer Control

The goal of prostate brachytherapy is to achieve biochemical control while avoiding overdosage of critical surrounding structures. To date, multiple studies have shown excellent correlation of postoperative dosimetry and bRFS. High-quality implants, as documented by D90 of greater than 90 % of prescription dose or >140 Gy for $I^{125}$ monotherapy implants, or by a V100 of >80 % or 90 %, correlates well with bRFS [16, 58, 59]. Centers should strive for 100 % achievement of these goals.

### Dose and Complications

The incidence of radiation proctitis increases as the rectal volume receiving 100 % of the prescribed dose (RV100)

increases, especially >1.0 cc on day 1 dosimetry and >1.3 cc on day 30 post-op dosimetry. The current goal is to achieve a consistently low RV100 on postoperative dosimetry in order to minimize the incidence of radiation proctitis. Modern implants on 1,131 consecutive patients performed by Blasko, Grimm, and Sylvester from 2005 to 2007 resulted in only 3 patients with D90 <87 % prescription dose and zero patients with an RV100 >1.0 cc on day 1 dosimetry. Thus, consistently excellent quality implants are achievable [63].

## Results

### Comparative Work of Prostate Cancer Results Study Group

The majority (75–80 %) of patients diagnosed today are of low risk and have favorable long-term results with most modalities. There is only one small, randomized trial comparing results among these modalities [64]. Multiple reported endpoints makes comparisons difficult and confusing. For example, since prostate cancer has a long natural history, the use of any survival endpoint is much less sensitive to the therapeutic effectiveness than biochemical control and makes a therapy look better or equal to another treatment. Biochemical relapse-free survival (bRFS) is considered the most sensitive endpoint for therapeutic effectiveness. The ASTRO definition (three consecutive PSA rise) of biochemical failure has been largely replaced by the Phoenix definition (PSA of nadir +2) as a measure of failure [65].

### Results: Low Risk

Figures 61.1, 61.2, and 61.3 [31–33, 42, 71–101] are a comparative analysis of all treatment studies from 2000 to 2010 that meet the Prostate Cancer Results Study Group criteria for comparability. A panel of 25 experts in all disciplines established the following set of criteria to allow for comparison of these largely retrospective studies [169]:

1. *Patients must be stratified into recognizable pretreatment-risk groups*: low, intermediate, and high risk by either D'Amico, Zelefsky, or NCCN stratification
2. *bRFS standard endpoint ASTRO*, *Phoenix*, *and PSA <0.2* (*surgery*)
3. *Clinical Staging No exclusions*: i.e., no pathologic staging
4. *All Treatment modalities considered*: *seeds*, *surgery*, *IMRT*, *HIFU*, *Cryo protons*, *HDR*
5. *Accepted results*: *peer reviewed journals only*
6. *Low-risk accepted minimum number 100 pts*
7. *Intermediate-risk accepted minimum number 100 pts*
8. *High-risk accepted minimum number 50 pts*
9. *Minimum median F/U*: *5 year*
10. *EBRT must be minimum 72 Gy IMRT/conformal*

The graph (Fig. 61.1) demonstrates an interesting range of results for the primary modalities and warrants close inspection. Overall approximately 80 % of patients in the low-risk group do well with any therapy. Brachytherapy as monotherapy consistently results in bRFS rates long-term of over 90 % in a fairly narrow range of 85–90 %, while surgery has an average of approximately 82 % with a wider range from 68 to 92 %. Proton studies are limited but promising to achieve good long-term results. The single long-term proton study from Zietman et al. demonstrated a 93 % long-term control [66]. High dose IMRT (81 Gy) as reported by Zelefsky et al. demonstrated an 89 % 7-year bRFS and 81 % 10 year in this group [28, 69]. The long-term Seattle experience with $I^{125}$ monotherapy evaluated 125 low-risk patients consecutively treated from 1988 to 1990 with $I^{125}$ implant to a dose of 144 Gy (TG-43). The average follow-up of the non-deceased patients was 94.5 months. The 15-year metastatic disease-free rate was 97 % and bRFS 85.6 % [70].

### Results: Intermediate-Risk Group

The Intermediate-risk group constitutes a diverse histologic group because of the predictive risk of extraprostatic disease varies widely in this group, making results subject to possible significant variables. However, these patients are more likely to have more disease and a higher likelihood of extraprostatic extension than low-risk patients [17]. Therefore, strategies need to address local and extraprostatic disease to maximize control rates.

PPB as either monotherapy or combined therapy in the intermediate risk group appears at least oncologically equivalent to external beam radiation or surgery (Fig. 61.2) [42, 85, 86, 102–122]. Theoretically, the high intraprostatic dose delivered by brachytherapy increases the local cancer control rate over EBRT, and the coverage of extraprostatic disease covers the disease beyond the gland. Long-term studies have demonstrated consistency among centers in achieving average rates of control in intermediate risk of approximately 85 % with PPB, either as monotherapy or combined with external beam radiation (Fig. 61.2). As previously discussed, the decision to add EBRT to PPB in the intermediate group is controversial. The rationale for EBRT is to deliver a wider area of treatment, which cannot be performed with an implant alone. The use of connected seeds has allowed for treatment volumes with monotherapy to be very similar to combined treatment, with the exception of the seminal vesicles. An increased risk of seminal vesicle involvement may therefore be the primary reason to add EBRT in this group. In the Seattle, 15-year study intermediate-risk patients experienced a 15-year bRFS of 79.9 % with combined treatment [70].

## Results: High Risk

In the D'Amico classification system, patients with high-risk disease are defined as PSA ≥20 ng/ml, *OR* > T2c or greater, *OR* Gleason score >7 or PSA 10–20, GS ≥7 Stg ≥ cT2 (2 or more factors) by Zelefsky criteria. Literature reports are somewhat varied, with selected groups within the high-risk category evaluated. Patients with high-risk disease are predicted by the Partin tables and other predictive models to have a very high risk of disease beyond the prostate and histologically would not be predicted to do well with local therapy alone [17]. An analysis of reported results (Fig. 61.3) [35, 42, 44, 45, 48, 67, 93, 98, 103, 109, 116, 118, 123–168, 170] lends support to this concept, as treatment with surgery alone or seeds alone have failure rates of 50–80 %. To date, there are no studies, which preoperatively identified "good" high-risk patients who could be good candidates for local treatment alone. Nguyen et al. [20] from the Cleveland Clinic demonstrated that for whatever definition and for whatever era of radical prostatectomy, the patients failed at a rate of 60–80 %. In our small Seattle monotherapy implant series of high-risk patients, the 5-year bRFS was 65 % [37].

More studies are now demonstrating that combined treatments utilizing EBRT and seeds with or without hormonal therapy (HT) have improved cancer control rates over other therapies (Fig. 61.3). The results with aggressive combined therapy (EBRT, seeds, and HT) are likely influenced by grade. Stock and Stone evaluated 181 men with high-risk disease, all having a Gleason score of 8–10. Treatment consisted of 3 months of an LHRH agonist followed by a 100 Gy 103-palladium implant. Two months later, external beam radiotherapy of 45 Gy was given covering the prostate with margin and the SVs, and, if positive, the pelvic nodes. The total duration of HT was 9 months. The 8-year recurrence-free survival was excellent for Gleason 8 (84 %), but worse for GS 9 (55 %), and for GS 10 (30 %) [67]. At present, combination therapy for high-risk disease is considered standard if permanent seed implantation is considered.

## Side Effects

### Short Term

Almost all patients have short-term side effects after permanent seed implantation. Acute postoperative side effects are common and are primarily RTOG grade 1–2 irritative and obstructive lower urinary symptoms, including increased urinary frequency, urgency, and weakening of the urinary stream [170]. Initially patients have dysuria for the first urinations. Severe bleeding requiring transfusions or admission to intensive care for any postoperative acute events and/or death have not been reported. Acute urinary retention rates are low typically ranging from 3 to 10 % [208]. Several factors have been implicated in single institution, univariate analysis, including large gland size, high pretreatment urinary symptom score, and pretreatment with androgen ablation. On multivariate analysis, most of these risk factors drop out or are not reproducible between various institutions.

Alpha blockers are routinely started a few days prior to the implant and continue until urinary obstructive symptoms subside. The primary effects for the next 6 months are frequency and urgency reaching a peak at approximately 2 months and then gradually decreasing over the next 12 months. In the small percentage of patients that experience retention of more than a few weeks duration, self catheterization is taught or a suprapubic catheter is placed until the swelling and retention spontaneously resolves. If retention does not resolve, surgical intervention with a transurethral urethrotomy (TUIP) or a minimal TURP is usually indicated. It must be emphasized that these procedures should not be performed until at least 9 months (preferably >12 months) after PPB due to risk of incontinence. Occasionally a staged procedure can minimize risk of incontinence.

A temporary increase in bowel frequency and urgency occasionally occurs and usually responds to diet modification or antidiarrheal medications. Hematuria and hematospermia is to be expected for at least a few days following PPB. One third of the sexually active patients will experience some level of pain with orgasm; this can persist for weeks to months, is usually mild, and typically responds to nonsteroidal anti-inflammatory drugs (NSAIDS). The prostatic and seminal vesicle fluid components (~90 %) of the ejaculate will decrease dramatically following PPB, but sperm can still be present. Whether or not the sperm is significantly damaged by the radiation exposure is unknown, but birth control measures are recommended for those couples that are still fertile. Ejaculation of a seed is rarely reported. The Seattle team is aware of less than five patients that have noted this event over the past 15 years. In our Seattle experience, of over 10,000 PPB procedures, there have no serious intraoperative or postoperative morbidity (infections) and no mortality.

### Long Term

Studies reporting side effects using a validated questionnaires and results prospectively and from a patient's starting point are rare. Most studies lump large groups of disparate functional starting points and use nonvalidated questionnaires.

Chen et al. [68] evaluated, in a 3-year prospective study, the results from nerve sparing RP, non-nerve sparing RP, EBRT, and brachytherapy. The findings are summarized in Fig. 61.4. These figures reflect a normal starting point. A full slide set can be requested from peter@grimm.com.

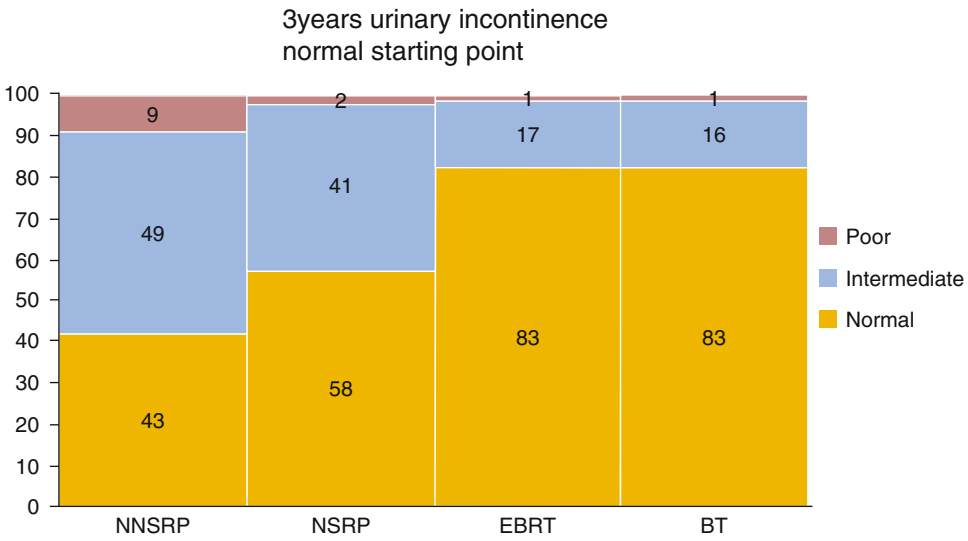


**Fig. 61.4** Urinary incontinence normal starting point for nerve sparing, non-nerve sparing external beam radiation, and brachytherapy [68]

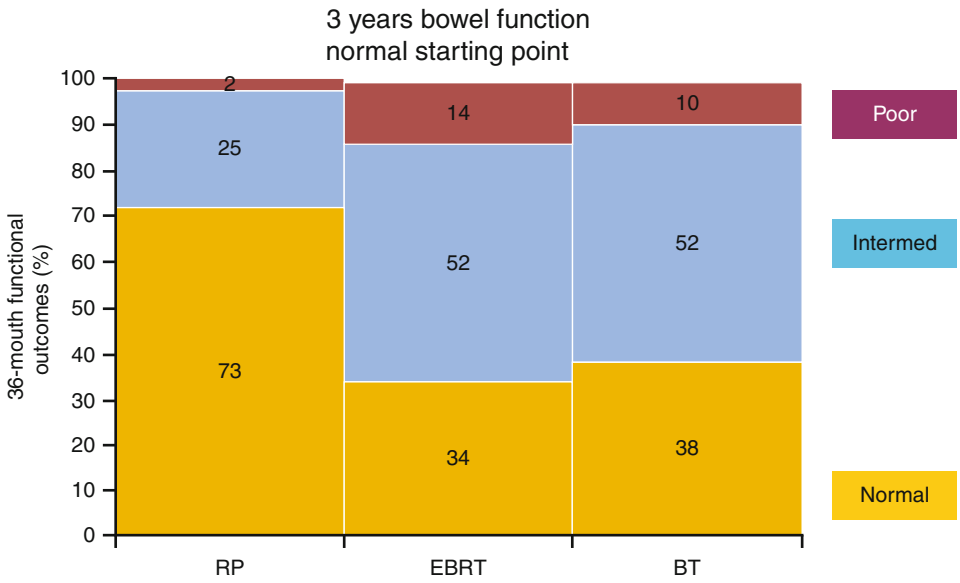


**Fig. 61.5** Bowel function normal starting point for nerve sparing, non-nerve sparing external beam radiation, and brachytherapy [68]

## Incontinence

Incontinence rates after PPB are low. Less than 1 % of our patients require a pad for any reason. Long-term approximately 15 % of patients will describe leaking a few drops (Figs. 61.4 and 61.5) but not requiring a pad.

## Bowel Function

Chronic or delayed minor rectal bleeding due to rectal changes from the implant occurs in a 2–10 % incidence. Studies have suggested that rectal bleeding may be reduced if the RV100 is kept below 1.0 cc. This "proctitis" may be managed with maintaining a soft stool, steroid suppositories, and sucralfate enemas. Additional measures for more persistent bleeding include formalin and hyperbaric oxygen. Significant rectal bleeding should be investigated with colonoscopy or flexible sigmoidoscopy. Biopsy or, electrocautery of the anterior rectum following PPB should not be done, due to risk of creating a rectal-urethral fistula. In Seattle, we recommend colonoscopy be performed prior to all PPB treatments [10].

## Bladder Symptoms

Chronic bladder complications include cystitis and overactive bladder. These occur with ~2 % incidence and can be managed with medications. Late urinary retention due to urethral stricture occurs with a 5–10 % incidence. This can be corrected in ~90 % of patients with dilation or urethrotomy.

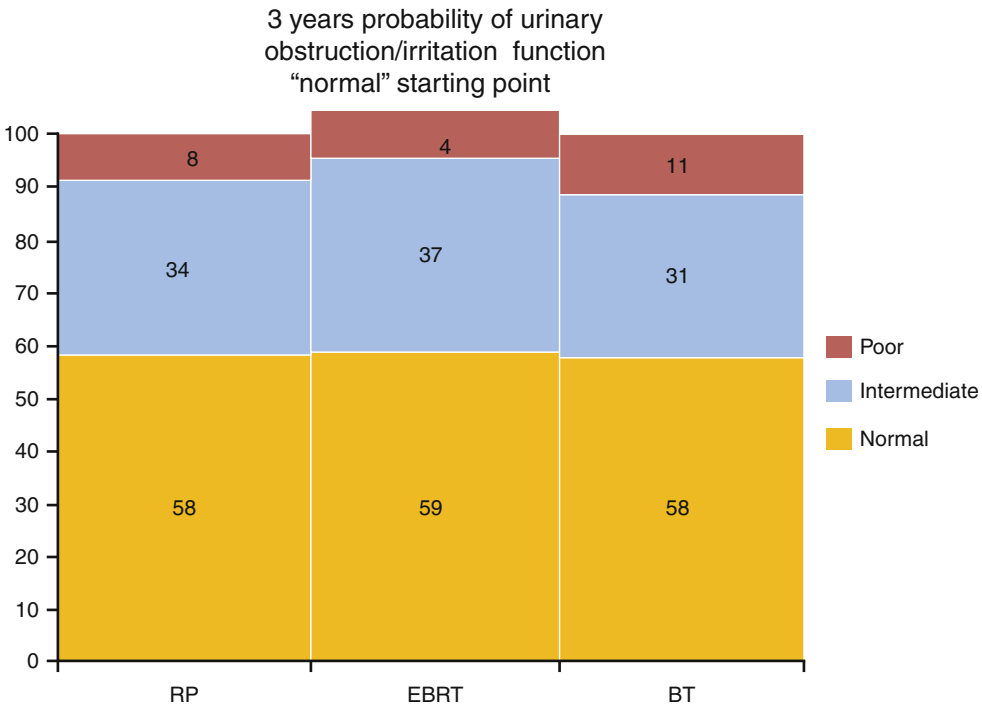


**Fig. 61.6** Obstruction, irritative status normal starting point for nerve sparing, non-nerve sparing external beam radiation, and brachytherapy [68]

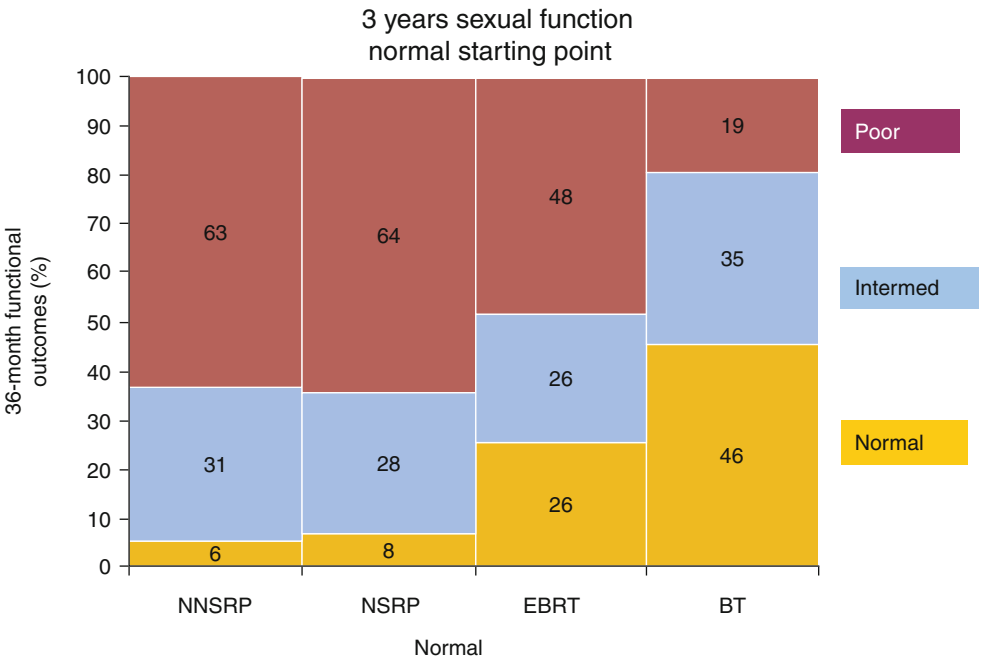


**Fig. 61.7** Sexual function normal starting point for nerve sparing, non-nerve sparing external beam radiation, and brachytherapy [68]

The problems of urinary obstruction or irritation occur in approximately equal frequency among therapies (Fig. 61.6).

## Erectile Dysfunction

Erectile dysfunction (ED) analysis after any prostate cancer treatment is difficult to interpret because of multiple factors, including the subjectivity of patient questionnaires, reliability of patients answering the questions, the age and health of the patient pretreatment, and the functional starting point of the patient. Most studies show surgery to result in significantly higher rates of erectile dysfunction than brachytherapy treated patients, despite the younger age of surgical patients. Chen, Talcot et al. have one of the few prospective studies comparing results (Fig. 61.7). Eighty-one percent of PPB patients with a normal starting point maintained their erection ability either naturally or with the

use of PDE-5 inhibitors. Young age may also have some effect. Ceasaretti and Stock reported on patients who were in their 50s at time of PPB and had a pretreatment SHIM score of >20; 92 % maintained the ability for erections adequate for intercourse 7 years after PPB. Although, data from EBRT-treated patients suggests a penile bulb dose related effect, but this is not completely clear for PPB. Despite this, care is taken to avoid high doses to the penile bulb. Rehabilitation programs, which include frequent erections and liberal use of PDE-5 inhibitors, are recommended at our center to attempt to improve function.

### Second Malignancies

The incidence of second malignancies after PPB is low. Our group reported on 10-year follow-up on this topic. There was no increase in secondary malignancy when PPB monotherapy was used when compared with age-matched cohorts; a small increase was associated with those receiving combination EBRT and PPB.

## Future Directions

The intermediate-risk group will need to be stratified further to allow for more directed care and resolve the issue of requirement for monotherapy or combined treatment. Improvements in postoperative dosimetry are exploring MRI techniques to better identify seeds as well as to accurately delineate anatomy. Frank et al. have recently described an MRI identifiable marker designed to facilitate seed identification on MRI. Efforts are currently underway to reduce urethral strictures by modifying the seed distribution. Our center and others are also evaluating the use of thinner needles and seeds. This new seed is 40 % thinner than the standard seeds currently in use and fits into a 20 gauge needle instead of an 18 gauge needle. In our initial analysis, these 20 gauge needles have been demonstrated a lower risk of bleeding and pain than the 18 gauge needle and a low risk of urinary retention of 3–6 %. The effect on dosimetry and on erection ability is also being studied [169].

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# Prostate Brachytherapy: High Dose Rate

62

Carl Salembier and Peter Hoskin

## Introduction

Prostate cancer is the most common male malignancy in the Western world. Over the past decade, a significant shift has taken place in stage at diagnosis, with most patients now presenting with localized disease. Options for treatment include radical prostatectomy and different radiation modalities including external beam radiotherapy, low-dose-rate brachytherapy with permanent seeds or high-dose-rate brachytherapy.

Evidence exists that radiation therapy for localized prostate cancer needs to deliver higher than conventional (64–70 Gy) doses in order to increase biochemical and local control [1–6]. As confirmed by Zelefsky et al. in a recent study, local failure is of clinical importance as a direct relationship between local control, distant metastases, and survival has been demonstrated. Especially in high-risk patients, the risk of distant metastases decreased with higher radiation doses [7].

The administration of higher than conventional doses to the prostate requires specialized radiation solutions in order to avoid major toxicity. With exclusive external beam radiotherapy, the solution can be searched in the use of intensity-modulated radiotherapy (IMRT). However, even the most sophisticated external beam solution still results in delivery of significant radiation doses to the adjacent (normal) tissues. Interstitial brachytherapy consists of the insertion of radioactive material directly into the target. This can be done using either a permanent seed implant (palladium-103 or iodine-131) or using temporary implants with a remote high-dose-rate (HDR) afterloading machine (iridium-192). Either form of interstitial radiotherapy (brachytherapy) delivers a high radiation dose directly into the target (prostate), with additional rapid dose falloff beyond the target. This results in high dose delivery to the target with rapid sparing of the surrounding normal tissues. High-dose-rate brachytherapy is applicable to virtually all stages of localized prostate cancer. Where initially HDR prostate brachytherapy was mainly used in combination with external beam radiotherapy (HDR as boost modality), it is nowadays also used as the only treatment modality (HDR monotherapy).

## Rationale

Studies on radiobiology of prostate cancer provide evidence that the $\alpha/\beta$ ratio for prostate cancer has an exceptionally low value. Using clinical data, Brenner et al. [8, 9] and Fowler et al. [10] estimated a ratio of 1.5 Gy. Most of this data modeling was based on the clinical finding that external beam radiotherapy and permanent seed brachytherapy with certain dosing regimens are equivalent in treatment outcome. In 2002, Brenner et al. [8] compiled and analyzed the data derived from a clinical study conducted at the William Beaumont Hospital using external beam radiotherapy plus HDR-BT boost. Radiobiological parameters for prostate cancer derived from this analysis were an $\alpha$-value of 0.026 $Gy^{-1}$ and an $\alpha/\beta$ ratio of 1.2 Gy. Wang et al. [11] reanalyzed these data with a 4-year posttreatment time end point (in contrast to a 3-year posttreatment end point in the Brenner analysis) and included in the analysis the clinical results from Memorial Sloan Kettering Cancer Center. This analysis provided further evidence to support that prostate cancer has a low $\alpha/\beta$-value, albeit a little higher around 3.1 in this dataset. Duchesne et al., based on a total of 3,756 patients treated with radiotherapy at three institutions (including 185 HDR-BT boost patients), derived an $\alpha/\beta$ ratio in the range of 2–5 Gy. This implies that the $\alpha/\beta$ ratio of prostate cancer cells is lower (or at least equal to) than the $\alpha/\beta$ ratio of the surrounding dose-limiting normal structures where a ratio of 3–5 Gy is generally accepted as the normal

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value. If this is the case, then a potential gain for treating prostate cancer with hypofractionated radiotherapy is likely. HDR prostate brachytherapy represents the optimal way to perform hypofractionated radiation therapy. In addition, HDR brachytherapy allows the possibility to improve the clinical results by implementation of a dose escalation in regard to what can be obtained by external beam radiotherapy. Both patients with intermediate- and high-risk prostate cancer have been shown to benefit from higher than conventional doses. HDR brachytherapy compares favorably with external beam radiotherapy in the delivery of a highly conformal radiotherapy for prostate cancer. Using HDR brachytherapy as a boost, significantly less rectal and bladder volume is irradiated in comparison with conformal external beam radiotherapy.

In summary, three major arguments can be provided in favor of the use HDR prostate brachytherapy:

1. Generally accepted evidence of the extremely low $\alpha/\beta$ ratio of malignant prostate cells favoring hypofractionated radiotherapy schedules
2. Importance of dose escalation, either in intermediate- or high-risk prostate cancer patients, easily obtained using HDR-BT
3. The ultimate conformal administration of the dose to the target volume using HDR-BT, reduction of surrounding normal tissue irradiation

With HDR-BT, a highly conformal radiation treatment can be delivered to the target. Treatment is performed using a stepping source, mostly iridium-192, which is automatically advanced into catheters or needles that have been placed into or nearby the target volume. The source is usually attached to (or embedded in) the end of a wire or cable. The source dwells in a preplanned position for a preset time before stepping along the catheter. This process repeats to create the required dose distribution. By varying the position and dwell time, the dose can be sculpted to provide dose geometry conformal to the target. The patient typically receives the total dose in a series of two or more treatment sessions, also known as fractions. The HDR dose rate is about 100 Gy/h, which is almost similar to the dose rate delivered by external beam linear accelerators. This is in complete contrast to low-dose-rate brachytherapy (LDR-BT) where dose rates are about 10 cGy/h and radiation dose is delivered over months as the isotope slowly decays. HDR-BT was first used in clinical practice for prostate cancer at the Kiel Institute in Germany. In the mid-1980s, Kovacs et al. started to use HDR-BT as a boost during a split course of external beam radiotherapy for locally extended or high-grade tumors. Given the good results, other centers worldwide followed this initial experience, and prospective trials were initiated. Clinical experience has been built up progressively, and the technique can nowadays be considered as effective and safe [12–20].

## Indications for Prostate HDR Brachytherapy

Indication for HDR treatment is histologically proven localized or locally advanced prostate adenocarcinoma (tumor stage T1b up to T3b and all Gleason scores). While initially HDR-BT was only used as a boost after a course of external beam radiotherapy for intermediate- and high-risk prostate cancer, centers started to use HDR-BT also as sole treatment for low- and intermediate-risk patients. Experience in this field remains small, but published data show equivalent results as obtained by low-dose-rate brachytherapy, external beam radiotherapy, or surgery in selected groups of patients.

HDR prostate brachytherapy has also been proposed as a salvage treatment for local failure after previous external beam radiotherapy. Some small published series suggest that this may be safe and effective. It cannot, however, at present be recommended as evidence-based practice.

## Contraindications for Prostate HDR Brachytherapy

As for low-dose-rate brachytherapy, urinary outflow restriction preimplantation predicts for those patients who will have greater incidence of complications including the risk of catheterization postimplant procedure. Objective criteria which have been defined include an IPSS of greater than 15 and/or a flow rate less than 15 ml/s.

Initial prostate gland size is less important for HDR than LDR brachytherapy since in general HDR brachytherapy is able to cover a larger volume than can be achieved by seeds. An important restriction, however, is the likelihood of pubic arch interference during the transperineal implantation which may compromise coverage of the peripheral gland. This factor may be judged from preimplant imaging.

A history of a transurethral resection of the prostate (TURP) was until recently regarded as an absolute contraindication for all prostate brachytherapy since early experience reported a significantly increased rate of urinary incontinence and urethral strictures in such patients. However, with time, a number of patients have now been treated post-TURP, and the complication rate does not seem as high as originally feared. Many centers will now implant patients who are more than 6 months to 1 year from TURP and who on imaging (ultrasound and/or MRI-imaging) do not have a significant resection cavity inside the gland.

Patients presenting a contraindication to undergo anesthesia are few. Individual centers will vary in their technique, some using conventional general anesthesia, others spinal anesthesia techniques, and a small minority describe local anesthesia techniques.

## Prostate HDR Brachytherapy Implantation Technique

A variety of different techniques of performing prostate HDR brachytherapy have been described. Whatever technique is used, all incorporate the following four steps: (1) placement of the afterloading catheters or needles into the prostate (and where indicated seminal vesicles) (Fig. 62.1); (2) acquisition of images with the catheters in place (Fig. 62.2); (3) treatment planning (Fig. 62.3); and (4) treatment delivery (Fig. 62.4). Hereafter, we describe the Mount Vernon Hospital technique of delivering HDR afterloading brachytherapy.

Preoperative bowel preparation starts 2–3 days before the implant date. It includes a low fiber diet and an enema the evening before or the morning of the procedure date. Procedure is performed under either general or spinal anesthesia. Patients undergo a transrectal ultrasound volume study in the lithotomy position. The prostate template is aligned to ensure that the urethra is positioned midway between the rows of template settings and that the base plane runs along the required inferior border of the implanted volume, including, where appropriate, the seminal vesicles. An indwelling catheter allows demarcation of the bladder base and urethra on ultrasound. Standard 2-mm diameter HDR flexible interstitial afterloading applicators are inserted transperineally using the prostate ultrasound template. With a combination of transverse and sagittal views, the applicators can be placed accurately using a 1-cm square grid within the prostate volume. A flexible template is used against the perineal skin and fixed with adhesive. It incorporates rubber O-rings, which hold the flexible afterloading catheters in position. Other techniques use one of the proprietary plastic templates which are sutured to the perineal skin. The aim is to place catheters around the periphery of the prostate with an inner ring which will give greater flexibility in sculpting the dose around the urethra and provide cover at the base and apex where the volume tapers in; whenever indicated, catheters should also be placed inside the seminal vesicles and any suspected extra-prostatic extension where tumor has been identified on previous staging. It is important to keep a close check on catheter coverage throughout the gland, particularly at the apex where peripheral catheters may not be able to contribute to the dose. The template will define the XY-plane; the Z-plane will be defined by ensuring the catheters are advanced to include coverage of the base of the gland and seminal vesicles as required. This may require tenting or even penetration of the bladder which is acceptable to avoid under dosage in these areas. At completion of the implant procedure, the rigid template is removed, and the applicator ends are capped to protect the afterloading channel.

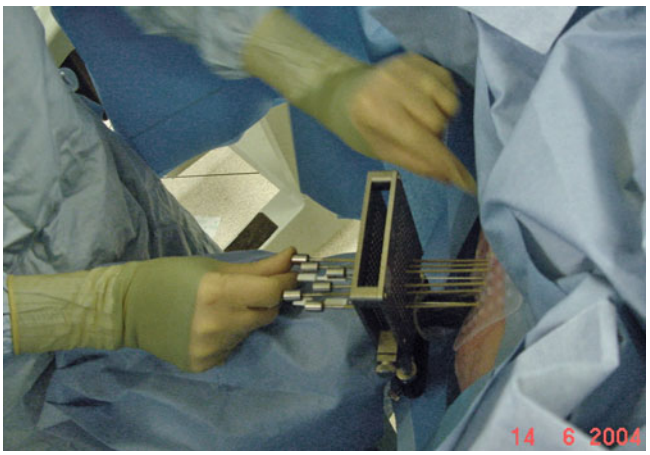


**Fig. 62.1** Setup and implantation of needles/catheters for high-dose-rate brachytherapy

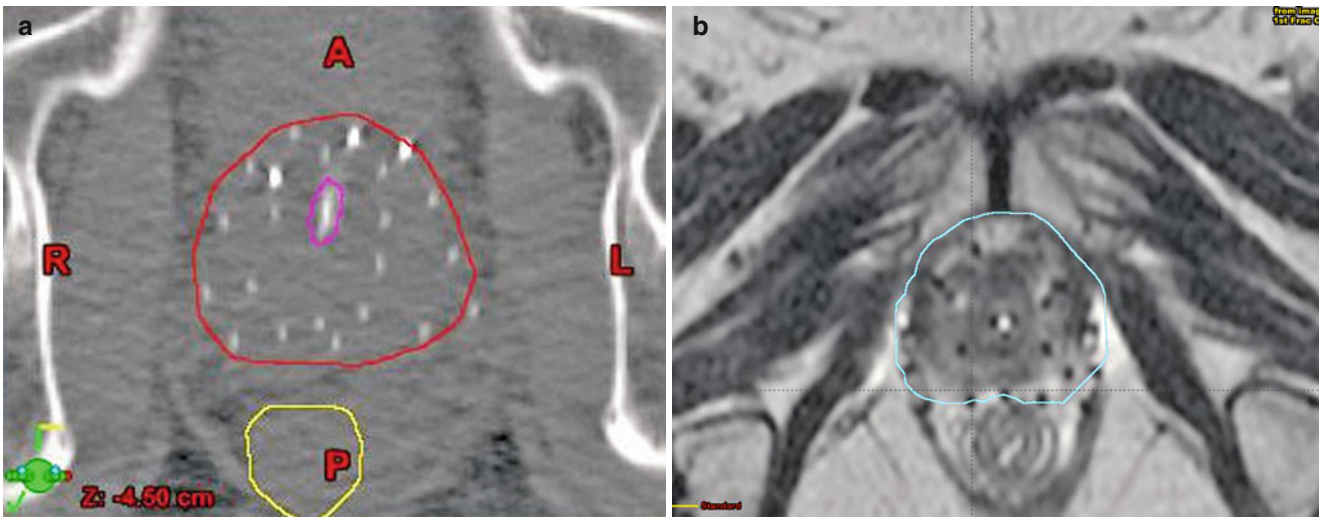


**Fig. 62.2** Acquisition of images with the catheters in place: (**a**) CT-scan based, (**b**) MRI-scan based

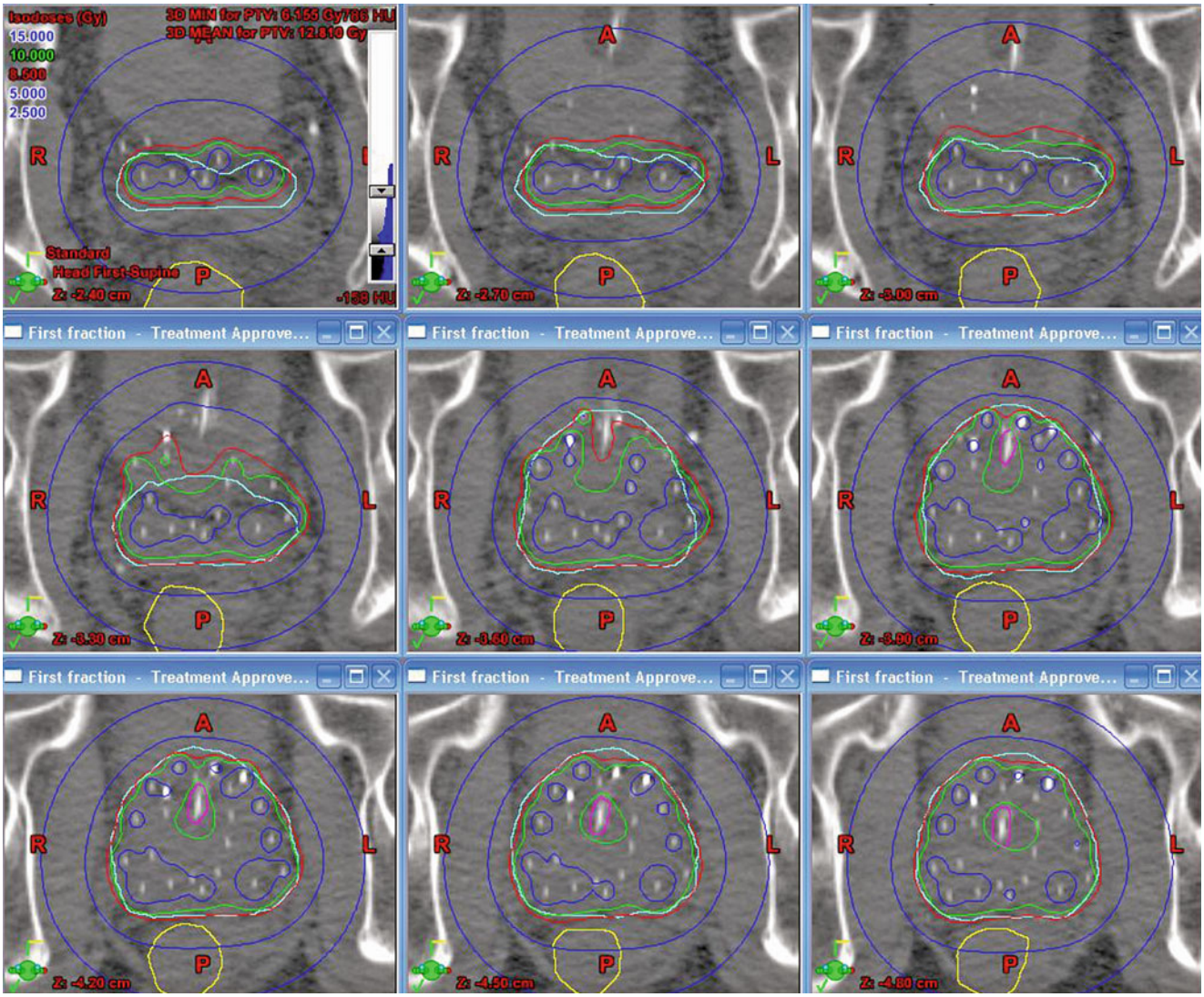


**Fig. 62.3** Treatment planning

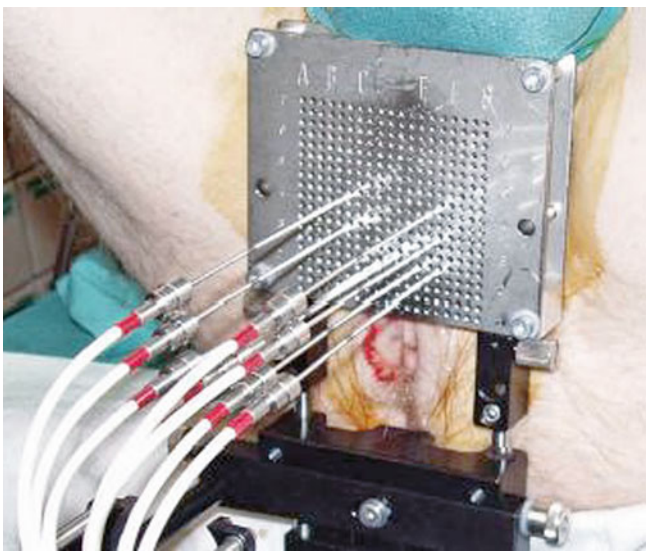

**Fig. 62.4** Treatment delivery

The applicator positions are checked by measurement from the rubber O-ring, enabling their position to be verified before each treatment exposure. Imaging in this technique is undertaken after recovery from anesthetic; however, other centers may use an ultrasound-based volume study obtained while the patient is still in the operating room followed by planning and immediate treatment delivery without moving the patient. Alternatively after transfer 5 mm transverse CT and/or MRI images are taken through the implant volume, and the target volume is defined on each scan. Dwell positions and times are then calculated along the length of each applicator to ensure a homogeneous dose within the target volume, aiming for a cold spot around the urethra. Treatment is given on the day of implant, with any additional fractions during the next days. Following the last fraction, the applicator tubes are removed manually without the need for additional anesthetic, and the flexible template is also removed. Typically, the patient will return home the same day.

## Target Volume, Dosimetry, Fractionation and Dose

### Target Volume

Temporary HDR-BT by using a stepping source offers the possibility to deliver a high dose to a well-defined volume with high precision and a rapid decrease of dose to nearby critical structures. However, interpretation of this "well-defined volume" differs from center to center. Comparison of administered dose/volume parameters was frequently impossible or at least fairly difficult. In 2005, GEC/ESTRO-EAU published recommendations on temporary brachytherapy using stepping sources for localized prostate cancer [20]. In this publication, the proposition was made (in order to obtain a common language in this field) that three different clinical target volumes (CTV) may be defined. The prostate CTV1 will be represented by the whole prostate gland as visible on the TRUS images. CTV2 represents only the peripheral zone of the prostate, and CTV3 describes the visible tumor infiltration area. In addition, a large number of centers apply a safety margin adding 3 mm to the CTV as defined above to cover potential routes of microscopic extra-capsular spread; this expanded volume will then define the planning target volume (PTV).

### Dose Distribution

The dose distribution is defined by varying dwell times using the HDR dosimetry program. There are two schools in implant dosimetry. Centers using peripheral weighting with catheters predominantly around the periphery of the gland with a smaller number of needles centrally prescribe the dose to the prostate gland (CTV1) or the gland with margin (PTV). Others use an individualized needle placement (typically in a horseshoe shape) concentrating the catheters in the peripheral zones of the gland, prescribing dose to the CTV2 (peripheral zone of the prostatic gland). In both schools, hot spot areas can be achieved by loading more needles or adapting dwell times to prescribe additional dose to the CTV3 (clinical visible tumor area).

### Fractionation Schedules

As already stated, HDR-BT for prostate cancer is ideal for hypofractionated treatment. This both exploits the typical radiobiological behavior of prostate cancer cells and delivers dose in the most conformal way avoiding adjacent organs at risk. Hypofractionation refers to a treatment scheme where larger than usual doses of radiation are administered per fraction (>2 or 2.5 Gy per fraction) and where the total number of fractions is lower than in standard fractionation schedules. This typically results in lower than classical total cumulative dose. However, given the greater impact of larger doses of radiation per fraction, the BED (biological effective dose) is at least equal to or larger than what could be obtained with the classical fractionation schedule. Most reports describe, in the multimodality setting, two to four fractions of HDR-BT in combination with external beam irradiation. In addition, the fractionated HDR-BT can be given following one implant procedure, requiring the patient to be treated as an inpatient or on an outpatient basis where each fraction is delivered after a separate catheter insertion. Either approach has advantages and drawbacks including cost, patient inconvenience, resources, and management of possible catheter displacement between the fractions and the time factor in the radiobiological calculations. In addition, the timing of the HDR-BT (before, during, or after the course of external beam) and the definitive administered total dose and fractionation may influence comparison between reports from different centers.

Since the start of prostate HDR-BT in Kiel in the early 1990s, a large variety of fractionation schedules and doses have been applied in different centers, and the optimum dose and fractionation for use in the combined approach (external beam radiotherapy with HDR-BT boost) or in the more recent unique approach (exclusive HDR-BT) is uncertain. A wide range of dose and fractionation schemes have been reported in literature. A large range of prescriptions are used in HDR-BT for prostate cancer given as a boost after external beam radiotherapy for intermediate- and high-risk locally advanced prostate cancer. Doses administered during external beam therapy vary between 39.6 and 45 Gy (administered in 1.8 Gy/day) and 50–54 Gy in 2 Gy fractions. The number of HDR-BT fractions varies between 2 and 4 with doses per fraction between 4 and 15 Gy; single doses of 12–15 Gy have also been reported. In Table 62.1, a summary of the different treatment schemes is shown. One should also take in account that the reported series may differ in external beam dose and fractionation, and also in how the dose is specified and how the brachytherapy relates to the external beam course. This large variation in the administration of HDR-BT in combination with an external beam irradiation results in a wide range of different biologically equivalent delivered doses. The total dose equivalents at 2 Gy per fraction for the reported schedules of combined external beam and HDR-BT regimens are listed in Table 62.2. Calculations were made with alpha-beta values of 1.5 Gy (prostate cancer), 3 Gy (late responding normal tissue), and 10 Gy (acute responding normal tissue).

HDR monotherapy programs have been initiated regarding lower-risk prostate cancer disease. The most common prescriptions used are 34–38 Gy in 4 fractions in 2 days, although further hypofractionation using 54 Gy in 9 fractions, 31.5 Gy in 3 fractions, and 26 Gy in 2 fractions has also been reported [33–41, 51]. In Table 62.2, a summary of the reported treatment regimes is given.

**Table 62.1** Dose and fractionation of combined external beam radiotherapy and high-dose-rate brachytherapy

| Reference | External beam dose | HDR regimen |
|---|---|---|
| Kovacs et al. [21] | 50 Gy (40 Gy on prostate) | 2 × 15 Gy |
| Borghede et al. [13] | 50 Gy | 2 × 10 Gy |
| Martinez et al. [22] | 46 Gy | 3 × 5.5 up to 11.5 Gy |
| Mate et al. [19] | 50.4 Gy | 4 × 3 or 4 Gy |
| Deger et al. [23] | 40–50.4 Gy | 2 × 9 or 10 Gy |
| Syed et al. [24] | 39.6–45 Gy | 3 × 5 Gy up to 4 × 6.5 Gy |
| Pellizzon et al. [25] | 45 Gy | 4 × 4 or 5 Gy |
| Demanes et al. [26] | 36 Gy | 4 × 6 Gy |
| Martin et al. [27] | 39.6–45 Gy | 4 × 5 up to 7 Gy |
| Curran et al. [28] | 50 Gy | 3 or 4 × 5.5 Gy |
| Hiratsuka et al. [29] | 41.8–45 Gy | 3 or 4 × 5.5 Gy |
| Chiang et al. [30] | 50.4–54 Gy | 3 × 4.2 Gy |
| Hoskin et al. [31] | 35.75 Gy (2.75 Gy/fraction) | 2 × 8.5 Gy |
| Hsu et al. [32] | 45 Gy | 2 × 9.5 Gy |

**Table 62.2** Dose and fractionation used in high-dose-rate brachytherapy monotherapy

| | |
|---|---|
| Grills et al. [33] | 4 × 9.5 Gy |
| Martin et al. [34] | 4 × 9.5 Gy |
| Yoshioka et al. [35–41] | 6 × 8 up to 9 Gy |
| Corner et al. [37] | 4 × 8.5 or 9 Gy or 3 × 10.5 Gy |
| White et al. [38] | 6 × 7.5 Gy |
| Martinez et al. [51] | 6 × 7 Gy (CED) – 4 × 9.5 Gy (WBH) |

When using HDR-BT monotherapy, quality assurance is important to ensure that catheters do not move between implantation and treatment delivery and between separate treatment administrations, particularly when more than one fraction is to be delivered with the same implant as is commonly the case. Prospective evaluation has documented that interfraction movement of catheters relative to the prostate gland, as derived from consecutive CT scans, may be important [42, 43]. Compared to the first fraction, the mean interfraction caudal movement relative to the prostate base was in this study 7.9 mm (fraction 2) (range 0–21 mm) between fractions 1 and 2, and 3.9 mm (fraction 3) (range 0–25.5 mm) between fractions 2 and 3. These movements (principally away from the base of the prostate) may have a significant impact on implant dosimetry unless corrected by repositioning the catheters. D90 % was reduced without movement correction by a mean of 27.8 % (fraction 2) and 32.2 % (fraction 3), compared with only 5.3 % (fraction 2) and 5.1 % (fraction 3) with catheter movement correction. Interfraction correction for catheter movement using pretreatment imaging is critical to maintain the quality of an implant. Without movement correction, there is a significant risk of tumor underdosage and normal tissue overdosage. Internal changes of the prostate or organs at risk are more difficult to simply assess, and a limited imaging series should be undertaken before each fraction to evaluate this. Dwell positions or catheter positions may need adjustment for each fraction.

## Dosimetric Parameters

The dose is prescribed to the PTV (that normally equals the CTV in prostate brachytherapy). The D90 (dose received by 90 % of the target volume) should be at least 100 % of the prescription dose. The V100 (the percentage of the target volume that receives the prescription dose) should be at least 95 % of the prescription dose.

The most critical organs in HDR-BT for prostate cancer are the urethra and the anterior wall of the rectum. Given the heterogeneity in dose and fraction size used in HDR-BT, a multitude of dose constraints for these organs at risks are published. It is critical that these are related to the dose per fraction. As a guide, dose constraints used at Mount Vernon are based on a urethral dose D10 (dose received by 10 % of the urethra) 130 % of the prescription dose and rectal D2 cc (dose received by 2 cc of the rectum) less than 100 % of the prescription dose.

In the RTOG 0321 study [32], the first multi-institutional phase II trial of combined high-dose-rate brachytherapy and external beam radiotherapy for adenocarcinoma of the prostate, the authors state that the goal of the protocol was to maximize the CTV(=PTV) coverage without sacrificing normal tissue sparing. The dose to the critical normal structures was kept to a minimum with dose constraints for 1 $cm^3$ of the bladder and rectum to receive no more than 75 % of the prescription dose (Vr75 < 1 $cm^3$ and Vb75 < 1 $cm^3$), and the volume of urethra receiving 125 % of the prescription dose had also to be kept below 1 $cm^3$ (Vu125 < 1 $cm^3$).

## Clinical Results with High-Dose-Rate Brachytherapy

The first reports of early experience using HDR-BT as a boost after external beam radiotherapy came from the University of Kiel (Germany). Kovacs and Galalae [21] treated with this combination therapy mostly patients that had intermediate- or high-risk disease. Ninety-nine percent of their patients had stage greater than T1, and 85 % had grade 2 or 3 tumors. Seventy-eight percent of the 171 treated patients remained disease-free at 10 years. Mate et al. [19] reported on 104 patients treated with a hypofractionation schedule. Seventy percent of the patients had stage 2 or 3, 52 % had PSA < 10, and 79 % a grade 1 differentiation tumor. With a median follow-up of 46 months, disease-free survival was 84 % (patients with initial PSA ≤ 20) and 50 % (patients with initial PSA > 20), respectively. Martinez et al. [22] at William Beaumont

Hospital reported on a dose escalation study in 207 patients who showed a disease-free survival of 68 % and local control rate of 98 % at median follow-up of 53 months. Borghede et al. [13] from Goteborg reported on 50, meanly T2 (68 %) and grade 2 (60 %), patients. At median follow-up of 45 months, 84 % disease-free survival was reported. Deger et al. [23] reported on 230 patients, 93 % at least stage T2 and 77 % grade 2 or 3. At 40 months, disease-free survival of 70 and 65 % for T2 and T3 disease, respectively, was noted. Other studies [24, 25, 27, 29, 32] confirm these good results.

One prospective randomized phase III trial was performed in the United Kingdom [31]. The trial has compared external beam radiotherapy alone with a dose-escalated schedule using high-dose-rate brachytherapy. Patients with histologically confirmed prostate cancer, no evidence of metastases, a pretreatment PSA < 50 ng/ml, no previous TURP, and fit for general anesthesia were included. Patients were randomized to receive either standard radiotherapy (UK-standard treatment schedule of 55 Gy in 20 fractions, 5 days a week over 4 weeks) or a combined schedule comprising external beam treatment delivering 35.75 Gy in 13 fractions, 5 days a week over 2.5 weeks followed by a temporary high-dose-rate afterloading implant delivering 17 Gy in 2 fractions over 24 h. A total of 220 patients were randomized, well balanced for all important prognostic parameters including tumor stage, initial PSA level, Gleason score, and use of adjuvant hormonal treatments. With a median follow-up of 30 months, a significant improvement in actuarial biochemical relapse-free survival was reported in favor of the combined brachytherapy schedule. The mean PSA relapse-free survival in the HDR-arm is 5.1 years (95 % CI 4.6–5.5) compared to 4.3 years (95 % CI 3.8–4.8) in the control arm. When analyzing the population by prognostic groups according to PSA, Gleason score, and T stage, the improvement is seen in all three groups. There was as would be expected greater use of antiandrogens in the high-risk group (93 %)) compared to the intermediate-risk group (67 %) and even less in the low-risk group (50 %). Use was balanced between the two arms of the study for each group, and no overall effect of adjuvant antiandrogens on biochemical relapse-free survival was seen.

Other studies, including the pooled analysis of 507 patients treated either at William Beaumont Hospital or at the University of Kiel, showed no evidence that the addition of an androgen deprivation therapy to HDR-BT improves the biochemical control (76 % without hormones, 74 % with hormones) [44].

## Toxicity and Side Effects

Acute and late-term morbidity related to HDR-BT seems equivalent or inferior to what is observed after external beam radiotherapy. Despite the large variation in techniques and doses used in the combination treatment of external beam radiotherapy and HDR-BT boost irradiation, reported acute and late toxicity remains very low.

### Acute Effects

Perineal bruising and soreness are inevitable and usually resolve within a few days. Acute toxicity consists mostly of temporary lower urinary tract symptoms. Dysuria may occur for a few days after treatment but tends to be less prominent and of shorter duration than with LDR seed implantation. Hematuria, bruising, and pain are relatively uncommon. Proctitis with bowel frequency and urgency may persist during and for several weeks beyond the period of brachytherapy. This is less severe when HDR brachytherapy is given than after an equivalent dose given with external beam irradiation. In combination therapy, acute rectal toxicity is probably related mostly to the accompanying external beam radiotherapy.

### Late Effects

Urethral stenosis or urethral stricture is the most commonly reported long-time side effect (5–14 %) [19, 23, 46–49]. This risk can be reduced by careful patient selection and attention to technique (midline needles, dose to urethra, irradiation of a long end of urethra). The overall risk of urinary incontinence is less than 1 %. In the series of Galalae et al., urinary incontinence was reported in 9 out of 144 patients (6 %) [45]. All but one patient had a history of TURP shortly before or after radiation treatment. Chronic frequency or dysuria happens in 2–12 % of the treated population. It is important to bear in mind that the treated population is often an older population, in which grade 1 or more lower urinary tract symptoms are already present in more than one-third of the patients before commencing treatment. The gastrointestinal late side effects are also low and include some degree of diarrhea, proctitis, or occasional rectal bleeding. Late rectal ulceration and rectourethral fistula formation are extremely rare and often related to surgical interference such as a biopsy or procedure for hemorrhoids.

Grade 1 or more urinary symptoms are frequently reported, although grade 2 symptoms are rarely present in more than 10 % of the treated population, whereas grade 3 toxicity is extremely rare. Martinez et al. [22] reported on 207 patients at a median follow-up of 3.8 years and a 5-year RTOG urinary grade 3 complication rate of 8 %. Duchesne et al. [50] reported only 8 % of men having grade 2 or more urinary symptoms at 5 years, and none had grade 3 late urinary toxicity. I-Chow Hsu et al. [32], reporting the early results of RTOG trial 0321, reported an estimated

rate of acute grade 3–5 urinary and gastrointestinal toxicity of 2.43 % and an estimated rate of late grade 3–5 urinary and gastrointestinal toxicity of 2.56 % (at 18 months) resulting in a hazard ratio of 0.0014/month. Hoskin et al. [31] reported acute and late toxicity in the only published external beam radiotherapy ±HDR-BT trial. Acute toxicity scores between the two arms of the study were comparable for all parameters of urinary and bowel function except for rectal discharge which was lower in the HDR-BT arm. No significant difference in late bowel and bladder reactions was seen between the two arms when considering grade 2 and greater severity. The dose escalation used in this prospective randomized HDR-BT study resulted thus in no increase in acute toxicity, and indeed, if rectal discharge is considered a surrogate for proctitis, there was a significant reduction in this particular acute toxicity. In addition, with a mean follow-up of more than 2 years, no difference in late toxicity was emerging. This confirms that the therapeutic ratio for prostate cancer is strongly in favor of using HDR-BT as a boost with external beam radiotherapy in intermediate- and high-risk localized prostate cancer.

Data on sexual function after HDR-BT is not well documented in most series. However, Duchesne et al. [50] evaluated erectile function following HDR-BT in a subset of men who had normal erectile function prior to treatment and who did not have androgen deprivation therapy combined with the radiotherapy. It was shown that dysfunction commonly developed in the first 24 months and subsequently had little recovery. At 5 years follow-up, 77, 47, and 30 % of patients had grade 1 or more, grade 2 or more, or grade 3 erectile dysfunction, respectively.

HDR-BT monotherapy data suggests that overall, it is well tolerated and toxicity may be even less than observed after seed implantation. The first report comes from Martin et al. [34], describing their initial experience and toxicity levels with HDR-BT monotherapy. In only 4 % of cases (2 out of 52 patients), acute grade 3 genitourinary toxicity was observed, and there was no greater than grade 1 gastrointestinal toxicity. The Michigan group [51] compared monotherapy by seeds (palladium-103) versus HDR-BT in a large patient group of 454 patients – 248 treated by HDR-BT monotherapy and 206 treated by palladium-103 seed implantation. HDR-BT alone was associated with significant decreased acute rates of grade 1–3 dysuria, urinary frequency/urgency, and rectal pain. Late toxicities were also decreased with HDR-BT, including long-term urinary dysuria, frequency and urgency. There was no difference in the rates of urinary incontinence, retention, or hematuria. However, the urethral stricture rates were 8 % in the HDR-BT alone versus 3 % for the seed implantation group. Impotence rate was also in favor of HDR-BT (20 % vs. 30 %).

## Take Home Messages

HDR-BT delivers a high biologically effective dose to the prostate in the most conformal way. HDR-BT used as a boost in combination with external beam radiotherapy compares favorably with the most modern forms of external beam radiotherapy. Published data, mainly single-institutional studies, report high local and biochemical control rates in association with low toxicity profiles. Large variations in treatment technique, patient characteristics, administered dose, and fractionation schedules have been used, and currently the optimal radiation dose, fractionation scheme, and sequencing are not known. Multi-institutional prospective randomized trials are needed to validate this experience.

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# Intensity-Modulated Radiotherapy

63

Bridget F. Koontz, Devon Godfrey, and W. Robert Lee

Intensity-modulated radiotherapy (IMRT) is a technique for delivering external beam radiation. IMRT is defined as a radiation treatment in which the number of photons delivered (or "fluence") varies within a field (Fig. 63.1). Such variability can be used to avoid normal structures with lower radiation tolerance than the cancer and increases the ability to provide focal treatment. Its use has become widespread in a variety of malignancies that require high radiation doses, avoidance of critical normal structures, or both. For prostate cancer, the cancer control benefit of dose escalation, which also leads to greater rectal toxicities, has driven a widespread adoption of IMRT for definitive external beam radiotherapy.

## History

### Development of IMRT

Radiation therapy has undergone an evolution in treatment field design over the past 25 years. Initial treatment of prostate cancer used nonconformal ("2D") techniques using skeletal anatomy to guide the design of treatment fields. Multiple fields with different angles were used to create a homogenous high-dose region internally while reducing peripheral dose. Beam shaping was performed by customized solid blocking (Fig. 63.2).

With computed tomography (CT), the tumor location and shape, as well as that of other nearby organs, could be individualized to each patient ("3D conformal" treatment). However, the dose delivered remained constant within each field, with multiple field plans still generating a homogeneous treatment volume.

Intensity-modulated radiotherapy (IMRT) was initially a mathematical solution to the problem of developing a heterogeneous treatment plan. In 1982, physicists in Stockholm published a mathematical method to generate an annulus of uniform dose with minimal central dose using a rotating modulated beam [1].

Techniques to accomplish delivery of IMRT were developed throughout the early 1990s with continued technical and dosimetric advances extending into early 2000s [2, 3]. Beam shaping evolved from the premade solid blocks to multileaf collimators (MLCs), small motorized "leaves" with variable positioning in the head of the linear accelerator (Fig. 63.2). Widespread availability of MLCs in linear accelerators allowed changes to how treatment plans were developed since numerous MLC shapes at a single gantry angle could be used to vary the number of photons delivered to differing areas of a single field [4]. While MLCs are not required for IMRT delivery, they are perhaps the most widely used technique for delivering an IMRT plan.

IMRT depends on high-quality imaging and computerized planning to individualize treatment fields to ensure adequate coverage of the target and avoidance of normal structures [4, 5]. It is best used when the proximity of target and critical organs requires a sharp penumbra [6]. IMRT treatment plans are often less homogeneous than 3D conformal plans, a characteristic which can be used to create concave treatment plans or escalate dose to certain areas within the target. For prostate cancer, IMRT plans have significant improvement in the dose distribution to the femoral heads, bladder, and rectum (Fig. 63.3) [7].

### Delivery Methods

Many different techniques have been developed to create an IMRT treatment plan. These are briefly described below [8]. The combination of multiple beam angles and field shape changes can result in longer treatment times compared to 3D conformal radiotherapy, but newer techniques have been designed to reduce treatment time.

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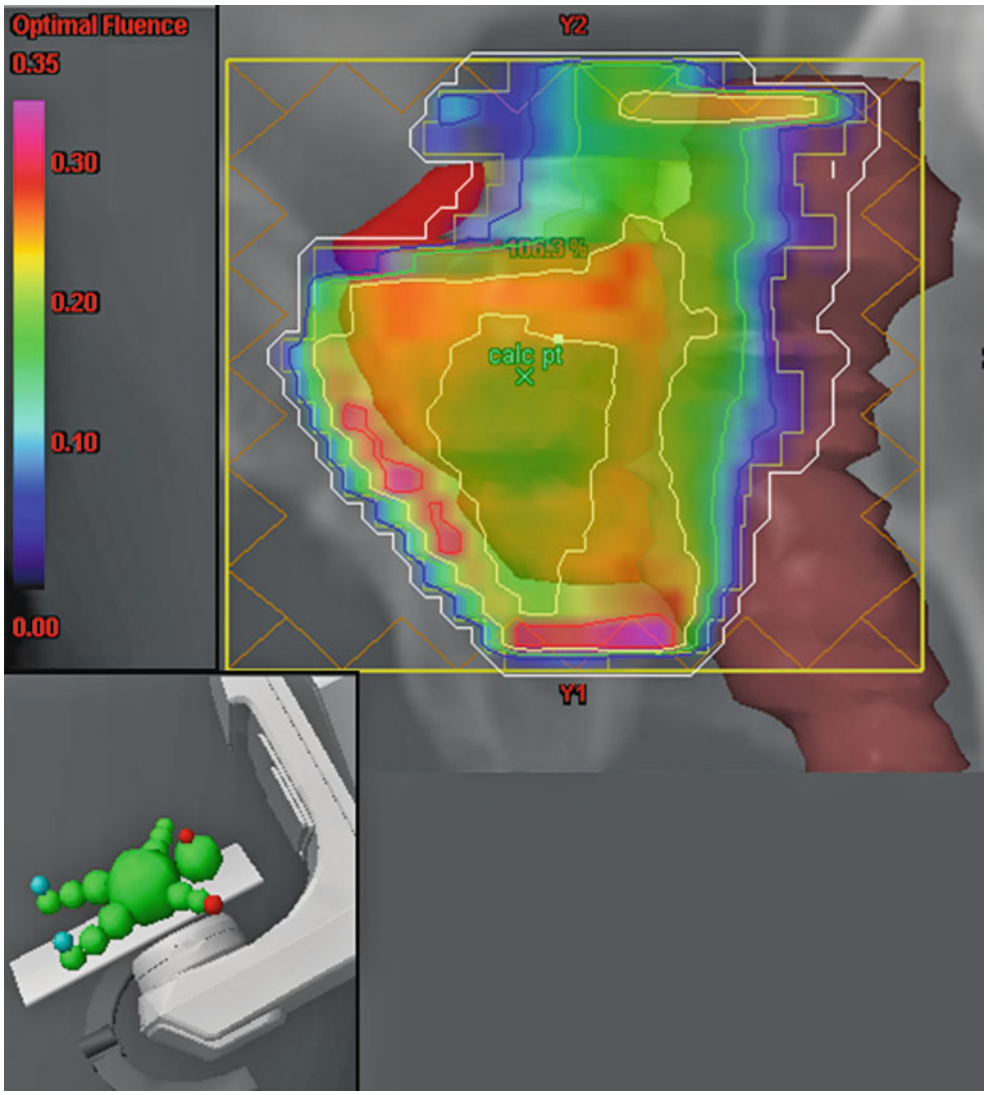


**Fig. 63.1** Fluence map from a single IMRT field showing the fraction of the beam that is transmitted at each location in the field. The planned target volume (*red*) and rectum (*brown*) are visible behind the fluence map. A schematic in the lower left corner illustrates that the field has a left posterior oblique orientation

- Static MLCs ("step and shoot" or "segmental IMRT") – at each gantry angle, the field is divided into multiple subfields with different MLC positions.
- Dynamic MLCs ("sliding window") – at each angle, MLCs move independently during beam-on time across the field aperture.
- Arc therapy – the beam remains active while the gantry is rotated. Often multiple arcs are used with either static or dynamic MLCs. Rotation speed can also be varied [9–11].
- Tomotherapy IMRT – treatment is delivered to a narrow "slice" using arc rotation and dynamic MLCs. Adjoining axial slices are used to complete coverage of the target [12]. Motion of the couch allows for helical tomotherapy delivery.
- Compensator-based IMRT – instead of MLC position changes, metal filters can be customized to patient and field to modulate intensity. This requires custom manufacturing of multiple filters as well as changing each filter prior to treatment of each field.
- Robotic linear accelerator – a linear accelerator mounted on a robotic arm with 6° of freedom will aim small beamlets at target [13], which sum to provide full target coverage.

## Planning

### Defining the Target

Most IMRT plans are developed using inverse planning, where a planning software system is given the target and avoidance structures, field angles, and parameters of dose (minimum, maximum, and/or how much of a structure can receive a given dose) by a user, and the system develops a fluence map and MLC positioning to achieve the user-specified dose constraints. Therefore, any area of concern must be delineated as a target structure, and any area to be avoided demarcated as such, to ensure coverage or avoidance in the final plan. In addition, the sharp penumbra often

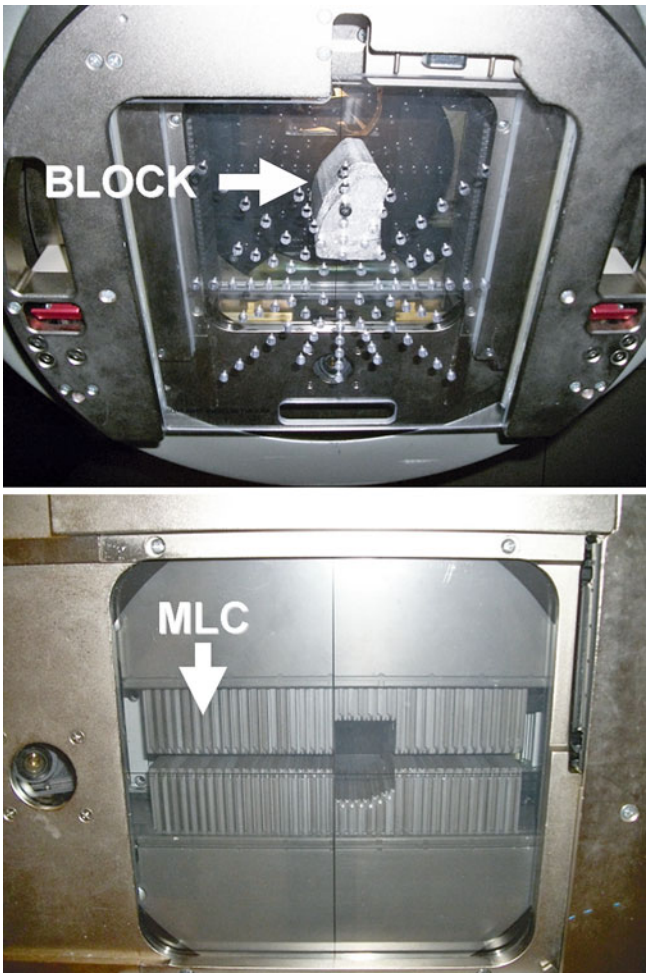


**Fig. 63.2** Fields were historically shaped using thick cerrobend blocks, mounted just after the radiation exit window (*upper image*). Today, most field shaping is accomplished using a programmable MLC, built into the head of a linear accelerator (*lower image*)

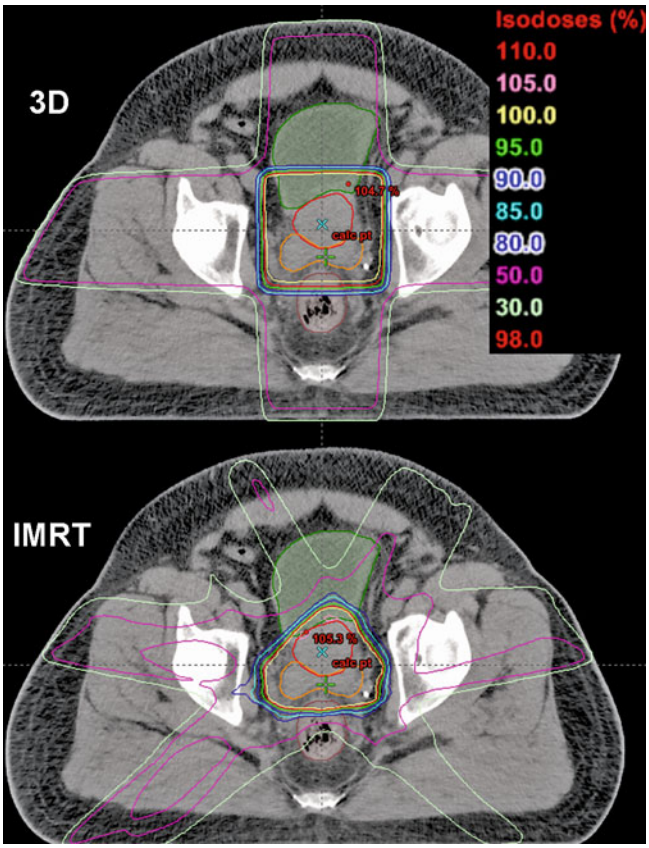


**Fig. 63.3** Axial CT slice showing the planned isodose distributions for typical 3D and IMRT radiotherapy to the prostate (*red contour*) and seminal vesicles (*orange contour*). The IMRT plan delivers and achieves better dose sparing of the rectum, bladder, and femoral heads

afforded by IMRT plans means that care must be taken in designing these volumes.

Currently most software systems rely on CT-based planning to calculate dose attenuation through tissue. Other imaging modalities can be useful in structure delineation, however, including magnetic resonance imaging (MRI). T2-weighted MRI offers improved soft tissue contrast between the prostate and periprostatic fat, connective tissue, and urogenital diaphragm, and is particularly useful in delineating the apex of the prostate [14–17].

Certain conventions rule the labeling of structures used in treatment planning (Fig. 63.4). These are defined below:

- Gross tumor volume (GTV) – visible tumor on imaging or exam.
- Clinical treatment volume (CTV) – includes the GTV plus additional areas at risk for subclinical disease through microscopic spread. The extent of expansion depends on tumor behavior and anatomic boundaries.
- Internal target volume (ITV) – expansion of the CTV to account for predicted target motion during treatment.
- Planning treatment volume (PTV) – includes the ITV plus margin for setup error.
- Organs at risk (OARs) – normal tissue or organs for which the planner wishes to set a dose limit in order to minimize injury to those organs.

Once the physician has outlined these structures and given the prescription dose to be delivered to the PTV and the dose constraints limiting the dose to be delivered to the OARs, the IMRT planning software will develop a treatment plan that will meet all such criteria. Evaluation of the treatment plan is typically done by reviewing the plan showing delivered dose overlaying the planning CT and by reviewing the amount of dose given to each structure, shown graphically in a dose-volume histogram (DVH; Fig. 63.5).

## Target Motion

Since the margin of full dose surrounding the defined target can be quite small, any motion, either physiologic organ

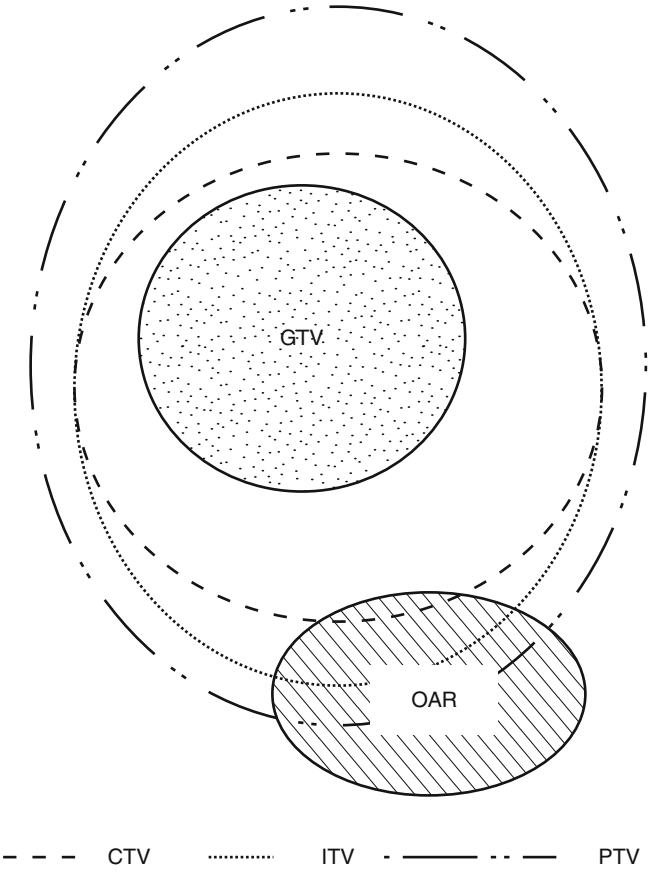


**Fig. 63.4** Diagram showing spatial relationship of different planning structures to each other and an organ at risk (*OAR*). *GTV* gross tumor volume, *CTV* clinical treatment volume (includes subclinical disease spread), *ITV* internal target volume (takes motion into account), *PTV* planning treatment volume (includes margin for setup error)

motion or changes in patient positioning from the planning CT, can result in underdosing of the prostate and overdosing of the normal structures at risk. Thus, careful consideration of patient setup including strategies to minimize setup error and understanding of typical physiologic motion that can occur during the time frame of a treatment must be taken into account during planning and treatment delivery.

Two types of motion need to be considered – interfraction motion, which includes differences in daily positioning as well as organ location, and intrafraction motion, which primarily involves organ motion during beam-on time, although patient movement can also play a role.

In the past decade, both have been extensively studied for prostate cancer. Table 63.1 shows data summarizing several studies' findings regarding setup and motion error, reported as margins required to cover motion seen. In general, interfraction motion is much larger than intrafraction motion [18] and depends on the type of setup performed (skin tattoos vs. various techniques to localize the prostate itself).

The degree of intrafraction motion varies significantly between patients [19] and is partly dependent on individual anatomy, as well as rectal filling [20, 21]. There is no significant difference in whether the patient is positioned supine or prone [22, 23]. One study showed that the prostate for 14 of 17 patients stayed within 5 mm of its original position over 90 % of the time [18]. The other three patients, however, had a substantial duration of their treatment with the prostate moving more than 7 mm from its starting position. Another study noted that, while on average prostate motion was less than 1 mm in any direction, displacement (as measured by implanted fiducial markers) as large as 9.5 mm was seen in some instances [24]. Seminal vesicle motion has also been studied and has a larger degree of motion than the prostate [25].

## Correcting for Motion

Minimizing the motion of the target allows for smaller margins and thus less normal tissue receiving high dose. Several methods to improve targeting accuracy in prostate cancer radiotherapy have been developed. These include daily use of abdominal ultrasound to position the prostate (B-mode, Acquisition, and Targeting or BAT; NOMOS Corp., Sewickley, PA), an endorectal balloon to reproduce rectal filling and fix the prostate against the pubic arch, imaging of permanently placed inert intraprostatic fiducial markers, placement of wireless transponders (Calypso Medical Technologies Inc, Seattle WA) to follow prostate position prior to and during radiotherapy, and CT-based imaging systems integrated with treatment accelerators to allow soft tissue matching prior to treatment. Each has advantages and disadvantages, as described below:

- Ultrasound imaging – a non-ionizing method of daily localization using transabdominal imaging through the bladder to image and reproduce prostate position daily prior to treatment [26]. However, it requires therapist training, consistent bladder filling for proper imaging, and has been shown to have significant inter-user variability [27, 28].
- Endorectal balloon – Placed daily during planning and treatment. Use of an endorectal balloon reduces the volume of rectum which receives high dose [29] and appears to reduce intrafraction motion [30] but may not effectively reduce interfraction prostate motion [31].
- Inert intraprostatic markers –Daily setup adjustment is highly reproducible [32] without significant migration of the markers [33–35] but requires additional procedure for placement and daily imaging, adding time and dose to overall treatment. Kilovoltage imaging reduces additional overall dose compared with imaging using the megavoltage treatment beam.
- Implanted electromagnetic wireless transponders – can be used as fiducials for pretreatment setup and will also

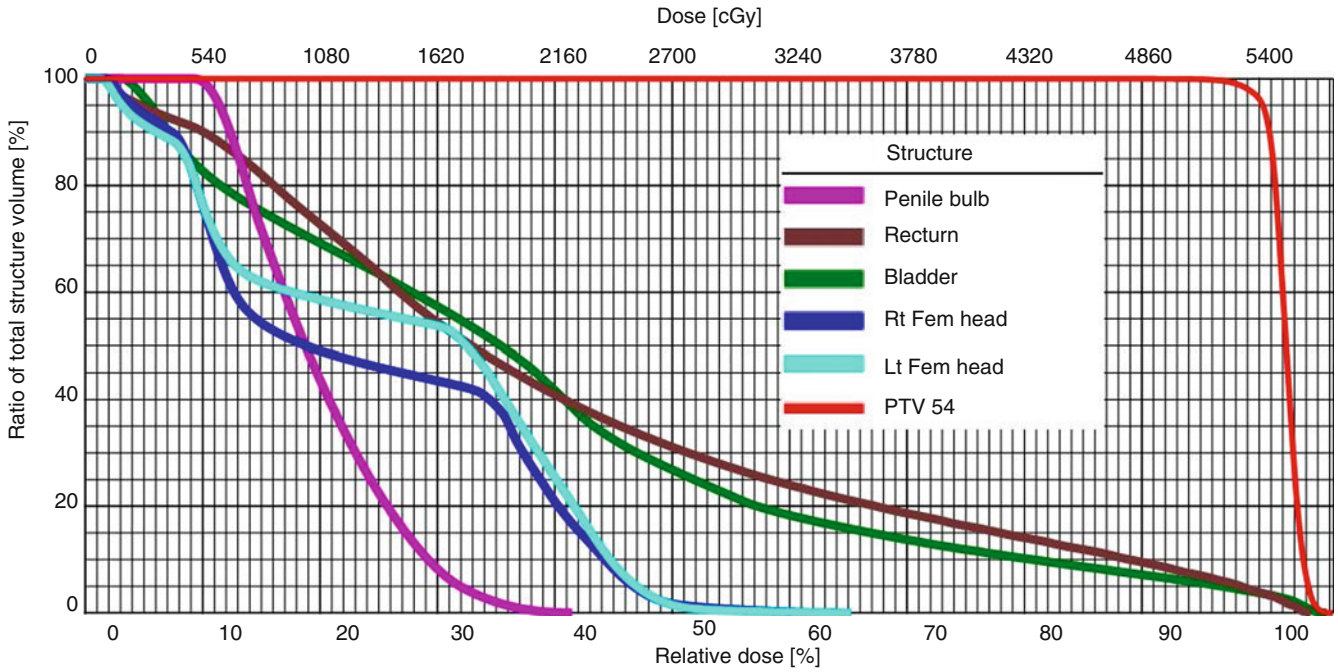


**Fig. 63.5** The dose-volume histogram for a primary IMRT plan targeting the prostate and seminal vesicles shows the percent volume of each structure that receives more than a specified dose. Ninety-five percent of the planned target volume is seen to receive at least 54 Gy, while dose to critical normal structures is minimized. A boost IMRT plan (not shown) would typically deliver approximately 20 Gy of additional dose to the prostate alone

**Table 63.1** Prostate motion between and during radiotherapy fractions

| | Interfraction motion (mm) | | |
|---|---|---|---|
| | L-R | S-I | A-P |
| Su et al. [18] | 8.4 | 10.8 | 14.7 |
| Khosa et al.* [74] | 3.6 | 7.3 | 4.7 |
| Graf et al. [75] | 7 | 9.5 | 9.5 |
| Skarsgard et al. [76] | 5.7 | 7.9 | 7.7 |
| Tanyi et al. [77] | 7.3 | 10.9 | 16 |
| Tanyi et al.* [77] | 1.6 | 8.9 | 10.5 |
| Perez-Romasanta et al. [78] | 10.5 | 12.4 | 17.8 |
| Beltran et al. [79] | 6.8 | 7.2 | 9.8 |
| Beltran et al.* [79] | 3.1 | 8.9 | 10.7 |
| Litzenberg et al. [80] | 8 | 10 | 7.3 |
| Schallenkamp et al. [35] | 5 | 5.1 | 7.3 |
| Su et al. [18] | 1.3 | 2.3 | 2.8 |
| Khosa et al. [74] | 1.2 | 1.9 | 3.1 |
| Graf et al. [75] | 1.3 | 2.2 | 1.7 |
| Adamson et al. [63] | 1.4 | 3.2 | 3.2 |
| Tanyi et al. [77] | 2.8 | 3.7 | 3.2 |
| Tanyi et al.† [77] | 1.4 | 2.6 | 2.3 |
| Skarsgard et al. [76] | 3.6 | 3.7 | 3.7 |
| Wilder et al. [22] | 0.6 | 1.6 | 1.7 |
| Beltran et al. [79] | 2.4 | 3.4 | 3.4 |
| Litzenberg et al.† [80] | 1.8 | 7.1 | 5.8 |

Interfraction motion based on skin markings except * where bony anatomy referenced. Intrafraction motion based on implanted fiducial markers except † where implanted transponders used
*L-R* left-right, *S-I* superior-inferior, *A-P* anterior-posterior

provide real-time monitoring of prostate positioning during treatment [36, 37]. Transperineal placement of the transponders requires a separate procedure, typically requiring sedation.

- On-board soft tissue imaging – can be accomplished using several methods incorporating CT imaging with treatment accelerator. This allows direct matching of prostate with planning contour [38], however, brings up additional issues of organ deformation [39, 40] and shrinkage across treatment course [41], as well as significantly increased dose given due to frequent imaging [42].

## Quality Assurance Issues

Due to the complexity of IMRT treatment plans, it is necessary to check each plan for accuracy in dose delivery. Because each field is often partially blocked by MLCs during delivery, the unblocked accelerator output is much greater than for conventional radiotherapy, and so the risk of injury is increased if treatment is not delivered as planned [43]. This risk is minimized through the implementation of strict periodic and patient-specific quality assurance (QA) protocols for IMRT, usually designed to comply with guidelines issued in task group reports from the American Association of Physicists in Medicine (AAPM) [44–46].

For MLC-based IMRT systems, periodic QA of the IMRT delivery system includes verification of MLC leaf positioning and velocity accuracy, as well as measurement of the radiation leakage through closed MLC leaves. Gantry angle and rotation speed accuracy are also verified on a routine basis for machines delivering arc therapy. For helical tomotherapy IMRT, additional checks of couch speed uniformity and the synchronization between couch translation and gantry rotation are necessary [47]. Periodic QA of the treatment planning system is also important and is accomplished by recomputing the dose for a standard IMRT plan and comparing the results with an established baseline (i.e., a "constancy check").

For each individual patient, IMRT dose calculations from the treatment planning system are validated using an independent "second check" dose calculation software. Manual verification ensures that the parameters in each plan have also been successfully transferred from the treatment planning system to the IMRT delivery database. Finally, and most importantly, actual delivered dose maps from each patient's IMRT plan are measured in advance, and compared to the dose predicted by the treatment planning system, to verify that both the treatment planning and the delivery systems are functioning properly for the specific plan in question. This analysis is usually performed on the 2D dose maps generated by each IMRT field, though composite 3D dose distributions are also sometimes evaluated.

## IMRT for Prostate Cancer

### Dose Escalation

The role of IMRT in the treatment of prostate cancer lies in its ability to provide focused treatments to a target with a sharp penumbra that can reduce the dose given to critical normal structures (i.e., rectum and bladder). Therefore, IMRT can be used to escalate dose while keep the risk of toxicity the same or lower compared to 3DCRT.

The benefit of dose escalation has been shown in multiple randomized trials (described elsewhere in this textbook) [48–52]. The update of the Dutch phase III trial randomizing 669 patients to 68 Gy or 78 Gy reported 70-month median follow-up and a statistical improvement in 7-year freedom from biochemical failure (45 % vs. 56 %, $p=0.03$, Fig. 63.6) [48]. The majority of patients were treated with 3DCRT. The update of the MD Anderson Cancer Center phase III trial of 70 Gy versus 78 Gy also showed an improvement in 8-year freedom from biochemical or clinical failure (59 % vs. 78 %, $p=0.004$) [50]. Both arms used 3DCRT. Zietman et al. reported improved 5-year biochemical control with 79.2 Gy equivalent (delivered with a proton boost) compared to 70.2 Gy given by 3DCRT (80 % vs. 61 %, $p<0.001$) [52]. The MRC RT01 trial of 64 Gy versus 74 Gy, both given with 3DCRT, gave similar results (5-year biochemical progression-free survival 71 % vs. 80 %, $p=0.0007$) [49].

While the individual trials showed mixed results when patient outcome was analyzed by risk group, a meta-analysis performed by Viani et al. reported that all subgroups benefit in biochemical control with higher radiotherapy doses (Fig. 63.6) [53]. No statistical improvement in cause-specific or overall survival was noted.

### Efficacy Data for IMRT

While no randomized trials exist between 3DCRT and IMRT, a few cohort studies comparing groups treated with each technique to similar doses do not show any differences in cancer control, while studies in which the IMRT group received higher dose do show a control advantage (Table 63.2) [54]. Kupelian et al. [55] reported on a series of 166 IMRT patients compared to contemporary cohort of 116 patients treated with 3DCRT. The IMRT patients underwent a slightly accelerated course, receiving 70 Gy in 2.5 Gy fractions, while the 3DCRT group received 78 Gy in 2 Gy fractions. Three-year outcomes using the ASTRO definitions of three PSA rises showed similar results: 94 % versus 88 % ($p=0.084$).

Vora et al. [56] described the experience of 271 patients undergoing 68.4 Gy by 3DCRT compared to a sequential group of 145 patients prescribed 76 Gy by IMRT. Five-year biochemical control did show an advantage to the IMRT group (85 % vs. 74 %, $p<0.03$). A third study performed a matched pair analysis of 376 men treated with either IMRT or 3DCRT [57]. With comparable treatment doses and risk characteristics, there was no difference in biochemical recurrence (18 % vs. 19 %, $p=0.675$).

The 2011 National Comprehensive Cancer Network recommendations are that doses for intact prostate cancer reach a minimum of 75.6 Gy. Memorial Sloan Kettering Cancer Center recently published outcomes of 170 patients treated to 81 Gy with IMRT [58]. Median follow-up was 99 months. Ten-year actuarial PSA relapse-free survival was 81 % for low-risk, 78 % for intermediate-risk, and 62 % for high-risk patients.

### Toxicity

Observational studies have shown that higher radiation dose is associated with greater toxicity, particularly for late rectal complications [48–50, 52, 53]. In the cohort studies comparing IMRT to 3DCRT, dose seems to play the largest factor in toxicity (Table 63.3). However, in cohorts prescribed

a similar dose, IMRT does appear to reduce the risk of late GI toxicity [59–61].

Results for late genitourinary toxicity are mixed, and variability in the volume of irradiated bladder may contribute to the disparity between study findings (Table 63.4). Zelefsky et al. [62] found the late Gr2+ GU toxicity was increased in patients treated with IMRT, although on multivariate analysis, the presence of acute GU symptoms and dose affected the likelihood of late GU toxicity.

## Future Directions

Adaptive radiotherapy is based on a set of images taken at one time point. It involves replanning intermittently throughout the treatment course to adapt the treatment plan to each patient's individual likelihood of organ motion. Most replanning occurs within the first several weeks of treatment and can reduce the margin size required for motion for many patients [63–65]. One study noted that after five fractions,

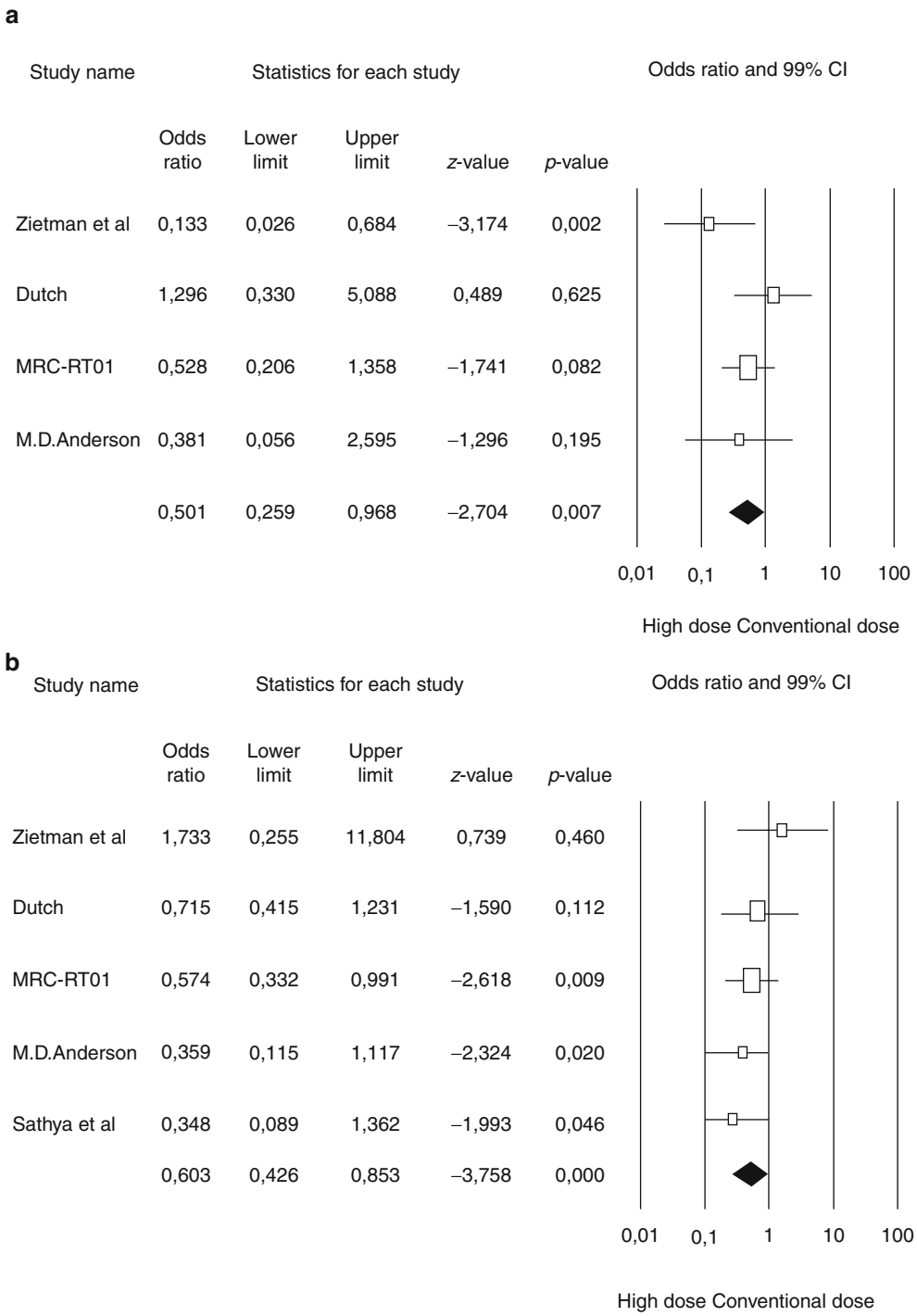


**Fig. 63.6** Viani et al. [53] meta-analysis regarding biochemical failure for the (**a**) low-, (**b**) intermediate-, and (**c**) high-risk groups based on dose (Reprinted with permission)

**Fig. 63.6** (continued)

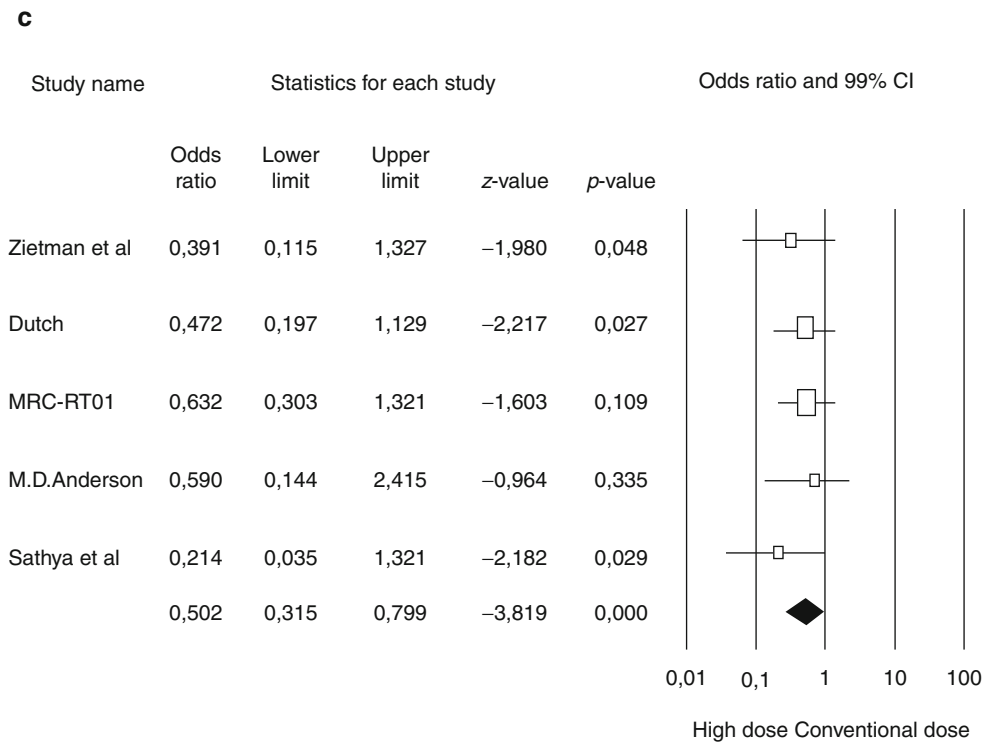


**Table 63.2** Comparison of biochemical relapse-free survival for IMRT versus 3DCRT

| | Median FU (months) | Failure definition | # IMRT patients | # 3DCRT patients | IMRT dose | 3DCRT dose | Actuarial time reported (years) | BRFS IMRT | BRFS 3DCRT | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| Kupelian et al. [55] | 25 | Three rises | 166 | 116 | 70[a] | 78 | 3 | 94 | 88 | 0.084 |
| Vora et al. [56] | 60 | Nadir +2 | 145 | 271 | 75.6 | 68.4 | 5 | 85 | 74 | <0.03 |
| Morgan et al. [57] | 35 | Nadir +2 | 188 | 188 | 81 | 80 | 4 | 82 | 81 | 0.67 |

*BRFS* biochemical relapse-free survival, *FU* follow-up, *IMRT* intensity-modulated radiotherapy, *3DCRT* 3D conformal radiotherapy
[a]Given in 2.5 Gy fractions

**Table 63.3** Comparison of late gastrointestinal toxicity for IMRT versus 3DCRT

| | Median FU (months) | # IMRT patients | # 3DCRT patients | IMRT dose | 3DCRT dose | Toxicity definition | Actuarial time reported | IMRT toxicity | 3DCRT toxicity | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| Kupelian et al. [55] | 30 | 166 | 116 | 70[a] | 78 | Gr2/3 | 30 months | 5 | 12 | 0.24 |
| | 30 | 166 | 116 | 70[a] | 78 | Gr3 | 30 months | 2 | 8 | 0.06 |
| Vora et al. [56] | 60 | 145 | 271 | 75.6 | 68.4 | Gr2/3 | Crude | 24 | 16 | 0.24 |
| | 60 | 145 | 271 | 75.6 | 68.4 | Gr3 | Crude | 1 | 2 | |
| Sharma [60] | 86 (3DCRT)<br>40 (IMRT)[b] | 123 | 170 | 76 | 76 | Gr2+ | 5 years | 8 | 20 | 0.01 |
| Zelefsky et al. [62] | 120 | 472 | 358 | 81 | 66–81 | Gr2+ | 10 years | 5 | 13 | <0.001 |
| Morgan et al. [57] | 35 | 188 | 188 | 81 | 80 | Gr2+ | 4 years | 4 | 9 | 0.06 |
| Kirichenko [59] | 63 (3DCRT)<br>30 (IMRT) | 489 | 928 | 74–78 | 70–79 | Gr2+ | 3 years | 6 | 10 | 0.05 |
| Martinez et al. [61] | 52 (3DCRT)<br>26 (IMRT) | 172 | 556 | 79.7 | 79.7 | Gr2+ | 3 years | 5 | 18 | <0.01 |

*FU* follow-up, *IMRT* intensity-modulated radiotherapy, *3DCRT* 3D conformal radiotherapy
[a]Given in 2.5 Gy fractions
[b]Mean FU

**Table 63.4** Comparison of late genitourinary toxicity for IMRT versus 3DCRT

| | Median FU (months) | # IMRT patients | # 3DCRT patients | IMRT dose | 3DCRT dose | Toxicity definition | Actuarial time reported | IMRT toxicity | 3DCRT toxicity | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| Vora et al. [56] | 60 | 145 | 271 | 75.6 | 68.4 | Gr 2/3 | Crude | 29 | 22 | 0.33 |
| Vora et al. [56] | 60 | 145 | 271 | 75.6 | 68.4 | Gr3 | Crude | 6 | 5 | |
| Sharma et al. [60] | 86 (3DCRT)<br>40 (IMRT)[a] | 123 | 170 | 76 | 76 | Gr2+ | Crude | 4 | 6 | 0.6 |
| Zelefsky et al. [62] | 120 | 472 | 358 | 81 | 66–81 | Gr2+ | 10 years | 20 | 12 | 0.01 |
| Morgan et al. [57] | 35 | 188 | 188 | 81 | 80 | Gr2+ | 4 years | 1 | 2 | 0.66 |
| Martinez et al. [61] | 52 (3DCRT)<br>26 (IMRT) | 172 | 556 | 79.7 | 79.7 | Gr 2+ | Crude | 8 | 12 | 0.12 |

*FU* follow-up, *IMRT* intensity-modulated radiotherapy, *3DCRT* 3D conformal radiotherapy
[a]Mean FU

the degree of future motion could be predicted with ~80 % accuracy [63]. Strategies to use online imaging through either CT on rails or CBCT allow for imaging taken at time of treatment to be used with the replanning software [66].

Focal tumor boost – IMRT allows dose escalation *within* a target structure so that as tumor imaging improves, it may be possible to boost doses to tumors within the prostate to even higher values [67, 68]. A simultaneous integrated boost (SIB) provides a greater dose per fraction to a target within the PTV, while respecting the tolerances of the rectum and bladder [69–71].

Hypofractionation – previously prohibited by toxicity, IMRT has allowed potential treatment to the prostate with higher doses per fraction and therefore shorter treatment courses. With limited follow-up, the efficacy of such treatment and its toxicity appears reasonable [72, 73]. Hypofractionation is discussed in more depth in the following chapter.

## Take Home Messages

IMRT is a radiation delivery technique that allows "dose sculpting" to improve target coverage while sparing normal tissues. It does require significant quality assurance and consideration of patient setup and target motion to ensure treatment accuracy. While the technique itself is not more efficacious in achieving biochemical control, its ability to spare normal tissues allows for dose escalation, which does provide improved prostate cancer control.

## Update

Presented at the 2011 Annual Meeting of the American Society for Radiation Oncology, the toxicity analysis of RTOG 0126 favored IMRT with reduction in early gastrointestinal/genitourinary toxicity. The dose escalation trial included 491 patients treated with 3DCRT and 257 with IMRT on the dose arm of 79.2 Gy. With median follow-up of 4.6 and 3.5 years, respectively, early grade 2+ GI/GU toxicity was significantly less in the patients treated with IMRT (14.3 % vs. 19.4 %, significant on multivariate analysis). A trend was also seen for reduction in late grade 2+ GI toxicity ($p = 0.099$). In addition, the volume of the rectum (≥15 %) receiving 70 Gy was independently associated with GI toxicity.

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## Suggested Reading

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# Proton Beam Therapy and Novel Radiotherapeutic Approaches to the Treatment of Prostate Cancer

64

Jeffrey J. Meyer, Jordan A. Holmes, and Ronald C. Chen

## Introduction

Radiation treatment of malignancies with curative intent requires maximizing the chance of tumor eradication while minimizing the risk of normal tissue injury, the so-called collateral damage of radiotherapy. There has been a gradual evolution in radiotherapy approaches over time in an effort to achieve this goal. Much of this evolution has centered on advances in the technological aspects of radiotherapy treatment planning and delivery. Appropriate delineation of clinical target volumes through improvements in imaging technology (CT, MRI, PET) is one example. Another example is in the development of three-dimensional conformal radiotherapy planning and the introduction of intensity-modulated radiotherapy (IMRT), discussed in the previous chapter.

The overwhelming majority of radiation treatments are delivered with high-energy photons (x-rays) or electrons. The interactions of photons with and their transfer of energy to tissue are in general well understood and can be modeled with treatment planning systems, allowing for creation of a specific radiation treatment plan for a given patient. Various techniques to overcome the dosimetric restrictions of x-ray therapy have been implemented over time. There is also considerable interest in using proton beams in radiotherapy treatments. This chapter describes the rationale for this interest, controversies associated with proton radiotherapy, and results in its use for the treatment of prostate cancer. Results with high-dose hypofractionated therapy delivered with stereotactic body radiation therapy will also be discussed.

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## Proton Therapy

### Physical and Biological Characteristics of Proton Radiotherapy

There is a critical difference in energy deposition (via ionizations or excitations) by protons versus photons in their interactions with tissues [1]. Protons gradually decelerate in tissue with a sharp rise in linear energy transfer (LET) at the end of their path; this has been termed the Bragg peak. Importantly, there is no further energy transfer/dose beyond the peak (i.e., no "exit dose"). This is in stark contrast to photon dosimetry, wherein dose is delivered beyond the target tissue. The physicist Robert Wilson realized in the mid-1940s that the Bragg peak phenomenon could be exploited in the treatment of tumors and that protons may offer a significant advantage over photons since there is less integral energy transferred to nontarget critical tissues [1]. As a result, the ratio of tumor control probability/normal tissue complication probability should be maximized.

Accelerating protons to the high energies required for treating deep-seated tumors requires the use of particle accelerators such as cyclotrons and synchrotrons. Much of the high cost associated with proton therapy treatment facilities is associated with use and maintenance of these accelerators. Much as with x-ray therapy, proton therapy can be delivered through isocentric gantries, allowing for use of multiple, nonaxial beam arrangements.

Most proton treatments are currently delivered using passive scattering systems, wherein proton energy and range compensators define the distal edge of the proton beam's penetration. Since the Bragg peak is so narrow, multiple Bragg peaks are "summed" together by beams of differing energies to create a "spread-out Bragg peak." There is also significant interest in pursuing spot scanning technology, in

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which individual "spots" of protons of varying energies are deposited within a tumor [2]. Spot scanning improves on the conformality of treatment plans relative to that achieved with passive scattering proton plans. Spot scanning should also reduce the amount of neutron contamination seen with passive scattering treatments [3].

Generally speaking, high-energy protons have a biological effectiveness similar to that of x-rays, although there is an increase in density of energy deposition toward the Bragg peak, with a concomitant increase in biological effect. Many, but not all, particle therapy centers employ a biological effectiveness correction of 1.1. That is, the physical dose delivered with protons is reduced by a factor of 1.1 relative to what would be delivered with photons to achieve the same biological effect [4]. The effective dose delivered with protons is given units of GyE (Gray equivalents).

## Proton Therapy: Treatment Planning Process

Proton treatments for prostate cancer are commonly delivered with opposed lateral beams, with one or two fields treated for each treatment session. With these arrangements, beams pass through but do not complete their range in the bladder and anterior rectal wall. A rectal balloon is often employed to mitigate intrafractional motion of the prostate and to distend the posterior rectum away from the lateral beam edge. Rectal balloons are not specific to proton therapy and can also be used for photon-based treatments [5]. The balloons are well tolerated by patients in general [6]. Harvard investigators have also reported on use of a single beam directed through the perineum [7]. Beam energies required for treatment are dependent on patient-specific anatomy and beam path length. Uncertainties in proton range must be determined during the treatment planning process and incorporated into additional margin around the distal edge of the clinical target volume [8].

## Preclinical Comparisons of Proton and Photon Therapy

Numerous groups have compared proton and photon treatment plans in order to evaluate potential dosimetric superiority of one modality versus the other [9–11]. In general, proton therapy with opposed lateral beams reduces doses to the rectum and bladder in the low-dose range, whereas in the high-dose range, intensity-modulated photon treatment plans can reduce dose to these structures compared to proton plans. Dose to the posterior rectal wall is quite low since the posterior wall is blocked in proton treatment plans. This may contribute to the low overall late rectal toxicity rates (discussed further below) (Fig. 64.1). In one study, IMRT was better able to spare the radiation dose to the femoral heads, a function of the multiple modulated beams used with IMRT as opposed to the two-beam opposed lateral configuration with most prostate proton treatments [10].

Integral energy transferred to the body is reduced with proton plans relative to photon treatments. Other modeling studies have shown that protons may be associated with a reduced risk of developing a secondary, radiation-induced malignancy in comparison with photons as a result of this reduced energy deposition [12].

## The Role of Proton Radiotherapy in Modern Radiation Oncology

The appropriate role of proton therapy in modern radiation oncology is controversial, particularly in the treatment of prostate cancer. The high costs associated with currently available treatment facilities and reimbursement for a course of treatment are a major factor in the controversy, with resulting debates over the cost-effectiveness of this treatment especially in the era of optimized 3D conformal and intensity-modulated x-ray therapy as well as the various brachytherapy methods [13–16]. These latter treatments allow for high-dose irradiation of the prostate with relatively low rates of acute and chronic GU and rectal toxicity. There have been arguments for and against the need for comparison randomized trials of proton and x-ray therapy made in the literature. It is important to note that similar clinical studies (of particle therapy versus "conventional" treatment) have indeed been conducted in the past [17]. As cost for facilities and treatments is reduced over time, and as intensity modulation methods are applied to proton therapy, cost-effectiveness debates will have to be readdressed [18].

## Proton Radiotherapy for Prostate Cancer: Clinical Results

### Institutional Experiences

Loma Linda University Medical Center (LLUMC) has extensive clinical experience employing proton therapy in prostate cancer management. In 2004, Slater et al. reported their experience with 1,255 patients with localized prostate cancer treated from 1991 to 1997 with protons or mixed proton/photon plans, without preceding surgery or androgen deprivation [19]. The radiation dose was 75 CGE in the patients treated with protons and photons and 74 CGE in the proton-alone patients. Lateral beams were used for the proton treatments. A rectal balloon was used for treatments. Median follow-up was 62 months. Estimated 5-year biochemical disease-free survival for all patients was 75 %. Initial PSA, PSA nadir, and Gleason score were all independently associated with

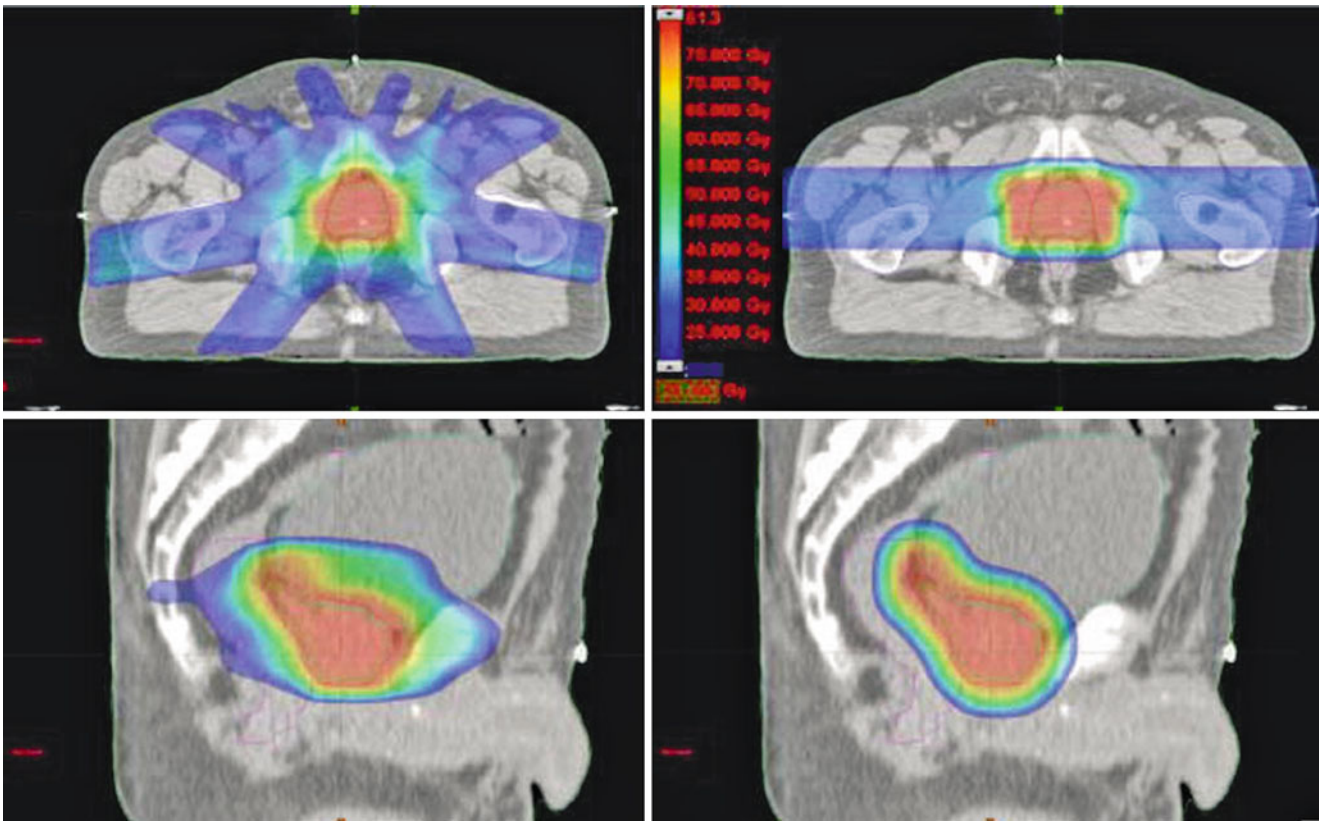

**Fig. 64.1** Comparison of IMRT (*top* panel, *left side*, and *bottom left* panel) versus proton (*top* panel, *right side*, and *bottom right* panel) treatment plans for a patient with prostate cancer. Multiple modulated photon beams are used in the IMRT plan as opposed to two (opposed lateral) beams for the proton plan. Colors correspond to different radiation doses as shown in the top panel (Reproduced, with permission, from Zhang et al. [11])

biochemical disease-free survival. Acute grade 3 or higher gastrointestinal (GI) toxicity was seen in <1 % of patients, and the estimated 5-year freedom from grade 3 or higher late toxicity was 99 %. Freedom from grade 3 or higher late genitourinary toxicity was similarly excellent at 99 %.

Investigators from the Hyogo Ion Beam Medical Center in Japan reported on acute toxicity data for 287 patients with localized prostate cancer treated with proton radiation therapy (dose: 74 CGE) [20]. About 70 % of patients received neoadjuvant androgen deprivation therapy. No patients developed grade 2 (NCI-CTC version 2.0) or higher acute GI toxicity. Thirty-nine percent and 1 % of patients developed acute grade 2 and 3 GU toxicity, respectively. Most patients responded to use of alpha-1 blocking agents to aid with urination difficulties. Bladder dosimetry was not related to acute GU toxicity in any clear manner. The authors emphasized the sparing of the posterior rectal wall made possible by the opposed lateral beam arrangement and the possible implications for preventing rectal toxicity.

## Clinical Trials

Investigators at Harvard began clinical studies with proton treatment for prostate cancer in the 1970s. Following early-phase clinical trials, a phase III study was conducted in which patients with locally advanced prostate cancer (T3–4, with or without involved pelvic lymph nodes) were treated with 50.4 Gy with photon therapy followed by a boost with 16.8 Gy with photons versus 25.2 GyE with protons (the latter delivered through a perineal-directed field) [21, 22]. A later report showed that the actual delivered dose for the patients in the proton-boost arm was 27 GyE for a total dose of 77.4 Gy. Although there were no differences in overall or disease-specific survival, likely a reflection of the locally advanced disease state, local control in the subset of patients with poor differentiation was higher in the high-dose arm. Grade 1–2 rectal bleeding was seen at a higher frequency in the high-dose arm. It is unknown if the rectal toxicity rates would have been even higher if the high-dose boost had been delivered with photons.

Gardner and colleagues reported on toxicity rates in long-term surviving patients treated on this protocol and on a preceding phase II study [22]. Thirty-nine patients were interviewed. Median follow-up was 13.1 years. Using the RTOG/EORTC Common Toxicity Criteria version 2.0, 15-year actuarial grade 2 or higher GI toxicity was 13 %, and grade 2 or higher hematuria was 47 %.

**Table 64.1** Late toxicity outcomes following prostate irradiation from selected phase III and institutional series

| Study (reference) | Dose (fractional dose) | Grade 2 GI (%) | Grade 3 GI (%) | Grade 2 GU (%) | Grade 3 GU (%) |
|---|---|---|---|---|---|
| *Photon studies* | | | | | |
| Peeters et al.[a] [26] | 68 Gy (2 Gy) | 27 | 4 | 41 | 12 |
| Randomized phase III trial | 78 Gy (2 Gy) | 32 | 5 | 39 | 13 |
| Kuban et al.[b] [27] | 70 Gy (2 Gy) | 13 | 1 | 8 | 5 |
| M.D. Anderson Cancer Center | | | | | |
| Randomized phase III trial | 78 Gy (2 Gy) | 26 | 7 | 13 | 4 |
| Dearnaley et al.[c] [28] | 64 Gy (2 Gy) | 24 | 6 | 8 | 2 |
| RT01 | | | | | |
| Randomized phase III trial | 74 Gy (2 Gy) | 33 | 10 | 11 | 4 |
| Alicikus et al.[d] [29] | 81 Gy (1.8 Gy) | 3 | 1 | 16 | 5 |
| Memorial Sloan-Kettering Cancer Center institutional series | | | | | |
| *Proton and photon-proton studies* | | | | | |
| Zietman et al.[e] [23] | 70.2 Gy (1.8 Gy) | 8 | 1 | 18 | 8 |
| PROG/ACR 95–09 | | | | | |
| Randomized phase III trial | 79.2 Gy (1.8 Gy) | 17 | 1 | 20 | 1 |
| Slater et al.[f] [19] | 74–75 Gy (1.8–2 Gy) | 1.2 % Grade 3+ | | | |
| Loma Linda University Medical Center institutional series | | | | | |

[a]Modified RTOG/EORTC toxicity scoring criteria. Actuarial results at 5 years
[b]Modified RTOG/LENT toxicity scoring criteria. Actuarial results at 10 years
[c]RTOG toxicity scoring criteria. Actuarial results at 5 years
[d]CTC v3.0 toxicity scoring criteria. Actuarial results at 10 years. Patients in this series were treated with intensity-modulated radiation therapy
[e]RTOG toxicity scoring criteria. Patients were treated with 50.4 Gy to the prostate with photons. The remainder of the treatment was delivered with protons to the prostate alone
[f]RTOG toxicity scoring criteria

LLUMC and Massachusetts General Hospital/Harvard investigators collaborated on the Proton Radiation Oncology Group/American College of Radiology (PROG/ACR) 95–09 protocol [23]. PROG/ACR 95–09 was not a direct test of the value of proton radiotherapy versus other types of prostate cancer treatments, but rather a randomized trial comparing two dose levels for patients with T1b–T2b prostate cancer, namely, 70.2 GyE versus 79.2 GyE (without androgen suppression). The trial is nonetheless important for the evaluation of proton therapy as it involved nearly 400 patients enrolled on a phase III, dual-institution study, and provides level I evidence regarding radiation dose selection in which a significant portion of the total dose was delivered with proton beams. All patients received 50.4 Gy with photon therapy to the prostate and seminal vesicles. Depending on the randomization arm, 19.8 or 28.8 GyE was delivered to the prostate alone with protons. At most recent report, median follow-up was 8.9 years. Patients in the high-dose group had a lower rate of biochemical failure (Phoenix criteria) at 10 years – 17.4 % versus 32.0 % in the low-dose arm. The difference in freedom from biochemical failure was especially pronounced in the subset of low-risk patients. Need for subsequent androgen deprivation therapy was lower in the high-dose arm, as well. There was no difference in overall survival between the two groups. Late grade 3 (RTOG criteria) or higher GU rates were 2 % for both dose arms; 1 % of patients in the high-dose arm had late grade 3 or higher GI toxicity.

ACR 03–12 is a phase II study evaluating efficacy and tolerability of high-dose radiation (82 Gy at 2 Gy per fraction) delivered with protons alone. Initial toxicity rates were recently published [24]. High-grade acute toxicity was uncommon, but investigators found an actuarial risk of grade 3+ late gastrointestinal/genitourinary toxicity rate of 6.08 %. There was no clear correlation between rectal wall radiation dose and rectal bleeding. Tumor control rates are awaited following further follow-up.

Mendenhall et al. at the University of Florida Proton Therapy Institute recently reported preliminary toxicity results from three institutional protocols treating low-, intermediate-, and high-risk prostate cancer patients [25]. Four of 211 patients experienced grade 3 GU toxicity, and 10 % of patients developed grade 2+ GI toxicity by 2 years following treatment.

Table 64.1 summarizes data regarding treatment-related toxicity from various phase III and institutional series [19, 23, 26–29]. Recognizing that differing toxicity criteria makes comparisons difficult, it is apparent that photon and proton treatments are both associated with relatively low rates of high-grade (grade 3+) gastrointestinal and genitourinary toxicity.

### Other Particles

Other particles such as neutrons, negative pi-mesons (pions), and carbon ions have also been studied as therapies for treating prostate cancer [30–32]. Neutrons are densely ionizing particles that tend to have a significantly higher biological effectiveness than photons, although this is not necessarily tumor specific and the actual therapeutic ratio does not appear significantly different than that achieved with photons. There may be an advantage to using neutrons for bulky and hypoxic tumors. Carbon ions share physical properties with protons (specifically, the Bragg peak) and also display some of the biological characteristics of neutrons. This combination is intriguing, and carbon ion facilities are conducting clinical studies evaluating the merits of carbon ion therapy for prostate and other cancers.

## Stereotactic Radiation Therapy

Stereotactic radiation is the highly precise irradiation of a target, with rapid radiation dose falloff at the periphery of the target, therefore minimizing radiation dose to nearby organs [33–36]. Although some treatments are indeed delivered with help of a defined stereotactic coordinate system, the term "stereotactic body radiation therapy" has become an umbrella term used to describe high-precision, high-dose radiotherapy typically made possible by image guidance. The precision results from target definition (usually involving CT scan fused with MRI during the treatment planning process), patient immobilization, and sophisticated image guidance (usually with CT or x-ray images) to localize the radiation target [37]. In contrast with conventionally fractionated radiation therapy and its protracted treatment course of several weeks, stereotactic radiation is typically delivered in one to five treatments (a high dose given per treatment). Both x-rays and particle irradiation can be employed in stereotactic hypofractionated treatment courses, although published studies to date have used x-rays.

### Stereotactic Radiation Technology

The target volume for radiation treatment includes the anatomical area of the cancer (e.g., prostate), which is expanded by a "margin" to account for imprecision of prostate location from 1 day to next (interfraction movement) and movement of the prostate during radiation treatment (intrafraction movement). In one study of 329 patients and 1,870 CT scans performed immediately prior to a daily radiation treatment, the prostate was found to vary in position by up to 2.5 cm left/right, 2.3 cm anterior/posteriorly, and 1.5 cm superiorly/inferiorly – although most were of much smaller magnitude [38]. Many centers in the United States now perform image-guided radiation treatment, using CT scans, fiducial markers (imaged with kilovoltage on-board imaging), or ultrasound to ascertain the location of the prostate prior to radiation treatment, therefore substantially reducing treatment setup error [39]. A potentially more difficult issue is the movement of the prostate during treatment, while the patient is on the treatment table and radiation is being delivered. This movement can be as much as 1 cm or greater and is unpredictable from patient to patient and from day to day [40, 41]. As mentioned above, use of prostate balloons can mitigate this motion. The need to radiate a larger area than the actual cancer to compensate for interfraction and intrafraction movement of the prostate means that parts of the nearby organs may also receive large doses of radiation treatment. For prostate cancer, these organs are the bladder and rectum, and radiation to these structures likely explains the long-term morbidity seen in some patients.

Similar to conventional radiation therapy, stereotactic radiation targets the entire prostate to a high dose of radiation. However, stereotactic radiation, with its ability to account for prostate interfraction and intrafraction movement, allows for reduction of the margin around the target, therefore reducing the amount of bladder and rectum irradiated [42]. Radiation planning studies comparing intensity-modulated radiation therapy (IMRT) to stereotactic radiation using the Cyberknife system showed that the latter can deliver a higher dose within the prostate, while reducing dose to the bladder and rectum [35, 42]. Therefore, stereotactic radiation holds promise for potentially increasing the effectiveness of treatment while reducing treatment-related toxicity.

Most of the currently published clinical data on stereotactic radiation for prostate cancer involve radiation delivery using the Cyberknife system. Cyberknife® (Accuray, Inc., Sunnyvale, CA) is a dedicated stereotactic radiation machine where a linear accelerator is mounted on a computer-controlled, six-joint, robotic arm [34, 43, 44]. The autonomous robotic arm allows delivery of radiation from coplanar and non-coplanar angles. The treatment table is also computer-controlled and has six degrees of freedom to allow for patient positioning adjustments. Prior to treatment, three to five fiducial markers (usually made of gold, 3–6 mm in length) need to be placed in the prostate via transrectal ultrasound by the urologist or radiation oncologist. Using a pair of diagnostic quality digital X-ray imaging devices, the Cyberknife system monitors the position of these fiducial markers (and thus the radiation target); the fiducial marker positions as detected on the x-rays are automatically interpreted by the system leading to adjustments to radiation delivery in real time [33, 42.]

Stereotactic radiation to the prostate can also be delivered using gantry-based (standard) linear accelerators (Linac-based

stereotactic radiation) with sophisticated image-guidance technology. Examples of such devices include the Novalis (BrainLab, Inc., Germany, Sweden), Trilogy (Varian, Inc., Palo Alto, CA), and Axesse (Elekta, Inc., Norcross, GA) treatment units [33, 34, 36]. The TomoTherapy Hi-Art System (TomoTherapy, Madison, WI), which uses a ring-shaped gantry delivering helical radiation therapy and on-board image guidance with megavoltage CT, can also be used.

Ideally, stereotactic radiation therapy, which uses a small margin around the prostate, needs to account for the intrafraction motion of the prostate [45, 46]. When a delivery system is used that cannot assess and/or track the prostate location in real-time during treatment, considerations for using immobilization devices such as the rectal balloon may be worthwhile.

## Biologic Rationale for Hypofractionation

In conventional prostate cancer radiation therapy, 1.8–2 Gy of radiation is delivered each day for a total treatment duration of 8–9 weeks. Hypofractionation is the delivery of higher doses of radiation in each treatment, reducing the number of overall treatments and thus the overall treatment time course. Radiation treatment, and decisions about dosing and fractionation, takes advantage of the differential sensitivities of the tumor versus adjacent organs to radiation in order to maximize the therapeutic ratio (i.e., maximize tumor kill while minimizing toxicity) [36]. For most tumors, low dose of radiation per treatment accomplishes this. However, multiple studies and radiobiologic calculations have suggested that prostate cancer may be different [47–49]. Compared to the adjacent organs (such as bladder and rectum), prostate cancer may be more sensitive to high doses of radiation per treatment. In radiobiology, the sensitivity of tissue (or tumor) to radiation dose fractionation is expressed as the $\alpha/\beta$ ratio. While most cancers are thought to have an $\alpha/\beta$ ratio of approximately 10 Gy, and therefore standard fractionation is used, the $\alpha/\beta$ ratio for prostate cancer may be as low as 1.5 Gy [36]. Since this value is less than the typical $\alpha/\beta$ value of 2–3 assigned to normal tissues, these data suggest that, for prostate cancer, hypofractionation may be a strategy to maximize the therapeutic ratio.

Extreme hypofractionation is the delivery of very large doses of radiation each day. An older British study treated 209 patients from 1962 to 1984 with nonmetastatic prostate cancer to 36 Gy in six treatments (6 Gy/fraction) [50]. This was done prior to the era of 3D radiation planning, intensity-modulated radiation therapy, or stereotactic radiation. With 22 years of follow-up, long-term disease control and morbidity outcomes were similar to historical controls from the same era – confirming its safety and potential effectiveness.

More recently, using high-dose rate brachytherapy (HDR), similarly high doses of radiation could be delivered to the prostate. Long-term disease control outcomes using HDR demonstrate the clinical efficacy of extremely hypofractionated radiation dosing schedules for the treatment of prostate cancer. Martinez et al. reported the results from 248 patients treated with HDR at William Beaumont Hospital (38 Gy in four treatments) and California Endocurietherapy Center (42 Gy in six treatments) for low- and intermediate-risk prostate cancer [51]. With a median follow-up of over 4 years, the 5-year biochemical control rate was 88–91 % and similar to a comparison cohort of patients treated with low-dose-rate brachytherapy at William Beaumont Hospital. Similar results were observed by Yoshioka et al., in a series of 112 patients with localized prostate cancer treated with HDR brachytherapy to a total dose of 54 Gy in nine treatments within 5 days [52]. At a median follow-up of 5.4 years, the local control rate was 97 %. Five-year biochemical failure-free survival for patients with low-, intermediate-, and high-risk disease were 85, 93, and 79 %, respectively.

While HDR is a treatment modality that can deliver high doses of radiation very accurately to the prostate, it is an invasive procedure with associated risks of infection, bleeding, and anesthesia. It requires hospital admission with narcotic pain medication to help patients manage the pain from indwelling catheters. With development of stereotactic radiation technology, this could potentially be a noninvasive method of delivering the same dosing regimen as HDR [53]. To deliver high doses of radiation externally requires a system with high precision of dose delivery, which is capable of adjusting for interfraction and intrafraction target motion. The stereotactic radiation systems described above have these capabilities. The technologic advances in radiation therapy – and development of these systems – have now made extremely hypofractionated radiation treatment for prostate cancer clinically feasible.

## Stereotactic Radiation as Monotherapy for Low- and Intermediate-Risk Prostate Cancer

Stereotactic radiation for low- and intermediate-risk prostate cancer has been a subject of intense study recently, with ongoing prospective trials accruing and multiple publications of institutional experiences. (Tables 64.2 and 64.3)

Boike et al. conducted a phase I dose escalation study of patients with low- to intermediate-risk prostate cancer [54]. Cohorts of 15 patients were successively treated to doses of 45, 47.5, and 50 Gy in five treatments, using LINAC-based stereotactic radiation with rectal balloon to minimize prostate motion. Median follow-up was 30 months. Biochemical control was achieved by 100 % of patients.

**Table 64.2** Published studies on stereotactic radiation therapy for prostate cancer and disease control outcomes

| First author | Study design | Stereotactic system | *N* | Risk group | Dose fractionation | Median follow-up (year) | Disease control measure | Death from prostate cancer |
|---|---|---|---|---|---|---|---|---|
| *Prospective trial* | | | | | | | | |
| Boike [54] | Phase I | LINAC | 45 | Low and intermediate | 45 Gy–50 Gy/5 fx | 2.5 | Biochemical control 100 % | X |
| Tang [66] | Phase I/II | LINAC | 30 | Low | 35 Gy/5 fx | 1 | X | X |
| King [56] | Phase II | Cyberknife | 41 | Low and intermediate | 36.25 Gy/5 fx | 2.75 | Biochemical control 100 % | – |
| Madsen [55] | Phase I/II | LINAC[a] | 40 | Low | 33.5 Gy/5 fx | 3.4 | 4-year FFBF 90 % | – |
| *Prospective or retrospective series* | | | | | | | | |
| Freeman [59] | Combined analysis (Florida retrospective and Stanford prospective) | Cyberknife | 41 | Low | 36.25 Gy/5 fx (Stanford), 35 Gy/5 fx (Florida) | 5 | bPFS 93 % | – |
| Friedland [58] | Single-institution | Cyberknife | 112 | Low, intermediate, and high | 35 Gy/5 fx | 2 | Biochemical control 97 % | 0 |
| Katz [60] | Single-institution | Cyberknife | 50 | Low (69 %), intermediate (27 %), and high (4 %) | 35 Gy/5 fx | 2.5 | Biochemical control 100 % | 0 |
| | | | 254 | | 36.25 Gy/5 fx | 1.4 | Biochemical control 98 % | X |
| Townsend [65] | Single-institution | Cyberknife | 37 | – | 35 Gy or 37.5 Gy in 5 fx | 1 | – | X |
| Bolzicco [57] | Single-institution | Cyberknife | 45 | Low (49 %), intermediate (51 %) | 35 Gy/5 fx | 1.7 | Biochemical control 100 % | 0 |
| Jabbari [46] | Single-institution | Cyberknife | 20 | Low or intermediate | 38 Gy/4 fx | 1.5 | Biochemical control 100 % | 0 |

*X* follow-up too short for meaningful results, *LINAC* linear accelerator, *Fx* fraction, *FFBF* freedom from biochemical failure, *bPFS* biochemical progression free survival
[a]Patients treated in flex-prone position

**Table 64.3** Acute and late GI and GU toxicity from stereotactic radiation therapy for prostate cancer

| | Acute (%) | | | | Late (%) | | | |
|---|---|---|---|---|---|---|---|---|
| First author | Grade 2 GI | Grade 3 GI | Grade 2 GU | Grade 3 GU | Grade 2 GI | Grade 3 GI | Grade 2 GU | Grade 3 GU |
| *Prospective* | | | | | | | | |
| Boike | 2.5[a] | 0[a] | 18[a] | 2[a] | – | – | – | – |
| Tang [66] | 7 | 0 | 13 | 0 | [b] | [b] | [b] | [b] |
| King [56] | – | – | – | – | 15 | 0 | 24 | 5 |
| Madsen [55] | 13 | 0 | 21 | 2 | 8 | 0 | 20 | 0 |
| *Retrospective* | | | | | | | | |
| Freeman [59] | – | – | – | – | 2.5 | 0 | 7 | 2.5 |
| Friedland [58] | – | – | – | – | – | – | – | – |
| Katz [60] (35 Gy) | 4 | 0 | 4 | 0 | 0 | 0 | 2 | 0 |
| (36.25 Gy) | 4 | 0 | 5 | 0 | 3 | 0 | 6 | 1 |
| Townsend [65] | 0 | 0 | 2 | 3 | – | – | – | – |
| Bolzicco [57] | 24 | 0 | 11 | 0 | 2 | 0 | 0 | 2 |
| Jabbari [46] | 17 | 0 | 39 | 0 | 3 | 0 | 8 | 5 |

*GI* gastrointestinal, *GU* genitourinary

[a]Worst toxicity was reported and did not distinguish between acute and late

[b]The percentage of patients with grade 2 or grade 3 GU and GI symptoms at 3 and 6 months were no higher than baseline

Madsen et al. published results of 40 patients with low-risk prostate cancer from the phase I/II trial of Stereotactic Hypofractionated Accurate Radiotherapy of the Prostate (SHARP) [55]. Patients were treated in the flex-prone position from 2000 to 2004 and received 33.5 Gy in five treatments. After a median follow-up of 41 months, three biochemical failures were seen. The 48-month actuarial freedom from biochemical relapse rate was 90 %.

A Stanford phase II trial treated patients with low- and intermediate-risk prostate cancer after 2003 [56]. Patients received 36.25 Gy in five treatments. In an interim report of 41 patients with median follow-up of 33 months, no patient experienced biochemical failure. The median PSA nadir was 0.32 ng/mL (range 0.03–2.65). Multiple other studies have confirmed that patients treated with stereotactic radiation therapy achieve a similarly low PSA nadir [55, 57, 58]. In a follow-up report pooling Stanford patients with long follow-up with patients from Naples, Florida (who received 35 Gy in five treatments), 5-year biochemical progression-free survival rate for patients with low-risk disease was 92.7 % [59].

Large retrospective series have confirmed the results from these trials. In a study of 304 patients treated at Winthrop University Hospital from 2006 to 2008, two dosing schedules were used. The first 50 patients received a total of 35 Gy (in five treatments), while the subsequent 254 patients received 36.25 Gy. Four patients experienced biochemical failure (two with low-risk and two high-risk disease) [60]. Friedland, reporting the full experience of patients treated in Naples, Florida, analyzed results from 112 patients with median follow-up of 24 months [58]. Three experienced biochemical failure.

Rates of acute and late gastrointestinal and genitourinary toxicity are similar to those reported for external beam radiation (photon) or proton radiation (Table 64.1). Acute grade 2 gastrointestinal (GI) toxicity has been reported at 0–24 % in different series, and grade 2 genitourinary (GU) toxicity at 2–39 % (Table 64.3). Late grade 2 GI toxicity ranged from 0 to 15 %, and GU toxicity 0–24 %. Grade 3 GI and GU toxicity is rare. It is important to note that these results are from early clinical experiences using stereotactic radiation for prostate cancer. With increased experience using this technology, toxicity rates will likely be lower.

Several studies examined patient-reported quality of life. In the SHARP study, median American Urological Association (also called the International Prostate Symptom Score) score measuring urinary symptoms increased at 1 month following treatment but returned to baseline values by subsequent follow-up time points [55]. Similarly, in the Stanford trial, the AUA score worsened by 3 months but improved to be better than baseline at 1- and 2-year time points [56]. This initial increase in urinary symptoms with subsequent recovery to baseline has also been reported by two large series and appears to be a consistent finding [58, 60]. The Stanford trial reported that patient-reported rectal symptoms, measured by the Expanded Prostate Cancer Index Composite (EPIC), showed increased rectal symptom at 3 months, and about 50 % of patients continued to report "very small/small problem" at 1 and 2 years. In contrast, Katz et al., using the same instrument, reported that bowel symptoms returned to baseline after an initial worsening [60]. Using a rectal assessment score, Friedland et al. reported resolution of symptoms by 4 months [58].

Patient reported sexual function has also been examined. Using the Sexual Health Inventory for Men (SHIM), Friedland reported decreased scores during treatment but return to baseline within 1 month [58]. Of patients who

**Table 64.4** Published dose-fraction schedules for stereotactic radiation therapy in prostate cancer

| Total dose (Gy) | Number of fractions | Dose per fraction (Gy) | Biologically equivalent dose (Gy) (when given in 2 Gy/fraction)[a] |
|---|---|---|---|
| 33.5 | 5 | 6.7 | 78 |
| 35 | 5 | 7 | 85 |
| 36.25 | 5 | 7.25 | 91 |
| 37.5 | 5 | 7.5 | 96 |
| 38 | 4 | 9.5 | 119 |

[a]Assuming $\alpha/\beta$ ratio of 1.5 for prostate cancer

reported erectile function sufficient for sexual intercourse at baseline, 82 % retained this ability at 1 year and 81 % at 2 years. Similar rates were reported in the Katz series (87 % patients maintained potency at median follow-up of 18 months) [60] and by the SHARP trial (77 % maintained potency at median follow-up of 30 months) [55]. Using the EPIC instrument, Wiegner reported sexual function results in 32 patients from the Stanford trial with at least 12 month follow-up [61]. This study demonstrated a gradual decline in the sexual domain summary score up to 48 months of follow-up. Age was found to be an important factor in patient's ability to maintain sexual function after treatment. For patients younger than 70 years, 60 % maintained satisfactory erectile function; in contrast, only 12 % of patients ≥70 years did ($p = 0.008$). No significant association was found between radiation dose to the penile bulb and sexual function.

As described above, there are currently multiple dose fractionation schedules for stereotactic radiation being used for prostate cancer treatment (Table 64.4). The biologically equivalent dose of these extremely hypofractionated treatment regimens, when compared to conventionally fractionated radiation given at 2 Gy per day, all represent dose-escalated radiation therapy. Some of the regimens may represent delivery of doses much higher than currently possible with conventional (nonstereotactic) radiation technology. The available literature shows that these schedules have promising results in disease control and toxicity, but the comparative effectiveness of the different schedules will require further study. In addition, some of the treatment regimens use "heterogeneous" dose planning, intentionally planning radiation treatment to mimic the doses given by HDR brachytherapy, with doses inside parts of the prostate (such as the peripheral zone) significantly higher (up to 40 %) than the dose to the periphery of the prostate [34, 46, 53]. The rationale for this type of planning and delivery is to deliver even higher radiation doses to within the prostate. Other institutions plan stereotactic radiation using "homogeneous" dosing, in order to deliver a relatively even dose to all parts of the prostate [34, 56, 58]. Both types of planning are currently being investigated in multicenter phase II trials. Whether heterogeneous or homogeneous dosing results in differential disease control and/or toxicity rates awaits further study as well.

## Stereotactic Radiation as a Boost for Intermediate- and High-Risk Prostate Cancer

For patients with intermediate- or high-risk prostate cancer, where the risk of extra-prostatic disease extension is higher, conventionally fractionated radiation therapy could be used to treat a larger area around the prostate and seminal vesicles, and stereotactic radiation used for additional high dose given to the prostate ("boost" radiation dose). Several retrospective series have been published, describing the tumor control efficacy and toxicity of this combination treatment regimen.

The largest published series included 73 intermediate- and high-risk patients treated at Winthrop University Hospital (Mineola, NY) with external beam radiation to 45 Gy (1.8 Gy per fraction) plus stereotactic radiation boost ranging from 18 Gy (in three fractions) to 21 Gy (in three fractions) [62]. Thirty-six patients (49 %) received androgen deprivation therapy also for a median duration of 4.8 months. With a median follow-up of 33 months, the 3-year actuarial biochemical control rates for intermediate-risk patients was 89.5, and 77.7 % for high-risk patients. Overall, 6.8 % of patients experienced acute grade 2 urinary toxicity, and 6.7 % grade 2 rectal toxicity; there was no acute grade 3 toxicity. Late grade 2 urinary and rectal toxicity rates were 4.1 and 8.2 %, respectively; one patient (1.4 %) experienced late grade 3 urinary toxicity.

In another series, 50 patients with mainly intermediate- and high-risk disease were treated with 64 Gy of conventionally fractionated radiation, followed by stereotactic radiation boost of 10–16 Gy in two fractions [63]. Thirty-three patients also received androgen deprivation therapy. Five-year biochemical disease-free survival was 98 %. The 5-year rates of grade ≥2 GI and GU toxicity-free survival were 72 and 82 %, respectively.

Results from additional smaller series of patients have shown results consistent with the above [46, 64, 65].

## Take Home Messages

Reduced overall irradiation to nontarget normal tissues remains the primary appeal of proton therapy. To date, a direct comparison of proton- and photon-based treatments for prostate cancer has not been performed. Although the rates of acute and late toxicity associated with proton therapy are encouragingly low (along with disease-control rates appropriate for the doses delivered), nonrandomized inter-study comparisons with published photon series present challenges. Moreover, long-term data regarding hip fracture incidence and erectile function following proton irradiation are not yet available. In the face of highly conformal external beam photon therapy and brachytherapy, the debate about cost-effectiveness of protons as a radiotherapy option for

prostate cancer will continue. Optimization of proton therapy for prostate and other tumors remains an active area of investigation that may provide new fuel for this debate.

Stereotactic radiation for prostate cancer holds promise to be a radiation treatment modality that increases efficacy (by delivering a high dose of radiation each day) and decreases long-term toxicity (by taking advantage of the radiobiologic differences between prostate cancer and adjacent organs and by the precise radiation delivery using stereotactic technology) compared to standard fractionation radiation therapy. Early results appear consistent with these hypotheses, and data from prospective trials continue to mature. Stereotactic radiation therapy represents a dramatic shift in the way radiation treatment is delivered for prostate cancer, and shortens treatment time from 8–9 to 1 week. With longer follow-up, if stereotactic radiation therapy is shown to be similar or better than other treatment modalities in terms of disease control efficacy and long-term toxicity, then the noninvasive nature and short treatment duration of this treatment may make it an attractive option [36].

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# Prostate Cryotherapy

# 65

Mohamed Ismail, Shwan Ahmed, and John Davies

## Introduction

Prostate cancer is the most commonly diagnosed malignancy in the UK representing 24 % of male cancers diagnosed; the death rate from prostate cancer is significant at 3 % of all male deaths [1]. Current curative therapies for early prostate cancer include radical prostatectomy (RP) (open, laparoscopic, or robotic techniques), external beam radiotherapy (EBRT), and brachytherapy (BXT). More recently, prostate cryotherapy has become available to treat localized and locally advanced prostate cancer. There is no randomized controlled trial comparing cryotherapy to the standard treatments. Nevertheless, there are several clinical centers that published their clinical experience with primary and salvage cryotherapy. There is adequate evidence to support the use of this procedure in patients with prostate cancer.

## History of Cryotherapy

The word "cryo" comes from the Greek word "kruos" for cold. Cryosurgery, also known as cryotherapy or cryoablation is a technique in which freezing is used to destroy undesirable tissues. Dr. James Arnott from Brighton, UK (1797–1883), was the first physician to use cold or congelation to treat cancers [2]. He used a mixture of saline and ice applied to advanced breast and cervical cancer to reduce pain, discharge, and hemorrhage.

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Several major developments took place at the end of the nineteenth century. In 1877, Cailletet of France and Pictet of Switzerland began developing adiabatic expansion systems for cooling gases. This led to liquefaction of oxygen, air, and nitrogen. In 1895, Linde of Germany and Hampson of the UK began using throttle expansion or the so-called the Joule-Thompson effect that enabled the production of continuous operating air liquefiers. These developments have enabled Dr. Campbell White from New York to use liquid oxygen (−190 °C) to treat various dermatological conditions [3]. Liquid nitrogen became commercially available in 1940s and was used clinically in 1950s by Allington of Oakland, California [4], but only to treat superficial skin conditions as delivery systems for deeper tissues were not available. One of the most important steps in the history of cryosurgery was the development of the closed liquid nitrogen system in 1961 by a neurosurgeon, Irving Cooper, and an engineer, Arnold Lee [5]. They designed a cannula capable of delivering liquid nitrogen to deep tissue, which was essentially the model from which future liquid nitrogen probes were manufactured. In 1964, Maurice J Gonder from New York and colleagues began experimenting on canine prostate [6] using liquid nitrogen. Two years later, the same group published the first report of prostate cryosurgery in 50 patients with BPH and prostate cancer [7, 8]. The prostate was frozen using a single 26 Fr diameter liquid nitrogen probe, only the tip of which was cooled (−160 °C). The probe was placed trough transurethral approach, and the freezing process was continuously monitored by a single thermocouple positioned between the rectal wall and the prostate and by regular digital examination. Freezing was stopped when the thermocouple temperature reached 0 °C or if any fixation of the rectal mucosa was felt. Although they achieved sufficient outcome in terms of BPH symptoms and cancer control, complications were significant. These included urethral sloughing of necrotic tissue which required removal, frequent infections such as epididymitis, prolonged catheterization, and incontinence. Despite technical modifications of cryotherapy including open perineal [9] and percutaneous transperineal

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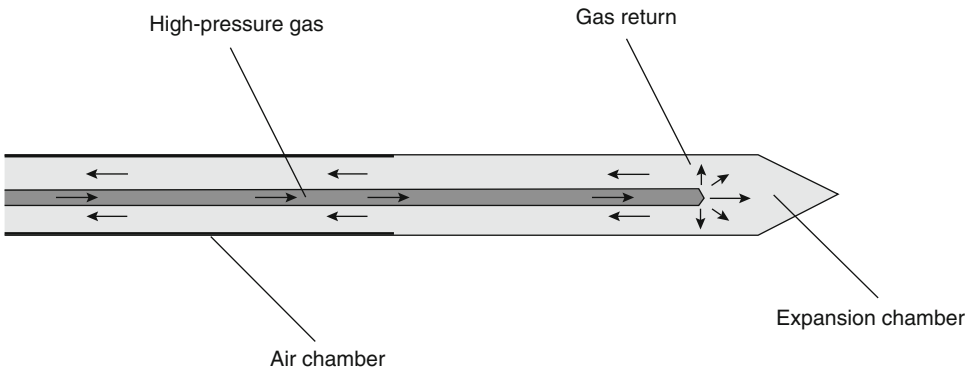


**Fig. 65.1** Diagram of the tip of a Joule-Thompson-type freezing probe

[10] approaches, complications remained a problem as surgeons were still unable to precisely place the cryoprobes or monitor the freezing process. Therefore, urologists lost interest in cryosurgery in the 1980s.

Another significant landmark in the development of modern cryosurgery which led to the revival of interest was the development of real-time transrectal ultrasound scan monitoring by Onik et al. [11]. This enabled surgeons to accurately place the cryoprobes and continuously visualize ice ball progression. At the same time, a multi-probe liquid nitrogen system (Accuprobe™) was introduced. This allowed a synergistically uniform and effective distribution of lethal low temperature throughout the ice ball. In the 1990s, cryosurgery developed rapidly. Lee et al. [12] described the use of transperineal thermocouple probes placed at specific points providing real-time temperature information of the ice ball, sphincter, and rectal wall. A year later, a double-lumen urethral warming catheter was developed [13] in order to preserve the urethral mucosa. These developments facilitated more effective tumor destruction and significantly reduced complications including incontinence, urethral sloughing, and rectourethral fistula. In the late 1990s, multiple-port high-pressure gas systems utilizing the Joule-Thompson effect were introduced. These systems use pressurized argon gas for freezing and helium for active thawing. They are compact, respond rapidly to user input, and able to create an ice ball faster with steeper internal temperature gradients than the liquid nitrogen systems (Fig. 65.1).

## Equipments Used in Prostate Cryotherapy

### Transrectal Ultrasound (TRUS)

Biplanar TRUS allows for viewing the prostate and monitoring the progression of the ice ball both in transverse and longitudinal views. The leading edge of the ice ball appears as a bright line as the sound waves reflect off the frozen/unfrozen interface (Fig. 65.2). The tissue behind the ice ball edge is concealed in the acoustic shadow; therefore, TRUS cannot monitor beyond the anterior boundary of the ice ball.

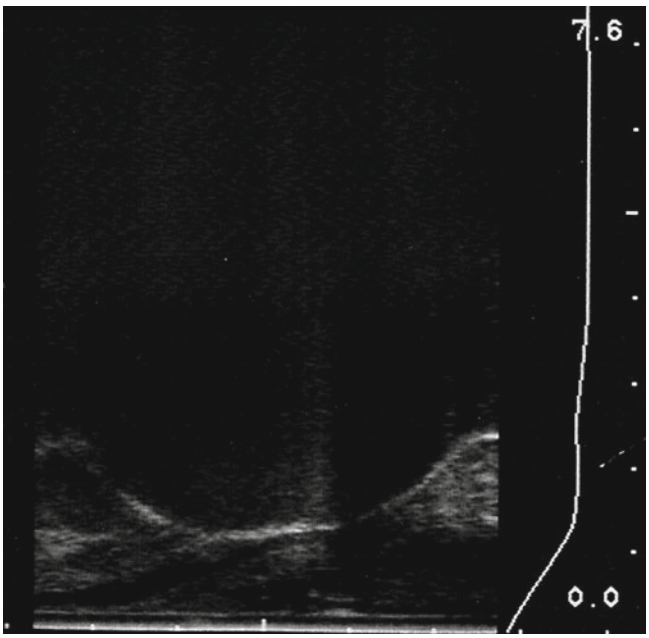


**Fig. 65.2** Sagittal view of the prostate showing ice ball formation

### Cryotherapy Systems

Two cryotherapy systems are available for prostate cancer treatment. The Cryocare CS™ system with built-in ultrasound scanner (Endocare Inc, Irvine, CA) allows the use of up to eight freezing probes and eight thermosensors. The system enables the user to control the rate of cooling by changing the rate of freezing gas flow rate between 5 and 100 % in 5 % increments.

The Seednet™ system (Galil Medical, Plymouth, Meeting, PA) allows the use of up to 30 cryoneedles and 5 thermosensors. The users can change the gas flow rate between 20 and 100 % in 20 % increments.


**Fig. 65.3** Ice ball formation on a cryoneedle

## Freezing Probes

Double-lumen cryoprobes are used, where high-pressure gas (up to 300 bar) is delivered via a thin central tube to the tip of the probe. The gas is then released to the expansion chamber where it expands rapidly as its pressure decreases to the atmospheric pressure (1 bar). The expanded gas is then circulated back to the cryogenic unit through the outer lumen of the cryoprobe and the supply hose where it is vented into the room (Fig. 65.3). This sudden change of gas pressure results in temperature change via the Joule-Thompson (J-T) effect. High-pressure argon gas is used for freezing as its temperature decreases to −186 °C, while helium is used for thawing (+67 °C) according to the J-T effect. The shaft and base of the probe is insulated with an air chamber to protect perineal tissue from freezing. The Cryocare CS™ system uses 2.4-mm-diameter probes, while the Seednet™ system utilizes smaller 1, 47-mm-diameter cryoneedles.

## Urethral Warming Device

Urethral warmer consists of a closed double-lumen catheter made of polyethylene membrane, through which heated saline (38–43 °C) is continuously circulated by a special pump.

## Thermosensors

To monitor the ice ball temperature, 1.5-mm-diameter probes with T-type 0.07-mm-diameter copper/constantan alloy thermocouple wire are used.

# The Joule-Thompson Effect

The Joule-Thompson effect is a process in which high-pressure gas changes temperature when expands adiabatically. Argon cools to −186 °C while helium warms to +67 °C.

For a fixed pressure, a gas has a Joule-Thompson inversion temperature which determines if the gas cools down or warms up upon expansion. The value of this temperature is −233 °C for helium and +450 °C for argon. Therefore, at room temperature, helium results in warming while argon causes cooling on expansion. The reason of this difference is explained by the difference in the intermolecular forces of each gas. In any gas, there are attractive and repulsive forces present between the molecules or atoms. When a system goes to a more stable state, it gives off energy; the process is exothermic, whereas if a system goes to a less stable state, energy must come from somewhere for the process to occur. In the process of gas expansion, this energy is in the form of heat. In the case of argon gas, the attractive forces predominate, upon expansion, a larger average separation of molecules leads to a less stable state, and energy in the form of heat is taken from the surroundings; hence, cooling is observed upon expansion. When helium is used, heating is observed upon expansion as the repulsive forces predominate, and a greater separation of molecules results in a more stable state, releasing energy in the form of heat.

# Cryobiology

The destructive effect of freezing on tissues can be due to many mechanisms: direct cellular injury, vascular injury, increased apoptosis, and a possible immunogenic effect.

## Direct Cellular Injury

Two biophysical changes occur in water during freezing and have been linked to direct cell injury. As the temperature falls to less than 0 °C, water crystallizes and ice starts to form. This first occurs in the extracellular spaces creating an

extracellular hyperosmotic environment. This in turn withdraws water from the cells causing cellular dehydration. The resulting high concentration of intracellular solute has been hypothesized to cause cellular injury by damaging vital enzymes and destabilization of the cell membrane through increased protease activity and lipid peroxidation, respectively. Effective cellular dehydration occurs predominantly between 0 and −20 °C and with relatively low cooling rates when the cells have sufficient time to dehydrate completely. Intracellular ice formation (IIF) occurs when temperature drops below −40 °C [14]. IIF is more efficient when the cooling rate is rapid, not allowing sufficient time for water to leave cells which keeps their solute freezing point higher. Lethal injury of ice crystal to the organelles and membranes is more lethal than that of the extracellular ice, although the precise mechanism whereby IIF destroys cells is still debated [15]. During thawing, ice crystals fuse to form larger crystals (a process called recrystallization) which can disrupt the cell membrane and causes additional cell damage. As the ice melts, the extracellular environment becomes hypotonic, and water enters the damaged cells which subsequently increases cell volume leading to cell membrane rupture [14].

### Vascular Injury

The initial response to the cooling of tissue is vasoconstriction, a decrease in the flow of blood and eventually the circulation ceases with freezing causing ischemia. During thawing, the circulation returns with vasodilatation. This hyperemic response is brief and associated with increased vascular permeability leading to tissue edema. Cryotherapy has also shown to cause endothelial damage which results in a further increase in capillary wall permeability and edema, platelet aggregation, and microthrombus formation resulting in stagnation of the circulation [16]. The loss of blood supply deprives all cells of any possibility of survival and results in tissue necrosis.

### Apoptosis

Apoptosis is a form of cell death designed to eliminate unwanted cells through activation of a coordinated, internally programmed series of events. Biochemical features of apoptotic cells include protein cleavage, protein cross-linking, and DNA breakdown. Apoptosis could happen in normal tissues such as endometrial cell breakdown during the menstrual cycle and also occurs in pathological conditions including cancers, cytotoxic chemotherapy, heat injury, and irradiation. Apoptosis is also seen after tissue freezing predominantly in the peripheral zone of the cryogenic lesion where the temperature was not sufficiently cold to kill all the cells [17]. Studies have shown apoptosis occurs at temperatures between 6 and −10 °C [15] and that cells were susceptible to entering the apoptotic state up to 8 h after rewarming [18]. Most of the studies examining the role of apoptosis in cold and freezing injury have been in vitro, and the effect of apoptosis in vivo is still unclear.

### Immunogenic Effect

Soanes et al. [19] have suggested a possibility of an "immuno-cryothermic response" following a spontaneous regression of metastatic lesions in two men after cryotherapy for primary prostate cancer. According to this hypothesis, after cryosurgery, the immune system of the host is sensitized to the tissue destroyed by the cryosurgery. Any tissue remaining undamaged by the freezing insult is destroyed by the immune system during the time after cryosurgery. Since then, many investigators have examined the role of cryoimmune response in animals; however, their results were inconsistent. While several studies showed immunogenic response, many showed little or no response and others have shown that cryosurgery increases tumor growth and metastasis [20].

## Physical Parameters of Prostate Cryotherapy

The degree of cryogenic injury is a function of five different physical parameters: target temperature, cooling rate, duration of freezing, thawing rate, and number of freeze-thaw cycles.

### Target Temperature

The temperature range over which cells die is −5 to −50 °C [21]. Extensive tissue damage occurs at −20 to −30 °C, but cell destruction is uncertain or incomplete. As explained before, IIF, which is more effective, occurs commonly in temperatures below −40 °C. Therefore, temperatures between −40 and −50 °C are essential to ensure complete damage of all cancer cells.

### Duration of Freezing

Increasing the duration of freezing can allow the intracellular space to equilibrate with the extracellular space, thereby increasing cellular dehydration. Holding longer at subzero temperatures can also increase the amount of IIF. Increasing hold time may also allow recrystallization, whereby smaller ice crystals fuse to form larger ice crystals [14]. It has been recommended that the prostate should be held in the frozen state for 5 min, although the optimum duration of freezing is not well defined [18].

### Thawing Rate

The rate of thawing should be as slow as practical and is best done by allowing the tissues to thaw passively with no assistance by heating. The longer the duration of the thaw, the greater the damage to the cells because of solute effects, ice-crystal restructuring (recrystallization), prolonged oxidative stress, and growth of ice crystals [22]. The large ice crystals that form during "warming" recrystallization create shearing forces which disrupt the tissues.

### Number of Freeze-Thaw Cycles

Repeating the freeze cycle produces faster cooling and more extensive tissue destruction and necrosis [23]. This means, in the prostate, the border of tissue destruction moves closer to the outer limit of the frozen volume, permitting a closer approach to the margins of the gland without endangering the rectum. Therefore, repetition of the freeze-thaw cycle is thought to be critical in the treatment of prostate cancer.

### Cooling Rate

The cooling rate should be as fast as possible to increase the potential to produce the more effective IIF. During prostate cryosurgery, rapid freezing of the order of 50 °C/min or more occurs only close to a cryosurgical probe. The further away from the probe, the lower is the cooling rate. At about 1 cm from the probe, the cooling rate is estimated to be between 10 and 20 °C/min. However, studies have shown that IIF occurs over a wide range of cooling rates ranging from 20 to 50 °C/min, and in tightly packed cells even a slower cooling rate may produce IIF [21]. From these variances, it appears that the cooling rate is less critical to cell injury than the mentioned other factors.

## The Cryogenic Lesion

This is characterized by a central uniform coagulation necrosis near the cryoprobe/cryoneedle where temperature reaches below −20 °C. The central area is surrounded by a peripheral zone (temperature ranges between 0 and −20 °C) which is characterized by partial necrosis and apoptotic cells. Soon after thawing, the tissue appears congested and hyperemic and becomes edematous, while the extent of necrosis becomes evident in about 2 days. The process of wound repair begins in the peripheral zone in the areas in contact with viable tissue. Inflammatory cells infiltrate and new blood vessels may grow into the injured tissue. Over the following weeks or even months, the dead tissue is slowly replaced by fibroblasts and new collagen formation. The end result is a contracted healed area.

## Patient Selection for Prostate Cryotherapy

### Primary Cryotherapy

Cryotherapy is infrequently used to treat organ-confined prostate cancer in the UK because of increasing competition from other treatment modalities such as radical prostatectomy, radical radiotherapy, and brachytherapy. The National Institute for Health and Clinical Excellence (NICE) has updated recommendations in 2008 stating that cryotherapy should not be considered for men with localized prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions. The European Association of Urology (EAU) guidelines on prostate cancer state that cryotherapy is a true therapeutic alternative for patients with clinically localized prostate cancer [24]. The American Urological Association has issued an update on their best practice policy statement on cryotherapy treatment for localized prostate cancer [25]. There is a scarcity of evidence that short-term outcomes for intermediate- and high-risk organ-confined disease may be similar to those from radiotherapy at follow-up durations <8 years. Cryotherapy has also been used to treat locally advanced primary prostate cancer. A recent randomized controlled trial evaluated the relative efficacy of cryotherapy versus external beam radiotherapy (EBRT) for the treatment of localized prostate cancer [26]. Patients were followed for 3 years, and the Phoenix definition was used to define biochemical failure. It was demonstrated that there is no difference in disease progression between the two treatments; nevertheless, fewer positive biopsies were documented after cryoablation than after radiotherapy. Patients with a contraindication to EBRT may wish to consider cryotherapy as primary treatment. Men with pathologically confirmed prostate cancer should have appropriate investigations to confirm staging prior to prostate cryotherapy [27]. The use of established staging nomograms (Roach et al. [28] or Partin et al. [29]), and lymph node sampling may be considered if lymph node involvement is suspected. Men with prostate volume of more than 40 cc may benefit from 3 months hormone therapy in order to facilitate the procedure and reduce the risk to the surrounding structures [30].

### Salvage Cryotherapy

EBRT remains one of the main treatment modalities for localized and locally advanced prostate cancer. Patients with unfavorable presentation (PSA level > 20 ng/mL or Gleason score ≥ 8 or clinical stage > T2b) are at higher risk of clinical failure after radiotherapy [31]. Failure rate of EBRT ranges between 24 and 85 % [32, 33]. Stamey et al. [34] reported that 80 % of men in the high-risk group treated with radiotherapy for localized prostate cancer had an increasing PSA level at a mean

follow-up of 5 years. Men with clinically localized prostate cancer, who failed their treatment either with radiotherapy or brachytherapy, are usually left with either watchful waiting or hormone treatment in which progression to androgen independence occurs in a few years [35]. Repeating radiation therapy is not successful as these tumors are radio resistant and is associated with high risk of toxicity. Salvage radical prostatectomy is a technically difficult procedure and has been associated with significant comorbidities [36]. This group of patients is potentially the largest group of patients who are suitable for prostate cryotherapy.

Rising serum PSA level is the first sign of treatment failure in prostate cancer. PSA levels may fluctuate in the first 18 months following radiotherapy [37]. With a persistent rise in PSA which meets the Phoenix definition of biochemical failure (the nadir PSA + 2 ng/ml), then staging investigations for salvage therapy may be instigated [38]. The possibility of lower urinary tract infection should be excluded. Restaging pelvic MRI scan and bone scan is mandatory to exclude metastatic disease prior to prostrate biopsy. Prostate biopsy is mandatory to confirm local recurrence. Saturation prostate biopsy (20–40 cores) is more sensitive than transrectal biopsy (12 cores) in detection of recurrent cancer in irradiated patients [39]. Patients at higher risk of having locally advanced disease (D'Amico high-risk category) should have pelvic lymph nodes biopsy prior to their procedure. Patients with radiological or histological evidence of pelvic lymph node involvement or metastatic disease should be excluded.

## Prostate Cryotherapy Procedure

### Preoperative Preparation

The majority of patients undergoing cryoablation of the prostate are elderly and have often undergone previous cancer treatment. These patients typically have other comorbidities and are commonly on multiple drugs including antihypertensive agents and alpha-antagonists. Useful preoperative investigations therefore include an electrocardiogram, full blood count, and serum urea, creatinine, and electrolyte levels. Other tests should be ordered according to clinical need. Patients are admitted the night before to receive bowel preparation (Picolax®). Intravenous antimicrobial prophylaxis (metronidazole and cefuroxime) is given immediately before surgery.

### Cryotherapy Procedure

Under general anesthesia, patients are placed in extended lithotomy position. A warming blanket (Bair Hugger®) is used to prevent systemic hypothermia. The lower abdomen, genitalia, and perineum are prepared with antiseptic solution and draped. A diagnostic flexible cystoscopy is performed initially to exclude urethral or bladder abnormalities. A urethral catheter is inserted and the bladder is filled with 200 ml of saline to increase the safety margins at the bladder neck. An aerated gel is placed within the catheter to visualize the urethra on ultrasound. Transrectal ultrasound scan (TRUS) is used to measure prostate dimensions and to guide transperineal cryoneedle insertion into the prostate. A stepping unit mounted either on the floor or attached directly to the operating table is used to hold the ultrasound probe and the template. Commercial software is available to optimize placement of the cooling probes based on the gland volume and the location of the critical structures (rectum and urethra); however, this is not widely used and most operators place the cryoprobes freehand via a perineal template. Two cryoablation systems are available: the Cryocare CS system (Endocare, Inc., Irvine, CA, USA) in which 4–6 cryoprobes (2.4 mm) are used to cover the prostate and the Seednet™ (Galil Medical, Plymouth Meeting, PA, USA) which uses 10–15 cryoneedles (1.47 mm). Once all probes are in place, a flexible cystoscopy is used to ensure that no probe had traversed through the urethra and to allow the placement of a guide wire over which a double-lumen urethral warming catheter is placed and warm normal saline (43 °C) circulated to protect the urethra. The two freeze cycles are then commenced with careful monitoring of the freeze using the temperature probes and the ultrasound images. The target temperature at the apex and anterior prostate is −40 °C and greater than 0 °C at the external sphincter and Denonvilliers' fascia. Following the procedure, the cryoprobes are removed and adequate pressure is applied to the perineum for a minimum 5 min to prevent bruising during which time the urethral warmer is left in place. Urethral warmer is then replaced with an indwelling urethral catheter which is removed after 2 weeks.

### Technical Consideration in Probe Placement

In prostate cryotherapy, cryoneedles should be placed precisely in order to cover the entire gland without damaging normal structures. Prostate size, tumor volume, and position and lethal ice ball dimension are important parameters to know when planning for a successful cryotherapy procedure. In salvage cryotherapy, the prostate size is usually small, and the safety margins superiorly and posteriorly are limited. The ideal lethal temperature is −40 °C which should be achieved and maintained within the prostate during freezing. The prostate is surrounded by two heat sinks which may interfere with freezing process, the bladder and the neurovascular bundles. We use the Seednet™ system with 17 gauge

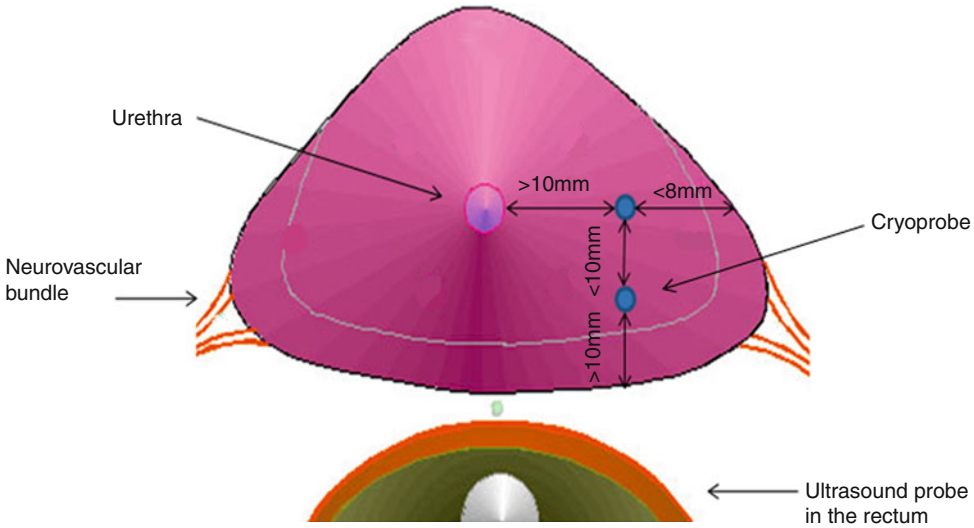


**Fig. 65.4** Technical consideration in cryoneedle placement. Cryoneedles need to be less than 8 mm from the lateral edge of the prostate, less than 10 mm apart, and more than 10 mm from the urethra and rectal wall

(1.47 mm) cryoneedles. Ice ball dimensions for the lethal zone (−40 °C) is 8×17 mm±2 mm, and it extends 5 mm cephalad from the tip of the probe. Cryoneedles are inserted into three imaginary levels of the prostate, anterior, middle, and posterior. Total number of cryoneedles depends on the size of the prostate. For a 40-g prostate, four cryoneedles are inserted anteriorly, four in the middle region and five posteriorly. Cryoneedles should be no more than 10 mm apart and less than 8 mm from the lateral edge of the prostate (Fig. 65.4). Cryoneedles should be placed at least 10 mm away from the urethra and the rectal wall. This permits lethal ice ball to advance laterally more quickly than posteriorly. The expansion of the ice ball is monitored precisely in the sagittal and coronal view. Extra cryoneedles can be placed as necessary. Four thermocouples are placed in four critical positions, i.e., anterior prostate, apex, Denonvilliers' fascia, and external sphincter. Additional two thermocouples can be placed to monitor the temperature around the neurovascular bundles. The anterior needles start the freeze, and once the entire width of the prostate is covered anteriorly, the middle and then the posterior row are switched on. Ice ball should be allowed to extend beyond the prostate capsule at the neurovascular bundles to ensure optimal freezing and better disease control. Ice ball from the posterior row should be allowed to coalesce in the midline and extend to the posterior prostate margin. Double freeze-thaw cycles are applied. Following the first freeze-thaw cycle, a pull-back technique may be necessary in long prostates.

## Postoperative Follow-Up

Patients can be discharged the following day on 1-week course of antimicrobial prophylaxis and 4 weeks of α-blockers. Patients are followed up every 3 months for the first year, every 6 months for the second year, and yearly thereafter. At the first postoperative visit, PSA level is recorded and patients are consulted for lower urinary tract symptoms and erectile function. The international prostate symptom score (IPSS) and international index of erectile function questionnaire (IIEF) can be completed and compared to the preoperative levels. PSA serum levels take few months to drop to nadir following prostate cryotherapy. Therefore, PSA level should be interpreted with caution postoperatively. Postoperative biopsy is optional and depends on the treating center.

## Clinical Response Following Prostate Cryotherapy

Serum level of PSA does not become undetectable following cryotherapy, due to either persistent cancer cells or residual benign tissue. Therefore, there is no definition of success for prostate cryotherapy leading to a great difficulty in evaluating clinical outcome. Serum PSA level and biopsy results have been used to define failure postcryotherapy. PSA level cutoffs of 0.1, 0.2 (above nadir), 0.3, 0.4, and 0.5 ng/ml have been used to define biochemical failure [40–44]. The American Urological Association best practice statement on cryosurgery for the treatment of localized prostate cancer published in 2008 failed to make a statement on endpoint definition of treatment success. ASTRO and Phoenix criteria have been applied recently to cryotherapy patients to assess outcome. Connolly et al. demonstrated that a PSA cutoff value of >0.5 ng/ml is a strong predictor of positive biopsy at 12 months postcryotherapy [45]. An initial PSA level of <0.6 ng/ml after salvage cryotherapy has been shown to have a prognostic value and is correlated with a favorable outcome [46].

**Table 65.1** Results of the primary cryotherapy series

| Series | Year | Number of patients | Follow-up (mean) months | Negative biopsy (%) | PSA failure | % BRFS (risk group) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Low | Intermediate | High |
| Cheetham et al. [47][a,b] | 2010 | 76 | 120 | 90 | Phoenix | 51 | | |
| Jones el al. [48] | 2008 | 1,198 | 24 | 76 | ASTRO/Phoenix | 85/91 | 73/78 | 75/62 |
| Cohen et al. [49] | 2008 | 370 | 150 | 76.9 | Phoenix | 80.5 | 74.16 | 45.5 |
| Hubosky et al. [50] | 2007 | 89 | 11 | N/A | ≤0.4 | 74 | 70 | 60 |
| Polascik et al. [51] | 2007 | 50 | 18 | 96 | <0.5 | 90 all patients | | |
| El Hayek et al. [52] | 2007 | 21 | 41 | 42 | <1 | 42.8 at 60 months | | |
| Prepelica et al. [53] | 2005 | 65 | 35 | 87.5 | ASTRO | 83 (high-risk patients) | | |
| Han et al. [43][b] | 2003 | 106 | 12 | N/A | <0.4 | 75 at 12 months | | |
| Bahn et al. [54] | 2002 | 590 | (65) | 87 | ASTRO | 92 | 89 | 89 |
| Donnelly et al. [55] | 2002 | 87 | (50) | 98.6 | <0.3 | 60 | 77 | 48 |
| Long et al. [56] | 2001 | 975 | 24 | 82 | <1 | 76 | 71 | 61 |
| Koppie et al. [57] | 1999 | 176 | (30.8) | 62 | <0.5 | 70 | | 45 |
| Wong et al. [58] | 1997 | 83 | 30 | 17[c]<br>90 | – | – | – | – |
| Shinohara et al. [59] | 1996 | 102 | – | 77 | Undetectable | 41 | 54 | 3 |
| Miller et al. [60] | 1994 | 62 | (24) | 79 | <0.4 | 51 at 20 months | | |
| Onik et al. [11] | 1993 | 55 | (23) | 93 | Biopsy results | – | – | – |

[a]Cases performed before January 1999
[b]Mixed primary and salvage cases
[c]Without temperature monitoring

## Oncological Outcome of Primary Cryotherapy of the Prostate

Biochemical recurrence-free survival (BRFS) rates following primary prostate cryotherapy were variable ranging from 60 to 90 %. It depends on the criteria used in defining the cutoff PSA recurrence rate. Outcome also varies depending on risk groups with better outcome in the low-risk patients (PSA level ≤ 10 ng/ml, a Gleason score ≤ 6, and a clinical stage <T2b) compared to the high-risk patients (PSA level > 20 ng/ml, a Gleason score ≥ 8, or clinical stage >2b) [31]. The use of preoperative hormone ablation therapy can make it difficult to interpret outcome following prostate cryotherapy. Table 65.1 summarizes the results of the recent case series studies of the primary prostate cryotherapy. Jones et al. [48] present the largest study of whole-gland cryotherapy for primary prostate cancer. Data from the Cryo On-Line Data (COLD) registry were analyzed, and a total of 1,198 patients were stratified according to D'Amico classification and followed for 24 months. The 5-year actuarial BRFS for the whole population was 77.1 and 72.9 % using the ASTRO and Phoenix criteria definition for biochemical failure, respectively. Stratified by risk group, BRFS were 85, 73, and 75 % (Phoenix 91, 78.5, and 62 %) for the low-, intermediate-, and high-risk groups, respectively. Cohen et al. [49] assessed 370 men who had undergone prostate cryotherapy as primary treatment for locally advanced prostate cancer. Using a nadir plus 2 ng/ml definition for biochemical recurrence, the 10-year actuarial BRFS for the low-, intermediate-, and high-risk groups were 80.56, 74.16, and 45.54 %, respectively. The 10-years positive biopsy rate was 23 %. Comparable results with regard to local cancer control were demonstrated recently [50]. Long et al. [61] presented multi-institutional report of primary prostate cryotherapy. A total of 975 patients were treated over 5 years. Two PSA thresholds were used (0.5 and 1 ng/ml) to define the biochemical failure. Overall, 75 % of the patients were stratified into the intermediate- and high-risk group. The 5-year actuarial BRFS rates were 60 % in the low-risk patients compared to 36 % in the high-risk group using PSA cutoff of 0.5 ng/ml. Positive biopsy rates ranged from 18 to 24 %. These results were comparable to the conformal radiotherapy and brachytherapy treatment. Bahn et al. [54] reported on 590 patients who underwent cryoablation of the prostate and followed for 7 years. The BRFS rate was defined as PSA level < 0.5 ng/ml. The 7-year actuarial BRFS rates were 61, 68, and 61 % for the low-risk, intermediate-risk, and high-risk groups, respectively, with a positive biopsy rate of 13 %.

## Oncological Results of Salvage Cryotherapy Series

Cryotherapy is an attractive option to treat patients with locally recurrent prostate cancer after radiotherapy, with the intention to provide local control and prolong survival. Several institutions have published their salvage cryotherapy

**Table 65.2** Results of salvage cryotherapy series

| Series | Year | No. of patients | Follow-up (mean) months | Negative biopsy (%) | PSA failure | % BRFS (risk group) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Low | Intermediate | High |
| Pisters et al. [62] | 2008 | 279 | 21.6 | 67.4 | ASTRO/Phoenix | 58.9 and 54.5, respectively | | |
| Eisenberg et al. [63] | 2008 | 19 | 18 | 90 | ASTRO | 50 % at 3 year | | |
| NG et al. [64] | 2007 | 187 | (39) | 83.4 | Nadir +2 | 56 all groups | | |
| Ismail et al. [30] | 2007 | 100 | (33.5) | N/A | ≥0.5 | 73 | 45 | 11 |
| Collins et al. [65] | 2007 | 195 | 46.5 | 70.59 | ASTRO | 69 all groups | | |
| Robinson et al. [66] | 2006 | 46 | 24 | N/A | ≥0.3 | 48 at 2 years | | |
| Lam et al. [67] | 2005 | 72 | 6 | N/A | N/A | 90 at 6 months | | |
| Bahn et al. [44] | 2003 | 59 | (72.5) | 100 | ≥0.5 | 61 | 62 | 50 |
| Ghafar et al. [41] | 2001 | 38 | 20.7 | N/A | >0.3 above nadir | 74 at 2 years | | |
| Chin et al. [42] | 2001 | 118 | (18.6) | 94 | >0.5 | 34 all groups | | |
| de la Taille et al. [40] | 1999 | 43 | (21.9) | 63(5/8) | <0.1 | 66 at 1 year | | |
| Pisters et al. [68] | 1997 | 150 | (13.5) | 77 (85/110) | ≥0.2 above nadir | 58 | | |
| Bales et al. [69] | 1995 | 23 | 12–23 | 59 (13/22) | <0.3 | 14 at 1 year | | |

results. Table 65.2 summarizes the outcome of the recent salvage cryotherapy reports in the literature. In our center, a total of 215 patients with locally recurrent prostate cancer were treated with salvage cryotherapy (unpublished data). Patients were followed with 3 monthly serum PSA level over a mean follow-up period of 63 months. The Phoenix criteria were used to define biochemical failure. The 10-year actuarial BRFS for the whole population was 50 %. Unsurprisingly, significant numbers of high-risk patients show disease recurrence at their last follow-up. This may reflect undetected subclinical systemic disease, persistent local cancer progression, or involvement of the seminal vesicle [68]. Cheetham et al. recently reported on long-term survival beyond 10 years of prostate cryotherapy [47]. A total of 76 men underwent primary or salvage cryotherapy for localized prostate cancer before January 1999. The overall survival rates were 60 and 55 %, and prostate cancer-specific mortality rates were 20 and 35 % for the primary and salvage cases, respectively. The BRFS for men who remain alive was 51 %. A recent retrospective case study reported on 279 patients who had undergone salvage cryotherapy for recurrent prostate cancer [62]. At 5 years, 59 % were showed freedom from biochemical failure and 67.4 % had a negative biopsy following the procedure. Bahn et al. [44] presented the longest follow-up series of salvage cryotherapy. At 7-year follow-up, the combined biochemical disease-free survival using PSA cutoff of 0.5 ng/ml was 59 %. At the London Health Sciences Centre in Ontario, 187 patients with locally recurrent prostate cancer have been treated with salvage cryotherapy using an argon-based system [64]. They reported a BRFS of 56 % with a mean follow-up of 39 months. Preoperative PSA level was an independent predictor for BRFS, and patients with preoperative PSA less than 4 ng/ml had better outcome.

## Complications of Primary Prostate Cryotherapy

Complication rates are low following primary prostate cryotherapy apart from erectile dysfunction which remains a serious problem [50]. Table 65.3 summarizes the complication rate following primary cryotherapy of the prostate. Impotence rate in the primary cryotherapy ranges from 53 to 96 %. Donnelly et al. [55] reported that the nerves have the potential to recover 12 months following cryotherapy, and half of their patients had their potency improved by 36 months. Rectourethral fistulae are very uncommon in modern primary cryotherapy series [51]. Incontinence rates varied considerably but remain less than 10 % in most reports.

## Complications of Salvage Prostate Cryotherapy

Almost all patients following salvage cryotherapy will have some degree of lower urinary tract symptoms (LUTS) secondary to urethral slough most of which will resolve in the first 6 months [70]. There was a significant reduction in the urethral sloughing since the introduction of urethral warming catheter which protects urethral mucosa during cryotherapy [42, 69]. Although urethral warming has been successful in reducing urinary morbidity, it can compromise cancer control by protecting a rim of prostatic tissue around the urethra from freezing. Gould et al. [71] demonstrated a significant improvement in biochemical disease-free survival in men undergoing total cryotherapy (without warming catheter) compared to men having standard cryotherapy (with warming catheter). In early reports of salvage prostate cryotherapy, urinary incontinence was reported to be as high as 95 % [69]. This may be related

**Table 65.3** Complication rates following primary cryotherapy of the prostate

| Series | Impotence (%) | Incontinence (%) | Rectourethral fistula % | Urethral slough (%) | Pain (%) | Stricture/retention (%) |
|---|---|---|---|---|---|---|
| Cheetham et al. [47] | N/A | N/A | N/A | N/A | N/A | N/A |
| Jones el al. [48] | 91 | 4.8 | 0.4 | 2.1 | N/A | 3.6 |
| Cohen et al. [49] | N/A | N/A | N/A | N/A | N/A | N/A |
| Hubosky et al. [50] | N/A | N/A | N/A | N/A | N/A | N/A |
| Polascik et al. [51] | 50 | 4 | 0 | 0 | 0 | 0 |
| El Hayek et al. [52] | 96 | 8 | 0 | N/A | N/A | N/A |
| Prepelica et al. [53] | N/A | 3.1 | 0 | N/A | 3.1 | 3.1 |
| Han et al. [43][a] | 87 | 8 | 0 | 5 | 2.6 | 3.3 |
| Bahn et al. [54] | 89.8 | 15.9 | 0.004 | N/A | N/A | 5.5 |
| Donnelly et a. [55] | 53 | 1.3 | N/A | 3.9 | N/A | N/A |
| Long et al. [56] | 93 | 7.5 | 0.5 | N/A | 2.3 | 13 |
| Koppie et al. [57] | N/A | N/A | N/A | N/A | N/A | N/A |
| Wong et al. [58] | 94 | 4 | 0 | 37 | N/A | 4 |
| Shinohara et al. [59] | 84 | 4 | 1 | N/A | 3 | 23 |
| Miller et al. [60] | N/A | 2.7 | 0 | 1.3 | N/A | 1.3 |
| Onik et al. [11] | 64 | 0 | 2.9 | 4.4 | N/A | N/A |

[a]Mixed primary and salvage cases

**Table 65.4** Complication associated with salvage cryotherapy

| Series | Impotence (%) | Incontinence (%) | Rectourethral fistula (%) | Urethral slough (%) | Pain (%) | Stricture/retention (%) |
|---|---|---|---|---|---|---|
| Pisters et al. [62] | 69.2 | 4.4 | 1.2 | 3.2 | N/A | 6.8 |
| Eisenberg et al. [63] | 60 | 6.6 | N/A | N/A | N/A | 6.6 |
| NG et al. [64] | N/A | 3 (severe) | 2 | | 14 | 21 |
| Ismail et al. [30] | 86 | 6 (severe) | 1 | 16 | 4 | 2 |
| Collins et al. [65] | N/A | 6.6 | 0 | 0 | 10.26 | 2 |
| Robinson et al. [66] | 56 | 29 (moderate to severe) | 2 (early series) | 24 (early series) | 16 | 6 (early series) |
| Lam et al. [67] | 83.3 | 17.5 | 0 | N/A | 5 | 9 |
| Bahn et al. [44] | N/A | 8 | 3.4 | N/A | N/A | N/A |
| Ghafar et al. [41] | N/A | 7.9 | 0 | 0 | 39.5 | 0 |
| Chin et al. [42] | | 6.7 | 3.3 | 5.1 | | 8.5 |
| de la Taille et al. [40] | N/A | 9 | 0 | N/A | 26 | 5 |
| Pisters et al. [68] | 72 | 73 | 1 | 22 | 8 | 67 |
| Bales et al. [69] | 100 | 95.5 | N/A | N/A | N/A | 40.9 |

either to the lack of protection of the urethra and external sphincter or periurethral scarring post-radiation therapy [68]. Currently, urinary incontinence rate is significantly lower with recent studies reporting incontinence rates of 3–6 % [51, 62]. The most serious complication of salvage cryotherapy is the development of rectourethral fistula. New treatment advances and better control of the procedure have significantly reduced this complication to 0–3 % in salvage cases [42, 67]. Erectile dysfunction is the most frequently occurring complication following prostate cryotherapy [70], primarily due to the ice ball extending into the neurovascular bundles when attempting to completely eradicate the tumor. Impotence rate in salvage cases range from 56 to 100 %. In salvage cryotherapy, most patients suffer from a degree of erectile dysfunction owing to previous hormone therapy and pelvic irradiation [95] (Table 65.4).

## Cost-Effectiveness

Prostate cryotherapy may be a cost-effective approach to treat prostate cancer. It has been estimated that the total cost of a cryotherapy procedure is approximately half of the total cost of radical prostatectomy. The cost saving reflects the length of hospital stay, 1.1 days for cryotherapy versus 3.5 days for radical prostatectomy [72].

## Modification of the Standard Prostate Cryotherapy

### Focal Prostate Cryotherapy

Focal therapy for prostate cancer intends to treat cancer within the prostate, while sparing the majority of the benign

prostate tissue. This approach avoids treatment effects in the surrounding structures and reduces morbidities associated with radical whole-gland treatment. In prostate cryotherapy, the entire gland is treated including the periprostatic tissue and neurovascular bundles. Therefore, the incidence of erectile dysfunction is high. Focal cryotherapy is a new concept with limited data available outside the experimental application. It was suggested that only a small group of men diagnosed with prostate cancer have completely unilateral cancers that would be amenable to focal ablation therapy [73]. Therefore, proper patient selection is crucial to optimize outcome. In a recent report, 77 men with unilateral prostate cancer were treated with focal cryotherapy and followed for 24 months [74]. Recurrent prostate cancer was identified in 13 % of the patients, of which 20, 70, and 10 % had ipsilateral, contralateral, and bilateral diseases, respectively. The overall actuarial biochemical recurrence-free survival were 75 and 50 % at 3 and 5 years, respectively. Onik et al. described focal nerve-sparing prostate cryotherapy where they treated part of the prostate which contain the tumor [75]. After a mean follow-up of 50 months, 95 % of the treated patients had stable PSA and 80 % maintained their potency. In a different approach, the neurovascular bundle was successfully preserved by active warming, but this resulted in an incomplete ablation of prostate tissue [76]. Lambert et al. presented their data primary focal cryotherapy. Eighty-four percent of patients had not experienced biochemical failure, and 14 % showed positive biopsy on the treated site. Potency was maintained in 71 % of patients, and none reported any worsening of lower urinary tract symptoms or incontinence [77]. Focal nerve-sparing cryotherapy has not been applied in salvage treatment.

## Rectal Wall Protection

The incidence of rectourethral fistula following prostate cryotherapy is low. Rectal wall injury can be avoided by allowing the ice ball to extend laterally more than posteriorly. Nevertheless, it may result in exposure to sublethal freezing temperature and preserving tumor cells posteriorly. Modifying the cryotherapy technique to protect healthy tissue without limiting the ablation of the unwanted tissue was attempted using different techniques. [94] inserted two cryoneedles into the Denonvelliers' fascia for active warming using the thawing phase when the temperature drops below 0 °C in the posterior prostate. This approach successfully maintained a PSA level of <0.5 ng/ml in 80.6 % of the patients treated and no rectal injury was reported. Other studies have addressed this issue by manipulating the transrectal ultrasound probe to increase distance between the rectal wall and the prostate. The mean distance was increased by 7.1 mm without impairing the ultrasound quality image [78]. Using laser irradiation heating for confining the freezing process around the vital structures was also described and referred to as laser-assisted cryosurgery [79].

## Adjuvant Treatment to Prostate Cryotherapy

It is well known that successful application of cryotherapy depends on several factors including tumor stage and thermal parameters in the freeze-thaw cycle [21]. It is crucial to optimize these parameters to achieve total tumor ablation in order to increase the efficacy of prostate cryotherapy. There are limitations to the maximum delivery of cold temperature to the prostate given the close relationship between the critical structures which surround the prostate. Therefore, complete ablation of the prostate sometimes fails, and a significant number of patients will have disease recurrence. Other options for improving outcomes include the application of treatments adjuvant to the application of cold.

## Cryochemotherapy

Cryotherapy alone may fail to kill prostate cancer cells completely, and combination with a sensitizing agent may be needed to improve the long-term clinical outcome. We demonstrated that concomitant treatment of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and cryotherapy represent a novel approach to increase the sensitivity to cryotherapy through increased necrosis [80]. As TRAIL is already under clinical evaluation as a cancer therapy, this combined approach may be feasible for locally advanced prostate cancer. Clarke et al. demonstrated enhanced efficacy of cryotherapy when combined with sublethal concentration of 5-fluorouracil in vitro [81]. The limitation of those studies has been the lack of a representative model which simulates the clinical situation in order to design strategies to enhance the killing effect further. Goel et al. investigated the ability of tumor necrosis factor alpha (TNF-α) to enhance cryoinjury in vivo [82]. Temperature threshold for necrosis was increased with the addition of TNF-α prior to cryotherapy, and the combined treatment resulted in growth delay of the tumor in the experimental animals. Systemic toxicity of TNF-α was reduced by delivering the drug combined with gold nanoparticles. Cryochemotherapy may represent a potentially effective therapeutic model for the treatment of prostate cancer, and further studies and clinical trials are required.

## Cryoimmunotherapy

Tumor destruction by cryotherapy releases large amounts of tumor antigens and inflammatory signals that trigger local dendritic cells (DC) maturation. Mature DC migrate to the

local lymph nodes to interact with immune effector cells resulting in tumor-specific immune response and tumor eradication [83]. Cryoimmune response has been studied in several animal models, and both immunostimulatory and immunoinhibitory effects were noticed [20, 84–87]. The precise mechanism of the immunostimulatory effect was not clear. Early cytokine-mediated response was reported [84]. Involvement of T cell immunity and enhanced natural killer (NK) cell cytotoxicity was also described [88]. Other reports suggested the development of antitumor antibodies following cryotherapy [89]. Most reports recognize that the cryoimmune effect is minimal and would require amplification by immune adjuvant in order to be clinically effective. We demonstrated that cryotreated prostate cancer cells result in phenotypic and functional activation of dendritic cells. Immunostimulatory cytokine genes were significantly upregulated in dendritic cells loaded with cryotreated tumor cells. Freezing injury stimulates dendritic cells in two different ways. First, it provides a pool of antigen from the cryonecrotic tumor tissue and second, by creating an immunostimulatory cytokine environment which enhance DC maturation [90]. Therefore, the combination of cryotherapy and dendritic cell vaccine may represent a novel method to increase the efficacy of cryotherapy especially at the peripheral zones of the prostate where cells are exposed to sublethal temperature and warrant further studies and application of similar protocols in clinical trials.

## Inhibition of Aquaporin Water Channels

The aquaporin (AQP) family of water channels are intrinsic membrane proteins that facilitate selective water and small solute movement across the plasma membrane [91]. Only recently, the role of AQP in tumor pathogenesis has been identified. Aquaporin 3 was found to be expressed in normal and malignant prostate tissue and may be involved in tumor initiation and development [92]. We described a novel role for AQPs expression in prostate cancer cells [93]. Modification of AQP3 expression has accentuated the established mechanism of cryoinjury. Inhibition of AQP3 was successful in increasing the sensitivity of prostate cancer cells to cryoinjury, and a significant increase in cell death was attained at −10 °C freezing temperature. The observed effect was possibly due to increased intracellular ice formation at higher freezing temperatures. Potential future developments include identification of AQPs inhibitor that can be used clinically.

### Conclusion

The application of cold temperature in the treatment of cancer is not a new concept. Prostate cryotherapy has evolved rapidly over the last decade, and with a modern cryotherapy value technology, the current status of prostate cryotherapy is promising. The most established role is currently in salvage treatment. The relative values of primary treatment with cryotherapy for localized and locally advanced disease have yet to be fully explored with comparative studies. Compared to other treatment modalities, cryotherapy is safe, well tolerated, and can be repeated. With better understanding of the cellular pathophysiology of freezing injury, future improvements are expected. Potential future developments include cryoimmunotherapy, cryochemotherapy, and aquaporin inhibition as alternative models to improve efficacy and reduce morbidities. Clinical trials evaluating the role of adjunctive treatment in addition to cryotherapy are invaluable to ensure that these treatments can be applied clinically.

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# Focal Therapies for Localized Prostate Cancer

66

Louise Dickinson, Hashim U. Ahmed, and Mark Emberton

## Introduction

With the increased uptake of PSA testing within both formal and informal screening programs, and increased public awareness of the disease, men are being diagnosed with prostate cancer earlier in its natural history. As a result, there has been a major shift in the incidence and prevalence of low- to intermediate-risk prostate cancer [1]. The benefits of screening and early cancer detection are equivocal. The European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a 20 % reduction in prostate cancer mortality in the screened population compared to the control arm [2]. However, this comes at a price as 1,410 men needed to be screened and 48 diagnosed and treated in order that one prostate cancer-related death was avoided over a 9-year interval.

At present, men diagnosed with low-risk localized prostate cancer face a difficult decision between two extremes of care: active surveillance and radical therapies. The former avoids the side effect risks of radical treatments but with the added burden of regular invasive tests (usually PSA blood tests 3–6 monthly and prostate biopsies every 1–3 years), the risk of progression, and the psychological morbidity of living with the disease. Radical therapies allow near certainty of cancer clearance but with an associated significant side effect profile including impotence, incontinence, and rectal toxicity. Thus, the screening related shift in disease profile has not been accompanied by an alteration in our approach to low-risk disease. Knowledge of which disease we need to treat, and which disease can be monitored over time, has not shifted in a parallel manner to the change in disease profile. As a result, the risk of overtreatment, and treatment-related harms, is significant. This risk becomes less of a problem if a treatment can be delivered that is cost-effective and associated with very low rates of harm, while eliminating potentially high-risk disease.

Focal therapy, the selective treatment of part of the prostate, may offer a middle way between these two extreme management strategies of active surveillance and radical therapies (Fig. 66.1). If cancerous tissue can be successfully and definitively treated while preserving normal tissue, men are potentially offered cancer treatment with minimal functional impact, as adjacent structures such as the neurovascular bundles, external urinary sphincter, bladder neck, seminal vesicles, and rectum are avoided. This move toward tissue-preserving therapies is a strategy that has well served other oncologic specialties. For example, there has been a move from mastectomy to lumpectomy for localized breast cancer and from nephrectomy to partial nephrectomy, or even focal lesion control (e.g., radiofrequency ablation) for localized renal cancers. Thus, the potential of focal therapy as a primary treatment for prostate cancer has been the focus of discussion by clinicians and researchers worldwide in recent years [3–13]. In addition, focal therapy may provide an option for cancer control in patients with recurrent disease, minimizing the acknowledged high rate of side effects that occur with other salvage treatments, while potentially delaying the need for systemic hormone ablation treatment.

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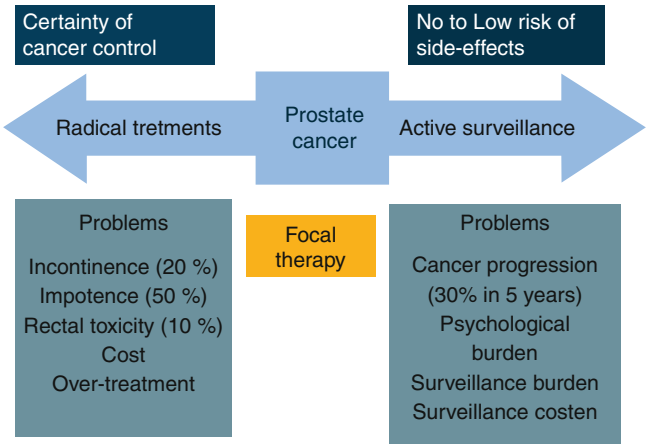


**Fig. 66.1** Focal therapy as an alternative treatment option for localized prostate cancer (Figure first published in *BJU International*, 2010)

## Focal Therapy as an Alternative Treatment Strategy to Current Standard Care

An international consensus expert panel recently defined focal therapy as "a type of treatment that aims to eradicate known cancer within the prostate and at the same time preserve uninvolved prostatic tissue with the aim of preserving genitourinary function" [14]. There are two patient cohorts that might potentially benefit from this strategy as a primary treatment: firstly, men with low-risk disease who opt for treatment over active surveillance and secondly, men with intermediate-risk disease for whom radical therapy has been offered, but who place particular value on preservation of functional status.

Defining who is and who is not a candidate for focal therapy is, in the absence of knowledge of the long-term outcomes of the intervention, a potentially contentious issue. The arguments are polarized to two schools of thought. First, that a novel intervention has, by definition, high levels of uncertainty associated with it and should only be offered to a group of men with a low chance of disease progression and thus a low chance of prostate cancer-related death (the active surveillance cohort). The second is to adopt the position that men with low-risk characteristics are not destined to die of prostate cancer over a 15–20-year window, [15] and therefore any intervention has a very low chance of conferring benefit and therefore can only confer harm. This position would encourage the inclusion of patients with characteristics that would increase their chances of disease progression if left untreated. In other words, a pragmatic strategy might be to incorporate men with higher-grade tumors but with an upper limit of tumor burden that is deemed feasible and safe to treat.

## Focal Therapy as an Alternative to Active Surveillance

Active surveillance is a strategy that enables maximum tissue preservation and hence genitourinary function but with planned delayed treatment of low risk or occasionally low-volume intermediate disease. It involves a regular program of PSA blood tests and prostate biopsies, with the associated interventional and psychological morbidities that these procedures carry. Many men undertake this "watch and wait" strategy in order to preserve function as long as possible. While approximately 10 % of men on active surveillance choose to have intervention despite the absence of biochemical or histologic progression, questionnaire surveys have shown that there are conflicting findings about the anxiety levels present in such cohorts [16]. The latest report from a large active surveillance cohort in Toronto has demonstrated that of 450 on active surveillance, approximately a quarter of the population was treated radically, with a median follow-up of 6.8 years [17]. In these 117 men, the PSA failure rate was 50 %, a relatively high rate, and upgrading occurred in 30 % of men.

Active surveillance relies on accurate baseline characterization of disease burden. It is likely that a significant proportion of those men that "progress" within 5 years do so not due to true cancer progression but due to the poor accuracy of diagnostic transrectal ultrasound-guided biopsies in ascertaining baseline burden [18]. In any case, despite this significant level of "disease progression," the 10-year actuarial prostate cancer survival rate was high at 97.2 %, again suggestive of overtreatment in patients with low-risk disease. However, it may be possible to alleviate patient anxiety by selectively treating cancer lesions and extend the period without side effects if focal therapy were to be carried out either at diagnosis or at the time of disease progression instead of radical therapy.

Thus, the two main arguments for focal therapy as an alternative to active surveillance are firstly, to reduce the potential psychological morbidity of delayed intervention with the approach that "some form of treatment is better than none," and secondly, to reduce the cancer progression and/or reclassification rate that currently occurs in about one-third of men who undergo active surveillance.

The arguments against men who are suitable for active surveillance undergoing focal therapy are that any treatment within this group is liable to be overtreatment and regardless of the encouraging functional outcomes that it may demonstrate, will carry greater morbidity than a management strategy in which two-thirds of men with low-risk disease can avoid treatment while the others can delay such morbidity.

## Focal Therapy as an Alternative Strategy to Radical Treatments

The benefit of "no treatment" versus radical treatment for localized prostate cancer remains uncertain. The Scandinavian Prostatic Cancer Group Study, which randomized 695 men to watchful waiting versus radical prostatectomy, demonstrated a reduction in disease-specific mortality of 14–9 % with radical surgery over a median follow-up period of 8 years [19] suggesting that radical therapies improve survival. However, the patient cohort in this trial involved mainly men with clinically palpable tumors and PSA levels of up to 50 ng/ml, a disease profile that differs from the PSA-screened population of today. In addition, the true effects of radical prostatectomy on disease-free survival should be tempered, as the result incorporated a higher percentage of men that were treated with hormone ablation therapy within the watchful waiting arm compared to the radical prostatectomy arm. In addition, the recent update showed no statistical difference in disease-related mortality in the two groups at a longer follow-up period of 12 years [20].

Even with significant recent advances in technology, and a move toward minimally invasive therapies, the functional outcomes and recovery periods for patients following radical therapies remain significant. Although there have been no prospective randomized trials comparing techniques, laparoscopic and robot-assisted laparoscopic data suggest that blood loss and length of hospital stay are favorable compared to the open radical prostatectomy approach [21]. However, the data does not currently support the belief that cancer control and functional outcomes will be significantly improved with the minimally invasive techniques. The side effect risks remain similar as the whole prostate is treated or removed, with unavoidable collateral damage to the surrounding structures. Radical surgery causes chronic urinary symptoms in one-third of men. The alternative radical therapy, i.e., radiotherapy, causes moderate anorectal and urinary side effects in 5–20 % of men. Both radiotherapy and radical surgery cause impotence in 30–90 % of men depending on which modality is used and the particular series looked at (high-volume centers of excellence generally get better results) [22].

A strategy that treats the cancer rather than the organ may reduce the side effect burden while allowing adequate cancer control. One strategy could be to selectively treat all clinically significant cancer and carefully monitor untreated tissue for *de novo* cancers and/or progression of clinically insignificant disease. This may obviate the need for any further radical therapies in future or delay it for a number of years during which the man is free of treatment-related side effects.

The theoretical problem posed by focal therapy is that selective treatment of a target volume of tissue deemed to contain a cancer may incur a miss due to poor targeting, poor staging, or both. The result would be that a cancer with metastatic potential may be given a time window to progress that would not have been available had radical whole-gland therapy been employed.

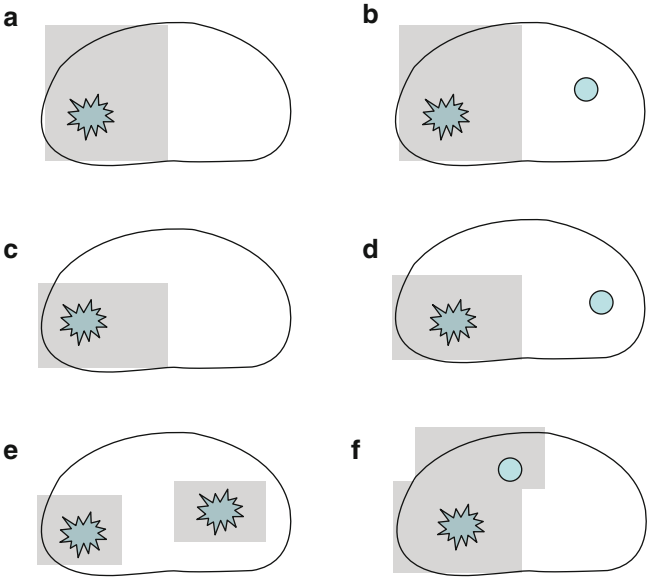


**Fig. 66.2** Example treatment protocols for "focal" therapy. (**a**) Hemiablation (all detected tumour). (**b**) Index lesion hemiablation. (**c**) Quadrant ablation. (**d**) Index lesion quadrant ablation. (**e**) Bilateral focal ablation (sparing at least one neurovascular bundle). (**f**) Hemiablation with anterior extension ("dog leg")

## Selecting Candidates for Focal Therapy

Focal therapy challenges our understanding of both the distribution of cancer foci within the prostate and which cancers we do and do not need to treat. As prostate cancer is a multifocal disease in most men, can targeted ablation really be a feasible option? One approach may be to treat only those men with unilateral or unifocal disease. An alternative approach may be to ablate only the "clinically significant" disease, with a surveillance strategy for the untreated "clinically insignificant" disease (Fig. 66.2). Both approaches require accurate methods for detecting, localizing, and characterizing cancer foci in order to plan treatment and for reliable follow-up of untreated foci.

### Disease Profile

#### Multifocal Versus Unifocal Disease

A number of studies now show that prostate cancer in the PSA screened era is increasingly unilateral or unifocal.

Indeed, unilateral disease has been shown to exist in 20–40 % of men, while unifocal disease in contemporary series may be present in 10–44 % of men with newly diagnosed localized prostate cancer [23–28]. However, the data on multifocality arises from verification studies performed on men who have undergone radical prostatectomy. It is possible that the group of men who are recommended to undergo radical prostatectomy are likely to overrepresent the proportion of men who have multifocal disease compared to those men with screen-detected disease who opt for other management strategies (surveillance, radiotherapy/brachytherapy, minimally invasive treatments). Thus, this group is subject to work-up bias. Although this is more likely in European countries, and particularly in the UK in which active surveillance is well established, it is difficult to verify. However, a larger proportion of men than previously thought may be suitable for focal therapy whereby all of the known disease is treated.

### The Index Lesion

Most men with multifocal disease have between two and three separate foci at diagnosis. Among these foci, there usually exists a dominant lesion that accounts for about 80 % of the total tumor volume (mean tumor volume varies between 0.5 and 2.3 cc) [29–32]. The implication of this observation is that the other 'nondominant' lesions account for 0.1–0.4 cc of tumor on average. By far, the majority of these small cancer foci will be of low grade and will conform therefore to most of the definitions of "indolence" [32, 33]. Lesions above 0.5 cc are the ones that tend to harbor Gleason scores of seven or greater and are responsible for extracapsular extension if present.

Epstein et al. [34] have classified foci into insignificant tumors and minimal, moderate, and advanced tumors using a radical prostatectomy series but drawing on the literature demonstrating pathological characteristics of tumors found in radical prostatectomy, autopsy studies, and cystoprostatectomy. Additional evidence pointing to the role of volume of cancer driving disease progression has emerged from retrospective cohorts evaluating rates of biochemical failure after surgery and radiotherapy [35–37]. Other studies have shown total tumor volume predicts failure on univariate analysis but not on multivariate analysis likely due to the strong influence of Gleason score [38, 39]. Evaluating the predictive power of the index lesion seems to demonstrate a relationship [40, 41]. This may explain some of the discrepancy evident in the literature.

Evidence from molecular genetic studies, which point to a single clone being responsible for metastases, demonstrates that there is usually only one clinically significant clone in the prostate and therefore presumably one clinically significant lesion. This study could not demonstrate whether the metastatic clone resided in the index lesion [42]. It may seem reasonable to propose that ablation of the dominant lesion(s) by volume and grade will give rise to disease control provided the remaining lesions can be well characterized in the pretreatment evaluation [43]. In fact, it could be argued that definitive knowledge of whether index lesions drive disease progression could only be answered within a clinical trial that involves careful selection and follow-up to ensure that progression of untreated areas of cancer is detected early.

## Disease Localization and Characterization

In order to evaluate suitability of candidates for focal therapy, an accurate assessment of the target disease to be treated is required. Using the arguments above for the prognosis of prostate cancer by pathological characteristics and lesion size, the test needs to adequately sample or visualize all of the lesions of clinical significance. The current "gold standard" of TRUS-guided biopsies is likely to be inadequate for this purpose. A number of alternative biopsy strategies and imaging modalities have been proposed or are currently under evaluation.

### Biopsy Techniques

TRUS-guided prostate biopsy techniques have advanced over the years, with improved ultrasound technology and an increase in the recommended number of cores taken. However, despite an increase from six cores to the current "extended" standard of between 10 and 12 cores, or even saturation biopsies, it is still recognized that this technique has a high false-negative rate, especially in the detection of anterior tumors [44]. In the context of focal therapy, accurate siding of the cancer lesions is a particular concern. Despite this, most focal therapy series to date have relied on TRUS-guided biopsies to assess eligibility, plan treatment, and assess response to treatment.

Some groups are now showing high cancer detection rates with the use of targeted transrectal biopsy of image-detected suspicious lesions [45]. If prostate imaging can meet the standards required to rule in and rule out "significant" disease, then this may provide the optimal diagnostic test, with histopathological confirmation of cancer on limited targeted biopsies of image-detected lesions. Until that time, an alternative approach may be required. The transperineal template-guided technique has been proposed as a more accurate method for "mapping" the prostate for cancer foci (Fig. 66.3). It involves biopsies taken via the perineal skin, with sampling of the prostate at 5 or 10-mm intervals through a brachytherapy grid, performed under general anesthetic. The technique has been shown to be approximately 95 % accurate in locating all significant tumor foci. Recently, the Colorado group demonstrated that prostate template mapping biopsies detected all tumor subsequently found on whole-mount radical prostatectomy specimens [46, 47].

As the prostate is sampled via a "clean" approach, sepsis rates are much lower compared with the transrectal approach.

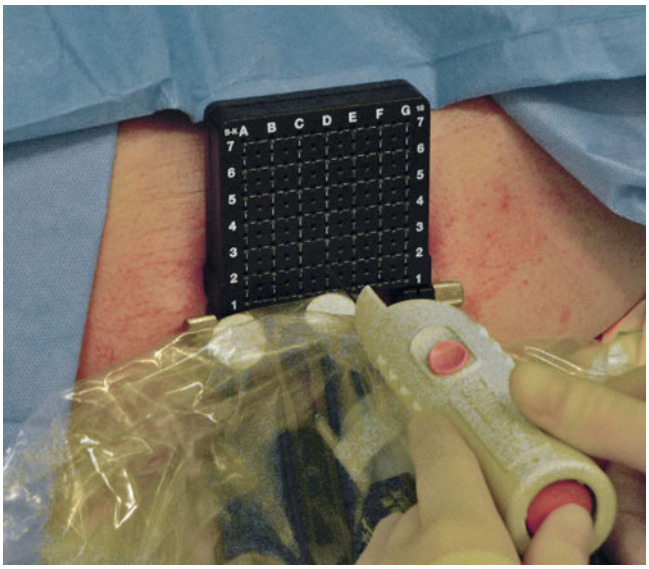


**Fig. 66.3** Transperineal template prostate biopsies

The main acknowledged risk of acute urinary retention can be limited with the use of perioperative alpha-blockers. Thus, despite the need for general anesthetic and theater time demands, transperineal template-guided biopsies have been proposed (and accepted by some groups), as the standard to which trials in focal therapy should evaluate patients' eligibility [6, 48].

## Imaging

As opposed to other solid organ cancers, imaging is not considered a component of the diagnostic pathway for prostate cancer. Instead, reliance is placed on histological sampling of the gland via prostate biopsies, with the aim of capturing cancer in a "blinded" manner. However, with improvements in technology and our understanding of the imaging phenotype of prostate cancer, imaging may now take an essential role in prostate cancer diagnosis and in the assessment of suitability for focal treatments.

### Ultrasound

Although cancers often show up as hypoechoic lesions on normal gray-scale TRUS, this modality is currently neither sensitive nor specific enough to accurately evaluate disease burden or identify the index lesion for focal therapy purposes. However, the addition of color Doppler ultrasound, which assesses regional blood flow, may have a future purpose in identifying the index lesion [49]. Other techniques using ultrasound are now emerging that demonstrate improved accuracy for prostate cancer detection and localization over gray-scale ultrasound. One is contrast-enhanced ultrasonography (CEUS), which uses microbubble contrast agents to visualize prostate cancers through alterations in microvascularity. It has already been used in the context of focal therapy, for monitoring ablative lesion formation [50]. Another is HistoScanning™, a tissue characterization modality that detects and localizes the acoustic signatures produced by tissue of altered morphology, i.e., tumors, compared with normal tissue (Fig. 66.4). Pre-trained algorithms are applied that interrogate raw backscatter 3D ultrasound data and translate them into visual, interpretable signals indicating the presence or absence of disease. Retrospective analyses using whole-mount step-sectioned radical prostatectomy specimens as the reference standard have demonstrated that HistoScanning™ can reliably detect and locate clinically significant lesions of at least 0.5 cc in volume [51, 52]. Finally, elastography is a method that assumes that malignant tissues have different elastic properties to benign tissue and has demonstrated sensitivities of around 85 %, with improved detection of high-grade disease [53].

### Multiparametric Magnetic Resonance Imaging

Traditional MRI uses T1- and T2-weighted sequences, but newer sequences such as diffusion-weighted (DW), magnetic resonance spectroscopy imaging (MRSI), and dynamic contrast enhancement (DCE) using intravenous gadolinium, have been used to improve the accuracy of this imaging modality (Fig. 66.5). A number of studies suggest that with the addition of these sequences, in the so-called multiparametric MRI (mpMRI), 90–95 % of lesions of greater than 0.2 and 0.5 cc in volume are detected [54]. Thus, imaging for prostate cancer with MRI has progressed from its initial use to stage the disease to its present-day capability to identify tumor burden and the precise location of tumor foci within the gland. In fact, a number of centers are now using mpMRI prior to prostate biopsies in order to detect, localize, and characterize prostate cancer [55]. Expert consensus is now being reached on the optimum conduct and interpretation of images for this purpose [56] in an attempt to standardize practice. In addition, mpMRI allows the morphological characteristics of the tumors to be visualized so that margins are better incorporated within a focal treatment plan [57].

## Therapeutic Options for Focal Therapy

There are a number of energy sources that can be used to ablate tissue in a focal manner. An ideal focal therapy is one that offers precise ablation within millimeters of tissue volume, with quick delivery, minimal impact to the patient in terms of discomfort and side effects, and within a day-case setting. Several methods are demonstrating promise in delivering these ideals. Cryotherapy, high-intensity focused ultrasound (HIFU) (Fig. 66.6), and photodynamic therapy (PDT) are the most established techniques to date, all having been evaluated within phase II studies. These are discussed in the following section, together with other possible focal therapies of the future.

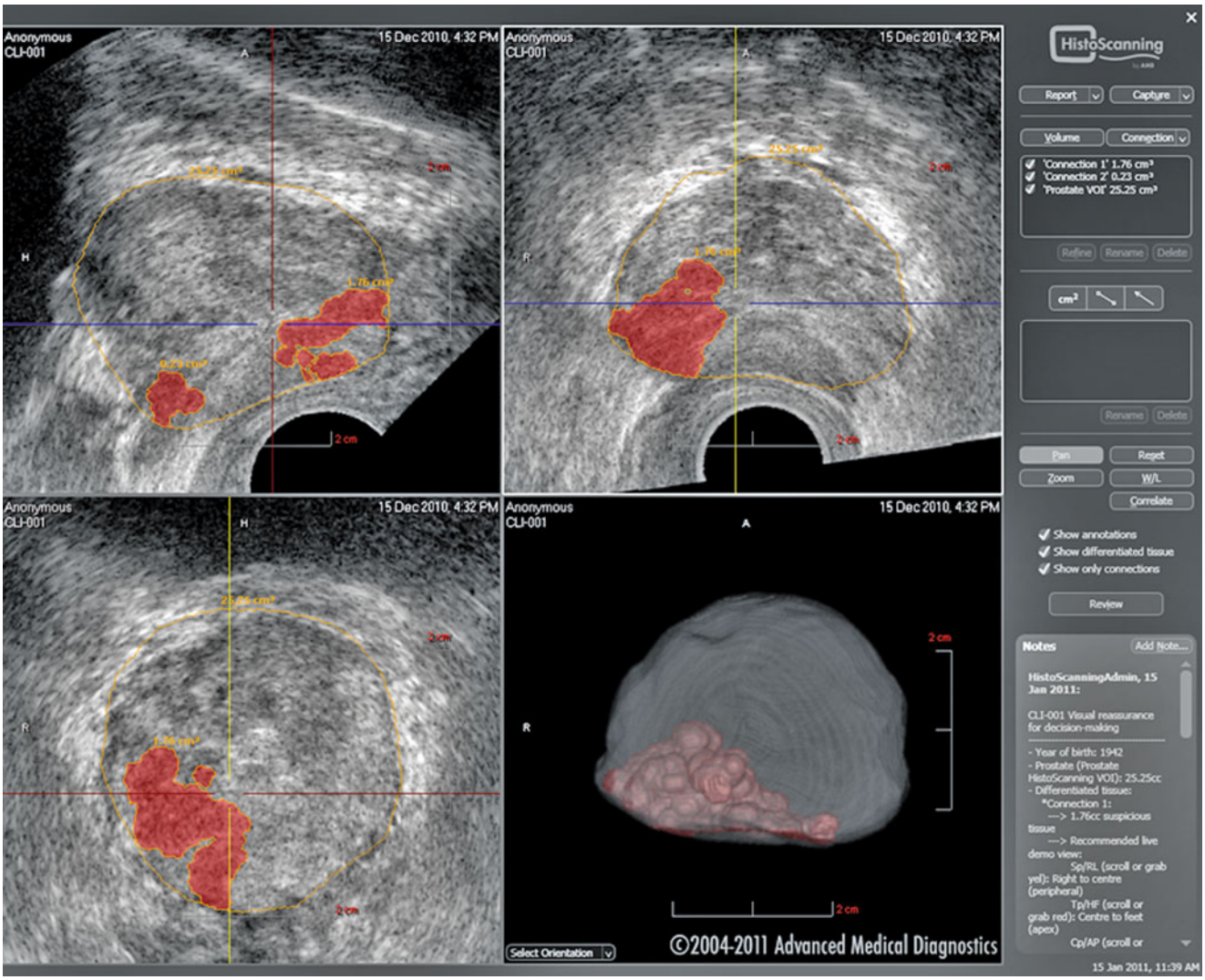


**Fig. 66.4** HistoScanning™ images indicating right-sided prostate cancer (Courtesy of Advanced Medical Diagnostics, Waterloo, Belgium)

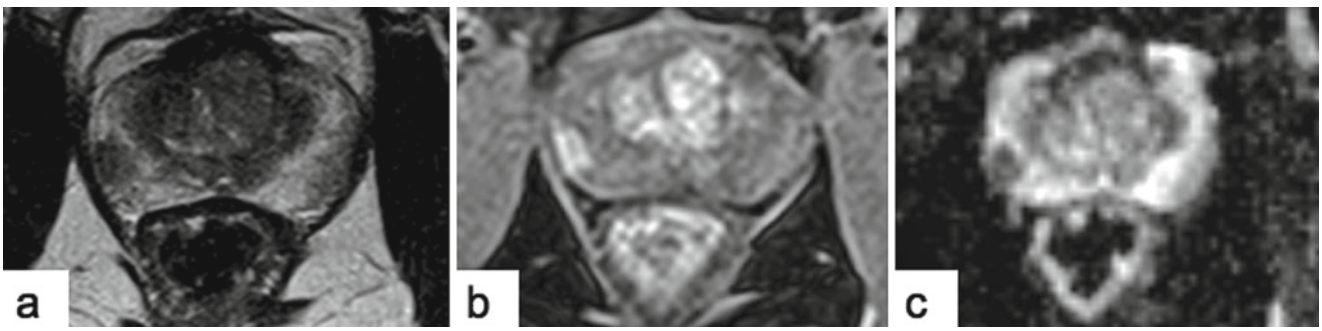


**Fig. 66.5** Multiparametric MRI sequences showing a right peripheral zone lesion. (**a**) T2-weighted. (**b**) Dynamic contrast-enhanced. (**c**) Diffusion-weighted

## Cryotherapy

### Background

Cryotherapy uses extremely low temperatures to treat prostatic cancer via percutaneously placed cryoprobes (Fig. 66.7). It has been demonstrated as a successful primary and salvage treatment for localized prostate cancer with the advantages of minimal blood loss, shorter hospital stay, and the ability to treat "difficult" tumors, such as high burden disease involving the capsule, with more ease than radiotherapy and radical

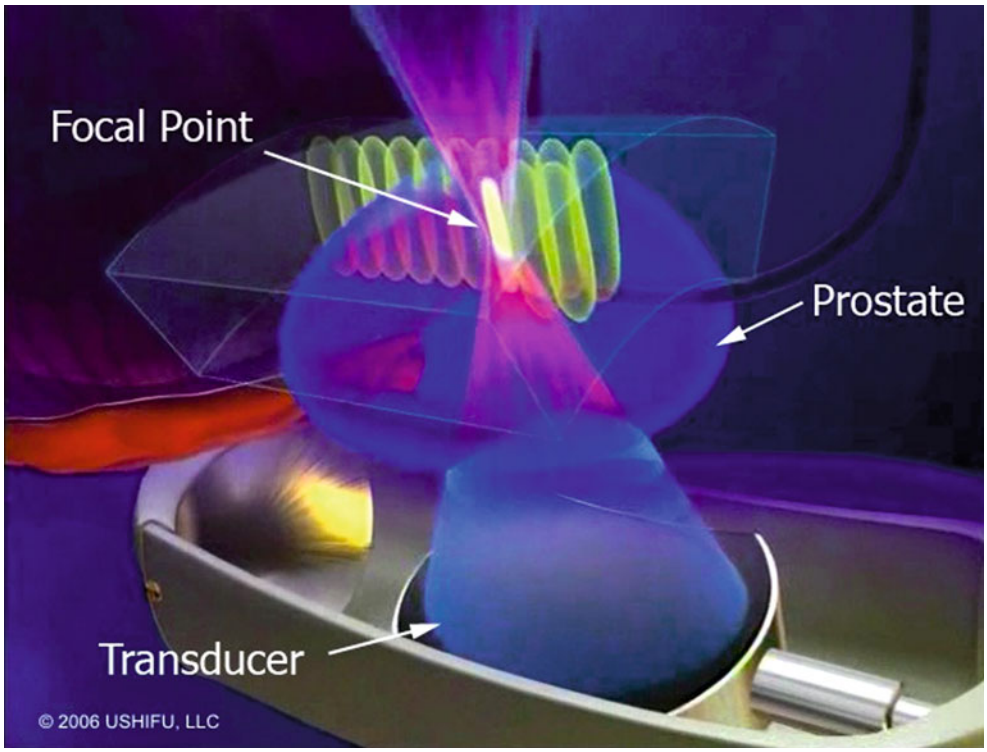


**Fig. 66.6** High-intensity focused ultrasound (Sonablate 500®). The ultrasound waves are focused on a target area depositing large amounts of energy (Courtesy of US HIFU, LLC, Charlotte, USA)

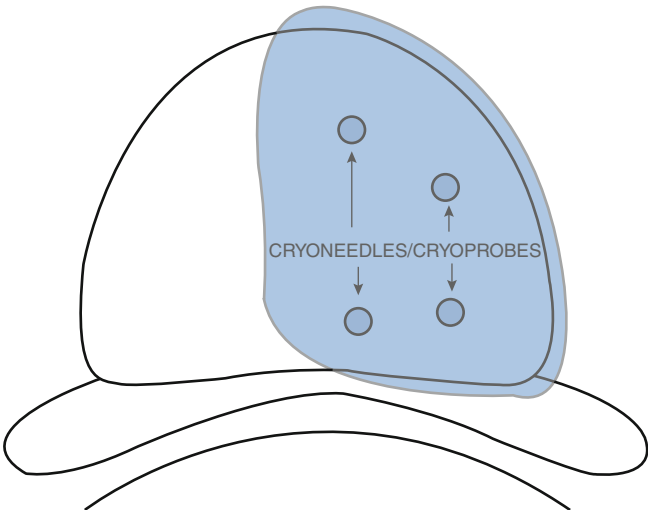


**Fig. 66.7** Example of a focal cryotherapy treatment (Figure first published in *Journal of Urology*, 2007)

prostatectomy. Cryotherapy was approved by the Centers for Medicare and Medicaid Services (CMS) as an alternative primary whole-gland therapy in 1999. In addition, it has been granted approval by the Food and Drug Administration for the treatment of localized prostate cancers. Over the years, cryosurgery has taken its place as an alternative primary treatment option to "conventional" treatments for localized prostate cancer but with limitations on functional outcomes. Subsequently, the cryotherapists were the first to explore whether a focal ablative approach, with preservation of at least one neurovascular bundle, might improve functional outcomes without compromising cancer control.

Cryotherapy was first proposed as an alternative form of radical therapy for localized prostate cancer in 1966, by Gonder et al [58]. Initially, liquid nitrogen was used, with needles placed transurethrally via an open perineal technique but without accurate visualization of the needle placement and the real-time freezing effect. Subsequent treatment of 229 patients demonstrated reasonable cancer control but significant associated morbidity, with a high rate of fistulae (particularly urethrocutaneous), urethral sloughing, and incontinence [59]. The technique was temporarily abandoned due to poor functional outcomes. However, refinement of the technique by Onik et al. caused a reemergence of its application. Visual feedback was introduced with ultrasound imaging guidance, and there was a move toward a percutaneous route of probe insertion. This change in access required several smaller (3 mm) probes in place of the single 8-mm probe, with better and more precise tissue coverage. As a result, cancer ablation improved and fistulae rates declined. Further adaptations to technique and equipment have improved oncological and functional outcomes further; free-hand probe insertion was replaced by the use of a fixed template, urethral warmers have reduced urethral sloughing rates, thermosensors provide local tissue temperature feedback, and intraoperative injection of saline into Denonvilliers' fascia to separate the rectum from the prostate has permitted increased periprostatic freezing to be tolerated in patients with high-risk disease [60]. A change from passive freezing with nitrogen to active freezing and

thawing, via pressurized argon and helium gas, respectively, permitted a further decrease in probe size (17 gauge). It was then possible to insert the probes via a brachytherapy grid, with increased precision of placement and freeze contouring. Other conceptual changes in practice were suggested through expert opinion in an attempt to improve outcomes yet further [61]. However, despite a significant improvement in technology and conduct, potency rates remained poor, with persistently high rates of erectile dysfunction. Thus, a move toward tissue preservation, particularly of the neurovascular bundle, was considered to evaluate whether improved functional outcomes could be achieved without compromising cancer control.

### Summary of Clinical Results

With nerve-sparing radical prostatectomy already demonstrating increased preservation of erectile function, the feasibility of nerve-sparing cryotherapy was addressed. A pilot study, published in 2002, was the first to attempt a "focal" approach to cryotherapy [62]. Patients with cancer confined to one lobe of the prostate (assessed on sextant TRUS biopsy as a minimum) were treated with sparing of the contralateral neurovascular bundle. Eleven patients in total received focal, nerve-sparing treatment, with 2 patients lost to follow-up. Of the remaining 9, all had stable PSA results over a mean follow-up period of 36 months (range 6–72 months); 6 received postoperative biopsies at 1 year, all of which were benign. Potency was preserved in 7 out of 9 men. Feasibility of nerve sparing was also assessed in canines by another group, with active warming of the nerve bundles demonstrating preservation of the neurovascular bundles on histopathological examination, albeit with adjacent unintentional preservation of prostatic tissue in some cases [63]. They also demonstrated more uniform and complete tissue ablation when a double freeze-thaw cycle was applied, compared to a conventional single cycle.

The notion of the "male lumpectomy" was first proposed by Onik et al., drawing on similarities with the tissue-preserving strategy by the breast oncologists in order to minimize the psychological and physical morbidities of losing a breast [64]. Focal cryotherapy was performed by his group in 48 men with localized prostate cancer with a follow-up period of at least 2 years. Of these, 94 % had stable PSA levels according to ASTRO criteria, and all 24 men who received postoperative biopsies at 1 year were cancer-free [65]. Four patients (8 %) with rising PSA levels and confirmation of residual disease on prostate biopsy received a second treatment. Pad-free continence was 100 %, and erectile function (defined as that sufficient for penetration and "satisfactory" sexual function, with or without oral agents) was maintained in 90 % of men.

Other groups were also adopting this technique. Lambert et al. retrospectively reviewed 25 patients who received focal cryosurgery confined to a single lobe at a single institution between 2002 and 2005 [66]. Patient eligibility was assessed on 12-core TRUS biopsy; those with Gleason grade 6 or 7 (3+4) confined to one lobe in up to two contiguous biopsy cores, and with a maximum tumor volume of up to 10 % had an ipsilateral lobe and neurovascular bundle treatment with sparing of the contralateral neurovascular bundle. The median follow-up period was 28 months (range 9–72 months). The median PSA level fell from 6.0 ng/ml to a median nadir of 2.4 ng/ml postoperatively. Sexual function outcomes were less favorable in this group. Of 24 previously potent men, 17 (71 %) remained potent, with the use of phosphodiesterase-5 inhibitors in 7. However, other than an episode of postoperative retention in 1 patient, no other adverse effects were reported.

Another small cohort received tissue-preserving cryotherapy between 1995 and 2004 [67]. This group of men were selected based on initial 6- or 8-core TRUS-guided biopsies, followed by color Doppler ultrasound with systemic and targeted biopsies of suspicious areas on ultrasound (including of the neurovascular bundle or seminal vesicle if extracapsular extension was suspected). There was no limitation to Gleason grade or PSA for inclusion. Over a mean follow-up period of 70 months (range 2–107 months) potency was preserved in 88.9 % (24/27) of men; 40.7 % required phosphodiesterase-5 inhibitors for preservation of function. Again, no patients suffered with incontinence (defined as leak at least 3 months following treatment) or other complications. Biochemical disease-free survival was defined by ASTRO criteria in this study, at a rate of 92.9 %. Of 25 patients receiving at least one postoperative set of biopsies, only one was found to have cancer on the contralateral side.

Ellis et al. treated 60 patients with stage T1 to T3 localized prostate cancer amenable to tissue-sparing therapy as assessed on standard TRUS biopsy [68]. Of 34 preoperatively potent men, 24 (70.6 %) retained potency at 12 months, with or without oral pharmaceutical assistance. The postoperative incontinence rate (with leak but pad-free) was 3.6 % in this cohort. ASTRO criteria were again used to define biochemical disease-free survival, with a rate of 80.4 %. However, cancer-free rates on follow-up bilateral biopsy were high with 14 of 35 men (40 %) having a positive result. Of 11 men who received a second focal treatment, following a period of impotence in 5 men, all regained potency by 12 months following re-treatment.

Thus, in small groups of men, improved functional outcomes compared to whole-gland therapy have been demonstrated as feasible with a focal approach, together with acceptable cancer control. Recently, the multicenter Cryotherapy On-Line Data Registry ("COLD") of whole-gland and focal treatments has begun. This has allowed analysis of outcomes in larger numbers of patients over a longer follow-up period. Focal results have been presented for 795 patients treated with "partial gland" cryoablation [69], with

reported "sexual activity", incontinence, and fistula rates of 65, 2.8 and 0.4 %, respectively, with a median follow-up period of 1 year. Accurate assessment of the data collected is difficult however, as the methods by which both functional and histological data have been obtained are variable. For example, only 18 % of patients underwent postoperative biopsies (performed at the physician's discretion). Of these, 25 % were positive for histology.

## High Intensity Focused Ultrasound

### Background

Due to the ability of high intensity focused ultrasound (HIFU) to treat small, localized areas of the prostate in a precise manner, this technology has shown promise as a focal ablative therapy, both as a primary treatment and as a focal salvage treatment for localized radio-recurrent disease. Additional prostate treatment is not precluded if cancer recurrence occurs after HIFU. Patients can either undergo further HIFU (whole gland or focal) or be considered for brachytherapy, cryotherapy, radiotherapy, or surgery. The majority of men choose redo HIFU, so the numbers undergoing other therapeutic modalities is low. Therefore, the outcomes of salvage radical therapies after HIFU are poorly reported but would be expected to be worse than for primary treatments.

Ultrasound applies cyclical sound pressures at varying frequencies passed through a piezoelectric material. The spectrum of frequencies allows ultrasound to be used for both diagnostic (1–20 kHz) and therapeutic purposes (0.8–3.5 MHz). Waves are propagated through tissue, causing alternating cycles of pressure, with compression and rarefaction of tissue. HIFU uses short wavelengths (mm) in combination with megahertz frequencies to cause a focused heating effect on a small volume of tissue. By applying heat over 55 °C for at least 1 s, irreversible tissue necrosis is caused. The heating effect is localized to ellipsoidal volumes of tissue measuring approximately the size of a grain of rice (as small as 1 × 8 mm).

HIFU uses the mechanisms of firstly, thermal ablation and secondly, cavitation to cause irreversible cell damage. The ultrasound waves are focused on a target area depositing large amounts of energy, which is absorbed by the tissue and converted into heat. Temperatures of up to 100 °C can be reached for a period of a few seconds causing necrosis and cell death within the target area without causing damage to the surrounding tissue. However, heats over 55 °C are sufficient for cell death. Some of the energy sourced at the transducer is deposited at the tissue interfaces that sit between it and the target tissue. However, as the frequency of the waves rapidly diminishes with proximity to the transducer, the heating effect is minimized to normal tissue. The vibrating effect of ultrasound on tissue causes rarefaction and the production of bubbles from released gas, with rapid collapse. The combination of thermal insult and cavitation causes tissue necrosis.

The therapeutic application of HIFU was first described in 1942 by Lynn et al. when neurological changes were noted in cats and dogs in whom brain tissue was treated [70]. The Fry brothers subsequently demonstrated successful ablation of neurological tissue with HIFU in both animals [71] and humans with neurological conditions [72] in the 1950s. In the same decade, HIFU was first considered as an ablative therapy for cancer tissue [73], and since that time, it has been evaluated in clinical practice for a number of benign and malignant pathologies. Currently, these include treatment of lesions in the liver, bladder, kidney, breast, uterus, brain, and bone. All of these treatments are at different stages of clinical development, with most undergoing evaluation of medium to long-term outcomes within ongoing clinical trials.

It was not until the 1990s that clinical application of HIFU on both benign and malignant prostate tissue is starting to become of interest. HIFU ablation of benign prostatic hypertrophy within phase II trials demonstrated only moderate medium-term improvement in lower urinary tract symptoms, and in one series, 43.8 % of men required a re-resection TURP (transurethral resection of the prostate), within 4 years [74]. Thus, HIFU was not proven as a successful alternative treatment of benign prostatic hyperplasia to TURP. However, it is its ability to ablate tumors with an acceptable side effect profile that has resulted in its adoption as a form of cancer therapy worldwide.

There are currently two HIFU devices available for the treatment of prostate cancer: the Ablatherm® (EDAP-TMS SA, Vaulx en Velin, France) and Sonablate 500® (Focus Surgery Inc, Indianapolis, Ind). There are differences in technology and conduct between them. However, both involve the delivery of treatment via a transrectal probe containing the transducer. Treatment effects can be monitored via real-time ultrasound. In most cases, the patient receives a general anesthetic. This allows for patient tolerance and restricts motion so that accurate targeting is possible. The rectum is cooled during treatment using continuous irrigation with degassed water in order to limit the potential adverse effects of heating such as fistula formation.

The Ablatherm® device consists of two "modules," the treatment module on which the patient lies in a lateral position to receive treatment and the control module at which the surgeon plans treatment and controls the position of the probe delivering HIFU. Treatment plans are automated to a preset protocol depending on whether it is a primary treatment, re-treatment, or salvage procedure.

The Sonablate 500® equipment consists of a monitoring module together with the transrectal probe which is inserted with the patient supine and in the lithotomy position on a

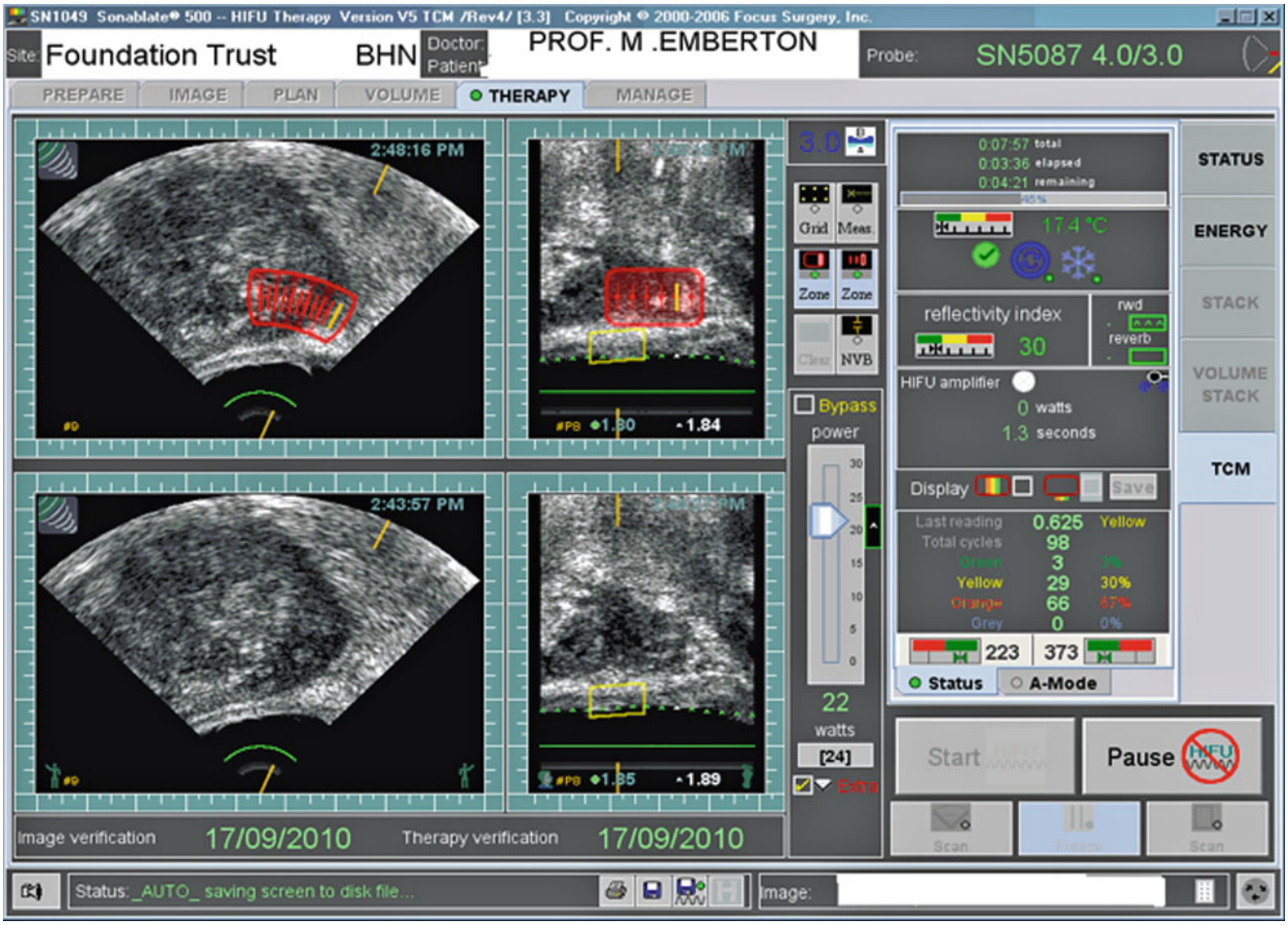


**Fig. 66.8** Ultrasound images of a focal HIFU treatment (Sonablate 500®). Live images are seen in the sagittal and transverse views, and power levels can be adjusted according to the visual effects seen

standard operating table. The Sonablate 500® is controlled manually by the surgeon, and the power of HIFU pulses can be altered according to real-time visual feedback from the ultrasound images.

Ultrasound real-time feedback of treatment effect is seen as gray-scale changes as the heating effect causes tissue damage. These so-called "Uchida changes" are also known as the "popcorn" effect due to the visual appearance of circular areas of echo-poor tissue. The changes are classified into grades I–III depending on the extent of the gray-scale changes within the targeted area. The power delivered can be altered immediately by the surgeon according to the real-time effects seen (Fig. 66.8).

Prostate-related contraindications to HIFU treatment include a large prostate size whereby the focal length for treatment would not reach the anterior part of the prostate. Some surgeons perform a TURP prior to HIFU to reduce the prostatic volume. Also, large calcium deposits within the prostate can prevent ultrasound wave propagation causing undertreatment. Both of these factors can be assessed at a preoperative transrectal ultrasound of the prostate. Non-prostatic reasons for HIFU exclusion include any anatomical or pathological abnormality limiting insertion of the rectal probe, e.g., tight anal stenosis and previous anorectal surgery.

## Summary of Clinical Results

HIFU is still a relatively new treatment for prostate cancer. The medium–long-term results of whole-gland treatment are now being published. Reported complication rates include urethral stricture 10–40 %, impotence 25–30 %, incontinence <2 %, and rectourethral fistula <0.5 %. As with other salvage procedures, the reported side effect profile and adverse functional outcomes of salvage whole-gland HIFU are greater, with cancer control of approximately 70 %.

As focal HIFU is a relatively new therapeutic concept, reported results are currently limited (Fig. 66.9). The results of focal HIFU were first reported in 29 men out of a total cohort of 70 that received HIFU for localized prostate cancer (low–high risk) [75]. The remaining 41 patients received whole-gland therapy. Treatment was evaluated and planned (whole gland versus focal) using 12-core tran-

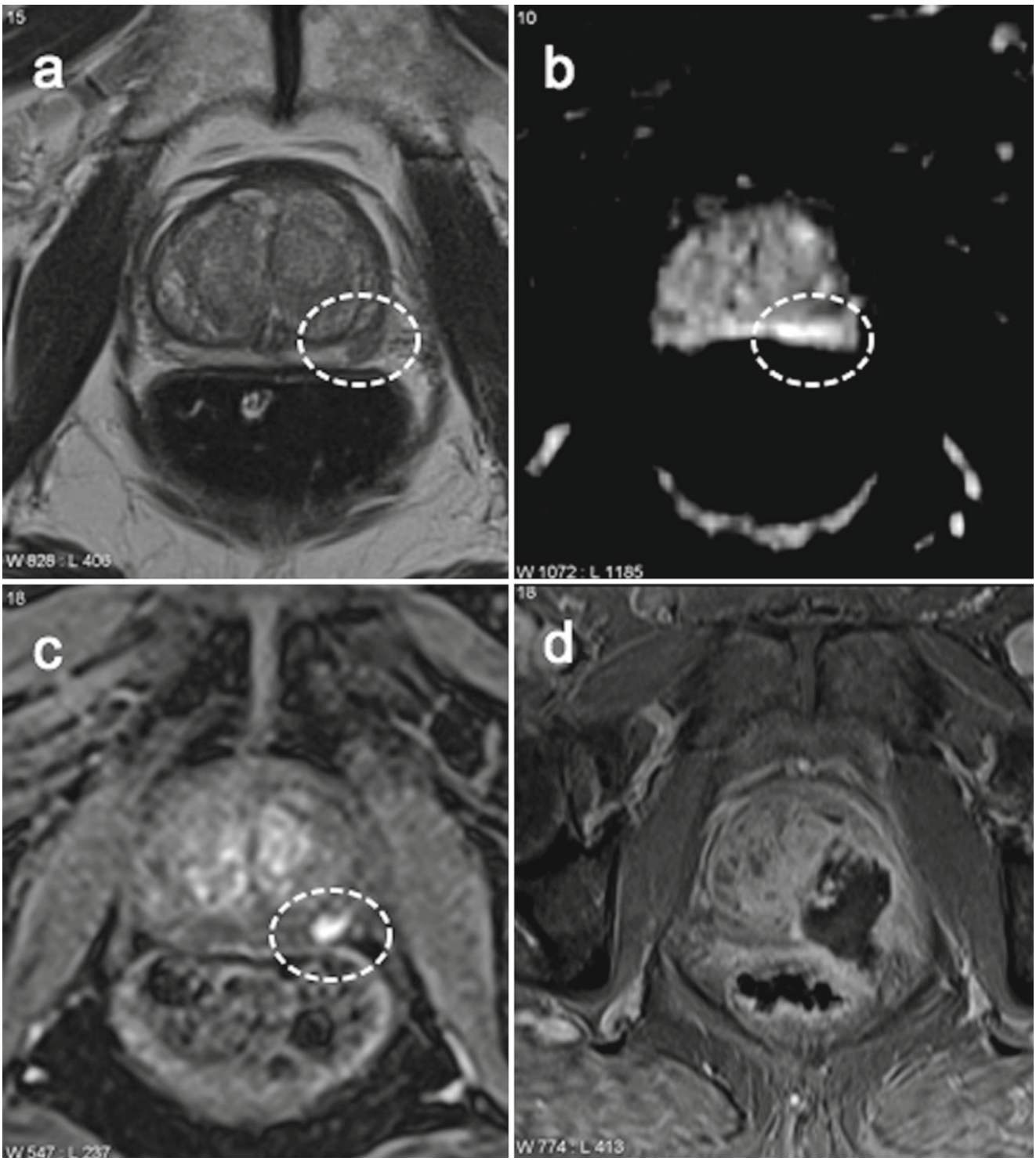


**Fig. 66.9** Focal ablation of a left peripheral zone lesion. Multiparametric images showing the preoperative lesion on (**a**) T2-weighted, (**b**) diffusion-weighted, (**c**) dynamic contrast-enhanced sequences, and (**d**) necrosis of the area seen on the early (2 week) postoperative MRI

srectal biopsies. Men receiving focal treatment had unilateral disease on biopsy. A third (34.3 %) of patients in total were receiving hormone ablation therapy prior to treatment, including 24 % of those patients treated focally. Focal treatment involved bilateral peripheral zone ablation and ipsilateral transition zone ablation according to the laterality of the positive biopsy cores. This group demonstrated comparable cancer control between the two groups; 84.4 % of patients were disease-free on 12-month postoperative prostate biopsy in the whole-gland group, compared

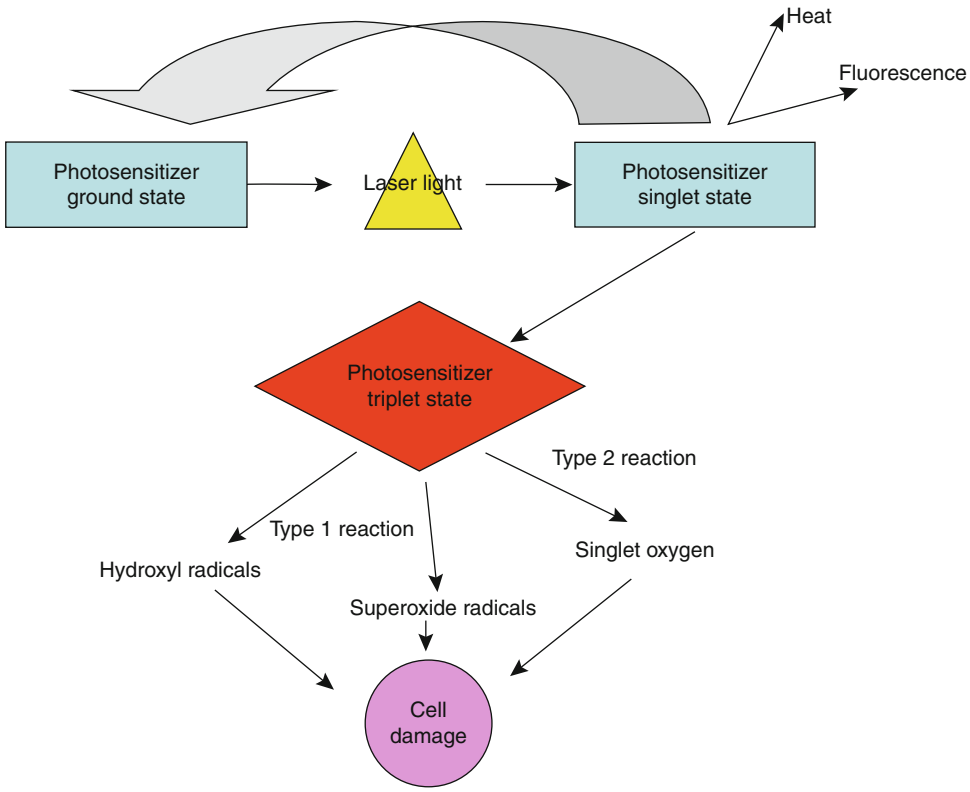


**Fig. 66.10** Photodynamic therapy. Activation of the photosensitizer occurs on exposure to light of a specific wavelength, with conversion of the inactive product to an unstable energized (singlet) state (Figure first published in *World Journal of Urology*, 2010)

to 76.5 % of the focal group. Surprisingly, despite preservation of some normal prostatic tissue, 2-year biochemical disease-free survival rates according to ASTRO criteria were also similar between the two groups, at 90.9 and 49.9 %, respectively, for low- and intermediate-risk disease with whole-gland ablation and 83.3 and 53.6 %, respectively, with focal ablation. However, the group did observe that in the group of patients not receiving hormone ablation therapy, serum testosterone levels were maintained following focal treatment but diminished following whole-gland treatment. If this outcome is reproducible, it may account for some of the functional loss following whole prostate treatment.

Published data for focal HIFU is otherwise lacking, although it is currently being evaluated within phase II clinical studies with promising early results that demonstrate potency and continence rates of approximately 90–95 % with 90 % early cancer control. The results of the first two of these trials have recently been published [87, 88]. Two further phase II trials are ongoing at University College London, UK. The first involves treatment of the index lesion only, i.e., ablation of clinically significant cancer as assessed on transrectal or transperineal biopsies, while sparing clinically insignificant disease for future surveillance. The second is a multi-centre UK study. This will provide further phase II data on a larger group of men and with a longer follow-up period (3 years).

## Photodynamic Therapy

### Introduction

Photodynamic therapy is the ablation of tissue using a photosensitizing drug that is activated by light of a certain wavelength, in the presence of oxygen. Interaction of the activated drug and oxygen results in the production of reactive oxygen species, which cause localized tissue necrosis. Photosensitizers are administered either topically, orally, or intravenously in their stable inactive form. Activation occurs on exposure to light of a specific wavelength, with conversion of the inactive product to an unstable energized (singlet) state (Fig. 66.10) [76]. Energy is emitted in this state in the form of heat or light. Conversion to a triplet, or intermediate state, occurs prior to the return to the unstable form. From the triplet state, the photosensitizer is capable of two types of reaction: type 1 is the production of superoxide and hydroxyl radicals, and type 2 is the conversion of molecular tissue oxygen to singlet oxygen. The output of both reactions causes localized cell death.

Photosensitizers can either be activated in the vasculature or in the tissue itself. Tissue-activated photosensitizers take several days to reach a maximal concentration in the target tissue, in comparison to the surrounding normal tissue. However, due to accumulation of the drug in other nontarget tissue, such as the eyes and skin, careful precautions are required to protect these areas from activation of the drug by

light such as strong sunlight or indoor light. These drugs can take several weeks to be cleared, requiring skin protection for several weeks. An example of a tissue-activated photosensitizer is amino levulinic acid (ALA). The second form of photosensitizer (vascular-activated) is activated within the vasculature within minutes of administration. In addition, it is cleared rapidly. As a result, both the photosensitizer and the light source can be administered as a same-day treatment, with no requirements for prolonged protection from light. Examples of this type include the palladium bacteriopheophorbide photosensitizers, padoporfin, and padeliporfin (Steba Biotech, Netherlands).

Since that time, the development of a light delivery system via optical fibers enabled its use as a treatment of solid organ tumors, including of the head, neck, and pancreas. For treatment of the prostate, optical fibers (hollow plastic needles) are inserted via a transperineal route, using a brachytherapy template.

### Summary of Clinical Results

The first clinical application of photodynamic therapy for prostate cancer was published in 1990 in the Lancet [77]. Two patients with localized prostate cancer were treated with tissue-activated PDT. Both patients were treated with tissue-activated hematoporphyrin-derivative photosensitizers, one with "Photofrin" (polyporphyrin) and the other with HpD. Light dosing was administered transurethrally 48–72 h later, 6 weeks after two separate prostatic resections (to ensure adequate resection). Follow-up prostate biopsies were benign 3 months postoperatively. PSA values fell from 10 and 6 μg/l preoperatively to 2.5 and 0.2 μg/l postoperatively, respectively. There were no adverse events reported. One patient died of previously undiagnosed lung cancer 6 months after treatment. However, the post-mortem evaluation of his prostate showed no histological evidence of residual cancer.

Another group at University College London, UK, performed two small clinical studies using PDT for localized prostate cancer. The first involved treatment of radio-recurrent localized disease with the tissue-activated photosensitizer temoporfin (meso-tetra-hydroxyphenyl-chlorine, mTHPC, Foscan®; biolitex AG, Jena, Germany) in 14 men [78]. A low light dose (20 J/cm) was given to the first 5 patients, 4 of which then chose to have a larger second dose after limited effects of treatment were seen on postoperative CT. The remaining 9 patients received a higher dose of 50 J/cm from the outset. Limited tissue ablation was performed based on preoperative biopsy and imaging results. Volumes of necrosis were variable on postoperative imaging, some of which were patchy, with a maximum treatment effect of 91 % necrosis for a bilateral treatment. Adverse events included one rectourethral fistula (possibly contributed to by, or caused by, a postoperative rectal biopsy), stress incontinence in 2 men, and acute urinary retention in 3 men. The second phase I/II study used the same photosensitizer (mTHPC) to treat primary localized disease in 6 men with Gleason 3 + 3 [79]. Focal treatment was given using up to four fibers inserted via the transperineal route and the positions checked using the open access MRI scanner. The light dose given was tailored to proximity of the treatment to the apex (50–100 J/cm). After a total of ten treatments (4 patients were offered re-treatment on the basis of cancer found on biopsy 1 month after the first treatment), the PSA fell after eight of these. Postoperative treatment effects were variable on the early postoperative MRI at 2–6 days. Healing of necrotic and edematous areas was seen at both the 1-month and the 2–3-month, postoperative MRI scans. The treatments were well tolerated. All patients had irritative voiding symptoms that lasted for up to 2 weeks, and two patients required temporary re-catherization after second treatments. One of these men developed transient incontinence that had resolved by 4 months.

Padorphin (WST-09, Tookad®; Steba Biotech, The Hague, The Netherlands) is a lipophilic vascular-activated photosensitizer. It requires a carrier in order to be given by intravenous infusion. It was also first evaluated within a phase I/II trial as a salvage treatment for radio-recurrent disease [80]. As this was the first application of this drug in humans, a dose escalation regimen was used. At an infused rate of 2 mg/kg, and with a half-life of about 20 min, photosensitizer levels were undetectable at 2 h. An increased volume effect of treatment was seen with the higher light dose, as assessed on early postoperative MRI scans. There was no residual skin photosensitivity, as assessed using a full spectrum of solar-stimulated light, 3 h after treatment. A similar dose-related effect was seen by the same group, when Padorphin was assessed as a whole-gland salvage treatment in 28 men with failed external beam radiotherapy (EBRT) [81]. In 13 men who received a light dose of at least 23 J/cm$^3$, 8 had negative biopsies 6 months following treatment. Two patients had rectourethral fistulae following treatment, one of which closed spontaneously at 6 months. Neither received a higher than average light dose compared to the rest of the group.

Padorphin has since been evaluated as a primary therapy within a dose escalation trial, and the results of this trial are awaiting publication [82]. Good volumes of necrosis were seen. Hypotension requiring fluid bolus and vasopressors had been seen previously. However, cardiovascular events (in two patients) and subclinical hepatotoxicity were additional adverse events seen in this study.

As a result of the systemic effect seen with padoporfin, a water-soluble version of the drug was developed, called padeloporfin (WST-11 Tookad® Soluble). This drug has undergone assessment within recent phase I/II clinical trials, within improved safety and tolerability levels seen compared to padoporfin. The results of these studies are awaiting publication. Furthermore, a European multicenter phase III trial

is underway, assessing the outcomes of PDT versus active surveillance in men with localized low-risk disease.

## The Future of Focal Therapy

A number of different ablative techniques are underdevelopment as potential focal therapies for localized prostate cancer. They all aim to provide greater precision by which abnormal tissue is ablated, within a minimum treatment timeframe and with the minimal postoperative recovery period and discomfort to the patient. The method by which tissue is rendered nonviable may not be the priority question however, in the assessment of whether focal therapy will take a position within the current "standard" treatments for localized prostate cancer. Rather, the most pressing area of need may be in the ability to accurately detect, localize, and characterize those cancers requiring treatment, with the ability to rule out significant disease elsewhere, both at the diagnostic stage, for planning focal treatment, and for follow-up. Additionally, imaging tissue characterization and cancer detection at the time of treatment would allow accurate tissue ablation of the cancer areas only, minimizing the area requiring ablation and with maximum preservation of surrounding normal tissue. Some important technological advances are currently underway with the aim of transferring imaging datasets from the diagnostic to the treatment platforms, with the potential for more accurate targeting. Finally, the ability to receive real-time visual feedback of tissue response would allow accurate delivery of the energy source, eliminating the risk of undertreatment (and poor cancer control) and overtreatment (with increased risk of side effects).

### Alternative Focal Therapies

Radiofrequency ablation (RFA) and brachytherapy are both established ablative techniques for renal and prostate cancers, respectively, with the ability to treat selective areas of the prostate. Transperineal RFA, using both monopolar and bipolar energy via needles of different configurations (to alter the volume of tissue treated), demonstrated effective focal ablation in the prostate, as published in 1998 [83]. However, this technique is not currently being evaluated as a focal therapy within prospective trials. Similarly, there is potential for selective treatment using different radiotherapy sources. For example, low-dose brachytherapy seeds could be placed in a selective manner, with maximal radioactivity delivered to distinct areas of the prostate. Similarly, CyberKnife is a new method for delivering hypofractionated sterotactic radiotherapy via a robotic arm. It allows dose distribution to be tailored to the tumor, with a steep dose gradient between the target tissue and the surrounding normal tissue. As a result, it is hoped that the bowel, urinary, and sexual function toxicities seen with external beam radiotherapy will be diminished. Although not designed as a form of focal therapy, the notion behind CyberKnife is equivalent, with maximum energy delivered to the tumor itself.

Microwave and laser therapies are examples of thermal ablative techniques with the potential for real-time monitoring of treatment effect using imaging. MR thermometry was used to monitor the temperature changes in tissue with microwave treatment radio-recurrent prostate cancer in 5 men [84], with good correlation between the visualized heating effect with the areas of tissue necrosis. More recently, after demonstrating the feasibility of photothermal laser ablation for low-risk prostate cancer within a phase 1 trial [85], one group subsequently performed real-time MR imaging-guided laser ablation in 2 patients [86] with successful ablation of the target area and correlation of the temperature changes seen on imaging.

Finally, direct injection of an antiandrogen into the prostate has been proposed as method of administering a maximum tissue concentration to the lesion itself with minimized systemic effects. Patients are currently being recruited for treatment with the antiandrogen 2-hydroxyflutamide (Liproca®, LIDDS pharma, Sweden) within a phase II trial.

## Take-Home Messages

With increased awareness of the potential for overtreatment and treatment-related burden from "traditional" whole-gland treatments for localized prostate cancer, focal therapy is showing promise as a new treatment concept in order to limit these risks. The cryotherapists have been the first group to demonstrate focal treatment in men, with consistently improved side effect outcomes compared with whole-gland cryotherapy. Since then, HIFU and PDT have also demonstrated success in the ability to ablate discrete areas of the prostate within phase I/II studies, with verification of treatment effects seen on imaging and histopathological specimens at follow-up. Functional outcomes have been encouraging across all three therapies.

Histological outcomes, although good in most series, have been less consistent. This inconsistency may be partly due to staging errors – preoperative TRUS biopsies for focal therapy eligibility may have been inadequate to adequately assess disease burden. Imaging and alternative biopsy techniques, such as transperineal template or image-targeted biopsies, need to continue to be evaluated within the focal therapy context to minimize staging errors in these patients. Secondly, focal treatment poses a dilemma for oncological follow-up. With the preservation of some normal prostate tissue, PSA levels are not expected to decrease to a negligible level. Currently, there are no defined biochemical treatment

failure criteria for focal therapy, although most studies use one of the many definitions for radical therapies as a surrogate measure, e.g., ASTRO criteria, Phoenix criteria. In addition, postoperative biopsy strategies currently differ across published data, making comparison of outcomes difficult. Imaging has been used for verification of treatment effect in many studies to date, and in the future, this may become the dominant technique for monitoring oncological success of a focal treatment.

In order to continue to assess focal therapy as an alternative treatment option in eligible men, longer-term data is now required. Registry data collections, such as with the COLD registry, will provide crucial information. In addition, further prospective trials in larger groups of patients, using validated patient questionnaires and consistent biochemical and histological verifications of treatment success, are required. In the meantime, new methods for selectively ablating tissue continue to be developed, together with improved technological advances such as in the concomitant use of imaging for guiding and monitoring treatment.

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# Part VI

# Failure and Management of Recurrent, Locally Advanced, and Advanced Disease

Andrew Armstrong, Ronald Chen, Richard Stock,
and John Sylvester

# Biochemical Failure in Prostate Cancer

67

Tian Zhang and Andrew Z. Wang

## Introduction

Prostate cancer treatment failure after local therapy can be detected through changes in PSA prior to any clinical evidence of disease. Therefore, posttreatment elevation, also called biochemical failure, has been utilized as a surrogate for disease recurrence. The ability to consistently define biochemical failure is important both for the prognostic risk stratification of patients for clinical recurrence and survival and for the standardization of research when comparing multiple series of patients who undergo the same treatment. Due to the difference in PSA posttreatment, the definition of biochemical failure varies between treatments. In this chapter, we will explore the definitions of biochemical failure for each type of prostate cancer treatment, the clinical workup at time of biochemical failure, and the management decisions that clinicians encounter after patients develop biochemical failure.

Although definitive treatments for prostate cancer are highly effective, many patients still suffer from recurrent disease after treatment. Recurrent prostate cancer can take months to years to be detected by imaging or to manifest clinically. Posttreatment elevation in PSA, also called biochemical relapse/failure, generally precedes clinical recurrence of prostate cancer. In order to detect disease recurrence early, biochemical failure has been used as a surrogate for disease recurrence. Indeed, biochemical failure is the most common end point in reporting prostate cancer treatment outcomes.

Defining biochemical failure after local radiation and surgical therapy has been challenging. The ability to consistently define biochemical failure is important both for the prognostic risk stratification of patients for clinical recurrence and survival and for the standardization of research when comparing multiple series of patients who undergo the same treatment. However, posttreatment PSA behavior varies dramatically between treatments. Thus, biochemical failure has been defined differently for different prostate cancer treatments and has been the subject of much debate in both urology and radiation oncology fields. In this chapter, we will explore the definitions of biochemical failure for each prostate cancer treatment, the clinical workup at time of biochemical failure, and the management decisions that clinicians encounter after patients develop biochemical failure.

## Definitions of Biochemical Failure After Surgical Treatment

Surgical treatment of prostate cancer generally removes all prostate tissue at the time of surgery, and therefore, PSA levels should become undetectable within 6 weeks in the postoperative setting. Hence, any PSA value higher than undetectable or zero would seem to be an obvious definition for biochemical failure, but the issue is not so simple. Detectable PSA after surgery may reflect residual normal prostatic tissue, which also produces PSA. In addition, normal tissues such as urethral glands have been known to produce low levels of PSA [1, 2]. Lastly, commercial PSA tests have different levels of sensitivities and detection thresholds. A patient's PSA may be undetectable by one test but detectable using a more sensitive test. Due to the above-mentioned factors, there were many definitions of biochemical failure after surgical management prior to 2007. In order to identify a biochemical failure definition that reliably predicts prostate cancer recurrence, the American Urological Association established guidelines on postoperative biochemical failure in 2007 [3]. They reviewed 145 articles of primary research for patients treated with radical prostatectomy; these articles combined had 53 different definitions of biochemical failure.

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After weighing the advantages and disadvantages of each definition, the urology panel found that the most accurate PSA levels predicting biochemical recurrence progressing to clinical recurrence were between 0.2 and 0.4 ng/mL. In debating between values within 0.2 and 0.4 ng/mL, they decided that a lower cut point would allow higher sensitivity in detecting biochemical failure as well as earlier initiation of potential salvage therapy. Ultimately, the panel recommended PSA level greater than 0.2 ng/mL, with a second confirmatory PSA level greater than 0.2 ng/mL, as the definition of biochemical failure after surgery.

Although the consensus has been widely accepted, advances in PSA testing may1 day lead to changes to this definition once more. Typical commercially available PSA assays have enough sensitivity to detect changes of 0.1 ng/mL with some ultrasensitive PSA tests that can detect changes of 0.01 ng/mL. A new technology which allows the detection of PSA in picograms (up to 300 times more sensitive than current assays) was reported [4]. In this study, 2 of the 18 patients whose serum was analyzed retrospectively had increases in PSA levels in the picogram range and also developed biochemical recurrence by the current definition. These authors suggest that the increasing PSA may be more important predictor of biochemical failure than absolute PSA levels. However, the era of ultrasensitive PSA testing has allowed detection of PSA even in women, with some studies suggesting that PSA may be a marker for benign breast disease [5, 6]. More studies need to be performed before using these tests in standard clinical care.

## Definitions of Biochemical Failure After Radiotherapy Treatment

Radiation therapy, which encompasses brachytherapy and external beam radiotherapy, has also been a mainstay of locoregional treatment in prostate cancer. Radiation therapy induces double-stranded DNA breaks and kills prostate cancer cells in a prolonged manner. Hence, PSA after radiation has a gradual decline over months to several years and eventually ends in a nadir value, which can be different for each patient. Although it is tempting to define biochemical failure after radiotherapy as any rise in PSA after nadir, a rise is not always associated with disease recurrence. In fact, radiation-induced prostatitis can also cause a transient elevation in PSA levels. In these cases, PSA levels will decrease back down to nadir if not below nadir levels. This type of benign elevation of PSA is termed "PSA bounce."

Retrospective analyses of patients treated with radiation have identified a range between 12 and 35 % of patients who experience PSA bounce, depending on the definition of the PSA bounce [7–10]. In the largest of these studies, Rosser et al. retrospectively investigated a cohort of 964 patients who had received external beam radiation at a single cancer center [11]. They defined PSA bounce as increase in PSA more than 0.5 ng/mL, then decreasing to PSA nadir less than 60 months after radiation therapy was complete. They found that 119 (12 %) of their patients experienced PSA bounce. PSA bounce was not associated with biochemical failure, and indeed, patients who experienced PSA bounce had biochemical relapse-free survival rates longer than those who did not experience PSA bounce. Similarly, brachytherapy with the implantation of radioactive seeds also causes a delayed cell death and slower decline in PSA levels. In these patients, PSA bounce has also been characterized retrospectively. One of the more comprehensive studies by Stock et al. compared three definitions of PSA bounce: (1) PSA increase more than 0.1 ng/mL, (2) PSA increase more than 0.4 ng/mL, and (3) increase in PSA > 35 % of the previous PSA level [12]. They found that in their study population of 373 patients, 31 % had PSA bounce with the first definition, 17 % experienced a bounce using the second definition, and 20 % had the transient bounce with the third definition. Using multivariate regression, PSA bounce was not associated with biochemical failure.

Defining biochemical failure in patients treated with radiation therapy is therefore much more difficult and has been the subject of much discussion over the past two decades. In 1996, the American Society of Therapeutic Radiology and Oncology (ASTRO) convened a consensus panel to define biochemical failure after radiation treatment [13]. Experts in the field delineated the data available at the time, examining large patient series after external beam radiation at six comprehensive cancer centers around the US. Discussion focused on whether to take absolute values of PSA levels or PSA trajectory into account when initiating treatment for biochemical failure. Given patients' propensity to progress to clinical recurrence after three consecutive rises in PSA, the inability to define absolute values for nadir PSA, and the need to avoid incorrect diagnoses of biochemical failure in patients experiencing PSA bounce, the consensus panel recommended three consecutive elevations in PSA after reaching a nadir as the definition for biochemical failure after external beam radiation therapy. In addition, they recommended that for purposes of clinical trials, the timing of the failure date should be half of the time between the nadir date and the first increase in PSA. This definition of biochemical failure is generally referred as the "ASTRO" definition.

Subsequently, several disadvantages of this initial consensus recommendation became apparent. First, there was bias in event-free survival depending on length of time in follow-up, with more bias in shorter follow-up PSA levels. In addition, the timing of biochemical failure could not be correlated with clinically relevant end points or timing of treatments. Finally, the initial consensus had been formulated based on patient series after external beam radiotherapy and

without the data from newer treatment options including brachytherapy and hormonal therapy. In order to overcome the above disadvantages of the initial ASTRO consensus guidelines, a second consensus panel was formed in Phoenix, AZ, in 2005. These "Phoenix guidelines" took into account clinical prognosis/survival as well as different types of therapeutic interventions (including androgen deprivation therapy and brachytherapy) and recommended that biochemical failure after radiation therapy be redefined as nadir PSA +2 ng/mL. Since most PSA bounce phenomena do not increase PSA levels more than an absolute 1 ng/mL, this definition's threshold of 2 ng/mL would decrease false-positive biochemical failure rates to 5 % or less. In other patient series in which patients had undergone hormonal therapy or brachytherapy, nadir +2 was also appropriate for defining biochemical failure [12, 14]. This definition of biochemical failure is also called the "Phoenix" definition. In one study where the ASTRO and the Phoenix definitions were compared, the Phoenix definition of biochemical failure was a more robust determinant of patient outcome such as distant metastasis, cancer-specific survival, and overall mortality [15]. Although the "Phoenix" definition is more current than the ASTRO definition, it is not always the better definition. The experts on the Phoenix consensus panel warned that in certain circumstances, particularly after either external beam radiotherapy or brachytherapy alone, the initial ASTRO consensus guidelines would be more appropriate.

## Definitions of Biochemical Failure After Other Types of Treatment

In addition to surgery and radiotherapy, other forms of treatments have been explored for prostate cancer. These include cryotherapy and high-intensity focused ultrasound (HIFU). These treatments have been primarily utilized for focal prostate cancer treatments, and the studies were recently reviewed [16]. Given the relative recent emergence of these treatments and limited experience with these treatments, there is no biochemical failure definition specifically defined for either cryotherapy or HIFU. Since the PSA behavior after these treatments is similar to radiotherapy, the cryotherapy and HIFU studies have been using ASTRO or Phoenix definitions of biochemical failure [16], which should be reasonable definitions for post-cryotherapy and HIFU therapies.

## PSA Change After Biochemical Failure and Clinical Outcomes

Biochemical failure can often occur months if not years prior to clinical recurrence but portends worse prognosis; PSA levels must therefore be monitored closely. The utility of PSA levels as a prognostic indicator and early surrogate of mortality from prostate cancer have been validated through multiple trials. PSA velocity (the rate of PSA increase) has now been shown to be associated with prostate cancer-specific mortality. In particular, in one multicenter cohort of 919 patients treated with either radiation or prostatectomy, D'Amico et al. showed that all-cause mortality and prostate cancer-specific mortality were both significantly associated with annual PSA velocity of more than 1.5 ng/mL [17].

One method to characterize the rate of change in PSA is PSA doubling time, the amount of time during which PSA levels double, which has been shown to have clinical relevance. In a study by Lee et al., a retrospective analysis of 621 patients with prostate cancer found that independent risk factors for clinical failure included PSA doubling time <8 months, higher Gleason score, and pretreatment PSA level [18]. In another large patient cohort, a short PSA doubling time (less than 3 months) was again found to be independently associated with higher risk of metastasis, clinical progression, and mortality from prostate cancer [19]. Indeed, in a third large prospective patient cohort, D'Amico et al. reported that patients with PSA doubling time of less than 6 months were found to have higher prostate cancer-specific mortality, a result which was statistically significant [20]. In another example of the importance of rate of PSA changes, a statistical model monitoring for disease recurrence found the slope of posttreatment PSA levels to be independently associated with risk for clinical recurrence [21]. Using a validation patient data set, their model was able to predict risk of clinical recurrence. It remains clear that the rate of change in PSA levels is an important factor as an early indicator for clinical progression of disease, metastatic disease, and ultimately prostate cancer-related mortality.

## Clinical Workup

Patients who are undergoing surveillance for disease recurrence after prostate cancer treatment should receive routine digital rectal exams yearly in addition to routine PSA testing every 6–12 months for 5 years. Although digital rectal exams in post-prostatectomy patients often cannot distinguish between postoperative changes and local recurrences, clinicians who follow patients longitudinally may be able to find differences in rectal exams upon local prostate cancer recurrence. In addition, if recurrence by rising PSA or by digital rectal exam, patients may be sent for prostate biopsy, along with bone scan, with consideration of abdominal/pelvic CT or MRI.

Upon biochemical failure as defined above with either post-prostatectomy or post-radiation therapy, a technetium-99 m bone scintigraphy scan can be utilized to detect sites of bony metastasis. A recent study analyzed 239 patients

with biochemical recurrence, on whom 414 bone scans had been performed. Fourteen percent of these bone scans showed metastatic disease [22]. Using multivariate analysis, PSA slope, velocity, and PSA at the time of the bone scan predicted the positive bone scan. From this result, Dotan et al. built a nomogram utilizing the independent predictors of positive bone scans [22]. If spinal cord compression is suspected from clinical symptoms and the physical exam, MRI of the spine is helpful to detect metastatic lesions that compress the spinal cord. In one series of 36 prostate cancer patients who underwent both MRI and bone scans, MRI found bone metastases in 7 patients who had negative bone scans [23].

The radionuclide indium-111 capromab pendetide imaging (Prostascint) has drawn attention in recent years. In limited, small studies, the positive predictive value of Prostascint for detecting disease recurrence ranged from 27 to 90 % [24, 25]. Therefore, this particular imaging study is not being used as a mainstream imaging study to detect disease recurrence.

## Management Decisions

When biochemical recurrence occurs, it is imperative first to work up whether the patient has local recurrence or distant metastatic disease. As above, bone scans and MRI can be helpful modalities in searching for distant metastatic disease. If the radiological workup is negative, local treatment options should be considered.

In the absence of metastatic disease, salvage treatment options should be offered to the patient, while paying attention to the patient's comorbidities and individual benefits from treatment. Patients who had previously been treated with radical prostatectomy can undergo salvage radiation to the surgical bed. If the patient had been previously treated with radiation, salvage options are limited but include cryotherapy, surgical resection, salvage low-dose radiation brachytherapy, and hormonal therapy.

If, however, the patient were found to have distant metastases, medical management should be explored with medical castration, cytotoxic chemotherapy, and novel agents still in development. Further details of salvage therapy will be covered in a subsequent chapter.

## Summary

Biochemical failure by measurement of PSA is immensely important in stratifying patients for disease recurrence and prognosis. The nature of the definitive first-line treatments has implications on the definition of biochemical failure after the treatment.

Current definitions of biochemical failure are as follows:

For surgical patients:

- PSA > 0.2 ng/mL twice for confirmation

For patients treated with radiation:

- ASTRO definition (2003):
  - Three consecutive elevations in PSA.
  - Date of failure is half the time between nadir PSA & first increase in PSA.
- Phoenix definition (2007):
  - Nadir PSA +2 ng/mL.
  - Date of failure is at the time that PSA increases to 2 ng/mL over nadir.

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# The Phenomenon of PSA Bounce After Radiation Therapy

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Peter Acher and Rick Popert

Prostate-specific antigen (PSA) is a 34-kDa serine protease secreted by prostate epithelial cells; it has a role in the liquefaction of semen. Low concentrations of PSA are found in the normal sera where it is exploited as a tumor marker. Following radical prostatectomy, serum PSA levels are expected to fall to undetectable levels within a few weeks, and subsequent detection of PSA signifies biochemical recurrence. The effects of radiotherapy treatments, however, depend on DNA damage and only become apparent during postmitotic events that may take several generations. Thus, the serum PSA level will fall slowly to reach a nadir often 3 years later [1]. During this time, the serum PSA value may rise before resuming its decrease without any therapeutic intervention – this is the phenomenon known as "PSA bounce", also known as PSA "bump" or "spike" [2]. Although it is a benign occurrence, it is a source of anxiety for patients and physicians alike since it may easily become confused with a persistently rising PSA that denotes recurrent disease that requires treatment.

Kent Wallner first described the bounce phenomenon ("spike") in the context of patients treated with combination interstitial brachytherapy and external beam radiation [2]. Since then, it has since been observed in all groups of primary radiotherapy patients with or without hormonal treatments (there are no data concerning salvage or metastatic therapies). With respect to external beam radiotherapy (EBRT), PSA bounce has been reported in series of conventional EBRT, 3-D conformal radiotherapy, intensity-modulated radiotherapy (IMRT), and more recently stereotactic body radiotherapy [3–7]. The incidence following EBRT alone ranges from 12 to 66 % depending on the definition of bounce used, i.e., the value of the PSA rise and fall, for example, defined by Rosser et al. as ≥0.5 ng/mL with a decrease to pre-bounce levels and by Pickles et al. as any increase followed by any decrease [4, 8]. The average time to bounce in these series ranged from 9 to 35 months [4, 5]. In a recent report on IMRT, one bounce occurred at 87 months posttreatment [7].

In the largest (multi-institutional) analysis of 4,839 patients treated with EBRT alone, 20 % of patients experienced bounce defined as an increase of ≥0.4 ng/mL over 6 months followed by any decrease [6]. One quarter of these patients experienced multiple bounces.

Pickles et al. reported on nearly 2,000 men treated with EBRT at British Colombia Cancer Agency and with a minimum follow-up of 4 years [8]. Androgen deprivation therapy (ADT) appeared to decrease the frequency of bounce from 66 to 55 % using a definition of any PSA increase followed by subsequent decrease. Bounces in the ADT group occurred earlier (median 5 months to start of bounce vs. 22 months), lasted longer (median 12 months vs. 6.7 months), and were of lower magnitude (median 0.59 ng/mL vs. 1.2 ng/mL) than the hormone naïve patients. Among 468 brachytherapy patients in the same report, 84 % experienced bounce. In contrast to the EBRT patients, those treated also treated with ADT were more likely to have PSA bounce (89 % vs. 71 %). Similarly though, bounces in the ADT group were recorded earlier (median 13 months vs. 18 months), lasted longer (median 14 months vs. 7 months), and were of lower magnitude (median 0.24 ng/mL vs. 0.78 ng/mL) than the non-hormone group. Twenty percent of all bounces were related to testosterone recovery, suggesting other mechanisms for the phenomenon.

Among the brachytherapy literature, there is wide variation in the frequency of bounce occurrence, again related to the definition used, and the frequency of PSA assay. When used as a monotherapy without external beam boost or ADT, the phenomenon occurs in 37–40 % of patients when a threshold of 0.2 ng/mL is defined [9, 10]. PSA bounce occurred at a median of 25 months in these studies, but with a wide range of 2–41 months, and lasted up to 50 months

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(but with usual resolution within a year). Most reports concern the use of iodine-125 isotope; however, Bostancic et al. reported that patients implanted with palladium-103 were much less likely (14 % vs. 46 %) to experience bounce in the absence of ADT, attributed to the faster dose delivery [11]. Bounce rates were comparable between the isotope groups when hormones were used (20–28 %).

## Significance of Bounce

The majority of studies of the relationship between bounce and biochemical control point towards no association. Comparison of the published data is difficult, however, due to the different patient populations, types of treatment, and definitions used.

Hanlon et al. observed patients treated with 3-D conformal radiotherapy and found bounce (defined by a rise of 0.4 ng/mL followed by *any* decrease) was related to lower dose and biochemical control: bouncers had a 52 % biochemical control compared to 69 % of non-bouncers [5]. Bounce was also related to low dose. This was only significant, however, in patients with pretreatment PSA values of less than 10 ng/mL. In the pooled analysis of 4,839 patients treated with EBRT (above) using a similar definition, bouncers were also more likely to fail (58 % vs. 72 % at 10 years), but no relationship with clinical or distant failure or overall survival was found [6]. In contrast, Rosser et al. using a bounce definition of rise to 0.5 ng/mL followed by a reduction to pre-bounce levels found an improved 5-year biochemical disease-free survival of 82 % compared to 58 % [4].

Patel et al. reported on 295 patients treated with prostate brachytherapy and found 100 % biochemical control at 5 years compared to 92 % of non-bouncers, using a definition of rise of 0.2 ng/mL with subsequent decline to the pre-bounce level [12]. Using a similar bounce definition, Cievski et al. reported comparable findings also after brachytherapy [13]. These differences in the association between bounce and biochemical failure may simply be due to the different definitions of bounce used: the studies that reported bounce as a predictor of biochemical control required the post-bounce PSA to reduce to the pre-bounce level, whereas "any" drop following a significant rise may simply be natural fluctuation as part of a longer-term significant PSA increase due to failure.

## Predicting Bounce

The only consistent pretreatment factor that appears to predict for PSA bounce is patient age at treatment, and this is reported in EBRT and brachytherapy papers. The largest EBRT study showed a modest but significant difference of 72 % bounce-free rate at 5 years for the under 70 years group compared to 75 % for older patients, considering a rise of 0.4 ng/mL followed by any subsequent drop [6].

Critz et al. considered 1,011 men treated with combination EBRT and interstitial brachytherapy: with a bounce definition of rise and fall of at least 0.1 ng/mL with a floor of 0.2 ng/mL and found frequencies of bounce of 57, 41, and 26 % in age groups 60 years and younger, 61–70, and 71 or older, respectively [14]. Pretreatment disease characteristics, treatment dose, and prostate volume were not significant factors in this large series.

Stock et al. evaluated 373 brachytherapy patients and found that age less than 66 years had a significantly higher bounce rate than those older (38 % vs. 24 %) at 5 years using a definition of 0.1 ng/mL but no difference when using a threshold rise of 0.4 ng/mL or of >35 % [15].

As well as the different testosterone kinetics in the young, another plausible explanation for this association is that since the PSA rises following ejaculation, the more sexually active population may have more benign PSA rises as a result. This is supported by Das' study in which ejaculation, recent instrumentation, and radiation proctitis accounted for 23 % of bounces [16].

## Causes of Bounce

The irradiated prostate gland is a heterogenous structure with varying grades of cancer within it and benign elements; radiation effects may then occur at different time points throughout the gland leading to differing PSA kinetics [17]. In brachytherapy, the situation is further exaggerated by dose inhomogeneity throughout the target. Merrick et al. found that transition zone index was associated with bounce in a population of brachytherapy patients [17]. It is thought that radiation effects on the benign epithelium causing a radiation prostatitis may account for benign bounce. Critz et al. found that a low post-treatment PSA of 0.2 ng/mL or less was a negative predictor for bounce, implying that there was very little remaining prostate tissue to produce PSA [18]. Stock et al. considered that patients were more likely to bounce if their glands were more than 35 $cm^3$, possibly due to more benign tissue. They also noted that the median time to bounce (20 months) in brachytherapy patients was similar to the time to develop other radiation effects on the bowel and erectile function [15].

## Differentiation Between Bounce and Failure

The rising PSA after radiotherapy is a source of anxiety for patients and physicians. As mentioned above, the results of radiotherapy may take several years to materialize following the treatment, particularly in the case of iodine-125 brachytherapy that takes approximately 10 months for the prescription dose to be fully delivered. Thirty percent of positive biopsies 12–18 months after EBRT ultimately converted

to subsequent negative biopsies in one study, and so these may simply add to the confusion [19].

In 1996, the American Society for Therapeutic Radiology and Oncology (ASTRO) held a consensus meeting in order to produce guidelines for PSA-monitoring and definition of treatment failure post-radiotherapy partly in order to prevent confusion between disease recurrence and benign bounce [20]. ASTRO defined three consecutive PSA rises of any amount as indicative of biochemical failure with the suggestion that serum samples be taken every 3 months for the initial 2 years after treatment, and then on a 6-monthly basis. This was updated, however, by a further consensus conference held in Phoenix in 2005 again, partly to reduce the false positives associated with benign bounce [21]. The "Phoenix definition" for biochemical failure requires the serum measurement of the PSA nadir plus 2 ng/mL. As compared to the initial ASTRO criteria, the Phoenix definition improves early outcomes by reducing the number of false positives due to PSA bounce, from 28 % to less than 5 % when treatment is combined with hormonal therapy [7]. Even so, false positives will still occur; in a series of monotherapy interstitial brachytherapy, 15 % of resolved bounces were more than 2 ng/mL above the preceding nadir [9].

## Avoiding Anxiety

There is still much to be learnt about PSA bounce, and further studies are needed to improve our understanding of this interesting but perplexing phenomenon. Importantly, the definition of bounce ought to be consistent in order to allow comparison and meta-analysis of different datasets. Since PSA values will vary by 34 % due to assay inconsistency and physiological changes in normal individuals even without prostatic manipulation, a defined bounce value would appear pragmatic in order to differentiate between bounce and natural variation [22].

In the meantime anxieties may be lessened by pre-intervention counseling of the phenomenon, avoiding too frequent sampling of PSA posttreatment and not sampling PSA after instrumentation, ejaculation, cycling, or during urinary tract infection. The timing of PSA increase is helpful, and rises within 2 years of therapy may be managed by observation or a search for distant spread if clinical suspicion is high [13]. Otherwise, the Phoenix definition of failure is useful for clinical practice.

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# Management of Locally Recurrent Disease

69

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## Introduction

Both radical prostatectomy (RP) and primary radiotherapy (RT) (external beam or brachytherapy, BT) are established treatment choices for clinically localized prostate cancer. Despite advances in surgical and RT techniques, treatment failures are still observed. The first sign of recurrent prostate cancer is a rise in serum prostate-specific antigen (PSA), referred to as a biochemical recurrence (BR), with the definition of failure depending on the primary treatment (Chap. 68). Literature supports the hypothesis that this PSA rise is often caused by local treatment failure (Table 69.1).

- Following radical prostatectomy, the failure pattern is predominantly local instead of metastatic [1, 2]. Of those local recurrences, approximately 2/3 of the relapses occur at the vesicourethral anastomosis (60 % posteriorly, 20 % anteriorly, and 15 % laterally), 1/5 retrovesical, 1/10 each at the bladder neck, and elsewhere (e.g., seminal vesicle remnants) [3–6] (Fig. 69.1a). In the observational arm of the EORTC trial 22911, the clinical local failure rate was four times higher than the systemic failure rate [1]. This finding was confirmed by the Southwest Oncology Group (SWOG) 8794 trial, which showed that the local failure rate was 1.5 times higher than the systemic failure rate [2]. Even for postoperative PSA levels <0.2 ng/ml, local failures occurred in 20 % of patients who did not receive adjuvant RT [2]. Based on current level 1 evidence, the optimal strategy to reduce the local recurrence rate [1, 2] and improve overall survival [7] in pT3N0M0 prostate cancer with or without positive margins appears to be immediate adjuvant postoperative RT.
- Following primary RT, local recurrences occur in 9–53 % depending on the prescribed dose and used definition (Table 69.1) [8–14]. The site of local recurrence appears to be at the original tumor location within the prostate [15, 16] (Fig. 69.1b). Therefore, it is advocated to increase the dose to the entire prostate [9, 11, 14] or selectively boost these regions to higher doses compared to the dose delivered to the whole prostate to avoid local recurrences. These higher doses to the prostate are able to reduce the rate of biochemical and local recurrences (Table 69.1). Advances in RT technique make this a feasible and safe procedure [14, 17, 18], and doses up to 93 Gy to the primary tumor region will be investigated in the near future [19].

Isolated local failure is of clinical importance, as there is a direct relationship between local control and distant metastasis [7, 11, 12, 20] and prostate cancer mortality [7, 11, 12]. The reseeding theory [20] hypothesizes that local failure may lead to a subsequent shedding of tumor cells and a late wave of metastases.

The above-mentioned incidences of local failure are apparently not convincing physicians to refer patients for curative-intent local salvage therapy at disease recurrence [21–24]. The Comprehensive, Observation, Multicenter, Prostate Adenocarcinoma Registry offers interesting insights into the practice patterns of US physicians treating

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**Table 69.1** Overview of local recurrence rates following primary therapy

| Author | Patients | Median follow-up | Dose | Local recurrence rate | Definition of recurrence |
|---|---|---|---|---|---|
| *A. Following radical prostatectomy* | | | | | |
| SWOG 8794 [2] | 374 | 10.2 | 60–64 Gy | 22 % | Digital rectal examination |
| EORTC 22911 [1] | 1,005 | 5 | 60 Gy | 15 % | Digital rectal examination |
| *B. Following primary radiotherapy with external beam radiotherapy or brachytherapy (BT)* | | | | | |
| Crook et al. [12] | 378 | 6.6 years | 66 Gy | 12 % | Positive biopsy |
| Stone et al. [13] (BT) | 508 | 6.7 years | 124–160 Gy | 7.7 % | Positive biopsy |
| | | | Low | 29.4 % | |
| | | | Intermediate | 6.1 % | |
| | | | High | 4.4 % | |
| Zelefsky et al. [139] | 339 | 10 years | <70.2 Gy to >81 Gy | 32 % | Positive biopsy |
| | | | <70.2 Gy | 45 % | |
| | | | 75.6–81 | 27 % | |
| | | | >81 Gy | 25 % | |
| Kuban et al. [9] | 164 | 8.7 years | 70–78 Gy | 10 % | Positive biopsy |
| | | | 70 Gy | 12 % | |
| | | | 78 Gy | 7 % | |
| Kupelian et al. [140] | 919 | 8 years | 60–78 Gy | 13 % | Positive biopsy or clinical presentation |
| Kuban et al. [141] | 4,839 | 6.3 years | 60–78 Gy | 9 % | NA |

PSA failures [22]. The dominant pattern of care appears to be a noncurative approach (observation in 74 % and androgen deprivation therapy in 22 %) [22], with less than 5 % of the patients receiving salvage local therapy [22]. In the majority of the patients (>90 %) with a PSA recurrence following RT, palliative androgen deprivation appeared to be the secondary treatment of choice [23, 24], with only 4 % of the patients receiving salvage surgery [24]. The rate of salvage RT following RP as primary treatment is somewhat better (40 %), although androgen deprivation remains the most popular option [24]. Nevertheless, salvage RT is the only therapeutic option offering a potential cure with improved prostate-specific [25] and all-cause survival [26] in this setting.

## Challenges

The low tendency for choosing secondary local treatments [21–23] might reflect two difficult challenges a physician is faced with at time of BR.

### PSA Recurrence: Local or Distant Progression?

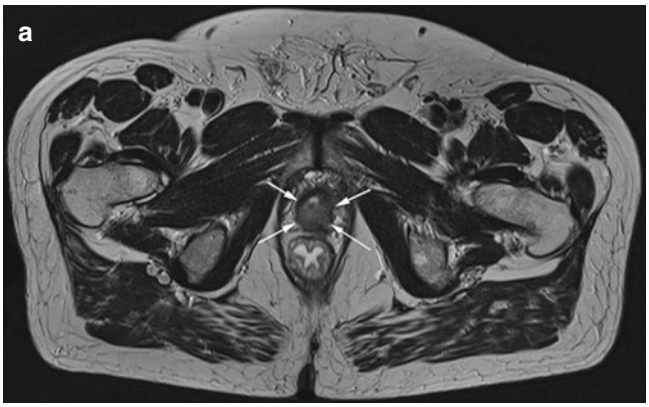
The key question remains whether a PSA rise is reflective of local or distant progression. The first requirement is indeed the identification of patients without metastatic disease, as local salvage treatments would otherwise expose patients to unnecessary morbidity. The diagnostic workup for PSA recurrences is presented below.

### Natural History of PSA Progression

Secondly, the natural history of a biochemical recurrence is very heterogeneous and might be long [27–30]. In the report of Freedland et al. the median time from BR following RP to prostate cancer-specific mortality was not reached after 16 years [27]. They identified three clinical parameters to predict the natural history: pathological Gleason score, time between surgery and biochemical recurrence, and PSA doubling time. Moreover, the 15-year prostate cancer-specific survival ranged from 1 to 94 %, depending on the clinical features [27]. In the updated series, the median time from BR to developing metastatic disease was 8 years, depending on the clinical features. From that point, the median time to prostate cancer-related death was another 5 years [28]. Although prostate cancer deaths were rare, they were seen as early as 1 year after PSA recurrence [27].

Following primary RT, the natural history of PSA recurrence is also variable. Within a median time of 7 years after BR, only 15 % prostate cancer-related deaths were observed [29]. The 10-year probability of PCSM is low for low-risk and intermediate-risk disease (0–6 %) [31]. However, this number may rise to 45 % in high-risk disease [31]. The most important factor for PCSM appears to be PSA-DT [30–32]. In a recent publication of Abramowitz et al. a BR (Phoenix definition) as such was associated with an increased risk of death, although the risk remained small [33].

The variable nature of a BR indicates that both clinical factors and patient factors (e.g., age, comorbidity, life expectancy) need to be taken into consideration when deciding between treatment options. Patients with a low probability of



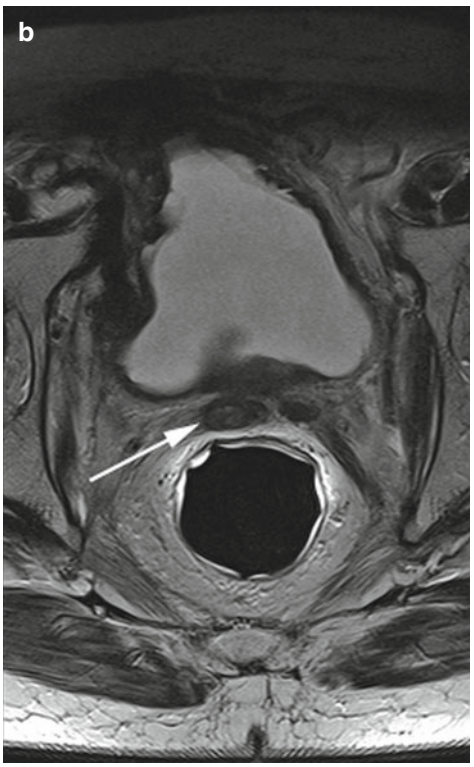




**Fig. 69.1** (**a**) A T2-weighted MRI axial slice of a local recurrence (*white arrows*) at the vesicourethral anastomosis following radical prostatectomy. (**b**) A T2-weighted MRI axial slice of a local recurrence (*white arrows*) at the seminal vesicle following primary radiotherapy

prostate cancer death, but short life expectancy due to comorbidity, could for example be suitable candidates for a more conservative approach compared to patients at high risk of prostate cancer death and a long life expectancy.

## Diagnostic Workup Prior to Local Salvage Treatment

There is currently no consensus regarding the use of imaging techniques prior to a course of local salvage therapy. These diagnostic procedures should be reserved for patients eligible for local salvage therapy. The first step is to exclude metastatic disease, followed by a local recurrence evaluation. Several nonimaging surrogates and nomograms might be used to improve patient selection [34], as the diagnostic yield of imaging studies at low PSA values and slow PSA kinetics might be poor. An overview of the different options with its limitations is given below and summarized in Table 69.2.

**Table 69.2** Workup recommendations prior to salvage treatment

| Modality | Recommendation |
|---|---|
| *A. Following primary radical prostatectomy* | |
| Transrectal ultrasound + biopsy | Not routinely recommended |
| Bone scan | Recommended if:<br>PSA doubling time <6 months or<br>PSA velocity >0.5 ng/ml/month or<br>Absolute PSA level >10 ng/ml |
| Abdominopelvic computed tomography | Not recommended |
| Magnetic resonance imaging | May be considered to assess pelvic nodes if PSA rises rapidly<br>Useful for identifying residual seminal vesicles |
| Positron emission tomography | Not routinely recommended<br>Deserves further investigation<br>Could play in patients with fast-growing PSA kinetics [53] |
| $^{111}$In-capromab pendetide scan | Not routinely recommended |
| *B. Following primary radiotherapy* | |
| Biopsy | Recommended |
| Bone scan | Recommended, although diagnostic yield might be low for trigger PSA <5 ng/ml and PSA doubling time >10 months |
| Abdominopelvic computed tomography | Recommended, although diagnostic yield might be low for trigger PSA <5 ng/ml and PSA doubling time >10 months |
| Magnetic resonance imaging | Recommended local restaging with endorectal T2-weighted MRI<br>May be considered to assess pelvic nodes if PSA rises rapidly |
| Positron emission tomography | Not routinely recommended<br>Deserves further investigation |

## Workup of a PSA Recurrence Following Radical Prostatectomy

### Metastatic Restaging

#### Imaging

- A *bone scan* should only be considered if there are symptoms of bone disease, a high baseline PSA (>10 ng/ml), or if the PSA kinetics (PSA doubling time <6 months, PSA velocity >0.5 ng/ml/month) are unfavorable at BR [35, 36]. In patients with a PSA level of less than 10 ng/ml, the risk of having a positive bone scan is less than 1 %

[36]. Two nomograms combining PSA kinetics, along with other patient characteristics, predicting the probability of radiographically detectable bone metastases after PSA recurrence, might be used to reduce the number of unnecessary scans [37, 38].

- An *abdominopelvic computed tomography* (CT) is not recommended for restaging, because of the low sensitivity at low PSA levels [35, 36, 39].
- New diagnostic imaging modalities that detect lymphatic and/or haematogenous metastases much earlier in the disease history are worth investigating to improve patient and target selection. *Lymphotropic nanoparticle-enhanced magnetic resonance imaging* (LN-MRI) has recently been investigated for the detection of lymph node metastases with high sensitivity and specificity rates [40, 41]. The preliminary results of *diffusion-weighted magnetic resonance imaging* (DW-MRI) for characterizing lymph nodes have been recently published, suggesting its superiority to size criteria to discriminate between benign and malignant lymph nodes [42]. The combination of DW and LN-MRI has also been explored with promising results [43]. *$^{11}$C-choline PET/CT* has also been investigated in this setting [44–51]. The reported sensitivity and positive predictive value in the postoperative setting ranges from 85 to 100 % and 80 to 90 %, respectively [44, 47, 51, 52], but with a low negative predictive value in some studies [44, 51]. Fuccio et al. concluded in their review that choline PET/CT could play a crucial role as the first diagnostic procedure in detecting lymph node or bone metastases for patients showing fast- growing PSA kinetics [53]. The *$^{111}$In-capromab pendetide scan* (ProstaScint®) utilizes an IgG monoclonal antibody that binds to the prostate-specific membrane antigen on prostatic epithelial cells. The results seem encouraging compared to conventional anatomical imaging at low PSA levels with reported sensitivity and specificity ranging from 76 to 86 % and 47 to 86 %, respectively [54–56]. On the other hand, the presence of extraprostatic radionuclide uptake does not necessarily predict a poorer outcome from postprostatectomy salvage RT or a favorable outcome if uptake is limited to the prostatic fossa [55, 57–60]. Because there are no large studies that include histologic confirmation in men with a positive scan after radical prostatectomy, longer follow-up is needed to routinely recommend this modality [35].

## Clinical Surrogates

Postoperative nomograms predicting the probability of developing metastatic disease are available to stratify patients into risk groups, helping clinicians in making decisions [61].

The following clinical factors might be used to determine the likelihood of systemic failure with an accuracy of more than 80 % following RP: a PSA increase <1 year after RP, a PSA doubling time (DT) of 4–6 months, a Gleason score of 8–10, and stage pT3b, pTxpN1 [62].

## Local Restaging

### Prostate Biopsy

Although positive biopsies are the only way to confirm local relapse, their role is debatable as a negative biopsy does not preclude local recurrence and a positive biopsy does not exclude systemic disease [35, 63]. According to the 2010 European Association of Urology guidelines, there is no indication for performing *ultrasound-guided biopsies* of the vesicourethral anastomosis to diagnose local relapse because of the low sensitivity and low predictive accuracy of this method in men with rising PSA levels <1.0 ng/ml [62]. This is supported by the systematic review of Beresford et al. [35].

### Imaging

According to the review of Beresford et al. the current practice is to treat patients with salvage therapy for a rising PSA without the need for imaging or biopsy evidence of local recurrence, accepting that current techniques may not be sensitive enough to detect small volume local disease [35]. The tumor volume in the postoperative setting is estimated to be <1 $cm^3$ for PSA levels <3.5 ng/ml [64], rendering it invisible for anatomical imaging such as *transrectal ultrasound* and *CT* [35], which are therefore not recommended. *T2-weighted MRI* (Fig. 69.1a) improves the detection of recurrences compared with aforementioned techniques, especially with the use of an endorectal coil [5, 65]. This offers excellent diagnostic sensitivity (71–95 %) and specificity (89–100 %), with accuracy that directly correlates with serum PSA levels and RP histopathology [5, 66, 67]. However, most patients in these studies had a PSA >2 ng/ml, corresponding to a local recurrence averaging 1.5 cm in diameter [5, 66, 67]. Further studies are needed to routinely recommended screening of every individual [62], especially at low PSA levels. Nevertheless, MRI information can be implemented in the planning of local salvage RT to better define the planning target volume and delineate organs at risk (e.g., penile bulb). Especially, the position and appearance of the seminal vesicles (SV) can be visualized, as a recent study found 22 % of the local postoperative recurrences within a retained SV, although only 6 % of the patients had SV invasion at radical prostatectomy [5]. Other acquisition techniques and imaging agents such as dynamic contrast-enhanced MRI (DCE-MRI) [68] and MRI spectroscopy [68] are also available and are described in detail in Chap. 42. These techniques deserve to be further investigated in the postoperative setting.

*$^{11}$C-choline PET/CT* may be able to detect local recurrences [49], but further studies are required to routinely recommend it for local staging [35].

### Clinical Surrogates

Local failure following RP is predicted with an 80 % probability by PSA increase >3 years after RP, a PSA DT >11 months, a Gleason score <6, and stage < pT3a pN0, pTany R1 [62].

## Workup of a PSA Recurrence Following Primary Radiotherapy

### Metastatic Restaging

#### Imaging

The probability of positive imaging studies for a PSA recurrence following RT is less investigated. Both *bone scan* and *abdominopelvic CT* are routinely recommended, although the yield is estimated to be low [69, 70]. As previously mentioned, new diagnostic imaging such as *$^{11}$C-choline PET/CT* and *lymphotropic nanoparticle-enhanced* and *diffusion--weighted magnetic resonance imaging* are currently under investigation. A nice overview of available and upcoming noninvasive molecular imaging techniques for detecting lymph node metastasis is given by Pouliot et al. [71].

#### Clinical Surrogates

A PSA failure caused by missed micrometastases at the time of initial RT is more likely in patients with adverse pre-RT factors (Gleason score ≥8, ≥T2c, PSA levels >20 ng/ml, and PSA velocity >2 ng/ml) [69]. Several post-RT factors (PSA failure within 1 year following RT, PSA doubling time <8 months, and a PSA level ≥10 ng/ml) are associated with an important risk for developing distant metastases [69]. The probability of developing distant metastasis can be estimated using the nomogram developed by Slovin et al. [38]. These factors could be used to improve the diagnostic yield of imaging modalities in the future.

### Local Restaging

#### Biopsy

Before treating patients with local salvage therapy, a biopsy is still recommended to verify local persistent disease [62, 69, 72]. However, there are important caveats to its use. Pathologists who are familiar with RT effects on the prostate should analyze prostate biopsies, as the interpretation is not unequivocal [73]. Moreover, the histologic regression of tumor cells after RT may be prolonged [74]. About 30 % of the positive biopsies 1 year after RT will convert to a negative biopsy 2 years posttreatment, while 20 % of the negative biopsies will turn positive [74]. Additionally, a biopsy-proven local recurrence does not rule out the presence of distant spread at low PSA values even with a negative metastatic restaging.

#### Imaging

Endorectal *T2-weighted MRI* is more sensitive compared to *transrectal ultrasound* for detection of local recurrences (Fig. 69.1b) and is recommended in the diagnostic workup of men with PSA relapse after radiation therapy, who might be candidates for secondary local salvage therapy with curative intent [62]. The reported sensitivities (26–44 %) and specificities (64–86 %) of T2-weighted MRI in the detection of tumor recurrence might be further improved with the use of additional techniques, especially *MR spectroscopy* and *DCE-MRI* [75]. More details can be found in Chap. 42.

*$^{11}$C-choline PET/CT* may be able to detect local recurrences [76], but further studies are required to routinely recommend it for local staging.

#### Clinical Surrogates

Ideally, candidates for salvage local therapy following RT are those who present initially with low-risk clinical features (PSA <10 ng/ml, biopsy Gleason score ≤6, T1c or T2a tumor status, pretreatment PSA velocity <2.0 ng/ml) [69]. Other factors which should be taken into account before salvage therapy: interval to PSA failure >3 years, PSA-DT >8–12 months, a presalvage PSA level <10 ng/ml and a presalvage Gleason score <7 read from a biopsy specimen without significant RT effect, and absence of bulky or locally advanced clinical T3/T4 disease at the time of salvage [69].

## Salvage Options Following Radical Prostatectomy

Salvage RT is the only therapeutic option offering a potential cure with improved prostate-specific [25] and all-cause survival [26] in this setting. A 3-fold increase in prostate cancer-specific survival with salvage RT was observed compared to those who received no salvage treatment [25]. The 5-year biochemical relapse-free survival ranges between 35 and 67 %. Tzou et al. give a nice overview of different studies reporting on biochemical failure [77].

### Timing of Salvage RT

Both in Europe and the USA, the consensus exists that early treatment is more likely to be successful than delayed treatment [62, 72]. The EAU guidelines suggest starting salvage RT at time of BR and before the PSA reaches 0.5 ng/ml [62]. More than a decade ago, the American Society for Therapeutic

Radiology and Oncology Consensus Panel recommended waiting for "a secure evidence of PSA failure (PSA ≥0.5 ng/ml)" before initiation of salvage RT, although preferably before a PSA level >1–1.5 ng/ml [72]. In view of recent published series [78, 79], the ASTRO suggestions need to be revised. Both a scoring algorithm and nomogram, based on clinical and pathological indices, are available predicting salvage RT response [78, 79]. One of the interesting findings is that patients with unfavorable indices should not be denied RT because a durable response is possible. For example, in patients with a presalvage PSA >1.5 ng/ml, a long-term biochemical response was seen in 20 % [78]. Patients with a high probability of metastatic spread with a PSA doubling time <6 months have a threefold increase in prostate cancer-specific survival when the prostate bed is irradiated, irrespective of pathological stage or Gleason score [25]. This might seem counterintuitive, as it is commonly believed that a short doubling time is indicative of distant disease and therefore a lack of benefit to salvage RT.

## Defining the Target

One of the first steps in RT planning is delineating the tumor. Errors in this step might result in an underdosage of the target and/or an overdosage of the normal tissues. However, the tumor burden is often microscopic in this setting, which renders it invisible for anatomical imaging. The RT field should therefore include the region at highest risk for disease relapse following prostatectomy [80], with approximately 2/3 of these relapses at the vesicourethral anastomosis, 1/5 retrovesical, and 1/10 at the bladder neck [3–6]. Delineation guidelines are developed to reduce intra- and interobserver variability. Different guidelines coexist, with different suggestions for the same target volume [80–84]. The guidelines all advocate including the vesicourethral anastomosis and surrounding periurethral tissue but differ on the exact position of these structures and on the amounts of additional tissue to be included. Two studies reported an increase in the delineated CTV volume and a decrease in the interphysician variability with the use of a guideline [82, 83]. In a recent evaluation of the EORTC guideline, only a moderate observer agreement was observed [85]. The authors made several recommendations to improve this guideline with the suggestion to include postoperative MRI information [85].

## Dose

It is suggested that the dose-response relationship of SRT and definitive primary prostate RT is similar [64]. According to the analysis of Bernard et al. and King et al. there is a strong dose-response relationship, and they both concluded that it is appropriate to consider doses above 66.6 Gy [86, 87]. This is in agreement with the advice of the American Society for Therapeutic Radiology and Oncology Consensus Panel, suggesting to use "the highest dose of radiation therapy that can be given without morbidity is justifiable [72]." However, in 1999, this dose was judged to be only "64 Gy or slightly higher [72]." The recommended dose according to the EAU guidelines is still only 64–66 Gy [62]. Only one group has explored doses up to 76 Gy resulting in a 5-year bRFS of 56 % [88]. Moreover, when SRT was applied early (PSA <0.5 ng/ml), the 5-year bRFS increased to 73 % [88]. Due to the heterogeneity in reported patient populations, it is difficult to assess whether this improvement in bRFS can solely be attributed to dose escalation. On the other hand, bRFS remains below 50 % with dose escalation, when patients are referred with PSA levels >1 ng/ml [88].

## Adjuvant Androgen Deprivation Therapy (ADT)

A potential benefit of ADT in addition to salvage RT has been reported in retrospective studies [88–91], but its definite role remains to be clarified by ongoing randomized trials: the RTOG 96–01 trial [92], the RTOG 05–34 SSPORT trial [92], the GETUG-16 trial (ClinicalTrials.gov identifier NCT00423475), and the RADICALS trial [93]. The preliminary results of the RTOG 96–01 trial were presented by Heney et al. at the annual meeting of the Society for Urologic Oncology (December 2010). After a median follow-up of 7 years, the freedom of biochemical progression was 40 % for salvage RT+ placebo arm versus 57 % for the salvage RT+ bicalutamide arm (150 mg during 2 years) [94]. In the bicalutamide arm, 7.4 % of the patients developed distant metastasis, compared to 12.6 % in RT alone arm. In one non-randomized study with high-dose salvage RT, the addition of ADT improved biochemical relapse-free survival on multivariate analysis [88].

## Toxicity

A dose up to 64.8 Gy delivered with conventional RT is rarely associated with severe long-term side effects (<5 % grade 3 gastrointestinal (GI) and genitourinary (GU) toxicity) [95–97]. Furthermore, compared to RP alone, the absolute increase in major urinary incontinence is <1 %, hematuria (usually transient) is <5 %, major rectal bleeding (usually transient) is 2–6 %, and bowel urgency/incontinence is <5 % [98]. Mendenhall et al. suggested that a dose exceeding 70 Gy in the postoperative setting "is likely not feasible because of the risk of late toxicity [99]." Indeed, dose escalation might be hampered by toxicity when using conventional 2D RT [100, 101]. 3D-conformal RT was a first improvement,

allowing for dose escalation to 68 Gy without increase in toxicity [102]. Additionally, IMRT offers the advantage of further reducing the dose to the bladder and rectum by creating concave dose distributions along the PB [88, 103–105]. Two studies using IMRT for moderate dose escalation (68–70 Gy) did not observe any grade 3 toxicity, although the median follow-up was ≤24 months [106, 107]. In the study of Ost et al. using a median dose of 76 Gy with IMRT, late grade 3 GI and GU toxicity was only observed in <1 % and 3 % of the patients, respectively, after a median follow-up of 5 years [88].

The results on erectile dysfunction are ambiguous. In a report of Hu et al. patients receiving salvage RT had a worse sexual function compared to men who had surgery only [108]. However, this report had several limitations such as a lower use of nerve-sparing procedures in the salvage arm and its retrospective nature. In the SWOG 8794 trial comparing surgery alone with surgery plus immediate postoperative RT, no difference was observed in erectile dysfunction [109]. Worth mentioning is the fact that >90 % of the men in both arms experienced sexual side effects [109]. With modern surgical techniques, these data would probably change.

## Salvage Options Following Primary Radiotherapy

Nguyen et al. concluded in their systematic review on local salvage therapies following RT that based on the current evidence, it is not possible to ascertain whether PSA outcome is best after salvage prostatectomy, cryosurgery, or BT [69]. However, the likelihood of cure by local salvage therapy is decreased in patients presalvage PSA levels >10 ng/ml, presalvage T3–T4 disease, or presalvage Gleason scores ≥7 on a rebiopsy sample without significant RT effects [69]. Another important comment when interpreting the below-reported salvage-related morbidity is the fact that most series report on patients treated with relatively low-dose RT as compared to modern standards [69]. Only one center has reported acceptable morbidity of 55 patients undergoing RP following "twenty-first-century" RT [110].

### Radical Prostatectomy

RP offers long-term cancer control with a 5-year failure-free survival of 54–63 % [111–113] and 10-year cancer-specific survival rates of 70–77 % [111, 113, 114]. Several predictors associated with improved outcome following RP have been identified: presalvage PSA ≤10 ng/ml [111, 113, 114], organ-confined disease, biopsy Gleason score ≤7 [110, 112], and absence of lymph node involvement [111]. According to the series of Heidenreich et al. organ-confined disease is predicted by the biopsy score prior to RP, number of positive biopsy cores, and a PSA-DT >12 months [110]. Salvage cystoprostatectomy is reserved for patients with locally advanced disease. However, it should be noted that 5-year BR-free survival is low (19–30 %) [113, 115], which call into question the usefulness of this procedure given its substantial morbidity [69]. It should be noted that in the absence of randomized data or consistent results from retrospective series, neoadjuvant ADT is not recommended prior to salvage RP [69].

The widespread use of salvage RP has probably been limited [24] because of the technical demands of the procedure [69, 116] as well as concerns regarding postoperative morbidity. Perioperative mortality is very low (0.2 %) [69]. Nguyen et al. has nicely summarized the morbidity of RP series published since the 1990s [69]. On average, 42 % of the patients will have urinary incontinence, with 24 % experiencing bladder neck strictures, and 4.7 % of rectal injuries [69]. Leibovici et al. have described interesting "tricks of the trade" of RP to reduce this morbidity [117] as there is a learning curve to this procedure [69, 116]. This is also reflected in the reduction of grade 2–4 complications for patients treated before 1993 versus after (33 % vs. 13 %) [69]. However, no marked reduction in incontinence rates or anastomotic strictures was observed [69].

### Cryosurgery

With the introduction of transrectal ultrasound guidance, urethral warming catheters, and argon/helium gas-based cryotechnology, cryotherapy has emerged as an alternative to salvage RP [118]. With this technique, the prostate is cooled down, and cancer cells are destroyed through the formation of ice balls. In a pooled analysis of six tertiary care referral centers in the USA, a biochemical failure-free rate of 40 % was observed at a median follow-up of 3.4 years [119]. On multivariate analysis of potential predictors of biochemical failure, they identified three important predictors of treatment outcome: serum PSA level at diagnosis, the initial biopsy Gleason score, and the initial clinical stage [119]. In a large single center, 176 patients have been treated with a median follow-up of 7.5 years. They observed a 10-year DFS of 39 % and a metastatic-free survival of 82 % [120]. Risk factors for recurrence included presalvage prostate-specific antigen, preradiation and presalvage Gleason score, and a PSA nadir >1.0 ng/dl. In a retrospective comparison between salvage cryotherapy and RP, RP resulted in an improved 5-year biochemical relapse-free survival (42 % vs. 66 %); however, disease-specific mortality was comparable [121]. Further improvements are expected with the introduction of third-generation devices.

Perioperative mortality is very low (0.2 %). Urinary incontinence rates occur on average in 36 % of the patients

[69], with severe incontinence rates below 5 % [122]. In the large series of Pisters et al. the incontinence rate requiring daily pad use was only 4.4 % [123]. Urethral sloughing was observed in 11 % of the patients [69] but can be reduced to 4 % with the use of a warming catheter [124]. Bladder neck stricture/retention and perineal pain were reported in 17 and 36 %, respectively [69]. The development of fistulas is an uncommon event and occurs on average in 2.6 % of the patients [69]. Furthermore, the majority of patients (69–86 %) will experience erectile dysfunction [122, 123, 125]. Technical advances over the last years might further improve cryotherapy-induced morbidity.

## Radical Brachytherapy

The long-term PSA control achieved with salvage BT appears to be comparable to salvage RP [69, 126–130]. The average grade 3–4 genitourinary complication rate was 17 % for series reported before 2008, with reported grade 3–4 gastrointestinal morbidity in 5.6 % of the cases [69]. The average urinary incontinence rate was only 6 %. Moreover, the rate of developing fistulas was <5 % on average. These toxicity rates are in agreement with more recently published series [126–129] and appear to be more favorable compared to salvage RP. An interval of <4.5 years between initial radiation and salvage irradiation was associated with an increase in grade 3–4 toxicity [69].

Several limitations should be taken into account when interpreting these results. Firstly, all series but one [130] are retrospective. Also, the number of patients in the reported series is small, with the largest series including only 49 patients [131]. Moreover, most series use a high rate of adjuvant hormonal therapy and different definitions of recurrence [69, 126–129, 132], making comparison of studies difficult. As with salvage RP, the centers reporting these series have extensive experience in BT. A prospective multi-institutional phase II trial (RTOG 0526) is currently testing the efficacy and safety of salvage BT in the setting of recurrent cancer following external beam RT. The proposed dose for a $^{125}$I implant is 140 Gy covering the planning target volume and 120 Gy for a $^{103}$Pd implant. This trial is currently recruiting patients (www.RTOG.org) and will help address the above-described limitations.

## High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is a minimally invasive salvage treatment option. Ultrasound waves of high intensity are targeted at the tumor site via an endorectally inserted ultrasound probe. Due to thermal and mechanical effects, prostatic tissue is destroyed, leading to coagulative necrotic lesions that are replaced by scar tissue within a few weeks following treatment. Only three articles have described this modality in the salvage setting, with a follow-up of less than 2 years [133–135]. In the largest series, a biochemical relapse-free survival of 53 % is reached [134].

The most common reported complications include urinary incontinence (grade 3 in 7–10 %), obstruction/retention (9–36 %), bladder neck/urethral stricture/stenosis (17 %), urinary tract infection (1–6 %), and rectourethral fistula (3–7 %) [133–135].

A recent systematic review only found very low evidence to support the use of salvage HIFU [136]; as a result the EAU guidelines only recommend HIFU as an alternative salvage option for patients who are well informed about its experimental nature [62].

## Photodynamic Therapy

Vascular-targeted photodynamic therapy (VTP) is the newest salvage modality being investigated [137, 138]. It uses light-activated drugs (palladium-bacteriopheophorbide photosensitizer) to selectively damage endothelial cells, resulting in vascular thrombosis and secondary tumor destruction [138]. Eight out of 13 patients receiving the highest light dose had a negative biopsy 6 months later. Important to mention is that two patients experienced rectal fistula. Further research is targeting the issues of light dosimetry and rectal sensitivity. As the experience with this salvage approach is very limited, it should not be performed outside clinical trials.

## Future Perspectives

Currently, all the above salvage treatment modalities are planned using the entire prostate as a target volume, leading to a high incidence of adverse effects. However, salvage cryosurgery, BT, and HIFU could be planned so that the dose to the primary tumor would be escalated, whereas the remainder of the prostate would receive a lower dose or no dose at all. If the primary tumor site were indeed the site of clinically significant tumor recurrence [15, 16], such a minimally invasive approach might still be able to achieve a cure, while minimizing the treatment side effects.

# Definition of Failure Following Salvage Treatment

Following salvage RT and radical prostatectomy, a biochemical recurrence is often recorded as a rising PSA above 0.2–0.4 ng/ml. However, the definitions of biochemical recurrence are less clear following salvage cryosurgery, HIFU, or BT [69], making interpretation and comparison of results difficult.

**Conclusions**

To conclude, we believe that every patient with a biochemical failure following radical treatment and a life expectancy exceeding the time to distant metastases should be referred for local salvage therapy.

Following RP, salvage RT is the only therapeutic option offering a potential cure with improved prostate-specific and all-cause survival. It is recommended to start RT as early as possible before the PSA reaches 0.5 ng/ml. Generally, a dose of 66 Gy is delivered to the prostate bed with less than 5 % grade 3 toxicity. Adjuvant androgen deprivation therapy with bicalutamide might be considered based on the preliminary results of the RTOG 96–01 trial.

Following RT, several options are available including prostatectomy, BT, and cryosurgery. Based on the current evidence, it is not possible to recommended one treatment over the other, and treatment choice should be balanced with possible side effects. Newer treatment techniques such as high-intensity focused ultrasound and photodynamic therapy should be considered investigational.

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# Management of High-Risk/Locally Advanced Disease

# 70

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## Definition and Incidence of Locally Advanced Prostate Cancer (PC)

Several definitions for locally advanced PC are used. In general, locally advanced PC includes stages T2c, T3, or T4. Besides T-stage, adding high-risk tumor features such as Gleason score and PSA level at presentation can extend the definition of locally advanced PC. Frequently used definitions of high-risk or locally advanced PC are presented in Table 70.1 [1–3]. The worldwide use of PSA screening has resulted in stage migration towards lower stage PC. Despite an initial decline in number of patients presenting with high-risk PC from 1990 to 2001, the proportion of patients with high-risk features has been relatively constant since that time [4]. Nowadays, 12 % up to 17–31 % of the patients with PC in Europe [5] and the USA [4], respectively, are diagnosed with locally advanced or metastatic disease. Over the years, there has been a change in distribution of high-risk clinical features. According to Cooperberg et al., high-risk PC patients diagnosed in recent years are more likely to present with higher Gleason scores, lower PSA, lower clinical stage, and lower percent of positive biopsy cores. The proportion of high-risk patients with more than one high-risk clinical feature has been essentially constant over time [4]. More recently, a small decrease of patients presenting with more than one high-risk feature has been reported [6]. The presence of multiple high-risk features is associated with an increased risk of biochemical recurrence, development of metastases, and PC death [6, 7]. Excellent clinical results have been published for patients with very low-, low-, and intermediate-risk PC treated with surgery, external beam radiotherapy (EBRT), or brachytherapy. Five-year actuarial PSA relapse-free survival rates, according to the Phoenix definition, of 98 and 85 % for the low- and intermediate-risk National Comprehensive Cancer Network (NCCN) prognostic groups have been reported after high-dose EBRT [8]. Comparable results have been published for patients treated with radical prostatectomy (RP) or brachytherapy. The long-term (5–10 year) PSA relapse-free survival rates after RP, EBRT, or brachytherapy for patients with high-risk PC features are much lower and range between 60 [9, 10] and 70 % [8, 11]. Men presenting with high-risk disease require therefore more aggressive therapies as they are at higher risk of PC death [12].

**Table 70.1** Definitions of high-risk prostate cancer

| Definition | Criteria |
|---|---|
| D'Amico et al. [1] | ≥T2c + PSA > 20 ng/ml or Gleason ≥ 8 |
| RTOG 99-02 and 05-21 [2] | Any stage + PSA 10–20 ng/ml, Gleason ≥ 7 or ≥T2, PSA < 100 ng/ml and Gleason ≥ 8 |
| NCCN [3] | ≥T3 or PSA > 20 ng/ml or Gleason ≥ 8 |

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**Table 70.2** Guidelines for extended PLND

| | Indications | Extent | Number of lymph nodes |
|---|---|---|---|
| AUA | PSA ≥ 10 ng/ml and Gleason score ≥ 7 | Not specified | Not specified |
| NCCN | Predicted probability of pelvic nodal metastases by nomograms ≥2 % | Removal of all node-bearing tissue from an area bounded by the external iliac vein anteriorly, the pelvic side wall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally | Not specified |
| EAU | Patients with intermediate (cT2b–cT2c or Gleason score = 7 or PSA = 10–20)-risk features with an estimated risk for positive lymph nodes >7 %<br>High-risk patients (≥ cT3a or N1 or Gleason score = 8–10 or PSA > 20) | Extended lymph node dissection (removal of nodes overlying the external iliac artery and vein, nodes within the obturator fossa cranially and caudally to the obturator nerve and the nodes medially and laterally to the internal ileac artery) | Mean of 20 lymph nodes |

## Diagnostic Work-Up

A correct local staging is important for treatment decisions. The accuracy of digital rectal examination and ultrasound in evaluating the tumor stage is limited resulting in understaging and overstaging. The accuracy of clinical staging is 81.4 % for T3a, 77.4 % for T3b, and 70.1 % for T4 [13]. Overstaging occurs in 27 % [10].

Staging accuracy can be improved by implementing magnetic resonance imaging (MRI). With MRI sensitivity, specificity, and accuracy rates of 69, 82, and 76 % and 60, 100, and 95 % for extracapsular extension and seminal vesicles invasion were reported respectively [14].

Both *CT* and *MRI* are disappointing in predicting the lymph node status with a sensitivity of 40 % [15]. Also, for PET-CT with $^{18}$FDG or $^{11}$C-choline, the reported sensitivity for lymph nodes of 60 % remains low [16].

The use of *lymphotropic ultrasmall superparamagnetic particles of iron oxide* (*USPIO*) enables the detection of metastases in normal-sized pelvic lymph nodes. It leads to an improvement in diagnostic accuracy [17] as USPIO combines a sensitivity of 91 % with a specificity of 98 %. The positive and negative predictive values are 95 and 98 %, respectively [17]. However, larger trials are imperative to confirm these encouraging results. Unfortunately, USPIO is not yet Food and Drugs Administration-approved.

A *pelvic lymph node dissection* (PLND) remains the gold standard for accurately determining the N-status. An important question is when and how to perform a PLND. Several preoperative risk-assessment nomograms were developed. The Partin tables, updated in 2007, are based on preoperative T-stage, PSA, and Gleason score. An external validation of the Partin tables showed excellent discrimination for positive lymph nodes with an area under the curve of 0.77 [18]. However, nomograms often underestimate the probability of metastatic lymph node disease – as they are based on limited instead of extended PLND. Briganti et al. developed a nomogram based on extended PLND including the following parameters: T-stage, PSA level, biopsy Gleason sum, and the number of lymph nodes. An internal validation demonstrated an accuracy of 76 % [19]. Besides nomograms, formulas can be used to predict the risk of nodal involvement. The Roach formula ([(2/3) × PSA + (Gleason score − 6) × 10]), derived from the Partin tables, is easy to use but overestimates the risk of nodal involvement [20]. The Yale formula ([Gleason − 5] × [PSA/3 + 1.5 × T], where $T = 0$, 1, and 2 for cT1c, cT2a, and cT2b/cT2c [21]) has been developed to overcome this problem. However, both formulas are not applicable for T3–T4 tumors. Seeing the limitation of nomograms and formulas, the decision to perform PLND is often left at the discretion of the physician. An extended PLND is recommended in locally advanced disease and high-grade PC.

The exact impact of extended lymphadenectomy on patient outcomes has not yet been clearly determined because prospective randomized trials are lacking. Recently, Masterson et al. reported that a higher number of nodes removed correlated significantly with biochemical non-evidence of disease (bNED) in men without nodal involvement [22]. Similar results were published by Joslyn and Konety [23]. Nodal resection might eliminate micrometastases that are not detected by routine histological examination. Another likely explanation is that nodal resection leads to stage migration. Using immunohistochemistry, occult lymph node metastasis are detected in 13.3 % of patients with pathologically node-negative high-risk PC [24]. The EAU, AUA, and NCCN recommendations of performing PLND are presented in Table 70.2.

## Treatment Options for T3–T4 N0 M0 PC

The possible treatment options for patients with locally advanced PC are RP, high-dose external beam radiotherapy (EBRT), brachytherapy, and hormone therapy (HT).

HT has been the primary treatment for patients with locally advanced PC for many years. Although the response rate is high, HT is not a curative therapy and has important side effects.

Several studies have compared the clinical outcome after RP and radiotherapy. However, most of them were non-randomized retrospective analyses and divergent results have been reported. Several studies concluded that RP remains the treatment of choice in high-risk PC [25–28] while other reported better results with radiotherapy [29, 30]. A few studies reported equivalent efficacy [31, 32].

Merglen et al. claimed that RP offers the best 10-year survival rates for T1–T3 PC patients, in particular for younger patients and patients with poorly differentiated tumors [25]. However, this study has some major shortcomings such as the lack of information on radiation dose as several randomized [33–36] and large single-institution trials [37, 38] demonstrated an increase in 5-year biochemical NED with higher radiation dose. In addition, parameters including Gleason score and PSA were not well balanced between the RP and radiotherapy group [25]. Zelefsky et al. compared the effect of RP and EBRT on the development of distant metastases in patients with localized PC [27]. RP was associated with a statistically significant reduced risk of developing metastases, especially for high-risk patients (difference of 7.8 % in 8-year metastatic progression rate). Similar results were published for cancer-specific mortality (8-year probability of cause-specific survival: 98.6 versus 95.3 % for the patients treated with RP and radiotherapy, respectively). As was recognized by the authors, this study has some limitations that could have influenced the results such as the study design (this is a non-randomized retrospective analysis with relatively short median follow-up), the use of incompletely balanced treatment groups (higher Gleason score and age in EBRT group) and the abbreviated course of adjuvant HT as well as the omission of elective lymph node irradiation in the EBRT group. An important limitation of the study is the difference in use and timing of salvage therapy between both groups [27]. Cooperberg et al. published comparable results [28]. They concluded that prostatectomy for localized PC was associated with a significant reduction in mortality relative to EBRT and HT monotherapy. Again, this was a non-randomized trial. More recently, Boorjian et al. performed a similar study only including high-risk (according to the NCCN criteria) PC patients. They observed that both RP and EBRT combined with HT were associated with a 10-year disease-specific survival rate of 92 % [31]. There was no significant difference in risk of systemic progression or prostate cancer death. The risk of all-cause mortality however was greater after EBRT plus HT than after RP. According to the authors, this difference can be explained by an imbalance between both treatment groups in terms of medical comorbidities [31].

Akakura randomized patients between RP and low-dose EBRT both combined with HT. The 10-year overall survival rates were better for the RP group, although not statistically significant. Moreover, the applied 60–70 Gy is insufficient to treat locally advanced PC [32]. In a retrospective matched case analysis, RP, brachytherapy, and multimodality radiotherapy (i.e., EBRT with brachytherapy boost and HT) were compared. bNED at 4 years was significantly improved with multimodality radiotherapy (multimodality radiotherapy, 72 %; brachytherapy, 25 % and RP, 53 %, $p < 0.001$).

A small retrospective intention-to-treat analysis showed a significantly better biochemical outcome after EBRT than after RP in patients with high-risk PC [29].

Based on available data RP, whether or not combined with adjuvant radiotherapy, and high-dose radiotherapy still have to be considered as equally effective.

## Radical Prostatectomy

Surgery consists of total prostatectomy with resection of the neurovascular bundle at the tumor-bearing side, seminal vesicles as well as the bladder neck in combination with an extended lymphadenectomy. The main advantage of performing a RP is the possibility to obtain pathological information and consequently improve staging. Several single institutions have proven the feasibility and efficacy of a surgical approach in T3–T4 PC patients. An overview is presented in Table 70.3 [9, 10, 39–42].

The most important postoperative side effects are urinary incontinence and sexual dysfunction occurring immediately after RP and tending to improve over time. The rate of these side effects is significantly reduced in high-volume hospitals. Nevertheless, persisting urinary incontinence after RP can have a tremendous impact on patient's quality of life. It has been reported in up to 8 % of patients [41, 43]. More recent papers report continence rates varying between 48 and 98 % at 12 months, 85 and 93 % at 18 months, and 95 and 97 % at 24 months. Return to baseline continence status at 12 months is 36 [44] to 74 % [45].

There is no uniform definition to score "continence rate," which might explain the inter-study differences. Sacco et al. tested the effect of different "continence rate" definitions on the incidence of being "continent" in 985 patients [46]. According to the applied definition, the incidence of continence at last follow-up varied from 83 to 93 % [46].

Sexual dysfunction is present in almost all patients as nerve-sparing procedures are often contraindicated.

RP alone might be a valuable treatment for low-volume high-risk PC with only a limited number of adverse prognostic factors. Pathological findings that have been correlated with increased risk of postoperative relapse are seminal vesicles invasion, extracapsular extension, and positive margins. Up to 50 % of the patients who undergo a RP have at least one of these high-risk features, resulting in a biochemical recurrence in >50 % [47]. Although surgical experience

**Table 70.3** Overview of studies regarding surgery for locally advanced prostate cancer

| Year | Author | Inclusion criteria | *N* | Follow-up in months | Time (years) | Overall survival | Cancer-specific survival | Progression-free survival | PSA relapse-free survival | PSM | N+ | SVI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2005 | Ward et al. [10] | T3 | 5,652 | 124 | 5/10/15[a] | 90-76-53 | 95-90-79 | 85-73-67 | 58-43-38 | 56 | 27 | – |
| 2006 | Berglund et al. [39] | ≥T2b, PSA ≥ 15 or Gleason ≥ 8 | 281 | 34 | 34[b] | – | – | – | 70.4 | 18.5 | 8.9 | 23.1 |
| 2006 | Carver et al. [40] | T3 | 176 | 77 | 5/10/15 | – | 94-85-76 | – | 44[c] | 24 | 21 | 31 |
| 2007 | Hsu et al. [48] | T3a unilateral | 235 | 71 | 5/10 | 96-77 | 99-92 | 96-85 | 59-51 | 33.5 | 8.5 | 16 |
| 2007 | Loeb et al. [41] | High-risk cT2b or T3 | 288 | 88 | 10 | 74 | 88 | 35 | – | 26 | 6 | 30 |
| 2009 | Villari et al. [42] | T4 | 106 | 86 | 5/10 | 75-57 | 80-75 | – | 40-38 | 23.6 | 29.2 | 69.8 |

*N* number of patients, *PSM* percentage positive surgical margin, *N+* percentage positive lymph nodes, *SVI* percentage seminal vesicle invasion
[a]At 5/10 and 15 years
[b]Time in months
[c]Figure at 10 years

results in a lower rate of positive surgical margin rates, they remain present in at least 10 % [48]. For patients with adverse pathological findings, immediate postoperative radiotherapy is advised as three randomized trials showed improved biochemical/clinical PFS in favor of adjuvant radiotherapy [49–51]. The SWOG trial 87–94 demonstrated a reduced risk of developing metastasis and a significant overall survival benefit in favor of adjuvant radiotherapy for pT3N0M0 PC patient [51]. Gastrointestinal (GI) and genitourinary (GU) toxicity after postoperative radiotherapy is satisfactory (<5 % grade 3 GI and GU toxicity) [49]. Nevertheless, after adjuvant radiotherapy to doses of 60–64 gray (Gy), 25 % of patients will progress biochemically within 5 years [49]. In analogy to primary radiotherapy, where there is ample level 1 evidence for improved bNED with higher doses [33–36], increasing the dose in the postoperative setting could result in better bNED. Cozarrini et al. confirmed the benefit of high-dose early adjuvant radiotherapy in high-risk PC patients [52]. Moreover, the recurrence pattern following RP alone in high-risk patients is predominantly local instead of metastatic [49]. In a retrospective, non-randomized trial, improved bNED was reported with doses >65 Gy [53]. King and Kapp estimated a 3 % gain per incremental Gy [54]. Modern radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), can allow further dose escalation without increasing the risk of developing toxicity, thanks to better sparing of the surrounding organs at risk. In a retrospective study, the feasibility of high-dose (median dose of 74 Gy) adjuvant radiotherapy in 104 patients was demonstrated with encouraging results regarding bNED and toxicity [55]. The role of hormonal therapy and chemotherapy in the pre- as well as in the post-prostatectomy setting remains unclear and needs further investigation. The long-term effects of a 3-month neo-adjuvant hormonal treatment in patients with localized PC treated with RP were evaluated in a randomized European trial [56]. Neo-adjuvant HT resulted in a clinical and pathological downstaging as well as a reduction in positive resection margins. This advantage, however, did not result in a significantly better PSA progression rate [56]. The absence of an improved overall and disease-free survival by adding neo-adjuvant HT prior to RP was confirmed in other randomized trials [57, 58]. A meta-analysis of randomized trials evaluating the role of neo-adjuvant HT concluded that neo-adjuvant HT prior to RP did not improve overall or disease-free survival but significantly reduced the incidence of positive margin rates and lymph node invasion and increased organ confinement [59]. Prolongation of the duration of neo-adjuvant HT results in a further improvement in positive surgical margin and organ-confined rates [59, 60].

Few studies have examined the role of post-prostatectomy adjuvant HT. A systematic review performed by Kumar et al. showed that the addition of hormones after prostatectomy as primary treatment did not improve overall survival [60]. The clinical benefits of (neo-) adjuvant HT need to be weighted against treatment costs, side effects, and impact on quality of life.

Preliminary results of the RTOG 96-01 trial, randomizing patients between 2 years of bicalutamide 150 mg + salvage EBRT versus placebo + EBRT after RP, are promising regarding biochemical control and presence of distant metastases and encourage the combined use EBRT and HT. Longer follow-up is needed to show a survival benefit. Randomized trials are ongoing to address issues such as timing of radiotherapy and HT and duration of HT [61].

Based on the available data, nevertheless, the use of androgen deprivation or chemotherapy outside clinical trials cannot routinely be recommended.

## Primary Radiotherapy Combined with HT

With conventional EBRT only, local recurrence rates of approximately 30 % at 10 years have been reported for patients with clinical stage T3–T4 PC [62]. Local failure is often the only site of recurrence but of clinical importance, as there is a direct relationship between local control and distant metastasis [62, 63] and survival [64]. Several randomized trials have demonstrated improved disease-specific and overall survival outcomes in patients with locally advanced stage disease when EBRT is combined with HT [65–69]. The rationale for this combined approach is to reduce the planning target volume, reduce the risk of local relapse and consequently metastatic disease and to improve the effectiveness of radiation [70]. Clinical or biochemical relapse is observed in a quarter of the patients 5 years after combined radio-hormonotherapy [66]. Extensive evidence exists that high-dose radiotherapy (dose ≥ 74 Gy) is superior to conventional-dose radiotherapy (dose 64–70 Gy) [33–36]. Zelefsky et al. confirmed the importance of dose escalation on outcome. They demonstrated a 6 % improvement in distant metastases-free survival (DMFS) by increasing the dose from <70 to >80 Gy [71]. A same trend was demonstrated by Pollack [33]. However, which dose is high enough? Based on the publication of Eade et al., a dose of at least 80 Gy is necessary for achieving optimal tumor control [72]. A recent meta-analysis demonstrated that a dose increase from 70 to 80 Gy resulted in a 5-year bNED increase of 19 % for high-risk patients [73]. The above reported dose-response relation should be interpreted with caution, as it could be artificial due to bias induced by stage migration, improved therapy, and shorter follow-up [74]. When 3D conformal therapy is used, there is an increased risk of toxicity when performing dose escalation [75]. IMRT allows safe implementation of higher doses. However, even with the best technical approach, it seems unlikely that doses of 90 Gy or more can be safely delivered to the prostate. According to Cellini et al. and Pucar et al., the highest rate of local relapses is observed at the initial tumor location (IPL)

[76, 77]. Consequently, increasing the dose to the IPL might further improve local control and consequently bNED. Information provided by MRI and MR spectroscopy enables us to localize the IPL and selectively boost it. Zelefsky et al. reported long-term results after high-dose radiotherapy for T3 PC. For patients treated to high doses (81 Gy) combined with HT, 5- and 10-year PSA relapse-free survival was 77 and 52 % for T3a stage and 53 and 49 % for T3b stage PC. Dose ≥ 75.6 Gy was an important predictor for improved biochemical control. With higher doses, 5- and 10-year local progression-free survival of 96 and 88 % were reported [78]. The combination of EBRT and HT is safe [79].

About 75 % of PCs arise in the peripheral zone. Due to the close vicinity of the rectal wall, dose escalation is a technical challenge. As a result of these anatomical considerations, dose levels administered with EBRT using current techniques may not be sufficiently tumoricidal for radical eradication of large-volume PC cancer. Achieving local tumor control is, nevertheless, of outmost importance as it is associated with a decrease in distant metastases and PC mortality [80]. Brachytherapy overcomes this problem partially, thanks to a sharp dose fall-off towards the anterior rectal wall at the price of virtually higher urethral doses (35). Combined brachytherapy with IMRT may be more favorable and is associated with the delivery of significantly higher biologic equivalent dose levels far beyond those achieved with 81–86-Gy IMRT. Although brachytherapy alone might not be suited for locally advanced and high-Gleason PC (36), there are several reports that have observed a low incidence of distant metastases at 5 years and longer survival for high-risk patients treated with combined brachytherapy (high-dose rate brachytherapy as well as seed implantation) and conformal radiotherapy techniques [81, 82]. Recently, the 10-year results of a prospective trial using pelvic EBRT with high-dose rate boost and hypofractionated dose escalation was published [83]. This study demonstrated a strong dose-response relationship for intermediate and high-risk PC patients. The 10-year biochemical failure rate, clinical failure rate, and distant metastases rate were 18.9, 7.7, and 5.7 %, respectively, and significantly better than when lower doses were applied [83]. Sylvester et al. published their 15-year results of transperineal interstitial permanent prostate brachytherapy combined with moderate-dose (45 Gy on a limited pelvic field) neo-adjuvant EBRT. None of the patients received HT. Fifteen-year bNED for patients with high-risk features according to D'Amico et al. was 67.8 % [11]. Similar results have been published by Stone et al. 648 men with high-risk PC were treated with a combination of EBRT, seed implantation, and 9 months of HT [84]. The reported 12-year bNED was 67 % [84]. In a paper published by Merrick et al., high-risk PC patients were treated with pelvic EBRT and Pd-103 or I-125 brachytherapy boost [85]. HT was initiated in 63 % of the patients. The 12-year cancer-specific survival, bNED, and overall survival were 94.2, 89, and 69.7 % [85]. These data indicate that the excellent long-term clinical outcome for EBRT and seed implantation in high-risk PC patients is reproducible. An overview of other studies on combined brachytherapy (mainly high-dose rate brachytherapy) and EBRT in high-risk PC patients is presented in Table 70.4 [86–92]. Little information is reported regarding the place and duration of HT when brachytherapy is applied.

Many questions remain unresolved concerning the value of pelvic irradiation. In case of localized (N0) PC, two large randomized trials failed to show an overall survival benefit [93, 94].

The Radiation Therapy Oncology Group (RTOG) 9,413 trial [93] favors pelvic radiotherapy. This study demonstrated a significant 7 % improvement in the 4-year progression free survival rate (PFS) when patients were treated with the combination of neo-adjuvant + concurrent HT and pelvic EBRT compared with prostate-alone EBRT for patients with intermediate- and high-risk PC. However, there was no significant benefit for pelvic EBRT when it comes to overall survival or DMFS. Moreover, an increase in late grade 2 and 3 toxicities was noted. The GETUG randomized trial [94] failed to show differences in PFS.

Two important shortcomings of these "older" trials are the low dose on the prostate and insufficient coverage of the lymph nodes. Historically, at the time of the study design set-up, the currently available level I evidence for dose escalation was not present yet. Therefore, the 70 Gy received by the prostate can be considered insufficient in the light of current knowledge.

The GETUG trial failed to show a significant difference in the groups < or ≥70 Gy, which is, after all, still a low dose [94].

A large retrospective study with high-dose BT also failed to demonstrate a benefit for pelvic irradiation [95], hereby suggesting that dose escalation to the prostate rather than pelvic radiotherapy is beneficial.

There has been reluctance towards the implementation of pelvic radiotherapy due to the fear of increasing toxicity. New radiotherapy techniques, such as IMRT and certainly rotational radiotherapy (such as IMAT), allow better coverage of the target volume with sparing of the organs at risk. These newer techniques also allow for dose escalation to the prostate and invaded lymph node areas that can lead to further improvement of disease outcome.

## Treatment Options for N1 M0 PC

A subpopulation of patients with PC will have lymph node metastasis (stage N1). The optimal management for these patients remains controversial. The outcome for these patients is however not necessarily poor as patients with low-volume nodal metastases can experience excellent survival rates.

**Table 70.4** Overview of studies regarding brachytherapy for locally advanced prostate cancer

| Year | Author | Inclusion criteria | *N* | Therapy | Follow-up in months | Time (years) | Overall survival | Cancer-specific survival | Progression-free survival | PSA relapse-free survival | Late grade 3 toxicity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2000 | Kestin et al. [57] | PSA ≥ 10.0 ng/ml, Gleason≥7, T2b to T3c | 161 | Pelvic EBRT + HDR | 54 | 5 | – | 95 | 78 | 67 | 4 % |
| 2002 | Galalae et al. [58] | T1–T3N0M0 | 144 | Pelvic EBRT + HDR | 96 | 5/8 | 80/70 | 90[a] | 77/69 | 74/69 | 4 % |
| 2005 | Sathya et al. [88] | T2–T3 | 51 | Lymphadenectomy + EBRT + IM | 98 | 5 | 94 | – | 71 | | 4 % GI/14 % GU |
| 2006 | Nickers et al. [89] | PSA ≥ 10.0 ng/ml, Gleason ≥ 7, ≥ T2b | 201 | EBRT + $^{192}$Ir LDR | 42 | 4 | – | 88 (84)[b] | – | 81 (65)[b] | 0 % GI/6 % GU |
| 2008 | Fang et al. [90] | T1c–T3b | 55 | EBRT + HDR | 56 | 5 | – | – | – | 67 (52)[c] | 0 % GI/1 % GU |
| 2009 | Viani et al. [91] | PSA > 20.0 ng/ml, Gleason ≥ 8, > T2b | 131 (66 high-risk patients) | EBRT + HDR | 63 (60) | 5 | – | – | – | 81 (71) | 0 % GI/4 % GU |
| 2010 | Yoshioka et al. [92] | T1c–T4N0M0 | 112 (68 high-risk patients) | HDR | 65 | 5 | 96 | – | 87 | 83 (79)[c] | 2 % GI/1 % GU |

*IM* iridium implant, *GI* gastrointestinal, *GU* genitourinary, *HDR* high-dose rate brachytherapy, *LDR* low-dose rate brachytherapy

[a]At 8 years

[b]Presence of 2 adverse factors (presence of 3 adverse factors)

[c]Number between brackets presents result for high-risk patients

The number of positive nodes involved determines the prognosis of patients with N1 disease. The clinical recurrence-free survival is increased by approximately 20 % when ≤2 lymph nodes are involved [96, 97]. Single-modality therapies such as HT [98], EBRT [99], or RP and pelvic lymphadenectomy [100] have reported 5-year clinical PFS rates of 55–67 %. A few prospective randomized trials have suggested that immediate adjuvant therapy after definitive local procedures (RP with pelvic lymphadenectomy or radiation) may reduce progression rates and improve survival in patients with locally advanced and node-positive prostate cancer [66, 101]. Excellent results were described for RP and HT for stage N1 PC with 5-year and 10-year PFS rates for patients with lymph node metastasis of 74 and 64 %, respectively, compared with 77 and 59 %, respectively, for patients without lymph node metastasis and 5-year and 10-year cancer-specific survival (CSS) rates of 94 and 83 %, respectively, compared with 99 and 97 %, respectively, for patients without lymph node metastasis. For patients with a single lymph node metastasis, the 5-year and 10-year CSS rates were 99 and 94 %, respectively [102]. Comparable 10-year CSS and bNED rates were published by Boorjian et al. [103]. In a retrospective study, EBRT + HT resulted in a significant gain of 5 and 10 % concerning bNED and CSS, respectively, when compared to HT alone in the post-prostatectomy setting [104]. Although there are a lot of shortcomings in this study, recognized by the authors, it represents an innovative approach that deserves further examination in randomized trials [104].

The combination of EBRT and HT is also an effective treatment for stage N1 PC, with an overall survival rate of 86, 72 and 53 % at 5, 8 and 12 years, respectively [105].

The importance of combining (long-term) HT to EBRT has, also for N1 disease, univocally been established in large phase III trials such as RTOG 86-10 [106] and RTOG 85-31 [107].

In analogy to the important dose-response relationship described for primary radiotherapy in high-risk prostate, we can assume that dose escalation to the prostate/seminal vesicles and pelvic lymph nodes will improve locoregional control and, consequently, reduce distant failure [62]. When using 3D RT technique, dose escalation will be limited by the spatial relationship of the pelvic lymph nodes and organs at risk such as the small and large bowel and the bladder. Therefore, modern RT techniques such as IMRT [108] or helical tomotherapy [109] are used to safely deliver pelvic RT. The feasibility of IMRT and rotational therapy in high-dose pelvic radiotherapy has been published with acceptable toxicity rates [110–112].

## Summary

High-risk prostate cancer can be defined by the assessment of pretreatment prognostic factors such as clinical stage, Gleason score, and PSA level. High-risk features include PSA > 20 ng/ml, biopsy Gleason score 8–10, and stage T3-T4 tumors.

Patients with locally advanced prostate cancer present a diagnostic and therapeutic dilemma and require more aggressive therapies as they are at higher risk of PC death. Herein, we examine the role of surgery, external beam radiotherapy, brachytherapy, and hormonal therapy in the management of locally advanced prostate cancer. Patients with adverse prognostic factors have historically fared poorly with monotherapeutic approaches. Multimodality treatment utilizing combined radical prostatectomy and/or radiotherapy and androgen suppression has improved survival rates for patients with high-risk prostate cancer.

So far, no established standard treatment has been proposed. Like other patients with prostate cancer, individualized therapeutic choices are essential and depend on a multitude of factors. Improved radiotherapy techniques that allow for dose escalation, as well as multimodality approaches, present promising future therapeutic alternatives for patients with high-risk prostate cancer.

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# Radiotherapy Plus Hormonal Therapy

# 71

Jordan A. Holmes and Ronald C. Chen

External beam radiation therapy (EBRT) plus androgen deprivation therapy (ADT) is an important and well-established treatment regimen for patients with high-risk and locally advanced prostate cancer, as demonstrated by multiple randomized trials. Radiation therapy is also an established treatment for patients who have recurrent disease after radical prostatectomy, offering patients a "second chance" at cure. The recent report of a randomized trial suggests that the addition of ADT to radiation therapy may also be of benefit for patients in this "salvage" treatment setting. This chapter will review the body of literature on and indications for radiation therapy with ADT for patients with high-risk, locally advanced, and recurrent prostate cancer.

## Need for Radiation Therapy in the Treatment of Patients with Locally Advanced Prostate Cancer

A Scandinavian trial (SPCG-7/SFUO-3) randomized 875 patients with locally advanced prostate cancer to ADT alone vs. ADT plus EBRT [1]. All patients had PSA <70, N0, and M0 disease; 78 % had T3 cancer. ADT consisted of 3 months of total androgen blockade (LHRH agonist plus flutamide) followed by flutamide until disease progression or death. Radiation treatment was to at least 70 Gy and targeted the prostate and seminal vesicles. After a median follow-up of 7.6 years, patients who received EBRT had significantly reduced biochemical recurrence (10-year rate 74.7 % for ADT alone vs. 25.9 % for ADT/EBRT, $p<.001$), prostate-cancer-specific mortality (23.9 % vs. 11.9 %, $p<.001$), and overall mortality (39.4 % vs. 29.6 %, $p<.001$). Long-term urinary, rectal, and sexual symptoms were slightly more frequent in the ADT plus EBRT group.

Intergroup T94-0110 confirmed these results in a cohort of 1,205 patients with similar disease characteristics [2]. All patients had N0M0 disease, and 88 % of the patients had locally advanced (T3/T4) prostate cancer. Patients were randomized to lifelong ADT (bilateral orchiectomy or LHRH agonist) vs. ADT plus EBRT to 65–69 Gy. After a median follow-up of 6 years, patients who received EBRT had significantly reduced disease-specific mortality (10-year rate 23 % vs. 15 %, $p<.001$) and overall mortality (hazard ratio 0.77, $p=.03$). Grade ≥2 late gastrointestinal toxicity was low and similar in both arms (proctitis 1.3 % ADT vs. 1.8 % ADT/EBRT).

These two randomized trials demonstrate that ADT alone is insufficient for the treatment of patients with locally advanced prostate cancer and establishes radiation therapy as a standard of care for these patients. Radiation therapy results in a 10 % absolute survival benefit with acceptable long-term side effects.

## Benefit of Adding ADT to EBRT

For patients with high-risk and locally advanced prostate cancer, the results from multiple randomized trials have consistently demonstrated that treatment outcomes are significantly improved when ADT is added to EBRT.

### ADT and EBRT in High-Risk Prostate Cancer

At least six randomized trials have examined the disease control and survival outcomes of ADT and EBRT for high-risk prostate cancer.

D'Amico et al. published results of the Harvard trial which randomized 206 patients to EBRT vs. EBRT plus 6 months of ADT [3, 4] (Table 71.1). This study included patients with intermediate- (74 %) and high-risk (26 %) prostate cancer. EBRT

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**Table 71.1** Randomized trials of external beam radiation therapy with androgen deprivation therapy for high-risk and locally advanced prostate cancer

| | Patients included | Median follow-up (yrs) | Treatment arms | Overall survival (%) | Cancer-specific survival (%) | Distant failure (%) | bFFS/DFS (%) |
|---|---|---|---|---|---|---|---|
| Harvard [3] ($N=206$) | 74 % intermediate-risk, 26 % high-risk | 7.6 | EBRT | (8-Yr) | (8-Yr) | NA | NA |
| | | | EBRT + 6 mo ADT | 74 | HR 4.1 ($p=.01$) | | |
| | | | | 61 ($p=.01$) | | | |
| RTOG 9408 [5] ($N=1,979$) | 35 % low-risk, 54 % intermediate-risk, 11 % high-risk | 9.1 | EBRT | (10-Yr) | (10-Yr) | NA | NA |
| | | | EBRT + 4 mo ADT | 57 | 93 | | |
| | | | | 62 ($p=.03$) | 96 ($p<.01$) | | |
| TROG 96.01 [6] ($N=802$) | 16 % intermediate-risk, 44 % high-risk, 40 % locally advanced | 5.9 | EBRT | NA | (5-Yr) | (5-Yr) | (5-Yr)[a] |
| | | | EBRT + 3 mo ADT | | 91 | 19 | 38 |
| | | | EBRT + 6 mo ADT | | 92 | 22 | 52 ($p<.01$) |
| | | | | | 94 ($p=.04$) | 13 ($p=.05$) | 56 ($p<.01$) |
| Quebec 1 [7] ($N=161$) | ~70 % T2, ~30 % T3 | 5 | EBRT | NA | NA | NA | (7-Yr)[b] |
| | | | EBRT + 3 mo ADT | | | | 42 |
| | | | EBRT + 10 mo ADT | | | | 66 ($p<.01$) |
| | | | | | | | 69 ($p<.01$) |
| Quebec 2 [7] ($N=296$) | 86 % T2, 14 % T3 | 3.7 | EBRT + 5 mo ADT | NA | NA | NA | (4-Yr)[b] |
| | | | EBRT + 10 mo ADT | | | | 70 |
| | | | | | | | 70 ($p=.55$) |
| Canadian [8] ($N=361$) | 26 % low-risk, 43 % intermediate-risk, 31 % high-risk | 6.6 | EBRT + 3 mo ADT | (7-Yr) | (7-Yr) | NA | (7-Yr)[c] |
| | | | EBRT + 8 mo ADT | 81 | 94 | | 58 |
| | | | | 79 ($p=.7$) | 93 ($p=.24$) | | 65 ($p=.18$) |
| RTOG 8531 [9] ($N=945$) | T3 or $N+$ (28 %) | 7.6 | EBRT | (10-Yr) | (10-Yr) | (10-Yr) | (10-Yr)[d] |
| | | | EBRT + indef ADT | 39 | 78 | 39 | 9 |
| | | | | 49 ($p<.01$) | 84 ($p<.01$) | 24 ($p<.01$) | 31 ($p<.01$) |
| EORTC 22863 [10] ($N=412$) | T1-2 (7 %), T3 (82 %), T4 (9 %) | 5.5 | EBRT | (5-Yr) | (5-Yr) | (5-Yr) | (5-Yr) |
| | | | EBRT + 3 Yr ADT | 62 | 79 | 29 | 45 |
| | | | | 79 ($p<.01$) | 94 ($p<.01$) | 10 ($p<.01$) | 76 ($p<.01$) |
| RTOG 8610 [11] ($N=456$) | Bulky tumors (5 × 5 cm). 70 % with Stage C (locally advanced) | 13[e] | EBRT | (10-Yr) | (10-Yr DSM) | (10-Yr) | (10-Yr)[f] |
| | | | EBRT + 4 mo ADT | 34 | 36 | 47 | 3 |
| | | | | 43 ($p=.12$) | 23 ($p=.01$) | 35 ($p<.01$) | 11 ($p<.01$) |
| RTOG 9202 [12] ($N=1,521$) | 45 % high-risk, 55 % locally advanced | 11.3[e] | EBRT + 4 mo ADT | (10-Yr) | (10-Yr) | (10-Yr) | (10-Yr)[g] |
| | | | EBRT + 28 mo ADT | 52 | 84 | 23 | 13 |
| | | | | 54 ($p=.36$) | 89 ($p<.01$) | 15 ($p<.01$) | 23 ($p<.01$) |
| EORTC 22961 [13] ($N=970$) | T2c-T4N0 (92 %), $N+$ (8 %) | 6.4 | EBRT + 6 mo ADT | (5-Yr OM) | (5-Yr CSM) | (5-Yr)[h] | (5-Yr BP) |
| | | | EBRT + 36 mo ADT | 19 | 4.7 | 14 | 38 |
| | | | | 15 ($p<.05$) | 3.2 ($p<.01$) | 6 ($p<.01$) | 15 |

*Abbreviations*: *bFFS* biochemical failure-free survival, *DFS* disease-free survival, *EBRT* external beam radiation therapy, *Mo* months, *ADT* androgen deprivation therapy, *Yr* year, *HR* hazard ratio, *NA* not available, *Indef* indefinite, *DSM* disease-specific mortality, *OM* overall mortality, *CSM* cancer-specific mortality, *BP* biochemical progression

[a]Biochemical failure defined as nadir + 2

[b]Biochemical failure defined as two consecutive rises in PSA with PSA value at least 1.5 ng/mL

[c]Freedom from any failure. Biochemical failure defined as nadir + 2

[d]Disease-free survival. Biochemical failure defined as PSA > 1.5 ng/mL

[e]Median follow-up for survivors

[f]Disease-free survival. Biochemical failure defined as PSA > 2 ng/mL at ≥1 year from randomization

[g]Disease-free survival. Biochemical failure defined as three consecutive rises in PSA, PSA > 4 ng/mL, or receiving additional ADT

[h]Distant metastasis or death due to disease

plus ADT resulted in an improved prostate-cancer-specific survival and overall survival over EBRT alone. The 8-year overall survival rates were 74 % (EBRT plus ADT) vs. 61 % (EBRT alone, $p=.01$) [3]. This survival benefit was apparent for both intermediate- and high-risk subgroups of men [14].

RTOG 94-08 included 1,979 patients with low- (36 %), intermediate- (53 %), and high-risk (11 %) prostate cancer and randomized them to EBRT vs. EBRT plus 4 months of ADT [5]. This trial also demonstrated an overall survival benefit from the addition of ADT. Ten-year overall survival

rates were 57 % (EBRT) vs. 62 % (EBRT plus ADT, $p = .03$). However, in subgroup analysis, no benefit from ADT was seen for low-risk patients.

A third trial, Trans-Tasman Radiation Oncology Group (TROG) 96.01, randomized patients with intermediate-risk (16 %), high-risk (44 %), and locally advanced prostate cancer (T3–T4, 40 %) to receive EBRT alone, EBRT plus 3 months ADT, or EBRT plus 6 months ADT [6]. EBRT plus ADT (either 3 or 6 months) improved biochemical failure-free survival and disease-free survival compared to EBRT alone. In addition, 6 months of ADT also reduced distant failures (HR 0.67 compared to EBRT alone, $p = .046$) and prostate-cancer-specific mortality (HR 0.56, $p = .04$).

Similarly, two trials from Quebec demonstrated a benefit from short-term ADT used with EBRT [7]. Laverdiere et al. randomized a cohort of patients (70 % with T2 disease) to EBRT vs. EBRT plus 3 months ADT vs. EBRT plus 10 months ADT. After 5 years of follow-up, the addition of ADT (3 or 10 months) improved biochemical relapse-free survival compared to EBRT alone. A follow-up study randomized patients to EBRT plus 5-month ADT vs. EBRT plus 10-month ADT. No difference was seen. In a third Canadian trial that randomized patients to EBRT plus 3-month ADT vs. EBRT plus 8-month ADT, there was no difference in overall survival, cause-specific survival, or freedom from any failure between the two arms [8].

These trials consistently demonstrate a disease control and survival benefit from adding ADT to EBRT for the treatment of patients with high-risk prostate cancer. It is important to note that these trials were conducted in an era when lower-dose radiation therapy was given for prostate cancer and therefore demonstrate that ADT improves outcomes when added to lower-dose EBRT. With 3D conformal and intensity-modulated radiation therapy (IMRT), higher doses can now be safely delivered. Three randomized trials have compared lower-dose (68–70 Gy) vs. dose-escalated (78–79 Gy) EBRT, all showing that dose-escalated radiation therapy improves freedom from disease failure [15–20]. For patients with intermediate-risk prostate cancer (which is not subject of this current chapter), whether ADT provides additional benefit in the setting of dose-escalated EBRT (and the magnitude of benefit) is unclear; this is currently being investigated by a randomized trial.

For patients with high-risk prostate cancer, there is a risk of distant micrometastatic disease and ADT is needed. The Harvard trial demonstrated that the addition of short-term ADT to EBRT improves overall survival [3]. RTOG 92-02 examined whether longer-term ADT can further improve disease control and survival outcomes. In this trial, patients with high-risk (T2, 45 % of patients) and locally advanced (T3/T4, 55 %) prostate cancer were randomized to receive radiation therapy, plus short-term (4 months) vs. long-term (28 months) ADT [12, 21]. Long-term ADT improved local control, disease-free survival, and cancer-specific survival. In addition, for patients with Gleason 8–10 disease, overall survival was improved with long-term ADT (10-year OS 31 % for short-term ADT vs. 45 % for long-term ADT, $p < .01$). In contrast, dose-escalated radiation therapy (without ADT) has not yet demonstrated a survival benefit over lower-dose radiation therapy in randomized trials. These results support the use of long-term (2–3 years) ADT with EBRT for patients with high-risk prostate cancer.

## ADT and EBRT in Locally Advanced Prostate Cancer

At least three randomized trials have demonstrated that the addition of ADT to EBRT improves disease control and survival outcomes in patients with locally advanced prostate cancer (Table 71.1).

In RTOG 85-31, 945 patients with T3 or node-positive (28 % of patients) prostate cancer were randomized to EBRT vs. EBRT plus indefinite ADT [9, 22, 23]. The primary analysis of this trial showed that the addition of ADT improved 10-year biochemical failure-free survival (9 % for EBRT alone vs. 31 % EBRT/ADT, $p < .01$), cancer-specific survival (78 % vs. 84 %, $p < .01$), and overall survival (39 % vs. 49 %, $p < .01$). However, many patients stopped ADT early. In a secondary analysis, patients who completed more than 5 years of ADT had improved disease control and survival outcomes compared to those who stopped prior to 5 years [24].

A second trial, RTOG 86-10, tested whether short-term ADT added to EBRT was beneficial [11, 25]. In this trial, 456 patients with bulky primary tumors (5 × 5 cm, 70 % patients had locally advanced disease) were randomized to EBRT vs. EBRT plus 4-month ADT. Patients who received ADT had improved local control, disease-free survival, and cancer-free survival. The 10-year overall survival rates were 43 % (EBRT/ADT) vs. 34 % (EBRT alone); however, this 9 % absolute difference was not statistically significant ($p = .12$), likely due to the small size of this trial and therefore lack of sufficient power.

The EORTC 22863 trial included 412 patients with T3 (82 %) or T4 (9 %) disease [10, 26]. Patients were randomized to EBRT vs. EBRT plus 3-year ADT. This trial confirmed results from RTOG 85-31 and demonstrated a benefit to long-term ADT in all endpoints, including overall survival.

While these three trials consistently demonstrated a survival benefit of adding ADT to EBRT in patients with locally advanced prostate cancer, whether short-term (RTOG 86-10) or long-term (RTOG 85-31 and EORTC 22863) ADT was needed required further study. Two randomized trials have examined this issue. As described above, RTOG 92-02 included a mixture of patients with high-risk and locally

advanced prostate cancer and showed that 28 months of ADT was better than 4-month ADT when combined with EBRT. EORTC 22961 randomized patients with locally advanced or node-positive (8 %) disease to EBRT, plus 6 vs. 36 months of ADT [13]. This study was designed as a non-inferiority trial, and at 5 years, the primary null hypothesis of non-inferiority in overall mortality for 6-month ADT could not be rejected. In post hoc analysis, short-term ADT was shown to be inferior to long-term ADT in overall survival. Taken together, RTOG 92-02, EORTC 22961, and the secondary analysis of RTOG 85-31 all support the use of EBRT with long-term ADT (2–3 years) for the treatment of patients with locally advanced prostate cancer.

### Type of ADT to Use with EBRT

There are two classes of drugs commonly used to induce androgen deprivation in conjunction with EBRT: luteinizing hormone-releasing hormone (LHRH) agonist and antiandrogens. LHRH agonists are also frequently referred to as gonadotropin-releasing hormone (GnRH) agonists and are synthetic analogs of the natural hormone which bind to the GnRH receptors on pituitary gonadotropin-producing cells. Binding causes the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH cause an initial increase in testosterone production from testicular Leydig cells, but this surge in testosterone eventually leads to downregulation of GnRH receptors in the pituitary and an eventual decline in LH and FSH release. The end result of this feedback loop is castrate levels of testosterone [27, 28]. In a study of the effects of GnRH analogs, 80 % of patients experienced a testosterone surge after receiving treatment, and the time from initiation of treatment to castrate testosterone levels was approximately 4 weeks [29]. Available LHRH agonists include leuprolide, goserelin, and triptorelin. A second class of drugs, antiandrogens, are synthetic compounds that bind directly to testosterone receptors in tissue and competitively inhibit binding of testosterone and dihydrotestosterone. Antiandrogens are often used in conjunction with an LHRH agonist to provide maximal androgen blockade. Available formulations include flutamide, bicalutamide, and nilutamide. A more detailed description of the different types of ADT agents and mechanisms of action is included in Chaps. 56 and 60.

In the randomized trials described above using EBRT with short-term ADT, maximum androgen blockade (MAB, LHRH agonist plus antiandrogen) was used in all trials [4, 6, 7, 30, 31]. In RTOG 92-02 and EORTC 22961, MAB was used for the first 4–6 months, and then LHRH agonist was continued until the end of the long-course ADT [13, 21]. However, when used with radiation therapy, whether MAB improves patient outcomes compared to LHRH agonist alone is unclear.

In the Harvard trial, a secondary analysis was performed examining the outcomes of patients who completed EBRT with 6 months of MAB, vs. those who stopped flutamide early [32]. All patients completed the 6 months of LHRH agonist. This study found that the risk of cancer recurrence decreased for each month of flutamide completed (HR 0.81, $p < .01$) – suggesting that the antiandrogen may have added benefit when combined with EBRT and LHRH agonist. A retrospective study of 628 patients with high-risk prostate cancer treated with radiation-based primary therapy had similar findings [33]. In multivariable analysis, patients who received MAB with radiation therapy had a lower risk of prostate-cancer-specific mortality compared to those who received LHRH agonist alone with radiation therapy (HR 0.18, $p = .04$).

## Use of EBRT After Prostatectomy

Radical prostatectomy is a standard treatment for patients with localized prostate cancer. At the time of prostatectomy, adverse pathological features are seen in 38–52 % of patients [34, 35] – this includes pathologic extension of cancer beyond the prostate, positive surgical margins, and/or invasion of the seminal vesicles. While radical prostatectomy provides excellent tumor control when the cancer is confined to within the prostate, patients with these adverse pathologic features have an increased risk of disease recurrence, progression, and death [36–38]. Radiation therapy has been used both in the adjuvant (for patients with adverse pathologic features, prior to disease recurrence) and salvage (patients with disease recurrence) settings and offers patients a second chance of cure.

### Adjuvant Radiation Therapy in Patients with Adverse Pathologic Factors

Three similarly designed randomized trials have been performed to examine the efficacy of adjuvant radiation therapy in patients with adverse pathological features on surgical pathology.

In the Southwest Oncology Group trial (SWOG 8794), 425 patients after radical prostatectomy with adverse pathological features were randomized to observation vs. radiation therapy. Median follow-up has reached 12.6 years on the most recent update [39]. Radiation treatment improved biochemical relapse-free survival ($p < .001$) [40], metastasis-free survival (10 years 61 % for observation vs. 71 % EBRT, $p = .016$) [39], and overall survival (66 % vs. 74 %, $p = .023$) [39]. The benefit of adjuvant radiation treatment was seen in all subgroups of patients, which were stratified by postoperative PSA level (detectable vs. undetectable), Gleason score

(2–6 vs. 7–10), and extent of disease (extracapsular extension or positive margin vs. seminal vesicle invasion) [39].

EORTC 22911 included 1,005 patients and had a similar randomization [41]. Median follow-up was 5 years. Radiation treatment improved biochemical progression-free survival (5 years 52.6 % for observation vs. 74.0 % EBRT, $p<.001$), clinical failure-free survival ($p<.0001$), and locoregional failure-free survival ($p<.0001$). The treatment benefit was seen in all subgroups of patients.

In a third trial conducted by the German Cancer Society (ARO 96-02/AUO AP 09/95), 307 patients were randomized to observation vs. radiation therapy [42]. At a median follow-up of 4.5 years, radiation treatment improved the 5-year biochemical progression-free survival rate (54 % for observation vs. 72 % EBRT, $p=.002$).

These trials consistently demonstrate that for patients who have undergone a radical prostatectomy and have adverse pathological features, adjuvant radiation therapy results in a 20 % absolute benefit in biochemical progression-free survival at 5 years [40–42]; in the SWOG trial which has sufficient follow-up, this translated to a 8 % overall survival benefit [39]. However, this benefits needs to be balanced against the potential long-term toxicity of radiation treatment. In the EORTC trial, the cumulative incidence of grade 3 GI or GU toxicity at 5 years was 2.6 % for the observation arm and 4.2 % for the radiation arm (absolute increase 1.6 %) [41]. The German trial reported one event of grade 3 toxicity (0.3 %) [42].

While ADT has consistently demonstrated benefit when added to EBRT in the treatment of patients with high-risk and locally advanced prostate cancer, it is unclear whether a similar benefit results from its use in the adjuvant setting. No prospective trial has compared adjuvant EBRT vs. EBRT/ADT.

## Salvage Radiation Therapy in Patients with Recurrent Disease

If adjuvant radiation treatment were not given, or for patients without adverse pathologic features, salvage radiation therapy given at the time of recurrent disease can also be beneficial. Stephenson et al., in a multi-institutional retrospective cohort of 1,540 patients who received salvage radiation therapy for recurrent prostate cancer after prostatectomy, demonstrated that approximately 50 % of patients achieved long-term disease-free survival if radiation therapy was delivered early after recurrence (PSA ≤ 0.5 ng/mL) [43]. Other favorable prognostic factors for 6-year progression-free probability included prostatectomy Gleason score 4–7 (vs. Gleason 8–10), positive surgical margin, and PSA doubling time of more than 10 months. Several other retrospective series have found similar prognostic factors [38, 44–49]. However, while these identified clinical factors predicted for good long-term outcomes, these studies were unable to demonstrate which subgroups of patients actually derived benefit from salvage radiation therapy. It is possible that patients who had favorable disease would achieve long-term disease control even without salvage treatment.

Recent studies have more directly demonstrated a potential benefit from salvage radiation therapy. In a retrospective series of 635 patients from Johns Hopkins who experienced biochemical failure and/or local recurrence after radical prostatectomy, Trock et al. compared the prostate-cancer-specific survival rates in patients who received no salvage therapy vs. salvage radiation vs. salvage radiation and androgen deprivation therapy [50]. Median follow-up was 6 years after recurrence (9 years after prostatectomy). Salvage radiation therapy was associated with a three-fold decrease in prostate-cancer-specific mortality compared to no salvage treatment (hazard ratio 0.32, $p<.001$), while adding ADT did not result in further benefit. Ten-year prostate-cancer-specific survival rates were 62 % (no salvage), 86 % (EBRT), and 82 % (EBRT/ADT). In stratified analysis, the benefit from EBRT was limited to patients with a PSA doubling time of less than 6 months and when salvage treatment was started within 2 years of biochemical recurrence. In another retrospective study, Boorjian et al. examined the outcomes of 2,657 men who experienced biochemical failure after radical prostatectomy, of these, 856 received salvage radiation therapy [51]. Compared to patients who received no salvage treatment, those who received salvage EBRT had a dramatic reduction in local recurrence (HR 0.13, $p<.001$) and systemic progression (HR 0.24, $p<.001$). The authors hypothesized that with longer follow-up, the systemic progression benefit from EBRT will likely translate into improved overall survival.

In the setting of salvage radiation therapy, the potential benefit of adding ADT was examined by RTOG 96-01 [52]. This trial included 771 post-prostatectomy patients who had pathologic T3N0 or T2N0 (positive margin) disease and who had elevated PSA. Patients were randomized to salvage radiation therapy alone vs. radiation therapy plus 24 months of bicalutamide (150 mg once a day). Median follow-up of surviving patients was 7.1 years. The 7-year rates of freedom from PSA progression were 40 % (EBRT alone) vs. 57 % (EBRT/ADT, $p<.001$). Benefit was seen in subgroups of patients with Gleason <7, Gleason 7, and Gleason 8–10 disease. Cumulative incidence of metastasis was 12.6 % (EBRT alone) vs. 7.4 % (EBRT/ADT, $p<.04$).

Taken together, these studies support the use of salvage EBRT with ADT in patients with early biochemical failure after radical prostatectomy. While RTOG 96-01 used bicalutamide with EBRT, in a dosage that is no longer commonly used, it may be reasonable to substitute with an LHRH agonist. Further, the randomized trials provide level 1 evidence

to support the use of adjuvant EBRT after radical prostatectomy in patients with adverse pathological features. A large absolute benefit in progression-free survival was consistently seen, applied to almost all subgroups of patients, with low risk of long-term grade 3 or higher morbidity. Whether early salvage radiation is as effective as adjuvant radiation therapy is unclear and is currently being examined in a randomized trial.

## ADT-Associated Side Effects

The benefit of ADT needs to be balanced against its side effects. Some patients are unable to tolerate a prolonged course of ADT. In RTOG 85-31 which randomized patients to EBRT vs. EBRT plus indefinite ADT, 44 % of patients in the ADT arm stopped treatment before 2 years.[23] Similarly, in EORTC 22961 (EBRT plus 6 vs. 36 months ADT), 22 % of men randomized to long-term ADT stopped treatment early [13]. Further, recent studies have demonstrated a potential link between ADT and an increased risk of diabetes and cardiovascular disease. This literature is summarized below, along with a review of potential supportive therapies to ameliorate ADT-associated side effects and improve treatment tolerability.

### Risk of Cardiovascular Disease and Patient Selection Considerations

Several retrospective studies have examined the correlation between ADT and cardiovascular disease (Table 71.2). The studies showing a statistically significant association between ADT and cardiovascular events and mortality included retrospective analyses of large patient databases such as SEER/Medicare [53, 54], the Veterans Administration [55], and Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) [59]. In these studies, the absolute increase in cardiovascular mortality attributed to ADT was estimated to be 4–10 deaths/1,000 person-years, and LHRH agonist (not antiandrogens) appeared to be the associated agent [53, 55]. Other studies have shown that ADT is associated with an increased risk of insulin resistance [56, 60], diabetes [53, 55, 61], and dyslipidemia [62, 63], as well as increased obesity and fat mass [62, 64, 65]. The metabolic changes associated with ADT often become apparent within a few months of treatment. Similarly, in the studies showing a statistically significant increase in cardiovascular mortality associated with ADT, this risk was observed even for patients receiving short-term ADT [53, 54, 57, 66]. D'Amico et al. conducted a post-randomization analysis of pooled data from the Harvard trial (EBRT vs. EBRT plus 6 months ADT), TROG 96.01 (EBRT vs. EBRT plus 3 months vs. EBRT plus 6 months ADT), and a Canadian trial (EBRT plus 3 months vs. EBRT plus 8 months ADT). Compared to radiation therapy alone, this study found that 6 months of ADT was associated with a shorter time to fatal myocardial infarction in men 65 years or older [66]. Long-term ADT does not appear to further increase this risk. EORTC 22961 reported similar rates of fatal cardiac events among patients receiving short-term or long-term ADT (4.0 and 3.0 %, respectively) [13]. Similarly, a post-randomization analysis of RTOG 92-02 did not find a difference in the risk of cardiovascular mortality on multivariable analysis between the short-term vs. long-term arms of the study (HR 1.02, $p = .90$) [58].

There are also several studies that found no significant increase in cardiovascular disease or mortality associated with use of ADT. Among the studies showing no significant association are post-randomization analyses of RTOG 85-31 [67] (EBRT vs. EBRT plus indefinite ADT) and RTOG 86-10 (EBRT vs. EBRT plus 4 months ADT) [11], as well as an analysis of the Ontario Cancer Registry [61]. The inconsistency in the results of the above studies is likely due to the fact that none of the large databases or prospective trials were designed to assess cardiovascular disease, plus inherent differences in study design and biases of retrospective data analyses. Thus, the findings of above studies – whether indicating a significant or null relationship between ADT and cardiovascular disease – are hypothesis-generating and require prospective validation with studies specifically designed to examine this issue. Further, it is possible that an effect of ADT may only manifest in certain subgroups of patients, such as those with baseline comorbidities or cardiovascular risk factors. Nanda et al. retrospectively analyzed a series of 5,077 patients treated with brachytherapy, of whom 30 % received short-term ADT [68]. There was no difference in the cardiovascular mortality rates among patients who received vs. did not receive ADT, except in the subgroup of patients with preexisting heart conditions.

Multiple randomized trials have consistently demonstrated a disease control and survival benefit from the addition of ADT to EBRT in the treatment of patients with high-risk and locally advanced prostate cancer. However, if the findings of Nanda et al. are validated, then it is possible that for some patients, the risks of ADT may nullify its benefit. In a post-randomization analysis of the Harvard trial, a survival benefit from adding 6 months of ADT to EBRT was only seen in patients with little or no baseline comorbidity [3]. Patients with moderate or severe comorbidity did not achieve a statistically significant benefit from ADT. Prospective trials that stratify patients by pretreatment comorbid conditions would be able to better answer this question in the future.

The American Heart Association, American Cancer Society, and American Urological Association recently published a joint statement about the potential risk of cardiovascular morbidity and mortality associated with ADT [69].

**Table 71.2** Studies examining the association between androgen deprivation therapy and risk of cardiovascular morbidity and mortality

| **Retrospective analyses of large patient cohorts** | | | | |
|---|---|---|---|---|
| | Median FU (yrs) | Comparison | Time to cardiovascular morbidity: AHR (95 % CI) | Time to cardiovascular death: AHR (95 % CI) |
| *Studies demonstrating a significant relationship* | | | | |
| SEER/Medicare [52] (*N* = 73,196) | 4.6 | ADT vs. no ADT | CAD: AHR:1.16 (1.10–1.21)<br>MI: AHR:1.11 (1.01–1.21) | Sudden cardiac death AHR: 1.16 (1.05–1.27) |
| SEER/Medicare [53] (*N* = 22,816) | NA | ADT vs. no ADT | AHR 1.20 (1.15–1.26) | NA |
| Veterans Healthcare Administration [54] (*N* = 37,443) | 2.6 | ADT vs. no ADT | CAD: AHR:1.19 (1.10–1.28)<br>MI: AHR:1.28 (1.08–1.52) | Sudden cardiac death AHR: 1.35 (1.18–1.54) |
| CaPSURE [55] (*N* = 4,892) | 3.8 | Local tx + ADT vs. local tx | NA | Surgery: AHR:2.6 (1.4–4.7)<br>RT or cryo: AHR:1.2 (0.8–1.9) |
| *Studies demonstrating no significant relationship* | | | | |
| Ontario [56] (*N* = 19,079) | 6.5 | ADT ≥ 6 mo vs. no ADT | MI: AHR: 0.91 (0.84–1.00) | Sudden cardiac death AHR: 0.96 (0.83–1.10) |

| **Secondary analyses of randomized trials** | | | | |
|---|---|---|---|---|
| | Median FU (yrs) | Treatment arms | Time to cardiovascular morbidity (ADT vs. no ADT): AHR (95 % CI) | Time to cardiovascular death (ADT vs. no ADT): AHR or point estimates (95%CI) |
| *Studies demonstrating a significant relationship* | | | | |
| Pooled analysis of Dana-Farber, Canadian, and TROG 96.01 trials [42, 57] (*N* = 1,372) | ~6 | EBRT + ADT vs. EBRT | NA | (Patients ≥ 65 years) shorter time to fatal MI in patients receiving ADT compared to those not treated with ADT ($p = .017$) |
| *Studies demonstrating no significant relationship* | | | | |
| RTOG 85-31 [58] (*N* = 945) | 8.1 | EBRT + indef ADT vs. EBRT | NA | AHR: 0.99 (0.58–1.69) |
| RTOG 86-10 [11] (*N* = 456) | 13[a] | EBRT + 4 mo ADT vs. EBRT | NA | 10-Yr fatal cardiac events: 9.1 % (EBRT) vs. 12.5 % (EBRT + ADT), $p = .32$ |

*Abbreviations*: ADT androgen deprivation therapy, *FU* follow-up, *Yrs* years, *AHR* adjusted hazard ratio, *CI* confidence interval, *CAD* coronary artery disease, *MI* myocardial infarction, *Tx* treatment, *RT* radiation therapy, *Cryo* cryotherapy, *EBRT* external beam radiation therapy, *NA* not available, *Indef* indefinite

[a]Median follow-up for survivors

In the statement, they recommend "that the treating physician weigh the potential risks and benefits of ADT in each patient's specific clinical scenario. For patients with aggressive prostate cancer in whom the addition of ADT is necessary, no further evaluation by an internist, cardiologist, or endocrinologist is recommended. Patients with cardiac disease should receive appropriate secondary preventive measures (such as statins, aspirin, and antihypertensive medications) and be monitored by their primary care physicians."

## Management of ADT-Associated Symptoms

For patients in whom the potential benefit of ADT outweighs its adverse effects, recognition of ADT-associated symptoms and the use of appropriate supportive therapies can help patients complete their prescribed treatment. Management strategies for the most common ADT side effects are described below.

Hot flashes – a feeling of intense warmth in the face and upper body, often accompanied by sweating and possibly nausea – affect approximately 80 % of men who receive ADT [70]. Hot flashes, if occurring at night, can also cause sleep disturbance. Selective serotonin reuptake inhibitors (SSRIs) can be helpful in reducing hot flash intensity and frequency. Quella et al. treated 16 patients with moderate to severe hot flashes with venlafaxine 12.5 mg twice a day. There was a significant reduction in the incidence of severe and very severe hot flashes from 2.3 to 0.6 events/day ($p = .003$) [71]. By 4 weeks of treatment, the hot flash score (frequency x severity) decreased by greater than 50 % in 10 of 16 patients. Paroxetine has demonstrated similar efficacy [72]. Gabapentin (300 mg three times a day) [73] and pregabalin (75 or 150 mg, twice daily) [74] can also reduce the frequency and intensity of hot flashes in men receiving ADT. In a randomized trial, gabapentin reduced hot flash frequency by 46 % (compared to 22 % reduction for placebo) and hot flash score by 44 % (27 % for placebo) [73]. Another randomized trial showed that pregabalin reduced hot flash frequency by approximately 60 % (compared to 36 % reduction for placebo) and hot flash score by approximately 66 % (50 % for placebo) [74].

Fatigue is also potentially modifiable side effect of ADT. In a cross-sectional study of prostate cancer survivors, 26 % of men who received EBRT alone reported chronic fatigue, compared to 39 % of men who completed EBRT and continued to receive ADT [75]. Randomized trials have shown that physical activity successfully reduces fatigue associated with ADT treatment. Segal et al. randomized 155 men receiving ADT to either a 12-week resistance training regimen, or to a waiting list [76]. In patient self-report, men in the exercise arm had reduced fatigue and improved quality of life at 12 weeks. In another trial by the same investigator group, resistance training was found to have a similar benefit in men receiving EBRT for prostate cancer.

Sexual dysfunction is another common side effect of ADT and can cause both a decline in sexual interest and erectile dysfunction [77, 78]. Phosphodiesterase type 5 (PDE5) inhibitors have been successfully used to treat erectile dysfunction in this patient population. In a study by Teloken et al., 152 men with erectile dysfunction following EBRT (with or without ADT) were given sildenafil [79]. The median age of patients in this cohort was 62 years. Among patients who received only radiation therapy, 61 % achieved erections sufficient for intercourse with sildenafil. The corresponding rate for men who received both EBRT and ADT was 47 %.

## Duration of Androgen Suppression

The symptoms described above are associated with androgen suppression, the duration of which is dependent on patient age, baseline testosterone level, and length of ADT [80–84]. After cessation of ADT, testosterone recovery takes longer in patients receiving long-term compared to short-term ADT. Yoon et al. conducted a prospective study of patients who received prostatic bed EBRT with 2 years of ADT and found that testosterone recovery to baseline levels occurred at a median of 22 months [84]. By 36 months after cessation of ADT, 93 % of patients were able to recover to non-castrate testosterone levels, including 72 % who recovered to baseline testosterone levels. Testosterone recovery depended on patient age. For men more than 60 years old, cumulative incidence of testosterone recovery was 66 % and median time to recovery 28 months; for those younger than 60, it was 86 % and 16 months. Other studies had similar findings [80–83].

## Summary

For patients with high-risk, locally advanced, and recurrent prostate cancer, external beam radiation therapy with androgen deprivation therapy is a well-established treatment regimen with disease control and survival benefits demonstrated consistently through numerous randomized trials. This is perhaps the most well-studied group of prostate cancer patients with prospective trials. Currently unanswered questions include whether patient comorbidities nullify the potential benefit of ADT in certain subgroups, whether the addition of ADT to adjuvant radiation therapy improves outcomes in patients with adverse features on surgical pathology, and whether early salvage radiation therapy is as good as adjuvant treatment. These subjects require further study.

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# Watchful Waiting in Advanced Prostate Cancer

72

Maria Carmen Mir and Nathan Lawrentschuk

Prostate cancer (PCa) is the most common type of cancer found in American and European men, other than skin cancer. The American Cancer Society estimates that 217,730 incident cases will be diagnosed in 2010, and 32,050 will die from PCa [1].

PCa is the second leading cause of cancer death in men (lung cancer being the first). One man in six will get PCa during his lifetime, while 1 man in 36 will die of this disease. PCa mortality has been declining steadily over the last two decades, which may be attributed to multiple reasons, including advances in treatment and early detection of the disease [2, 3].

## Background to Watchful Waiting

According to the Surveillance, Epidemiology and End Results (SEER) database of the US National Cancer Institute, the median age at diagnosis of PCa is 68 years, and 72 % of deaths due to PCa occur in men aged over 75 years [4]. With the exponential aging of the population and the increasing life expectancy, the burden due to PCa is expected to increase dramatically in the future. An ongoing debate surrounds the optimal treatment for men diagnosed with PCa, both in early disease and in men with advanced disease. The key dilemma for both is the need for aggressive treatment upfront or the option of expectant management with treatment upon progression. Recently, Brasell et al. [5] revealed age over 70 years to be a significant predictor of biochemical recurrence after radical prostatectomy; for the group of 3,650 men evaluated being over 70 showed to have more aggressive parameters in pathological as well as surgical margin status and also higher biochemical recurrence and shorter overall survival rate. For disease in predominantly younger men, the option of active surveillance versus radical treatment exists. Tewari et al. described their experience with robot-assisted minimally invasive radical prostatectomy [6] with excellent results regarding perioperative complications (1.64 %), anastomotic stricture (0.54 %), biochemical failure (4.7 %), and the need for salvage therapy (4.0 %). This makes surgery more attractive, particularly in men with limited comorbidities. Furthermore, Bill-Axelson et al. [7] in an update of their RCT of radical prostatectomy versus WW, a small reduction on risk of death from PCa at 10 years follow-up was demonstrated. As a result, therapeutic approach to PCa has become increasingly complex due to the various therapeutic options available which appear to have equal oncological efficacy but significantly different treatment-related side effects. In more advanced disease in men not considered for radical therapy, the timing of hormonal manipulation, particularly in asymptomatic men without metastases, is debated because of the recognition of side effects related to such treatment. Alternatives such as waiting for a specific PSA level to be reached, treating when symptoms arise before treatment, and/or even aggressive treatment strategies in some cases are still practiced with none having a clear mandate.

The impact of mortality from PCa was documented in a large, population-based study [8]. The probability of death from PCa within 15–20 years of diagnosis depended on the Gleason sum of the cancer and the age of the patient at diagnosis. Patients with a well-differentiated cancer (Gleason sum 2–4) had a low probability of death from cancer within 20 years; high-grade cancers took a substantial toll even among older men. Interestingly, since the time of this study,

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Gleason 2–4 has all but disappeared with us now being left with well-differentiated (Gleason 6), intermediate (Gleason 7), and poorly differentiated (Gleason 8–10) disease. The main reason for the disappearance was the low concordance between biopsy and prostatectomy Gleason scores when low Gleason biopsy were assigned . This stage migration means that we may apply the findings of Gleason 2–4 to Gleason 6 [9, 10]. This change in Gleason classification has led PCa into what is called Will Rogers phenomenon [11, 12]. Albertsen et al. looked at the same cohort of patients prior to changes in Gleason classification, so the same cohort of patients was examined with different criteria, coming to the result that there was an improvement in patient survival as mortality rate decreased by 28 %. The lengthy time between diagnosis and death results in data whereby we base decisions today on what is almost always in less relevant environment due to changes in reporting, disease detected, and the increasing life expectancy of males, all making decisions more difficult. However, data from long-standing studies such as the Baltimore aging study and Connecticut still provide some insights. Further, Ercole et al. in their outcome series on active surveillance found no evidence that a delay in treatment compromised future outcomes on correctly selected patients [8, 13–15].

## Watchful Waiting Versus Active Surveillance

Watchful waiting (WW) is also known as "deferred treatment" or "symptom-guided treatment". WW is an active decision not to treat the patient, who instead is followed closely. The term was firstly used in the pre-PSA screening era (1990s) and referred to as the conservative management of PCa until the development of local or systemic progression, at which point the patient would be treated palliatively with transurethral resection of the prostate (TURP) or other procedures for urinary tract obstruction and hormonal therapy or radiotherapy for the palliation of metastatic lesions [16]. Therefore, the main difference in relation to active surveillance (AS) approach is that the aim of men treated with WW is to avoid treatment as far as possible, so when the treatment is required the only option is palliative, but may extend for many years in the case of those men who do respond to treatments (e.g., hormonal manipulation).

The rationale behind WW is the observation that PCa often progresses slowly and is diagnosed in older men in whom there is a high incidence of comorbidity and related high competitive mortality. This limits treatment time and side effects and hopefully assists in maintaining quality of life. The ability to extend life has never been proven with WW, but it also has never been disproved. Hence, it is important that we do not confuse WW with active surveillance, of which the latter aims to diagnose, observe stringently, and then act with an intention to cure the PCa only when necessary thus avoiding unnecessary morbidity from overtreatment of disease [17].

A distinction also needs to be made between localized, locally advanced, and advanced prostate cancer. Localized is obvious as organ confined; locally advanced in most instances includes extraprostatic extension and/or seminal vesicle involvement, and some include pelvic nodal disease (others argue that it represents more widespread metastatic disease and hence advanced), while most agree that those with metastases have advanced disease. This chapter will focus mostly on the dilemma of curative intent versus expectant management in men with localized or locally advanced disease. Advanced disease is also relevant, but this is more the dilemma of when (or if) to start treatment as opposed to curative intent.

## Data Regarding Watchful Waiting

Literature reports on locally advanced PCa (defined as stage T3–4, Nx–0, M0) and WW are unclear. There are no randomized controlled trials (RCT) comparing active treatment versus deferred treatment. The vast majority of patients that progress after a WW approach on a locally advanced PCa will be candidates for androgen deprivation therapy (ADT).

As stated, the opinion of most urologists regarding ADT has shifted toward a more conservative approach due to negative side effects related to androgen blockade. Nevertheless, two different meta-analyses on early versus deferred androgen suppression in the treatment of advanced PCa conclude that early androgen suppression for treatment of advanced PCa reduces disease progression and complications due to progression. As a result, early ADT may provide a small but significant improvement in overall survival at 10 years [18, 19]. Recently, a prospective randomized clinical phase III trial (EORTC 30891) analyzed immediate versus deferred ADT in patients with PCa not suitable for local treatment with curative intent [20]. Studer et al. randomly divided the population (985 patients with T0–4 N0–2 M0 PCa) into two groups: immediate ADT or receiving ADT only on symptomatic disease progression or occurrence of serious complications. After a median follow-up of 7.8 years, the overall survival hazard ratio was 1.25 (95 % CI: 1.05–1.48) favoring again immediate treatment. However, the median time to start off deferred treatment after study entry was 7 years, and in this group 25 % of patients died without ever needing treatment. The conclusions drawn from this RCT show that immediate ADT resulted in a modest but statistically significant increase in overall survival, but no significant differences in PCa mortality or symptom-free survival were found. Moreover, the authors identified significant risk fac-

tors associated with a significantly worse outcome: in both arms, patients with a baseline PSA > 50 ng/mL were at >3.5-fold higher risk of dying of PCa than patients with baseline PSA less than 8 ng/mL. When PSA was between 8 and 50 ng/mL, the risk of PCa death was approximately 7.5-fold higher in patients with a PSADT <12 months [21]. Practice cannot be based on one study alone, and in our practice each individual must have circumstances weighed up including the side effects of ADT. As such, delayed treatment or ultimately no treatment at all if significant comorbidities exist may be appropriate in many instances.

## Potential Indications for Early Androgen Deprivation Therapy

Currently, we consider a few potential indications to start ADT at first presentation of men with PCa: symptomatic M1, selected asymptomatic M1 (depending on patient characteristics and life expectancy), more than two positive nodes after radical prostatectomy with extended lymphadenectomy [22], in association with curative intent on radiotherapy for intermediate and high risk [23], biochemical recurrence after radical prostatectomy in Gleason >7 or PSADT <12 months [24], locally advanced PCa patients not suitable for curative treatment when PSA > 50 ng/mL or PSA 8–50 ng/mL, and PSADT <12 months [21]. WW for patients with biochemical recurrence is another accepted form of minimizing side effects from ADT or radiotherapy that should be regarded as an option for low-risk patients (Gleason 6 or 7 and/or PSADT >12 months) as shown by Moul et al. [24] since in the overall cohort, early ADT did not show to have an impact on clinical metastases.

To summarize, we can basically define two clinical scenarios where WW in a locally advanced PCa would result in a solid treatment option: (1) an elderly patient without relevant past medical history that incidentally is screened for PCa and has it diagnosed or (2) a younger patient with multiple comorbidities (e.g., multiple cardiovascular or respiratory risk factors, another life-threatening malignancy etc.). Both scenarios are essentially limited by determining life expectancy and health status when taking a therapeutic decision.

## Life Expectancy and Prostate Cancer

Life expectancy is a major determinant of the potential for benefit from therapy beyond palliative care, yet it varies substantially between individuals within a given age group. Life expectancy estimates apply to a population and represent a useful tool for public healthcare but are not valid for a given individual. For example, 75-year-old men are expected to live for a further 8.3 years, but 25 % (the upper quartile) will live for at least 14.2 years, whereas another 25 % (lower quartile) will live for 4.9 years. Thus, although it is not possible to calculate the exact chance of survival for an individual, variables such as the number and severity of comorbidities and the extent of functional impairment can be used to predict the chance of surviving within an age group. As stated by the Connecticut Tumor Registry database analyses, the risk of death from PCa is established by Gleason score at prostate biopsy, facing a 4 % risk of death for Gleason 2–4 and 87 % for Gleason 8–10 within 15 years of diagnosis [13]. Tewari et al. [25] demonstrated that comorbidity evaluated by Charlson Comorbidity Index was the strongest predictor of death from other than PCa in men with localized PCa treated with radical prostatectomy.

Health status influences patient survival and might affect the ability to tolerate treatment-related side effects. As stated by SIOG (International Society of Geriatric Oncology) [26], the most important factors to consider for the evaluation of health status in older men with PCa are comorbidities, dependence status, and nutritional status.

Comorbidity is the major predictor of nonprostate cancer survival [25]. Nowadays, the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) is the best available tool for assessing the risk for death unrelated to PCa. CIRS-G rates not only lethal comorbid conditions (Charlson Comorbidity Index) but also nonlethal.

The level of dependence in daily living activities influences survival in senior adult patients [27]. Dependence can be easily evaluated using the activities of daily living (ADL) and instrumental activities of daily living (IADL) scales. The ADL scale rates a patient's ability to accomplish basic activities of daily living (bathing, dressing, toileting, transferring, continence, feeding). One ADL impairment is considered abnormal in older men with PCa, with the exemption of incontinence. The IADL scale rates activities that require a higher level of cognition and judgment. Four items apply to men with PCa: ability to manage money, to manage medications, to use transportation, and to use the telephone. One ADL impairment is considered abnormal in older men with PCa.

Malnutrition has also been shown to be associated with an increased mortality rate in senior adult patients [28]. Nutritional status can be estimated simply by the variation of weight during the previous 3 months: good nutritional status (<5 % of weight loss), risk of malnutrition (5–10 % of weight loss), and severe malnutrition (>10 % weight loss).

These tools enable older men with PCa to be classified into four health status categories: healthy, vulnerable, frail, and too sick (Fig. 72.1).

In summary, the decision-making is based on the evaluation of the competition between the risk of dying from PCa and the risk of dying from health status impairment.

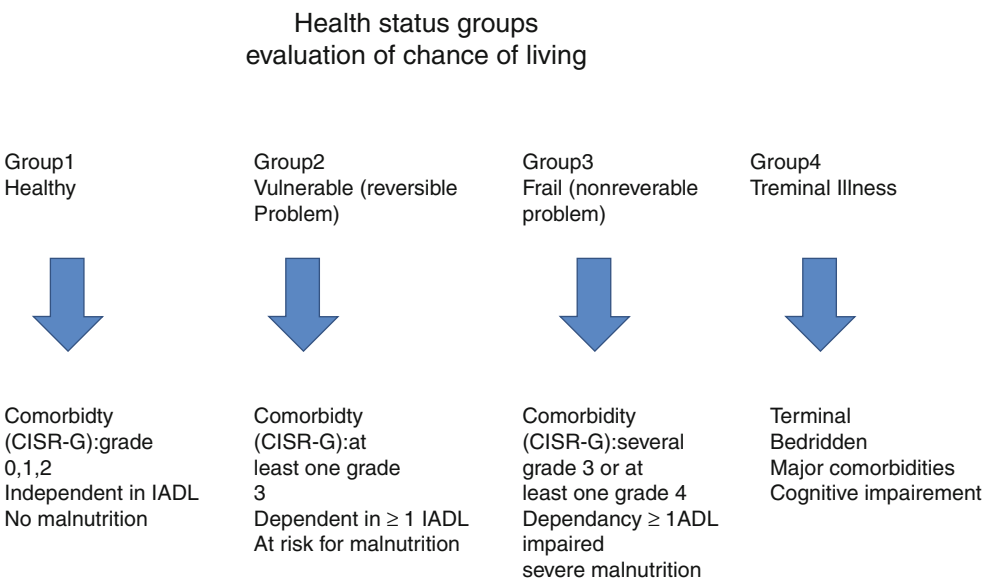


**Fig. 72.1** Health status groups (According to SIOG guidelines Droz et al. [26])

## Health-Related Quality of Life Effects and Prostate Cancer

Another item to take into consideration when discussing treatment options with PCa patient in this scenario is health-related quality of life effects (HRQOL). HRQOL has gained importance since survival of patients diagnosed with PCa has increased due to early detection. There has been a concern that the quality of life (QOL) of the patients is affected by the knowledge of living with an untreated tumor. However, in the studies published on this topic, the views differ radically. Schapira et al. [29] found no change in the QOL in patients on WW, whereas patients under curative intent (radical prostatectomy/radiotherapy) had significant symptoms affecting their QOL. A potential deficiency of this study was the short follow-up at 12 months. Bacon et al. [30] found that patients who had radical surgery had a better generic quality of life than those managed by radiotherapy, WW, or ADT. Siston et al. [31] stated that among the 98 men with localized prostate cancer, significant disease-specific QOL changes noted at 3 and 12 months included worsening of urinary and sexual function among men treated with radical prostatectomy or radiotherapy and worsening of urinary function among those who opted for watchful waiting.

Steninga et al. [32] were assessing psychological and decision-related distress after the diagnosis of localized prostate cancer. Authors found no change in overall QOL for WW, while those treated actively had problems with sexual, bowel, and urinary function. Even though no change was found on QOL, a consistent finding was that those who had problems deciding on treatment had worse QOL. Same findings for Steginga et al. [32] Katz et al. [33] with decline on QOL for patients treated with curative treatment versus WW. Hoffman et al. [34] found that aggressive treatment was associated with significant decreases in disease-specific HRQOL due to urinary and sexual problems. However, men who were aggressively treated for localized cancer had a minimally reduced absolute risk of dying from prostate cancer. There is one RCT on HRQOL comparing radical prostatectomy versus WW [35]; Steineck et al. found differences in symptoms (erectile dysfunction, urinary leakage, urinary obstruction), but no differences were described in overall QOL at 4 years follow-up. Subsequently, Johansson et al. [36] published an update on this RCT stating that anxiety and depressed mood were less common, and sense of well-being and self-assessed QOL were better throughout in the radical prostatectomy group than in the WW group. As the number of physical symptoms increased, all psychological variables became worse and more prominent in the WW group. After a follow-up time of 6–8 years, a significant decrease in quality of life ($p=0.03$) was seen in the WW group. So, adverse effects of WW take longer time to develop but reach the same level as of radical prostatectomy.

Alternately, Arredondo et al. [37] reported the HRQOL outcomes in men with PCa who were enrolled in the CaPSURE (Cancer of the Prostate Strategic Urological Research Endeavor health survey) registry and selected WW. Authors concluded that population in this study had better or similar HRQOL outcomes compared to men without PCa at the start of the study, that many of the scores decreased over time, and the physical domain scores as well as sexual function scores decreased more than expected from the aging process alone.

The differences in WW group may be due to different follow-up and higher clinical stage for the Scandinavian group. Thus, patients with early stage PCa who underwent WW had greater declines in general HRQOL and urinary obstruction, more than 5 years after diagnosis, than did

patients who underwent radical prostatectomy. In the basis of these findings, patients on WW may benefit from psychological intervention years after starting surveillance to maintain QOL items [38].

## Consequences of Androgen Deprivation Therapy

Finally, another reason to delay treatment on this pool of patients is the side effects derived from aggressive treatment, either radiotherapy or ADT. Radiotherapy affects erectile function, increases risk of developing secondary malignancies of the rectum and bladder, and causes acute GU and GI toxicity. Potosky et al. [39] compared 5-year outcomes among radical prostatectomy patients versus radiotherapy patients showing a heavy decline in erectile function between 2 and 5 years from treatment probably due to microvessel and neural inflammation over time. In a retrospective study of men undergoing EBRT or RP, the risk of being diagnosed with rectal cancer increases 1.7-fold in comparison with the surgery group [40] and 2.34-fold when bladder cancer was watched [41]. ADT not only shows physical side effects but also HRQOL are declined when using ADT. As described by Johansson et al. [36], 24 % of androgen-deprived patients assigned to WW in the Scandinavian group reported high self-assessed quality of life compared with 60 % in the radical prostatectomy group. Well-known side effects of ADT are divided into two groups: (a) non-life-threatening but bordering, *vasomotor* flushing (in up to 70 % of men under ADT [42]), *erectile dysfunction*, and *gynecomastia* (at complete androgen blockage), and (b) dangerous (should get follow-up), *osteoporosis*, *sarcopenia*, *anemia*, *cardiovascular disease, depression, cognitive disorders, and frailty syndrome*. Regarding recent data on ADT side effects on a review of major adverse effects, Taylor et al. [43] state that men who underwent ADT for PCa have a significantly increased risk of overall fracture of 23 % compared with men who have PCa but do not undergo ADT, a 17 % increase in cardiovascular mortality and 36–49 % increase in incident diabetes. Bone health is now at the forefront of the management of patients with PCa. This has predominantly been driven by our understanding of the side effect of osteoporosis related to ADT but also recognition that bone health in elderly men who may suffer from osteoporosis independent of PCa is a significant issue. This has implications both for ADT and metastatic disease with the increased risk of fractures. There is currently no standard protocol for men undergoing WW, but we recommend exercise, a well-balanced diet as well as calcium and vitamin D supplementation. In an ideal world, all men should undergo bone densitometry prior to WW, but more often this takes place prior to ADT [44] in many institutions depending on availability of resources. Morote et al. described a 42.9 % prevalence of osteoporosis at 2 years ADT and 80.8 % at 10 years of ADT [45]. Shainian et al. demonstrated an increase in the risk of fracture in patients under ADT [46]. Because of that, urological community has started to pay attention into general measures for osteoporosis prevention such as dietary calcium intake, smoking cessation, reducing alcohol intake, or exercise. Further studies reveal the importance of adding bisphosphonates in order to prevent bone loss. Greenspan et al. [47] showed an improvement of bone mineral density on men with PCa and ADT treated with once weekly oral alendronate for 1 year: on the follow-up manuscript, same authors state that second year of alendronate therapy provides additional skeletal benefit, whereas discontinuation results in bone loss and increased bone turnover. Other trials using zoledronic acid show prevention of bone loss in ADT PCa patients [48, 49]. Planas et al. [50] assessed the risk of fracture at femoral neck on ADT PCa patients before starting the treatment and demonstrated a decrease on the risk of fracture at 1 year of alendronate. Nowadays, a new molecule named denosumab is beating the market by showing in recent published data an increase in bone mass in all locations and a decrease in fracture risk [51]. Denosumab directly acts over RANK-L (receptor activator for nuclear factor ligand) blocking its linkage to RANK and stopping the bone turnover cascade.

A higher prevalence of metabolic syndrome in men with PCa undergoing long-term ADT has been observed. Braga-Basaria et al. [52] in 2006 were the first to describe a 50 % prevalence of metabolic syndrome among this population; meanwhile, the prevalence of metabolic syndrome (MS) in general US population was stated in 22–24 % [53]. MS was described in 1988 by Gerald Reaven as X syndrome. MS has received considerable attention in recent years because of its association with increasingly common pathophysiologic states such as heart failure [54], type II diabetes mellitus [55], and erectile dysfunction [56]. MS is considered the main threat for public health in the twenty-first century and is associated with an increased risk of cardiovascular disease irrespective of which MS definition is used. Currently, three definitions for MS have been set (Table 72.1). Traish et al. [57] on its review on MS and erectile dysfunction point the role of androgen deficit on cardiovascular disease. Actually, testosterone therapy has shown to improve lipid profile in men, reduce fat percentage, increase lean muscle mass percentage, lower blood pressure, and decrease fasting glucose levels, all of them related with an increase risk of MS. Cardiovascular mortality is the first cause of death in PCa under ADT [58, 59].

## Other Considerations

It is important to note that it is becoming a standard of care to discuss patients' treatment and options in multidisciplinary meetings. Thus, some men may be appropriate to have curative

**Table 72.1** Metabolic syndrome definitions

| | WHO | NCEP-ATP III | IDF |
|---|---|---|---|
| Required for diagnosis: | Criterion 1 plus 2 of the other 4 | ≥3 of 5 criteria | Criterion 2 plus 2 of the other 4 |
| 1. Hyperinsulinemia, hyperglycemia | FBS ≥ 110 mg/dL (≥6.1 nmol/L), insulin elevation, or IR or DM2 | FBS ≥110 mg/dL (≥6.1 nmol/L) or DM2 | FBS ≥ 100 mg/dL or DM2 |
| 2. Increased body size | WHR > 0.9, WC ≥ 94 cm, BMI ≥30.0 | WC ≥ 102 cm | WC ≥ 94 cm |
| 3. Triglycerides | ≥150 mg/dL (≥2.3 mmol/L) combined with HDL | ≥150 mg/dL (≥2.3 mmol/L) | ≥150 mg/dL (≥2.3 mmol/L) |
| 4. HDL cholesterol | >35 mg/dL (>0.9 mmol/L) | >40 mg/dL (>1.03 mmol/L) | >40 mg/dL (>1.03 mmol/L) |
| 5. BP | ≥140/90 mmHg or HTN on Rx | Systolic BP ≥130 mmHg, diastolic BP ≥85 mmHg, or HTN on Rx | Systolic BP ≥130 mmHg, diastolic BP ≥85 mmHg, or HTN on Rx |

WHO: World Health Organization (2002), NCEP-ATP III: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001). (Adult treatment panel III), IDF: International Diabetes Federation (2007)
*BMI* body mass index, *BP* blood pressure, *FBS* fasting blood sugar, *HDL* high-density lipoprotein, *HTN* hypertension, *IR* insulin resistance, *Rx* prescription, *DM2* diabetes mellitus type 2, *WC* waist circumference, *WHR* waist-hip ratio

treatment when all factors are balanced. Locally advanced patients may also appropriately receive combined therapy with androgen blockade and radiation where benefit may occur. Finally, advanced patients may ultimately require radiation to bony disease and eventually newer agents and chemotherapy upon progression. Such subtleties are ripe for discussion, but the overall thrust remains that a balance between factors in each case is the key. When cure is enacted or radiation early on, the patient is not really having WW, and thus the discussions of such matter have been limited in this chapter.

### Conclusions

To conclude, the WW approach on locally advanced PCa patients remains a treatment option for selected patients with short life expectancy and asymptomatic well-differentiated tumors. Exact parameters are difficult to glean from the literature were randomized trials are lacking. However, the literature provides some guidance whereby those men with a PSA < 50 ng/mL and PSADT > 12 months would appear more suitable. The concept that no active treatment equals shorter cancer-specific survival is probably irrelevant as most of our patients are elderly and with comorbidities, so aggressive treatment does not necessarily imply a positive outcome. Individualized treatment remains the key, and as such, patient age, comorbidities, life expectancy, and desire for treatment, disease type, and tempo as well as an understanding of the side effects of treatment all deserve equal weighting for decisions made.

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# Androgen and Androgen Receptor-Directed Therapy as Initial Treatment for Prostate Cancer

73

Bruce Montgomery and Peter S. Nelson

## Introduction

Androgenic hormones are critical for the normal development of the prostate gland, and they influence signaling cascades that regulate the proliferation, survival, and secretory activity of prostate epithelium at maturity. The primacy of androgens in maintaining normal prostate function led Huggins and Hodges to exploit androgen suppression for the treatment of prostate cancer [1]. Androgen deprivation therapy (ADT) is defined by an effective block of androgenic ligand-mediated androgen receptor (AR) activation, either through suppression of androgen production or by pharmacological agents that interfere with receptor-ligand interactions. Many variations on this theme have been explored, but the standard approach remains suppression of testosterone production by the testes. Although the effectiveness of ADT in suppressing androgen-regulated processes such as the secretion of prostate-specific antigen (PSA) approaches 100 % in men with prostate cancer, its ability to improve both duration of survival and quality of life is influenced by disease stage and the ability of some tumors to adapt to low levels of serum androgens. Recent developments in studies of ADT have been marked by the recognition that the benefits do not always outweigh the side effects, and the all too frequent escape from androgen deprivation may in many cases be mediated by tumoral upregulation of either ligand and/or receptor. This chapter will review developments in the history of ADT, the data supporting its use in specific clinical settings, and new approaches which are attempting to offset toxicities of therapy.

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## Molecular Endocrinology of Prostate Cancer

Androgens are steroidal hormones required for development of the male reproductive system and secondary sexual characteristics. Androgens are defined by their ability to activate the AR, and in the normal male, the principal androgens made by the testis are testosterone and dihydrotestosterone (DHT). Over 90 % of circulating testosterone is synthesized in the testis, while 25–35 % of DHT is of testicular origin and the other 65–75 % derives from metabolism of testosterone in peripheral tissues, including the prostate gland, by 5α-reductase action. The potency of DHT ranges from 2- to 10-fold that of testosterone depending on whether potency is measured as an effect on tissue growth or transcription from the androgen receptor. DHT concentrations in prostate tissue are 10–20-fold higher than in serum, and tissue DHT is at least twice as high as tissue testosterone [2, 3]. The activity of type 1 and 2 isoenzymes of 5α-reductase (SRD5A1 and SRD5A2) in the prostate has provided a pharmacologic target for the SRD5A inhibitors finasteride and dutasteride which effectively block conversion to DHT. Testosterone in circulation is bound to sex hormone-binding globulin or albumin except for approximately 1 %, which is free and immediately available for receptor binding. The majority of the other androgens present in serum are 19-carbon steroids produced in the adrenal gland, including dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), androstenedione, and androsterone. These androgens are substantially less potent than testosterone or DHT, but their higher concentrations in serum make them a potentially

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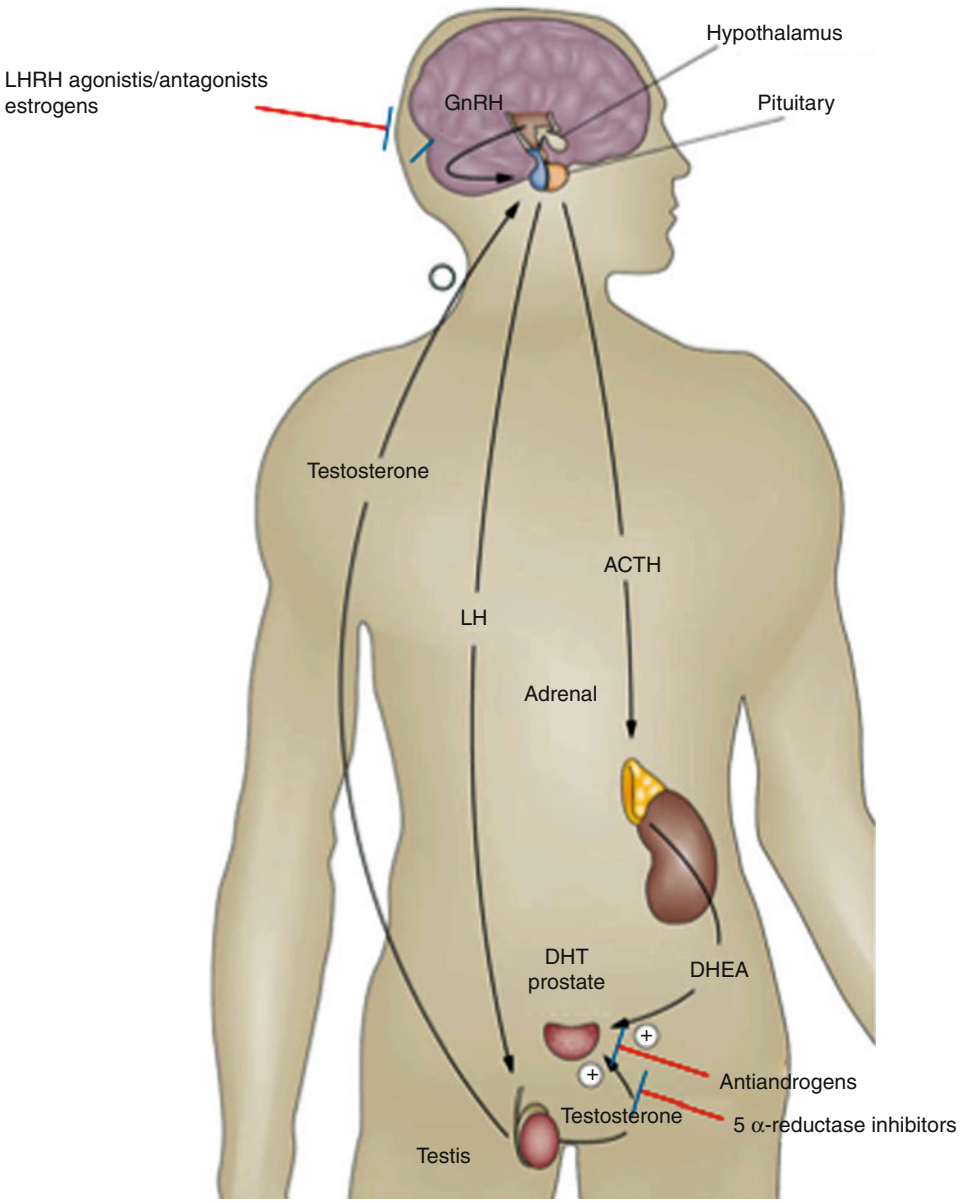


**Fig. 73.1** Hypothalamic-pituitary-gonadal axis and androgen deprivation therapy (*ADT*). The normal physiology of androgen production involves the secretion of gonadotropin-releasing hormone (*GnRH*) from the hypothalamus which stimulates the secretion of the gonadotropin leutinizing hormone (*LH*) from the anterior pituitary. LH stimulates Leydig cell production of testosterone in the testis, which produces trophic effects on prostate epithelium and stroma and also provides feedback inhibition to the hypothalamus/pituitary to maintain serum androgens within a eugonadal range. Approaches for ADT include: LHRH agonists and antagonists designed to suppress gonadotropin stimulation of testicular androgen production; direct competitive blockade of the androgen receptor (*AR*) with antiandrogens; and suppression of the potent androgen DHT by inhibition of 5-alpha-reductase activity within the prostate

important reservoir for conversion to more potent androgens. Synthesis of all steroidal hormones proceeds through metabolism of cholesterol in the endocrine organs of testis and adrenal gland (and ovary in women), with the skin and prostate participating in the peripheral conversion of testosterone to DHT (Fig. 73.1). The majority of circulating testosterone is produced through initial metabolism of progestins to DHEA by CYP17A1, followed by conversion to testosterone. Another potentially important "backdoor" pathway has also been defined, in which progestins are first metabolized by 5α-reductase, followed by CYP17A1, providing a direct path to DHT without the intermediate conversion from testosterone [4]. Import of these androgens into the prostate and prostate cancer has been thought to occur through passive diffusion into tissue where conversion to DHT then occurs. The regulation of androgen production and secretion originates in the hypothalamic-pituitary axis. Recent work has described a class of pituitary peptides called kisspeptins which bind to the GPR54 receptor expressed on gonadotropin/luteinizing hormone-releasing hormone (GnRH/LHRH) neurons in the hypothalamus. Release of LHRH stimulates release of luteinizing hormone (LH) from the pituitary with subsequent end-organ effects on Leydig cells in the testis, initiating the cascade of metabolism of cholesterol to testosterone. The pituitary also secretes adrenocorticotropic hormone (ACTH), which regulates synthesis of glucocorticoids, mineralocorticoids, and androgens in the adrenal cortex.

Androgens function through their action on the androgen receptor (AR), a member of the steroid hormone receptor family of nuclear transcription factors. Compared with testosterone, DHT binds the AR in a more stable manner, leading to a five- to ten-fold increase in transcriptional activation,

which makes DHT the primary ligand and effector of AR-mediated signaling at the level of the prostate epithelial cell [5]. The AR resides in the cytoplasm, bound to heat shock proteins, which stabilizes the AR and allows androgen binding. Upon ligand interaction, the AR homodimerizes, undergoing phosphorylation and translocation to the nucleus, where it interacts with androgen response elements (AREs) to modulate the transcription of target genes involved in cell cycle regulation, survival, protease (e.g., PSA) secretion, and other functions.

Depriving prostate cancer cells of androgen initiates a cascade of events that includes the induction of apoptosis, cell cycle arrest, and glandular involution, all of which provide potential therapeutic benefits. Early events after androgen withdrawal (days 0–3) include downregulation of the AR and expression of the negative cell cycle regulators p21 and p27. Studies of ADT in prostate cancer xenografts found that proliferation rate, as measured by Ki67, begins to decrease at day 3, with an associated increase in cell cycle arrest. Apoptosis in response to androgen withdrawal ranges from 0 to 20 % within the first 7 days after androgen deprivation depending on the method of assay and the tissue evaluated [6, 7]. Apoptosis after ADT in men treated with castration increases within the first 24 h, with a maximum effect (2.5–3 % apoptosis) at 3–4 days with subsequent declines in the numbers of apoptotic cells to baseline over the following week [8, 9].

The application of "hormone therapy" to treat prostate cancer involves approaches that target the production of gonadal androgens or the blockade of interactions between androgenic ligands and the AR. While surgical removal of the testis was used initially as an effective method to eliminate gonadal sources of androgens, the development of luteinizing hormone-releasing hormone (LHRH) agonists, or more recently LHRH antagonists, has largely replaced orchiectomy as the most widely used method to achieve low serum levels of androgens. Normally, free testosterone enters prostate cancer cells by diffusion, with subsequent metabolism by 5α-reductases to dihydrotestosterone (DHT). The suppression of testicular androgen production to achieve "castrate" serum testosterone concentrations produces substantial tumor responses in most men with prostate cancer, followed by subsequent tumor progression after several years. In this disease sequence, once cancer growth has resumed despite adequate suppression of testicular androgens, prostate cancers have been categorized as "hormone independent" or "androgen independent." However, many lines of preclinical and clinical data support the concept that AR signaling continues to play a role in driving progressive prostate cancer growth. Thus, a more appropriate term for this disease state is *castration-resistant prostate cancer* (CRPC), a descriptor that though accurate does not define the mechanism(s) contributing to growth in the absence of serum testosterone. Importantly, studies from several groups have shown that "hormone-independent" primary prostate cancers actually contain physiologic levels of testosterone [10], and metastatic CRPC contains higher levels of testosterone than untreated primary cancers [11]. Levels of the AR increase in prostate cancer cells upon their transition to CRPC, and deletion of the ligand-binding domain abrogates the ability of overexpressed receptor to transform cells, suggesting the continued importance of receptor-ligand interactions in maintaining tumor survival and growth [12]. Recently, new agents targeting the AR signaling axis in CRPC have shown substantial clinical benefit, both in phase II and phase III studies [13, 14]. Collectively, these results provide strong support for the continued focus on the AR axis as an important therapeutic target in prostate cancers that progress despite suppression of circulating androgens (Fig. 73.2).

## Clinical Studies Targeting Androgens and the Androgen Receptor for Prostate Cancer Therapy

Huggins and Hodges took note of the observations made by other investigators that orchiectomy in prepubertal males prevented the development of the prostate gland and that castration of adult males reduced prostate size and caused epithelial atrophy. They also noted that in dogs, prostatic hyperplasia was most commonly present in those animals with hyperactive testicular tumors, and both orchiectomy and estrogens reversed this hyperplastic growth [15]. They extrapolated the potential impact of those findings to prostate cancer, presuming the tumor to be derived from prostate epithelium, and suggested that these malignancies might also regress in response to orchiectomy [1]. Their original observation that orchiectomy resulted in "improvement greater than we have observed in any case in which far advanced or metastatic cancer was treated in any other way" led to the current standard of care treatment for metastatic prostate cancer. The nearly universal clinical efficacy of androgen suppression, characterized by PSA declines and improvements in symptoms in 80–90 % of patients, is unique in clinical oncology and provides the most compelling evidence that androgens and particularly testosterone and dihydrotestosterone are critical for the growth and proliferation of prostate cancer.

*Orchiectomy*: Many approaches have been evaluated for their effectiveness in inhibiting AR signaling in the clinical setting (Table 73.1). The earliest treatment explored by Huggins and Hodges was orchiectomy, which remains the gold standard for efficacy. For many years, the maximal effect of this therapy has been the ability to achieve and maintain anorchid or "castrate" levels of testosterone

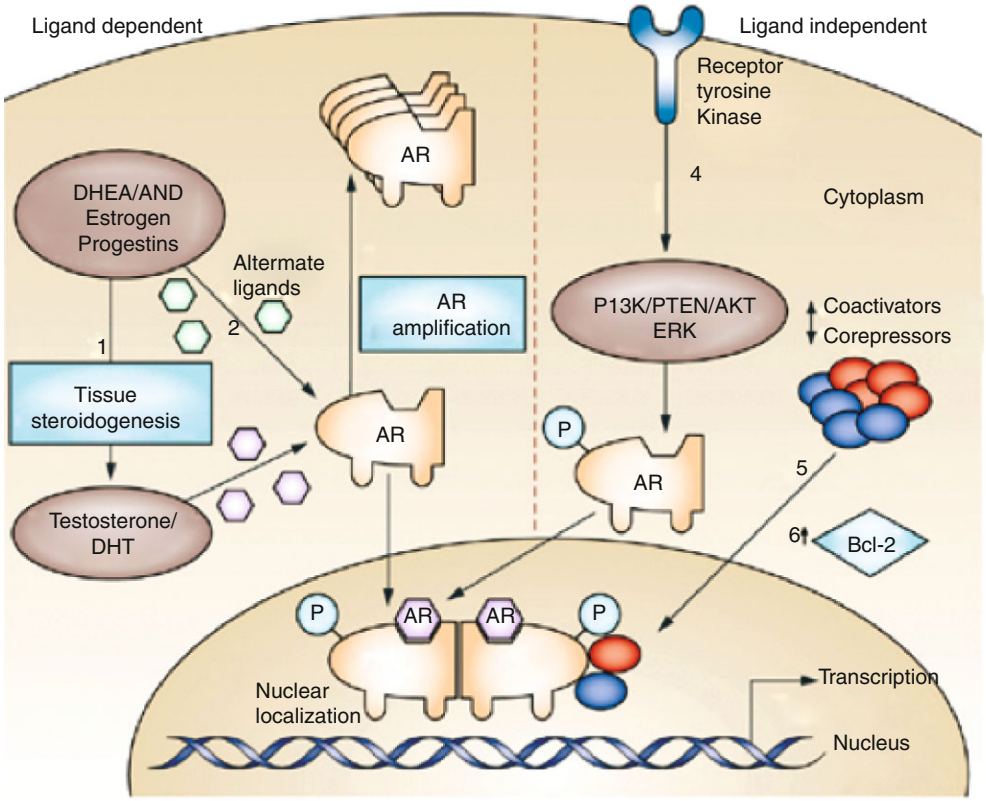


**Fig. 73.2** Androgen receptor signaling. The androgen receptor (*AR*) is activated through the binding of ligands, such as testosterone (*T*) generated by the testis [1]. In specialized tissues such as the prostate, testosterone is converted to the more potent androgen DHT by 5-alpha-reductases. Engagement of the AR C-terminal ligand binding domain by T or DHT induces a conformation shift with attendant transport to the nucleus, and subsequent recognition and binding to specific DNA sequences termed androgen response elements (*AREs*). AR binding to these DNA regions prompts the assembly of a complex of co-activator proteins leading to the transcription of messenger RNAs that encode androgen regulated proteins such as PSA. In prostate cancer cells, several mechanisms have been demonstrated to activate AR signaling in the setting of absent or low serum androgen levels. These include: (*1*) tissue steroidogenesis; (*2*) use of alternative ligands such as estrogen; (*3*) AR amplification; (*4*) cross-talk with other growth factor pathways; (*5*) changes in coactivator activity; and (*6*) alterations in cell death programs [68]

**Table 73.1** Mode of androgen deprivation

| | Class | Examples | Dosing |
|---|---|---|---|
| Hormonal suppression | LHRH agonists | Leuprolide | 7.5 mg IM/SC monthly, 22.5 mg IM/SC every 3 months |
| | LHRH antagonists | Degarelix | 240 mg once, and then 80 mg monthly 28 days later |
| | Estrogens | Transdermal estradiol | 0.6–0.8 mg topically every 24 h |
| | | Diethylstilbestrol | 1–5 mg PO daily |
| | CYP inhibitors | Ketoconazole | 200–400 mg PO TID (with steroids) |
| | 5-alpha-reductase inhibitor | Dutasteride | 0.5 mg PO daily |
| | Intermittent vs. continuous | | See text |
| Androgen receptor antagonism | Nonsteroidal | Flutamide | 250 mg PO TID |
| | | Bicalutamide | 50 mg PO daily |
| | | Bicalutamide (high dose) | 150 mg PO daily |
| | | Nilutamide | 300 mg PO daily for 30 days then 150 mg daily |
| | Steroidal | Cyproterone | |

(≤20–50 ng/dL). Residual levels of testosterone above zero were presumed to be derived from alternative sources such as the adrenal gland. These very low serum androgen concentrations have been the de facto benchmark reflecting effective endocrine therapy, as these levels reflect the complete removal or functional ablation of the most prominent source of prostate cancer growth-promoting factors. No other approaches have yet been shown to have greater

clinical benefit through more effective suppression of serum androgens. However, the definition of adequate suppression has been a topic of discussion, as has the relevance of these residual low levels of circulating androgens in contributing to prostate cancer progression.

*Estrogens*: The use of the synthetic estrogens diethylstilbestrol (DES) and stilbestrol for the treatment of prostate cancer was pioneered by Huggins and Hodges, who showed that the use of estrogen suppressed serum tumor marker values as effectively as orchiectomy [16]. Estrogens may suppress tumor growth by multiple mechanisms, but the best defined is the feedback inhibition of LHRH and LH release, with subsequent suppression of testosterone. The ease of oral use of DES and apparent equivalence to orchiectomy led to multiple studies carried out through the VA Cooperative Urologic Research Group and others. These studies established that DES given at a dose (3 mg or higher) which reproducibly suppressed testosterone into the anorchid range provided equivalent or better cancer control compared to orchiectomy but at a significantly higher risk of cardiovascular toxicity [17]. Multiple studies attempting to offset cardiovascular toxicity have shown that aspirin and low-dose warfarin cannot prevent these complications [18]. In addition, the use of estrogens is associated with a high rate of gynecomastia and mastodynia, requiring intervention in the form of other drugs or breast irradiation. The advent of LHRH agonists and legal issues related to carcinogenic effects of DES led to suspension of commercial production. However, DES continues to be prescribed through compounding pharmacies in the United States. It was recognized that the use of estrogens had potential advantages with regard to maintenance of bone density, cognitive function, and other metabolic parameters. This led to more recent studies in men with hormone-naïve and castration-resistant disease using transdermal formulations which allow bypass of the enterohepatic circulation, with less induction of coagulation factors, potentially offsetting the cardiovascular toxicities seen with oral estrogens. A series of studies described the results of a phase I study carried out in the United Kingdom using transdermal estradiol patches, suggesting feasibility of the approach and improvements in bone density [19–21]. Other studies in men with CRPC demonstrated a definable but low response rate to secondary estradiol and improvements in cognition in men treated with transdermal estradiol [22].

*LHRH Agonists*: The molecular endocrinology of prostate cancer indicated that methods to suppress the production of pituitary LH would result in suppression of circulating testosterone, effectively providing a means of chemical orchiectomy. Extensive efforts focused on defining the optimal analogs with long half-life and ease of administration, and the resulting clinically useful agents centered on compounds with luteinizing hormone-releasing hormone (LHRH) agonist activity [23–25]. LHRH agonists bind to LHRH receptors in the pituitary and cause a transient surge in release of LH, followed by a testosterone "surge" or flare. The continuous release of LHRH agonist from the various depot formulations available ultimately causes downregulation of LHRH receptors, decrease of LH release, and testosterone declines to castrate levels over the ensuing 14–30 days. With continued therapy, testosterone levels remain in the anorchid range indefinitely.

The registration studies for agents which suppress testosterone including the various classes of LHRH agonists (goserelin, leuprolide, triptorelin, historelin) and LHRH antagonists have documented that 94–97 % of patients have anorchid serum levels by day 28 and that the remainder achieved and maintained those levels by day 42. The majority of the studies followed serum concentrations for at least 1 year and reported that no patients subsequently showed escape of androgen suppression. However, there have been case reports of patients in whom LHRH agonists did not achieve and maintain anorchid serum levels in some cases, suggesting that up to 5 % of patients will have levels above 50 ng/dL during the course of treatment [26]. Reasons for this escape remain uncertain, although there are patients with LH-secreting pituitary adenomas and testosterone-secreting adrenal tumors. LHRH agonists suppress testosterone less effectively in obese patients, with total and free testosterone at 48 weeks after initiation of therapy which are 1.8- and 2.3-fold higher than normal weight patients [27]. Despite higher levels, all patients achieved and maintained total testosterone levels less than 20 ng/dL. When LHRH agonists do achieve anorchid testosterone levels, orchiectomy remains the treatment option of choice.

*Androgen Receptor Antagonists*: Targeting the androgen receptor with the use of steroidal and nonsteroidal androgen receptor antagonists, commonly known as antiandrogens, is an attractive approach, which was developed contemporaneously with LHRH agonists. The majority of these agents competitively inhibit the binding of androgens to the ligand-binding domain (C-terminus) of the androgen receptor, thereby suppressing activation of the receptor. Antiandrogens have the advantage of oral administration and maintenance of serum testosterone and estradiol, which may offset some of the side effects of androgen suppression. The most commonly prescribed agents are the nonsteroidal antiandrogens, including flutamide and bicalutamide, with nilutamide often reserved for the treatment of castration-resistant disease. Side effects more common with antiandrogens compared to orchiectomy or LHRH agonists include mastodynia and gynecomastia which are a result of unopposed stimulation of the estrogen receptor and hepatotoxicity. Both flutamide and nilutamide are associated with a higher incidence of gastrointestinal side effects, and nilutamide causes changes in color vision and accommodation to light changes and has been reported to cause interstitial pneumonitis. Steroidal

antiandrogens include cyproterone acetate, a derivative of 17-hydroxyprogesterone. Cyproterone has a number of effects independent of AR blockade, including progestational and glucocorticoid activity, with hepatotoxicity being the main side effect seen in clinical studies. Cyproterone has been used alone and in combination with LHRH agonists in randomized studies, with cyproterone alone providing equivalent survival to diethylstilbestrol and flutamide in patients with metastatic disease [28, 29], although time to progression was inferior to LHRH agonist alone in another study [30]. Cyproterone acetate continues to be used as a component of combined blockade in randomized studies of neoadjuvant therapy with prostatectomy and intermittent versus continuous therapy [31, 32]. The use of antiandrogens at standard doses as monotherapy has been shown to be inferior to orchiectomy or LHRH agonists in randomized studies in men with locally advanced or metastatic prostate cancer [33]. The use of high-dose bicalutamide at 150 mg daily has been used as part of the Early Prostate Cancer trial as well as other studies with mixed results. In patients with metastatic disease, survival with the 150 mg dose was inferior to standard therapy [34]. Studies using this dose in earlier stage disease have compared bicalutamide 150 mg to standard androgen deprivation or to placebo and have shown equivalence in locally advanced cancers [35, 36]. The insights gained into mechanisms of resistance to standard forms of androgen deprivation have provided critical information about why both androgen suppression and antiandrogens have not provided better cancer control. Upregulation of tissue androgens occurs in a significant proportion of tumors as resistance develops and would be anticipated to circumvent antiandrogen effects when androgen levels are high [11]. Upregulation of full-length androgen receptor levels also occurs as an adaptation to androgen suppression, and the generation of androgen receptor variants which do not contain the ligand-binding domain could also limit antiandrogen efficacy [12, 37–39].

The concept of combining antiandrogens with orchiectomy or LHRH agonists has been explored as a strategy to improve the effectiveness of AR pathway blockade [40], and the rationale to suppress androgen production by the testis and to block the androgen receptor concurrently has had a long and controversial history. Complete elimination of testicular sources of androgen by orchiectomy does not achieve zero levels of serum testosterone primarily because of production from the adrenal gland, and the residual levels of both tissue and serum testosterone are well within a range capable of activating the androgen receptor in the laboratory [2, 10, 41]. Though conceptually sound, demonstrating clinical benefit has been more elusive. The proponents of combined blockade suggested that the addition of an AR antagonist provided apparent improvements in clinical outcomes in patients with advanced prostate cancer [42]. Numerous phase III randomized clinical trials have been published or presented with conflicting conclusions [43, 44]. The most widely accepted meta-analyses that assess the outcomes of these trials have shown that the addition of an antiandrogen to LHRH agonist or orchiectomy in men with metastatic prostate cancer provides a statistically marginal overall survival benefit of between 2 and 5 % [45]. As a result of this small overall demonstrable benefit, coupled with the potential for side effects, the standard of care has been monotherapy with orchiectomy or LHRH agonist alone. The reasons for the failure of combined blockade to provide a greater benefit are uncertain. One of the primary tenets of combined therapy was that androgen deprivation by orchiectomy or LHRH antagonism suppressed tumor androgens to quite low levels, and an antiandrogen would have to antagonize a very limited level of tissue testosterone. However, the historical and more recent intratumoral androgen measurements have shown that tissue testosterone levels may be nearly equivalent to those found in men with an intact gonadal axis. In this setting, the lack of greater efficacy of clinically approved antiandrogens, which typically have affinities for the androgen receptor at least tenfold lower than the natural ligand, could simply be due to their overall limited ability to block ligand-receptor interactions. Further, several of these antagonists can exhibit agonist function in the setting of an amplified AR, a characteristic specifically avoided in the development of newer agents currently undergoing clinical evaluation.

## Current Clinical Approaches to Androgen Deprivation

Initial therapy for patients may include orchiectomy, LHRH agonist, LHRH antagonist, antiandrogens, and much less commonly estrogens, ketoconazole, or combinations of these agents. Although androgen deprivation is the most widely used systemic therapy for prostate cancer, there are a limited number of settings in which its use is supported by randomized studies.

*Indications*: The use of standard forms of androgen deprivation (orchiectomy or LHRH agonists) is supported by randomized studies for men with newly diagnosed metastatic and locally advanced prostate cancer, settings in which androgen deprivation prolongs overall survival, produces an objective response in bone and soft tissue metastatic disease and relieves bone pain, and prevents complications of disease [46]. While initial response to therapy is common, ADT in metastatic disease is considered palliative. The duration of ADT responses vary, with 5–10 % of patients remaining alive 10 years after initiating androgen deprivation [47], though the median response is between 18 and 36 months [48]. Often, the first indication of ADT failure is a rise in serum PSA concentrations, followed by symptomatic or radiographic progression.

Multiple randomized trials provide evidence of benefit for androgen deprivation with definitive radiation therapy in men with locally advanced or high-grade disease. The majority of studies have shown significant improvements in long-term local, distant, and biochemical control, with improvement in overall survival in the majority of studies using long-term ADT [49–51]. Adjuvant androgen deprivation improves overall survival in men with nodal metastasis found at prostatectomy. A randomized, multi-institutional study of immediate long-term ADT versus deferred hormonal therapy for men with nodal metastasis found at radical prostatectomy demonstrated improved overall survival, cancer-specific survival, and progression-free survival, compared with deferred hormonal therapy with a difference in median survival of almost 2 years [52, 53].

*Methods of Suppressing AR Activity*: The history of orchiectomy, LHRH agonists, and combined blockade has been reviewed in some detail, and the use of these approaches in the clinic varies, depending on the clinician and the country. Orchiectomy has been the gold standard for adequate suppression of testosterone, but in the USA, this procedure is used rarely except when compliance, cost, or impending cord compression are the primary issues. The more widely used LHRH agonists rely on downregulation of LHRH receptors, and there is a transient increase of LH and testosterone that follows initiation of LHRH agonists. The need to block this testosterone surge or flare is dictated by the clinical status of the patient. Patients with evidence of significant urinary obstructive symptoms, cord compression, or bulk disease which might cause significant organ dysfunction or pain if there were any additional growth require rapid inhibition of ligand-receptor interaction. The most rapid achievement to anorchid serum levels is provided by orchiectomy (3–12 h), LHRH antagonists (>90 % of patients by day 3), or high-dose ketoconazole [54, 55]. Alternative approaches include addition of antiandrogens before or concurrent with LHRH agonists. Several small studies have used this approach, and a large randomized study of monotherapy compared to combined blockade initiated synchronously showed improvement in pain control in patients on combined blockade compared to monotherapy, suggesting that concurrent initiation of combined blockade may be adequate [43]. The increase in testosterone after initiation of LHRH agonist occurs at approximately 48 h and then returns to baseline or below by day 8, which informs the duration of treatment with antiandrogen. LHRH agonists provide similar response and survival to orchiectomy as supported by multiple randomized studies and meta-analyses [17].

The use of LHRH antagonists circumvents the LH and testosterone surge which the agonists induce. Two agents, abarelix and degarelix, have been FDA approved for the treatment of prostate cancer, although abarelix is no longer commercially available. In randomized studies, the use of degarelix with a loading dose followed by various doses used as maintenance showed continued testosterone suppression equivalent to leuprolide (96–98 % maintenance of anorchid levels) [56]. LHRH antagonists offer an alternative initial approach for patients with impending complications from prostate cancer. The advantages of the immediate suppression of testosterone for longer-term control of cancer are uncertain. Preclinical studies suggested that degarelix and castration provided better tumor control than LHRH agonists in animal models [57], but data from clinical trials are not yet available to support or refute this potential advantage.

Alternatives to the standard androgen deprivation strategies described above have been developed with the objectives of reducing toxicity and potentially circumventing mechanisms of resistance to therapy. Strong preclinical data suggested that allowing testosterone recovery after a limited duration of androgen deprivation would prevent the development of resistance by decreasing selection pressure for tumor growth in low-androgen conditions [58]. Early institutional series of this discontinuous approach showed feasibility, and phase III studies have demonstrated equivalence of intermittent androgen suppression (IAS) to standard continuous therapy in men with nonmetastatic cancers. The first reported phase III trial evaluated 766 patients with locally advanced or metastatic prostate cancer who were randomized to IAS or combined androgen blockade showed no difference in overall survival, although there was a trend to earlier progression to CRPC in the intermittent arm [31]. A higher rate of progression to CRPC was offset by a higher rate of nonprostate cancer death in the continuous therapy arm. Two other phase III studies have been reported. A randomized trial of intermittent ADT versus continuous therapy in 335 patients with locally advanced or metastatic prostate cancer demonstrated equivalent survival [59]. The JPR7 study randomized 1,386 men with PSA recurrence after radiation therapy to intermittent androgen suppression with monotherapy during the majority of an 8-month "on-treatment" cycle versus the same regimen as continuous therapy. At a median of 7 years follow-up, median survival reached the threshold for noninferiority [60]. The SWOG 9346 study randomized 3040 patients with newly diagnosed and untreated metastatic prostate cancer to goserelin plus bicalutamide for 7 months, and all patients who achieved a PSA < 4 (1535 eligible patients) were then randomized to intermittent therapy or continuous therapy with combined blockade [69]. The study was designed as a noninferiority trial, with overall survival as the primary endpoint. At the median followup of approximately 9 years, the study failed to meet the prespecified parameters for noninferiority, with median survival of 5.8 months in those patients treated with continuous therapy versus 5.1 months in men treated with intermittent therapy. Based on these results, demonstrating a roughly 10% decrement in survival with the use of intermittent therapy, continuous therapy should be considered the standard approach for patients with newly diagnosed

metastatic disease [69]. Those patients with less responsive disease were not included in the overall survival analysis, and the efficacy of intermittent therapy in these patients is uncertain. The design of IAS studies has varied substantially, for example, employing GnRH agonists with or without a nonsteroidal antiandrogen, on-treatment cycles lasting 3–9 months, and different triggers for initiation of subsequent cycles. Detailed discussion of the modes of intermittent androgen suppression, duration of therapy, and thresholds for reinitiation of treatment is beyond the scope of this chapter but are discussed in detail in several recent reviews [61, 62].

## Toxicities of Androgen Deprivation

Androgen deprivation is associated with a number of adverse effects on quality of life, including sexual dysfunction, muscle atrophy, osteoporosis, hot flashes, fatigue, gynecomastia, anemia, and, in some patients, depression and cognitive dysfunction [63]. These symptoms and side effects mirror those occurring in men with hereditary or acquired hypogonadism without prostate cancer. Recognition that androgen deprivation increases the metabolic syndrome, diabetes, and cardiovascular morbidity and mortality has led to a clearer sense that the benefits and risk of androgen deprivation must be weighed for each individual patient [64, 65]. The approaches for monitoring and treating these side effects are detailed in Chap. 80.

## Prediction of Response and Survival

The ability to predict outcomes for patients initiating ADT is imperfect. Meta-analyses of the multiple randomized studies of ADT for patients with metastatic disease demonstrated a remarkably consistent median survival of 2.5 years for the group as a whole. Many factors have been found to influence response and survival, including Gleason grade, number of bone metastases, presence of visceral metastases, PSA level, pain level, and performance status. The initial report of response data from SWOG 9346, a randomized study of intermittent versus continuous androgen deprivation for patients with metastatic prostate cancer, analyzed multiple pretreatment prognostic factors, as well as PSA nadir during the first treatment cycle [48]. Although the report for the primary endpoint of the study, survival outcomes for intermittent versus continuous therapy, has not been reported, the survival from the eligible patients treated on study demonstrates that patients achieving and maintaining a PSA nadir of 0.2 ng/mL or less at the end of induction had a median survival of 75 months, compared to 44 months with a nadir between 0.2 and 4, and 13 months for patients not reaching a PSA less than 4 ng/mL. Approximately 20 % of patients did not achieve a PSA of 4 during induction. The prognostic factors which predicted for shorter survival within the study group were higher pretreatment PSA, Gleason score 8 or above, presence of visceral or distant nodal metastases, poor performance status, and the presence of bone pain. Improving the ability to anticipate poor outcomes for patients starting androgen deprivation will be critical in order to circumvent the molecular mechanisms of resistance at initiation of therapy rather than after induction.

## Mechanisms of Resistance to "First-Line" Androgen Deprivation Therapies

When progression occurs despite maintenance of anorchid serum androgen levels, the disease has been considered to be "androgen independent" or "hormone refractory." These labels resulted from an assumption that serum and tumoral androgen concentrations are equivalent and that androgen receptor signaling is no longer driving tumor progression in the absence of circulating testosterone. As discussed above, evidence suggests that patients with anorchid serum testosterone concentrations maintain prostatic androgen levels sufficient to support AR signaling and cancer cell survival. Early reports demonstrated that in patients with localized prostate cancer, orchiectomy or medical castration suppressed intraprostatic DHT levels by only 75–80 %, leaving tissue DHT levels well within a range anticipated to activate the androgen receptor [66]. Analysis of normal prostate tissue from men treated with short-duration androgen deprivation demonstrates that tissue testosterone and DHT levels are reduced by 70–80 % [2]. In patients with established CRPC, prostate tumors contained testosterone levels equivalent to those found in the prostatic tissue of untreated men, with DHT levels decreased to 20 % of those in untreated tissue. Soft tissue metastases in patients with anorchid serum testosterone contain levels of testosterone that are up to three times higher than those in prostate tumors in eugonadal men [11]. Transcript levels of enzymes involved in androgen synthesis were upregulated in the same tumors (8–30-fold), suggesting that tumoral synthesis of androgens from cholesterol might occur. Bone metastases in patients with CRPC also contain intact enzymatic pathways for the conversion of adrenal androgens to DHT [67]. Continued signaling through the AR has been postulated to occur through AR amplification or AR mutation that increases sensitivity to DHT and nonandrogenic steroid molecules or antiandrogens. Other possible AR-dependent mechanisms include activation of the AR or downstream effectors via cross talk with activated tyrosine kinase receptors, such as EGFR, or a change in the balance of coactivators and corepressors. Most proposed mechanisms

implicate increased sensitivity of the AR to low-level androgens, consistent with the finding that, for wild-type AR, the ligand-binding domain is necessary for the development of resistance to castration. Other hypotheses suggest that resistance develops via bypass of intact AR pathways and protection of cells from castration-induced apoptosis through androgen-independent upregulation of antiapoptotic molecules. Many of these potential resistance mechanisms are the focus of ongoing laboratory studies and clinical trials.

## Future Directions

More than 70 years since prostate cancer was found to be remarkably sensitive to circulating concentrations of androgens, suppressing testosterone remains the standard of care for the initial treatment of men with metastatic prostate carcinoma. Pharmacological approaches have largely replaced orchiectomy, and endocrine manipulation is highly effective in reducing testosterone levels in the circulation. Gratifying responses are usually observed, even in the setting of high tumor burden and advanced symptoms. Though responses are sustained for months or years, disease progression is essentially universal. Of great importance is the finding that prostate cancers progressing in the setting of androgen deprivation are still dependent on or sensitive to persistent activity of the AR program. It is likely that greater clinical benefit from combining additional AR-targeted therapeutics such as AR antagonists with androgen suppression has not been realized is due primarily to marginally effective drugs rather than a logical flaw in their application. This conclusion is supported by the recent development and ongoing clinical evaluations of newer, more potent inhibitors of androgen synthesis that target CYP17 and AR antagonists with improved affinity for the AR, without detrimental agonist activity. It is likely that the future use of these agents will employ combination strategies to enhance suppression of AR signaling and reduce drug resistance, and they may find clinical utility earlier in the disease course either as enhanced first-line therapy for advanced disease or as more effective adjuncts to radiation and prostatectomy.

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# Hormone-Based Therapies for Castration-Resistant Prostate Cancer

74

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## Introduction

Androgen deprivation therapy (ADT) remains the primary treatment modality for patients with metastatic prostate cancer (PCa) but is uniformly marked by progression to castration-resistant prostate cancer (CRPC) over a period of about 18 months, with an ensuing median survival of 1–2 years. Continued activation of androgen receptor (AR) signaling despite suppression of circulating testosterone (T) appears to remain a critical driving force in tumor progression [1]. Accumulating data emphasize that "androgen-independent" or "hormone-refractory" tumors retain a clinically relevant degree of hormone sensitivity and highlight the continued importance of AR axis activity in advanced tumors [2]. Accordingly, therapeutic strategies designed to more effectively ablate androgen signaling are required to improve clinical efficacy and prevent disease progression. Herein, we review AR-dependent mechanisms underlying PCa progression following standard androgen deprivation strategies (summarized in Table 74.1) and discuss the rationale and status of new hormone-based therapies targeting the AR axis, which are currently in clinical and preclinical development (summarized in Table 74.2).

## Significance of Intratumoral Androgens in CRPC

Ample evidence demonstrates that castration does not eliminate androgens from the prostate tumor microenvironment, that residual androgen levels are well within the range capable of activating the AR and AR-mediated gene expression [9–12], and that intratumoral androgens are clinically relevant in driving growth of castration-resistant tumors.

## Persistence of Intratumoral Androgens Despite Castration

The efficacy of ADT is routinely based on achieving castrate levels of serum T, defined as <20 ng/dl. However, prostatic tissue androgen levels in the setting of benign prostatic hyperplasia (BPH), locally recurrent PCa, or metastatic CRPC have consistently demonstrated that castration does not eliminate androgens from the prostate tumor microenvironment. Geller et al. examined prostatic DHT levels by radioimmunoassay (RIA) and demonstrate that castration by orchiectomy (or megace plus DES) reduced prostatic DHT levels by 75–80 % to 1 ng/g in some but not all patients, epithelial and stromal cell protein synthesis were strongly correlated with tissue DHT levels, and prostatic DHT levels were further reduced when castration was combined with adrenal androgen blockade by ketoconazole [9, 13–17]. These and other studies led early investigators to conclude that even low amounts of residual DHT may be sufficient to stimulate tumor growth (or at least maintain cell survival) and that the goal of therapy should be to decrease prostatic DHT to as low as possible.

Incomplete suppression of tissue androgens by castration has been confirmed in numerous studies of short- and long-term castration therapy. Treatment of BPH patients for 3 months with an LHRH agonist decreased intraprostatic T levels by 75 % to about 0.1 ng/g and DHT levels by 90 % to 0.48 ng/g [18]. A similar 70–80 % decrease in prostate tissue androgens was reported after 1 month of ADT in normal healthy men [12]. In prostate tumors, 6 months of neoadjuvant ADT with castration and flutamide reduced prostatic DHT levels by 75 % to about 1.35 ng/g [11]. Moreover, tumor differentiation based on Gleason grading was correlated with change in tissue DHT, with an 85 % decrease measured in

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**Table 74.1** Mechanisms of resistance to androgen deprivation therapy

| AR pathway dependence | Alteration | Effect |
|---|---|---|
| AR mediated and ligand dependent | Intracrine androgen synthesis | Utilization of circulating adrenal androgens |
| | | De novo androgen synthesis from cholesterol or progesterone precursors |
| | Expression of steroid transport proteins | Potential for enhanced uptake of circulating T and adrenal androgens |
| | AR amplification | Increased sensitivity to low ligand |
| | AR overexpression | Increased sensitivity to low ligand |
| | AR mutation (LBD) | Altered ligand specificity (e.g., progesterone, adrenal androgens, steroidal antiandrogens) |
| | Altered coregulator recruitment | Stabilization of AR at low ligand levels |
| | | Conversion of AR antagonists to agonist activity |
| AR mediated and ligand independent | AR mutation (NTD) | Coactivator binding and transactivation without requirement for ligand occupancy |
| | AR splicing variants (LBD) | Deletion of LBD with constitutive AR nuclear localization and transactivation |
| | Altered coregulator recruitment | Possible ligand-independent AR transactivation |
| | Activation of AR cross talk pathways | AR transactivation via alternate signal transduction pathways (IGF, EGF, KGF, IL-6, Her2/neu) |
| AR and ligand independent | Activation of AR bypass pathways | Upregulation of antiapoptotic molecules (clusterin, bcl-2, survivin, hsp-27) |
| | | Deregulation of survival pathways (MAPK, PTEN/AKT, Src, Myc) |

*LBD* ligand-binding domain, *NTD* N (amino)-terminal domain

Gleason 6 cancers but only a 60 % decrement in Gleason 7–10 tumors [19]. This finding indicates that tumor type-specific changes in androgen metabolism (synthesis or utilization) may impact responses to systemic T suppression.

In advanced PCa, Mohler et al. found that prostatic T levels in castrate patients with locally recurrent tumors were *equivalent* to those of BPH patients and that intratumoral DHT levels were only reduced by 80 % to about 0.4 ng/g [10]. Further, T levels in metastatic tumors obtained via rapid autopsy from men with CRPC were found to be approximately threefold higher than levels within primary prostate tumors from untreated (eugonadal) patients [20]. Adrenal androgens have also been detected at significant levels in prostate tissue of castrate men. Prostatic levels of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and androstenedione (AED) were decreased by about 50 % in castrate patients with recurrent PCa and far exceeded values of T and DHT in recurrent tumor tissue [10]. A separate study found no decrease in prostatic levels of 5-androstenediol (a primary metabolite of DHEA and a direct precursor of T, Fig. 74.1) after castration [22], which is of particular significance as this androgen has been shown to bind wild-type AR without being inhibited by flutamide or bicalutamide [23].

## Activity of Intratumoral Androgens in CRPC

Data derived from in vitro and in vivo studies have determined that tissue DHT levels of 0.5–1.0 ng/g, the range observed in prostatic tissue of castrated patients, are sufficient to activate the AR, stimulate expression of AR-regulated genes, and promote androgen-mediated tumor growth [10, 24–27]. Activity of intratumoral androgens in CRPC tumors is generally evidenced by reconstitution of tissue and serum PSA levels. Maintenance of PSA expression in neoplastic prostate epithelial cells has also been shown at 3 or 9 months of castration therapy [28]. The importance of intratumoral androgens in mediating CRPC tumor growth is confirmed by clinical responses produced by therapeutics that target residual androgen pathway activity. These include historical responses described in response to adrenalectomy and/or hypophysectomy [29, 30], the limited but consistent ~ 5 % overall survival benefit seen in meta-analyses of combined androgen blockade (CAB) trials [31–33], the observation that nearly 30 % of recurrent prostate tumors demonstrate at least transient clinical responses to secondary or tertiary hormonal manipulation [34], and most recently, the striking clinical response observed with the novel AR axis inhibitors abiraterone and MDV3100 (discussed below) [3, 5].

## Ligand-Dependent Mechanisms Mediating AR Transactivation in CRPC

Resistance to AR pathway inhibition may include ligand and/or AR-dependent and independent mechanisms (Table 74.1). Castration-resistant tumors are characterized by elevated tumor androgens and by steroid enzyme alterations, which may potentiate de novo androgen synthesis or

**Table 74.2** Androgen receptor and CYP17A steroid synthesis inhibitors in clinical development

| Class and agent | | Company | Target | Mechanism of action | Phase | Major trials | Identifier[a] | Efficacy | References |
|---|---|---|---|---|---|---|---|---|---|
| CYP17A inhibitors | Abiraterone (Zytiga) | Johnson & Johnson | CYP17A | Inhibitor of hydroxylase and lyase activities of CYP17A | Phase III metastatic CRPC | COU-AA01, docetaxel treated; COU-AA02, docetaxel naïve | COU-AA01 completed NCT00887198 (chemo naïve) | FDA approved in postdocetaxel setting based on improvement in overall survival from 10.9 (placebo) to 14.8 months (abiraterone) in COU-AA01 | [3] |
| | TAK-700 (orteronel) | Millennium/ Takeda Oncology | CYP17A | Inhibitor of CYP17 lyase activity | Phase II nonmetastatic CRPC, phase III metastatic CRPC | | NCT01046916 (nonmetastatic), NCT01193257 (chemo treated), NCT01193244 (chemo naïve) | 11 of 20 patients with metastatic CRPC showed PSA declines >50 % in phase I data | [4] |
| AR inhibitors | MDV3100 | Medivation | AR (LBD) | Competitive AR antagonist. Impairs nuclear translocation, DNA binding, and coactivator recruitment without partial agonist activity | Phase III metastatic CRPC | AFFIRM, docetaxel treated; PREVAIL, docetaxel naïve | NCT00974311 (chemo treated), NCT01212991 (chemo naïve) | >50 % PSA declines in 62 and 51 % of chemo-treated and chemo-naïve patients, with median time to PSA progression of 41 and 21 weeks, respectively, reported in phase I/II study | [5, 6] |
| | EPI-001 | Ipsen | AR (NTD) | Inhibits AR transactivation by disrupting AR N/C interaction and cofactor recruitment. Does not prevent ligand binding or nuclear translocation | Phase I/II under development | | | Not available | [7] |
| Mixed | VN/124-1 (TOK-001) | Tokai | CYP17A, AR (LBD) | Dual CYP17A inhibitor and competitive AR antagonist | Phase I/II metastatic and nonmetastatic CRPC | ARMOR1 docetaxel naïve | NCT00959959 | Not available | [8] |

[a]All ongoing clinical trials can be accessed at http://clinicaltrials.gov

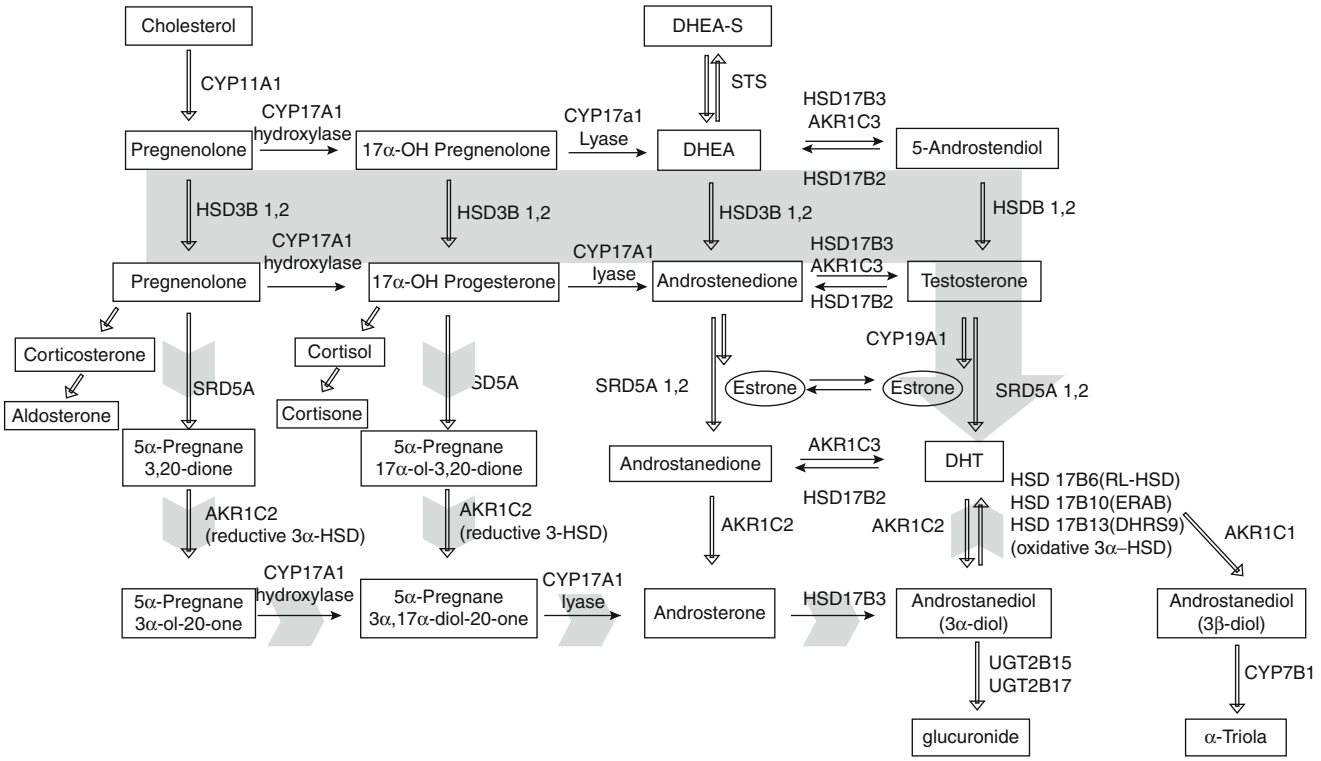


**Fig. 74.1** The classical and backdoor pathways of androgen biosynthesis. In the classical pathway (*solid gray arrow*), C21 precursors (pregnenolone and progesterone) are converted to the C19 adrenal androgens DHEA and androstenedione (*AED*) by the sequential hydroxylase and lyase activity of CYP17A1. Circulating adrenal androgens (including the sulfated form of DHEA, DHEA-S) enter the prostate and can be converted to testosterone by a series of reactions involving the activity of HSD3B, HSD17B, and AKR1C enzymes. Testosterone is then converted to the potent androgen DHT by the activity of SRD5A. In the backdoor pathway to DHT synthesis (*short gray arrows*), C21 precursors are first acted upon by SRD5A and the reductive 3α–HSD activity of the AKR1C family member AKR1C2, followed by conversion to C19 androgens via the lyase activity of CYP17A1. DHT is subsequently generated by the action of HSD17B3 and an oxidative 3α–HSD enzyme, including HSD17B6 (also called RL-HSD) or HSD17B10 (as well as RODH4, RDH5, and NT 3α–HSD, not shown) (Adapted from Mostaghel and Nelson [21], with permission)

utilization of circulating adrenal androgens [10, 20, 35, 36]. The dependence of CRPC on intratumoral androgen metabolism has been modeled in vitro and in vivo [37–39]. These observations suggest that tissue-based alterations in steroid metabolism contribute to development of CRPC and underscore these metabolic pathways as critical targets of therapy.

In the classical pathway of androgen synthesis, C21 steroids generated from cholesterol such as pregnenolone and progesterone are first converted to C19 steroids DHEA and AED via sequential hydroxylase and lyase activity of CYP17A1 (Fig. 74.1). These adrenal steroids are then acted on by HSD3B, HSD17B3, and SRD5A to generate T and then DHT. Recent data also suggest steroidogenesis in some tumors may proceed from adrenal androgen intermediates to DHT via androstenedione rather than T [40]. In steroidogenic tissues in which both CYP17A1 and SRD5A are expressed, an alternate route to DHT is possible wherein C21 steroids are first acted upon by HSD3B and SRD5A, followed by CYP17A1 and HSD17B3 [41]. This "backdoor pathway," wherein steroid flux to DHT bypasses conventional intermediates of AED and T, has also been postulated to be operative in prostate tumors (Fig. 74.1) [39].

## Steroidogenic Enzymes in CRPC

Enhanced expression of transcripts encoding key enzymes in the cholesterol biosynthetic pathway has been demonstrated in CRPC tumors, including expression of squalene epoxidase (SQLE), the rate-limiting enzyme in cholesterol synthesis [36]. Altered expression of genes encoding many steroidogenic enzymes including upregulation of FASN, CYP17A1, HSD3B1, HSD17B3, CYP19A1, and UBT2B17 has been reported in CRPC metastases, suggesting that castration-resistant tumors have the ability to utilize progesterone as androgenic precursors [20, 35]. Differential expression of several 17beta-hydroxysteroid dehydrogenase family members (HSD17B) occurs in PCa, suggesting a shift in tumoral androgen metabolism toward formation of T and

DHT, with increased expression of reductive enzymes catalyzing conversion to active androgens (HSD17B3 and HSD17B5—also known as aldo-keto reductase AKR1C3) and decreased expression of oxidative enzymes catalyzing the reverse reaction (HSD17B2) (reviewed in [21]). A selective loss of AKR1C2, which mediates catabolism of DHT to androstanediol (3α-diol), has been observed in primary prostate tumors, accompanied by a reduced capacity to catabolize DHT and an increased level of tumoral DHT. PCa cell lines and human prostate tissue have also been demonstrated to express oxidative enzymes capable of mediating back conversion of 3α-diol to DHT. Enzymes with this capacity include RODH4, RDH5, DHRS9, HSD17B6 (RODH-like 3αHSD or RL-HSD), and HSD17B10 [42, 43].

## Experimental Models of De Novo Steroidogenesis

Studies of in vitro and in vivo models of CRPC support the concept of intratumoral androgen synthesis. The androgen-independent LNCaP derivative (C81) demonstrated higher expression of steroid metabolic machinery, including steroidogenic acute regulatory (StAR) protein, cytochrome P450 cholesterol side chain cleavage (P450scc), and CYP17A1 compared to its androgen-dependent counterpart (C33) and was shown to directly convert cholesterol into T [44]. Increases in expression of genes responsible for accumulation of free cholesterol and cholesterol synthesis, low-density lipoprotein receptor (LDLR), scavenger receptor (SR)B1, ATP-binding cassette ((ABC)A1), StAR, acyl-coenzyme A cholesterol acyltransferase (ACAT) 1 and 2, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA), and side-chain cleavage enzyme (CYP11A1) were also demonstrated in a xenograft LNCaP model [45–47]. Also detected were increases in transcripts encoding CYP17A1, AKR1C1, AKR1C2, AKR1C3, HSD17B2, and SRD5A1 [45]. Conversion of acetic acid to 5α-DHT was observed in these xenografts, and tumors were shown to metabolize progesterone to six different intermediates upstream of 5α-DHT, via both classic and "backdoor" pathways [45]. Collectively, these data suggest that PCa cells may be capable of de novo steroidogenesis from cholesterol.

## Stromal-Epithelial Interactions and Intratumoral Androgen Biosynthesis

Androgen metabolism in PCa cells may also be facilitated by bone marrow and PCa-associated stromal cells. Compared to monocultures of LAPC-4 PCa cells stimulated with DHEA, coculture of LAPC-4 cells with PCa-associated stromal cells resulted in marked stimulation of PSA expression. This effect was likely mediated by stromal cell generation of T from DHEA, as T was detected in a time- and dose-dependent manner in PCa stromal cell monocultures treated with DHEA [48]. Similarly, the impact of DHEA on PSA promoter activity in LNCaP cells was markedly enhanced in the presence of PCa-derived stromal cells [38]. Knockdown of AR in LNCaP cells abrogated this effect, while coculture with PCa stromal cells transfected with AR shRNA did not, suggesting paracrine factors secreted by stromal cells act on the LNCaP AR. Furthermore, following DHEA treatment, T and DHT concentrations were ~ 5-fold higher in PCa stromal/LNCaP coculture versus LNCaP monoculture. Interestingly, PSA expression was also induced by normal prostate stroma, bone marrow stroma, lung stroma, and bone-derived stromal cells, although strongest effects were noted with PCa-derived stromal cells. Resting mesenchymal cells in a separate study of bone marrow stromal cell were also found to express HSD3B and SRD5A protein, while incubation with DHEA additionally resulted in expression of HSD17B5 [49]. These findings indicate that maintenance of intratumoral androgen levels in CRPC tumors may be facilitated by metabolism of androgen precursors in cancer-associated stromal cells.

## Alterations in Cellular Uptake of Steroid Hormones

Despite the generally accepted view that steroid hormones transit from circulation to intracellular compartments via free diffusion across lipid membranes, recent studies suggest a potential role for steroid transport proteins in actively mediating uptake of androgen into PCa cells. The organic anion-transporting polypeptides (OATP; encoded by the SLCO gene family) are variably expressed throughout liver, kidney, and steroidogenic tissues, and several SLCO genes are overexpressed in CRPC metastases versus untreated PCa [50]. These transporters mediate import of substrates such as bile acids, xenobiotics, and steroidogenic precursors, and single-nucleotide polymorphisms (SNPs) in SLCO genes can markedly alter substrate-specific transport efficiency [51]. Notably, OATP1B3 actively transports T in transiently transfected COS-7 cells [52]. Furthermore, a nonsynonymous SNP of OATP1B3 displayed a twofold decrease in T uptake, which correlated with a longer median survival, improved 10-year survival, and a longer time to androgen independence in two small studies of men with CRPC [53]. In a parallel study, OATP2B1 was shown to mediate uptake of DHEA-S in transiently transfected LNCaP cells, and a nonsynonymous SNP which displayed impaired DHEA-S import was correlated with a longer time to progression in men with CRPC receiving ADT [54]. Together, these studies imply that active hormone uptake may contribute to elevated androgen levels observed in CRPC tumors and progression of advanced disease.

## AR-Based Alterations Mediating AR Transactivation in CRPC

Numerous molecular features have been shown to contribute to AR signaling in context of low or absent androgen levels in CRPC (Table 74.1). Collectively, characterization of these molecular events indicates that AR activation may occur via both ligand-dependent and independent mechanisms. These include changes in expression and structure of the AR itself, as well as alterations in associated cofactors which regulate AR transactivation. As a consequence, AR ligand specificity can be broadened, and efficiency of AR activation at low or absent ligand levels can be enhanced.

### Overexpression and Genomic Amplification of Wild-Type AR

AR overexpression is a well-recognized feature of CRPC and believed to be a critical driver of CRPC progression. In preclinical PCa models, Chen et al. identified AR as the most common gene upregulated following androgen deprivation. AR overexpression supported in vitro proliferation of transfected cells at fivefold lower androgen levels than untransfected cells and was both necessary and sufficient to induce tumor formation when placed in castrate SCID mice compared to untransfected controls [1]. Importantly, AR overexpression not only mediated sensitivity to low ligand concentrations but converted antiandrogens such as bicalutamide and flutamide from antagonists to agonists via changes in composition of coactivators recruited to the AR promoter. While rarely identified in primary prostate tumors, AR gene amplification leading to AR overexpression is present in approximately 30 % of clinical CRPC specimens [55]. Additional mechanisms that mediate increased AR transcription and/or AR stability are likely operative, as increased AR expression is frequently observed in the absence of AR amplification. Recent data suggest that dimerization of AR with ligand-independent AR splice variants (discussed below) may increase AR levels by preventing AR protein degradation [56].

### AR Mutations

Mutations in the AR are found in approximately 20–40 % of CRPC tumors, though are rare in hormone treatment-naïve PCa [57]. Multiple mutations are frequently isolated from the same tumor, demonstrating the high degree of heterogeneity present in PCa [58]. Several hundred AR mutations have been described following ADT, but >90 % are nonsense or missense in nature and result in a nonfunctional AR. A number of clinically important AR mutations occur in the ligand-binding domain (LDB), and it is notable that none have been identified in this region in the absence of ADT. The most common mutation occurs at or around amino acid 877. The Thr877Ala mutation was originally described in the LNCaP human PCa cell line. This mutation permits binding of an expanded repertoire of steroid ligands, such as progestins and estradiol, as well as the antiandrogen flutamide, converting antiandrogen of the latter to an agonist [59]. Gain of function mutations also occur in both N- and C-termini, which can alter N/C interactions involved in cofactor recruitment. Although AR mutations are associated with castration resistance, none of them occur with a frequency that would suggest they are responsible for development of castration resistance. However, potential agonist activity of steroidal antiandrogens in the setting of AR amplification and/or AR mutation has spurred development of AR antagonists without agonist properties.

### Alterations in AR Coregulators

Several hundred AR coregulators have been described which influence AR activation via multiple mechanisms, including recruitment of transcriptional machinery, modulation of chromatin-remodeling enzymes, and initiation of RNA polymerase activity [60]. A number of AR coactivators are increased in CRPC including TIF-1, MAGE-II, SRB-1, NFKB, and ARA70, while corepressors such as SMRT are downregulated. Whether alterations in the balance between AR and its coregulators can activate AR in the absence of ligand in CRPC is not clear. However, altered coregulator expression may sensitize the AR for activation under low-androgen conditions, as well as converting AR antagonists into agonists via corepressor downregulation and/or corepressor dismissal from the AR complex [61]. Inhibition of AR coregulators has been proposed as a target for suppressing AR activity in CRPC [62].

### Activation of AR by Peptide Ligands

Several studies have determined that peptide growth factors can transactivate AR in absence of ligand via cross talk through well-characterized signal transduction pathways. These include insulin-like growth factors (IGF-I and IGF-II), epidermal growth factor (EGF), keratinocyte growth factor (KGF), and cytokines such as interleukin 6 (IL-6) (reviewed in [63]). The impact of these factors in vivo in terms of maintaining AR signaling is not known, although inhibition of IGF-IR by the IGF-IR inhibitory antibody A12 affects AR translocation and transactivation in preclinical models [64]. Probably, the most convincing of these potential AR peptide ligands is IL-6, which binds

the LBD and transactivates AR as determined by ARE-luciferase reporter constructs or by increased expression of androgen-regulated genes. Additionally, induced nuclear translocation of AR by IL-6 has been described. However, clinical relevance of IL-6 in PCa is not clear. While IL-6 is significantly elevated in serum and bone metastases of patients with advanced PCa, a recent clinical trial of men with CRPC treated with an IL-6 inhibitory antibody showed no evidence of benefit [65].

## Constitutively Active AR Splice Variants

Differential splicing of pre-mRNA is a frequent mechanism for generation of protein variants with oncogenic activity [66], and the expression of posttranscriptional AR splice variants with capacity for constitutive AR transactivation has recently been recognized as a potential mechanism of CRPC progression [56, 67–72]. Approximately 25 variants have been identified in human prostate tissues and cell lines [56, 67, 69, 71–73]. Some of these variants have no predicted function, while others appear to enhance effect of the full-length wild-type receptor. Most significant are those in which the carboxy-terminal AR LBD is lost, resulting in ligand-independent constitutive AR activation. Among the variants identified to date, ARV7 (which encodes the same protein as AR3) and $AR^{v567es}$ appear to be the most clinically relevant, with detection of ARV7 in radical prostatectomy (RP) tissues associated with an increased risk of biochemical relapse [67, 69] and ARV7 or $AR^{v567es}$ in CRPC metastases associated with shorter survival [68]. Notably, markedly higher expression of ARV7 and $AR^{v567es}$ has been observed in CRPC versus primary PCa, with $AR^{v567es}$ showing nearly exclusive expression in CRPC [56, 68, 69].

Mechanisms responsible for generation of AR splice rearrangements are thought to reflect a cellular response to ligand deprivation, as variants most prevalent in human CRPC tissues are those most consistently found following androgen deprivation in vitro. The emergence of specific AR isoforms including ARV7/AR3 and $AR^{v567es}$ in vitro and in vivo following suppression of intratumoral androgens [56, 73] suggests growth of these tumors is dependent on AR variants in low-androgen environments. Moreover, truncated AR variants can potentiate activity of full-length AR under low-ligand conditions, essentially functioning as AR ligands themselves. Sun et al. have demonstrated that $AR^{v567es}$ can form a heterodimer with full-length AR, leading to efficient nuclear translocation and AR transactivation in the absence of ligand. Recently, Dehm et al. have demonstrated that high-level expression of AR variants may be associated with intragenic rearrangement of alternative AR exons, although the clinical prevalence of this mechanism remains to be established [74].

Whether truncated AR variants have a pathogenic role or simply recapitulate wild-type AR transactivation is unknown but has significant implications for understanding CRPC tumor behavior. Several studies have shown that expression of ARV7 or $AR^{v567es}$ portends more clinically aggressive disease [67–69]. Moreover, emerging data demonstrate that AR splice variants transactivate an overlapping but not identical repertoire of gene targets compared to wild-type AR [56, 67, 73]. Differences in transcriptional output may reflect structural changes resulting in alterations in coregulator recruitment, as *in silico* analyses suggest loss of the LBD may affect interactions with NCOA1, NCOA2, TIP60, and ARA54 [60, 75]. Notably, expression of $AR^{v567es}$ and high-level expression of ARV7 in CRPC bone metastases were associated with shorter cancer-specific survival and with gene expression changes indicative of disturbed cell cycle regulation and increased invasiveness (e.g., CDK1, CYCLINA2, CDC20, C-MYC, HSP27, and UBE2C) [68].

From a therapeutic standpoint, tumors expressing AR splice variants may present a significant clinical challenge depending on their sensitivity to AR antagonists that are designed to target the AR LBD (e.g., bicalutamide, TOK-001, or MDV3100). Emerging data suggest that truncated AR variants may function in part via binding and promoting nuclear localization of full-length AR, and thus, the presence of carboxy-terminal AR variants does not necessarily preclude a response to ligand-binding inhibitors such as MDV [73]. While expression of LBD-deficient AR variants alone results in AR transcriptional activity, expression of AR variants has generally been reported to occur in conjunction with expression of full-length AR. Watson et al. recently demonstrated that in the presence of both truncated and full-length AR variants, targeting full-length AR with the antiandrogen MDV3100 suppressed AR activity and cell growth as efficiently as when only full-length AR was present, suggesting that activity of certain AR variants is mediated through full-length AR [73]. Additional studies are required to determine if all AR variants require full-length AR to activate the AR transcriptional program and maintain cell survival and growth, as unpublished observations suggest coexpression of ARV7 or $AR^{v567es}$ can mediate resistance to LBD-directed AR inhibition (Stephen Plymate, personal communication 2012).

## Secondary Hormonal Manipulation After Failure of First-Line ADT

The contribution of ongoing androgen pathway activity in CRPC progression is supported by response rates ranging from 20 to 60 % in studies of secondary hormonal manipulation [76]. Importantly, serum T levels <50 ng/dl should be documented prior to making a designation of CRPC. Breakthrough T levels >50 ng/dl were documented on one or

more occasions in nearly 25 % of patients in a study of LHRH agonist therapy administered as a 3-monthly depot over a 6–48 month period of time [77]. Interestingly, LHRH antagonists have been reported to induce durable androgen suppression in patients in whom LHRH agonists were not effective in maintaining castrate (<50 ng/dl) serum T levels and may be of value in this setting [78].

Once CRPC has been documented, standard strategies targeting residual AR pathway activity include antiandrogen withdrawal (AAW), alternative antiandrogens such as flutamide or nilutamide (after progression on bicalutamide), high-dose bicalutamide, addition of 5-α reductase inhibitors such as finasteride or dutasteride, the nonspecific CYP17A1 inhibitor and adrenolytic agent ketoconazole, estrogenic agents such as DES or transdermal estradiol, and palliative glucocorticoids. The choice and sequence of agents is largely physician dependent and often driven by side effect profiles, as numerous studies of secondary ADT have demonstrated prolongations in PFS, but none have reported improvement in overall or cancer-specific survival, reviewed in [76]. In general, PSA responses >50 % have been observed in 20–50 % of patients undergoing secondary hormonal maneuvers, with duration of median response ranging from 2 to 8 months.

Recent observations suggest that androgen levels may be useful in stratifying patients likely to sustain durable benefit from second-line therapies. In a randomized study of AAW alone versus AAW plus ketoconazole, PSA responses were observed in 10 % of men on AAW versus 32 % treated with the combination. Importantly, men with a >50 % PSA response while on ketoconazole experienced significantly longer survival (41 vs. 13 months, $p > 0.001$), and patients with higher baseline levels of androstenediol were most likely to demonstrate responses to ketoconazole [79]. A small study of second-line therapy using flutamide (after progression on bicalutamide) also reported an association between PSA response and baseline androstenediol levels [80]. In a separate study of either flutamide or bicalutamide for second-line therapy, men with T levels higher than 5 ng/dl demonstrated significantly higher response rates (77 vs. 37.5 %, $p = 0.04$); serum T level <5 ng/dl prior to initiation of second-line therapy was reported as an independent predictor of PSA-free progression at 1 year (0 vs. 53 % in men with pretreatment T > 5 ng/dl, $p = 0.002$) [81].

## New Agents Targeting Intratumoral Androgens

Potent therapies targeting ligand and/or AR-driven activation of the AR axis are currently in clinical development (Table 74.2). Alterations in a number of critical enzymes responsible for DHT synthesis and catabolism provide mechanistic support for the role of intracrine androgen production in maintaining the tumor androgen microenvironment in CRPC and underscore these metabolic pathways as critical therapeutic targets.

### Inhibitors of CYP17A1

CYP17A1 is a single enzyme that catalyzes sequential steps in the conversion of C21 progesterone precursors to C19 adrenal androgens, DHEA and AED. Ketoconazole (a weak inhibitor of CYP11A and CYP17A1) has been utilized for suppression of residual adrenal androgens but has limited efficacy and significant treatment-related side effects. This has prompted development of a number of potent CYP17A1 inhibitors, including agents exhibiting both CYP17A1 inhibition and antiandrogen activity [82].

Abiraterone is a pregnenolone derivative that acts as a selective irreversible inhibitor of both the 17 alpha-hydroxylase and C17,20-lyase activity of CYP17A1. Abiraterone suppressed T levels by >50 % in eugonadal men, accompanied by a corresponding rise in luteinizing hormone (LH) levels, while in castrate men, abiraterone further suppressed serum T levels by >75 % [83].

Phase I/II studies in chemotherapy-naïve metastatic CRPC demonstrated durable PSA declines >50 % in approximately two-thirds of patients, with partial radiographic responses (by RECIST criteria) in 37.5 % and a median time to progression of 32 weeks [84, 85]. PSA responses >50 % were observed in 47 % of patients with prior ketoconazole treatment versus 64 % of patients without [86]. DHEA levels were suppressed by approximately 75 %, and DHEA-S, AED, and T levels became essentially undetectable [85, 86]. As observed in studies of ketoconazole, patients achieving >50 % PSA declines had higher baseline levels of DHEA-S, DHEA, and AED, and, in contrast to progression on ketoconazole, increases in T, AED, or DHEA levels were not observed on progression with abiraterone [79, 84].

In a phase II study of postdocetaxel-treated CRPC patients, PSA declines >50 % were observed in 51 % of patients, with a median time to progression of 24 weeks [87]. In a postchemotherapy study in which 41 % of patients had received prior ketoconazole, abiraterone (in combination with prednisone, 5 mg twice daily) achieved PSA declines >50 % in 45 % of ketoconazole-naïve patients and 26 % of ketoconazole-treated patients, with a median time to progression of 28 and 14 weeks, respectively [88].

Phase III studies of abiraterone in combination with prednisone versus prednisone alone are ongoing in the chemotherapy-naïve (COU-AA-302) and postdocetaxel setting (COU-AA-301). Notably, the COU-001 study was unblinded at the interim analysis as improvement in OS exceeded the preplanned criteria for study termination. Among 1195 patients randomized 2:1 to abiraterone versus placebo, OS

was 14.8 in the abiraterone-treated patients versus 10.9 months in the placebo-treated group (HR = 0.646, $p<0.0001$), representing a 35 % reduction in risk of death with abiraterone [3]. Interestingly, phase II data suggest that at 3 months after starting abiraterone, over 30 % of patients may demonstrate an increase in bone scan intensity followed by improvement or stability of findings at 6 months [89]. The positive results in the phase III setting strongly suggest that bone scan findings early after starting treatment should not be used as criteria for early discontinuation of therapy.

Side effects with abiraterone have been related to expected increases in C21 steroids upstream of CYP17A1 (including a 10-fold increase in deoxycorticosterone and 40-fold increase in corticosterone). These were primarily manifested as symptoms of mineralocorticoid excess (including grade 1 and 2 hypertension, hypokalemia, edema, and fatigue) and responded to treatment with eplerenone or low-dose glucocorticoids (spironolactone was avoided due to potential AR agonist activity). Decreases in serum cortisol (twofold) with concomitant elevations in ACTH (fivefold) were also observed. Interestingly, 4 of 15 patients progressing on abiraterone responded to addition of dexamethasone, which decreased ACTH and deoxycorticosterone levels to below baseline [85], consistent with reports that steroids upstream of CYP17, including progestins and corticosteroids, can stimulate AR. At present, abiraterone in combination with low-dose prednisone or dexamethasone is recommended to prevent treatment-related rise in ACTH and attendant side effects.

TAK-700 is a nonsteroidal CYP17 inhibitor designed to have selectivity against C17,20-lyase over 17-alpha hydroxylase activity of CYP17. In a phase I/II dose escalation study, 11 of 20 patients with metastatic CRPC receiving >300 mg twice daily showed PSA declines >50 %, and 4 had reductions >90 %. At 4 weeks, median T and DHEA-S levels decreased from 4.9 to 0.6 ng/dl and 53.8 ug/dl to undetectable, respectively. Adverse effects included fatigue, nausea, constipation, and anorexia. Consistent with the agent's selective inhibition of 17,20-lyase over 17 alpha-hydroxylase activity, a significant incidence of hypertension was not observed [4]. The phase II portion is ongoing, including an arm evaluating concomitant use of prednisone.

VN/124-1, a heteroaryl steroid, is a potent dual CYP17 and AR inhibitor currently being evaluated in a phase I/II study under the trade name TOK-001. VN/124-1 exhibits three- and four-fold stronger inhibition of CYP17 activity than abiraterone and ketoconazole, respectively, and is also a potent inhibitor of the AR, both as a competitive antagonist (with a binding affinity comparable to bicalutamide) and as a dose-dependent inhibitor of AR protein expression, mediated in part via an increase in AR degradation [8] Notably, VN/124-1 has similar AR inhibitory activity against wild-type AR and the T877A AR mutant. VN/124-1 was significantly more effective than castration or bicalutamide in suppressing growth of androgen-sensitive LAPC4 xenografts. Moreover, VN/124-1 maintained potent downregulation of AR in vivo, leading to a tenfold reduction in tumor AR levels compared to castration or bicalutamide (both of which demonstrated a two- to three-fold increase in AR expression). Interestingly, this agent also inhibits growth of AR-negative PCa cells via induction of the endoplasmic reticulum stress response [90].

## Inhibitors of Other Steroidogenic Enzymes

The metabolic pathway from cholesterol to DHT offers several potential candidates for targeting steroid synthesis inhibition, either singly or in combination for maximal efficacy in reducing the production of tumor androgens.

The conversion of T to the more potent androgen DHT is carried out by steroid 5-alpha reductases SRD5A1 and SRD5A2 (and possibly SRD5A3, although the function of this enzyme has not been fully established) [91]. SRD5A2 is the primary isoform in benign prostate tissue, while PCa shows a relative increase in SRD5A1 expression and activity. Finasteride (a specific inhibitor of SRD5A2) and dutasteride (a dual SRD5A inhibitor) are 4-azasteroids extensively used in the treatment of BPH and have been explored for prevention and treatment of PCa. While dutasteride alone has limited activity in men with CRPC, a phase II study of ketoconazole, hydrocortisone, and dutasteride (KHAD) demonstrated PSA responses >50 % in 56 % of men and a median time to progression of 14.5 months, nearly twice that observed in phase II studies of abiraterone, leading the authors to postulate that intratumoral DHT synthesis may contribute to abiraterone resistance [92].

The final steps in T and DHT biosynthesis (reduction of the adrenal androgens AED and androstenedione, respectively) are catalyzed by HSD17B3 and/or AKR1C3. HSD17B3 is primarily expressed in testicular Leydig cells, while AKR1C3 mediates production of T and DHT in peripheral tissues. Increased expression of these enzymes in CRPC tumors suggests they may be important targets for inhibition [20, 35, 93]. The AKR1C family members AKR1C1 and AKR1C2 mediate catabolism of DHT (to 3β and 3α−diol, respectively), and a selective loss of these enzymes has been reported in prostate tumors (accompanied by a reduced capacity to metabolize DHT and an increase in tumoral DHT levels) [94].

Agents which selectively target AKR1C3 (but not the highly related AKR1C1 and AKR1C2) and HSD17B3 are under development. AKR1C family members are inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs) and the COX-2 selective inhibitor celecoxib [95]. Indoleacetic acids (e.g., indomethacin) are among the most potent agents

targeting the AKR1C family. Indomethacin analogs that selectively target AKR1C3 but do not inhibit COX-1, COX-2, AKR1C1, and AKR1C2 have been reported [96]. Small molecule inhibitors of HSD17B3 have been developed and shown to reduce systemic androgen levels (reviewed in [97]). However, to date, no studies of these agents in PCa have been reported.

The conversion of delta 4 steroids such as DHEA and androstenediol to delta 5 steroids AED and T, respectively, is mediated by 3BHSD. 3BHSD is required for de novo biosynthesis of androgens from cholesterol (via either classical or backdoor pathways) as well as for pathways converting adrenal androgens to T and DHT. The type 1 isoform is expressed in adrenal, ovary, and testis and type 2 in peripheral tissues such as prostate. Transcripts encoding both isoforms have been observed in CRPC metastases. Several studies have demonstrated that DHEA or androstenediol can directly activate wild-type and mutated AR [22], while others have demonstrated a requirement for 3BHSD-mediated conversion to downstream metabolites first [98], implicating 3BHSD as a therapeutic target for CRPC. Epostane, a competitive inhibitor of 3BHDS1, has been used in human studies for medical termination of pregnancy via inhibition of progesterone synthesis and has been shown to inhibit DHEA-induced proliferation of breast cancer MCF-7 cells [99], suggesting a study in PCa may be warranted.

Hydrolysis of inactive sulfates of estrogen and DHEA to biologically active steroids is carried out by steroid sulfatase (STS). PCa cell lines express functionally active STS, as demonstrated by hydrolysis of estrone-S and DHEA-S to unconjugated forms. STS expression in prostate tumors has been confirmed by immunohistochemical analyses (reviewed in [21]). STS inhibitors have been evaluated in breast cancer and may have efficacy in preventing prostatic utilization of the adrenal androgen DHEA, which primarily circulates as the inactive sulfate DHEA-S. A phase I study of the steroid sulfatase inhibitor BN83495 in men with advanced CRPC has recently completed accrual, and results are pending (NCT00790374) [100].

Apoptone (HE3235) is a synthetic analog of 3-beta androstanediol (a naturally occurring metabolite of DHT formed in prostate tissue). This agent has been shown to suppress tumor growth, decrease AR expression and nuclear localization, and suppress levels of intratumoral androgens in CRPC xenografts [101, 102]. While its mechanism of action has not been fully elucidated, HE3235 appears to inhibit conversion of d-cholesterol to d-pregnenolone, without inhibition of CYP17A1. HE3235 is currently under study in a phase I/II clinical trial of men with CRPC [103].

Production of androgens by the testis is under control of the hypothalamic-pituitary-testicular axis via sequential release of luteinizing hormone-releasing hormone (LHRH) and luteinizing hormone (LH) from the hypothalamus and pituitary, respectively. Variants of GnRH and LHRH receptor have also been demonstrated in prostate epithelium [104]. Thus, GnRH antagonist therapy may have direct antitumor effects [105], and LHRH receptors on prostate tumors may serve as targets for LHRH analogs hybridized to cytotoxic moieties. An analog of LHRH conjugated to doxorubicin has been clinically tested in women with gynecologic tumors expressing LHRH receptors [106]. Interestingly, receptors for LH itself have also been described in PCa specimens. Exposure of both androgen-sensitive (LNCaP) and androgen-independent (22RV1 and C4-2B) PCa cell lines to LH increased protein levels of steroidogenic enzymes including STAR, CYB5B, CYP11A, and 3BHSD, and a 2.5-fold increase in progesterone synthesis was observed in LH-treated C4-2B cells compared to controls [104]. LH may have a role in the regulation of steroid biosynthesis in PCa cells, with the LH receptor serving as a potential therapeutic target.

## New Agents Targeting the AR and AR Signaling Mechanisms

### Androgen Receptor Antagonists

AR antagonists prevent the AR from achieving the transcriptionally active conformation required for stable DNA binding via inhibition of chaperone dissociation, alterations in subcellular AR localization, recruitment of nuclear corepressor complexes, or ineffective recruitment of coactivator proteins (reviewed in [107]). Several mechanisms by which nonsteroidal antiandrogens function as AR agonists have been described, including AR mutations and/or alterations in cofactor recruitment. This has been a critical impetus for the development of novel, potent AR inhibitors without agonist activity against wild-type or mutant ARs (Table 74.2). The recent description of constitutively active AR variants lacking the C-terminal ligand-binding domain has also raised significant interest in the development of N-terminal-targeted antiandrogens.

MDV3100 is a second-generation diarylthiohydantoin competitive AR antagonist which binds to the AR with five- to eight-fold greater affinity than bicalutamide and only two- to three-fold lower affinity than DHT. Preclinical studies in VCaP xenografts (with endogenous AR gene amplification) or LNCaP xenografts engineered to express high AR levels have demonstrated that, compared to bicalutamide, MDV3100 potently decreased the nuclear translocation of AR, markedly reduces chromatin occupancy at canonical AREs, and is significantly more effective in suppressing tumor growth [6]. Importantly, MDV3100 did not elicit agonist activity against LNCaP tumors overexpressing the AR or against T877A or W741C AR mutations, situations in which bicalutamide demonstrates agonist activity. Moreover, targeting full-length

AR with MDV3100 in cells expressing both truncated and full-length AR variants led to suppression of AR activity and cell growth. These data suggest certain classes of AR variants act via an interaction with full-length AR and that MDV3100 may have clinical efficacy even in patients whose tumors express ligand-independent AR variants [73].

While preclinical studies show that MDV3100 is highly effective in tumors driven by an amplified AR, androgen was able to overcome the AR inhibitory effects of MDV3100 in vitro, raising a question as to whether MDV3100 will be equally effective in the setting of a nonamplified AR, particularly if residual tumor androgens are present. AR is amplified in about 20–25 % of CRPC cases [55] and in up to 50 % of CRPC cases when circulating tumor cells (CTC) are evaluated [108], and these may represent cases in which MDV3100 will have most efficacy.

A phase I/II study of MDV3100 in 140 men with CRPC demonstrated maximum PSA declines >50 % in 62 % of chemotherapy-naïve patients and 51 % of docetaxel-treated patients ($p=0.23$). At 12 weeks, the proportion of patients with declines >50 % was greater in the chemotherapy-naïve group (57 vs. 36 %, $p=0.02$), and median time to PSA progression (defined as 25 % or greater increase from nadir) was 41 versus 21 weeks, respectively [5]. PSA declines >50 % were achieved in 37 % of patients with prior ketoconazole treatment versus 71 % of those without, and 10 of 22 patients who were assessed by [18F]-FDHT PET scans showed >25 % declines in FDHT accumulation. Responses were dose dependent up to 150 mg/day. Fatigue, nausea, dyspnea, anorexia, and back pain were the most common adverse events, with 240 mg/day determined to be the maximum tolerated dose. Two seizures were observed at 360 and 600 mg doses (also observed with the experimental AR antagonist BMS-641988, and potentially due to GABA-A antagonist activity of AR antagonists) [109]. A phase III randomized placebo-controlled trial of MDV3100 in docetaxel-treated men with metastatic CRPC is ongoing.

An alternative to pharmacological approaches that target the AR ligand-binding domain is development of N-terminal domain (NTD) AR inhibitors. The NTD is essential for both ligand-dependent and independent AR activation. Agents such as MDV3100 or nonsteroidal antiandrogens do not inhibit ligand-independent transactivation of the AR NTD (such as bypass mechanisms mediated by IL-6 and other peptide growth factors) nor do they directly target constitutively active AR splice variants lacking the LBD. At present, the most promising compound that has been published is EPI-001, which is a degradation product of bisphenol A and was found by testing a library of products isolated from marine sponges [7]. EPI-001 binds to the amino terminus of the AR and inhibits AR transactivation. EPI-001 does not alter AR nuclear translocation or prevent ligand binding but disrupts the AR N/C interaction thereby inhibiting cofactor recruitment. EPI-001 blocked ligand- and nonligand-dependent AR transactivation in LNCaP cells stimulated with R1881 or IL-6, as well as blocking AR activity in 22RV1 cells which express full-length and truncated AR variants. When given to castrate mice, EPI-001 decreased the size of AR-positive LNCaP xenografts but not AR-negative PC-3 tumors. No apparent toxicity has been noted in animals, and it has 85 % bioavailability after oral administration. The combination of a LBD and ligand-targeting agents has significant potential for robustly suppressing AR activity.

## Modulators of AR Expression, Stability, and Downstream Signaling

Agents which do not target the AR directly but alter cellular pathways involved in maintaining expression, stability, and downstream signaling components of the AR axis are also under investigation for PCa therapy. Heat shock protein (HSP) chaperones, histone deacetylases (HDACs), and mammalian target of rapamycin (mTOR) are among those in development for men with CRPC.

HSP90 is an ATP-dependent chaperone protein involved in maintaining stability, localization, and activity of the AR as well as other oncogenic client proteins such as Her2 and AKT. Geldanamycin is an ansamycin antibiotic which binds the ATP-binding pocket of HSP90 leading to degradation of client proteins. Tanespimycin (17-AA-geldanamycin) inhibited growth of AR-positive PCa xenografts, accompanied by an 80 % decrease in AR expression [110]. Agents with improved solubility characteristics are currently being evaluated, as phase I studies have not shown significant clinical activity with current agents in men with CRPC.

Histone deacetylase (HDAC) inhibitors have been shown to modulate AR signaling and have demonstrated antitumor effects toward several malignancies. Transcriptional activity of numerous genes involved in cell survival and differentiation is regulated by chromatin remodeling, which is determined by the balance of histone acetylation versus deacetylation. HDAC inhibitors can decrease transcription of AR, inhibit AR-mediated transcription (by blocking recruitment of RNA polymerase to the promoter of HDAC-dependent AR target genes), and promote AR degradation (via acetylation-induced inhibition of HSP90 ATP binding) [111]. The combination of the HDAC inhibitor vorinostat (SAHA) with bicalutamide has shown synergistic activity in suppressing PCa cell proliferation in vitro [112]. A phase I study of vorinostat with docetaxel and a phase II study of single-agent vorinostat in the postchemotherapy setting showed minimal clinical response and significant dose-limiting toxicity, suggesting alternative agents in this class with a more favorable toxicity profile will be required. A phase I/II study of panobinostat (LBH589) in combination with bicalutamide in men with CRPC is ongoing.

Alterations in the PI3K/Akt/mTOR pathway (including loss or mutation of the negative regulator PTEN) are present in 30–50 % of prostate tumors, and this pathway is central to a number of signaling cascades mediating cell growth and survival. The Akt/mTOR pathway can also activate AR in the absence of androgen. Many agents targeting PI3K, Akt, and mTOR have been evaluated in both in vitro and in vivo models of PCa. Multiple phase I and II trials with the mTOR inhibitors rapamycin and its analogs everolimus (RAD-001) and temsirolimus (CCI-779) are ongoing [113]. Recent studies demonstrate a reciprocal feedback between PI3K and AR signaling, such that cotargeting the AR pathway may be significantly more effective than PI3K pathway inhibition alone [114–116].

Src kinases have been implicated in androgen-induced proliferation of CRPC cells and are nonreceptor protein tyrosine kinases involved in signal transduction downstream of multiple cell surface receptors, including EGFR, PDGFR, and VEGFR. A dual Abl and Src family kinase inhibitor dasatinib has been shown to inhibit AR phosphorylation and activation in vitro [117], as well as targeting osteoclast and osteoblast activity [118]. In a phase II study of chemotherapy-naïve men with CRPC, progression occurred in 60 and 80 % of patients at 12 and 24 weeks respectively, although nearly half the patients showed a decrease in markers of bone metabolism [119]. A randomized phase III study of dasatinib in combination with docetaxel (with skeletal-related events as one end point) is ongoing.

## Conclusions

Data regarding the molecular responses of PCa to therapeutics targeting the AR pathway continues to emerge, providing critical insights into cellular growth and signaling pathways that may be exploited as treatment targets. The optimal timing, sequence, and potential combinatorial strategies for novel AR pathway inhibitors entering clinical practice are critical questions in the treatment of men with CRPC. The introduction of potent steroidogenic inhibitors in combination with novel AR antagonists holds significant promise for the concept of multitargeted AR pathway blockade, as the presence of residual androgens and persistent activation of the AR signaling axis in CRPC suggest that a multitargeted treatment approach to ablate all contributions to AR signaling within the prostate tumor will be required for optimal antitumor efficacy.

While the clinical response to agents such as abiraterone and MDV3100 in men with CRPC has been impressive, the duration of response has been variable, mechanisms of resistance are not well understood, and optimal treatment strategies for men who develop resistance to abiraterone or MDV3100 have yet to be established. Whether these tumors now represent cancers that are entirely independent of AR pathway activity or still retain dependence on the AR signaling axis is a central question for selection of therapy in this setting. In this regard, recent data in preclinical models have shown that abiraterone treatment may variously result in upregulation of wild-type AR, AR splice variants, and CYP17A expression [120, 121]. Importantly, the effect of abiraterone on tumor tissue from patients is poorly understood, and the extent to which the therapeutic efficacy of agents targeting the AR axis is influenced by either baseline or treatment-induced differences in these resistance mechanisms is unknown. Delineating mechanisms and biomarkers of resistance to novel AR pathway inhibitors will be critical for rational trial design and for the stratification of men with CRPC to treatment strategies with the highest likelihood of durable efficacy.

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# Toxicity of Androgen Deprivation Therapy in Hormone-Sensitive Prostate Cancer

75

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## Introduction

The introduction of androgen deprivation therapy (ADT) for prostate cancer (PC) was a seminal event in oncology, as one of the first widely successful methods of systemic therapy and one of the first examples of "targeted therapy" [1]. These drugs have significantly prolonged the median survival of patients with high-risk, locally advanced, or metastatic PC. As patients taking ADT are living longer, they may experience a variety of previously underrecognized, but clinically important side effects include metabolic derangements such as hyperlipidemia and diabetes mellitus (DM), osteoporosis, anemia, gastrointestinal disturbances, and psychiatric disorders. They are also at an increased risk of cardiovascular death when compared to age-matched men not treated with ADT. The majority of these side effects are attributable to both the short- and long-term sequel of testosterone deficiency and withdrawal. Recognition and management of these toxicities is an essential to the care of patients undergoing ADT for PC. Below, we will review the adverse effects of this pharmacologic class and present an evidence-based approach to managing these effects.

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## Metabolic Syndrome

The metabolic syndrome (TMS) is a systemic disease characterized by a constellation of laboratory and physiologic abnormalities. The American Heart Association/National Heart, Lung, and Blood Institute recently published revised criteria for the diagnosis of TMS [2]. Three of five of the following criteria must be met to make the diagnosis in men: waist circumference of 40 or more inches, a triglyceride level of 150 mg/dl or more, high-density lipoprotein (HDL) cholesterol of 40 mg/dl or less, blood pressure greater than 130 mmHg systolic or greater than 85 mmHg diastolic, and an elevated fasting glucose of 100 mg/dl or more. A variety of other diagnostic schemas share similar criteria. The metabolic syndrome is an important risk factor for the development of DM and cardiovascular disease (CVD). Furthermore, there is evidence that this syndrome is associated with a systemic inflammatory state as evidenced by elevations in C-reactive protein (CRP) and decreases in adiponectin, an anti-inflammatory marker [3].

As discussed above, ADT induces changes reminiscent of TMS [4]. ADT has been shown to cause insulin resistance (IR), DM, and hyperlipidemia [5–8]. There is also evidence that ADT leads to increased abdominal girth. A prospective study of 81 men treated with ADT, for up to 24 months, had significant gains in adiposity and losses of lean body mass [9].

In a cross-sectional study 20 men with PC treated with ADT for at least 12 months, ADT therapy was associated with a statistically significant increased risk for developing TMS. Men treated with ADT had an increased prevalence of hyperglycemia, hypertriglyceridemia, and abdominal obesity than controls. Low-density lipoprotein (LDL) cholesterol and hypertension were not significantly different between the two

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**Table 75.1** Comparison of the classic metabolic syndrome (TMS) with the metabolic changes induced by ADT

| Criteria | The metabolic syndrome | ADT therapy |
|---|---|---|
| Waist circumference | Visceral adiposity | Subcutaneous adiposity |
| Serum glucose | Increased | Increased |
| HDL cholesterol | Decreased | Increased |
| Triglycerides | Increased | May be increased |
| Hypertension | Present | No change |

groups, but overall 55 % of men treated with ADT met criteria for TMS while only 22 % of men in the control group met these criteria ($P > 0.01$) [10]. In a study of 26 men treated with leuprolide, [96] examined the effect of ADT on body composition and blood pressure. They found that body mass index increased by 3.1 ± 0.9 %, waist circumferences increased by 3.5 ± 0.8 %, and body fat increased by 11.2 ± 1.5 % within a 12-month period. The waist to hip ratio was not significantly affected and the majority of fat accumulation was subcutaneous rather than visceral as assessed by computed tomography. There was no change in blood pressure during treatment, but levels of high-density lipoproteins (HDL) and low-density lipoproteins (LDL) were statistically increased [8]. A key feature of this study is that the authors measured adiponectin and CRP levels. As mentioned earlier, in the classic metabolic syndrome, CRP level increases and adiponectin level decreases. This study demonstrated an increase in adiponectin levels by 36.4 ± 5.9 % in men treated with ADT, and there was no increase in CRP levels [11]. This highlights important differences between TMS and the metabolic alterations induced by ADT therapy. The classic metabolic syndrome is characterized by visceral obesity, insulin resistance, low HDL cholesterol, and hypertriglyceridemia. ADT, however, increases serum HDL cholesterol and may or may not cause hypertriglyceridemia. ADT does not cause hypertension, and it causes accumulations of subcutaneous fat, which is not associated with the metabolic syndrome [12]. Furthermore, ADT is associated with low levels of circulating inflammatory markers such as CRP. Although changes in inflammatory markers are not diagnostic criteria for the metabolic syndrome, these differences do suggest a difference in the pathophysiology of these two entities. Further research is necessary to elucidate the potential impact of ADT-induced metabolic changes in this patient population. A brief description of differences between TMS and the metabolic side effects of ADT is provided in Table 75.1.

## Insulin Resistance and Diabetes Mellitus

ADT is an independent risk factor for the development of IR and DM [5]. Men treated with ADT had an average fasting plasma glucose level 28 mg/dl higher than controls after controlling for age and body mass index [6]. Furthermore, men with locally advanced PC treated with leuprolide and bicalutamide combination therapy have a decreased insulin sensitivity by 12.8 ± 5.9 % ($P = 0.02$) by homeostatic model assessment. These men also develop a 25.9 % increase in fasting plasma insulin and a small increase in glycosylated hemoglobin levels [7].

The data are consistent with those obtained from healthy men with testosterone deficiency showing derangements in glucose metabolism. After controlling for confounding factors, men with a 4-ng/dl decrease in testosterone from normal levels are almost 60 % more likely to develop DM [13]. The risk of glucose intolerance is proportional to the degree of testosterone deficiency; men with extremely low levels of free testosterone are approximately four times more likely to develop diabetes than men with higher free testosterone levels [14]. The causal relationship between testosterone deficiency and IR is corroborated by the fact that testosterone replacement improves insulin sensitivity and decreases the serum concentration of glycosylated hemoglobin [15].

The underlying pathophysiology behind the development of IR in hypogonadal patients is incompletely understood at this time but is thought to be due, in part, to increases in adipose tissue that accompanies testosterone deficiency. Increased adiposity leads to the accumulation of lipid-based substrates that compete with glucose in aerobic metabolism, leading to increases serum glucose concentrations. This causes elevations in serum insulin in order to correct the incident hyperglycemia. Over time, chronic elevations in serum insulin blunt its ability to regulate serum glucose.

In addition to IR, several large-scale observational studies of men treated with ADT have established it as a risk factor for the development of overt DM. In a study of 73,196 men with PC from the Surveillance, Epidemiology and End Results (SEER)-Medicare registry, patients treated with LHRH agonists had a hazard ratio of 1.44 for the development of DM [6]. Another large retrospective study compared 19,079 men with PC treated with ADT with 40,798 matched controls found a hazard ratio of 1.26 for incident diabetes attributable to ADT [16]. Finally, in a small retrospective study of 396 patients treated with ADT therapy, there was an incidence of 11.3 % of new onset diabetes and an average increase of 10 % in hemoglobin A1c among patients with preexisting diabetes [17].

To date, there have been no studies specifically addressing the management of hyperglycemia and DM in this population, but we also find no evidence that men with PC on ADT are protected from the sequel of DM. Therefore, we recommend that all patients treated with ADT be screened for diabetes and that standard measures should be taken to control serum glucose using dietary and exercise interventions with pharmacologic measures with oral hypoglycemic agents and insulin therapy when otherwise indicated. Though not

specifically studied prospectively in this population, based upon epidemiologic data, metformin might be a reasonable choice of initial pharmacologic therapy [18–20]. Given the potential far-reaching consequences, studies to determine proper screening intervals as well as proper pharmacologic approaches are warranted. In the interim, those without the proper expertise should refer to primary care or endocrinology specialists.

## Dyslipidemia

Independent of a complete metabolic syndrome, ADT has been linked to changes in lipid profiles. In a study of 16 men after a short duration of LHRH agonist therapy, total cholesterol and serum HDL increased by 6 and 22 %, respectively. But serum TG and LDL were not significantly changed [21]. In a study of 53 men with BPH treated with leuprolide, average total cholesterol levels increased by 10.6 %, HDL cholesterol increased by 8.2 %, and triglycerides increased by 26.9 % with no change in average LDL levels [22].

In contrast, observational studies found increases in triglycerides and LDL cholesterol, known risk factors for cardiovascular disease. In a study comparing 16 men with PC treated with ADT to PC patients treated with surgical resection and normal eugonadal controls, after adjusting for BMI, men who had undergone ADT had higher levels of total and LDL cholesterol and lower levels of HDL cholesterol than controls [23]. Furthermore, in a study of 40 men treated with a LHRH agonist, patients experienced statistically increased levels of total cholesterol (9.0 ± 2 %), HDL cholesterol (11.3 ± 2.6 %), LDL cholesterol (7.3 ± 3.5 %), and triglycerides (26.5 ±10 %) [8].

The significance of these alterations in lipid fractions is unclear at this time. Nevertheless, it makes sense that PC patients with a reasonable life expectancy should not be treated differently than the standard population and should establish care with a primary care physician in order to monitor lipid profiles at regular intervals. Diet modification and exercise counseling should be provided to all patients with evidence of dyslipidemia. Other treatment modalities should be considered as well. In a multicenter, double-blind, placebo-controlled trial from fracture prevention study, men with PC treated with ADT, who were also treated with toremifene, a selective estrogen receptor modulator, were found to have significantly reduced total cholesterol, LDL cholesterol, triglycerides (TGs), and significantly increased HDL cholesterol [24]. Furthermore, exercise therapy is being explored as a means of mitigating cardiovascular risk factors. Although there are data supporting the use of exercise in treating a wide array of ADT side effects, its use in treating the metabolic side effects of prostate cancer is currently under investigation. A large randomized controlled trial of exercise therapy from the Randomised Androgen Deprivation and Radiotherapy (RADAR) trial is currently underway [25].

## Cardiovascular Morbidity and Mortality

Cardiovascular disease (CVD) is the most common cause of death among men with PC who do not die from their underlying disease [26], but the data to support the claim that ADT increases CV mortality are conflicting. Several large retrospective observational studies clearly establish a link between ADT and CVD. An observational study of 73,196 patients from the Surveillance Epidemiology and End Results (SEER)-Medicare registry found that men treated with LHRH agonists had a statistically significant increase in the risk of developing coronary artery disease (CAD), myocardial infarction (MI), and sudden cardiac death (SCD) [27]. A second retrospective cohort study of 22,816 PC patients from the same registry, by Saigal et al., examined the cumulative incidence of CV morbidity in 22,816 men with PC patients treated between 1992 and 1996. This report found a 20 % greater incidence CVD in patients receiving ADT than in the control group. The increased risk was apparent 12 months after the initiation of ADT [28]. A retrospective analysis of 37,443 PC patients treated through the Veterans Affairs hospital system found an increased risk of CAD, MI, and SCD among patients who were treated with LHRH agonists. The incidence of stroke was also increased within this patient population [29]. Finally, there is evidence that patients 65 and older treated with ADT experience fatal myocardial infarctions an average of 2 years earlier than matched controls [30].

There are several published studies that dispute the association between ADT and poor CV outcomes. A large retrospective cohort study of 19,079 older men with PC from the Ontario Cancer Registry, half of whom were treated with ADT for at least 6 months, found no association between ADT and the risk of acute MI and SCD [16]. Furthermore, a series of prospective randomized controlled trials from the Radiation Therapy Oncology Group (RTOG) failed to discern an increased risk of cardiac death in patients treated with ADT and external beam radiation [31–33]. These conflicting results may be due to differences in the patient populations studied, proportions of patients receiving various treatment modalities (LHRH agonists vs. androgen receptor blockers vs. orchiectomy), selection bias among men offered ADT, and the limited number of cardiovascular events in some studies.

The American Cancer Society (ACS), in conjunction with the American Heart Association (AHA) and the American Urological Association (AUA), has published a statement instructing clinicians how to proceed given the possibility of increased CV risk due to ADT. The ACS advises careful

consideration of candidate's comorbidities and CV risk factors prior to the initiation of ADT. Of note, a large retrospective study suggests lack of a benefit for primary ADT in elderly men with PC [34]. There are CV risk factors associated with ADT; no particular intervention has been shown to mitigate this risk. Given the potential to increase CVD, one must weigh the risks and benefits of ADT for a given individual against the PC risks. For example, a man with low-risk PC, but with CV risk factors, should avoid unnecessary ADT, whereas a man with high-risk (or metastatic) PC and comorbidities would benefit from ADT. In addition to counseling, known modifiable CV risk factors should be addressed [35]. A summary of various studies about CVD and ADT and implications of radiation therapy have been described in Table 75.2 [16, 27–33, 35–37].

## Anemia

Although anemia associated with advanced PC is a common occurrence, the actual incidence of this condition can only be inferred from limited data. In a group of patients who underwent bilateral orchiectomy for PC, 78 % experienced a mild anemia, with a decrease in hemoglobin (Hgb) level of 1 g/dl from baseline, and 29 % demonstrated a decline of 2 g/dl or more [38]. In a study by Strum and colleagues of 133 patients undergoing ADT, 13 % experienced a decline in Hgb level of 25 % or more [39]. In a similar study by Asbell et al., 2 months of CAB led to anemia in 75 % of patients, compared with fewer than 5 % of patients who received goserelin acetate alone [40]. Furthermore, approximately 30 % of PC patients with metastases to the bone have anemia at the time of diagnosis [41].

The incidence of anemia in the setting of cancer is multifactorial. Castration is a well-documented cause of anemia, as testosterone is required for the enhancement of erythropoietin formation in the kidney as well as for the marrow action of erythropoiesis. It has been demonstrated that, after castration, red blood cell mass decreases 10 %, red blood cell diameter decreases 40 %, and osmotic fragility increases [42].

The production of inflammatory cytokines by PC may also cause a relative decrease in erythropoietin production, leading to anemia [43]. This myelosuppressive effect on red blood cell supply is believed to be mediated by moieties such as integrins, collagens, laminins, and other bone-derived proteins. While an additional mechanism may be possible, the major role of androgens in the release and action of GH and how ADT acts other than its effect on erythropoietin to cause a decline in Hgb is unclear [44]. The anemia associated with ADT is common, though not always clinically significant (i.e., symptomatic). Trials comparing CAB and monotherapy have been conducted but as these studies were not designed to look primarily at anemia, it is difficult to conclude how much of an impact CAB has in relation to LHRH monotherapy.

Johansson et al. described a benefit with the use of recombinant erythropoietin in PC patients: namely, a decrease in transfusion requirements and an improvement in quality of life [45], though one must use caution in using erythropoiesis-stimulating agents [46]. Low doses of dexamethasone are also being evaluated for the treatment of anemia related to PC. An increase in hemoglobin was noted in 65 % of patients receiving 0.5–2.0 mg of dexamethasone daily [47].

The most common manifestation of anemia is fatigue, though other presentations may occur. All underlying causes of anemia should be addressed before the start of ADT [48]. Although underlying anemia can be corrected with subcutaneous erythropoiesis-stimulating agent injections, the treatment is not risk free and Hgb levels due to ADT alone usually do not warrant intervention. Improvement in anemia usually occurs eventually after cessation of therapy, assuming other factors (such as cancer) are controlled [49].

## Musculoskeletal Side Effects

In the United States, ADT successfully treats one-third out of two million cancer survivors. However, some of these survivors may suffer from musculoskeletal side effects, including osteoporosis and sarcopenia. Many prospective studies have demonstrated that ADT causes immediate and sustained decrease in bone mineral density (BMD) [50, 51]. The mechanism of BMD decline includes increased bone turnover with increased osteoblastic and osteoclastic activity. This activity may peak at 6 months of ADT [51, 52]. It has been observed that change in sensitivity of bone to parathyroid hormone might also contribute to increasing osteoclastic activation and hence decreased BMD [53].

The increased bone turnover from ADT results in increased risk of bone fractures. Fragility fractures are a common occurrence in older men [54]. Hypogonadism, chronic glucocorticoid therapy, and excessive alcohol intake are among the most common risk factors for developing osteoporosis in men [55]. ADT with a LHRH agonist causes severe hypogonadism and significantly increases fracture risk [56, 57]. According to one claims-based analysis, men with PC receiving LHRH agonists were 1.4 times more likely to develop fractures compared to men with PC but have not received LHRH agonists [56]. In men with PC, pelvic 3D conformal external beam radiation therapy (EBRT) was associated with a 76 % increased risk of hip fracture. However, the combination of ADT and EBRT led to 40 % relative increase in hip fracture risk as compared to EBRT alone [58].

Sarcopenia can be defined as the age-related loss of muscle mass, strength and function [59]. Many factors, including physical inactivity, motor-unit remodeling, decreased hormone levels, and decreased protein synthesis, may all contribute to

**Table 75.2** Cardiovascular toxicity associated with androgen deprivation therapy (ADT)

| Data source | Type | Population | CV events | HR (95 % CI) | Conclusions |
|---|---|---|---|---|---|
| SEER/Medicare [27] | Retrospective cohort | 73,196 men >65 with local/regional disease | CAD: 15,116<br>MI: 3,917<br>SCD: 3,301 | MI: 1.11 (1.01–1.21)<br>CAD: 1.16 (1.10–1.21)<br>SCD: 1.16 (1.05–1.27) | ADT associated with CAD, MI, and SCD |
| SEER/Medicare [28] | Retrospective cohort | 22,816 men >65, all stages | 4,321 | CV event 1.20 (1.15–1.26) | ADT is associated with increased CV morbidity |
| Veterans Health Administration [29] | Retrospective cohort | 37,443 with local/regional disease | CAD: 4,775<br>MI: 857<br>SCD: 1,337 | LHRH agonist:<br>CAD: 1.19 (1.10–1.28)<br>MI: 1.28 (1.08–1.52)<br>SCD: 1.35 (1.18–1.54)<br>Orchiectomy:<br>CAD: 1.40 (1.04–1.87)<br>MI: 2.11 (1.27–3.50)<br>SCD: 1.29 (0.76–2.18) | LHRH agonists and orchiectomy increase risk of CAD, MI, and SCD. Oral antiandrogens do not significantly increase risk. Combined androgen blockade does not increase risk above that of LHRH agonists alone |
| CaPSURE [35] | Retrospective cohort | 4,892 with localized disease (3,262 prostatectomy, 1,630 radiation) | 131 CV deaths | Radical prostatectomy:<br>CV death: 2.6 (1.4–2.7)<br>Radiation:<br>CV death: 1.2 (0.8–1.9) | Patients treated radical prostatectomy in combination with ADT had increased risk of cardiovascular mortality. Patients treated with radiation therapy and ADT had a trend towards increased CV mortality |
| Nanda et al. [35] | Retrospective single-institution cohort | 5,077 with local/regional dz | 419 all-cause deaths | Mortality:<br>No risk factor: 0.97 (0.72–1.32)<br>Single CAD risk factor: 1.04 (0.75–1.43)<br>CHF/MI: 1.96 (1.04–3.71) | No increased all-cause mortality attributable to neoadjuvant ADT in patients with no or one cardiac risk factor. Patients with prior MI or CHF and ADT had a statistically increased risk of mortality |
| Ontario Cancer Registry [16] | Retrospective cohort | 19,079, men>66<br>ADT≥6 months | MI: 2,034<br>SCD: 835 | MI: 0.91 (0.84–1.00)<br>SCD: 0.96 (0.83–1.10) | ADT use is not associated with an increased risk of MIs or SCD |
| RTOG 85-31 [31] | Prospective randomized trial | Total: 189<br>RT + AD (indefinite)<br>RT (alone) | CR of CV death:<br>11 %<br>14 % | NS | Median f/u of 8.1 years CV-related deaths = 117<br>Treatment-related increase in CV mortality = No<br>At 9 years CV mortality for men receiving adjuvant goserelin = 8.4 %<br>Men treated without adjuvant goserelin = 11.4 % (Gray's $P = .17$) |
| RTOG 86-10 [32] | Prospective randomized trial | Total: 471<br>RT + AD (4 months)<br>RT (alone) | CR of CV death:<br>14 %<br>11 % | NS | In patients with Gleason score 2–6 , a short course of androgen ablation administered before and during radiotherapy has been associated with significant improvement in local control, reduction in dz progression, and overall survival |

(Continued)

**Table 75.2** (continued)

| Data source | Type | Population | CV events | HR (95 % CI) | Conclusions |
|---|---|---|---|---|---|
| RTOG 92-02 [33] | Prospective randomized trial | Total: 1,554<br>RT + AD (28 months)<br>RT + AD (4 months) | CR of CV death:<br>13.5 %<br>11 % | NS | The LTAD-RT arm showed significant improvement in all efficacy end points except overall survival (OS; 80.0 vs. 78.5 % at 5 years, $P = .73$), compared with the STAD-RT arm |
| D'Amico [36] | Prospective randomized trial | 241 men with clinically localized or advanced PC having RT + ADT or RT alone were selected | | Treatment with RT and ADT compared with RT was associated with a longer time to PSA recurrence ([HR], 0.22; 95 % CI, 0.14–0.35; $P < .001$). PCSM (HR, 0.23; 95 % CI, 0.09–0.64; $P = .005$), and all-cause mortality (HR, 0.30; 95 % CI, 0.16–0.58; $P < .001$) | Treatment using 6 months of ADT and RT compared with RT was associated with a longer time to PSA recurrence, PCSM, and decreased all-cause mortality |
| D'Amico [37] | Prospective randomized trial | 206 men with localized but unfavorable-risk PC were randomized to receive RT alone or RT + ADT | | A significant increase in the risk of all-cause mortality ([HR], 1.8; 95 % [CI], 1.1–2.9; $P = .01$) was observed in men randomized to RT compared with RT and ADT. Increased risk in all-cause mortality appeared to apply only to men randomized to RT with no or minimal comorbidity (HR, 4.2; 95 % CI, 2.1–8.5; $P < .001$). No increased risk of all-cause mortality for men with moderate or severe comorbidity, randomized to RT alone vs. RT and ADT: HR, 0.54; 95 % CI, 0.27–1.10; $P = .08$ | The addition of 6 months of ADT to RT resulted in increased OS in men with localized but unfavorable-risk PC. However, the benefit appeared to be negated in men with comorbidities |

*LDL* low-density lipoprotein, *TG* triglyceride, *HDL* high-density lipoprotein, *LHRH* luteinizing hormone-releasing hormone, ↑ increase, ↓ decrease, *HR* harm ratio/adjusted harm ratio, *PC* prostate cancer, *CV* cardiovascular, *MI* myocardial infarction, *CHF* congestive heart failure, *DZ* disease, *SCD* sudden cardiac death, *DM* diabetes mellitus, *CAD* coronary artery disease, *OS* overall survival, *CI* 95 % confidence interval, *CR* crude rate, *RT* radiation therapy, *ADT* androgen deprivation therapy, *flu* follow-up, *LTAD-RT* long-term androgen deprivation-radiation therapy, *STAD-RT* short-term androgen deprivation-radiation therapy, *PCSM* prostate cancer-specific mortality, *RT* radiation therapy

**Table 75.3** Recent phase III fracture prevention trials

| Name | | Population | Treatment | Conclusion |
|---|---|---|---|---|
| Toremifene (SERM) [72] | Multicenter phase III trial | 1,392 men 50 years or older with prostate cancer receiving androgen deprivation therapy were randomized to 80 mg toremifene per day or placebo | Toremifene 80 mg or placebo | Toremifene at a dose of 80 mg/day significantly increased BMD of the hip and spine in men receiving ADT |
| Denosumab (RANK ligand inhibitor) [73] | Randomized double-blind phase III study | The randomized, placebo-controlled trial included 1,468 men with histologically confirmed PC who were receiving ADT with an expected duration of on-study treatment of 12 or more months | Subjects were randomly assigned to receive subcutaneous injections of 60 mg denosumab or matching placebo every 6 months | Denosumab was associated with increased bone mineral density at all sites and a reduction in the incidence of new vertebral fractures among men receiving androgen deprivation therapy for nonmetastatic prostate cancer |

sarcopenia. The pathophysiology of sarcopenia is multifactorial and complex. It appears that the decrease in anabolic hormones (testosterone, GH, and estrogen), a concomitant increase in cytokines (interleukin [IL]-1β, tumor necrosis factor alpha, and IL-6), as well as nutritional factors, and atherosclerosis all contribute to the resulting loss of muscle mass [60].

Fatigue along with sarcopenia is an important manifestation of ADT. In a study with an aim to determine the prevalence, severity, and correlates of fatigue in a convenience sample of outpatients with PC, fatigue was found to be an important but underrecognized side effect of ADT [61].

Resistance exercises and psychological motivation may be effective tools for treating the symptoms and improving quality of life associated with osteopenia, sarcopenia, and fatigue. Exercise appears to be the best treatment to combat sarcopenia [60]. Multiple studies have demonstrated an improvement in muscle mass with exercise programs, particularly resistance training, in the elderly. No formal studies of exercise with PC patients have been performed. A small phase II study demonstrated a 37 % improvement in muscle strength with vitamin D replacement in patients with metastatic PC [62]. A recent trial has shown that relatively brief exposure to exercise significantly improves muscle mass, strength, physical function, and balance in hypogonadal men compared with normal care [63].

Bisphosphonates such as pamidronate, zoledronic acid, and alendronate as well as the receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor denosumab improve BMD and decrease the markers of bone metabolism in patients on ADT [64, 65]. Selective estrogen receptor modulators are also known to increase BMD and decrease the bone turnover [66]. Only one completed randomized controlled trial has evaluated bisphosphonate treatment among men with metastatic PC who are responding to first-line ADT. In that study, MRC PR05, clodronate failed to produce benefit [67]. After a median follow-up of 59 months, the clodronate group had no significant improvements in bone PFS (HR, 0.79; $p = .066$) and OS (HR, 0.80; $p = .082$) [68]. CALGB/CTSU 90202 (NCT00079001) is an ongoing randomized controlled trial that is designed to clarify the role of zoledronic acid in castration-sensitive metastatic PC [69]. The US Food and Drug Administration (FDA) recently granted approval for denosumab as a treatment to increase bone mass in patients who are at high risk of fracture from receiving ADT for nonmetastatic PC or adjuvant aromatase inhibitor (AI) therapy for breast cancer. In men with nonmetastatic PC, denosumab also reduced the incidence of vertebral fracture. The approvals were based on results from two international randomized (1:1), double-blind, placebo-controlled trials in patients receiving ADT. In men with PC, apart from effect on BMD, denosumab also significantly reduced the incidence of new vertebral fractures at 36 months. At 36 months, the proportion of men with new vertebral fracture was 1.5 % in men treated with denosumab compared with 3.9 % in men treated with placebo [absolute risk reduction (ARR) 2.4 %, 95 % CI (0.7, 4.1); relative risk reduction (RRR) 62 % (22, 81); $p = 0.0125$] [70]. The National Institutes of Health has recommended supplementation of calcium and vitamin D in men and women above 65 years to prevent the development of osteoporosis. However, their use to prevent the mineral loss in ADT is inconclusive [71]. Recently, completed clinically significant phase III fracture prevention trials are displayed in Table 75.3 [72, 73].

## Gastrointestinal Disturbances

Gastrointestinal (GI) toxicities from ADT may manifest in the form of anorexia, diarrhea and/or constipation, abdominal pain and nausea/vomiting, and liver damage, though the exact mechanisms of many GI side effects are not clear [74].

Many GI disturbances are related to oral hormonal drugs. For example, in a study assessing the combination of LHRH agonists and the antiandrogen flutamide, resulted in more diarrhea and nausea compared to leuprolide alone [75]. According to a study done by Langenstroer et al., the overall prevalence in 106 cases of GI side effects with flutamide was

**Table 75.4** Gastrointestinal side effects of hormonal therapy

| Study type | Patient population | Therapy | Toxicity |
|---|---|---|---|
| Phase II prospective trial [46] | 60 patients with high-risk prostate adenocarcinoma (having either a clinical stage of ≥T3a or an initial prostate-specific antigen [PSA] level of ≥20 ng/ml or a Gleason score of 8–10 or a combination of a PSA concentration of >15 ng/ml and a Gleason score of 7) | A LHRH agonist (leuprolide acetate, 22.5 mg), administered subcutaneously every 3 months) was prescribed for up to 6 months neoadjuvant, followed by concurrent hormonal therapy during RT and continuing after RT for 2–3 years | Acute toxicity was analyzed by RTOG toxicity criteria. 31 (51.7 %) patients had grade 1 GI toxicity, 21 (35 %) patients had grade 2 GI toxicity, and no patients had grade 3 or higher GI toxicity score |
| (CALGB 9583) Phase III randomized trial [47] | 260 patients with Progressive metastatic and androgen-independent PC having testosterone of <50 ng/ml were recruited in the study and divided in to two groups<br>1. Antiandrogen withdrawal = 128<br>2. Antiandrogen withdrawal + keto = 132 | Anti-androgen and Ketoconazole | Grade 3 or 4 hepatic toxicity was observed in 2 % of patients receiving ketoconazole |
| Retrospective study [48] | 1,091 consecutive patients treated for stage C or D PC with the antiandrogen flutamide and the luteinizing hormone-releasing factor (LHRH) agonist | Flutamide and LHRH agonist | An increase in AST and ALT at fourfold or more above upper normal limits was observed in four patients (0.36 %) and two of those developed clinically manifested liver failure |
| Phase III randomized trial [49] | Patients with histologically confirmed, previously untreated advanced (stage C/D) prostate cancer were recruited. Patients = 205<br>1. Bicalutamide 80 mg combination therapy = 102<br>2. LHRH agonist alone = 105 | Bicalutamide and LHRH agonist | Liver-related AE and ADRs:<br>Bicalutamide comb. therapy<br>ALT 7.8 %, 2.9 %<br>AST 7.8 %, 3.9 %<br>LHRH agonist alone<br>ALT 13.9 %, 9.9 %<br>AST 12.9 %, 10.9 % |
| Phase II trial [50] | 16 men with histologically confirmed PC not amenable to curative surgery or RT were eligible for the study if they had radiographic or PSA progression on at least one antiandrogens (not nilutamide) despite continued androgen suppression and standard antiandrogen withdrawal periods | Nilutamide | This study was closed after a planned analysis showed that there were only three partial responses. There were no grade ¾ toxicities and only three patients had grade ½ constipation |

*LHRH* luteinizing hormone-releasing hormone, *CALGB* Cancer and Leukemia Group B, *ADT* androgen deprivation therapy, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

22 %. Though some GI disturbances can be attributed to use of radiation therapy, this study of flutamide concluded that irradiated cases are not at greater risk for the development of GI side effects, suggesting that drug-induced local toxicity does not mediate GI distress [76].

Table 75.4 shows various studies involving different hormonal agents and their gastrointestinal toxicity profiles [77–81].

The incidence of drug-induced liver injury is on the rise in the United States; Ricker et al. reported a case of a patient who had histrelin (VANTAS) implant and later on went on to develop severe liver injury (necroinflammatory injury with bridging necrosis) [82]. Oral hormonal therapies including flutamide, bicalutamide, nilutamide, and ketoconazole have long been associated with liver toxicity and some of the newer oral drugs may be associated as well. The diagnosis of drug-induced liver injury may be difficult to prove retrospectively once the event is completed. Therefore, successful data gathering and testing should be performed as the event is unfolding.

## Psychological and Cognitive Side effects

ADT in patients with PC may result in many cognitive, neurological, and psychiatric side effects. Psychiatric side effects in such patients include moodiness, temper tantrums, depression,

anxiety, and crying with minimal provocation. Cognitive side effects include impaired memory concentration and verbal skills [83]. Many studies have been inconclusive in finding the relationship between these side effects and low testosterone levels. A weak relationship has been shown by some studies.

Recently, in an effort to find out more about the association between ADT and psychiatric and cognitive functions, a systemic search of various databases was performed. Studies have shown that 47–69 % of men on ADT declined in at least one cognitive area, most commonly in visuospatial abilities and executive functioning [84]. Significant progress has been made to determine the prevalence of cognitive impairment in men treated with ADT and to assess changes in cognitive performance over time. However, there is a high prevalence of lower than expected cognitive performance among a sample of patients starting ADT for PC, and there is no consistent evidence that 12 months of ADT use has an adverse effect on cognitive function in elderly men with nonmetastatic PC [85, 86].

There is no well-established treatment of the psychological and cognitive side effects. Exercise, especially resistance exercise, has helped to improve psychological side effects in patients receiving hormonal manipulation [74]. Other than physical activity and exercise, there is no well-established treatment to treat psychological and cognitive adverse effects of ADT.

## Sexual Side Effects

The most commonly and acutely encountered sexual side effects of ADT are loss of libido and erectile dysfunction (ED). Testosterone is not the only factor responsible for the libido effect; other factors that might contribute in this context include age, physical fitness, and psychological factors including cancer diagnosis and pretreatment testosterone levels may have an impact. Loss of libido, ED, genital shrinkage, low self-esteem, and diminished masculinity are associated with undergoing ADT. These losses frequently lead to changes in primary partner relationships. Clinicians should carefully select intervention strategies for helping couples maintain a strong relational bond for this population because of these unique and profound changes [87].

The first-line therapy for the men with ED is usually PDE-5 inhibitors. Several randomized phase III studies have suggested that intermittent hormonal therapy (IHT) may be as efficacious as continuous therapy in biochemical and locally advanced PC with some evidence in the metastatic setting as well. There seems to be no significant difference in terms of patient survival; however, there may be better sexual function as well as favorable economical effects on the individuals and community [88]. Other important therapeutic interventions include intraurethral medications, intracavernosal injections, vacuum constriction devices, and penile prosthesis.

## Breast Toxicity

Both gynecomastia and mastalgia may be seen with ADT. In men, estrogen has many physiological effects, and ADT may result in altering the ratio of estrogen to testosterone that is then responsible for the manifestations of the side effects like gynecomastia and mastalgia [68]. Breast problems may be especially bothersome with unopposed antiandrogen therapy, which results in higher circulating testosterone levels and estrogen aromatization via negative feedback from the pituitary. Antiandrogen monotherapy for PC is associated with breast toxicity incidence range of 30–79 %, estrogens 40–77 %, orchiectomy 1–14 %, and LHRH agonists 1–16 % [89]. Unfortunately, little is known regarding the physiological impact that gynecomastia has on men; however, gynecomastia for many men can be psychologically distressing, even to the point of requiring psychological support or intervention. If gynecomastia has been present for less than 1 year, it may be resolved only with cessation of the therapy. With further therapy, breast tissue may become fibrosed and hyalinized, so it becomes difficult to treat. The most common modalities for treatment include RT, subareolar mastectomy, and medical treatment. In a randomized Scandinavian trial, SPCG-7/SFUO-3, 253 patients underwent prophylactic breast irradiation, and the results showed significant decrease in the risk of ADT-induced gynecomastia and breast tenderness (78 vs. 21 % in non-RT and RT, respectively, $p < 0.001$) [90]. Aromatase inhibitors and tamoxifen are also used for the treatment of breast tenderness [91].

## Vasomotor Side effects (Hot Flashes)

Vasomotor symptoms or hot flashes are subjective sensation of heat often followed by excess perspiration. The essential attributes of hot flashes in men consist of physiologic (e.g., warmth, sweating, chills) and psychological (e.g., anxiety, impaired memory, agitation) factors. In men undergoing treatment for PC with ADT, the incidence is as high as 70 %, with different rates between men who have undergone surgical castration and patients undergoing LHRH agonist therapy. Lack of symptoms in those with congenital hypogonadism supports the prevailing theory of change in sex hormone level as the most likely causative factor. In a recent phase III trial of a new formulation of leuprolide acetate, the most common treatment-related adverse event was hot flashes seen in 72 of 160 men (45.0 %) [92]. Another study investigated hot flashes and quality of life during CAB therapy, using steroidal or nonsteroidal antiandrogens. More hot flashes were experienced in patients taking bicalutamide, and the results suggest that CAB using a steroidal antiandrogen such as chlormadinone might induce fewer and less-distressing hot flashes than CAB with bicalutamide [93].

Several studies have examined the utility of pharmacologic treatment of ADT-induced hot flashes. A randomized double-blind clinical trial compared the efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flashes, demonstrating efficacy for all of the drugs in treating the symptoms [94]. Another clinical trial has shown that paroxetine is more effective than fluoxetine in the treatment of hot flashes. A randomized trial of 235 men showed decrease in frequency of hot flashes experienced by patients receiving high-dose gabapentin as opposed to patients receiving placebo or low-dose gabapentin [95]. Alternatives to pharmacologic intervention include acupuncture and lifestyle changes such as weight control and smoking cessation.

## Newer Hormonal Agents

We now recognize that the vast majority of what used to be termed "hormone refractory" PC cases are now simply castration resistant, and newer, more powerful hormonal agents are being investigated. Most of the toxicities seen with the newer agents are similar to those seen with standard ADT (though could be more severe). While prospective randomized phase III trials for most of these agents are ongoing, it appears that some toxicity is different than those seen with simple ADT. Unopposed CYP17 inhibitors such as abiraterone acetate and orteronel may lead to mineralocorticoid excess, clinically manifesting as hypertension, hypokalemia, and/or fluid retention. Addition of low-dose corticosteroids or mineralocorticoid antagonists can ameliorate some of these toxicities, though appropriate mineralocorticoid antagonists are not widely available (spironolactone should not be used). With increasing experience and longer-term follow-up, additional toxicities may be discovered.

### Conclusions

ADT for PC is a powerful tool in the armamentarium of an urooncologist. However, toxicities exist and their indiscriminate use is not warranted. Every physician should maintain a careful balance between risk of potentially dangerous toxicities and beneficial antitumor efficacy for each individual in conjunction with personal preferences.

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# Chemotherapy and Novel Systemic Approaches in the Treatment of Metastatic Castration Resistant Prostate Cancer

76

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## Introduction

Prostate cancer is the most commonly diagnosed non-skin cancer in men in North America, and it is the second leading cause of cancer-related death [1]. Although the majority of men diagnosed with prostate cancer can be cured with definitive local therapy [2–13], many will subsequently have recurrent disease and others will have metastatic disease at presentation. Although metastatic prostate cancer is incurable, there exist several systemic treatment options with the goal of disease control, prolongation of life, and palliation of symptoms. The natural history of prostate cancer is extremely heterogeneous, but in the vast majority of men with recurrent disease there is a period of hormone sensitivity when patients can be treated with androgen deprivation therapy [14, 15]. Inevitably, the disease evolves to a castration resistant state which is defined as a rising PSA and/or clinical progression despite castrate levels of testosterone. The mechanisms mediating the development and evolution of castration resistant disease have been identified as being related to the androgen receptor (i.e., amplified, hypersensitive, and promiscuous androgen receptor) but can also bypass it [16, 17].

Median survival for patients with metastatic castration resistant prostate cancer (CRPC) is on the order of 18–24 months [18, 19], although there is wide variation around this median. Prognostic factors that are well validated in the setting of localized prostate cancer (stage, initial PSA, Gleason score) are no longer applicable in mCRPC. Prognostic factor s for mCRPC that have been identified include PSA doubling time, the presence of visceral versus bone-only metastasis, a variety of laboratory parameters (including hemoglobin, alkaline phosphatase, and LDH), and, most recently, the presence of circulating tumor cells [20, 21]. Despite these and other prognostic factors in mCRPC, we are sorely lacking in markers that are predictive of response to various treatments, and this is an area that, given the rapid evolution of treatments in this disease setting, will require significant effort to develop.

Historically, docetaxel chemotherapy has been the only intervention shown to improve overall survival in the context of CRPC [22]; however, more recently, several additional treatment options with a diversity of approaches have been shown to be efficacious in this disease [23–25] reflecting the evolution in our understanding of the biologic underpinnings of CRPC (Table 76.1).

Within this chapter, we will review standard systemic therapies for CRPC and also explore areas of ongoing research directed at mechanisms that drive the development and progression of CRPC with a focus on those areas for which novel targeted therapies have been developed and are in testing (Table 76.2).

## Classes of Drugs with Approved Therapies

### Chemotherapy

Mitoxantrone, an anthraquinone that is structurally similar to anthracyclines, was the first cytotoxic chemotherapy

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**Table 76.1** Agents demonstrating positive benefits in phase III trials for CRPC

| Name of agent | Class of agent | Patient population | Comparator arm | Primary endpoint benefit | Notable adverse events | Potential future applications |
|---|---|---|---|---|---|---|
| Mitoxantrone + prednisone [26] | Chemotherapy (Anthracenedione) | CRPC with pain symptoms and no prior chemotherapy | Prednisone | Palliative pain response (29 vs. 12 %) | Febrile neutropenia (<2 %), cardiotoxicity (<4 %) | After taxane chemotherapy |
| Docetaxel + prednisone [22] | Chemotherapy (Microtubule stabilizer) | CRPC, no prior chemotherapy | Mitoxantrone + prednisone | Overall survival (median 18.9 vs. 16.5 months) | Febrile neutropenia (3 %), diarrhea (32 %), sensory neuropathy (30 %) | Earlier use in disease process |
| Cabazitaxel + prednisone [27] | Chemotherapy (Microtubule stabilizer) | CRPC, prior docetaxel | Mitoxantrone + prednisone | Overall survival (median 12.7 vs. 15.1 months) | Febrile neutropenia (8 %), diarrhea (47 %) | Earlier application in the first-line chemotherapy setting |
| Abiraterone acetate + prednisone [23] | CYP17 inhibitor | CRPC, prior docetaxel | Placebo + prednisone | Overall survival (median 10.9 vs. 14.8 months) | Mineralocorticoid excess: edema (31 %), hypokalemia (17 %) | Phase 3 study in the CRPC, chemotherapy-naïve setting is completed |
| Denosumab [28] | Fully human monoclonal antibody against RANK ligand | CRPC with bone metastases | Zoledronic acid | Delay in first, on-study SRE (median 17.1 vs. 20.7 months) | Hypocalcemia (13 %), osteonecrosis of the jaw (2.3 %) | Prevention of bone metastases |
| Sipuleucel-T [29] | Autologous cellular immunotherapy | Asymptomatic CRPC | Placebo | Overall survival (25.8 vs. 21.7 months) | Grade 1–2 myalgias, fever, fatigue | Earlier use in disease process |
| Alpharadin [24] | Radiopharmaceutical | CRPC, prior docetaxel or unfit for docetaxel | Placebo | Overall survival (median 14.0 vs. 11.2 months) | Grade 3–4 neutropenia (2 %) and thrombocytopenia (4 %) | Earlier use in disease process |

**Table 76.2** Examples of agents in development in CRPC

| Target | | Agents |
|---|---|---|
| Androgen receptor signaling | Biosynthesis | Abiraterone |
| | | orteronel |
| | Receptor | MDV-3100 |
| | | ARN-509 |
| | | AZD-3514 |
| | | EZN-4176 |
| | | BMS-641988 |
| | Both | TOK-001 |
| Chaperone proteins | HSP90 | STA-9090 |
| | | IPI-504 |
| | Clusterin | OGX-011 |
| | HSP27 | OGX-427 |
| DNA repair | PARP | ABT-888 |
| Apoptosis | Bcl-2 family | AT101 |
| | Survivin | LY2181308,YM155 |
| Lysine deacetylases | | SB939 |
| | | LBH589 |
| Immune | CTLA-4 | Ipilimumab |
| | PD-1 | CT-011, MDX-1106 |
| | Vaccine | PROSTVAC-VF |
| | | CV9103 |
| | | TroVax (MVA-5 T4) |
| Cell signaling | IGF1R | Cixutumumab |
| | ErbB | Afatinib |
| | VEGF + other | Aflibercept |
| | | Cabozantinib |
| | | Cedirinib |
| | | TKI-258 |
| | | Vandetanib |
| | | Pazopanib |
| | C-Met | AMG 102 |
| | PI3K | PX866 |
| | | BKM120 |
| | mTOR | Temsirolimus |
| | | Everolimus |
| | Src | Dasatinib |
| | | Bafetinib |
| | | KX2-391 |
| | PDGFRα | IMC-3 G3 |
| | Integrins | CNTO 95 |
| Other/multiple | Angiogenesis, immune, cytotoxic | Lenalidomide tasquinimod |

approved for use in metastatic CRPC. The US Food and Drug Administration approval for mitoxantrone in this setting was based not on an improvement in overall survival, but rather due to the drug's ability to palliate symptoms. Tannock and colleagues demonstrated the palliative benefits of mitoxantrone in a relatively small trial randomizing patients to mitoxantrone plus prednisone versus prednisone alone [30]. The primary endpoint was pain control which was met. Improvement in progression free survival was also demonstrated favoring the mitoxantrone plus prednisone arm; however, there was no overall survival benefit. Subsequent trials evaluating mitoxantrone in the then termed "hormone refractory" population also failed to demonstrate an improvement in overall survival [26, 31].

It was 2004 before any systemic intervention was shown to have an impact on overall survival in CRPC. The TAX-327 trial randomized patients to one of three intervention arms: mitoxantrone plus prednisone versus docetaxel plus prednisone administered weekly versus docetaxel plus prednisone delivered every 3 weeks [22]. The primary endpoint was overall survival. There was a statistically significant improvement in overall survival in the docetaxel plus prednisone given every 3 weeks arm compared with the mitoxantrone arm (HR = 0.76, $p = 0.009$); this translated into an absolute survival benefit of 2.5 months (median survival 16.4 months in mitoxantrone arm and 18.9 months in the docetaxel plus prednisone q3weeks arm). Docetaxel administered every 3 weeks also demonstrated a statistically significant reduction in pain compared with mitoxantrone, and there was a statistically significant improvement in quality of life. Docetaxel administered weekly did not achieve significance in any of the survival, pain, or quality of life endpoints and is therefore not recommended. Following the completion of this trial, docetaxel plus prednisone administered every 3 weeks became the standard of care for the first-line chemotherapy treatment of metastatic CRPC, and it remains so to this day.

The most commonly reported toxicities from docetaxel included fatigue, alopecia, diarrhea, and nail changes. The rate of febrile neutropenia in the q3weekly docetaxel arm was 3 versus 2 % in the mitoxantrone arm.

Decreases in PSA are often not observed until two to three cycles of docetaxel chemotherapy have been administered, and therefore early cessation, particularly in the absence of worsening symptomatic disease, is not advisable. For men who do achieve PSA and symptomatic responses with docetaxel, the duration of therapy has not been established. Among many practitioners, it is generally accepted that ten cycles is the standard maximum, as per the TAX-327 study and as patients are approaching or have exceeded the tolerance of docetaxel by that point (particularly with regard to peripheral neuropathy), others treat until progression as defined by clinical parameters.

Multiple attempts at improving outcomes by combining docetaxel with other cytotoxic agents have been made. Docetaxel has been combined with vinorelbine [32], capecitabine [33], epirubicin [34], and estramustine [35, 36]. In the majority of cases, these combinations have been assessed in the context of phase II trials, and although activity has been shown for most, the activity has not superseded the historical benefit of single-agent docetaxel. Further, the toxicity profile was found to be, expectedly, worse with combination chemotherapy.

Combining weekly docetaxel with high-dose calcitriol, which has antiproliferative and pro-apoptotic effects in a variety of tumor models, was initially of great interest after a randomized phase II trial demonstrated a survival advantage for the combination compared with weekly docetaxel alone [37]. This lead to a phase III trial with results that were recently reported [38]. Patients were randomized to docetaxel plus prednisone given every 3 weeks versus weekly docetaxel plus high dose calcitriol. The trial was stopped early after an interim safety analysis revealed more deaths in the intervention arm. The final results showed a statistically significant decrease in overall survival for the weekly docetaxel and calcitriol arm (16.8 vs. 19.9 months, $p=0.002$). Whether this worsening of outcome is related to the calcitriol or to the schedule of docetaxel delivery (weekly vs. every 3 weeks) is unclear.

Until recently, there was no standard second line systemic option that afforded survival benefit. Typical second-line options have historically included retreatment with docetaxel, mitoxantrone, or enrollment in clinical trials. Cabazitaxel is a semisynthetic taxane that was developed to overcome taxane resistance. A randomized phase III open label clinical trial comparing cabazitaxel (25 mg/m$^2$) to standard mitoxantrone in patients with metastatic CRPC who had progressed after having received docetaxel chemotherapy has been conducted [39]. Seven hundred and fifty-five men were randomized, and there was a statistically significant overall survival benefit in the cabazitaxel group compared with the mitoxantrone group (15.1 vs. 12.7 months, HR = 0.70, $p<0.0001$). Although cabazitaxel was the first agent found to offer a substantial survival benefit in patients who are progressing after prior docetaxel, there can be significant toxicity associated with treatment. Adverse events associated with cabazitaxel included febrile neutropenia which occurred in 8 % (vs. only 1 % in the mitoxantrone arm), and 5 % of patients died within 30 days of last dose of drug from causes including neutropenic sepsis. This emphasizes the need for appropriate patient selection and toxicity management, including G-CSF support, when considering second-line chemotherapy in this frequently elderly and frail patient population.

Given the efficacy but significant toxicity of cabazitaxel, a randomized phase III trial is currently underway evaluating the relative effects of different doses of cabazitaxel (20 vs. 25 mg/m$^2$) in patients with mCRPC previously treated with a taxane chemotherapy (NCT01308580). Cabazitaxel was developed to overcome resistance to previous taxanes; however, the potency of cabazitaxel was similar to that of docetaxel in cell lines. There is now a question of whether or not cabazitaxel should be administered before docetaxel in mCRPC. A 3 arm randomized phase III trial is presently accruing in an attempt to address this question. Patients with mCRPC who have not had a previous taxane will be randomized to either docetaxel 75 mg/m$^2$, cabazitaxel 25 mg m$^2$, or cabazitaxel 20 mg/m$^2$; all three treatment arms will receive concurrent prednisone (NCT01308567).

Other cytotoxic agents have been evaluated in metastatic CRPC, but none have been incorporated into standard practice. Satraplatin (an orally bioavailable platinum agent) was studied in a randomized phase III trial comparing it to placebo in men who had progressed after first-line chemotherapy [40]. There was a statistically significant improvement in progression-free survival in the treatment arm but no difference in overall survival. Epothilones are a new class of non-taxane tubulin-polymerizing agents. Ixabepilone [41, 42], and patupilone [43] have been studied in the phase II setting in CRPC demonstrating clinical responses.

## Androgen Receptor Signaling

Androgen receptor (AR)-mediated signaling plays a pivotal role both in normal prostate development and in prostate cancer initiation and progression. In the normal prostate, the androgen receptor regulates the differentiation program of luminal epithelial cells, controls expression of specific prostatic proteins (such as PSA), and maintains and stimulates vascularity of the prostate. The critical role of AR-mediated signaling in prostate cancer is underscored by the clinical responsiveness of the tumor to therapies that deplete levels of the AR ligands, testosterone and dihydrotestosterone (LHRH agonists/antagonists or surgical castration), or directly antagonize AR function (bicalutamide).

While the relevance of continued AR signaling in prostate cancer is underscored by the clinical experience, the molecular mechanisms by which the AR mediates this effect are less apparent. These may relate to driving prostatic epithelial cell survival and growth [44, 45] as exemplified by the relevance of the gene fusion between the androgen regulated TMPRSS2 gene and the Ets transcription factor (primarily ERG) in primary prostate cancer and adjacent PIN lesions, creating a potent androgen-egulated transcription factor that might drive prostate cancer development [46–48]. The adaptive response of the AR signaling machinery to hormone therapy induced depletion of circulating androgens remains a matter of intense research and indeed speculation.

A plethora of immunohistochemical studies have demonstrated that expression of the AR is elevated in the majority of CRPC tissues [49–51], a finding corroborated by a number of studies confirming elevated AR gene transcription in CRPC compared with primary hormone-naive prostate tumor tissue [52–54]. The elevated levels of AR gene transcription and protein expression may be introduced by AR gene amplification which occurs in a significant fraction of CRPC tissues [55, 56].

However, it has been known for some time that current androgen-depleting therapies, as exemplified by LHRH

agonists and antagonists, while effective in inducing marked 90–95 % declines in systemic androgen levels only result in declines of 70–80 % in intra-prostatic androgen levels [57–61]. Furthermore, the residual levels of androgens present in the prostatic tissue are sufficient to drive AR-mediated signaling pathways [62].

The elevated levels of androgens present intraprostatically may be due to increased androgen synthesis within the prostate, via decreased catabolism of systemically acquired androgens, or via a combination of both of these mechanisms.

The raised androgen synthesis may derive from conversion of peripheral circulating weak androgens, mostly derived from the adrenals such as androstenedione or dihydroepiandrostenedione, DHEA, or even from de novo synthesis of androgens from circulating precursors such as cholesterol or progesterone [63], though the relevance of this in the clinical setting has yet to be determined [64]. Normal prostate stromal cells can catalyze the conversion of the weak adrenal androgen androstenedione to testosterone via the aldo-keto reductase family 1C3 (AKR1C3 or 17β-hydroxy steroid dehydrogenase type 5, 17β-HSD5) protein [65–69].

Production of the weak adrenal antigens, such as androstenedione, is not affected by standard first-line hormonal therapy such as LHRH agonists/antagonists implying that agents that might deplete adrenal androgen synthesis could be effective as second-line therapies in CRPC.

Given that our knowledge surrounding the mechanisms of castration resistance has expanded exponentially in recent years, it is unsurprising that extensive research has been directed toward developing more potent inhibitors of extragonadal androgen production and antagonists of the androgen receptor [70]. Two promising agents that exert their effect by targeting mechanisms of androgen receptor activation are abiraterone acetate (Couger Biotechnology Inc.) and MDV3100 (Medivation Inc.). Results from early phase clinical trials were encouraging and served to clinically confirm that CRPC often remains dependent on androgen receptor signaling; both agents subsequently entered into phase III testing.

Orally administered abiraterone acetate inhibits the cytochrome P450 enzyme CYP17A1. CYP17A1 has dual function as both a 17α-hydroxylase and a $C_{17,20}$-lyase, and both of these functions are required to synthesize androgens from cholesterol precursors. An initial phase I trial demonstrated good tolerance of the drug at all treatment levels in chemotherapy-naïve patients with CRPC [71]. Common toxicities were associated with mineralocorticoid excess and included hypertension, hypokalemia, and edema. These side effects were expected given the mechanism of action of abiraterone acetate, as inhibition of CYP17 decreases cortisol levels resulting in a compensatory increase in adrenocorticotrophic hormone (ACTH) and a subsequent increase in deoxycorticosterone and corticosterone. These side effects could be controlled by the administration of a mineralocorticoid antagonist (eplerenone) or corticosteroids to suppress ACTH. In this phase I trial, PSA declines of ≥30 and 50 % were observed in 66 and 57 % of patients, respectively.

High rates of PSA response have been reported in several phase II trials of abiraterone acetate in patients with CRPC in both the pre- and post-docetaxel patients settings with rates of PSA response ranging from 50 to 85 % [72, 73]. High-dose ketoconazole is a treatment option for those patients who have exhausted all standard therapies. It, like abiraterone acetate, suppresses steroidogenesis through P450 dependent enzymes. A phase II trial reported differences in efficacy of abiraterone dependent on previous exposure to ketoconazole; PSA declines of ≥50 % were seen in 45 % of ketoconazole-naïve patients but in only 26 % of patients previously treatment with ketoconazole [74].

A randomized, double-blind, placebo controlled trial of abiraterone acetate plus prednisone was undertaken and the results have recently become available [23]. The study enrolled 1,195 men with CRPC who had progressed after treatment with docetaxel. Patients were randomized 2:1 in favor of abiraterone plus prednisone versus placebo. The primary endpoint was overall survival with several secondary endpoints including time to PSA progression, radiographic progression-free survival, and PSA response rate. At the first predetermined interim analysis, the data monitoring committee recommended that the study be unblinded as there was a significant improvement in outcomes for those patients randomized to receive abiraterone. Median overall survival for patients in the abiraterone and placebo groups was 14.8 and 10.9 months, respectively (HR = 0.65, $p < 0.0001$). Time to PSA progression, radiographic progression free-survival, and PSA response rates were also all significantly improved in the abiraterone arm. Mineralocorticoid-related toxicities were more commonly reported in the treatment arm; however, these toxicities were grade 3 or 4 (severe or life-threatening) in fewer than 4 % of abiraterone acetate treated patients and overall adverse events were similar in the placebo treated patients. The results of this trial confirm that inhibition of extra-gonadal androgen synthesis with abiraterone acetate exerts substantial clinical benefits even in patients with late stage disease.

It is unknown at this point whether abiraterone is equally as efficacious in the population of patients who have not yet received docetaxel; however, a second phase III trial has completed accrual evaluating abiraterone acetate in patients who are chemotherapy naïve and asymptomatic or minimally symptomatic (not requiring opiate analgesics) to address this question. The primary endpoints for this study are overall survival and progression-free survival (NCT00887198).

Similar to abiraterone acetate, TAK-700 is also a potent inhibitor of CYP17A1 currently in clinical development.

Data from a phase I/II study was presented at the 2010 American Society of Clinical Oncology Annual Meeting. In the phase I portion of this open-label dose-escalation study, 26 patients with metastatic CRPC were enrolled, 11 of whom had received prior ketoconazole [75]. Treatment at all five dose levels was reasonably well tolerated, although all patients had at least grade 1 adverse events. The most commonly reported toxicities were fatigue and GI events (nausea, constipation, anorexia, vomiting). All patients who received ≥300 mg daily had a PSA response (PSA response ≥50 and ≥90 in 80 and 27 % of those patients who received ≥3 cycles, respectively), and the phase II dose was determined to be 300 mg BID. Phase III trials in patients who have had prior docetaxel chemotherapy (NCT01193257) or chemotherapy naïve (NCT01193244) are now accruing.

MDV3100 is a potent novel small AR antagonist that prevents nuclear translocation and DNA binding of AR. Unlike bicalutamide, no agonistic activity is described with MDV3100. A first-in-man, multicenter phase I/II dose-escalation study has been reported and demonstrated encouraging clinical results [76]. Treatment was well tolerated with fatigue as the most commonly reported grade 3/4 adverse event. PSA responses of ≥50 % were observed in 56 % of patients, and the median time to radiologic progression was 47 weeks. Given this, a dose of 160 mg/day has been selected as the dose for a phase III trial in which approximately 1,200 patients with CRPC who have progressed after docetaxel were randomized 2:1 in favor of MDV3100 versus placebo (NCT00974311). The primary endpoint of the trial is overall survival. As of November 2010, accrual has been completed and data are maturing. A second phase III trial is still recruiting patients, and it is evaluating MDV3100 versus placebo in the chemotherapy-naïve population of patients with mCRPC (NCT01212991).

There are a number of other novel drugs targeting the androgen receptor signaling cascade. ARN-509 is a second generation antiandrogen that is currently being assessed in a phase I/II trial in patients with mCRPC previously treated with docetaxel (NCT01171898). TOK-001 is a unique drug that impacts the androgen cascade in three ways: it is an androgen receptor antagonist, it is an inhibitor of CYP-17-lyase, and it decreases the level of the AR in prostate tumor tissue. TOK-001 is in early clinical testing, and there is currently a phase I/II dose escalation study accruing in the mCRPC, chemo-naïve population (NCT00959959).

## Bone Targeting

Given that the vast majority of patients with metastatic prostate cancer have bone metastases, therapies directed at inhibiting bone progression are rational. Bisphosphonates are an established treatment for men who have bone metastases, and studies continue with the aim of further defining their use in earlier disease stages. Additional agents targeting the biologic underpinnings of bone metastases' development and progression are under clinical development.

### RANK Ligand

Receptor activator of nuclear factor kappa B (RANK) and its ligand (RANK-L) have been identified as mediators that increase osteoclastogenesis. RANK-L is expressed by osteoblasts and is a member of the TNF superfamily. The binding of RANK-L to RANK is both necessary and sufficient to stimulate osteoclast-cell differentiation, proliferation, and inhibit osteoclast apoptosis. Osteoprotegerin (OPG) is a secretory glycoprotein that blocks the effects of RANK by acting as a decoy receptor for RANK-L; the effect is that OPG hinders the ability of RANK-L to stimulate bone resorption. Critical in the pathogenesis of bone metastases in advanced prostate cancer is the interplay between OPG, RANK-L, and RANK [77–79].

Denosumab (Amgen Inc.) is a fully humanized monoclonal antibody delivered via subcutaneous injection that is directed against RANK-L. In patient with physiologic or treatment-related bone loss, denosumab has demonstrated activity in reducing bone resorption and increasing bone density (when compared with either placebo or bisphosphonates) [80, 81].

A phase III randomized double-blind placebo-controlled trial of denosumab versus zoledronic acid (a potent bisphosphonate) in patient with CRPC who have bone metastases has recently been reported [28]. The primary endpoint was time to first skeletal-related event (as defined by pathologic fracture, need for radiation or surgery, or spinal cord compression). Patients were randomized 1:1, and 1,901 patients were accrued. Denosumab significantly delayed the time to first skeletal-related event (SRE) compared with zoledronic acid with the median time to first SRE as 20.7 and 17.1 months between the groups, respectively (HR = 0.82; 95 % CI: 0.71–0.95; $p = 0.008$). In correlative studies, it was shown that denosumab resulted in greater suppression of bone turnover markers compared with zoledronic acid. Rates of overall and serious adverse events were similar between groups. There were, however, more reports of hypocalcemia in the denosumab arm (13 vs. 6 %) and for the first time osteonecrosis of the jaw was a reported toxicity from denosumab (2.4 vs. 1.3 % in the denosumab and zoledronic acid groups, respectively). There was no difference in overall survival between groups.

More recently, a large phase III multicenter randomized double-blind placebo controlled trial evaluating denosumab in a population of patients with CRPC, but no bone metastases has been preliminarily reported (NCT00286091). In this study, 1,432 patients with CRPC who were at high risk for the development of bone metastases (PSA ≥8, and/or PSA

doubling time of ≤10 months) were randomized to receive either placebo or subcutaneous denosumab every 4 weeks. The median bone metastasis-free survival was 29.5 months with denosumab and 25.2 months with placebo (HR = 0.85, $P = 0.028$). The median time to bone metastasis was 33.2 months with denosumab and 29.5 months with placebo (HR = 0.84, $P = 0.032$). Although these results are notable as the first demonstration that an agent can delay the development of bone metastases, whether this benefit is worth the potential adverse events associated with denosumab, such as osteonecrosis of the jaw, remains to be decided and currently denosumab has not been approved for this indication.

### Endothelin-1

Endothelins (ET) are mediators of the osteoblastic response of bone to metastatic disease that are elevated in men with metastatic prostate cancer [82]. Three forms of ET have been described (ET-1, -2, -3) which bind to two receptors, ET receptor A and B (ET-A, ET-B). Osteoblasts stimulate metastatic prostate cells in bone to produce ET-1, and consequently, osteoblasts are stimulated by ET-1 to proliferate. The end result is new bone formation and osteoblastic metastases which contributes to a vicious cycle of progression [83].

Atrasentan (Abbott Laboratories) is an orally bioavailable competitive inhibitor of ET-1 that binds with 1,800-fold selectivity to the ET-A receptor (i.e., compared to ET-B). Treatment with atrasentan is well tolerated, and reported side effects (which include peripheral edema, rhinitis, and headache) appear to be mechanistically related to vasodilation. There have been occasional reports of heart failure, and both hypotension and hyponatremia were dose limiting in phase I trials. In a randomized double-blind placebo-controlled phase II study, 288 patients with metastatic CRPC received atrasentan (either 2.5 or 10 mg) or placebo [84]. In the intention to treat analysis, a nonstatistically significant increase in time to progression was observed in the 10-mg dosing group (183 vs. 137 days). A multinational double-blind placebo-controlled trial was subsequently undertaken [85] in which 809 patients with metastatic CRPC were randomized to receive either atrasentan 10 mg daily or placebo. There was confirmation of the biologic effect of atrasentan as evidenced by a delay in the increase in bone alkaline phophatase as a marker of bone deposition. Despite this, the primary endpoint of delayed time to progression was not met. A second phase III trial comparing atrasentan to placebo was carried out in patients with non-metastatic CRPC with time to progression as the primary endpoint. As in the phase III trial reported above [85], biologic effects were observed with a decreases in bone alkaline phosphatase and PSA in the atrasentan group; however, time to progression was not statistically different [86]. Development of atrasentan continued in combination with docetaxel; however, a large phase III trial involving approximately 1,000 patients with metastatic CRPC conducted by the Southwest Oncology Group comparing docetaxel and prednisone ± atrasentan (with OS as the primary endpoint) has recently been reported as negative (NCT00134056).

Zibotentan is a more specific inhibitor of ET-A with no demonstrated binding to ET-B. In a randomized phase II trial comparing patients who received zibotentan (at either a 10 or 15 mg daily dose) with those who received placebo, no difference was observed in the primary endpoint of progression [87]. A difference in overall survival, however, emerged in favor of both the zibotentan 10 and 15 mg treatment groups (24.5 and 23.5 months, respectively, versus 17.3 months for the placebo group). Multiple phase III trials evaluating zibotentan in various stages of CRPC have all been either negative or halted early secondary to projected futility.

### Src Family Kinases

The prototypical member of the Src family of non-receptor tyrosine kinases is Src, and it is involved in signal transduction downstream of multiple cell surface receptors (including EGFR, PDGFR, VRGFR, and integrins); as a result, Src is implicated in multiple cellular processes essential for malignant progression such as differentiation, proliferation, adhesion, and migration. Src, related kinases, and their upstream cell surface receptors are frequently overexpressed in CRPC and have been implicated in prostate cancer progression. Beyond this, increases in the activity of Src family kinases have been correlated with the presence of distant metastases and poor outcomes [88]. In preclinical models, it has been determined that Src signaling is important for normal functioning of osteoclasts and bone resorption, as well as osteoblast proliferation and bone deposition, and is implicated in the progression of bone metastases [89].

Dasatinib (Bristol-Myers Squibb Co.) was initially developed for its activity against the Bcr-Abl tyrosine kinase associated with chronic myelogenous leukemia. In preclinical models of prostate cancer, dasatinib was subsequently shown to have activity against Src family kinases resulting in direct antitumor effects (i.e., suppression of cell adhesion, migration, and invasion) [90]. Phase II trials of dasatinib in patients with prostate cancer have been carried out in twice-daily [91] and once-daily [92] dosing regimens. Although only one patient in each of the trials had a PSA response of >50 % decline, lesser declines were noted and decreases in markers of bone turnover (serum bone alkaline phosphatase and urinary N-telopeptide) were also observed providing proof of principal biologic activity data. Dasatinib in combination with docetaxel was found to be safe and well tolerated in a phase I/II trial, and PSA responses were observed in 41 % of patients [93]. Among the 31 patients who had bone scans, 30 had best response of either improved (32 %) or stable (65 %) disease at ≥6 weeks. A randomized phase III trial of docetaxel with or without dasatinib is now being conducted with a

primary endpoint of overall survival and a planned accrual of over 1,300 patients (NCT00744497).

AZD-0530 (AstraZeneca) is another orally administered Src-kinase inhibitor that is currently in clinical testing. A phase II study randomizing patients with bone metastases from either breast or prostate cancer to receive either AZD-0530 or zoledronic acid has completed accrual, and data are maturing (NCT00558272). The primary objective of the study is to compare changes in markers of bone turnover.

## Radiopharmaceuticals

For patients with multifocal painful bone metastases not amenable to (or refractory to) palliative intent external beam radiation, one option is treatment with radiopharmaceuticals. Samarium-153-ethylene diamine tetramethylene phosphonic acid ($^{153}$Sm-EDTMP) is a bone-targeted radiopharmaceutical that has previously been assessed as a single agent for its palliative properties. Durable improvement in pain control as a result of treatment with $^{153}$Sm-EDTMP compared with placebo was observed in two randomized placebo-controlled trials [94, 95]. The most common toxicity associated with treatment was transient myelosuppression. In preclinical models, there is evidence that there may be a synergistic effect when $^{153}$Sm-EDTMP is combined with docetaxel, and early phase studies have been reported evaluating the safety and efficacy of this combination [96–98]. Docetaxel and $^{153}$Sm-EDTMP was tolerable with, again, transient marrow toxicity as the most common adverse event. A phase II study of 43 patients with CRPC who had achieved response/disease stability following four cycles of docetaxel/estramustine has been completed. Patients went on to receive consolidation docetaxel (20 mg/m$^2$) weekly for 6 weeks in combination with $^{153}$Sm-EDTMP (given during week 1) [97]. There was a 77 % PSA response rate and a 69 % pain response rate, and 1- and 2-year rates of survival were 77 and 56 %, respectively. As assessed by the visual analogue scale, pain response was durable. Overall, these data may suggest that the combination of docetaxel and $^{153}$Sm-EDTMP is safe and may have more activity than either agent alone [99].

The alpha-emitter radium-223 ($^{223}$Ra, also known as alpharadin) is a newer radiopharmaceutical. It is a bone-seeking radionucleotide that has been studied as a single agent in a multicenter randomized phase II study [100]. Patients who had metastatic CRPC and bone pain that required palliative external beam radiotherapy were assigned to either four intravenous injections of $^{223}$Ra ($N=33$) or placebo ($N=31$) given every 4 weeks. Primary endpoints were time to first skeletal-related event and change in bone alkaline phosphatase. There was an improvement in the median bone alkaline phosphatase during treatment favoring the $^{223}$Ra group, but there was no difference between groups with regard to time to first SRE. The HR for overall survival, once adjusted for baseline covariates, was 2.21 (1.13–3.98; $p=0.020$) in favor of $^{223}$Ra. Based upon these results, a phase III study was conducted in patients with metastatic CRPC [24]. In this multicenter phase III study, 922 patients with CRPC and bone metastases were randomized 2:1 in favor of alpharadin versus placebo. Patients either had to have received previous docetaxel or be unfit to receive docetaxel. Primary endpoint was overall survival. At the first planned interim analysis, the data and safety monitoring board recommended stopping the trial early due to a significant benefit observed in the treatment arm. Median OS was 14.0 versus 11.2 (HR = 0.695, CI: 0.552–0.875 $p=0.00185$) in favor of alpharadin. Time to first skeletal-related event was also significantly longer for the treatment group (13.6 versus 8.4 months, HR = 0.610; 95 % CI: 0.461–0.807, $p=0.00046$). It is worth noting that the median survival for the study population is shorter than one would have anticipated as many patients had not received prior docetaxel, reflecting the fact that this population was unwell at baseline. Rates of grade 3–4 adverse events were not significantly different between groups, and overall alpharadin was extremely well tolerated. This is the latest in a recent rash of drugs of varying classes that have demonstrated OS benefit in mCRPC.

## Immunotherapy

An oncologic therapeutic strategy that has long been sought is the harnessing of the body's own immune system to elicit an antitumor effect and overcome the immunologic tolerance of malignancies. The goal of immunizing a patient with tumor- specific antigens is to induce an immune-mediated antitumor effect in a process known as active-specific immunotherapy. Dendritic cells, which are an example of antigen-presenting cells, are an essential component in the processing and presentation of antigens (via major histocompatibility complex [MHC] class I and II molecules) to T cells to elicit a specific immune response.

Sipuleucel-T (Dendreon Corp.) is a dendritic cell-based vaccine that has been designed to stimulate T cell immunity against prostatic acid phosphatase (PAP). PAP is abundantly expressed in both benign and malignant prostate epithelium but is expressed only in very low levels in non-prostatic tissues. Each vaccine is patient specific, and preparation of the treatment is laborious. Initially patients undergo a 1.5–2.0 blood volume mononuclear cell leukapharesis and then antigen-presenting cells (APC) are isolated from the leukapharesis product at a central facility. The APCs are cultured with a fusion protein that consists of PAP linked to granulocyte-macrophage colony-stimulating factor (GM-CSF); as a result, the APCs are activated, and they load and process the PAP antigen for presentation to T cells upon reintroduction into the patient. The goal is that the host will subsequently mount an immune response against any cell expressing high

levels of PAP. This approach was deemed feasible based on phase I and II trials, and evidence of immune responses to the fusion protein as well as antitumor effects were observed [101]. A phase III trial was designed with a primary endpoint of time to progression as defined by clinical progression (such as increasing measurable disease or cancer-related pain) but not by PSA progression [102]. One hundred twenty-seven patients with asymptomatic CRPC (pre-docetaxel) were randomized 2:1 in favor of the vaccine arm in this double-blind placebo-controlled trial. Crossover was allowed for patients randomized to the placebo arm who met criteria for progression. There was no significant difference in time to clinical progression between groups of patients treated with either sipuleucel-T or placebo (11.7 vs. 10.0 weeks, respectively; $p = 0.052$). Despite not meeting the primary endpoint, an overall survival benefit was observed favoring the vaccine group (HR = 1/70, 95 % CI: 1.31–3.44). A second similarly designed trial was conducted, and this demonstrated a non-statistically significant trend toward improved overall survival in the sipuleucel-T group [103].

As a result of these findings, a third phase III trial was conducted, this time with a primary endpoint of overall survival [25]. Five hundred and twelve patients with metastatic CRPC who were chemotherapy-naïve were randomized 2:1 in favor of sipuleucel-T in this double-blind placebo-controlled phase III trial. Treatment was administered every 2 weeks for a total of 3 intravenous infusions. At the time of disease progression, patients were unblended to treatment allocation, and those patients in the placebo group were allowed to cross over. There was a statistically significant improvement in overall survival in the treatment group with a median overall survival of 25.8 and 21.7 months in the vaccine and placebo groups, respectively (HR = 0.78; 95 % CI: 0.61–0.98; $p = 0.03$). The treatment effect was preserved after adjustment for subsequent use of docetaxel off study. There was no difference observed between groups with regard to time to progression. Sipuleucel-T was well tolerated with only 3 of 338 patients unable to receive all three infusions. Immune reactions manifested by fever, chills, fatigue, and nausea were common within 1–3 days of infusion. Cerebrovascular events were reported in 2.4 % of the vaccine group compared with 1.8 % in the placebo group ($p = 1.00$). The combined results of these trials are exciting in that they serve to introduce yet another treatment option for men with metastatic CRPC that is associated with an overall survival benefit. Concerns remain, however, as to the feasibility of delivering such a treatment in publically funded regions given the enormous burden (both financial and resource) associated with it.

Prostvac VF is a generic vaccine product that, unlike sipuleucel-T, does not require personalized manufacturing. This vaccine is similar to the small pox vaccine in that it is based on a viral backbone; the target antigen (PSA) is incorporated as part of a vaccinia backbone. In an attempt to further stimulate the immune response, ProstVac VF has incorporated three additional molecules as well as the target antigen. The tolerance of this agent has been demonstrated in number of single-agent and combination trials. In a phase II trial evaluating this vaccine, 125 men were randomized 2:1 to receive either ProstVac VF or placebo [104]. The primary endpoint, which was TTP, was not met at the time of the primary analysis. However, longer follow-up showed an OS benefit (25.1 vs. 16.6 months, HR = 0.56, $P = 0.006$). A phase III trial assessing the potential OS benefit of ProstVac VF in men with asymptomatic CRPC is scheduled to begin in 2011.

Another approach to vaccine therapy has been to use whole cells as an antigen source in order to provoke an immune response to multiple antigens. The GVAX platform (Cell Genesys, Inc.) employs this method, and for prostate cancer it utilizes the LNCaP and PC3 cell lines modified to express human GM-CSF to induce APC growth, maturation, and induction. Prior to patient administration, the cell lines are irradiated to prevent proliferation. The safety of this approach was demonstrated in phase I/II trials in which no dose-limiting toxicities were observed. The primary limitation to administration was the number of injections that could feasibly be performed [105]. Immune response was evidenced by immunoblot analyses of lysates of the two modified cell lines against patient sera at baseline and post-treatment. Although PSA responses of >50 % were rare, lesser responses were observed in several patients, and those patients who received higher doses of GVAX appeared to have longer time to progression and survival. Two phase III studies in patients with CRPC were subsequently conducted, both with a primary endpoint of overall survival. Both trials were terminated early, one due to an imbalance in deaths observed in the immunotherapy arm (NCT00133224) and one due to futility (NCT00089856).

A third approach to immunotherapy is through blockade of the cytotoxic T-lymphocyte antigen-4 (CTLA-4) costimulatory molecule expressed on the surface of T-cells. Following presentation of antigen to T cells by APCs, activation, and proliferation is mediated by recognition of the antigen/MHC complexes by the T cell receptor in conjunction with a costimulatory signal. This costimulatory signal is delivered through CD80 and CD86 on the APC and through CD28 on the T cell. Once the T cells are activated, they express CTLA-4 which also binds to CD80 and CD86 but mediates an inhibitory signal providing a negative feedback loop. Therefore, by blocking CTLA-4 signaling, it may be possible to enhance and maintain the activation and proliferation of tumor-specific T-cells [106]. The potential risk associated with this is breaking self-tolerance thereby inducing autoimmunity. Blockade of CTLA-4 has demonstrated successful induction of tumor immunity and rejection in vivo [107].

Ipilimumab (Medarex, Inc.) is a fully humanized monoclonal antibody against CTLA-4. A pilot study of single dose ipilimumab (3 mg/kg) was undertaken in men with CRPC [108]. Of the 12 patients who were treated, 2 had a >50 % decrease in PSA from baseline. Clinical autoimmunity was observed in one patient who has grade 3 rash/pruritis requiring corticosteroids. A phase one trial of ipilimumab alone or in combination with radiation was subsequently conducted [109]. The rationale for including radiotherapy in the protocol was based on the evidence that in preclinical models radiation has been shown to result in tumour antigen release and enhancement of the antitumor effects of CTLA-4 blockade. At the time of presentation, doses of up to 10 mg/kg were being delivered and 33 patients had been enrolled. Life threatening immune related adverse events (grade 3 and higher) included colitis (24 %), hepatitis (18 %), and rash (3 %); these appeared to be dose related. One patient died from an opportunistic infection after 3 months of immunosuppression for colitis. With regard to efficacy, 21 % of patients had a PSA decline of >50 % from baseline and one patient had a complete response in measureable disease. Several clinical trials using ipilimumab in various clinical settings are underway in patients with prostate cancer: a phase II neoadjuvant trial in patients prior to radical prostatectomy (NCT01194271), a phase III trial of ipilimumab versus placebo following radiation in men with CRPC who have previously received docetaxel (NCT00861614), and a phase III trial in minimally symptomatic men with CRPC who are chemo-naïve (NCT01057810). Combining various immunotherapies is also under investigation in an effort to enhance immune response to vaccine therapy [110, 111].

## Classes of Drugs in Development

### Insulin-Like Growth Factor Receptor

The insulin-like growth factor (IGF) axis is composed of two peptide growth factors (IGF-I and -II), two transmembrane receptors (IGF-IR and –IIR), six IGF binding proteins (IGFBP-1 to –6), and IGFBP proteases. Tyrosine kinase activity is initiated when the ligand of IGF-1R is bound with resultant stimulation of proliferation, survival, transformation, metastasis, and angiogenesis [112, 113] via the downstream signaling cascades of the PI-3 K/AKT/mTOR and Ras/Raf/MEK/ERK pathways [114]. There is a wealth of evidence linking upregulation and overexpression of various components of the IGF axis to numerous malignancies. High circulating levels of IGF-1 have been correlated with an increased risk of developing colon, prostate, breast, lung, and bladder cancers [115–120]. It has further been shown that tumor levels of IGF-1R are correlated with poor prognosis in renal cell cancer, colorectal cancer, non-small cell lung cancer, and ovarian cancer. In preclinical human tumor xenograft models inhibition of IGF-1R has been achieved using antisense [121], anti-IGF-1R antibodies [121–124], and small molecule inhibitors [125]; all of these methods have resulted in reduction of tumor growth.

In prostate cancer, elevated concentrations of IGF-I and risk of prostate cancer have been correlated, and high plasma IGF-I and low IGFBP-3 have been associated with more advanced stage prostate cancer [115, 126]. IGF-IR, IGF-I and –II, and IGFBP-2 have all been reported to be overexpressed in human primary prostate cancer compared with normal prostate tissue. Levels are also increased in advanced and metastatic disease [127]. An increasing body of evidence has linked activation of the IGF axis with androgen independent progression of prostate cancer [128]. As the IGF axis has been implicated in numerous malignancies, including prostate cancer, targeting the IGF axis is an attractive therapeutic avenue to explore in prostate cancer. A variety of methods have been employed to block IGF signaling thus supporting this theory [129].

Clinically, humanized monoclonal antibodies specific to the IGF-1R have been tested in prostate cancer in a variety of disease settings. IMC-A12 (cixutumumab) was tested as a single agent in asymptomatic chemotherapy-naïve patients with castration resistant prostate cancer [130]. Thirty-one patients were enrolled on two different dosing schedules (q2weekly and q3weekly dosing). Common toxicities included fatigue and hyperglycemia; other reported adverse events were thrombocytopenia, hyperkalemia, and pneumonia. Disease stability for over 6 months was achieved in 29 and 30 % of the q2wk and q3wk cohorts, respectively. A phase I/II combining cixutumumab with temsirolimus (an mTOR inhibitor) in metastatic CRPC is currently underway (NCT01026623) [131]. Cixutumumab is also being evaluated in combination with androgen deprivation in men with high-risk prostate cancer prior to prostatectomy; the primary endpoint of this phase II trial is rate of pathologic complete response at the time of definitive local surgery (NCT00769795) [132]. A phase II study of androgen withdrawal therapy with or without cixutumumab in patients with hormone sensitive metastatic prostate cancer is also being conducted by the Southwest Oncology Group (SWOG) (NCT01120236).

CP-751,871 (figitumumab) is another monoclonal antibody that has been shown to be safe in phase I studies [133], and testing in combination with docetaxel is ongoing (NCT00313781). Figitumumab was evaluated in the neoadjuvant setting in a recent phase II preoperative study in treatment-naïve patients who subsequently went on to have a radical prostatectomy [134]. In this study, 16 patients were accrued and received three cycles of figitumumab (20 mg/kg IV) q3weeks followed by radical prostatectomy (within 1 week of the last dose of figitumumab). The primary endpoint was inhibition of IGF-1R expression as demonstrated

by immunohistochemistry. PSA response and alteration in the expression of effectors downstream from IGF-R were also evaluated. One incidence of grade 3 hyperglycemia was reported in a patient with pre-existing diabetes. Paired biopsy and prostatectomy specimens demonstrated decreased IGF-1R expression by IHC visual score. PSA responses of ≥25, ≥30, and ≥50 % were seen in 94, 88, and 31 % of patients, respectively. Neoadjuvant studies such as this allow for evaluation of the direct biological impact of treatments and aid in identifying biomarkers of response.

Humanized monoclonal antibodies are not the only means by which we may interrupt the IGF axis, and other methods are under evaluation. Nordihydroguaiaretic acid is a small molecule inhibitor of IGF-1R that has been assessed in a phase II study of patients with non-metastatic hormone responsive prostate cancer [135]. Early results indicate that treatment with nordihydroguaiaretic acid may be associated with a lengthening of the PSA doubling time, but does not induce significant PSA declines. It is unknown if further studies are planned.

## Phosphatidylinositol 3-Kinase (PI3K)-Akt Signaling Pathway

Downstream of growth factor receptors like IGF-1R is the PI3K-Akt pathway (which is also known as the protein kinase B pathway). PI3Ks catalyze the transfer of a phosphate group to generate phosphatidylinositol-3,4,5 trisphosphate (PIP3) from phosphatidylinositol-4,5 bisphosphate (PIP2) following activation by receptor tyrosine kinases. PIP3 then serves to recruit Akt to the inner cell membrane where it is activated. The result of Akt activation is phosphorylation of a number of downstream targets such as mTOR (mammalian target of rapamycin) and others. Consequently, phosphorylation of these downstream targets has an effect on critical cellular functions including proliferation, growth, apoptosis, glucose homeostasis, nutrient response, and DNA damage. PTEN is a tumor suppressor gene whose product is a lipid phosphatase that negatively regulates the PI3K-Akt pathway by regenerating PIP2 from PIP3 [136, 137]. In prostate cancer, some of the rationale for targeting the PI3K-Akt pathway is based on evidence that this pathway contributes to castration resistant progression via mechanisms such as activation of the androgen receptor and androgen responsive genes [138, 139]. Further, PTEN (a negative regulator of the PI3K-Akt pathway) is frequently deleted in prostate cancer and has been identified as a negative prognostic factor [140, 141].

Given the robust body of evidence supporting the role of the PI3K-Akt pathway and downstream regulators in the progression of prostate cancer, it is rational that these have emerged as therapeutic targets in recent years. Sirolimus (also known as rapamycin) is an mTOR inhibitor that has a long history of clinical use as an immunosuppressive agent used following solid organ transplantation. It is also used as an antiproliferative agent in coronary artery stents. In the oncologic setting, sirolimus was been tested in a small phase I study in 13 patients with CRPC and showed some low-level activity [142, 143]. Additional mTOR inhibitors, either alone or in combination, are also under clinical investigation in prostate cancer; these include deforolimus (NCT00110188), temsirolimus (NCT00919035) [144], and everolimus (NCT00629525). Simultaneous targeting of the androgen receptor and the PI3K/mTOR pathway in cell lines has been shown to be more effective than targeting either alone [145], and this had been borne out clinically in a phase I/II study combining bicalutamide and everolimus in CRPC [146]. Eight patients will be enrolled in the phase I lead-in portion of the study, and all will receive combination treatment. In the phase II portion of this study, 80 patients with progressive CRPC who are already being treated with androgen deprivation will be randomized to receive either bicalutamide alone or in combination with everolimus. Thus far, eight patients have been enrolled, all of whom have received combination treatment. The combination of bicalutamide and everolimus has been well tolerated with only one episode of grade 3 pneumonitis reported that was deemed attributable to everolimus; it resolved with dose reduction and treatment with corticosteroids. Six out of eight patients have had a PSA decline of at least 30 %, and two patients have stable disease. Enrollment continues for the phase II portion of the study.

Another phase II trial combining the mTOR inhibitor everolimus with bicalutamide in CRPC has been reported [147]. Primary endpoint was a composite of PSA, bone scan, and CT responses. Thirty-six patients were enrolled; of these, 30 had received prior treatment with bicalutamide and 32 had metastatic disease. PSA response was observed in 44 % (≥30 % in 17 %, ≥50 % in 11 %). Median time to progression was 8 weeks; however, two patients continued with treatment for >32 weeks. Although the majority of adverse events reported were grade 1–2 (mucositis, rash, fatigue, diarrhea, nausea), 36 % discontinued treatment for physician discretion or toxicity. There are no plans to pursue this combination further.

One explanation for the seemingly low activity associated with mTOR inhibition is that it may induce feedback activation of Akt signaling through IGF-1R [148]. Thus, combined blockade of IGF-1R and mTOR inhibition is a rational approach and is being evaluated clinically (see Insulin-like Growth Factor Receptor section of this chapter).

Alternatively, upstream targeting of PI3K and Akt directly is an attractive prospect, and several inhibitors are in early phase clinical development. The selective Akt inhibitor, MK2006, has been assessed in two phase I trials of patients with advanced malignancies [149, 150]. The drug, administered orally, is well tolerated at doses of 60 mg given on

alternating days. Given the long half-life, once weekly dosing is also being evaluated. Testing continues. XL765 is a potent and selective inhibitor of PI3K isoforms (as well as TORC1 and TORC2) that has shown antitumor activity in multiple human xenograft models. A phase I trial of XL765 in patients with advanced malignancies was recently reported [151]. Maximum tolerated dose was 50 mg po BID, and the most commonly reported toxicities were nausea, diarrhea, anorexia, elevated liver enzymes, skin toxicity, and vomiting. Pharmacodynamic evaluation of the PI3K and ERK pathways revealed significant modulation of signaling.

## Chaperone Proteins

The molecular chaperone complex, heat shock protein-90 (Hsp90), is required to ensure the stability and maturation of the androgen receptor, and as such, it has been identified as a potential therapeutic target in CRPC. Not only does Hsp90 stabilizes the androgen receptor, it also serves as a chaperone to numerous other client proteins that are known to be associated with malignant progression: Akt, Raf-1, HER2, and hypoxia-inducible factor-1α [152]. In its role as a chaperone, Hsp90 is ATP dependent, and a number of specific inhibitors have been developed to disrupt its ATPase activity. HDAC inhibitors (small molecule inhibitors of histone deacetylase) can cause loss of Hsp90 ATP binding activity by acetylating and subsequently degrading the androgen receptor [153–156]. The TMPRSS2:ETS gene fusion occurs frequently in prostate cancer [46] and may result in epigenetic reprogramming with the consequent manifestation being upregulation of HDAC-1 and downregulation of its targets [157]. In light of this, HDAC inhibitors are of interest in prostate cancer as there may be an increased susceptibility to theses agents as a result of said epigenetic changes [158].

A benzoquinone ansamycin antibiotic, 17-allylamino-17-demethoxygeldanamycin (17-AGG), is under investigation. Antitumor activity was exhibited in preclinical models, and the proposed mechanism of action is that it binds to the Hsp90 ATP binding site. The agent demonstrated safety and tolerability in humans in phase I trials. Unfortunately, a phase II trial in patients with CRPC demonstrated only minimal clinical activity [159]. Likewise, HDAC inhibitors that have been assessed in phase II trials involving patients with CRPC have failed to yield any clinically significant activity thus far [160]. Despite these early failures, evaluation of other HDAC and Hsp90 inhibitors continue.

Another chaperone protein that has emerged as a novel therapeutic target for prostate cancer is clusterin. The Clusterin gene, located on chromosome 8p21-p12 codes for two secretory isoforms of clusterin (sCLU-1, sCLU-2), originating from transcriptional start sites in exons 1 and 2, respectively. sCLU is an ER-targeted, 449-amino acid polypeptide that represents the predominant translation product of the human gene. Proteolytic removal of the ER-targeting signal peptide produces a 60-kDa ER-associated, high mannose, cytoplasmic form (sCLUc). sCLUc is further glycosylated in the Golgi and cleaved into two 40-kDa α- and β-subunits. These subunits are assembled in an antiparallel manner into an 80-kDa mature, secreted, and heterodimeric form (sCLUs). Although sCLU is cytoprotective and anti-apoptotic, a pro-apoptotic activity 55-kDa nuclear (nCLU) splice variant lacking exon II and the ER signal peptide has been described [161].

Clusterin expression is induced following therapeutic stress and functions as a cytoprotective chaperone not dissimilarly to an ATP-independent small heat shock protein. Clusterin is transcriptionally activated by heat shock factor-1 [162]. In addition, clusterin has been shown to induce apoptosis through inhibition of activated Bax, a critical pro-apoptotic member of the Bcl-2 family [163]. Further, overexpression of clusterin results in activation of the PI3K/Akt pathway via the megalin cell surface receptor [164]. The expression of clusterin increases in response to cell stress induced by a variety of factors in xenograft models. Further, resistance to radiation, hormone therapy, and chemotherapy is conferred by forced overexpression of clusterin whereas inhibition of clusterin expression enhances apoptotic-mediated death from these treatment modalities [165]. In preclinical models of prostate cancer clusterin has been associated with androgen independent progression [166]. Clusterin has been shown to be overexpressed in a variety of human malignancies including prostate cancer. In prostate cancer clusterin expression increases after castration and with castration resistant disease [167].

Given the wealth of preclinical data supporting the role of clusterin in the development and progression of prostate cancer and treatment resistance, clusterin is a rational therapeutic target to enhance treatment efficacy. OGX-011 (OncoGenex Pharmaceuticals Inc.) is a second-generation phosphorothioate antisence molecule with a prolonged tissue half-life. In vitro and in vivo, OGX-011 has been shown to significantly decrease sCLU expression via inhibition of clusterin mRNA translation. The ability of OGX-011 to inhibit clusterin expression in prostate cancer tissues has been established by testing in phase I trials. These studies have also shown that standard doses of chemotherapy can be safely delivered in combination with OGX-011 at biologically active doses [168, 169].

In a randomized phase II trial of OGX-011 in combination with either mitoxantrone or docetaxel in patients with CRPC who had previously progressed on or within 3 months of completing docetaxel both regimens were found to be tolerable, but interesting antitumor activity was also demonstrated [170]. Twenty-seven percent of patients treated with the combination of mitoxantrone and OGX-011 had a PSA

decline of >50 %, and median overall survival was 11.4 months. In the OGX-011 in combination with docetaxel arm, 40 % of patients experienced a >50 % PSA decline from baseline including patients who had progressed while receiving prior docetaxel, and the median overall survival was 14.7 months.

A second phase II study with OGX-011 randomized 82 patients who had chemotherapy-naïve metastatic CRPC to receive first-line docetaxel with or without OGX-011 [171]. Although PSA response rates were similar between groups, there appeared to be fewer patients with progression as best response and a longer time to progression in the docetaxel + OGX-011 group. Mature results from this study have been reported. The median overall survival in the docetaxel group was 16.9 months, and in the docetaxel + OGX-011 group, it was 23.8 months; however, this was a secondary endpoint, and the study was not designed to detect overall survival differences [172]. Factors significantly associated with improved overall survival based on multivariate analysis were an ECOG performance states of 0 versus 1, presence of bone or lymph node metastases only versus other metastases (i.e., visceral), and treatment arm assignment to OGX-011 plus docetaxel versus docetaxel alone (HR = 0.50, 95 % CI: 0.29–0.87). A phase III trial comparing docetaxel + OGX-011 versus docetaxel alone in patients with chemotherapy-naïve metastatic CRPC has recently opened and accrual is ongoing (NCT01188187). The primary endpoint of this study is overall survival.

Like Hsp90, Hsp27 is a chaperone protein that affects multiple pathways implicated in cancer progression and the development of treatment resistance. OGX-427 is a second generation antisense oligonucleotide that has been developed to inhibit Hsp27 thereby resulting in cell growth inhibition, apoptosis, and enhanced response to chemotherapy. Hsp27 is also implicated in prostate cancer progression through interactions with ligand-activated AR that enhance AR stability, shuttling, and transcriptional activity [173].

A phase I trial assessing the safety of OGX-427 either alone or in combination with docetaxel in patients with metastatic CRPC, ovarian cancer, breast cancer, or non-small cell lung cancer (all solid organ malignancies that have are known in the literature to express Hsp27) has recently been reported [174]. Thirty-six patients were treated with OGX-427 alone, and 12 patients received combination therapy. Twenty-seven patients had CRPC. Infusion reactions were seen at dose levels >600 mg, and the most commonly seen toxicities were dyspnea and elevated creatinine. In patients who had measurable disease, 13 % had confirmed minor response or stable disease. A PSA decline of ≥30 % was seen in 19 % of patients with CRPC who received OGX-427 alone and in 56 % of patient who received docetaxel + OGX-427. At the maximum dose tested (1,000 mg) OGX-427 was well tolerated, and the feasibility of combining it with docetaxel chemotherapy was confirmed. Further, combination studies are planned. A randomized phase II study in men with metastatic chemotherapy-naïve CRPC has recently opened and will randomize patients to either prednisone alone or in combination with OGX-427 (NCT01120470).

## Vascular Endothelial Growth Factor and Receptor

In order for a malignant tumor to grow beyond a few millimeters and develop the ability to metastasize, it must first recruit new vasculature in a process known as angiogenesis. Angiogenesis is a complex process that is mediated by several factors. Chief among these is the vascular endothelial growth factor (VEGF) which signals through VEGF receptors (VEGFR) 1 and 2 to promote angiogenesis. In the TRAMP model of prostate cancer elevated VEGFR, particularly VEGFR-2, has been associated with progression of prostate cancer. VEGFR-2 is also overexpressed in human prostate cancers [175]. It has further been demonstrated that in patients with metastatic CRPC increased plasma VEGF, either as a continuous or dichotomous variable, has been correlated with disease progression and poor prognosis [176]. Inhibiting the VEGF/VEGFR pathways in experimental models of prostate cancer has been shown to induce and antitumor effect [177]. By combining VEGF inhibition with chemotherapy the thought is that one may be able to create and indirect antitumor effect by enhancing permeability via vascular normalization [178]. Given the sound preclinical rationale, as well as clinical success in other solid organ malignancies, targeting the VEGF pathway is a reasonable therapeutic approach for patients with prostate cancer. Three inhibitors of angiogenesis have been assessed in phase III clinical trials: bevacizumab (Genetech), aflibercept (Sanofi-Aventis), and sunitinib (Pfizer Inc.).

Bevacizumab is a monoclonal antibody directed against VEGF-A, and it causes potent inhibition of VEGFR signaling and angiogenesis. Bevacizumab currently has wide clinical indication and use. Single agent activity has been demonstrated in renal cell cancer [179], and bevacizumab is approved for use in combination with chemotherapy for patients with metastatic colorectal, breast, and non-small cell lung cancer. Typical toxicities associated with bevacizumab have been well documented and reproduced in several clinical trials; they include hypertension, thromboembolism, hemorrhage, gastrointestinal perforation, and proteinuria.

In prostate cancer, bevacizumab has been tested in a number of different clinical settings. The CALGB has conducted a phase II trial of bevacizumab in combination with docetaxel-estramustine chemotherapy in patients with metastatic CRPC [180]. In this study, PSA decline of >50 % from pretreatment baseline occurred in 81 % of patients. The median

time to progression, from either measurable disease or PSA progression, was in the range of 9 months. Median overall survival for the study population was 21 months. A phase III randomized placebo-controlled trial comparing docetaxel + prednisone to docetaxel + prednisone + bevacizumab in men with metastatic CRPC has subsequently been conducted and results have recently been presented [181]. In this study conducted by the CALGB, 1,050 patient with chemotherapy-naïve metastatic CRPC were enrolled. The primary endpoint was overall survival. There was a statistically significant improvement in progression-free survival in the bevacizumab group (9.9 vs. 7.5 months; HR = 0.77, 95 % CI: 0.68–0.88; $p < 0.0001$), however there was no overall survival benefit observed (median OS = 22.6 vs. 21.5 months; HR = 0.91, 95 % CI: 0.78–1.05; $p = 0.181$). Further, the rate of ≥grade 3 adverse events was significantly higher in the bevacizumab arm (74.8 vs. 55.3 %).

Bevacizumab has been tested in combination with docetaxel and RAD001 (an mTOR inhibitor also known as everolimus) in chemotherapy-naïve patients [182], as well as in combination with satraplatin (an oral chemotherapy) in patients who had previously been treated with docetaxel [183]. Although both combinations were reasonable well tolerated, more later-phase experience will be necessary to establish efficacy and to determine if either of these combinations will find a role in the standard treatment of metastatic CRPC.

Another angiogenesis inhibitor under investigation in CRPC is aflibercept (also known as VEGF Trap). Aflibercept is a recombinantly-produced fusion protein that consists of human VEGF receptor extracellular domains fused to the Fc portion of human immunoglobulin (Ig) G1. Aflibercept potently inhibits VEGF-A, VEGF-B, and other VEGF family members (such as placental growth factors that bind to VEGFR-1 and VEGFR-2) by binding to and thereby inactivating these circulating factors [184]. Clinically, the toxicities seen with the use of aflibercept are similar to those seen with bevacizumab; this is unsurprising given the similar mechanisms of action. The safety of aflibercept in combination with docetaxel has been demonstrated in phase I trials [185], and a phase III randomized double-blind placebo-controlled trial is underway for patients with metastatic CRPC (NCT00519285).

Sunitinib, an orally administered multi-targeted tyrosine kinase inhibitor, blocks the receptor kinase activity of VEGFR, platelet-derived growth factor receptor (PDGFR), and KIT. Sunitinib is approved for first-line use in metastatic renal cell cancer where it has been shown to significantly improve progression-free survival compared with interferon [186]. A phase II study evaluating sunitinib in patients with metastatic CRPC has been reported [187]. In this trial, progression of disease was based upon clinical and radiological (i.e., non-PSA based) parameters, and the primary objective was to determine if treatment with sunitinib was associated with a clinical progression-free survival of 12 weeks in >30 % of patients. The study population was heavily pretreated with all participants having received one or two prior chemotherapy regimens, including docetaxel. In 78.9 % of patients a 12 week progression free survival was attained. PSA responses of >30 and >50 % decrease from baseline were seen in 21 and 12 % of patients, respectively. Despite evidence of efficacy, 53 % of patients discontinued therapy due to toxicity and there were two early deaths that were deemed possibly related to the treatment. Fatigue and anorexia were the most commonly reported grade 3 toxicities. For patients with CRPC progressing after docetaxel chemotherapy, a phase III trial has been conducted that randomized patients to receive either sunitinib or placebo (2:1 randomization in favor of sunitinib). The trial was terminated at the first planned interim analysis due to futility (NCT00676650). There is a phase II trial currently recruiting patients that will assess the role of sunitinib as maintenance therapy following completion of docetaxel in patients who responded to chemotherapy (NCT00550810). Sunitinib has also been evaluated in combination with docetaxel as a first-line treatment in a phase II trial [188]. Fifty-five patients with metastatic CRPC were enrolled. Efficacy results were encouraging with 56 % of patients exhibiting a PSA response, but the combination resulted in an undue increase in adverse events. The rate of febrile neutropenia was 15 % and dose reductions were required for both sunitinib (26 % of patients) and docetaxel (33 % of patients).

Other VEGFR-targeting agents have been studied in prostate cancer, albeit less vigorously thus far. Sorafenib, like sunitinib, is an orally administered multi-targeted kinase inhibitor and has inhibitor action against Raf kinase, PDGFR, VEGFR-2 and −3, and c-kit pathways. Sorafenib is approved for the treatment of renal cell cancer [189] and hepatocellular cancer [190] based upon proven efficacy in these malignancies. In prostate cancer, two phase II trials of single agent sorafenib (administered in either the pre- or post-docetaxel setting) reported only modest activity with low rates of PSA responses and median progression-free survival in the range of 2–4 months [191, 192]. The combination of sorafenib and docetaxel has been evaluated in a number of phase I and II studies. Efficacy was challenging to determine based upon discordance between PSA and clinical/radiologic responses. Further, the combination was found to be toxic with high rates of febrile neutropenia [193, 194]. Cediranib is a potent orally administered small molecule inhibitor of VEGFR tyrosine kinase. Preliminary results from a phase II study using cediranib after progression on docetaxel are available show modest activity [195].

Although the results with a VEGFR TKI approach have thus far demonstrated only a low level of clinical activity, it may be that additional pathways need to be targeted for

greater clinical effects. Cabozantinib is a multi-targeted tyrosine kinase inhibitor that blocks both c-MET and VEGFR. The c-MET receptor is upregulated in a variety of tumor models and has been demonstrated to increase with prostate cancer progression particularly in bone metastases [196, 197]. There are several direct kinase substrates downstream in the c-MET signaling pathway, most of which have been implicated in tumor growth and progression; these include RAS, RAF, PI3K, Akt, SRC, STAT3/5, and SHP2 among others. c-MET has also been shown to cross talk with several other membrane protein members resulting in additional signaling response modulation. Results from a phase II randomized discontinuation trial with cabozantinib were presented in 2011 [198]. In this study, patients with mCRPC who had progressive measurable disease were enrolled in a 12-week lead-in phase in which all patients received cabozantinib 100 mg orally once daily. Beyond week 12, treatment was determined based upon the response observed during the lead-in phase: those patients with progressive disease discontinued treatment, and those patients with partial responses continued on open-label treatment. Patients with stable disease were randomized to placebo versus cabozantinib. Primary endpoint was objective response rate during the lead-in phase. The study was halted early based on an observed high rate of clinical activity, and at the time of reporting, 100 patients were evaluable for the lead-in phase. PR/CR, SD, and PD were observed on bone scan in 86, 12, and 2 % of patients, respectively. In those patients who reported bone pain at initiation of the study, 64 % had improvement in pain and 46 % were able to reduce/discontinue narcotic pain medications. Interestingly, PSA responses did not appear to correlate with clinical activity. Phase III trials of cabozantinib are planned.

Lenalidomide is another antiangiogenic agent that is in late phase clinical testing in prostate cancer. Thalidomide has been shown to have some clinical activity in late stage CRPC [199–202], however the mechanism by which it exerts its antiangiogenic effect has yet to be clearly elucidated. Further, significant peripheral neuropathy is a common toxicity that often limits treatment. Lenalidomide (Celgene Corporation) is an oral analogue of thalidomide that has been shown to inhibit angiogenesis in preclinical models [203, 204]. The tolerability of lenalidomide in men with CRPC has been demonstrated in phase I trials [205, 206]. Numerous early phase trials are underway combining lenalidomide with a number of cytotoxic and immunomodulatory agents (NCT00933426, NCT01093183, NCT00988208, NCT00939510) in men with CRPC, and there is a phase III trial randomizing patients with metastatic CRPC to docetaxel ± lenalidomide (NCT00988208).

Tasquinimod is a quinoline-3-carboxamide derivative that has antiangiogenic properties and has displayed antitumor activity in prostate cancer models. Phase I studies of tasquinimod in prostate cancer have determined it to be a well tolerated treatment. A randomized phase II trial of tasquinimod in chemotherapy-naive patients with metastatic CRPC has recently been reported [207]. Primary endpoint was proportion of patients without disease progression at 6 months. Two hundred six patients were enrolled and randomized (2:1) to receive either once daily tasquinimod or placebo, and 200 patients are available for evaluation. Six-month progression free proportion for the tasquinimod and placebo groups was 57 and 33 %, respectively. Likewise, median progression free survival for the two groups was 24.7 versus 12.9 weeks. Serious vascular events (myocardial infarction, heart failure, or stroke) were more common in the treatment group compared to the placebo group (3 vs. 0 %). Deep vein thrombosis was also more common in the treatment group (4 vs. 0 %). Grade 3–4 adverse event occurred with a frequency of 38 % in the tasquinimod group. Despite the toxicities, the efficacy results were encouraging enough that a phase III trial is planned (NCT01234311).

Despite the documented clinical response of some solid malignancies to antiangiogenic agents directly targeting VEGF itself (i.e., bevacizumab) or the tyrosine kinases downstream of VEGF (i.e., sorafenib, sunitinib) targeting VEGF signaling appears to be insufficient to halt all tumor angiogenesis, most likely through the development of resistance and selection of hypoxia-resistant cells or by switching on alternate pro-angiogenic signaling pathways [208].

VEGF gene expression is itself regulated by the transcription factor, hypoxia inducible factor I alpha, HIF-1α [209]. HIF-1α signaling is precisely coordinated either by post-translational modification involving acetylation of key residues mediate by histone acetyltransferases (HATS) or via HDACs. HDACs stabilize the HIF-1α protein by protecting it from interaction with the proteosomal ubiquitination degradation machinery, and reverse the actions of HATS through both indirectly and directly regulating HIF-1α protein levels. HIF-1α overexpression has been reported in numerous solid tumors including those of prostate [210, 211].

This infers that targeted therapeutics acting at different points in the pro-angiogenic signaling cascade are required to improve clinical outcomes for patients with solid malignancies. Targeting HDACs through specific inhibitors should therefore result in increased degradation of HIF-1α in the tumor hypoxic environment and compromise the development of the tumor pro- angiogenic environment and tumor associated vasculature. HDAC inhibitors can also have profound effects on gene regulation and interestingly one of the proteins strongly up regulated following treatment with HDAC inhibitors in a variety of cancer cell lines is clusterin [212]. Clusterin acting via its anti-apoptotic function could counteract the overall effects of HDACs and may be implicated in rendering tumor cells resistant to a HDAC inhibitor induced growth arrest and apoptosis [213].

A rationale therefore exists for exploratory combination clinical studies with HDAC inhibitors, whose clinical results have been disappointing as monotherapies, with agents such as OGX-011 the anti-clusterin agent as well as with direct anti-VEGF therapeutics such as bevacizumab for CRPC. By utilizing such combination therapeutics in future prostate cancer clinical trials a more profound antiangiogenic growth arrest signal might be expected to ensue, with clinical response rates superior to those currently observed with these agents as monotherapies.

## Poly (Adenosine Diphosphate-Ribose) Polymerase (PARP) Inhibition

PARP inhibition exploits the inherent vulnerability of tumor cells during DNA repair. DNA repair is an exquisitely sensitive and complex endeavor that involves in excess of 150 genes. Although there are multiple forms of DNA damage, double-stranded DNA breaks are of particular interest in malignancy as they induce cellular death as a result of many treatment modalities (including radiation and some chemotherapeutic agents). One of the primary repair mechanisms for double-stranded DNA breaks is homologous recombination which is dependent on BRCA1/2. PARPs are a family of nuclear enzymes that regulate multiple cellular processes (such as DNA repair and gene transcription) by polymerizing poly(adenosine diphosphase-ribose) [214]. The role of PARP1 is to repair single-strand DNA breaks, which, if left unchecked, may develop into lethal double-strand breaks. If PARP1 is inhibited and a double-strand break subsequently occurs, DNA repair is dependent on homologous recombination; in those cells deficient in homologous recombination (i.e., cells with BRCA1/2 mutations) cell death ensues [215]. Although the majority of clinical experience with PARP inhibitors has been in malignancies with known BRCA1/2 mutations, there is emerging evidence that this class of drugs may have efficacy in sporadic tumors with deficient mechanisms of homologous recombination [216–219]. Although BRCA1/2 are important in mediating homologous recombination (HR) DNA repair, numerous other proteins are involved, and any epigenetic or genetic disruption of those proteins may impede HR DNA repair. In light of this, there is likely a much broader clinical applicability for PARP inhibitors than simply those tumors with BRCA1/2 mutations.

As discussed earlier in this chapter, PTEN is a tumor suppressor gene that is frequently mutated or deleted in malignancies, and loss of PTEN is observed in 50–70 % of prostate cancers [220, 221]. It has been shown that cell lines with loss of PTEN are deficient in HR DNA repair and are selectively sensitive to PARP inhibition. When expression of PTEN is restored to these cell lines, resistance to PARP inhibition is observed [222]. A phase I study of ABT-888 (an oral PARP inhibitor) in combination with temozolamide is currently underway in patients with metastatic CRPC progressing after standard lines of therapy (NCT01085422), and other studies assessing the role of PARP inhibition in CRPC are planned.

## Clinical Context and Conclusions

In the past two decades, there has been an exponential increase in our understanding of the biological underpinnings driving the evolution and progression of castration resistant prostate cancer. This explosion of knowledge has resulted in a veritable embarrassment of riches when it comes to targets for rational drug development, and as a result, there are now five treatments for patients with metastatic CRPC that have demonstrated clinical benefits in phase III trials. The challenge now is determining how to individualize these treatment options, in which sequence to administer these treatments, and in whom they will exert the most benefit. This task is made more difficult as the rapid pace of development has meant that these new treatment options have been developed in relative independence of each other, and at present there is a paucity of predictive biomarkers.

The following is a suggested algorithm for the treatment of patients with mCRPC, in keeping with the current levels of evidence and the National Comprehensive Cancer Network (NCCN) guidelines. For a patient who develops castration resistant disease, one of the primary determinations is whether or not they have metastatic disease. For men with a rising PSA in the absence of metastatic disease, enrollment in a clinical trial is always something to consider. There is no evidence-based treatment with proven benefit in this population; however, most clinicians opt for second-, third-, and fourth-line hormonal maneuvers. These can included any (or even all, in sequence) of antiandrogen withdrawal, switching to a different antiandrogen, treatment with low-dose prednisone, or ketoconazole. PSA responses are certainly observed with these maneuvers, but whether that has any impact on either time to development of metastatic disease or survival is unknown. Recently, denosumab has been shown to decrease the time to development of bone metastases; however, it is currently not approved for this indication and the risk/benefit ratio must be carefully considered.

When a patient has CRPC in the context of documented metastatic disease, there are a number of things to consider, chief among them is whether or not the patient is symptomatic. As tremendously exciting as all of the advances in mCRPC are, it is essential to remember that this is an incurable disease, and there is no need to expose patients to potentially toxic interventions if they are not unwell from their disease. The two caveats to that are as follows: firstly, if a patient has visceral disease, a PSA that is rising rapidly, or a heavy burden of metastatic disease that is likely to become

symptomatic imminently, it is reasonable to intervene with standard of care docetaxel; secondly, recent evidence suggests that stepping in with treatments such as sipuleucel-T is most effective in the asymptomatic or minimally symptomatic patient. Unfortunately, sipuleucel-T carries a significant financial burden and is currently not widely available. Other options for patients with asymptomatic mCRPC include second-line hormonal maneuvers (as above) or enrollment in clinical trials.

In the symptomatic patient with mCRPC, docetaxel remains the standard first-line treatment, provided one is well enough to tolerate it. Post-docetaxel options include abiraterone or cabazitexel, both of which have shown an overall survival benefit. Certainly, abiraterone is the less toxic option in this population, but it is unclear in what order these post-docetaxel treatments are best delivered. Although not yet approved, alpharadin has also shown survival benefit in this setting. Although no survival benefit has been documented, certainly retreatment with docetaxel (particularly in patients who had a durable response and tolerated it well previously) or treatment with mitoxantrone are also options. Throughout all phases of treatment, best supportive care with targeted radiation as needed, narcotic analgesics, and bisphosphonates are essential.

Intensive efforts continue in order that we may discover and develop drugs that will expand the armamentarium for mCRPC, and any drugs that demonstrate efficacy in heavily pretreated populations will likely be brought forward to earlier disease settings. The results of studies evaluating drugs like abiraterone and MDV3100 in the pre-docetaxel setting are eagerly anticipated. Essential to this endeavor is ongoing elucidation of the many interactions between the various signaling pathways described in this chapter. In the coming years, there will be a growing need to understand how various novel targeted therapies could best be used in combination and how to best individualize treatment options. It is also, however, of paramount importance to recognize that mCRPC remains an incurable disease and that maintenance of quality of life should always be highly valued as we incorporate the treatments described into everyday clinical practice.

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# Immunotherapy

77

Nicola E. Annels and Hardev Pandha

## Introduction

Recent advances in the characterization of tumor antigens and a more precise knowledge of the regulation of cell-mediated immune responses have led to the development of multiple novel immunotherapy strategies that are being tested in clinical trials. Cancer immunotherapy involves activating a population of effector T cells that can migrate to the tumor site and mediate the specific lysis of cancer cells. However, tumor cells have multiple mechanisms to evade or suppress host immunity. These include weakly immunogenic target antigens, the production of high circulating levels of immunosuppressive cytokines, the production of regulatory immune cells and the ability of tumors to take advantage of the normal immune checkpoints. In this chapter, we will discuss some of these issues that relate to immunotherapy and several immunotherapy approaches to date that have tried to overcome these problems and advanced to clinical trials.

Several characteristics of prostate cancer make it an ideal target for immunotherapy. Firstly, prostate cancer is a relatively slow-growing tumor thus allowing sufficient time for immunological interventions to overcome immunosuppressive factors in the tumor microenvironment and to generate a clinically meaningful immune response. In addition, prostate cancer has many well-described tumor-associated antigens (TAA) [1]. These TAAs are ideal targets for immunotherapy because they are either specific to the cancer or are minimally expressed in normal tissues, and thus they can be used to direct the immune response to the cancer cells while sparing normal tissue. Furthermore, even if an autoimmune response to prostate cells were to develop, the fact that the prostate is a nonessential organ means this would not adversely affect the patient. Proteins expressed in prostate cancer include prostate-specific antigen [2], prostatic acid phosphatase [3], and prostate membrane antigen [4] all of which are potential immunologic targets for immunotherapy. Thirdly, there is evidence that prostate cancer is more immunogenic than previously thought. Not only are the prostate glands of men with cancer frequently infiltrated with both CD4+ and CD8+ T cells [5], but their tumors also have the ability to induce spontaneous autoantibodies [6]. Indeed, there is considerable preclinical data suggesting that anti-tumor immune responses can be elicited against prostate cancer cells. Thus, these multiple characteristics of prostate cancer together with the relative safety of immune-based therapies have resulted in the clinical development of several immunological approaches for prostate cancer. The increasingly important role of the tumor microenvironment in the development of tolerance to evolving malignancies has been supported by a large number of recent studies. In these, the interplay between immunosuppressive and immunostimulatory T cells (regulatory T cells, M1 and M2 macrophages, myeloid-derived suppressor cells) has been described as well as the expression of cytokines and immunosuppressive factors such as arginase, indole acetic acid, and nitric oxide (recently reviewed in [7]). Modulating this hostile environment will increase the likelihood for vaccine approaches to benefit patients.

## Vaccine-Based Approaches

Since most human cancers develop in immunologically intact hosts, TAAs are weakly immunogenic. Thus, cancer vaccines are designed to overcome this immune tolerance and elicit a specific anti-tumor response to tumor antigens to stimulate cell-mediated and humoral immune responses.

There is growing evidence that precise scheduling and dosing of commonly used chemotherapeutic agents modulate anti-tumor immunity in a vaccine-like fashion. This may be a direct effect or reflect the effects of these agents on the tumor microenvironment and the particular immune

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**Table 77.1** Recently completed and ongoing prostate cancer vaccine studies

| Immunotherapy agent (trial) | Endpoint | # of patients | Outcome | Reference |
|---|---|---|---|---|
| Sipuleucel-T (IMPACT) | OS | 512 | Prolonged OS (25.8 vs. 21.7 months for placebo ($P=0.03$)), no change in time to progression | [9] |
| Sipuleucel-T (D9901) | TTP | 127 | Prolonged OS (25.9 vs. 21.4 months for placebo ($P=0.01$)), no change in time to progression | [10] |
| PSA-TRICOM | TTP | 125 | Prolonged OS (25.1 vs. 16.6 months for placebo ($P=0.0061$)), no change in time to progression | [11] |
| GVA (VITAL-1) | OS | 626 | No difference in median OS (20.7 vs. 21.7 months, $P=0.78$) | [12] |
| GVAX (VITAL-2; prematurely terminated) | OS | 408 | OS shorter in docetaxel/vaccine arm vs. docetaxel/prednisone arm (12.2 vs. 14.1 months $P=0.0076$) | [13] |

| Immunotherapy agent (trial) | # of patients | Primary endpoint | Design | Reference |
|---|---|---|---|---|
| *Ongoing randomized phase III trials of prostate cancer immunotherapy* | | | | |
| Ipilimumab | 600 | OS | Chemotherapy-naïve; ipilimumab 10 mg/kg IV or placebo | [14] |
| PSA-TRICOM | 1,200 | OS | Chemotherapy-naïve; vaccine alone or vaccine with adjuvant doses of GM-CSF | [15] |
| Ipilimumab | 800 | OS | Post-docetaxel; ipilimumab 10 mg/kg IV or placebo following radiotherapy | [16] |

cells involved in creating a state of tolerance to the cancer [8]. Four distinct vaccine strategies have been investigated, namely, dendritic cell-based vaccines, cellular vaccines, vector-based vaccines, and DNA-based vaccines. Examples of recent and ongoing studies are summarized in Table 77.1.

Following vaccine treatment, markers of response have traditionally consisted of in vitro-based readout such as antigen-specific recall response to the injected immunogen (by ELISPOT and/or cytotoxic T-cell response), humoral response or changes in cytokine profile and evidence of change from the so-called tolerant Th2 to a more stimulatory Th1 or Th17. It is clear that traditional radiological parameters such as RECIST and clinical endpoints such as overall survival may not be appropriate post-vaccination. These endpoints were designed for cytotoxic therapy, and the kinetics of anti-tumor immune responses is quite different. This has been recently exemplified by studies with ipilimumab where response to treatment was delayed for 6 months and followed visual and radiological evidence of disease progression. In order to harmonize the evaluation of immunotherapeutic agents, specific endpoints have been debated and coherent terms of reference recently published. New immune-related response criteria were defined to more comprehensively capture all response patterns. Recent studies have shown delayed separation of Kaplan-Meier curves in randomized immunotherapy trials can affect results. Altered statistical models describing hazard ratios as a function of time and recognizing differences before and after separation of curves may allow improved planning of phase III trials. Furthermore, consortia such as CIMT are involved in harmonizing the laboratory evaluation of immune responses. This will allow more relevant comparison across studies involving very different vaccine agents and strategies.

To properly immunize a patient with a tumor-specific antigen, inducing an anti-tumor effect, antigen-presenting cells must process and present the antigens to T cells. Thus, DC-based vaccines are thought to hold the most potential, due to the fact that DCs are the most potent APCs and are essential for initiating and maintaining immunity. Various strategies have been used to induce a specific anti-tumor response by isolating DCs and loading them with peptides, proteins and tumor lysates, infected with viral vectors, TAAs and mRNAs, or fused with tumor cells [17]. However, the disadvantage of autologous DC-based vaccines is that their production is costly and labor-intensive. It is necessary to culture large amounts of peripheral blood mononuclear cells in the presence of several cytokines before being engineered and reintroduced into patients. Despite this, the first antigen-specific immunotherapy approved by the USA Food and Drug Administration (FDA) for cancer treatment used such an approach.

Sipuleucel-T (Provenge; Dendreon Inc.) is an autologous dendritic cell-based vaccine designed to stimulate T-cell immunity against prostatic acid phosphatase (PAP), which is expressed in benign and malignant prostate epithelia alike. The vaccine preparation involves using the patient's own antigen-presenting cells, which are isolated by leukapheresis and then cultured with a fusion protein that consists of prostatic acid phosphatase (PAP) linked with granulocyte macrophage-colony-stimulating factor (GM-CSF). The GM-CSF portion of the vaccine is intended to activate and mature the monocytes into functional APCs capable of activating PAP-specific CD4+ and CD8+ T cells when re-infused in the patient. These activated antigen-specific T cells are then thought to home to tumor lesions mediating an anti-tumor response. To date, three randomized, placebo-controlled trials of sipuleucel-T have been

conducted in patients with asymptomatic metastatic castrate-resistant prostate cancer (CRPC). The first involved 127 patients and suggested a relative reduction in the risk of death of 41 % in men receiving vaccine. The second suggested a trend toward improved survival on vaccine, and the third study, IMPACT, was designed to address a possible survival benefit definitively. The pivotal IMPACT study was a double-blind, placebo-controlled, multicenter phase 3 trial, where 512 patients were assigned in a 2:1 ratio to receive either sipuleucel-T (341 patients) or placebo (171 patients) administered intravenously every 2 weeks, for a total of three infusions. The primary endpoint was overall survival. Although the time to objective disease progression was similar in the two groups, sipuleucel-T was associated with a relative reduction of 22 % in the risk of death as compared with the placebo group (hazard ratio, 0.78; 95 % confidence interval 0.61–0.98; $p = 0.03$). This reduction represented a 4.1-month improvement in median survival (25.8 months in the sipuleucel-T group vs. 21.7 months in the placebo group). The 36-month survival probability was 31.7 % in the sipuleucel-T group versus 23.0 % in the placebo group [18] (Fig. 77.1).

The survival advantage for the vaccine group remained irrespective of the type of treatment patients received later such as docetaxel and despite patients initially randomized to placebo being allowed vaccine treatment after study completion (i.e., crossover). Furthermore, the impressive outcomes were achieved without significant toxicity. The most common adverse events in the sipuleucel-T group within 1 day after infusion were chills (in 51.2 %), fever (22.5 %), fatigue (16.0 %), nausea (14.2 %), and headache (10.7 %). Adverse events of grade 3 or more within 1 day after infusion were reported in 6.8 % in the sipuleucel-T group and 1.8 % in the placebo group. The detailed immune readouts from these studies were interesting in that a significant antibody response against the immunizing antigen PA2024 was observed in 66.2 % in the sipuleucel-T group and only 2.9 % in the placebo group. Antibody response against PAP was seen in 28.5 % in the sipuleucel-T group compared to only 1.4 % in the placebo group. At week 6, T-cell proliferation responses to PA2024 were observed in 73.0 % in the sipuleucel-T group compared to 12.1 % in the placebo group. An antibody response of >400 titre against PA2024 or PAP was associated with a survival benefit compared with patients where a lesser response (<400) was observed ($p < 0.001$ and $p = 0.08$, respectively), by the log-rank test.

Thus, the results of these studies have provided not only a "proof of principle" that sipuleucel-T does provide significant clinical benefit but also the viability of such an active and relatively nontoxic immunotherapy approach to cancer. The high cost and complex preparation of sipuleucel-T has very clearly impacted on its general adoption by clinicians.

## Cellular Vaccines

The second approach is the use of cellular vaccines. However, cancer cells themselves are generally nonimmunogenic, and in particular, patients' tumor cells are extremely variable in terms of viability and transduction efficiency. Thus, a cell-based immunotherapy product was created to overcome these difficulties which used allogeneic cell lines transduced to produce an appropriate stimulatory cytokine, i.e., GM-CSF that is thought to attract dendritic cells to the vaccination site and activate efficient tumor antigen presentation [19, 20]. The GVAX (Cell Genesys) vaccine uses two allogeneic prostate cancer cell lines (PC-3 and LNCaP), genetically modified to secrete GM-CSF [19]. LNCaP was derived from disease metastatic to a lymph node and expresses a number of prostate epithelial antigens including PSMA and PSA. PC-3 is an androgen-refractory line derived from a bone metastasis and expresses several cancer-associated proteases. Thus, this approach of using whole cells as an antigen source has the advantage of potentially provoking an immune response to multiple tumor antigens and thus minimizes the potential for antigen escape. The first phase I/II clinical trial using GVAX in 21 men with hormone-naive, biochemically relapsed disease demonstrated not only safety but also immunological activity as evidenced by the detection of novel antibodies reactive with the LNCaP and PC-3 lines [21]. Based on these encouraging phase II data, two large randomized phase III studies of GVAX immunotherapy (VITAL-1 and VITAL-2) were initiated in 2004 and 2005, respectively. VITAL-1 randomized 626 men with asymptomatic CRPC and no prior chemotherapy to GVAX or docetaxel/prednisone. VITAL-2 was expected to enroll 600 patients with symptomatic metastatic CRPC with treatment randomization to docetaxel plus GVAX versus docetaxel plus prednisone. The primary endpoint of these trials was overall survival, but both studies were terminated early. In the case of VITAL-1, the study was closed when a futility analysis revealed a <30 % likelihood of the study meeting its primary endpoint, whereas VITAL-2 was terminated because of a higher number of deaths in the GVAX arm. The reasons for failure of these studies are unclear. The issues of more defined patient selection and extent of disease burden (related to degree of immune suppression) have been debated as well as the possible changing of immunogenicity and expression of GM-CSF of the cells lines with time. The GVAX approaches did not address a key limiting factor increasingly recognized in later and current studies – that of reducing local and systemic immune suppression concomitantly with vaccine. Examples of this include the use of low-dose cyclophosphamide to target regulatory T cells and ipilimumab to overcome immune checkpoint.

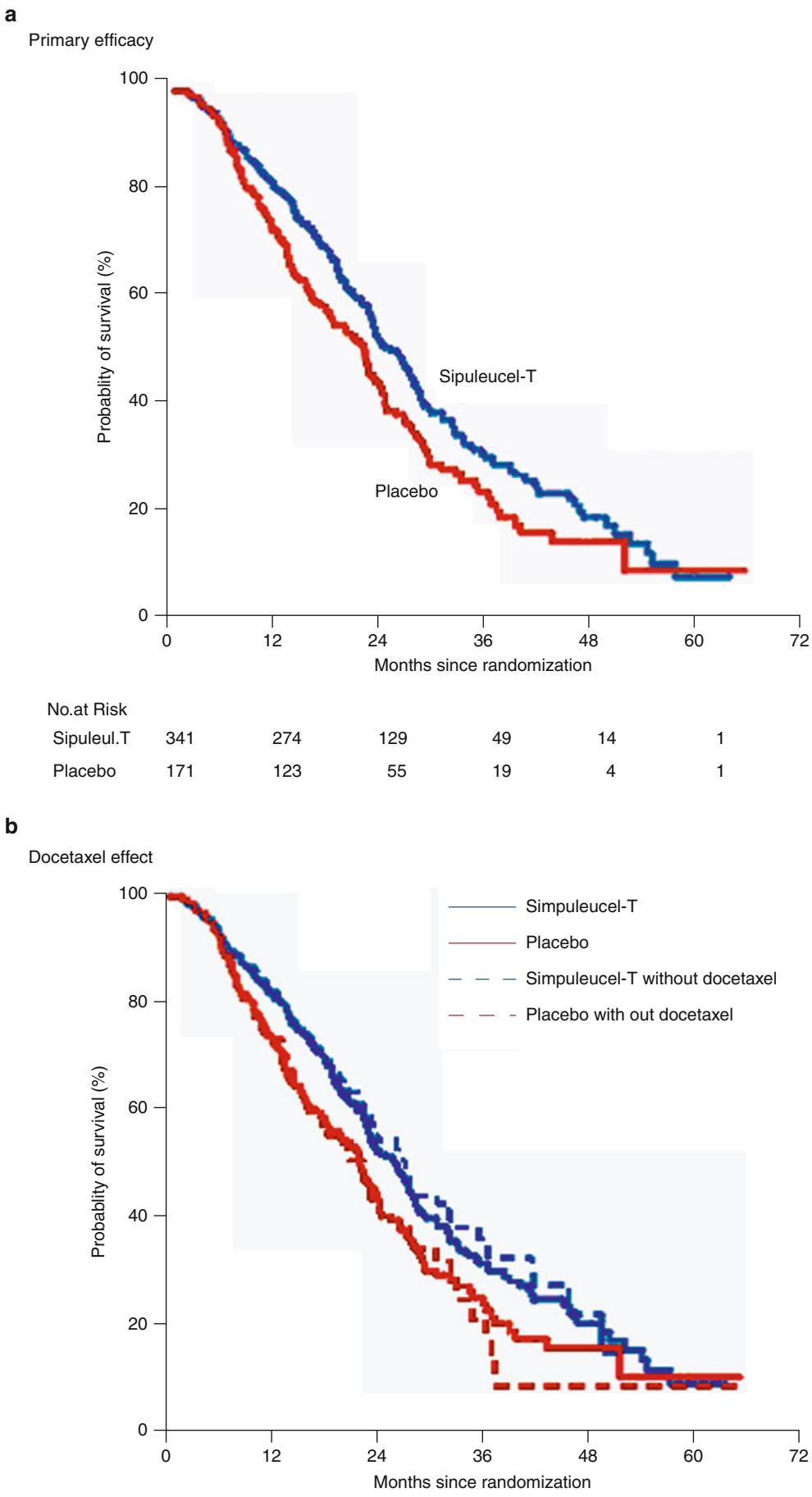


**Fig. 77.1** The efficacy of sipuleucel vaccine versus placebo (**a**). Panel (**b**) shows the results of the analysis with and without censoring at the time of the initiation of docetaxel therapy after study treatment (With permission *N Engl J Med*)

## Vector-Based Vaccines

The third vaccination approach using vectors such as viruses, bacteria, or yeasts has long been known to be a convenient vehicle for vaccine delivery. As is the case for the two approaches described above, vector-based immunotherapy approaches have both advantages and disadvantages. The advantages of using vectors are that these agents are prepared with standard cell-culture techniques making them relatively easy to manufacture and distribute. In addition, the fact that some of the vectors used have large genomes allows for the insertion of multiple genes for TAAs, costimulatory molecules, and cytokines. These vectors are generally quite efficient in priming an immune response, inducing an inflammatory response at the injection site and instigating migration of APCs to the site. Furthermore, these vectors can infect the APCs, allowing for better antigen processing. However, the major disadvantage of the use of vectors is that repeated immunization with these agents results in host-induced antibodies directed against the vector itself rather than the encoded target antigen, thus limiting its efficacy [22]. To date, considerable clinical development has focused on a viral vector approach administering a recombinant vaccinia virus encoding PSA (ProstVac) to men with biochemically relapsed prostate cancer [23]. Vaccinia virus has been used as a vector in many vaccines and has an excellent safety profile. However, in order to overcome the known problem that vaccinia-based vaccination would be limited by an antibody-mediated response against the viral backbone, initial phase II trials used vaccinia-based vectors in the priming phase, followed by monthly boosting with a replication-deficient pox-virus-based vector (fowlpox) targeting PSA. This scheduling of vaccinia-PSA and fowlpox-PSA vectors was shown to give an optimal immune response and even suggested an improvement in progression-free survival in treated patients [24]. In an attempt to further improve this approach by augmenting the immune response, three costimulatory molecules (B7.1, ICAM-1, and LFA-3) were added to the recombinant vaccinia-PSA/recombinant fowlpox-PSA combination. This agent, ProstVac VF (Bavarian Nordic, Mountain View, CA), has now been utilized in a large number of trials both alone and in combination with conventional therapies for prostate cancer in both early-stage and later-stage disease. However, the most notable results have come from a recent 43-center randomized phase II trial comparing ProstVac VF to placebo in men with asymptomatic, metastatic castrate-resistant prostate cancer. In this study of 125 patients, ProstVac VF extended median overall survival by 8.5 months ($p=0.015$) and had a favorable safety and tolerability profile. A subsequent 32-patient study of minimally symptomatic metastatic castrate-resistant prostate cancer patients provided additional evidence of immune response in vaccinated patients. All patients received an rV-PSA-TRICOM prime and monthly boosts of rF-PSA-TRICOM, resulting in declines in PSA (38 % of patients) and PSA velocity (47 % of patients) [25]. Median overall survival among all patients was 26.6 months. In view of these studies, a large multicenter randomized phase III study will commence in late 2011.

## DNA-Based Vaccines

A further vaccine approach targeting individual antigens to elicit a CD8+ T-cell immune response is the use of DNA vaccines. Although DNA vaccines are thought to be less immunogenic than, for example, viral-based vectors, they do have the advantage of being used for multiple immunizations without the need for heterologous vaccine strategies [26, 27]. The safety and immunological efficacy of such a DNA vaccine approach was demonstrated in a phase I clinical trial led by McNeel et al. [28]. Patients with stage $D_0$ PSA-recurrent prostate cancer were immunized six times at biweekly intervals using a DNA vaccine encoding PAP. They demonstrated that in addition to very little toxicity, PAP-specific T-cell responses were detectable in 10 of 22 individuals. Furthermore, this antigen-specific T-cell response appeared to be associated with an increased PSA doubling time in the treated men. Following on from this study, more detailed longitudinal immune analysis investigating the immunologic efficacy of subsequent booster immunizations showed that antigen-specific cytolytic T-cell responses were amplified after immunization in 7 of 12 human leukocyte antigen-A2-expressing individuals and that multiple immunizations seemed necessary to elicit PAP-specific immune responses. Moreover, among individuals who experienced a ≥200 % increase in prostate-specific antigen doubling time, long-term PAP-specific T-cell responses were detectable in 6 of 8, but in only 1 of 14 individuals without an observed change in prostate-specific antigen doubling time ($p=0.001$) [29]. In an effort to improve the delivery of DNA, a further study by Low et al. evaluated the use of electroporation (EP) to deliver a novel DNA vaccine, p.DOM-PSMA [30]. This vaccine encodes a domain (DOM) of fragment C of tetanus toxin to induce CD4+ T-cell help, fused to a tumor-derived epitope from prostate-specific membrane antigen (PSMA) for use in HLA-A2+ patients with recurrent prostate cancer. Such a DNA fusion vaccine design has previously been shown to overcome tolerance and induces high levels of tumor epitope-specific CD8+ T cells, able to suppress the growth of solid tumors in murine models [31]. In this phase I/II two-arm, open-label, nonrandomized study, they were able to demonstrate that the use of electroporation in patients is safe and tolerable. Evaluation of the humoral responses to DOM revealed low anti-DOM IgG antibody responses after intramuscular injection of DNA without EP. These could be

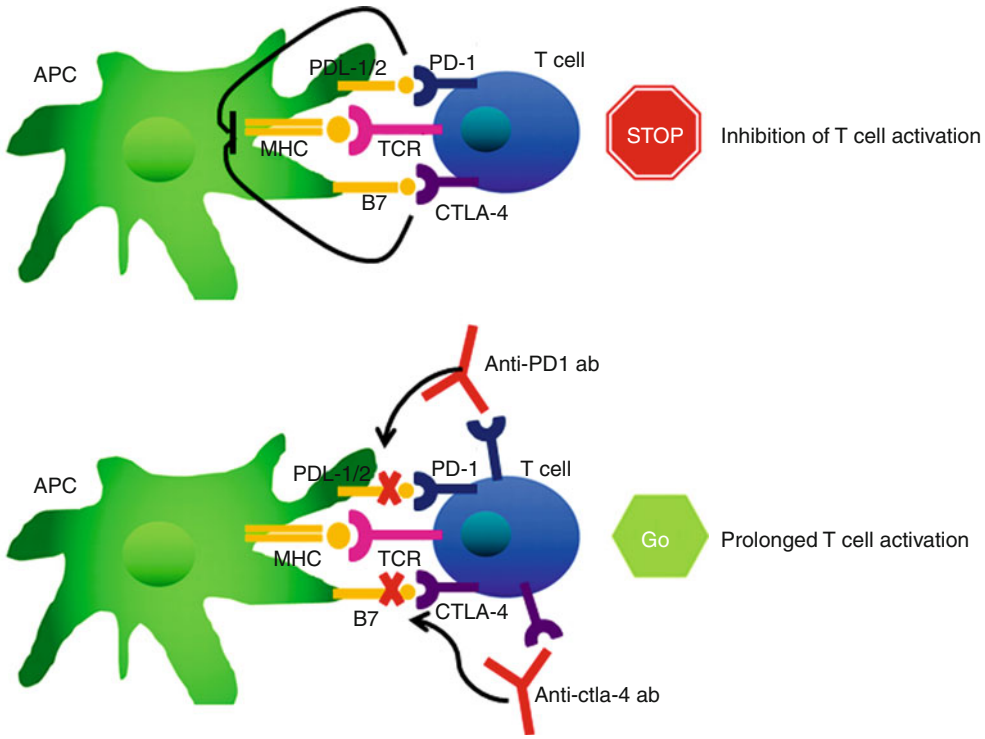


**Fig. 77.2** Two signals are required for full T-cell activation. T-cell activation involves binding of T-cell receptor to antigen-bound major histocompatibility complex (*MHC*) on the antigen-presenting cell (*APC*). Full activation also requires binding of costimulatory receptors (e.g., B7) on the APC to receptors (e.g., CD28) on the T cell. After T-cell activation, two other receptors, cytotoxic lymphocyte antigen-4 (*CTLA-4*) and programmed death-1 (*PD-1*), are up-regulated and compete for binding to B7 and down-regulate T-cell activation. Anti-CTLA4 and PD-1 monoclonal antibodies inhibit interaction of B7 and CTLA-4/PD-1, thus prolonging T-cell activation (Adapted from Robert and Ghiringhelli [36])

boosted by delivery of DNA+EP at later time points. However, delivery of multiple dosing of DNA+EP yielded the highest levels of anti-DOM antibody with responses persisting to 18 months of follow-up [30]. Thus, compared to other DNA vaccines which have previously been shown to be inadequate at inducing an antibody response [32], this study has shown promising results establishing EP as an improved delivery strategy for DNA vaccines in particular being a potent method for stimulating humoral responses induced by DNA vaccination in humans.

## Immune Checkpoint Blockade

While vaccination approaches as a form of prostate cancer immunotherapy have shown clinical promise, the full potential of this approach is still restrained by the multiple mechanisms that tumors and their associated stroma have to evade immune attack [33]. In particular, tumor cells have co-opted the normal immune checkpoints that are expressed on the surface of CD4 and CD8 T cells that function to limit an ongoing immune response. As prostate cancer-infiltrating lymphocytes express a number of such molecules, most notably, cytotoxic lymphocyte antigen 4 (CTLA-4) and programmed death-1 (PD-1) tumors are able to impede an anti-tumor response [34, 35]. This led to the proposition that interfering with these inhibitory immune regulatory checkpoints that act to constrain immune responses and help to maintain peripheral tolerance may represent an alternative strategy to traditional vaccination approaches in tumor immunotherapy. Indeed, a number of antibodies have already been generated that can block inhibitory checkpoint proteins or promote the activity of activating molecules (Fig. 77.2). Furthest along in clinical development are humanized antibodies specific for CTLA-4 (ipilimumab (MDX-010; Bristol-Meyers Squibb/Medarex) and tremelimumab (CP-675206; Pfizer)). CTLA-4 is a T-cell surface glycoprotein that is up-regulated following T-cell activation to inhibit the immune response. In addition to CTLA-4, T cells also express CD28 on their surface, and both of these receptors bind to the same ligands or costimulatory molecules on the surface of APCs (B7.1 and B7.2, also known as CD80 and CD86). Whereas binding of these costimulatory molecules to CD28 activates T cells, interactions with CTLA-4 deliver an inhibitory signal for T-cell activation. Early studies blocking CTLA-4 with a neutralizing antibody showed the ability to sustain and potentiate immune responses [37]. The first confirmation of the huge clinical potential of ipilimumab was recently

reported in the context of patients with malignant melanoma, with the first ever report of improved overall survival (11.2 vs. 9.1 months ipilimumab plus dacarbazine vs. dacarbazine) in this condition with any agent [38]. The toxicities associated with ipilimumab were significant. The major toxicity associated with this therapy is the emergence of autoimmune phenomena, referred to as IRE or "immune-related adverse events." Virtually, every organ and tissue has been described as a potential site of autoimmune events in the setting of this therapy. The most common sites involved are skin and bowel but have also affected the eye and pituitary. In 2–3 % of cases, these events were fatal, but in the majority of patients, toxicities are mild to moderate and required only symptomatic management. With careful surveillance, corticosteroids were employed to ameliorate severe autoimmune events. In cases where autoimmunity and response were occurring simultaneously, the introduction of immunosuppressive medications does not appear to impact tumor response. In view of the nature of these toxicities a "risk evaluation and mitigation strategy" has been set up to inform prescribers of the potential risks. Interestingly, the development of IRE has been correlated with increased likelihood of anti-tumor effects [39].

Ipilimumab has now been evaluated in several phase I and phase II trials in patients with prostate cancer, with objective clinical responses and declines in PSA levels reported [40, 41]. Based on those data, a randomized phase III trial comparing ipilimumab with a placebo has recently been initiated in men with castration-resistant metastatic prostate cancer who have not responded to chemotherapy. In addition, this trial also includes low-dose radiotherapy prior to immunotherapy in an effort to prime an anti-tumor response through the release of antigen from irradiated tumor cells.

In addition to ipilimumab, a monoclonal antibody targeting another immune checkpoint mediated by PD-1 (programmed cell death-1) is also in early-stage clinical trials. The ligand for PD-1, the B7 family molecule B7-H1, is widely expressed by cancers. Several studies have now demonstrated that the interaction of B7-H1 to PD-1 can induce a negative regulatory signal and inhibits T-cell responses [42, 43]. In animal studies, PD-1-deficient mice develop systemic and organ-specific autoimmune diseases and infusion of neutralizing monoclonal antibody against PD-1 increased the incidence of experimental autoimmune encephalitis and experimental diabetes [44, 45]. Most importantly, PD-1 blockade has been shown to potentiate an anti-tumor immune response, thus highlighting the potential role for PD-1 blockade in cancer immunotherapy [46, 47]. In humans, PD-1 has been found to be expressed by tumor-infiltrating lymphocytes including CD8+ T cells that infiltrate the prostate gland of men with cancer [35]. To date, only one phase I clinical trial of a fully human monoclonal antibody targeting PD-1 (MDX-1106; Bristol-Meyers Squibb) has been completed [48]. This was conducted to determine the safety and tolerability of anti-PD-1 blockade in patients with treatment-refractory solid tumors, including men with castrate-resistant prostate cancer, and to preliminarily assess anti-tumor activity, pharmacodynamics, and immunologic correlates. Not only was this agent well tolerated but several objective clinical responses were noted in patients with various types of cancer. Thus, these initial promising results warrant further exploration with this agent especially in combination with other therapies such as vaccines. Such studies will also reveal whether vaccination is still necessary or whether the release of existing anti-tumor T cells restrained by immune checkpoints may be sufficient to mediate an anti-tumor response. However, such an approach still requires caution as in at least some patients, a significant population of self-specific T cells may also be held at bay by identical mechanisms which could induce severe autoimmunity. Despite this, both ipilimumab and anti-PD-1 monoclonal antibody targeting have provided clear clinical evidence that cancer patients can mount clinically significant anti-tumor responses.

## Combination Therapies

While some of the aforementioned immunotherapeutic approaches appear promising, studies suggest that clinical combinations of immunotherapy and conventional treatments for prostate cancer such as radiation, androgen-deprivation therapy (ADT), and certain chemotherapies may result in more effective treatment for men with prostate cancer. This is probably due to the fact that many conventional treatments for prostate and other cancers have beneficial immunological effects. A good example of this is the immunological effects of androgen ablation. Preclinical studies have shown that in aged mice, androgen ablation causes regeneration of the thymus and the output of new T cells in the peripheral blood [49]. Similarly, in humans, androgen ablation before prostate cancer surgery results in the infiltration of predominantly CD4+ T cells displaying an oligoclonal pattern of TCR restriction [50]. Further evidence for the pro-immunogenic role for androgen ablation came from another study in which an increase in tumor-associated autoantibody responses was demonstrated in patients receiving neoadjuvant ADT for prostate cancer [51]. Based on this strong scientific evidence, several groups have attempted to make use of these effects in clinical trials. In an early study, the combination of one dose of vaccinia virus-PSA (ProstVac) with androgen ablation was found to be well tolerated [23]. Furthermore, in a later randomized study, immune responses to ProstVac were more commonly observed in men who received androgen ablation after active immunotherapy compared to receiving androgen ablation before immunotherapy [52].

Despite the cytotoxic effects of radiation therapy, radiation can augment the immune response to prostate cancer. Radiation can result in the uptake of dying tumor cells by APCs, the up-regulation of the expression of some TAAs as well as the induction of a pro-inflammatory microenvironment [53, 54]. Evidence for these effects has been demonstrated in prostate cancer patients who showed the induction of new antibody specificities following radiotherapy treatment [51]. This induction of an anti-tumor response was further demonstrated in a randomized phase II trial that evaluated immune responses in patients undergoing primary radiotherapy for prostate cancer [55]. A total of 30 patients were randomized to receive radiation alone or in combination with a poxviral-PSA vaccine. In total, 13 out of 17 patients in the combination arm had a threefold or greater increase in PSA-specific T cells, compared with no increase in the radiotherapy-only arm ($p<0.0005$). Indeed, in patients on vaccine for 3 months prior to radiation therapy, there was evidence of immune-mediated tumor killing, with the formation of de novo immune responses to prostate-associated antigen not found in the vaccine.

Similar to radiotherapy, chemotherapy has traditionally been thought to blunt the ability of a vaccine to activate an immune response. However, it is now appreciated that certain chemotherapy agents also elicit the same immunostimulatory effects as radiation and positively modulate the immune response [56]. Preclinical data have shown that administration of docetaxel prior to immunotherapy with cell-based immunotherapy leads to improved clinical outcome, without an increase in toxicity [57]. However, a randomized phase II study of patients with metastatic CRPC in which a poxviral-PSA vaccine was compared with or without weekly docetaxel demonstrated no difference in PSA-specific T-cell response [58]. This lack of a response was probably due to an impaired immune response in patients heavily pretreated with chemotherapy, and thus careful selection of not only the chemotherapy agent and scheduling but also the patients to be treated will be necessary.

## Summary

Although the development of effective chemotherapy and more recently hormonal regimens for CRPC has led to significant improvements in overall survival, prognosis for advanced disease still remains guarded, and better treatment options are needed. Immunotherapy represents one such alternative treatment option as not only have a number of clinical trials suggested a survival benefit for immunotherapy in metastatic prostate cancer but also that these agents are generally well tolerated. However, due to the number of immune evasion barriers which are predominant in advanced prostate cancer, it seems likely that clinical combinations of active immunotherapy with immune checkpoint blockade or combinations involving conventional therapy will result in more effective treatment for men with prostate cancer.

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# Bone Health: Prevention of Skeletal-Related Events and Palliative Care

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## Abbreviations

| | |
|---|---|
| ADT | Androgen-deprivation therapy |
| BALP | Bone-specific alkaline phosphatase |
| BMD | Bone mineral density |
| BP | Bisphosphonate |
| CRPC | Castration-resistant prostate cancer |
| CTC | Circulating tumor cell |
| CTIBL | Cancer treatment-induced bone loss |
| CTX | C-telopeptide of type I collagen |
| DTC | Disseminated tumor cell |
| GU | Genitourinary |
| HR | Hazard ratio |
| N-BP | Nitrogen-containing bisphosphonate |
| NTX | N-telopeptide of type I collagen |
| OS | Overall survival |
| PC | Prostate cancer |
| PO | Oral(ly) |
| PSA | Prostate-specific antigen |
| RANK | Receptor activator of nuclear factor kappa B |
| RANKL | Receptor activator of nuclear factor kappa B ligand |
| RP | Radical prostatectomy |
| SC | Subcutaneous(ly) |
| SRE | Skeletal-related event |
| ZA | Zoledronic acid |

## Introduction

Prostate cancer is the most diagnosed cancer in North America, with 223,307 new cases and 29,093 deaths from the disease reported in 2007 by the CDC (US cancer statistics working group) [1]. Most of these patients die with metastatic disease and experience bone complications prior to death. The treatment of metastatic prostate cancer has witnessed a steady refinement during the last 10 years, especially since the introduction of taxane-based chemotherapy. Patients are being maintained on multiple lines of treatments, and survival is possibly being significantly prolonged particularly in patients being enrolled on an ever-increasing number of new research protocols. Besides systemic cancer-directed treatments that are mostly aimed to improve quality of life, bone-directed therapies have also become standard of care, and their use is widely disseminated. These therapies may even possess anticancer activity.

Patients with metastatic prostate cancer usually have reached advanced stages of their disease, yet their survival perspectives are not so somber due to the protracted nature of prostate cancer progression. Preventing and treating bone complications due to metastasis should help improve quality of life before attaining the terminal stages of the disease. The ideal strategy in this patient population is to focus on prevention of symptoms and to delay the appearance of complications related to metastases.

## Natural History

Since the advent of the PSA era, the appearance of metastases in patients who have received definitive local treatment is being long antedated by biochemical recurrence [2]. Even if these patients receive androgen-deprivation therapy (ADT) only when metastases are documented, they may still have a median 6 years survival [3]. Nevertheless, it is anticipated that almost half the patients with castration-resistant disease will develop metastases an average 1.5–3 years following PSA rise on hormone therapy [4, 5]. When hormonal therapy is initiated upfront with no local treatment in nonmetastatic patients (probably in a high-risk population), median time to metastases development after initiation of ADT is often more than 5 years [6, 7].

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At the other end of the spectrum, patients who present with metastases rarely regress completely to a non-detectable metastatic state with the initiation of hormonal therapy [8–10]. Yet in a review of 12,500 patients from the CaPSURE database, Ryan et al. demonstrated that this group of patients still had a protracted course, with 5-year survival exceeding 70 %, and many of the patients (36 %) dying of non-related conditions [11]. Given this indolent course, the effects of prolonged exposure to hormone-deprivation therapy will become a concern, and complications not only related to metastases but also associated with osteoporosis and osteopenia are to be prevented.

Although prostate cancer metastasizes to bone more than any other cancer [12], many patients present with symptoms resulting from lymph node or visceral metastases; the management of which is significantly different from their osseous counterpart and will not be discussed in this chapter.

## Patients with Asymptomatic Metastases

Seven to twenty-five percent of patients with metastatic prostate cancer do not have pain [13]. In this patient population, it is probably best to initiate preventative measures early in order to prevent bone complications, as will be discussed later. Beyond the basic treatments for bone preservation that are applicable in the nonmetastatic setting, such as vitamin D and calcium, active treatment to prevent bone complications from metastases seems indicated. In a sub-analysis of a randomized clinical trial assessing zoledronic acid (ZA) for the prevention of bone complications in metastatic patients, it was demonstrated that the drug was more efficacious in patients that did not have any or had minimal pain [14].

## Patients with Symptomatic Metastases

Eventually, all patients with metastatic disease to bone will develop pain, which may necessitate palliative local radiation therapy or may prompt systemic treatment. Pain can be related to the local effect of the osseous metastasis per se on the bone and periosteum, but this is not always the case. Many patients report pain at a different site than what is observed on imaging. Furthermore, pain can result from nerve compression by a metastatic lesion manifesting in a referred pattern. The development of pain seems to be an independent predictor of cancer-specific death [3, 15, 16].

Symptoms related to other metastatic sites include lower limb lymphedema from pelvic and retroperitoneal node metastases, liver failure with jaundice related to liver metastases, respiratory failure related to lung metastases, and neurologic symptoms associated with central nervous system metastases.

## Preventative Measures

### Definition of SREs

Trials pertaining to the prevention of bone complications in prostate cancer patients have focused on endpoints defined as skeletal-related events (SRE) which include: (1) pathological bone fractures; (2) need for surgery or palliative radiotherapy to bone due to fracture or pain, respectively; (3) spinal cord compression due to vertebral metastases; and (4) hypercalcemia of malignancy [17, 18].

### The Molecular Biology of Bone Metabolism and Conceptual Avenues for Preventing SREs

Possibly the best way to prevent SRE is to avoid a metastatic state in the first place by preventing implantation of circulating tumor cells in the bone matrix. A helpful concept that may lead to an interventional strategy in this regard is the "seed and soil" theory, which has been put forth as early as the late 1800s [19]. In essence, this theory suggests that circulating tumor cells (the seeds) would not implant in organs (the soil) that are unfavorable to their growth. One of the major requirements for tumor seeding in prostate cancer may be increased bone turnover. It is well established that bone matrix is in constant dynamic turnover, with equilibrium between bone resorption (mediated by osteoclasts) and bone deposition (mediated by osteoblasts) [20]. These two cell lines interact with each other through the secretion of receptor activator of nuclear factor κβ ligand (RANKL) by the osteoblasts. RANKL will specifically and avidly bind its receptor RANK on osteoclasts, thus activating these cells to degrade bone matrix. In a normal state, this interaction is regulated by the endogenous protein osteoprotegerin, which will bind RANKL and prevent it from attaching to RANK on osteoclasts [20, 21]. The presence of tumor cells alters this balance by driving the activation of osteoblasts through secretion of various cytokines and growth factors including VEGF, IGF, FGF, TGF-β, Wnt, and others. Activated osteoblast will increase their RANKL secretion, thus activating osteoclasts and increasing bone matrix degradation. In addition, osteoclast activation will lead to secretion of a number of mediators by these cells including PDGF, BMPs, FGF, and IGF. These mediators will drive the proliferation and growth of tumor cells, thus closing the loop and creating a vicious cycle. Amplifying even further, this phenomenon is a reduction of osteoprotegerin in prostate cancer, as has been shown in vitro [22]. Cancer cells therefore create a favorable soil for their implantation in bone, and a way of preventing this implantation is possibly to break the cycle that these cells create.

There are conceptually at least two means of preventing the deleterious effects of metastases: primary and secondary

preventions. Primary prevention is concerned with delaying metastatic disease in the first place; secondary prevention aims to delay SREs once metastases have occurred. After metastatic onset, most patients will eventually progress to a symptomatic state. Obviously, most SREs occur mainly in patients that are symptomatic from their osseous metastases, but ideally, if a prophylactic treatment is to be considered, it should start before pain settlement. In fact, patients seem to benefit most from preventative measures when these are initiated in the asymptomatic stages of their disease [23, 24]. Multiple agents have been assessed for their preventative activity in the setting of metastatic prostate cancer including pamidronate [25], zoledronic acid [17, 18], and most recently denosumab. Only the last two molecules have yielded positive results and are the subject of the following discussion.

## Prevention of SREs

### Zoledronic Acid (ZA)

ZA is an intravenously administered bisphosphonate. It is the only bisphosphonate that has shown a significant reduction of SREs in a randomized controlled trial assessing patients with metastatic prostate cancer, and only this agent has received worldwide regulatory approval for use in this setting [17, 18].

#### Mechanism of Action

ZA is a second-generation bisphosphonate that contains nitrogen within a heterocyclic ring. It is a pyrophosphate analogue that acts by inhibiting protein prenylation in osteoclasts through farnesyl diphosphate synthase inhibition (an enzyme in the mevalonate pathway), which leads to reduction in osteoclast activity [26]. This reduction freezes bone metabolism and breaks the vicious circle of bone turnover. ZA is administered intravenously once a year to prevent bone resorption and monthly for the indication of SRE prevention in metastatic prostate cancer patients.

#### Clinical Studies

ZA is one of the most potent new-generation bisphosphonates. It was the first bisphosphonate to show activity in reducing SRE in metastatic castrate-resistant prostate cancer in the setting of a randomized controlled trial (secondary prevention) [17]. This multicentric study included 643 patients who received 4 mg ZA or placebo every 3 weeks for a total of 2 years. There was a 22 % relative reduction in SREs in the active treatment group compared to placebo (38 % vs. 49 %, $p=0.028$), and these results compare to similar studies in metastatic breast cancer. Time to first SRE was increased by 5 months (488 vs. 321 days; $p=0.009$). Additionally, there was a reduction in the mean annual incidence of skeletal complications in the ZA group (0.77 vs. 1.47 events per year, $p=0.005$) as well as in the ongoing risk of these complications by 36 % in both the 15- and 24-month data analysis [17, 18]. Importantly, ZA (4 mg) consistently reduced bone pain with statistically significant differences at 3, 9, 21, and 24 months through the trial ($p \leq 0.05$) [18].

ZA has also been studied in the setting of nonmetastatic prostate cancer and has shown activity in the prevention of cancer treatment-induced bone loss (CTIBL) in patients under androgen-deprivation therapy [27]. Additionally, ZA (4 mg IV every 3 months for 12 months) also increased bone mineral density (BMD) with respect to baseline, especially in the lumbar spine. These results hold true when ZA is administered yearly, showing prevention of CTIBL in men with prostate cancer on ADT [28]. Considered under the light of the "seed and soil" theory, this makes ZA conceptually a promising agent in the prevention of metastatic disease. The assessment of this agent in patients with nonmetastatic disease in phase III trial is underway, and data pertaining to its prophylactic activity in preventing metastases should be available soon. Additionally, a phase III study is presently accruing to evaluate whether earlier initiation of ZA in hormone-sensitive metastatic prostate cancer may be more beneficial than its standard actual use in castration-resistant disease.

#### Antitumoral Activity of ZA

ZA may also possess antitumoral activity according to preclinical studies and to exploratory analysis of available randomized trials.

As discussed above, using bone-targeted molecules to disrupt the cycle induced by tumoral cells may result in reduced tumor-bone interaction and delay metastatic progression, which has been shown in a number of preclinical models [29–31]. Bisphosphonates and particularly ZA may also have a direct action on cancer cells inducing apoptosis or acting synergistically with cytotoxic chemotherapy [32–38].

### Denosumab

#### Mechanism of Action

Denosumab is a fully human monoclonal antibody directed specifically against RANKL, which results in an action similar to that produced by endogenous osteoprotegerin, namely, the inhibition of osteoclast activity, and consequent reduction in bone turnover [39]. Indications for denosumab administration in prostate cancer patients include the prevention of bone loss and fractures in patients with nonmetastatic prostate cancer on ADT and prevention of SREs in patients with hormone-refractory metastatic prostate cancer.

#### Clinical Studies

In a randomized multicentric phase III clinical trial, denosumab (120 mg S/C every 4 weeks) was tested against ZA

(4 mg IV every 4 weeks) for the prevention of SREs in metastatic castrate-resistant prostate cancer patients (secondary prevention). The trial included 1901 patients, and the primary objective for non-inferiority testing against ZA was time to first on study SRE, whereas secondary objectives included, additionally, time to first and subsequent on study SREs (multiple events). On final analysis, there was an 18 % risk reduction with respect to time to first SRE in the denosumab arm compared to the ZA arm. This rate of risk reduction was maintained for the secondary objective assessing multiple SREs. Overall progression and survival were however identical in both groups. Adverse event rate was also similar in both groups, albeit the denosumab group presented more hypocalcemia and muscle spasms, whereas the ZA group had more pyrexia and flu-like symptoms [38].

Denosumab has also shown activity in the primary prevention setting. In a phase 3 randomized, multicentric trial of this agent against placebo in 1,432 men with castrate-resistant nonmetastatic prostate cancer, denosumab significantly improved median bone metastasis-free survival by 4.2 months (HR = 0.85, 95 % CI 0.73–0.98, $p = 0.03$) compared to placebo, which was the primary endpoint of the study. A secondary endpoint was also met, with significantly improved time to first occurrence of bone metastases. However, denosumab did not improve overall survival over placebo [54]. Dosing in this study was 120 mg every 4 weeks. Adverse events were similar between denosumab and placebo, but the active agent presented more hypocalcemia and osteonecrosis of the jaw than the placebo group [54].

Finally, in a study addressing bone loss and fracture risk, denosumab resulted in an increase of BMD in a population of nonmetastatic prostate cancer patients on ADT. In a phase III randomized, multicentric, placebo-controlled study of 1,469 patients, denosumab (60 mg every 6 months) resulted in BMD improvement at 24 months in the lumbar spine (6.7 %, $p < 0.001$), total hip (4.8 %, $p < 0.001$), femoral neck (3.9 %, $p < 0.001$), and distal radius (5.5 %, $p < 0.001$) [40]. One may thus conclude that by increasing BMD and breaking the vicious cycle of tumor cells-osteoblast-osteoclast interaction, the implantation of metastases may be hindered or at least delayed. Caution must be exercised though in this inference, since dosing for bone preservation is different from that used in metastases prophylaxis and the timing of administration is also different in the two settings (men on ADT vs. men with castrate-resistant disease). Of note is that denosumab has not been approved by the FDA for use in the nonmetastatic prostate cancer patients.

## Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) was initially described as a complication of IV bisphosphonate therapy [41], but has also been observed, albeit to a lesser extent, with oral bisphosphonates. Patients typically present with exposed bone in the maxillofacial region, and healing can take more than several weeks. Precipitating events in patients on bisphosphonate therapy include preexisting oral pathology, poor dental hygiene, use of dentures, and oral surgery while on treatment. Fortunately, ONJ is a very rare event (1/10,000 to <1/100,000 patient-treatment years) when bisphosphonates are used, at therapeutic or prophylactic doses for osteoporosis. Most recently, denosumab has also been associated with ONJ when used in a monthly regimen, which implies that this clinical entity is not related to a class effect of bisphosphonates, and is most likely associated with osteoclast inhibition. It is noteworthy however that ONJ is practically inexistent when denosumab is used for prevention of bone loss in the nonmetastatic setting, as dosing in these patients is not monthly but only twice a year. Prevention of ONJ during bone-targeted therapy includes keeping appropriate dental hygiene, periodic dental checkup, and avoidance of invasive dental procedures [42–44].

## Biomarkers in Prevention

The presence of multiple available bone-targeted therapies begs the questions as to which agent takes precedence, what is the most appropriate sequential use (if any) of these agents, and what is considered treatment failure. Biochemical bone biomarkers may provide an answer to these questions. The most characterized and easily accessible markers include N-telopeptide (NTx) and C-telopeptide (CTx) of type I collagen for bone degradation and serum bone-specific alkaline phosphatase for bone formation [45]. These seem to correspond to the ongoing metabolic activity of bone turnover in prostate cancer patients [46].

Increased levels of bone marker have been associated with increased rates of recurrence, disease progression, and reduced survival [47–50]. Inversely, retrospective analyses on available data from a randomized trial of ZA in CRPC patients demonstrate that subjects who have a normalization of their NTx levels have a 59 % reduced risk of death compared to subjects with a persistently elevated NTx [51]. This held true in a more recent study showing increased overall survival (OS) in patients on ZA that had decreased bone markers after 3 months of ZA therapy [52]. Finally, it appears that patients with elevated bone markers at the onset of treatment seem to benefit most from bone-targeted therapy [53]. Considered together, these findings suggest that failure of a bone-targeted therapy may translate into failure to normalize bone markers, which should reasonably indicate the need to change treatment. Further prospective studies are needed however to consolidate such an observation.

## The Future

Multiple studies are underway in the field of bone health and prevention of metastatic disease complications in prostate cancer, and they promise groundbreaking findings. Namely, the RADAR study is assessing the ability of ZA to prevent CTIBL and delay metastases in patients with prostate cancer at the start of ADT treatment (NIH 2009); the STAMPEDE trial aims to evaluate the anticancer activity of ZA in association with different chemotherapeutic agents (ISRCTN78818544); and finally the ZEUS trial is assessing ZA in the prevention of metastases in patients with biochemical progression under ADT (NIH 2008). Taken together, the results of these trials will certainly help shed some light on the optimal timing of bone-targeted therapies as well as the best combination with available cytotoxic agents.

### Conclusions

An increasing body of evidence points toward the fact that delaying progression in prostate cancer lies in creating a hostile environment for tumor cells within bone, this organ being the most frequent site of metastasis. Understanding bone metabolism has allowed targeting specific checkpoints using bone-targeted agents, and these are proving to be active through different phases of the disease, preventing skeletal-related events, and probably delaying metastases occurrence. The challenge now lies in identifying which agent is best adapted to which patient, and the answer probably lies in the development of valid bone markers. Future data from ongoing trials will hopefully help shed the light on the antitumoral activity of the available bone-targeted agents.

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# Part VII

# Outcomes and Complications After Treatment

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# Assessment of Treatment Outcomes Following Prostate Cancer Therapy

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Paul Cathcart and Mark Emberton

## Introduction

In this introductory chapter, we discuss why it is important to measure outcomes of prostate cancer therapy, which outcome measures are commonly reported, and which tools have been developed to enable such reporting.

## Why Is It Important to Measure Outcomes of Prostate Cancer Treatment?

Over the last 20 or 30 years, the importance of knowing how successful an episode of medical care has been together with capturing information concerning a patients experience of their medical care has increasingly been recognized in all aspects of medical care – not only urological oncology [1–3]. This recognition stems from the acknowledgment that patient experience of medical care can vary markedly depending on where and when they received their care [4].

Outcomes research – one aspect of health services research developed out of the need to understand more about variation in medical care. Key to outcomes research was the development of valid outcome measures [5]. In the early era of outcomes research, very few outcome measures existed; the result of which was that outcomes achieved from different medical institutions could not be evaluated, monitored, or compared. Good care therefore could not be differentiated from suboptimal care and as such attempts to improve overall patient care and quality were limited. Prostate cancer therapy was certainly one area in which outcome measures were initially lacking, although over the two decades much work has been done to improve on this [6].

One reason why appropriate outcome measures of prostate cancer therapies were lacking is that the toxicity of therapy was hard to quantify. For example, unlike cardiac bypass surgery or esophageal cancer surgery where a significant proportion of patients die within 30 days of undergoing surgery [7], few patients die following radical prostatectomy. Therefore, the use of 30-day mortality as an outcome measure to contrast quality by healthcare providers is meaningless. Furthermore, unlike death, many of the long-term sequelae of prostate cancer therapy, such as erectile dysfunction, are soft outcomes. Such adverse events are therefore difficult to capture due to their ambiguous nature. Thus, attempts to report them were fraught with difficulty. Recently, much work has been done to develop and validate instruments that are able to quantify such so-called "soft" outcomes, the incidence of which varies by surgeon and institution. Furthermore, they are known to dramatically affect a patient's quality of life following prostate cancer therapy [8].

## Which Outcomes Are Important to Report upon Following Prostate Cancer Treatment?

Outcome following prostate cancer therapy may be divided according to whether the outcome relates to adverse events

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following therapy – the majority of which occur soon after treatment, although adverse events following external beam radiotherapy, for example, can occur many years after therapy, whether the outcome relates to the oncological success of the particular therapy or whether the outcome relates to the long-term toxicity of therapy upon functionality – for example, erectile function and urinary continence. There is no hierarchy of outcome suffices to say a successful overall therapy outcome is likely to represent a balance between minimal perioperative and functional morbidity together with acceptable rates of oncological success.

## Assessment of Adverse Events in the Peritherapy Period Following Prostate Cancer Treatment

Perioperative mortality following prostate cancer therapy is a poor outcome measure to assess quality as few patients die following prostate cancer therapy [9]. Alternative outcomes measures include estimated blood loss, length of stay, and the occurrence of adverse events following surgery [10, 11].

The accuracy of adverse event reporting was long been known to be poor, a factor that has made comparison among different hospitals and between different therapies very difficult. Furthermore, it has been difficult to evaluate quality of care over time within institutions. Dindo and Clavien [12, 13] recognized the need for a standardized classification of adverse events to enable comparisons Thus, they devised a 4-level severity grading system for complications following surgery and have subsequently applied their system to many different surgical procedures, including both open and robotic radical prostatectomy [10, 14]. Interestingly, use of the Clavien-Dindo system has resulted in a dramatic increase in the reported incidence of complications following radical prostatectomy, as milder complications are increasingly identified [15].

Reporting of adverse events following prostate radiotherapy has also been standardized. The US Radiation Therapy Oncology Group (RTOG) [16] has identified four different levels or "grades" of adverse event occurring following radiotherapy. The vast majority of studies reporting outcome of radiotherapy have adopted this grading system, which has greatly facilitated the comparison of outcomes.

While use of both grading systems is highly recommended, it is generally accepted that the accuracy of such is highly dependent on whether the data are collected prospectively or retrospectively, with the former strategy widely considered superior.

## Assessment of Oncological Outcome Following Prostate Cancer Treatment

A number of different outcomes can be used to assess oncological outcome following prostate cancer therapy including overall survival, disease-specific survival, uptake of salvage therapies, clinical and biochemical progression-free survival, and surgical resection margin status.

## Overall, Disease-Specific and Progression-Free Survival as Outcome Measures Following Prostate Cancer Therapy

Although all cancer therapies should ultimately be evaluated on their ability to provide a survival benefit, prostate cancer offers a unique challenge given the prolonged duration between cancer diagnosis and subsequent cancer death, irrespective of whether the man underwent therapy [17, 18]. As such, although overall survival is free of lead and length time biases and represents the most robust and clinically useful end point, few studies have used this outcome due to the need for very large study populations with prolonged follow-up. For example, Bill-Axelson and colleagues, [19] with over 8 years of follow-up, demonstrated a survival advantage with surgery compared to watchful waiting. However, despite the many person years of follow-up, the difference in overall survival was only 6.6 percentage points.

Disease-specific mortality is another desired oncological outcome that is seldom reported due to problems with cause of death ascertainment and relatively small numbers of events. Data concerning the impact of prostate cancer therapy on disease-specific mortality is desperately required as disease-specific mortality is in effect demonstrating the "true" effect of therapy on the disease by excluding deaths from competing causes. However, care must be taken when interpreting this outcome measure to assess what proportion of patient's die of the disease of interest. For example, a recent study utilizing comparative data from the CaPSURE database [20] demonstrated that the risk of prostate cancer death in those undergoing radiotherapy was twofold higher than for men undergoing radical prostatectomy. However, one could argue the clinical significance of this finding given that very few men died of prostate cancer in the study (3 %) when compared to the number dying of competing causes (17.2 %).

Progression-free survival (PFS) is increasingly used as an outcome measure, not in therapeutic prostate cancer studies but in studies evaluating chemotherapeutic regimes in men with castrate resistant prostate cancer. Recently, PFS has been shown to be related to overall survival. Progression-free survival simply refers to the absence of further metastatic disease as identified on medical imaging or clinical examination

during follow-up. Due to the aggressive nature of advanced castrate-resistant prostate cancer, progression-free survival is a useful study end point and has been used to demonstrate the utility of taxanes and abiraterone in this patient population [21, 22].

## Biochemical-Free Survival as an Outcome Measure Following Prostate Cancer Therapy: Surgery

In contrast to the other oncological outcomes mentioned earlier, biochemical-free survival is commonly used to report outcome of prostate cancer therapy. Following surgery, there should be no residual PSA in the absence of local/residual or metastatic disease. Despite this, a number of different definitions for biochemical recurrence (BCR) following surgery have emerged. However, the current American Urological Association endorsed definition for postprostatectomy BCR is a postsurgical serum PSA of >0.2 ng/ml which remains above 0.2 ng/ml on subsequent confirmatory testing [23].

The clinical implications of BCR following surgery are very variable with many men not needing adjuvant therapy or developing clinical progression despite a postsurgical detectable PSA. As a result, the link between BCR and overall survival is not clear [24–26]. Why this is so is likely to relate to the prolonged time between the development of BCR and clinical progression, metastases, and death. For example, Pound and colleagues [27] reported on just under 2,000 men undergoing surgery for localized prostate cancer between 1982 and 1997. The authors established that the median time to clinical metastases after biochemical failure was 8 years, while the median time to death after the development of metastases was 13 years.

## Biochemical-Free Survival as an Outcome Measure Following Prostate Cancer Therapy: Radiotherapy

Although serum PSA should fall dramatically following radiation therapy to the prostate, serum PSA rarely becomes completely undetectable. A number of different definitions of BCR radiotherapy have been advocated. The American Society for Therapeutic Radiation and Oncology (ASTRO) initially defined BCR following radiation as three consecutive rises in serum PSA after a PSA nadir, with the date of failure being the point halfway between the nadir date and the first PSA rise or [29].

This definition has largely been superseded by a newer ASTRO-endorsed definition, the Phoenix definition, which defines BCR as having occurred if a patient's serum PSA rises more than 2 ng/ml above the serum PSA nadir [30]. The initial ASTRO criteria were abandoned due to noncomparability of survival estimates based on different follow-up periods. The current definition has been demonstrated to have a sensitivity and specificity of 66 and 77 %, respectively, for predicting for clinical failure at 10 years following prostate radiation therapy.

## Biochemical-Free Survival as an Outcome Measure Following Prostate Cancer Therapy: Minimally Invasive Therapies

New emerging treatments such as cryotherapy and high-intensity focused ultrasound have often utilized radiation criteria for BCR due to the lack of validation studies assessing outcome after such therapies. However, Blana and colleagues in a multi-institutional study evaluating PSA dynamics on 285 men undergoing whole gland HIFU therapy with subsequent posttherapy verification prostate biopsy or clinical course developed that a post-HIFU serum PSA more than 1.2 ng/ml above the PSA nadir predicted ablation failure [31].

Measuring outcomes following emerging treatments of focal therapy, irrespective of the treatment platform used, poses a new challenge given that a significant amount of residual PSA-secreting prostate tissue is left in situ [32]. However, a number of studies are currently underway evaluating this treatment paradigm which will no doubt evaluate markers of effective outcome [33]. Imaging is likely to play a vital role in the follow up of these patients, not only identifying residual cancerous tissue but also directing biopsy strategies. Furthermore, work is being directed toward evaluating different PSA derivatives such as percentage drop in total serum PSA, posttherapy free-to-total PSA, and posttherapy PSA density to detect residual/recurrent disease.

## Serum PSA Values

In addition to the criteria above, serum PSA can be used in other ways to assess outcome of prostate cancer therapy. For example, both PSA nadir and time to PSA nadir have persistently been demonstrated to predict outcomes after external beam radiotherapy [34]. Furthermore, PSA pretherapy PSA velocity has been demonstrated to predict outcome of both radical prostatectomy and radiation therapy [35, 36]. However, interestingly, serum PSA has not been found to represent a surrogate marker for prognosis in trials evaluating outcomes in patients with hormone refractory prostate cancer.

### Margin Status

Surgical margins status after radical prostatectomy has been suggested as a marker of surgical quality. Data concerning surgeon experience and margin status does suggest that those surgeons with greatest experience have the lowest positive surgical margin rates [37]. The advantage of using surgical margin rates as a proxy for quality is that a surgeon's margin status can be calculated immediately without the need for prolonged follow-up. However, surgical margin status is highly dependent on the patient population. Furthermore, recent data suggest that while surgical margin status clearly is important, it does not appear to be a strong surrogate for long-term biochemical control [38].

### Initiation of Hormone Therapy

Some have suggested that time to initiation of hormone therapy may be a useful surrogate marker for overall survival in patients with prostate cancer. Indeed there are a number of ongoing clinical trials that use this outcome as a study end point. Its use is clearly aimed at reducing the duration of study follow-up. However, there are little data to support its use. Ray and colleagues [39] have developed a new prostate cancer study end point – referred to as general clinical failure – which incorporated initiation of androgen therapy along with other outcome variables and have shown that this outcome can predict prostate cancer survival at 10 years following radiation therapy.

## Assessment of Quality of Life and Functional Outcome Following Prostate Cancer Treatment

Impaired functional outcome – erectile, urinary, and bowel dysfunction – is well known to occur following prostate cancer therapy. However, functional impairment has traditionally been difficult to quantify. As such, comparison of functional outcomes between the different prostate cancer therapies has been difficult. This has made the evaluation of new emerging prostate cancer therapies, such as cryotherapy and high-intensity focused ultrasound, challenging.

As a result, much work has been done to develop tools that can reliably quantify – in a reproducible manner – the impact of different prostate cancer therapies on a patient's functional outcome [40]. Furthermore, much work has also been done to develop tools that are able to quantify, in a reliable and reproducibly manner, the impact of the different prostate cancer therapies on a patients general "quality of life," given that the majority of men seeking therapy for early prostate cancer will be asymptomatic with a good pretreatment "quality of life."

A number of tools now exist that have and may be used to evaluate the toxicity of prostate cancer therapy [41]. Each tool has been developed through a complex process of psychometric validation that requires the tool to be tested and retested to determine its reliability, reproducibility, and clinical value. Imperative to their use is the need for all tools to be employed in a prospective manner with all patients completing baseline assessments prior to undergoing therapy so that comparison can be made after therapy. Furthermore, following therapy, a single postprocedure assessment is often insufficient with multiple repeated assessments required over time to attain meaningful outcome measures.

Below, a few of the many tools used to assess functional outcome after prostate cancer therapy are discussed.

### International Index of Erectile Function (IIEF)

The IIEF was first developed by Rosen and colleagues in 1997 [42] and identified five domains of male sexual function – erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. These five domains were identified following a review of the literature concerning preexisting sexual function questionnaires and by interviewing men reporting sexual dysfunction. The result was a psychometrically sound 15-item questionnaire that accurately evaluated a man's sexual function. Although the IIEF is well validated and familiar to urologists, it has been suggested that the questionnaire concentrates on function alone rather than evaluating the impact that impaired function may have on a man's quality of life. Subsequently, an abridged version of the IIEF score has been developed for ease of patient use.

### UCLA-PCI

The University of California, Los Angeles Prostate Cancer Index was devised by Litwin and colleagues in 1995 and includes the RAND-36 health survey [43]. It represents a prostate-cancer-specific quality of life tool and contains 20 items. To date, it has been translated – from English – and validated in five different languages including French, German, Italian, and Japanese. The questionnaire, originally 273 men with and without prostate cancer, assesses urinary, sexual, and bowel function together with bother and as such represents a thorough assessment of the common side effects following both radical prostatectomy and external beam radiation to the prostate. One limitation of the questionnaire is that questions concerning urinary function are limited to assessing incontinence and neglect irritative lower urinary tract symptoms which are often common following other prostate cancer therapies such as brachytherapy for instance.

### Expanded Prostate Cancer Index Composite (EPIC)

John Wei and colleagues in 2000 [44] developed and validated the expanded prostate cancer index composite or EPIC for men with prostate cancer. The EPIC represents an expanded version of the 20-item University of California, Los Angeles PCI augmenting the index with items regarding orgasm and a multi-item set regarding bother. Overall, there are 50 items included in the questionnaire. The tool assesses erectile dysfunction and urinary dysfunction together with the toxicity induced by androgen deprivation. Overall, the composite is scored from 0 to 100 with higher scores representing better sexual health. Although generally regarded as excellent to compare toxicity profiles of patients undergoing brachytherapy, external beam radiotherapy, or radical prostatectomy, some have argued that the composite lacks brevity. Furthermore, the composite does not assess quality of life and as such has to be paired with another general health-related quality of life questionnaire.

### International Prostate Symptom Score (IPSS)

This symptom index – originally devised by Barry and colleagues [45] in 1992 on behalf of the American Urological Association – is composed of eight different items pertaining to a number of specific urinary complaints including urinary frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency. The symptom score is well known to urologists having been devised to assess lower urinary tract symptoms in men with symptomatic benign prostatic hyperplasia. The index is well validated; however, it is not exhaustive. For example, the symptom score does not have specific domains for urinary incontinence or dysuria.

### RAND SF-36

The RAND (Research ANd Development) Corporation is a not-for-profit global think tank that among many other projects completed the RAND Medical Outcomes Study – a multiyear, multisite study from which a 36-item health survey was developed to assess general health-related quality of life and as such it is a generic as oppose to a prostate-cancer-specific questionnaire. It has been well validated since its initial development and represents the benchmark tool for assessing general health-related quality of life. Its generability is often cited as its weakness as it does not have domains specific to early prostate cancer therapies and as such should always be completed in addition to a prostate-cancer-specific quality of life questionnaire.

### FACT-P and FACT-G

The FACIT (Functional Assessment of Chronic Illness Therapy) measurement system is a collection of quality of life questionnaires targeted to the management of chronic illness. The measurement system began with the generic core FACT-G (Functional Assessment of Cancer Therapy-G) questionnaire which included a 27-item questionnaire of general questions assessing physical well-being, social/family well-being, emotional well-being, and functional well-being. The FACT-G questionnaire has been validated on numerous occasions and can be applied to cancers in general, not just prostate cancer. Given its generality, the FACT-G is obviously unable to quantify disease-specific quality of life impairment, and as a result it is often paired with the FACT-P disease-specific subscale.

FACT-P, as mentioned above, is a disease-specific adjunct to the FACT measurement system and encompasses a 12-item prostate cancer subscale. Although the FACT-P questionnaire is thought to be a useful tool, it does not assess urinary incontinence specifically rather focusing on overall lower urinary tract symptoms.

In addition to the tools listed above, a number of other scales have been used, most notably the Hospital Anxiety and Depression Scale (HADS) which represents a self-report of depression and anxiety. The score is rated out of 10 with 1 being considered to identify patients suitable for clinical psychiatric care, while a score of 10 is considered normal. The scale has been used extensively in research and clinical practice to determine psychopathology and distress following diagnosis of prostate cancer and is likely to be used increasingly in the future to capture men experiencing anxiety and depression following early prostate cancer therapy.

## Combining Outcomes: The Trifecta

Authors have recently tried to combine information concerning oncological and functional outcome to generate a composite outcome – often referred to as the trifecta [46, 47]. Increasingly, surgical series report overall trifecta rates, that is to say the proportion of men that are free of biochemical recurrence, who are pad free and leak free and who are potent following surgical therapy. Published trifecta rates vary dramatically from as high as 76 % to less than 20 % and as yet, data concerning the trifecta outcome appears limited to surgical series, although a publication recently reported a trifecta rate of 89 % following focal HIFU [33].

Initially, the concept of combining the three domains of prostate cancer surgical outcome seemed contradictory as it was thought that oncological, sexual, and urinary outcome were inversely proportional. However, a recent study suggests that surgeons with the "best" oncological outcomes are

also able to achieve the highest rates of continence and sexual function, supporting the notion of a trifecta rate [28]. What period of follow up is required before a trifecta rate can be reported remains controversial. Clearly, sufficient time is required for men to fail biochemically; furthermore, the recovery of potency – the main determinant of the trifecta outcome – can take up to 3 years following therapy. Furthermore, some have argued that it is overly simplistic to reduce sexual and urinary function to an all or none response given that sexual and urinary dysfunction are highly complex, multidimensional entities [48].

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# Urinary Incontinence

80

Ted A. Skolarus

## Introduction

Urinary incontinence is a common side effect of prostate cancer treatment. While nearly one in five men over the age of 60 years reports some degree of urinary incontinence, one of the greatest risk factors for incontinence is the diagnosis and treatment of prostate cancer. Despite advances in our understanding of pelvic floor anatomy, surgical technique, and radiation delivery, nearly all local treatments for prostate cancer adversely impact urinary function. Because over 200,000 US men will be diagnosed with prostate cancer in 2012 and nearly one in six men will receive the diagnosis in their lifetime, the burdens of urinary incontinence will likely continue. Moreover, the economic burden of urinary incontinence following prostate cancer treatment is substantial. This chapter examines the implications of prostate cancer and its treatments on urinary function. After a review of the epidemiology and anatomic considerations surrounding urinary incontinence, its measurement and prostate cancer treatment outcomes are discussed. Finally, treatment options for men with urinary incontinence after prostate cancer treatment are reviewed.

## Overview of Urinary Incontinence

Many men have increasing urinary symptoms with increasing age and a variety of other conditions that impair urinary control (e.g., functional and cognitive dysfunction, diabetes, neurologic disorders) [1]. For instance, by the age of 60 years, nearly 20 % of men report some degree of urinary incontinence [1]. Because of its prevalence, the estimated economic burden of male incontinence is nearly $4 billion in direct costs annually [1, 2]. Annual individual health-care expenses for men with incontinence are approximately double those for men without the disorder [1, 2]. The additional spending may be for protective pads, condom, and indwelling urinary catheters, each altering lifestyle [3]. As illustrated in Fig. 80.1, the age-adjusted rates of urinary incontinence among US men increase with age [1, 4]. Because the median age at prostate cancer diagnosis is 67 years [5], urinary incontinence already affects a nontrivial percentage of these men.

One of the most common conditions contributing to lower urinary tract symptoms in the aging male is benign prostate hypertrophy or enlargement [6–8]. However, as men age, they may also have to deal with prostate cancer and its effects on urinary control, especially after treatment. While urgency, frequency, and even urge incontinence are the typical symptoms of benign urologic disease, the majority of urinary incontinence after surgical prostate cancer treatment is characterized as stress incontinence [9]. According to one study, nearly all patients with postprostatectomy incontinence were found to have stress urinary incontinence on urodynamic studies [10]. For men undergoing radiation therapy, irritative and obstructive symptoms may be exacerbated leading to urge and potentially even stress incontinence [11, 12].

There is no standard definition of urinary incontinence after prostate cancer treatment leading to a wide variety of reported outcomes [13, 14]. Unfortunately, patient-reported urinary incontinence after prostate cancer surgery may be as high as 65 % at 1 year, depending on the definition, and significantly impairs quality of life [15–21]. Not surprisingly, patient reports only moderately correlate with provider assessments of incontinence after treatment, which typically underestimate the severity [15, 16, 22]. Underestimation of the degree of incontinence facing prostate cancer patients indicates that systematic approaches to measurement are essential for adequate assessment and treatment of these men [15, 16, 22].

Urinary symptoms vary by treatment modality with each having potential for long-term urinary complications

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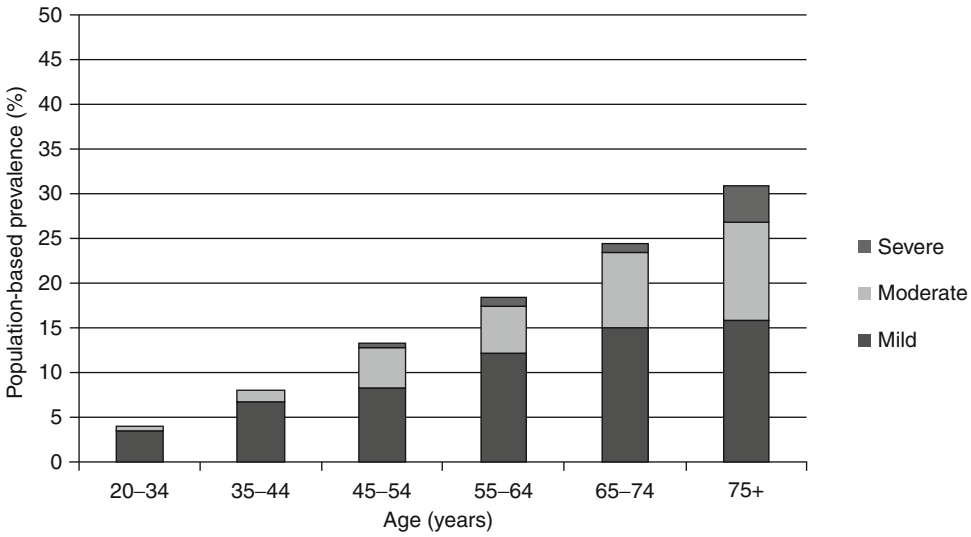


**Fig. 80.1** Prevalence of urinary incontinence among US men according to age group (Modified from Markland et al. [4] *Journal of Urology*). Median age at diagnosis of prostate cancer is 67 years [5]

**Table 80.1** Overview of urinary incontinence according to prostate cancer treatment type

| Treatment | Early urinary symptoms | Late urinary symptoms |
|---|---|---|
| Radical prostatectomy | Stress incontinence, de novo detrusor instability | Persistent stress incontinence, urgency, frequency |
| Radiation therapy (external beam and brachytherapy) | Urgency, frequency, dysuria, urinary retention | Occasional persistent symptoms |

**Table 80.2** Measures and instruments used to determine urinary outcomes after prostate cancer treatment

| Objective measures | Patient-reported questionnaires |
|---|---|
| Urine diary | Expanded prostate cancer index composite (EPIC) |
| 24-h pad use | UCLA prostate cancer index (PCI) |
| 24-h pad weight | International consultation on incontinence questionnaire—short form (ICIQ-SF) |
| 1-h pad weight | International prostate symptom score (IPSS) |
| Pads/day | AUA symptom index (AUASI) |
| Postvoid residual | Incontinence impact questionnaire (IIQ) |
| Flow rate | Functional assessment of cancer therapy —prostate (FACT-P) |
| Urinalysis | Male urogenital distress inventory (MUDI) |
| Urodynamics | Male urinary symptom impact questionnaire (MUSIQ) |
| Urethrocystoscopy | King's health questionnaire (KHQ) |
| | Stamey classification—mild, moderate, and severe |

[23, 24]. Even with the latest advances in surgical technology (i.e., robotic-assisted surgery), postprostatectomy incontinence persists [25–27]. For example, up to 14 % of patients at least 18 months from surgery in expert hands may have some degree of urinary incontinence, particularly depending on their age [28, 29]. According to another study, 15 % of men 5 years following radical prostatectomy may report urinary incontinence [30]. Fortunately for most men this is not the case, and the majority recover urinary control within 3 months of surgery [31]. Moreover, even the most advanced radiation therapy approaches (e.g., proton beam, intensity-modulated radiation therapy) are associated with adverse urinary side effects [32–34]. Patients undergoing radiation therapy may have less urinary incontinence compared to surgery, though higher than previously thought, and they still suffer from other treatment-related side effects (e.g., irritative urinary symptoms, bowel symptoms) [23, 30, 35]. Because localized prostate cancer represents over 90 % of disease, many men are treated with curative intent using one of these treatments [5, 36]. Therefore, considering the urinary implications of prostate cancer treatments is critical to optimizing patient outcomes and satisfaction following treatment [13, 37] (Table 80.1).

The measurement of urinary outcomes after prostate cancer treatment has evolved tremendously over the past several decades. According to Stamey, urinary incontinence can be pragmatically defined as *mild*—leakage with stress, e.g., cough and sneeze; *moderate*—leakage with minimal stress, e.g., walking; and *severe*—leakage at rest. These and other early urinary outcomes were measured by provider-reported continence, followed by patient-reported functional measures of continence (e.g., pad use) [38] and now validated measures of urinary function and bother (e.g., UCLA-PCI, EPIC) [39, 40]. Most of the current urologic literature uses selected questions from these instruments or other measures as shown in Table 80.2. An agreement on the definition and measurement of urinary incontinence after prostatectomy is needed [14, 41]. Ideally, pretreatment function is needed to examine within patient changes. Another

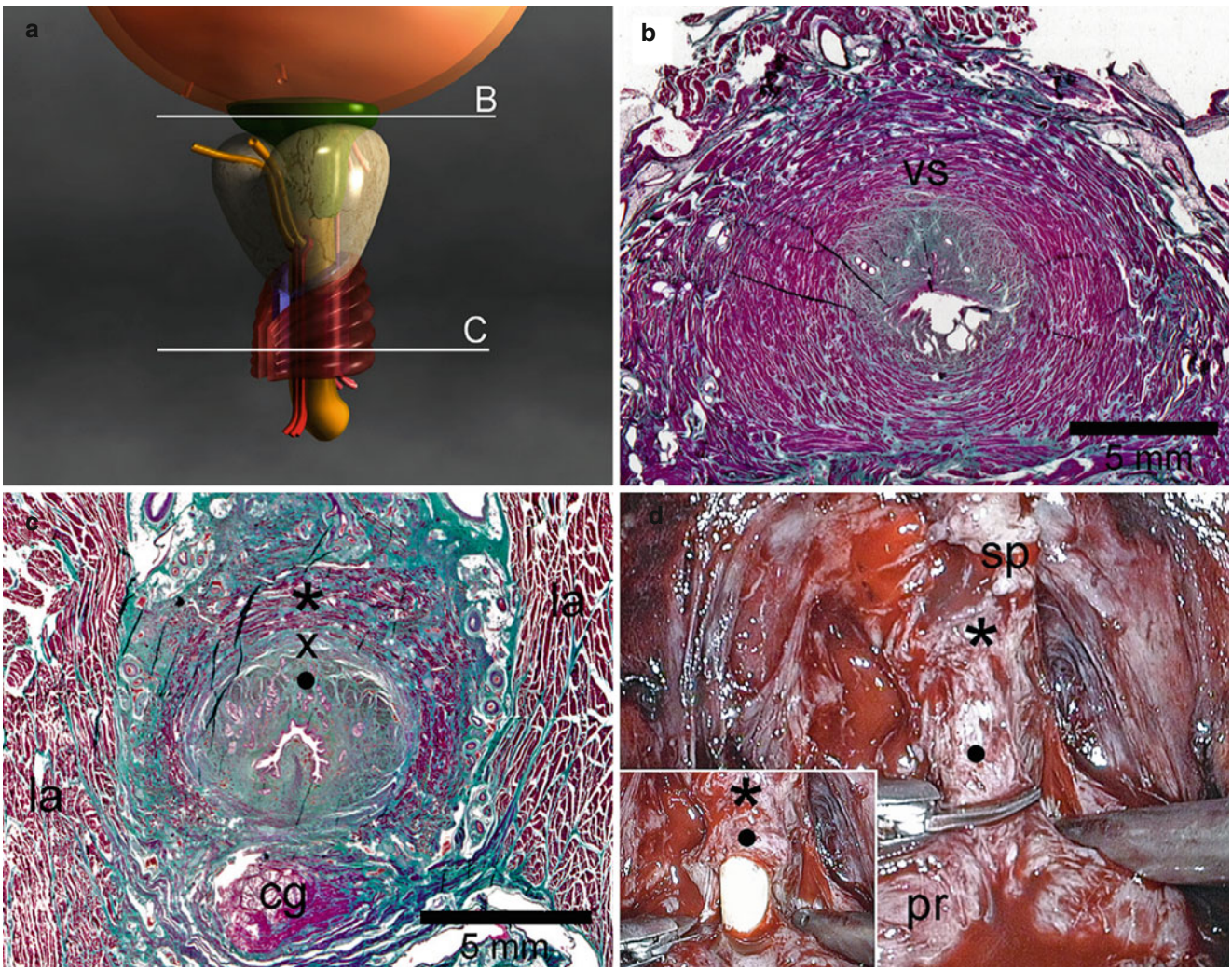


**Fig. 80.2** Anatomy and histology of the male urethral sphincter complex (Modified from Stolzenburg et al., *European Urology* [44]). The internal or proximal urethral sphincter is situated at the base of the bladder, highlighted in green in a dorsolateral view of the region (**a**). The internal sphincter completely encircles the bladder neck as shown in the histological section (**b**). The external urethral sphincter, *red* and *blue* in (**a**), ventrally overlaps the prostate and is horseshoe shaped, consisting of an inner smooth muscular part (*X*) and outer striated part (*) as shown in the histological section (**c**). A further smooth muscular part of the urethra (longitudinal musculature) is evident close to the urethral lumen (• in **c**). During apical dissection, the Santorini plexus, the urethral sphincter (striated and smooth muscular components—* in **d**), and the inner longitudinal smooth muscular layer of the urethra (•) are dissected in steps. After incision of the inner smooth muscular layer, the urethral catheter becomes visible (*inset* in **d**). Cowper's gland (*cg*), levator ani (*la*), vesical sphincter (*vs*), Santorini plexus (*sp*), prostate (*pr*)

major consideration when following treatment outcomes for localized prostate cancer is how they evolve over time, i.e., long-term effects [23, 24].

## Anatomic Considerations of Urinary Incontinence After Prostate Cancer Treatment

Urinary continence in men depends on adequate bladder function as well as a competent urethral sphincter [42, 43]. The urethral sphincter mechanism involves two functionally separate units: the proximal urethral (internal) sphincter and the distal (external) urethral sphincter [43]. The proximal sphincter is ring shaped and is sacrificed during prostatectomy leaving only the distal urethral sphincter to maintain urinary control [44]. As illustrated in Fig. 80.2, the components of the distal urethral complex include the prostatomembranous urethra, the omega-shaped external rhabdosphincter that surrounds the prostatomembranous urethra and is deficient posteriorly, the paraurethral musculature (e.g., levator ani), and the pelvic floor connective tissues [44]. The external urethral rhabdosphincter is comprised of both outer striated, mostly slow-twitch type 1, muscle fibers that provide continence through tonic contraction and inner smooth

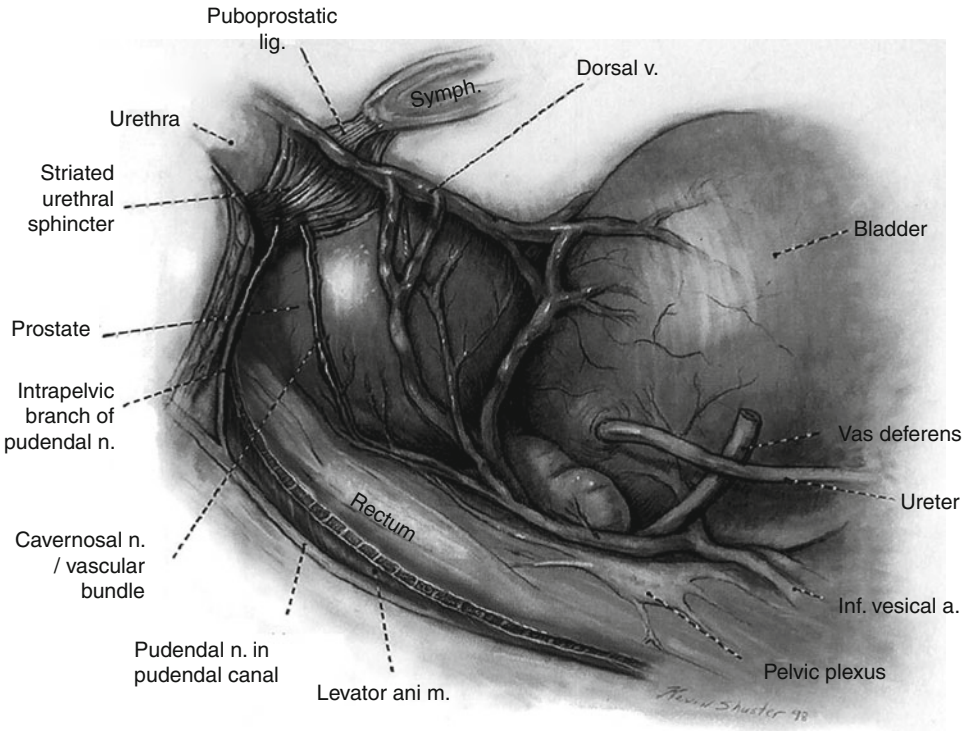


**Fig. 80.3** Neuroanatomy of the external urethral sphincter (from Hollabaugh et al., *Urology* [47]). The obturator internus muscle has been removed as was part of the levator ani muscle in this lateral view of the external urethral sphincter. The pudendal nerve travels in the pudendal canal, which is formed by a split in the obturator muscle fascia adjacent to the levator ani muscle. After leaving the pudendal nerve, the intrapelvic branch of the pudendal nerve courses along the levator ani muscle until it reaches the junction of the external urethral sphincter with the levator ani muscle where it enters the external urinary sphincter at the 5 and 7 o'clock positions. The cavernosal nerves travel along the urethra at the 3 and 9 o'clock positions

muscle fibers [42, 45]. Moreover, the levator ani and pelvic floor musculature are comprised of both type 1 and fast-twitch type 2 fibers, the latter necessary for maintaining continence during acute rises in intra-abdominal pressure [42, 45, 46]. The interaction between these two mechanisms provides both passive and active continence after prostatectomy. Furthermore, the complex innervation of the urethral sphincter mechanism is supplied from both the autonomic nervous system (i.e., pelvic nerve and inferior hypogastric complex) and the somatic nervous system (i.e., pudendal nerve) (Fig. 80.3) [47]. For this reason, denervation of the bladder neck and urethra has been implicated in postprostatectomy incontinence suggesting preservation of trigonal innervation improves urinary outcomes after surgery [48].

## Surgery and Urinary Incontinence

Surgical approaches (open, laparoscopic, and robotic-assisted radical prostatectomy) obliterate the internal, or proximal urethral, sphincter and may impair the integrity of the external urethral sphincteric complex through a variety of mechanisms described below [43, 47, 49]. There are also immutable patient characteristics that place patients at risk for urinary incontinence and/or delayed return of urinary function following prostate cancer treatment. Such risk factors include increasing patient age, obesity, large prostate size, prior prostate surgery, decreased membranous urethral length, and weak pelvic floor musculature [50–59] (Table 80.3). Older men and those with greater BMI may be slower to recover and less likely to return to their baseline following surgery [60]. One of the potential reasons older men are predisposed to stress incontinence is because apoptosis of the urethral rhabdosphincter cells increases with age and compromises urethral closure [61]. Although conflicting reports exist regarding the effects of obesity on postoperative continence, it is associated with increased intra-abdominal pressure that may overwhelm the external sphincter complex thereby

**Table 80.3** Factors associated with incontinence and prostate cancer surgery

| Patient | Operative | Postoperative |
|---|---|---|
| Age | Surgeon experience | Pelvic floor muscle therapy |
| Preoperative bladder function | Surgical techniques for apical and bladder neck dissection | Biofeedback and electrostimulation |
| Prostate size | Nerve sparing | Behavioral and diet modification |
| Disease stage | Preservation and restoration of vesicourethral anatomy | Medical therapy |
| Obesity | | Surgical therapy |
| Pelvic floor musculature and anatomy, e.g., functional urethral length | | |

worsening urinary control [56, 62–64]. Preoperative membranous urethral length has also been shown to be predictive of postoperative function. For example, preoperative MRI has demonstrated that longer membranous urethral length was associated with decreased time to urinary control after surgery [65, 66]. This has led some to preserve an intraprostatic portion of the membranous urethra to hasten urinary recovery [67]. Finally, surgery in the setting of prior radiation therapy (i.e., salvage prostatectomy) results in worse urinary incontinence than in standard settings due to postradiation tissue changes [68].

The integrity of the pelvic floor is compromised after radical prostatectomy and may lead to postprostatectomy incontinence. Opening of the endopelvic fascia, apical dissection, and disruption of the suburethral musculofascial plate alter the structural anatomy of the pelvis [69]. For this reason, reconstruction of the posterior rhabdosphincter to restore anatomic relations is one approach to improve urinary outcomes [70–72]. Based on an improved understanding of the male continence mechanism, anatomic restoration of the vesicourethral junction has also been postulated to improve early continence outcomes [42, 73, 74]. Moreover, the fascial investments of the rhabdosphincter fuse anteriorly with the pubourethral, i.e., puboprostatic ligaments—extensions of the arcus tendineus, and provide stabilization to the continence mechanism [42, 49]. This has led some to implicate transection of the puboprostatic ligaments in postprostatectomy incontinence [49, 75, 76]. Anterior urethropexy, i.e., placement of a paraurethral suspension suture, may help stabilize the external sphincter complex thereby mitigating these effects and leading to improved urinary outcomes [77, 78].

Along these lines, others suggest that nerve-sparing techniques hasten urinary recovery [17, 79, 80]. Cadaveric studies demonstrate that pelvic and pudendal nerve fibers track toward the external urethral sphincter at the 5 and 7 o'clock positions at the prostatic apex (Fig. 80.3). In fact, neurovascular bundle stimulation intraoperatively increases urethral pressure [81]. This suggests that meticulous apical dissection, nerve sparing, and avoidance of anastomotic sutures in this region might lead to improvements in urinary continence [47, 82, 83]. Others note that passage of the right-angle clamp posterior to the urethra during open prostatectomy may damage the contralateral nerve fibers of the external sphincter leading to worsened postoperative continence [47]. Furthermore, overlap of the prostatic apex with the membranous urethra, either anteriorly or posteriorly, has also been shown to adversely impact urinary outcomes by complicating the apical dissection [84]. Bladder neck sparing [85], intussusception [42, 85, 86], and hypothermia [87] have all been reported to improve recovery of postoperative continence.

During the anastomosis of the bladder neck to the urethral stump, sutures are placed into the urethra potentially causing scar tissue and decreased urethral compliance [47, 88]. Such trauma to the rhabdosphincter complex generally leads to sphincteric weakness, i.e., intrinsic sphincter deficiency, predisposing patients to incontinence [43, 89, 90]. For example, postoperative urethral and periurethral fibroses identified on MRI have been associated with worsened urinary control, likely through decreased elasticity of the urethral sphincter [66]. Anastomotic strictures can also occur up to 10 % of the time and are a risk factor for postprostatectomy incontinence likely due to their subsequent treatment [52, 91]. However, most series report bladder neck contracture incidence at less than 5 %, especially with the robotic-assisted approach [25, 91–93]. Anastomotic leakage is not uncommon after prostatectomy and usually not related to anastomotic stricture formation [94, 95]. Most strictures are successfully managed with dilations or incision although refractory cases may necessitate more aggressive management [91, 96–99]. Mucosal eversion and intussusception of the bladder neck as a way to prevent anastomotic strictures may or may not be effective but might help with early return of continence [86, 100, 101].

Even in the most experienced hands, temporary stress urinary incontinence after prostatectomy is common in most men [19, 72]. On the other hand, irritative urinary symptoms following radical prostatectomy could improve, especially for men with larger prostate glands [102–104]. However, these men may struggle with long-term continence issues compared to men with smaller prostates [57]. De novo detrusor overactivity and impaired detrusor contractility can also occur but are unlikely to be the source of long-term urinary incontinence [10, 90, 105, 106].

Urinary outcomes after radical prostatectomy continue to improve over 12–24 months, and increasing surgeon experience is strongly associated with improved urinary continence after prostectomy [23, 60, 103, 107–110]. A review of urinary outcomes following open, laparoscopic, and robotic prostatectomy is shown in Table 80.4 [25]. Fortunately, most men are continent within 1 year of treatment, especially in the hands of high-volume surgeons [25, 28, 110, 114, 116]. As most urinary outcomes are comparable at 1 year, achieving urinary continence more quickly (e.g., at 1 and 3 months) appears to be the next frontier for radical prostatectomy [42].

## Radiation Therapy and Urinary Incontinence

Radiation therapy impacts urinary continence through different pathobiologic mechanisms, sparing the gross disruption of pelvic anatomy, and results in less frequent incontinence, on average, than prostatectomy [33, 122–124]. Acute urinary dysfunction is primarily due to mucosal inflammation and denudation in the prostatic urethra and bladder neck that occurs 2–3 weeks after initiation of treatment [125]. Acute

**Table 80.4** Selected radical prostatectomy series and urinary continence outcomes

| Study | Cases | Urinary continence | |
|---|---|---|---|
| | | 6 months | 12 months |
| *Robotic-assisted radical prostatectomy* | | | |
| Krambeck et al. [111] | 294 | – | 92 |
| Murphy et al. [112] | 400 | ~87 | 91 |
| Zorn et al. [113] | 300 | 68 | 90 |
| Patel et al. [114] | 500 | 95 | 97 |
| Mottrie et al. [115] | 184 | 85 | – |
| Menon et al. [116] | 2,652 | – | 84 |
| *Laparoscopic radical prostatectomy* | | | |
| Guillonneau et al. [117] | 550 | 73 | 82 |
| Stolzenburg et al. [118] | 2,000 | 85 | 92 |
| Curto et al. [119] | 677 | 95 | 95 |
| Rassweiler et al. [120] | 5,824 | – | 85 (72–94) |
| *Open radical prostatectomy* | | | |
| Lepor et al. [103] | 500 | 87 | 92 |
| Stanford et al. [107] | 1,291 | 39 | 61 |
| Rocco et al. [71] | 161 | – | 95 |
| Bianco et al. [121] | 1,288 | – | 91 |
| Sacco et al. [97] | 985 | 78 | 87 |

**Table 80.5** Grading genitourinary acute and late toxicity after radiation therapy according to the Radiation Therapy Oncology Group (RTOG) [130]

| Grade | Acute description | Late description |
|---|---|---|
| 0 | No change | None |
| 1 | Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication | Slight epithelial atrophy<br>Minor telangiectasia (microscopic hematuria) |
| 2 | Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, and bladder spasm requiring local anesthetic (e.g., Pyridium) | Moderate frequency<br>Generalized telangiectasia<br>Intermittent macroscopic hematuria |
| 3 | Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain, or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage | Severe frequency and dysuria<br>Severe generalized telangiectasia (often with petechiae)<br>Frequent hematuria<br>Reduction in bladder capacity (<150 cc) |
| 4 | Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis | Necrosis/contracted bladder (capacity <100 cc)<br>Severe hemorrhagic cystitis |

Ref. [130]

urinary side effects represent a combination of obstructive and irritative symptoms including dysuria, frequency, urgency, and even transient urinary retention. [123, 126] These symptoms typically resolve after reepithelialization is complete several weeks later [125]. Symptoms occur in the setting of brachytherapy as well as external beam radiation therapy [23, 127]. Unless patients undergo subsequent prostate resection, late urinary incontinence remains low in the postradiation population [12]. Neoadjuvant androgen deprivation may be one way to decrease the impact of radiation on urinary symptoms [128].

Urinary outcomes vary depending on the type of radiation therapy and the definition of incontinence [125, 129]. The current Radiation Therapy Oncology Group acute and late toxicity effects are shown in Table 80.5. These do not include a measure of urinary incontinence, rather descriptions of worsening lower urinary tract symptoms, decreasing bladder capacity, and hematuria [130]. However, the National Cancer Institute's latest version of the Common Terminology Criteria for Adverse Events version 4.0 captures a variety of urinary outcomes including urinary incontinence [131] (Table 80.6). Some studies use health-related quality of life instruments to compare outcomes among the different radiation therapy types [23].

## External Beam Radiation Therapy

The typical short-term side effects of external beam radiation therapy (EBRT) consist of dysuria, urinary urgency, and frequency which wane over time for most patients, especially with modern conformal techniques [132–135]. According to one large study, the acute urinary toxicity following 3-D conformal radiation therapy included 58 % for grade 0/1 and 42 % for grade 2 side effects. The long-term toxicity was 91 % for grade 0/1 and 8 % for grade 2 side effects and was generally better than those for brachytherapy [136]. For some patients, the long-term side effects of EBRT include urinary incontinence and ongoing irritative symptoms [23, 137, 138]. Worsened outcomes, at least in the short term, may be present for patients with larger prostates and those who have had prior transurethral resection of the prostate [12, 126]. Bladder neck contractures and urethral stricture disease occur infrequently (~2 %), however may be associated with long-term detriments to urinary control [129, 136].

## Brachytherapy

Urinary symptoms following brachytherapy occur immediately postprocedure followed by increasing irritative and obstructive symptoms 2–3 weeks after treatment. These symptoms typically peak at 1 month and resolve by 1 year [125]. Transient flares may occur up to 5 years after treatment [139, 140]. A large study demonstrated the following

**Table 80.6** Grading genitourinary toxicity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) and Common Toxicity Criteria (CTC) v4.0

| Grade | Bladder spasm | Urinary frequency | Urinary incontinence | Urinary retention | Urinary tract obstruction | Urinary tract pain | Urinary urgency | Urine discoloration |
|---|---|---|---|---|---|---|---|---|
| 1 | Intervention not indicated | Present | Occasional (e.g., with coughing, sneezing), pads not indicated | Urinary, suprapubic, or intermittent catheter placement not indicated, able to void with some residual | Asymptomatic, clinical or diagnostic observations only | Mild pain | Present | Present |
| 2 | Antispasmodics indicated | Limiting instrumental ADL, medical management indicated | Spontaneous, pads indicated, limiting instrumental ADL | Placement of urinary, suprapubic, or intermittent catheter indicated, medication indicated | Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; urethral dilation; urinary or suprapubic catheter indicated | Moderate pain, limiting instrumental ADL | Limiting instrumental ADL, medical management indicated | – |
| 3 | Hospitalization indicated | – | Intervention indicated (e.g., clamp, collagen injections), operative intervention indicated, limiting self-care ADL | Elective operative or radiologic intervention indicated, substantial loss of affected kidney function or mass | Symptomatic and altered organ function (e.g., hydronephrosis or renal dysfunction), elective radiologic, endoscopic, or operative intervention indicated | Severe pain, limiting self-care ADL | – | – |
| 4 | – | – | – | Life-threatening consequences, organ failure, urgent operative intervention indicated | Life-threatening consequences, urgent intervention indicated | – | – | – |
| 5 | – | – | – | Death | Death | – | – | – |

Ref. [131]
*ADL* activities of daily living

urinary toxicities within 60 days of brachytherapy: grade 1—37 %, grade 2—41 %, and grade 3—2 % [141]. Urinary symptoms may be partially reduced by alpha-blocker therapy [142]. The long-term urinary morbidity for patients undergoing brachytherapy is generally worse than for EBRT [136], however may be worsened acutely for patients with large prostates or lower urinary tract symptoms prior to treatment [129, 143, 144]. In fact, some patients may be recommended to undergo androgen deprivation to decrease their prostate size prior to brachytherapy to prevent urinary retention, especially if they have bothersome lower urinary tract symptoms prior to therapy [145–149]. Transient urinary retention following treatment may occur up to 15 % of the time and is related to gland size, particularly for patients with prostates >60 g, and can be mitigated by a course of corticosteroids [141, 150]. Moreover, urethral strictures occur in ~10 % and may contribute to urinary incontinence following brachytherapy [136, 151]. Despite potential improvements in long-term urinary symptoms for some patients undergoing brachytherapy, urinary incontinence may still be problematic for others [127, 152–156].

## Other Prostate Cancer Treatments and Urinary Incontinence

### Minimally Invasive Therapies

An alternative prostate cancer treatment is cryotherapy which may damage the urethral sphincter leading to intrinsic sphincter deficiency and stress incontinence in approximately 5–8 % [157–163]. The degree of incontinence depends on the definition, generation of technology, and clinical setting (salvage associated with greater incontinence than primary cryotherapy) [157–163]. Sloughing of the urethra occurs infrequently with the use of a urethral warming catheter, and urethral stricture or bladder neck contracture, while rare, may also contribute to urinary incontinence after treatment [164, 165]. High-frequency ultrasound ablation (HIFU) outcomes are increasingly reported in the literature. Two reviews report urinary incontinence ranging from 1 to 34 % after the procedure [159, 166].

### Active Surveillance

Active surveillance is the least likely treatment to impair urinary control [13, 167]. Most men are spared the potential incontinence and worsening of lower urinary tract symptoms posed by the above treatment approaches [13]. On the other hand, selected men undergoing surgery or radiation may benefit in terms of obstructive urinary symptoms compared to those on active surveillance.

### Watchful Waiting and Androgen Deprivation Therapy

Urinary symptoms tend to be stable or progress from an obstructive standpoint among men undergoing watchful waiting [168, 169]. For men with locally advanced disease, obstructive symptoms may worsen necessitating transurethral resection which is associated with an increased risk of complications including urinary incontinence [170].

## Clinical Evaluation of Urinary Incontinence After Prostate Cancer Treatment

As illustrated in Fig. 80.4, an initial clinical examination is central to defining the type of incontinence and management options for men with prostate cancer [9, 171]. Initial assessment should include a complete history and physical exam, urinalysis, postvoid residual testing, a questionnaire to document incontinence severity, and an assessment of pad usage [73]. A maximum flow rate, urine diary, and 1- or 24-h pad test may also be considered. It is important to consider other causes of urinary incontinence during this evaluation (e.g., neurologic disorders), and urodynamic testing may be necessary [172]. Decreasing stream and increasing postvoid residual after surgery can indicate an anastomotic stricture warranting cystoscopy [91, 97]. Gross hematuria should always be referred to a urologist for evaluation along with persistent or refractory urinary symptoms after radiation therapy.

## Treatment of Urinary Incontinence

Treatments for urinary incontinence following prostate cancer treatment continue to evolve and range from behavioral and medical approaches to surgical interventions. The approaches described below depend on the severity of incontinence and patient preferences [9].

## Postprostatectomy Incontinence

### Behavioral Therapy

Recruiting the pubococcygeus and levator ani muscles to improve postprostatectomy incontinence was originally described in 1926 by Young et al. [173]. Several randomized studies have since demonstrated earlier return to continence following prostatectomy with behavioral therapy including pelvic floor muscle training [174–176]. However, the effectiveness of behavioral therapy and pelvic floor muscle therapy has been challenged. For example, a Cochrane Review concluded there was insufficient evidence to support pelvic

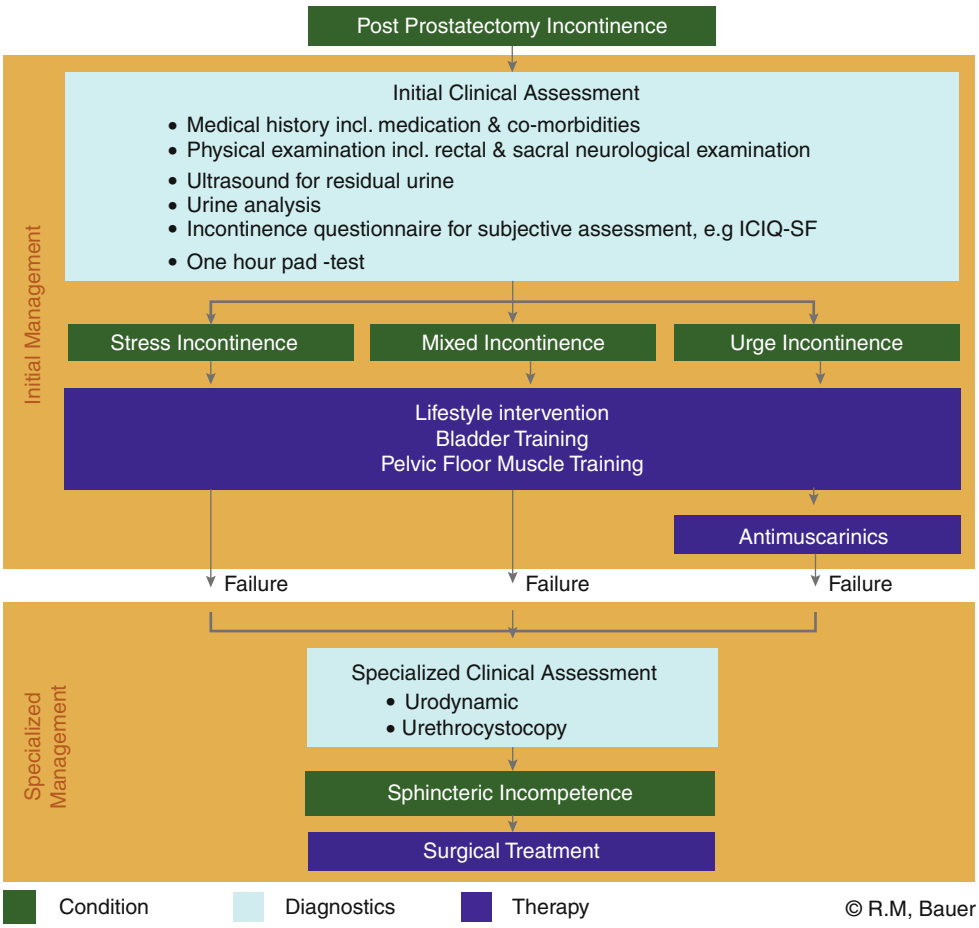


**Fig. 80.4** Assessment of urinary incontinence after prostate cancer surgery according to the European Association of Urology 2008 guidelines (From Bauer et al., *European Urology* [9])

floor muscle training after prostate cancer treatment [177]. On the other hand, a recent randomized trial demonstrated improvements in urinary control with behavioral therapy among prostate cancer survivors from 1 to 17 years after treatment [175]. Despite the seemingly conflicting evidence, Kegel exercises after surgery are routinely recommended, potentially with biofeedback, to recruit the proper muscle groups necessary for urinary control. Other behavioral strategies to improve urinary control following prostate cancer treatment include avoidance of bladder irritants (e.g., coffee, acidic juices), limiting fluid intake, weight loss, and smoking cessation [178]. Incontinence pads and undergarments may be used to prevent local irritation, and external compression devices may prevent leakage [178].

## Medical Therapy

Medical therapy for postprostatectomy incontinence includes anticholinergic therapy, imipramine, and potentially duloxetine [9]. For men with bothersome urgency and frequency, anticholinergic medications (e.g., oxybutynin, tolterodine, trospium, solifenacin, and darifenacin) may help. Imipramine is unique in that it exerts its effects through an anticholinergic relaxation of the bladder and a sympathetic activation of the bladder neck to improve urinary control [179]. Duloxetine is a serotonin-norepinephrine reuptake inhibitor typically used to treat stress incontinence in women by promoting detrusor relaxation and increasing urethral sphincter tone [180, 181]. Postprostatectomy incontinence has been treated with duloxetine with a randomized study demonstrating improvements in urinary symptoms and quality of life [182]. However, because of marginal success in the postprostatectomy setting, the use of these medical therapies has been limited.

## Surgical Therapy

More severe incontinence following an observation period (e.g., 12 months) may warrant surgical intervention. In fact, up to 6 % of men will undergo surgical treatment for their incontinence after radical prostatectomy [183, 184]. Surgical approaches include injection of bulking agents (e.g., collagen) into the bladder neck, urethral slings, and artificial urinary sphincters [185]. Each is discussed below and highlighted in Table 80.7. For men who wish to manage their incontinence conservatively, collection devices and compression devices may limit the impact of urinary incontinence on their day-to-day lives [177].

**Table 80.7** Postprostatectomy incontinence and success of surgical interventions[a]

| Reference | *n* | Dry/continent (%) | Improved (%) |
|---|---|---|---|
| *Collagen injection therapy* [186] | | | |
| Martins et al. [187] | 46 | 24 | 41 |
| Smith et al. [188] | 62 | 8 | 39 |
| Sanchez-Ortiz et al. [189] | 31 | 6 | 29 |
| Klutke et al. [190] | 20 | 10 | 35 |
| Westney et al. [191] | 322 | 17 | – |
| *Urethral sling* | | | |
| *Bone anchored* | | | |
| Carmel et al. [192] | 45 | 36 | 40 |
| Guimares et al. [193] | 62 | 65 | 23 |
| Giberti et al. [194] | 40 | 55 | 13 |
| *Transobturator* | | | |
| Rehder et al. [195] | 118 | 74 | 17 |
| Cornu et al. [196] | 102 | 63 | 18 |
| Bauer et al. [197] | 124 | 56 | 27 |
| *Artificial urinary sphincter*[b] | | | |
| Trigo Rocha et al. [198] | 40 | 90 | – |
| Wilson et al. [199] | 37 | 66 | – |
| Venn et al. [200] | 100 | 84–92 | – |
| Elliot et al. [201] | 323 | 88 | – |

[a]Some analyses include incontinence after transurethral resection and radical prostatectomy
[b]Female patients may be included in artificial urinary sphincter series

## Bulking Agents

The injection of urethral bulking agents to treat intrinsic sphincter deficiency following prostatectomy has been used since the 1970s [191, 202–206]. Collagen is the most extensively studied of the injectable agents although other agents such as polydimethylsiloxane (Macroplastique), hyaluronic acid/dextranomer (Deflux), and polytetrafluoroethylene paste (Teflon) (no longer used due to migration to lung, lymph nodes, and spleen) [207] have also been used [188, 208–214]. Stem cell injections with autologous myoblasts and fibroblasts have also been shown to improve urinary control; however, limited literature in the postprostatectomy setting is available for this complex approach [215]. The low success and improvement rates (8–40 %), repeat injections due to migration (2–4 times), and infrequent durable responses limit the effectiveness of this approach, particularly in severe incontinence [212, 216]. Antegrade injections have also been attempted with similar outcomes [217, 218]. On the other hand, it is a minimally invasive procedure compared to the alternatives (i.e., urethral sling and artificial urinary sphincter) that can improve but rarely cure mild to moderate stress urinary incontinence.

Complications following the injection of urethral bulking agents are relatively limited. Collagen skin testing prior to injection is necessary to confirm a lack of allergic response to the bovine-derived agent [219]. Otherwise, the incidence of urinary tract infection and urinary retention is low. Patients may experience hematuria and a period of dysuria [9]. Given the high failure rates for the procedure and the need for multiple injections, more definitive approaches discussed below often need to be considered [206].

## Urethral Slings

Urethral slings for stress urinary incontinence after prostatectomy increased in popularity in the 2000s. They are mostly used for mild to moderate stress urinary incontinence, however may have success in the severe incontinence setting [192]. For the bone-anchored suburethral sling, a synthetic material (e.g., silicone-coated polyester) is placed at the level of the bulbar urethra through a perineal approach and anchored using titanium screws to the ischiopubic rami (Invance) (Fig. 80.5). Synthetic slings have been shown to have better results than other materials (e.g., biologic), and surgical approaches continue to expand [220]. In 2007, a transobturator approach was reported, and recent studies indicate moderate success rates (Advance) [185, 195, 196, 221–224]. This approach is thought to enable functional lumen occlusion rather than the pure urethral compression from the artificial urinary sphincter [9]. Two other systems use an adjustable compression approach to improve continence—either through soft silicone suburethral compression (Argus) or a suburethral readjustable sling (REMEEX)—both with cure rates as high as 50 % [225, 226]. For patients who have failed bone-anchored sling placement, artificial urinary sphincter placement has been shown to significantly improve urinary control [227].

Cure rates range from 37 to 65 % with success/improvement rates even higher depending on the definition [193, 196, 228]. Outcomes for continence/cure are typically defined as no pad or one dry pad/day with improvements defined in some studies as a decrease in pad use by 50 % [196, 221]. For example, one study of bone-anchored synthetic slings demonstrated a 55 % cure rate at 3 years [194]. In fact, a reference chart is available to predict the success of bone-anchored perineal sling placement (Fig. 80.6). For example, patients with a 423-g 24-h pad weight preoperatively have a 71 % chance of success defined as very much or much improved following sling placement [229]. As shown in Table 80.7, the transobturator approach has similar success rates with the potential for no changes in maximum flow rates after the procedure [224]. Repeat retrourethral transobturator sling has been reported with some success [230]. When given the choice, patients are likely to choose a urethral sling over an artificial urinary sphincter [231].

Complications of suburethral sling placement include infection, urethral erosion, urinary retention, scrotal and perineal numbness, and pelvic pain [192, 194, 223]. The

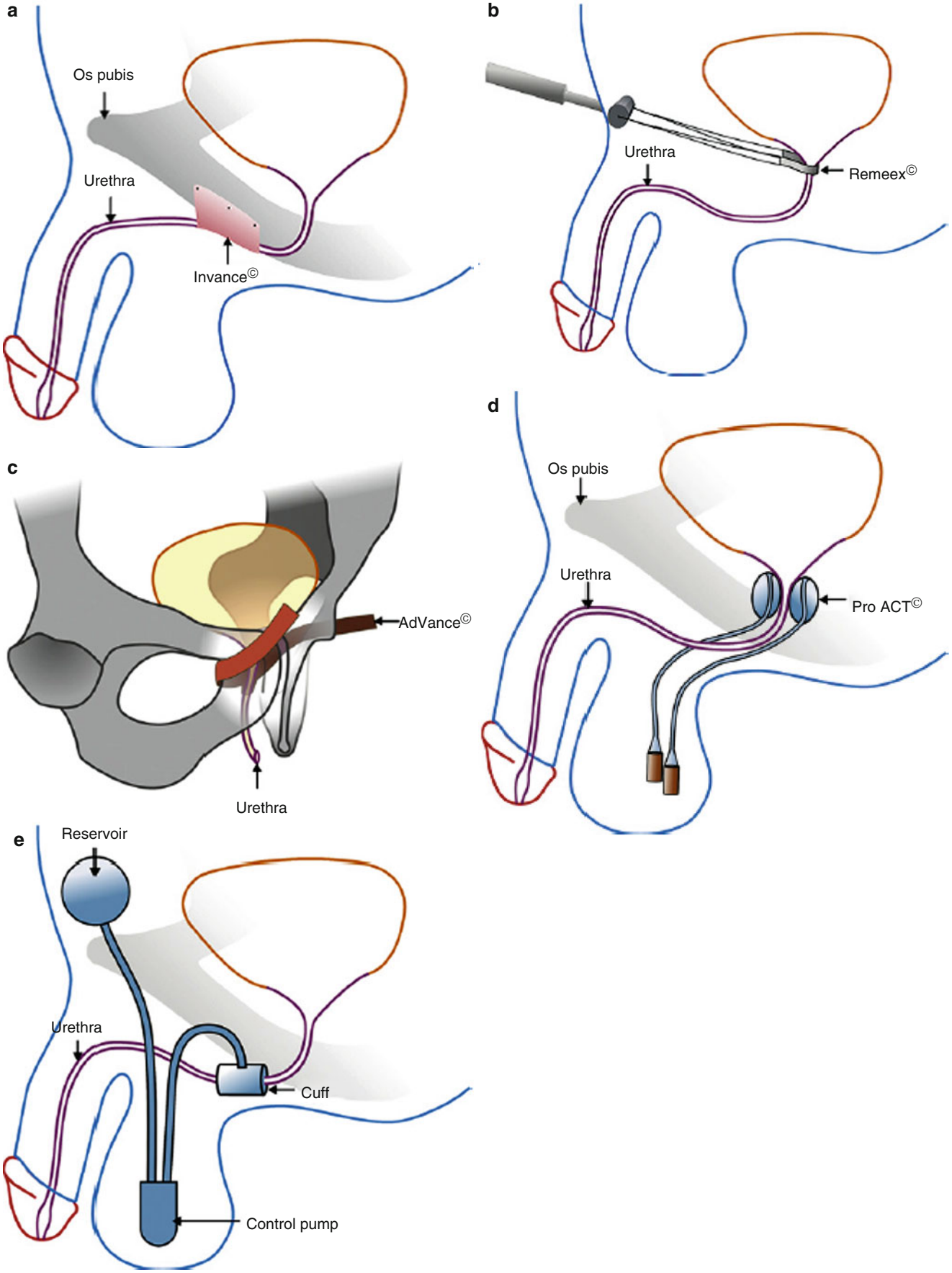


**Fig. 80.5** Surgical armamentarium for postprostatectomy urinary incontinence—urethral slings and compression devices. (**a**) Invance sling. (**b**) REMEEX system. (**c**) AdVance sling. (**d**) ProACT system. (**e**) Artificial urinary sphincter, AS-800 (From Bauer et al., *European Urology* [9])

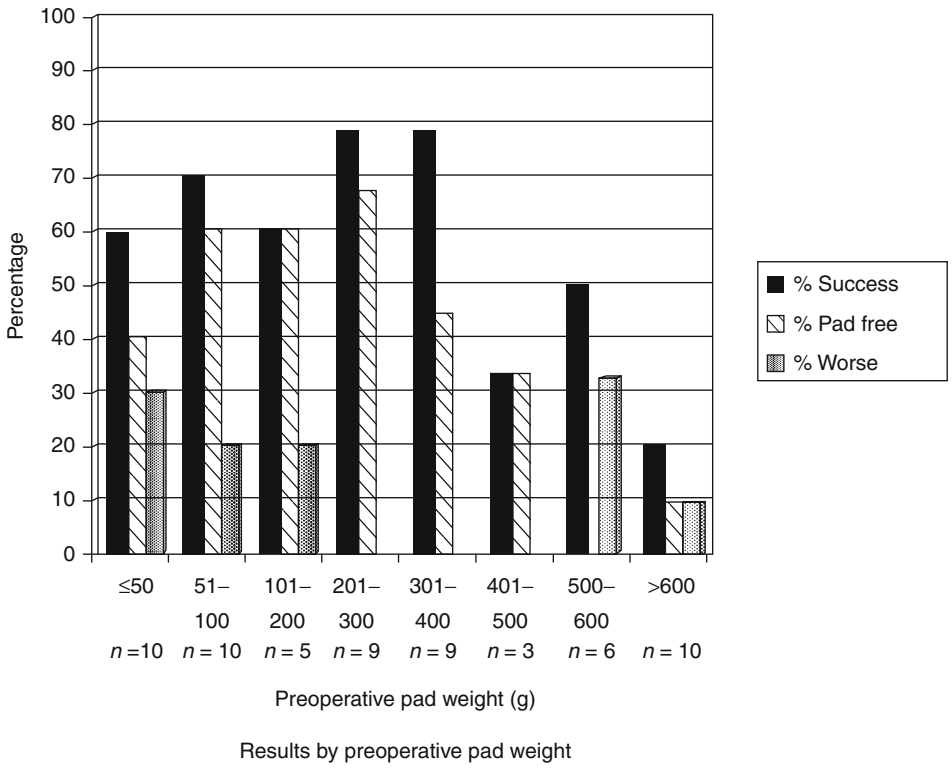


**Fig. 80.6** Success of the bone-anchored suburethral sling according to 24-h pad weight (From Nitti et al., *Journal of Urology* [229])

quality of life for men following the bulbourethral sling placement generally improves. For example, at a median follow-up of 3 years for men with moderate to severe incontinence, 72 % of patients were satisfied or very satisfied with their results [192].

## Artificial Urinary Sphincter

For men with moderate to severe incontinence after surgery, artificial urinary sphincters remain the standard treatment [232]. The current devices are largely based on the efforts of Scott et al. in 1974 [233]. Interestingly, Foley described an external periurethral compression device as early as 1947 to improve urethral resistance [234]. However, American Medical Systems (Minnetonka, MN, USA) placed the first patent on the artificial sphincter, AS 721, and has continued to modify the device to improve continence and decrease mechanical and nonmechanical complications [201, 232, 235]. The current device has four major components: a fluorosilicone-coated urethral cuff, kink-resistant tubing, an activation button for scrotal placement, and the pressure reservoir. Although placing the device at the bladder neck was associated with good success in early series, current approaches use a perineal or transcrotal approach to the urethra due to postsurgical changes at the bladder neck [199]. More recently, a conditional occlusion mechanism for the artificial sphincter was under investigation to regulate urethral pressure in situ, increasing urethral occlusion pressure during periods of increased intra-abdominal pressure [236]. As illustrated in Fig. 80.5, a variety of other devices for the treatment of postprostatectomy incontinence are under investigation, including a periurethral balloon compression device (Pro-ACT) with reported success rates of ~60 % [237, 238].

Patient selection (i.e., adequate manual dexterity and mental capacity) is essential to operate these devices. In addition, patients need to make their other medical providers aware in case urethral instrumentation is necessary [9]. The cuff should be deactivated for 6 weeks after surgery to allow healing and reduce erosion risk. Moreover, adverse preoperative factors on urodynamic evaluation prior to AUS implantation (e.g., low bladder capacity, decreased maximum flow rate) have not convincingly been shown to adversely impact continence outcomes [239].

Urinary continence following AUS placement is achieved in 27–75 % of patients with postprostatectomy incontinence [240–243]. Again, the definitions of continence, improvement in urinary control, model of sphincter, indications (radical vs. transurethral prostatectomy), and patient satisfaction vary widely [244]. Significant improvements in urinary control may be as high as 87 % in the short term [245, 246] and may persist up to 10 years indicating the durability of the procedure [198, 200, 247]. In one study, 90 % of patients had a functional AUS at 5 years with nearly three-quarters requiring no revision [201]. Patients with prior irradiation and cryotherapy may have similar outcomes

compared to other patients [248, 249]. Men over the age of 75 years may also benefit from AUS placement, although might need deactivation due to other health conditions [250]. Patients with bladder dysfunction (e.g., decreased compliance, detrusor overactivity) appear to benefit to similar degrees compared to patients with normal bladder function [198, 239, 245, 251, 252].

Despite evidence suggesting double-cuff placement for severe incontinence may improve urinary control or quality of life outcomes [253–255], longer-term follow-up suggests patients may not experience better outcomes and may be more likely to require surgical revision [256]. Revisions are necessary over time; however, most patients still maintain satisfaction following repeated surgery and can achieve satisfactory urinary outcomes [257–259].

The complications from artificial urinary sphincter placement are categorized as mechanical and nonmechanical and early and late [232]. Mechanical failures have improved since the introduction of the device, and failures necessitating revision occur in ~8 % of cases [232]. Mechanical failures include device leakage from tubing or reservoir, malfunctioning of the pump, and insufficient urethral occlusion pressure. Leakage may be due to microfractures, while pump malfunction is due to obstruction from airlock, debris, blood, contrast solution, or antibiotic crystals. These are all preventable with appropriate handling of the device during implantation and taking care not to kink the tubing [232, 260].

Nonmechanical complications include infection, urethral atrophy, persistent stress incontinence, and cuff erosion [261]. Infections may occur early, likely from a surgical infection, or late from hematogenous implantation and remain rare at less than 2 % [262–264]. While Staphylococcus epidermidis has been the traditional infectious agent for genitourinary prosthetics, recent data implicate a variety of organisms including Staphylococcus aureus and gram-negative bacilli in AUS infections [262]. Surgical explantation is the recommended treatment with the possibility for reimplantation typically after 3–12 months [265].

Urethral atrophy can occur up to 10 % of the time causing recurrent incontinence, while cuff erosion occurs less than 5 % of the time in most cases [201, 243, 261]. Causes include an undersized cuff, excessive reservoir pressure, radiation therapy, infection, and trauma [232, 260]. Deactivating the cuff is critical with urethral instrumentation to decrease the risk of erosion. Other preventive techniques include lowering the reservoir pressure in irradiated fields and appropriate cuff sizing. An additional cuff can be placed; [255, 266] the existing cuff size can be downsized [267] or moved proximally in the bulbar urethra [268], or the reservoir pressure increased to improve urinary control in the setting of urethral atrophy and persistent stress incontinence.

Patient satisfaction following AUS placement is excellent with as many as 80 % of patients satisfied with their results [198, 246, 249, 257]. Artificial urinary sphincter placement has demonstrated sustainable improvements in quality of life despite need for revisions [235]. Prior collagen injection therapy and radiation therapy do not appear to impact patient satisfaction and quality of life [206]. Moreover, upfront placement of an AUS may be cost effective compared to repeated collagen injections given the former's high success rates and patient dissatisfaction with failed collagen injection therapy [206, 269].

## Urinary Incontinence After Radiation

Urinary incontinence after radiation is typically due to irritative urinary symptoms (urgency, frequency) and may be due to decreased bladder capacity over the long term. Patients are at risk for urethral stricture disease that can lead to overflow incontinence [123, 129]. Although the urinary toxicity of radiation therapy typically wanes over time, long-term side effects may persist. The most common treatments for urinary toxicity are anticholinergics, alpha-blockers (e.g., tamsulosin, terazosin, alfuzosin), and phenazopyridine [125, 130, 270–272]. Some men may continue to have obstructive symptoms after radiation therapy necessitating transurethral resection. However, the risk of incontinence in this setting is increased after either EBRT or brachytherapy [273, 274].

## The Future of Incontinence and Prostate Cancer

Advances in the treatment of postprostatectomy incontinence may come in the form of improved devices, minimally invasive approaches, tissue engineering, an improved understanding of the pelvic floor functional anatomy, and surgical quality improvement collaboratives. Updating the current artificial sphincter mechanism to allow for conditional urethral occlusion in the setting of increased abdominal pressure and further decreasing the need for revision may improve outcomes. Innovative approaches to urethral sling design may also benefit patients. Furthermore, minimally invasive approaches like using ultrasound guidance for percutaneous placement of urethral occlusion devices may improve the morbidity of the procedure [275]. Using skeletal muscle stem cells has the potential to rejuvenate damaged external urethral sphincter musculature and improve the lives of men with postprostatectomy incontinence. Radiation therapy approaches can increase their ability to spare local tissues thereby limiting its urinary toxicity. Lastly, the creation of surgical quality improvement collaboratives to help identify and disseminate best practices from providers with the best urinary outcomes to those

with less optimal results could benefit the future pool of prostatectomy patients [276].

In the meantime, urinary incontinence continues despite our best prostate cancer treatments. Perhaps the best way to avoid detriments to urinary control is to avoid curative treatment [13]. Reduction of overtreatment for men with clinically insignificant disease and increases in active surveillance programs will limit the urinary incontinence burden among men surviving a prostate cancer diagnosis.

## Update

### Collagen Discontinued

The Collagen Corporation and C. R. Bard Inc. gained Food and Drug Administration marketing approval for injectable collagen treatment of stress urinary incontinence in 1993.[1] In January 2011, the company discontinued production of injectable bovine collagen as a bulking agent for stress urinary incontinence.[2]

1. http://www.nytimes.com/1993/10/02/business/company-news-collagen-bard-treatment-of-incontinence-is-approved.html. Accessed 2 Jan 2012
2. Personal communication, Bard Medical Customer Service 2 Jan 2012

### AUS Learning Curve Addressed

Reviewing manufacturer data for over 65,000 AUS cases, the authors find a long learning curve for AUS placement and discuss opportunities to potentially decrease reoperations.[3]

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### New Approaches to Male Slings

Recent updates in the field of male urethral slings highlight transobturator approaches.[4,5]

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# Erectile Dysfunction

# 81

Maarten Albersen and Tom F. Lue

## Erectile Dysfunction Following Prostate Cancer Treatment

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection with sufficient rigidity to perform satisfactory penetrative sexual activity [1]. ED is strongly associated with age and cardiovascular risk factors. Aside from these factors, ED is a frequent long-term complication of the treatment of prostate cancer (PCa). Various treatment options for PCa currently are available, including radical prostatectomy (RP), external beam radiation (EBRT), brachytherapy (BT), and androgen deprivation therapy (ADT); for most urologists, RP is the preferred treatment option for the majority of men with organ-confined disease [2]. The maintenance of a satisfactory quality of life is the principle concern in almost half of the men who elect treatment for localized PCa [3]. Furthermore, sexual dysfunction has been reported to be an independent determinant of a poorer general health-related quality of life at 2 years after primary treatment for PCa [4]. The development of ED over time is not uniform among different treatment options (Fig. 81.1). While following (nerve-sparing) RP, almost every patient develops ED shortly after the surgery; a recovery of erectile function is seen with nerve regeneration until a plateau in erectile function is reached about 18–24 months after surgery. In non-nerve-sparing RP, the same effect is seen, but recovery is only seen in few patients. Following radiotherapy, a gradual decline in potency is seen following treatment, which continues over a long period of time (reported up till 5 years). This effect may explain why in short-term outcome studies, radiotherapy may be perceived as less harmful to erectile function compared to surgical treatment. The "PCa outcomes study," however, showed similar low potency rates in a large cohort of patients treated with RP compared to those treated with EBRT 5 years after initiation of treatment [5]. The difference in evolution of ED following various treatments was also reflected in the fact that health-related quality of life remains stable between 2.6 and 6.2 years after RP, while, in patients treated with BT or EBRT, this continued to decline in the studied interval [6]. Following ADT, there is a rather quick drop in potency which generally persists during the treatment period which is also reflected in a decrease in quality of life during the first year after initiation of ADT [7].

Many studies on ED following nerve-sparing RP have been published, revealing widely disparate potency rates among various groups in different studies [8]. This variation in potency rates may be due to patient selection, surgeon and hospital volume, and the proportion of nerve-sparing procedures. However, nonuniform data collection, the assessment method, and the definition of potency also influence the reported erectile function outcome. In a recent systematic review, the weighted mean potency rates for patients who underwent unilateral or bilateral nerve-sparing prostatectomy in high-volume centers at 12-month follow-up were 43.1 and 60.6 % for retropubic, 31.1 and 54 % for laparoscopic, and 59.9 and 93.5 % for robot-assisted laparoscopic prostatectomy [9]. In another systematic review summarizing available outcome data on retropubic, laparoscopic, and robot-assisted prostatectomy, potency rates ranged between 10 and 93%, 42 and 76 %, and 70 and 80 %, respectively [10]. However, the lack of randomized trials precludes definitive conclusions on the best technique for potency preservation. ED is also the most common long-term adverse event of radiotherapy for PCa, affecting 36–59 % of patients after EBRT [11–13] and 24–50 % after BT [14–16]. Following initiation of ADT, approximately 80 % of patients experiences ED, starting from the first year of treatment [7].

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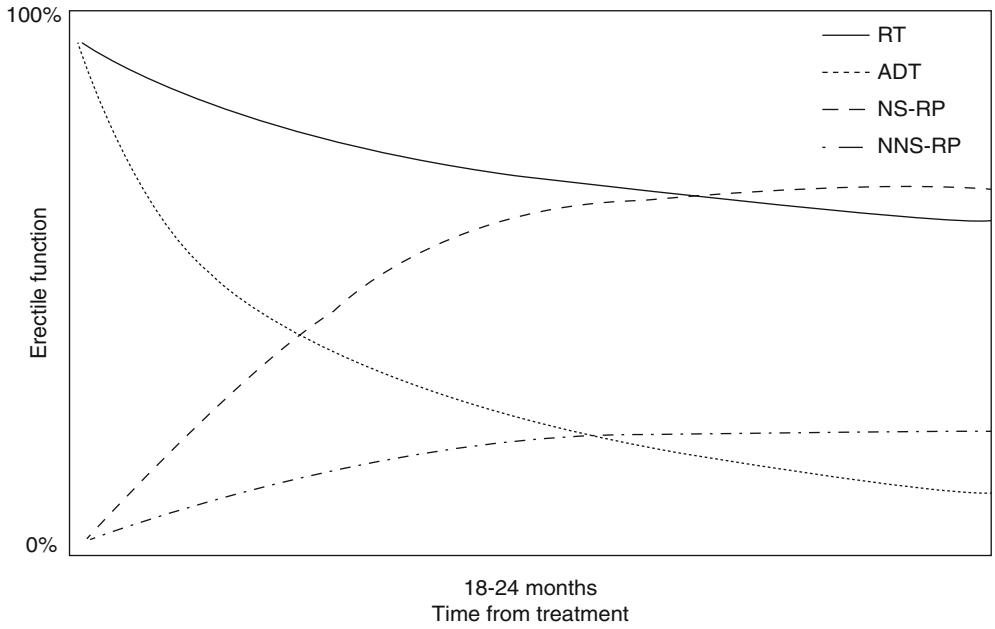


**Fig. 81.1** Evolution of ED following treatments for prostate cancer. Percentages are indicative only. Following both radiotherapy and initiation of ADT, a gradual decline is seen over time, whereas following RP, recovery of erectile function is seen until a plateau is reached 18–24 months following surgery. It is important that patients should be counseled about these time-dependent changes in erectile function

It is of paramount importance that patients should be informed correctly of the sexual side effects of PCa before making a choice about what treatment option is preferred. Naturally, this choice should always be made in the light of what is oncologically safe and what is not. Various authors state that newer, minimally invasive treatment options such as microwave ablation, high-intensity focused ultrasound (HIFU), and cryoablation of the prostate result in lower sexual bother; however, long-term data are not available on these techniques. In this chapter, we focus on pathophysiology, prevention, and treatment of ED following RP, radiotherapy, and ADT.

## Penile Erection

### Anatomy of Penile Erection

Upon sexual stimulation, the hypothalamus is exposed to input of various substances, of which dopamine appears to be the primary erectogenic neurotransmitter and serotonin the principle erection-inhibiting neurotransmitter. Dopamine-containing nerve endings impinge on oxytocinergic cell bodies in the paraventricular nucleus which project onto extrahypothalamic central nervous system components such as the hippocampus, the ventral medulla, and the spinal cord, where centrally originating impulses are received by the sacral spinal erection center (S2–S4). In addition to receiving signals from the brain, the sacral spinal erection center receives afferents from sensory neurons which generate signals in response to direct tactile stimulation of the penis. These sensory fibers travel through the dorsal penile nerve which is in turn derived from the pudendal nerve. Exiting through the sacral neuroforamina, efferent neurons from the sacral erection center pass anterior and lateral to the rectum as the nervi erigentes to reach the pelvic plexus. In this location, preganglionic fibers relay in ganglia, and postganglionic nonadrenergic, noncholinergic (NANC) fibers pass into the inferior hypogastric plexus [17, 18].

The most caudal portion of the inferior hypogastric converges into the cavernous nerves (CNs) which lie in close contact with the tips of the seminal vesicles where they travel between the layers of the lateral endopelvic fascia. Further caudally, the CNs are located mainly at the posterolateral surface of the prostate capsula, although their fibers are spread out over lateral aspect of the prostatic surface. The main component of the neurovascular bundle however lies in close contact to the anterolateral surface of the rectal serosa and lateral to the prostatic capsular vessels which therefore can be used as a landmark for the location of the CNs during RP (the neurovascular bundle of Walsh and Donker) [19]. During RP, the neurovascular bundle is most vulnerable at the apex of the prostate, where they closely approach the prostatic capsule at the 5- and 7-o'clock positions. The CNs then run in close relationship to the membranous urethra, where several superficial nerve branches penetrate and innervate the striated urethral sphincter. The CNs penetrate the urogenital diaphragm both medially at the 3- and 9-o'clock positions alongside the urethra and laterally approximately 5 mm from the sphincter. The nerve bundles then enter the corpora cavernosa at the level of the corporeal crura dorsomedially from, and alongside, the cavernous arteries. The CNs branch into small branches which accompany the helicine arteries into the erectile tissue to innervate both these arteries as well as the smooth muscle surrounding the sinusoids of the corpus cavernosum [17, 18, 20].

Blood supply to the penis is derived from the infralevatoric internal pudendal artery, a branch of the internal iliac artery. Alternatively, a supralevatoric accessory pudendal artery may supplement or completely replace branches of the common penile artery [20]. This accessory artery is particularly vulnerable to damage during apical dissection in RP due to its intimate anterolateral relation to the prostatic apex. The pudendal and internal iliac arteries are susceptible to vascular damage in external beam radiation therapy as these arteries commonly coarse through the field of pelvic irradiation. The cavernous arteries run centrally in the crura and the corpora cavernosa and branch into helicine arteries which are spiraloid and therefore able to accommodate length and girth changes during erection. These helicine branches in turn drain into the sinusoids of the corpus cavernosum, which are hollow spaces lined by smooth muscle in two layers oriented in different directions. Relaxation of the circular, outer, smooth muscle layer increases penile girth, while relaxation of the longitudinal, or inner, smooth muscle cell bundles allow for increase in penile length. The sinusoids are supported by a system of trabeculae, which consist of fibrous tissue and elastic fibers which both are interwoven with the smooth muscle fibers surrounding the sinusoids. This structural arrangement is essential for the unique fibroelastic properties of the erectile tissue which allow both for relaxation of the sinusoidal walls and for compression of the subtunical venules against the tunica albuginea.

Venous blood drains from the sinusoids of the corpus cavernosum to the subtunical veins, which in turn drain into the deep dorsal vein of the penis. The latter originates at the base of the glans and then runs through a groove formed by both corpora cavernosa and drains into the preprostatic plexus (Santorini's plexus). Although this venous complex is divided in RP, this maneuver has not been associated with the development of ED following this surgical procedure.

## Physiology of Penile Erection

Nitric oxide (NO) is released from NANC nerve terminals of the CNs in the corpus cavernosum in response to a neural stimulus and also from the endothelium in response to (1) the release of acetylcholine (Ach) by parasympathetic endothelial nerve endings and (2) the shear stress elicited by increased blood flow in the corporeal sinusoids. NO is synthesized in the nerve terminals and in the endothelium by action of the tissue-specific enzyme nitric oxide synthase (neuronal and endothelial NOS, respectively), which catalyzes the production of NO and citrulline from oxygen and L-arginine. Both the endothelium and the nerve endings of the CNs lie in close contact with the smooth muscle cells in the penile arteries and sinusoids. NO passively diffuses into cavernous smooth muscle cells where it binds to soluble guanylyl cyclase (sGC) and thereby activates this enzyme, which catalyzes the breakdown of guanosine triphosphate (GTP) into cGMP. In turn, cGMP incites a cascade of protein kinase G (PKG)-mediated intracellular events. Although being the most important pathway leading to smooth muscle relaxation, it is supported by other pathways with cAMP as a second messenger, which activates protein kinase A (PKA). These cAMP-dependent pathways are activated mainly by endogenous prostaglandins. PKG and PKA activate a series of cellular events via phosphorylation of various targets, ultimately leading to relaxation of the cavernous smooth muscle cells and thus increasing blood flow in the sinusoids and their supplying arteries. This results in an increase in the volume and pressure in the sinusoids, and the subsequent engorgement of the corpus cavernosum leads to penile erection. Blood then becomes trapped in the corporal bodies by compression of subtunical venules against the tunica albuginea leading to the full erection phase. Erectile rigidity is further enhanced by contraction of the voluntary ischiocavernosus muscle in the rigid erection phase [17, 18] (Fig. 81.2).

## Pathophysiology of Erectile Dysfunction Following Prostate Cancer Treatment

### Pathophysiology of Erectile Dysfunction Following Radical Prostatectomy

ED following RP is the result of injury to the CNs, combined with changes in the corpus cavernosum secondary to denervation of the erectile tissue. Some authors have further suggested that division of the accessory pudendal arteries contributes to ED post-prostatectomy. Even if the CNs are macroanatomically rendered intact at the end of the procedure, ED develops in the large majority of patients during the first 9–18 months following surgery. This time frame represents the time needed for the CNs to regenerate following neuropraxia and subsequent neurodegeneration. In neuropraxia, the affected (cavernous) nerve is injured by stretching, crushing, electrocoagulation, or blunt trauma. Thus, the nerve is injured although it macroscopically may appear intact. While a large majority of axons initially indeed do remain intact, these relatively minor injuries suffice to initiate a neurodegenerative process termed Wallerian degeneration (Fig. 81.3). Wallerian degeneration is initiated within minutes to hours following the nerve injury and begins with degradation of axoplasm and axolemma accompanied by the development of axonal as well as myelin debris, which is subsequently phagocytozed by resident Schwann cells but also by macrophages invading the degenerating neural environment. The influx of macrophages is the result of a neuroinflammatory reaction which is coordinated by the resident Schwann and glial cells. It was shown that in peripheral

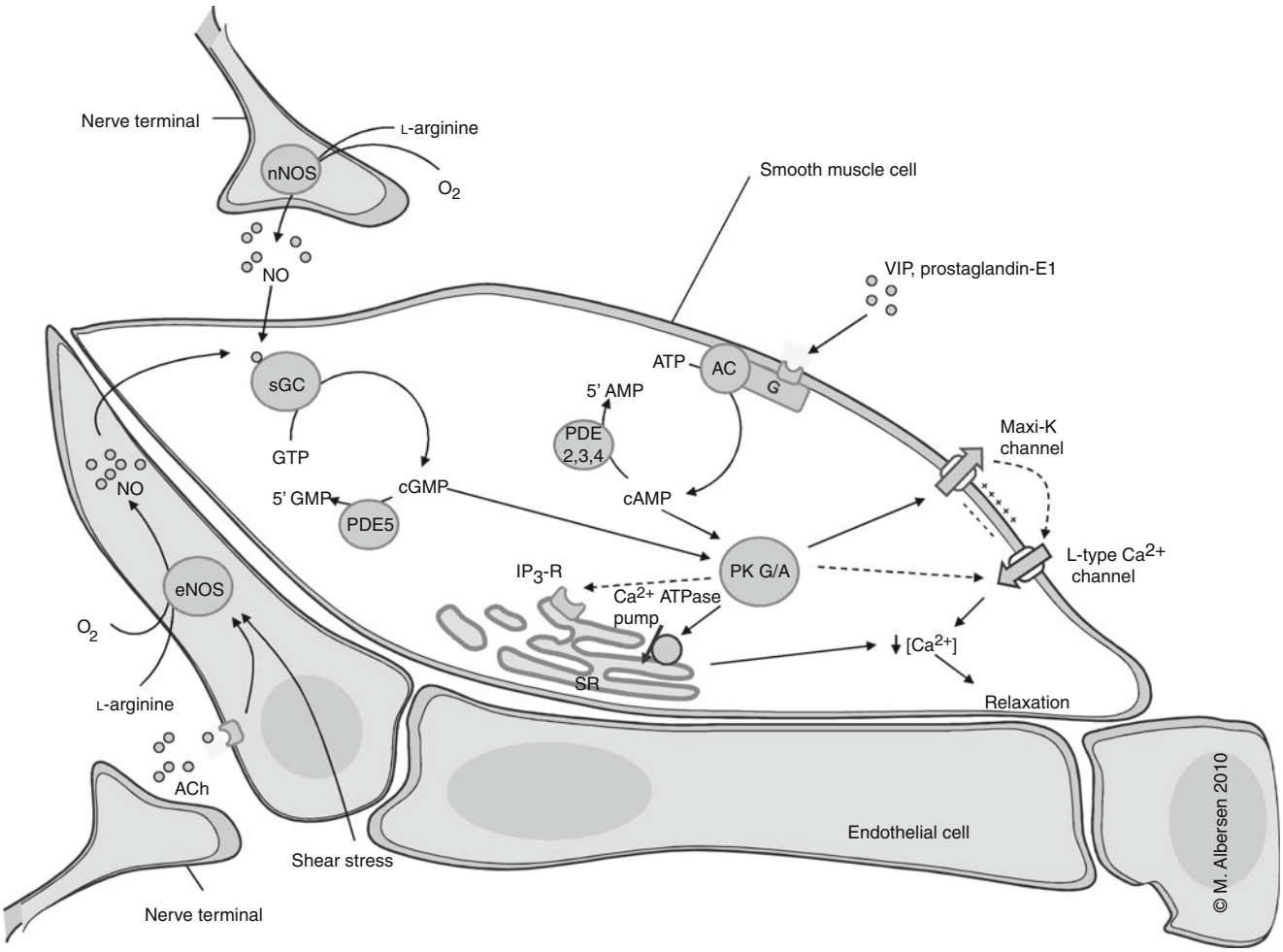


**Fig. 81.2** Physiology of smooth muscle cell relaxation. NO is released from nerve terminals in the corpus cavernosum in response to a neural stimulus and from the endothelium in response to the release of acetylcholine (*Ach*) and to the shear stress elicited by increased blood flow in the corporeal sinusoids. NO binds to soluble guanylyl cyclase (*sGC*) and thereby activates this enzyme, which catalyzes the breakdown of guanosine triphosphate (*GTP*) into cyclic guanosine monophosphate (*cGMP*). Other pathways, which are initiated by VIP and prostaglandin-E1, activate a G protein (*G*)-coupled receptor, leading to activation of adenylyl cyclase (*AC*), which catalyzes the breakdown of adenosine triphosphate (*ATP*) into cyclic adenosine monophosphate (*cAMP*). cGMP and cAMP exert analogous effects by activating protein kinase G and A, respectively, which modulate potassium and calcium channels in the cell membrane; and the inositol triphosphate receptor (*IP3-R*) and the calcium–ATPase pump in the membrane of the sarcoplasmatic reticulum (*SR*). These events lead to a lowering of the cytosolic calcium concentration, which causes dissociation of calcium from calmodulin. Calmodulin in turn dissociates from myosin light-chain kinase, thus inactivating it in turn leading to smooth muscle relaxation and, ultimately, to penile tumescence (Adapted from Ref. [18] with permission from Informa Healthcare)

nerves, an upregulation of proinflammatory cytokines takes place in both the endoneurium and perineurium in the first days and weeks after the injury [22]. These cytokines initiate an inflammatory cascade resulting in the expression of chemoattractant molecules not only at the site of injury but also at the cell body of the affected nerve fiber (in this case, the pelvic ganglia). The inflammatory reaction potentially affects the whole nerve and thereby results in disruption of initially uninjured axons as well. These findings in other research fields have led to the application of immunomodulatory therapies in preventing ED following CN injury with various success rates (vide infra).

The process of Wallerian degeneration results in axonal interruption and thus denervation of the erectile tissue it innervates. Denervation of the erectile tissue in turn results in loss of smooth muscle content and fibrotic changes in extracellular matrix of the penis [23]. Aside from substantiating ED, these changes in penile tissue architecture are often held responsible for penile shortening, and the increased incidence of Peyronie's disease observed after RP. It is believed that these changes are not only the direct result of denervation but also indirect due to a state of penile hypoxia resulting from the absence of erectile activity.

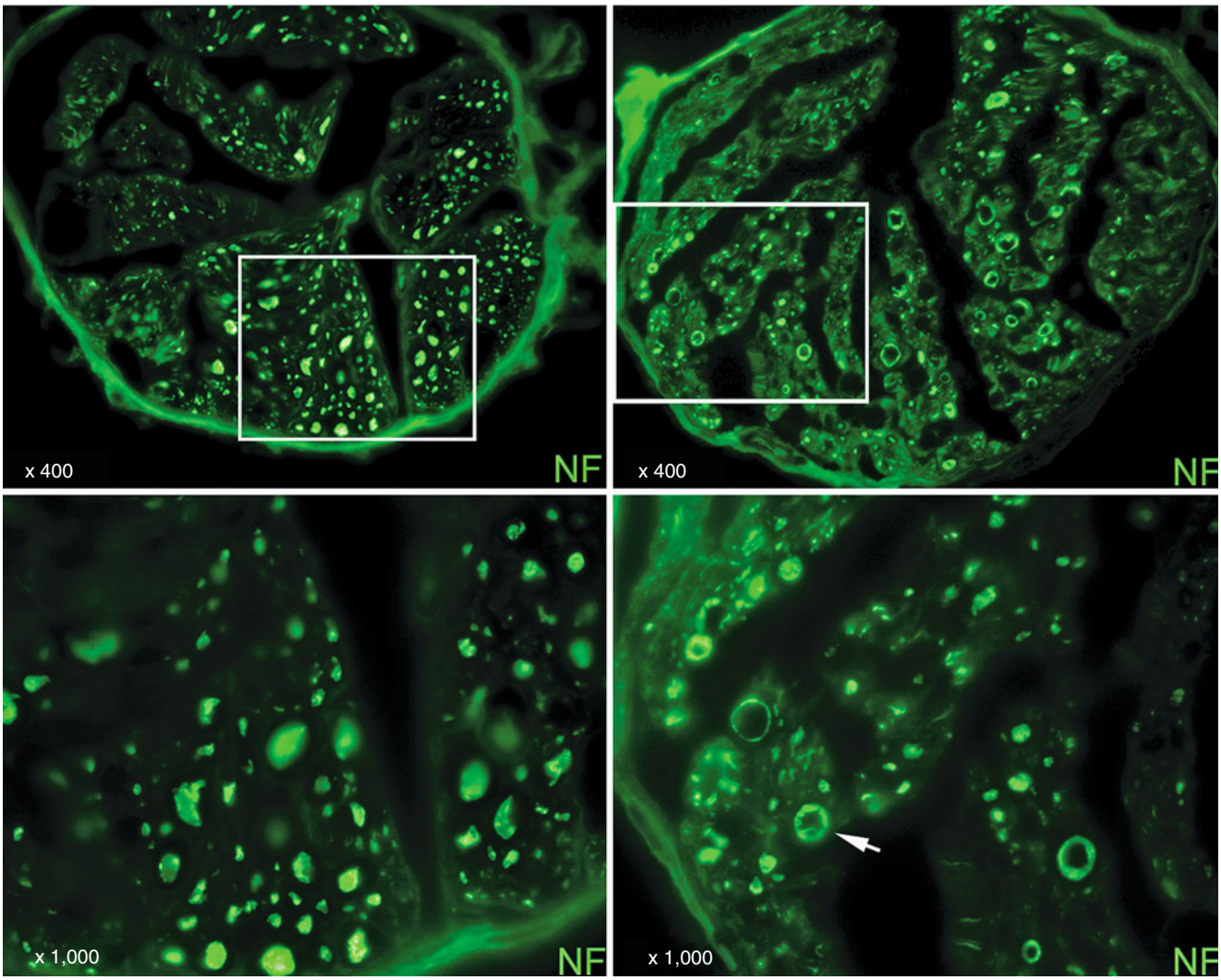


**Fig. 81.3** Wallerian degeneration following cavernous nerve injury. Rat cavernous nerve sections distal from the site of experimental cavernous nerve injury. Sections were immunostained for neurofilaments. Original magnification ×400 and ×1,000. Note microanatomical signs of Wallerian degeneration, including an overall distortion of normal nerve anatomy, axonal swelling, and axonal vacuolization (*arrows*) in the cavernous-nerve-injured rat (Adapted from Ref. [21] with permission from Elsevier). Normal cavernous nerve: left; injured cavernous nerve: right.

Azadzoi and colleagues showed in a canine model that subtunical oxygen tension in the flaccid penis was close to 100 mmHg, consistent with an arterial circulation, whereas central cavernosal measurements showed an oxygen tension characteristic of venous blood. With CN electrostimulation or after injection of vasoactive agents, oxygen tension in the central region of corpus cavernosum increased to a level consistent with arterial blood [24]. Thus, regular erectile activity keeps the cavernosal tissue oxygenized. Bannowsky and colleagues showed a significant decline in nocturnal penile tumescence episodes following non-nerve-sparing prostatectomy [25]. This denervation-induced loss of spontaneous erectile activity is not without consequences. While in the healthy male the cavernous tissue is supplied with arterial oxygen levels during REM sleep 3–5 times a night during 30–45 min, these nocturnal penile tumescence episodes diminish after CN damage, rendering the penis in a continuous flaccid state and thus a state of permanent relative hypoxia. This hypoxia is believed to be responsible for various changes in the cavernosal tissue.

A low oxygen tension has direct effects on the resistance of the arterial bed of the penis and on the relaxation of cavernosal trabecular smooth muscle. Kim et al. showed that relaxation of isolated human and rabbit corpus cavernosum tissue strips in response to electrical stimulation was progressively diminished when oxygen tension was decreased from arterial to venous $PO_2$. Furthermore, they showed that hypoxic conditions reduced basal levels of cGMP, prevented cGMP accumulation induced by nerve stimulation, and inhibited NOS activity. Loss of oxygen supply thus results in loss of NO availability in the erectile tissue [26].

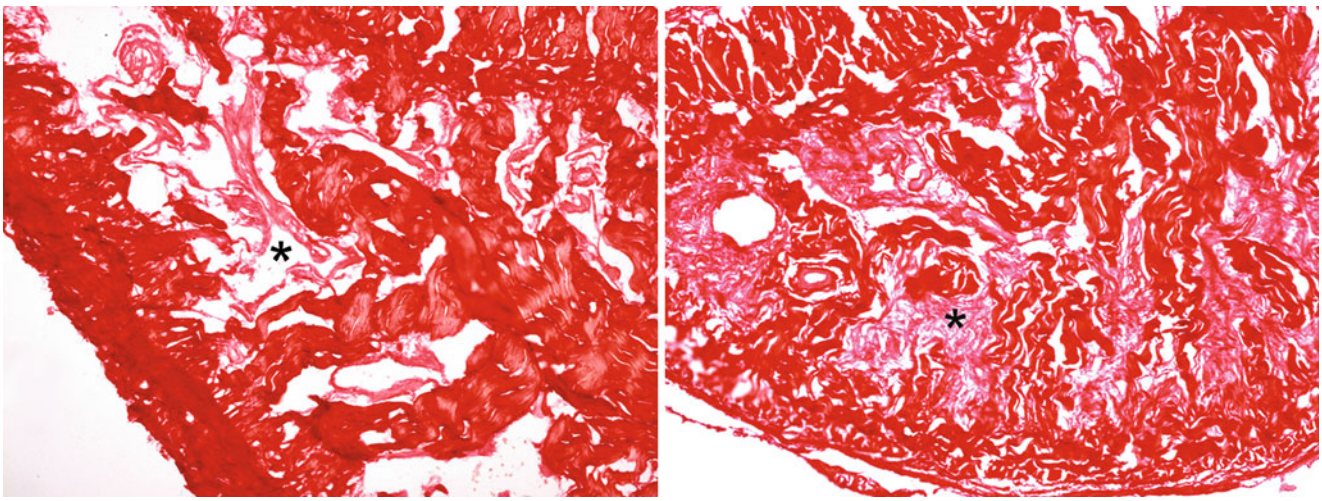


**Fig. 81.4** Fibrosis of the corpus cavernosum following cavernous nerve injury. Rat corpus cavernosum transverse sections with and without experimental cavernous nerve injury. Sections were stained for collagen using a picrosirius red staining method. Original magnification ×100. Collagen is located mainly in the trabeculae and the tunica albuginea where it consists of thick, bright red bundles. Reticular collagen fibers further are visible as thin fibrils forming a subendothelial meshwork. Note the deposition of reticular collagen (collagen subtype III) in the sinusoids following crush injury (*asterisk*) (Reprinted from Ref. [32] with permission from John Wiley and Sons)

The hypoxic state in the penis following cavernous neurotomy has been shown to induce overexpression of a variety of cytokines and other signaling substances in the corpus cavernosum. The most characterized are hypoxia-inducible factor 1α (HIF-1α), transforming growth factor beta 1 (TGF-β1), and endothelin-1 receptor B (ETB) [23]. HIF-1α is a transcription-inducing factor that is expressed when mammalian cells are subjected to hypoxia. The finding that this cytokine is upregulated confirms the theory that hypoxia of the erectile tissue occurs after CN injury. These findings were further corroborated by Vignozzi and colleagues at the University of Florence who showed in vivo hypoxia by administration of a so-called hypoxyprobe which was then visualized by immunohistochemistry. Hypoxia was detected predominantly in the endothelial and muscular compartments of cavernous spaces [27]. ETB has been linked to the penile hypoxic condition in cavernous neurotomized rats and is profibrotic [28]. It thus may play a role in the development of fibrosis in the hypoxic erectile tissue. Penile overexpression of TGF-β1 has repeatedly been identified following CN injury in both rat and mouse models [29]. TGF-β1 is a cytokine involved in numerous biological actions, including regulation of inflammation and production of extracellular matrix proteins. In both human corpus cavernosal smooth muscle cells and fibroblasts, it has been linked to production of collagen [30, 31]. This is in line with the finding that following RP in humans or CN injury in animal models, fibrosis of the erectile tissue is observed (Fig. 81.4). As stated above, this fibrosis is also suspected to be responsible for penile shortening and the higher prevalence of Peyronie's disease following prostatectomy. The increased collagen deposition and fibrotic changes in the penis provoke mechanical alterations, which reduce the elasticity and compliance of the cavernosal tissue. These alterations cause an impaired expandability of the sinusoids which normally compress the emissary veins against the tunica albuginea, resulting in corporeal veno-occlusive dysfunction (CVOD).

Diminished penile smooth muscle content has been raised as an important component of ED following CN injury. Whether this is a result of the denervation itself or from the resulting hypoxia is a matter of debate. Our group has observed a decline in smooth muscle content in multiple animal studies and was able to show detailed anatomical changes in the bilayered smooth muscle surrounding the cavernosal sinusoids in rats (Fig. 81.5). Various authors have shown increased smooth muscle apoptosis following CN injury. Klein et al. found the presence of condensed and fragmented cell nuclei (characteristic of apoptotic cells) within the erectile tissue in denervated rat penises versus a sham-operated control group [33]. User and colleagues have elucidated the role of apoptosis in the pathophysiology of post-prostatectomy ED in a rat model [34]. Rats were therefore randomized to bilateral or unilateral CN transection versus a sham operation. They found that bilateral cavernous neurotomy induced significant apoptosis, and the authors demonstrated that apoptotic cells were predominantly smooth muscle cells. In addition, it was found that most apoptotic cells were located just beneath the tunica albuginea where the subtunical venular plexus is located. This finding again may play an important role in the development of CVOD following RP.

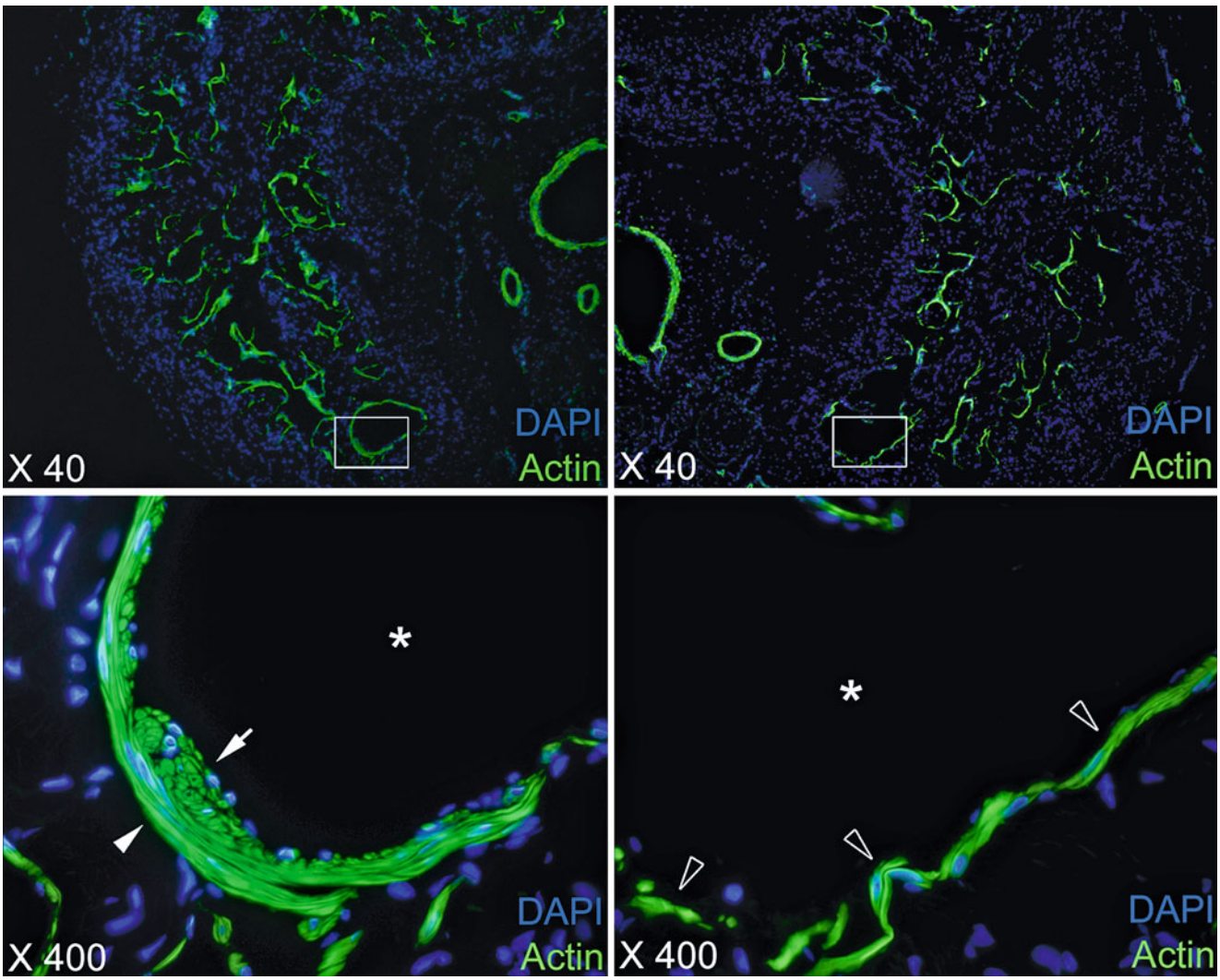


**Fig. 81.5** Loss of smooth muscle content in the corpus cavernosum following cavernous nerve injury. Rat corpus cavernosum transverse sections with and without experimental cavernous nerve injury. Sections were stained for smooth muscle (actin) and nuclei (DAPI). Original magnification ×40 and ×400. Images show detailed changes in the structure of cavernous smooth muscle surrounding sinusoids (*asterisk*). The sinusoid indicated by the white box is depicted in high magnification in the lower panel. Loss of smooth muscle structure was more pronounced in the longitudinal, or inner, layer of smooth muscle cells (*closed arrows*) rather than the circular, or outer, layer (*closed arrowheads*). *Open arrowheads*: architectural changes such as a decrease in cell number in both layers are observed following injury of the cavernous nerves (Adapted from Ref. [21] with permission from Elsevier)

Sonic hedgehog homolog (SHH) plays a key role in vertebrate organogenesis and remains important in the adult. SHH has been suggested to play a role in apoptosis of smooth muscle cells. In a series of experiments by Podlascek et al., bilateral CN resection resulted in significantly decreased SHH in the smooth muscle of the corpora cavernosal sinusoids and extensive morphological changes, including increased apoptosis. The SHH cascade acts to establish normal penile morphology. Nerve injury disrupts the SHH cascade and corpora cavernosal homeostasis after which morphological changes in sinusoid structure ensue, resulting in ED. Bond et al. illustrated that neural activity and a trophic factor from the pelvic ganglia or CNs are necessary to regulate SHH protein and smooth muscle abundance in the penis [35]. While others have proposed hypoxia as the main element responsible for smooth muscle apoptosis, these experiments suggest a direct link between denervation and loss of smooth muscle. Further research is necessary to further elucidate these mechanisms.

Summarizing, the pathophysiology of ED following RP has been extensively studied in animals but also in humans. A hypoxic state following denervation results in apoptosis of key cellular populations and the induction of fibrosis by upregulation of various profibrotic signaling molecules.

These changes in the erectile tissue lead to CVOD which further deteriorates erectile function, besides interruption of innervation of the corpus cavernosum. The identification of hypoxia as a key mechanism in ED following prostatectomy has led to the advent of strategies aimed at preservation of penile oxygenation to prevent development of penile fibrosis and thus CVOD. These "penile rehabilitation" regimens will be discussed later in this chapter.

## Pathophysiology of Erectile Dysfunction Following Prostate Radiation Therapy

While the mechanisms behind ED following RP have been extensively studied, the pathophysiology of post-radiotherapy ED remains largely unclear. In recent years, an increasing number of both animal and human studies have been questioning which anatomical structures are involved in loss of erectile capacity following pelvic irradiation and what structural alterations occur in the erectile tissue and penile neurovascular supply in these patients. Most attention has been given to the neurovascular bundles (of Walsh), the arterial supply of the penis, and the penile bulb. Initially, the latter structure does not seem important for achieving erectile rigidity, as the pressure in the corpus spongiosum during erection is only one-third to half of the pressure in the corpora cavernosa [36]. This is due to a lack of venous occlusion in the corpus spongiosum because a thick tunica albuginea is absent. The rigidity of the penis therefore depends predominantly on the corpora cavernosa. While the role of the penile bulb is questionable, the radiation dose to the penile bulb is correlated with the dose in the proximal-most region of the corpora cavernosa, the crura. Furthermore, the cavernous arteries and nerves penetrate the tunica albuginea at this level and might be susceptible to radiation-induced tissue damage. Van der Wielen and associates have summarized the available data on irradiation dosing to anatomical regions involved in erectile function in EBRT and BT and have concluded that the larger studies did not find a significant correlation between post-radiation ED and the radiation dose to the penile bulb [37]. Other groups have focused on the neurovascular bundles alongside the prostatic capsula. While most of these studies were performed on smaller patient populations, there was no clear correlation found between radiation dose to the neurovascular bundle and erectile function. Since both the penile bulb and the cavernous neurovascular bundles are in close proximity to the prostatic apex, a reduction in radiation dose to these structures is only implicated when it does not compromise oncological safety.

Arterial alterations seem to play a role in the development of ED following pelvic irradiation therapy. It has been shown that patients suffering from ED following radiotherapy for PCa have a decreased arterial flow rate in the cavernous artery when evaluated by duplex ultrasound [38]. This can possibly be explained by changes in the corpus cavernosum or cavernosal arteries themselves but could also be caused by an obstruction of the arterial flow before it reaches the cavernosal arteries. The internal pudendal arteries provide the arterial blood supply for the penis and are located in the radiation field for external beam radiation therapy (EBRT). During brachytherapy (BT), these vessels receive radiation as well, although this radiation dose is supposedly lower than during EBRT. Surprisingly, the literature on the role of these arteries in post-radiation ED is scarce, and a correlation between the dose on these vessels and ED has not been investigated.

Erectile biology following radiotherapy in experimental animals has been underinvestigated, and up till today, only four preclinical studies have been geared towards elucidating penile changes following radiotherapy. Carrier et al. at UCSF investigated the changes in the rat penile dorsal nerves after increasing dosages of radiation to the prostatic area and observed a dose-dependent decrease in intracorporeal pressure both upon CN electrostimulation and after injection of the vasoactive substance papaverine. They concluded that radiation to the prostatic area resulted in a defective neural and vascular supply to the corpus cavernosum [39]. When examining the penis histologically, they found a significantly decreased number of nNOS-containing nerve fibers. In another study, early post-radiation changes in the corpus cavernosum were interstitial edema and vascular congestion, which were linked to increased levels of reactive oxygen metabolites [40]. Reactive oxygen species may induce an inflammatory condition in the erectile tissue with an increase in proinflammatory cytokines such as seen after CN injury, which is particularly likely as certain cytokines (interleukin (IL)-1beta, IL-6, and TGF-β) are upregulated the plasma of patients who underwent prostatic irradiation [41]. Hypothetically, increased oxidative stress mediated through superoxide radicals and other reactive oxygen species may be central to impaired cavernosal function in ED following radiation therapy, by damaging penile NO transmission and smooth muscle relaxation [42]. Furthermore, propagation of endothelial dysfunction by reactive oxygen species may result in impairment of penile vascular function [42]. In a study by van der Wielen et al., indeed the penile vascular function was impaired as rats subjected to fractionated irradiation of the prostatic area had developed loss of vascular smooth muscle cells, thickening of the intima, and occlusion of the cavernosal arteries (Fig. 81.6) [43]. Arterial blood flow following pelvic irradiation may be further diminished by upregulation of endothelin-1, as was shown in irradiated rats by Merlin and colleagues [44]. In summary, currently available data indicate that prostatic radiotherapy appears to upregulate reactive oxygen species and endothelin-1 in the erectile tissue and causes impaired neural and vascular input leading to ED.

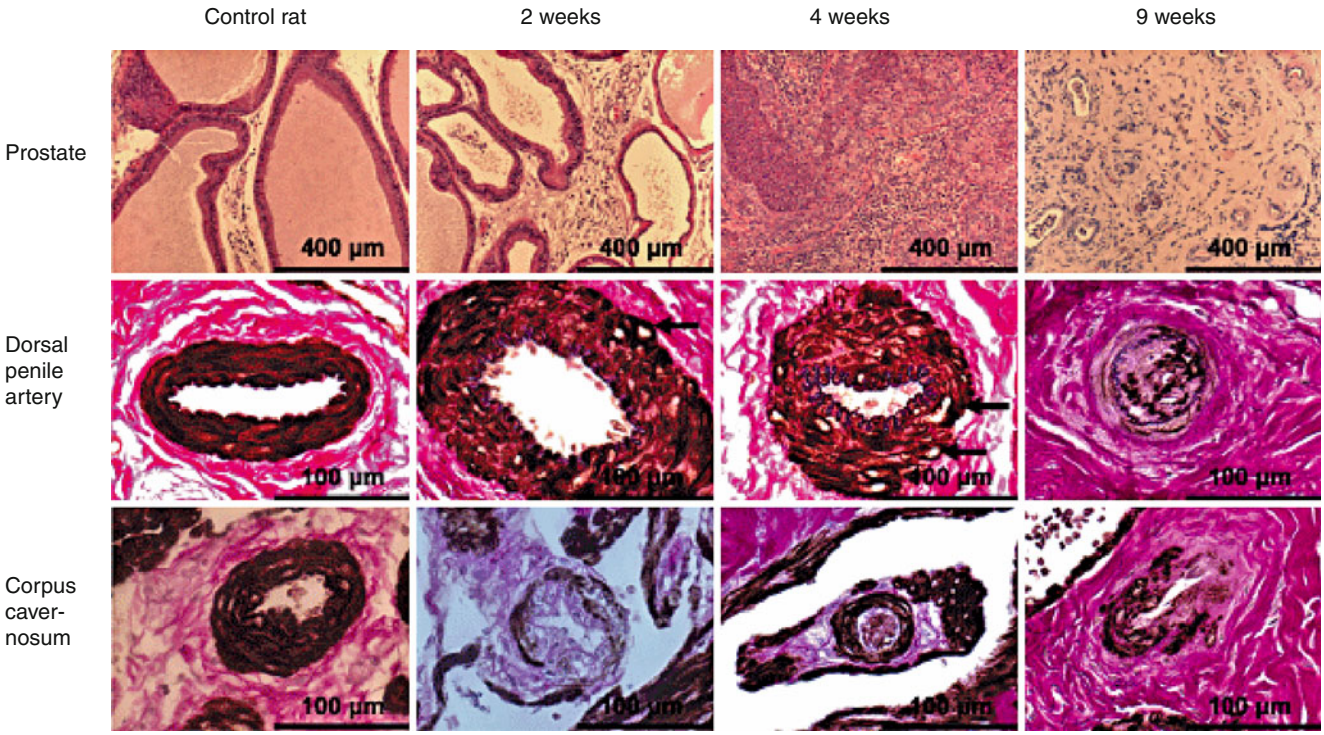


**Fig. 81.6** Changes in arteries and corpus cavernosum of the rat following experimental prostatic irradiation. Histology of prostatic and penile tissue of a control rat and rats sacrificed at 2, 4, and 9 weeks after irradiation. The *first row* (prostate) shows the prostate stained with hematoxylin–eosin. Two weeks after irradiation, edema is observed, followed by inflammation at 4 weeks and fibrosis at 9 weeks after irradiation. The *second row* (dorsal penile artery) shows the dorsal penile artery with resorcin–fuchsin and α-smooth muscle actin staining. The histology after irradiation shows smooth muscle cells (*brown*) in apoptosis (examples indicated with an *arrow*) and an increase in collagen in the arterial wall (*pink*). At 9 weeks, an artery is shown with severe thickening of the intima and loss of most smooth muscle cells expressing α-smooth muscle actin. The *third row* (corpus cavernosum) shows arteries in the corpora cavernosa with resorcin–fuchsin and α-smooth muscle actin staining. Again, there is a decrease in smooth muscle expressing α-smooth muscle actin. The tissue sample at 4 weeks after irradiation shows an occlusion of an artery caused by a thrombus (Reprinted from Ref. [43] with permission from John Wiley and Sons)

## Pathophysiology of Erectile Dysfunction in Androgen-Deprived Patients

Penile erection is a complex neurovascular phenomenon modulated by several biochemical and psychological factors. One of these influencing factors is androgen regulation of penile erection. Disruption of these hormonal control mechanisms holds the potential for causing not only ED but also other sexual dysfunctions in men treated with androgen deprivation therapy (ADT) for PCa. As testosterone has various effects on homeostasis of the erectile tissue, ADT may result in ED. Furthermore, libido is generally diminished in androgen blockade which raises the question whether these patients are inclined to request therapy for their ED. Erections and sexual desire are two interrelated processes that vary significantly with androgen deprivation, but both tend to decline gradually. Regardless of this discussion, an understanding of pathophysiological mechanisms can aid both the patient and the physician in understanding the side effects of hormonal therapy.

Androgens are deemed critical for penile tissue development, growth, and maintenance of erectile function; however, their role in erection, especially in humans, remains controversial. While some hold the view that androgens are not critical for erections, this view may be distorted by the fact that the threshold of androgen levels required for maintaining erections in humans is lower than that needed for maintaining other tissue functions [45]. Furthermore, in a study by Peters and Walsh, an LHRH analog lowered testosterone to castration levels and induced ED in men which resolved after discontinuation of the LHRH therapy [46]. Treatment with LHRH analogs also resulted in a significant reduction in frequency, duration, and rigidity of nocturnal erections [47]. The other way around, androgen supplementation therapy in hypogonadal patients has been shown to have beneficial effects on erectile function [45].

In humans, it has been recognized that androgens play a critical role in the development and growth of the penis. This is illustrated by the finding that children with defects in their androgen metabolism develop microphallus and that supplementation of testosterone, either systemically or locally, in

children with microphallus resulted in penile growth and marked enlargement of an abnormally small penis [45]. The role of androgens in maintaining penile health after development is less clear and subject of discussion. Castration of the human male after attainment of sexual maturity does not result in a marked reduction in penile size. This is in contrast to findings in various animal models, in which a reduction of penile size following bilateral orchiectomy is noted. One must keep in mind, however, that the human adrenals produce dehydroepiandrosterone and 4-androstenedione, which serve as sources of androgens by peripheral conversion in target tissues to testosterone and 5α-dihydrotestosterone. This adrenal androgen production is putatively absent in animal models [45]. In either surgically or medically castrated animal models, it has been demonstrated that androgen deprivation results in a significant reduction in trabecular smooth muscle content and a marked increase in connective tissue deposition in the corpus cavernosum [45]. Furthermore, smooth muscle appeared disorganized following castration, while in normal rats, smooth muscle cells were clustered together in an organized fashion. Reduction of smooth muscle content and increased deposition of collagen in the corpus cavernosum has at multiple instances been linked to the development of ED. The corpus cavernosum extracellular matrix consists of a network of fibrillar collagen and elastin fibers which are intimately connected to the trabecular smooth muscle. As described above, these changes lead to impaired sinusoidal expandability and, ultimately, CVOD. Other changes that have been observed in orchiectomized animals include the accumulation of adipocyte-like cells containing droplets of fat in the subtunical regions of the corpus cavernosum [48]. This is interesting to note as it is possible that the presence of fat cells in the subtunical region of the corpus cavernosum may further contribute to CVOD in the orchiectomized animal. That these tissue changes indeed cause CVOD in experimental animals has been shown by dynamic infusion cavernosometry and cavernosography [45]. Aside from changes in the corpus cavernosum, decreased fiber density and thinner myelin sheaths were observed in the CN of orchiectomized rats compared to controls, potentially indicating decreased conductivity of these nerves innervating the penile tissue [49]. Functionally, the observed changes resulted in decreased intracavernosal pressure following electrostimulation of the CNs.

Aside from structural alterations in the penile tissue, androgen deprivation therapy may have important effects on protein expression and function of both NOS and PDE5 which may explain the clinically observed decreased erectile response to PDE5-inhibitor (PDE5i) therapy in men under ADT. In animal studies, androgen deprivation reduced various NOS isoforms and PDE5 mRNA and protein expression, while testosterone supplementation restored PDE5 gene and protein expression. Androgen deprivation reduced the effect of PDE5 inhibitors on neurogenic relaxation in vitro, and this was restored in tissues of castrated animals treated with testosterone [50]. This finding has been contested by others, who state that PDE5 may not be directly regulated by androgen levels; the decline in PDE5 expression after castration in a rat model has been shown to be the result of decreased penile smooth muscle content rather than by an isolated decline in PDE5 expression [51].

## Techniques to Prevent Erectile Dysfunction in Prostate Cancer Patients

### Radical Prostatectomy

#### Nerve-Sparing Surgery

Until 1982, virtually every patient who underwent RP became impotent, many had significant urinary incontinence, and when performed via the retropubic approach, excessive perioperative bleeding was common. In 1982, however, the surgical treatment of PCa was revolutionized by introducing the "anatomical RP" which was based on one of the defining and seminal discoveries in urology by PJ Donker and PC Walsh in 1981, when they dissected out the CNs running close to the prostatic capsula in a stillborn male infant. During the next year, intraoperative observations identified the capsular arteries and veins of the prostate as a landmark that could be used in the adult male pelvis to identify the microscopic CNs. The first patient that purposefully underwent a nerve-sparing RP was operated on April 26, 1982, and had complete recovery of sexual function within 1 year following surgery and had undetectable PSA during follow-up [52]. By now, various nerve-sparing techniques have evolved based on ongoing anatomical insights and technical development. An increasing body of literature discusses the various extrafascial, interfascial, and intrafascial dissection approaches to the posterolateral portion of the prostate for sparing the neurovascular bundles without compromising cancer control. The preoperative decision whether to spare or resect the neurovascular bundles is based on the location of the lesion (apex vs. base), the probability of capsular extension, and whether or not there is perineural invasion. However, intraoperative findings finalize the decision whether neurovascular bundle resection is necessary and include (1) induration in the lateral pelvic fascia, (2) adherence of the neurovascular bundle to the prostate while it is being released, and (3) inadequate tissue covering the posterolateral surface of the prostate once the prostate had been removed, leading to secondary wide excision of the neurovascular bundle [53]. Starting in the late 1990s, laparoscopic nerve-sparing RP has been widely employed but is currently progressively abandoned in favor of robot-assisted laparoscopic RP, which is rapidly on its way to becoming the most

**Table 81.1** Potency rates following nerve interposition during radical prostatectomy

| Author | Nerve type | *N* | Follow-up (month) | Graft potency rate (%)[a] | Control potency rate (%)[a] |
|---|---|---|---|---|---|
| *Unilateral interposition nerve graft* | | | | | |
| Kadmon et al. | Sural | 38 | 20–22 | 64.7 | N/A |
| Wood et al. | Sural | 27 | 13 | 48 | N/A |
| Kim et al. | Sural | 20 | 18 | 65 | 47 |
| Zorn et al. | Sural | 23 | 26 | 47.8 | 56 |
| Namiki et al. | Sural | 19 | 36 | 60 | 18 |
| Hanson et al. | Sural | 40 | 19 | 72 | N/A |
| Sim et al. | Sural | 41 | 27 | 63.2 | 26.5 |
| Nelson et al. | Genitofemoral | 22 | 14 | 63 | N/A |
| Joffe et al. | Genitofemoral | 22 | 23 | 32 | N/A |
| Davis et al. (phase 2 trial) | Sural | 107 | 24 | 71 | 67 |
| *Bilateral interposition nerve graft* | | | | | |
| Kim et al. | Sural | 23 | 23 | 43 | 0 |
| Wood et al. | Sural | 30 | 22 | 43 | N/A |
| Secin et al. | Sural | 44 | 60 | 34 | N/A |
| Chang et al. | Sural | 30 | 23 | 72 | N/A |
| Nelson et al. | Genitofemoral | 5 | 14 | 20 | N/A |

Adapted from Ref. [54] with permission from Elsevier
[a]PDE5i-aided potency

popular nerve-sparing surgical approach in Western countries. In spite of these advances, the functional results of robot-assisted versus open surgery are still a matter of debate, with authors reporting varying outcomes for both techniques. Furthermore, the learning curve for achieving optimal cancer control combined with preservation of erectile function and continence (also termed "trifecta") seems to be quite long. For a more elaborate discussion of surgical aspects of RP and nerve-sparing technique, we refer the reader to prior chapters in this book.

## Nerve Reconstruction Techniques

If unfavorable pathologic features are encountered during the work-up of PCa, many men require resection of one or both CNs to optimize adequate cancer control. This is especially the case for locally advanced PCa, in which surgical treatment is gaining acceptance in the uro-oncology field. The potency rates in the subset of men who undergo non-nerve-sparing prostatectomy are expectedly dismal and have led to the novel inception of interposition nerve grafting.

When a nerve is transected, the cut end sprouts minifascicles in an attempt to regenerate. When considerable gaps between cut ends are present, as is the case in non-nerve-sparing prostatectomy, functional healing is frequently impaired or inefficient. The nerve graft provides a scaffold for orderly nerve fiber regeneration, and the Schwann cells present in these grafts release neurotrophic agents beneficial for the restorative process. An orderly, staged nerve regeneration ensues in which axons grow down the graft, reconnect to the target tissue, and eventually restore coordinated neural functions. The time to this functional recovery is dependent primarily on the length of nerve that needs to be regenerated. In the setting of CN resection, graft-aided regeneration is expected to take close to a year [54].

While initial reports were promising, conflicting outcomes of subsequent studies prevented the translation of nerve grafting to routine practice in non-nerve-sparing RP. The first successful feasibility studies were conducted in the early 1990s in which genitofemoral nerve grafts were used to aid in the restoration of erectile function in rats [55]. However, note must be taken of the fact that in rats, the CN is a well-defined structure, making it an ideal model for experimental studies. In humans however, there are multiple nerves dispersed in a plexus surrounded by vessels which make accurate nerve interposition anatomically complicated. In humans, Walsh performed the first genitofemoral nerve interposition graft during retropubic RP in men who underwent unilateral nerve-sparing surgery [53]. The results were inconsistent, and there was uncertainty whether the return of potency was a result of graft interposition or a result of sparing the contralateral nerve. Moreover, the genitofemoral nerve was potentially of an inadequate caliber to serve as a frame for consistent regeneration. Therefore, the sural nerve was explored as an interposition graft with promising initial results that fueled the initiation of follow-up studies and trials at multiple centers (Table 81.1). Multiple initial studies focusing on sural nerve grafts have shown significantly better potency outcomes and a quicker return to potency among men who underwent unilateral grafting and contralateral nerve sparing compared with patients who underwent contralateral nerve sparing alone [54]. However, in a large-scale randomized phase II trial in patients who underwent unilateral nerve-sparing prostatectomy versus unilateral nerve-sparing prostatectomy with contralateral sural nerve graft

who were followed up for a minimum of 2 years, the results were rather disappointing and engendered questions regarding the future use of interposition grafting after unilateral nerve-sparing prostatectomy [56]. The true benefit of interposition nerve grafting still needs to be determined. However, based on the initial positive results and the reproducible success of nerve reconstruction in plastic surgery, the conceptual basis of interposition grafting appears sound [54]. Therefore, ongoing preclinical and clinical research is focusing on the improvements in surgical techniques and technologies that facilitate more precise nerve identification, preparation, and reapproximation, as well as on the use of neurotrophic agents and (either or not cell seeded) conduits [54].

### Radiotherapy

#### Radiation Field

Based on recent publications, the capital predictive factor of erectile function preservation following radiotherapy seems to be the chosen treatment modality. Even with newer techniques such as 3-D conformal radiotherapy (CRT), the preservation rate of erectile function was low [57]. Namiki et al. reported a study comparing conformal and conventional radiotherapy and intensity-modulated radiotherapy (IMRT) with respect to effect on sexual function. In the CRT group, sexual function decreased at 3 months and remained substantially lower than the baseline level. However, the IMRT group showed no significant difference from the baseline level, and at 18 months, sexual function in the IMRT group was better than in the CRT group [57]. Vessel-sparing prostate radiotherapy is another treatment option for sparing potency after treatment. This approach is based on decreased cavernosal artery flow rates following radiotherapy, the data observed in animal studies, and the finding that narrowing of the internal pudendal artery is the most common cause of impotence in the general population. It is conceivable that radiation may contribute to this process [58].

#### Radiation Dosing

On the basis of available data, it seems prudent to keep the mean dose to 95 % of the penile bulb volume to <50 Gy. It is acknowledged that the penile bulb may not be the critical component of the erectile apparatus (vide supra), but it seems to be a surrogate for yet to be determined structures critical for erectile function for at least some techniques, such as the cavernous arteries and the corporeal crura [59]. The relationship of the internal pudendal artery to the prostate is variable and complex. The vessel follows the lateral curvature of the prostate in some patients, and sparing is therefore possible only with an MRI and IMRT approach to reduce radiation dosage to the internal pudendal artery [58]. For BT, controversy exists about the impact of the radiation dose to the neurovascular bundles. While some authors claim that the presence and severity of ED correlates significantly with the bilaterally average maximum dose received by neurovascular bundle, others have not been able to confirm this finding [60, 61]. Differences in the length of follow-up, patient selection, and the mode of data collection can be responsible for the wide range of observed potency rates in patients treated with BT. It is therefore not clear whether a dose reduction to the neurovascular bundles, if oncologically safe at all, would be of benefit for preservation of erectile function.

## Evaluation of Erectile Dysfunction Following Prostate Cancer Treatment

Assessment of complications of the chosen PCa treatment is essential in the follow-up of the patient. Patients who are in follow-up during, or after, treatment of their PCa should be routinely and regularly questioned for the presence and severity of ED. Compared to the evaluation of ED in the general population, the assessment of ED following PCa treatment is rather limited as the cause and underlying mechanisms of the erectile problem are known. An interview should assess for the use of drugs or substances and comorbidities which can potentially contribute to ED. Formal investigation of the erectile problem is often unnecessary, although a penile duplex ultrasound investigation can be useful in the assessment of CVOD in the absence of response to intracavernous injection therapy when counseling the patient for penile prosthesis implantation.

The impact of ED on both general well-being and sexual satisfaction is an important issue, not only for the patient himself, but also for the partner. The sexual relationship with the partner should be assessed as well as whether the need for intercourse or other forms of intimacy persists within the couple at the current age and in the setting of PCa. Open communication within the couple should be stimulated. As patients and their partners are likely bothered by discussing sexual issues, it is important that the clinician maintains an attitude of comfort and flexibility throughout the evaluation process and does not assume a patriarchal role when guiding the PCa survivor with ED.

The use of standardized questionnaires such as the international index of erectile function (IIEF) and the expanded PCa index composite (EPIC) can be useful instruments in assessing the severity of ED, in screening for concomitant sexual or other complications, and in evaluating effects of ED pharmacotherapy. However, questionnaires should not substitute for a detailed personal sexual history. Aside from evaluating individual patients, these questionnaires are often used in the reporting of potency rates following RP and pelvic radiation therapy series, and it has previously been shown

that the choice of assessment method or questionnaire significantly influences the reporting of potency in this setting. For example, Albersen et al. showed that reported potency rates were significantly higher when using single-item assessment (in which potency was defined as "having erections firm enough for intercourse") versus an abridged version of the international index of erectile function questionnaire [8], while the latter has been validated and is generally assumed reliable in this specific setting. A group of researchers of the Memorial Sloan–Kettering Cancer Center investigated what ED measures have been validated in a PCa population. They found that the majority of ED measures follow acceptable item development practices, are multidimensional, and report good psychometric properties. They concluded that the IIEF and EPIC are the most extensively validated measures for use in PCa patients, and therefore, the use of these questionnaires is advised when reporting on and evaluating ED in PCa survivors [62].

## Treatment of Erectile Dysfunction Following Prostate Cancer Treatments

The goal of treatment of ED in PCa patients is twofold. The immediate goal is to provide the patient and his partner with a safe and effective therapeutic option that allows them to resume sexual relations in a timely fashion following PCa treatment; this is also termed "on-demand treatment." The second goal of initiating treatment is the prevention of secondary changes to the cavernosal tissue integrity which occur as a result of either surgery or radiotherapy. Only recently has evidence for this second therapeutic goal emerged, and various treatment regimens are being developed to pursue erectile tissue preservation under the common denominator of "penile rehabilitation therapy" [23].

### On-Demand Treatment

#### Selective Phosphodiesterase-5 Inhibitors

Historically, treatment of ED was limited to surgical options and intracavernosal or intraurethral application of vasoactive drugs. Since the early 1980s, research on the mechanisms of penile erection has done much to clarify erectile physiology and pathophysiology. Research focusing on the mechanisms of corpus cavernosum smooth muscle relaxation led to the discovery of NO as the most important peripheral neurotransmitter in erectile physiology. Following this discovery, important advances have been made in the knowledge of the complex signaling pathways in the cavernosal smooth muscle and endothelium, leading to the development of phosphodiesterase-5 inhibitors (PDE5i). The introduction in 1998 of the first commercially available PDE5i – sildenafil – and the accompanying publicity in the media made therapy for ED easily accessible and lowered the threshold for patients to seek treatment for ED. Guidelines on the treatment of ED nowadays generally recommend PDE5i as the initial and reference treatment for ED, irrespective of the cause [63]. In patients who underwent surgery, radiotherapy, or hormone therapy for PCa, this guideline applies, although efficacy of these drugs is expected to be significantly lower than in the general population.

PDE5i are nonhydrolyzable analogs of cGMP and exert their beneficial effects on smooth muscle relaxation by competitively binding to the catalytic site of PDE5, the enzyme responsible for breakdown of cGMP to GMP. By slowing the degradation of cGMP by PDE5, these drugs produce a rise in intracellular cGMP concentration in the smooth muscle cells in the corpus cavernosum and in the walls of the supplying arteries. This accumulation of cGMP results in persistent activation of corresponding protein kinases and a decrease in intracellular calcium which keeps the smooth muscle in a relaxed state [18].

#### Efficacy After Radical Prostatectomy

As the efficacy of PDE5i depends on the integrity of the NO pathway for the production of cGMP, it is evident that patients in whom this pathway is disturbed or defective will benefit far less from PDE5i use than the general population. In RP patients, in whom the nerve supply to the erectile tissue is impaired, less NO is released upon sexual stimulation, and therefore there is less intracellular cGMP available as a second messenger in the smooth muscle. It logically follows that patients who underwent uni- or bilateral nerve-sparing surgery respond better to PDE5i than do patients who underwent non-nerve-sparing surgery. Zippe and associates first reported on the efficacy of sildenafil in the post-prostatectomy population. In the bilateral nerve-sparing group, the unilateral nerve-sparing group, and the non-nerve-sparing group, 71.7, 50, and 15.4 % of patients achieved successful vaginal intercourse after using a PDE5i, respectively [64]. Age is also an important factor in the efficacy of PDE5i following prostatectomy. In patients who underwent bilateral nerve-sparing surgery under 55 years versus patients older than 55 years, response rates to sildenafil 50 and 100 mg were 80 and 45 %, respectively. Furthermore, sildenafil appeared ineffective in the first 9 months after prostatectomy, and early spontaneous erectile recovery seems indicative of efficacy of sildenafil [65]. These facts illustrate that nerve recovery and nerve preservation both increase efficacy of PDE5i. Subsequent trials testing the potency of vardenafil and tadalafil in the post-prostatectomy population yielded similar results [2].

#### Efficacy Following Radiation Treatment and Androgen Deprivation

Also following radiotherapy, a decreased efficacy of PDE5i is noted. The reduction in efficacy appears to be time

dependent, which points to the progressive nature of neural, arterial, and corporeal changes contributing to ED after radiotherapy. Shortly after the clinical introduction of sildenafil, Zelefsky and colleagues evaluated the efficacy of the drug taken on demand and found significant improvement in erectile function in 74 % of the patients [66]. They further observed an inverse relationship between the response to sildenafil and the degree of post-irradiation ED. While this initial evaluation was highly promising to post-irradiation ED patients, it was not conducted with standardized questionnaires and the follow-up time was limited to one and a half years. With the increasing recognition that ED worsens with time after radiotherapy, less positive results emerged in studies with longer follow-up. Mulhall and colleagues studied the temporal changes in efficacy of sildenafil following pelvic radiation therapy and observed a serial decline in response to sildenafil. They studied patients who underwent either BT or EBRT. The respective response rates in men who underwent BT/EBRT at less than 12, 13–24, and 25–36 months were 76 %/68 %, 54 %/46 %, and 44 %/38 %, respectively. As tachyphylaxis to sildenafil has not been reported, it is probable that the serial decrease in sildenafil efficacy is the result of progression of neural, arterial, and erectile tissue damage [67]. Thus, while PDE5i on-demand are efficacious in patients who suffer from ED following pelvic radiation therapy in the early months post-radiation, patients should be counseled that these beneficial effects putatively are not persisting over time.

As approximately two-thirds of patients receiving ADT have received radiation or prostatectomy prior to hormonal ablation, it is rather complex to evaluate and comment on the isolated effects of ADT on the efficacy of PDE5i in these patients [68]. Another complicating factor in assessing PDE5i efficacy is loss of libido, as few patients seek or desire pharmacological treatment for ED caused by ADT. Diblasio et al. retrospectively studied the efficacy of on-demand PDE5i following either primary or salvage ADT and reported a success rate of 44 % [68].

### Safety and Adverse Events

The safety profile of the currently available PDE5i is excellent, based on postmarketing data and further demonstrated by the recent FDA approvals for daily use of PDE5i. In postmarketing pharmacological surveillance, no increase in myocardial infarction rates in patients who received these agents has occurred compared to expected rates in age-matched populations [18]. In spite of these data, there are certain heart-related precautions in the use of PDE5i. PDE5i are relatively contraindicated in patients with unstable angina pectoris, recent myocardial infarction, certain arrhythmias, and poorly controlled hypertension. Furthermore, patients who are treated with nitrates or nitrate donors should not take PDE5i, and use of PDE5i with certain α-blockers may result in postural hypotension [18]. The most common adverse events from PDE5i are attributable to specific inhibition of PDE5 resulting in vasodilatation in tissues other than the penis and include headache, facial and ocular hyperemia, nasal congestion, myalgia, and back pain. Adverse events account for about 25 % of cases in which PDE5i are discontinued, with the most common reason for discontinuation of PDE5i being lack of efficacy [18]. There have been rare reports of serious adverse events such as seizures, nonarteritic ischemic optic neuritis, and acute hearing loss. While the role of PDE5i in causing these disorders remains a controversial issue, the majority of reports on the topic have been rather anecdotal. Other adverse events can be attributed to cross-reactivity with other PDE isoforms. Vision disturbances, which are believed to result from cross-reactivity of PDE5i against PDE6 (an isoform of PDE that is abundantly present in the cones of the retina), have been reported with PDE5i use. Tadalafil has been shown to cross-react with PDE11 to some extent, although no consequences of this cross-reactivity are currently known. None of the available PDE5i has shown clinically significant cross-reactivity with PDE isoforms other than PDE6 [18].

### Self-Injection Therapy and MUSE®

Penile injection of vasoactive substances has been utilized since the 1980s as a treatment for ED and provides a good safety profile and has a rapid onset of action. The efficacy of injection of intracavernous injection of papaverine was first demonstrated by a French vascular surgeon Ronald Virag in 1982 [69]. An accidental intracavernous injection of that drug during an arterial epigastric cavernous anastomosis, a vascular procedure proposed to treat vasculogenic ED, had produced a rigid erection lasting for 2 h. While Virag and others first employed the substance for diagnostic testing in ED, soon it became the first medical treatment available, whereas before then, ED could only be treated by surgical procedures with rather low success rates. Nowadays, three substances are widely used for intracavernous injection therapy: alprostadil, phentolamine, and papaverine.

The most commonly utilized substance, and currently the only one with FDA approval as a treatment of ED, is prostaglandin E1 (PGE1), or alprostadil. Alprostadil activates adenylyl cyclase, thereby facilitating cleavage of ATP to cAMP, a second messenger with downstream effects analogous to cGMP in the establishment of smooth muscle relaxation (vide supra). Recommended dosages for PGE1 are 5–40 μg. Alprostadil is also available for intraurethral administration (medicated urethral system for erection, MUSE®).

Other drugs which are commonly used for intracavernous injection therapy include phentolamine and papaverine. Phentolamine is a competitive, nonselective α-adrenoreceptor antagonist that acts on both pre- and postsynaptic receptors. In addition, it is believed to open potassium channels,

antagonize endothelin, and activate NOS to some extent [69]. It is not often administered alone but is often used to potentiate the effects of papaverine or PGE1. It is given in dosages ranging from 0.5 to 2 mg.

Papaverine, as discussed above, was the first substance used for intracavernous injection therapy. It is a non-opiate derivate from *Papaver somniferum* (poppy plant) and is a nonselective PDE inhibitor which increases both intracellular cAMP and cGMP. It may also have an additional inhibitory effect on L-type calcium channels. Recommended dosages range from 30 to 110 mg [69]. These three substances can be injected alone, or when limited efficacy is observed, they can be administered in combination (so-called bimix or trimix). Vasoactive intestinal peptide and forskolin are available for intracavernous injection therapy in some countries although their efficacy is rather low and they are typically only used as a component in combination therapy.

### Efficacy

The effects of these vasoactive substances are independent of the NO pathway, and therefore these treatments are particularly useful as a treatment for ED after RP in the case of PDE5i failure. Overall efficacy rates with intracavernous PGE1 therapy are 64–85 % in the post-prostatectomy group [70, 71], while continuation of therapy was 70 % in one small study in the post-radiotherapy population [72]. In patients with extensive fibrosis of the corpus cavernosum and/or extensive corporeal smooth muscle loss following PCa treatment, CVOD may occur, and this may limit the efficacy of intracavernous self-injection therapy. Starting intracavernous injections on a regular basis early after surgery or radiotherapy may help reduce the fibrotic alterations in the erectile tissue and improve response to PDE5i; this is further elaborated in the section on penile rehabilitation therapy.

Costabile and colleagues performed a retrospective review of the MUSE® clinical trial for assessing the efficacy and safety of the drug in post-prostatectomy patients. They found that, of the 384 patients in whom RP was identified as a cause of ED, 70.3 % gained an erection sufficient for intercourse in the clinic and 57.1 % on active medication had sexual intercourse at least once at home [73]. The authors attributed the lower home success rate to the psychological impact of PCa and concluded that the severe neurovascular deficit associated with prostatectomy does not limit the efficacy of the compound. Concerning safety, the percentage of patients with urethral pain/burning was higher in the post-prostatectomy group than in patients with other organic causes of ED.

### Safety and Adverse Events

The major disadvantages of injection therapy include the risk of priapism and variable degrees of pain with injection in 50 % of patients. Patients using injection therapy should undergo a thorough training program prior to initiation of therapy. MUSE may have some side effects in common with intracavernous injection of PGE1 and may also be associated with hypotension, syncope, urethral burning or pain in the patient, and vaginal irritation in the partner. While these therapies provide a valid alternative for patients who do not respond to oral therapy, the self-injection or urethral administration is a major drawback for many patients compared to oral therapy.

## Vacuum Erection Device

The concept of a vacuum erection device (VED) dates back to the nineteenth century when an American physician named John King described improvement of erectile function by applying a small vacuum pump. Only in 1982, the first FDA-approved VED was introduced on the market. Modern-day VEDs are composed of a plastic cylinder, whose lower edge is made airtight with the application of lubricant gel, is then applied over the penis, and firmly pressed against the body. Following application of the cylinder, a vacuum is created within the cylinder via a pump. The device thus creates negative pressure around the penis, thereby initiating passive engorgement of the sinusoidal spaces and creating an erection. Maintenance of erection is facilitated by application of a rubber cuff worn around the base of the penis. Although effective in up to 90 % of patients, the use of a vacuum device might be perceived as disruptive, especially by younger men [63]. The erection that is achieved with a VED is not a natural-like erection. Because the constriction ring can only be applied at the base of the penis, the crura do not get engorged and the penis pivots at the level of the constriction ring, causing some degree of instability and often needing manual assistance when inserting the penis into the vagina. Due to the fact that blood is passively trapped, the subcutaneous tissues also become engorged with venous blood and the penis has a cyanotic, cool aspect and an increased glans volume. The constrictive band can cause obstructed ejaculation which can be perceived as uncomfortable. This is not an issue in the post-prostatectomy patients as they develop anejaculation following surgery. The unnatural aspect of the erection and the discomfort of the device cause high drop-out rates up to 60 %. Of those who do continue usage, satisfaction rates range from 65 to 83 % in the largest series [74].

### Safety and Adverse Events

Local side effects are relatively minor and include bruising and some discomfort. It is advised to limit the use of the constriction band to 30 min to avoid skin necrosis. Contraindications to VCD use include bleeding disorders and the use of anticoagulants [63].

## Penile Prosthesis Implantation

Surgical treatment of ED in PCa patients is indicated in patients who have the desire to achieve erections and in whom conservative pharmacotherapy has failed, or in those

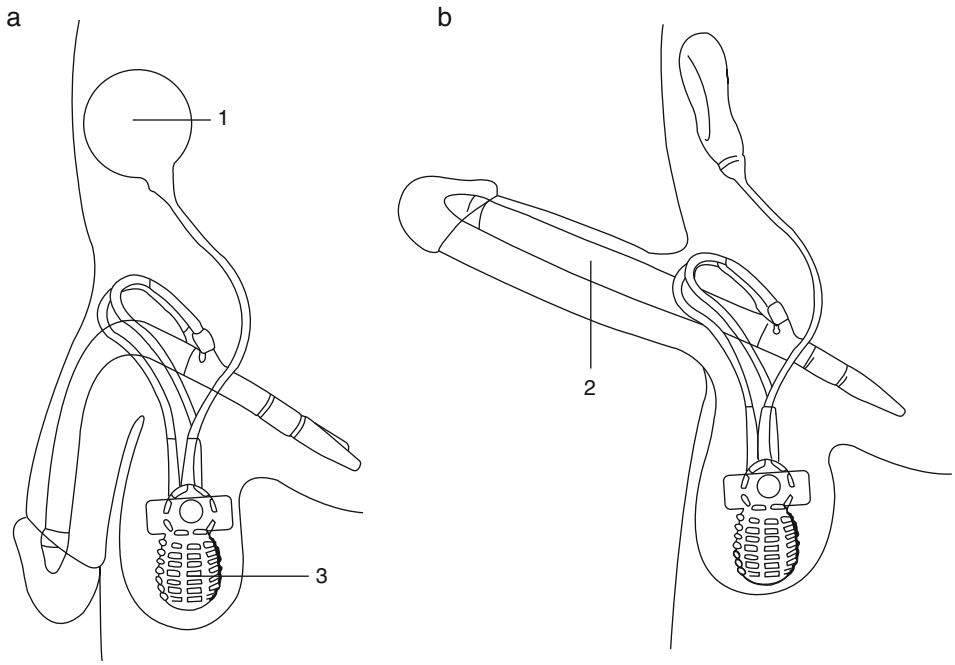


**Fig. 81.7** Three-piece inflatable penile prosthesis. Figure shows a three-piece inflatable penile prosthetic device. (**a**) In flaccid, or deflated, position. (**b**) After inflation, in erect position. *1*: reservoir, which is implanted in the retropubic space. *2*: inflatable cylinders, implanted in the corpora cavernosa. *3*: pump, placed in the scrotum

declining pharmacotherapy. The penile prosthesis has been the only efficacious treatment option for ED for a long time before pharmacological treatments such as intracavernous self-injection therapy and PDE5i became available. Early implants were wooden splints that supported the penis in a semirigid state, or wooden pipes, which were mainly intended to help patients after traumatic penile amputation facilitate urination in the standing position, and not for the treatment of ED. The first real implant for the treatment of ED consisted of rib cartilage, which unfortunately had limited long-term success as natural resorption of the graft occurred [75]. The first prosthesis surgery consisted of the intracavernosal implantation of acrylic rods by Egyptian surgeon GE Beheri [75], followed by the introduction of the three-piece inflatable device in 1973 by Scott and colleagues. Implantation of the inflatable device required more extensive surgery and entailed higher chances of mechanical failure but was revolutionary as the result approximated the natural physiologic state better than all other available modalities [75].

Currently, there are three types of penile prosthesis: 2- or 3-piece inflatable devices, semirigid devices, and soft-silicone devices. The latter device is being abandoned as it was a supportive prosthesis and patients with partial ED now commonly respond to the now-available pharmacotherapy. The three-piece inflatable prosthesis is currently the preferred device and consists of two inflatable rods, connected to a pump device which is placed in the scrotum and a reservoir which is placed in the preperitoneal space in the lower abdomen (Fig. 81.7). Three-piece penile implants are placed under general or regional anesthesia. A short-acting spinal is ideal for the procedure, as local anesthesia is inadequate for reservoir placement [75]. The semirigid (malleable) device is indicated in patients with limited manual dexterity and can be used when the patient is unable to undergo spinal or general anesthesia, as the corpora cavernosa and the skin incision can be anesthetized locally. Surgical implantation of penile prostheses can be carried out using a variety of surgical approaches. While malleable prosthesis can be implanted through a distal penile approach, two- or three-piece devices can be implanted using either an infrapubic or a penoscrotal approach. There does not appear to be a clear advantage in either outcome, infection rate, or patient satisfaction for either approach [75]. Both patient and partner satisfaction are very high, and satisfaction rates reach 90–98 % for the three-piece inflatable devices [75]. Careful counseling before placement of a penile prosthesis is of capital importance and limits postoperative dissatisfaction issues.

### Safety and Complications

There are a number of intra- and early postoperative complications. These include corporal crossover of rods or cylinders and corporal and urethral perforation. While the latter is rather rare, it is vital that the surgeon recognizes these events during surgery. Superficial wound separation and/or infection and scrotal hematoma are the most common complications in the early postoperative phase. Also in the long term, several complications of penile prosthesis implantation can be observed. The most common long-term complication is mechanical failure. Currently implanted prosthesis has reported survival rates of approximately 60 % at 15 years [75]. Infection of the prosthesis is the bane of genitourinary prosthetic surgery and occurs in approximately 1–2 % of the

patients [75]. However, these percentages are decreasing due to novel coating techniques. These coatings consist of a hydrophilic layer that significantly enhances antibiotic coating of the device surface following immersion in an antibiotic solution. The prostheses are coated with polyvinylpyrrolidone, a hydrophilic substance that reduces bacterial adherence and absorbs and elutes the antibiotics which the device is immersed in intraoperatively [76]. The operating surgeon thus has the ability to choose appropriate antibiotics for device immersion. Another long-term complication is prosthesis or reservoir erosion although this is quite rare in three-piece devices [75]. Bothersome long-term effects of penile prosthesis placement are autoinflation, which can occur during increases of the intra-abdominal pressure, and downward drooping of the glans due to inappropriately sized implant cylinders, inadequate distal corporal dilation, or a constitutionally hypermobile glans. This effect has been termed supersonic transport (SST) deformity, in analogy with the tip of the concorde airplane. This SST deformity can be bothersome or esthetically disturbing only, or may lead to difficulty with penetration or irritation of tissue overlying the ends of the corporal body, in which corrective surgery is indicated. Some patients also complain of a lack of glandular engorgement during erection. This has been successfully treated with concomitant PDE5i therapy or MUSE pellet insertion.

#### Timing of Penile Prosthesis Implantation

In the adequately counseled patient undergoing RP without the option of sparing the neurovascular bundles, penile prosthesis implantation at the time of prostatectomy has been suggested. In the first published series on concomitant prosthesis surgery and RP, an additional operative time of 82 min was noted, but no differences in postoperative morbidity, analgesia use, blood loss, or hospital stay were observed compared to patients who underwent prostatectomy only [77]. The infection rate of the combined procedure was comparable to those in the literature for penis prosthesis implantation alone. In a later report by the same group, overall and sexual quality of life after the combined approach was higher than in those patients who underwent non-nerve-sparing RP, but not significantly better than those who underwent nerve-sparing prostatectomy [78]. Thus, simultaneous placement of a penile prosthesis appears feasible in well-informed patients who are not eligible for nerve-sparing surgery.

Most penile prosthesis are placed some time following surgery or radiotherapy for PCa and those placed following prostatectomy compromise between 9 and 25 % of all penile implants [79]. Safety and success of penile implantation surgery following prostatectomy were similar to those in ED of other origin [79]. Prosthesis implantation following RP and radiotherapy can be somewhat complicated by fibrosis of the corpora cavernosa which complicate the insertion of the dilating rods. Timing is essential in planning penile prosthesis surgery following prostatectomy as (either or not spontaneous) erectile function continues to improve until 24 months after the initial surgery. Thus, conservative treatment of ED during this initial 2 years following surgery is warranted. On the other hand, penile prosthesis placement can be discussed and considered in patients with significant ED not responding to intracavernous injections or severe ED at 12 months following surgery [79]. This timing is of less note in patients who received pelvic irradiation as ED develops rather progressively following this treatment without spontaneous recovery some time following irradiation. In a retrospective study performed by Dubocq and colleagues, it was concluded that penile prosthesis surgery can be safely and effectively performed after radiation therapy with minimal intraoperative and postoperative complications and an excellent patient satisfaction rate [80].

## Penile Rehabilitation Therapy Following Radical Prostatectomy

### Rationale

The finding that poor oxygenation of the erectile tissue induces cavernosal structural damage which causes ED following RP led to the hypothesis that preserving the oxygenation of the corpora cavernosa by improving blood flow might improve ED [23]. This is in analogy with the paradigm "use it or lose it" which is not only used for penile health but also in brain (cognition and memory), skeletal muscle following nerve injury, and various other organ systems. The rationale behind the hypothesis of penile rehabilitation therapy is that local or systemic therapies can minimize penile smooth muscle alterations and the development of fibrosis and subsequent CVOD after CN injury. If the erectile tissue can be maintained in good health while the CNs regenerate, ED may be prevented, or at least response to pharmacotherapy may improve. Oxygenation of the corpus cavernosum is achieved by erection, and therefore the accent of research has been on erectogenic drugs such as vasoactive substances and PDE5i.

Penile rehabilitation therapy following RP is gaining popularity among healthcare providers who follow up prostatectomy. In a recent survey among members of the international society for sexual medicine, 87 % of all respondents used some form of penile rehabilitation therapy. As part of the primary rehabilitation strategy, 95 % used PDE5i, 75 % used intracavernosal injections, 30 % used vacuum device, and 9.9 % used MUSE®. Fifty-four percent commenced rehabilitation immediately/just after urethral catheter removal, and 37 % within the first 4 months after RP [81]. Despite many well-designed studies attempting to demonstrate

efficacy of rehabilitative approaches, there currently is not enough evidence to incorporate it into the standard of care in the post-prostatectomy patient. On the other hand, no significant harm of rehabilitation has been demonstrated provided the patients understand the side effects and costs of the proposed treatment [82]. It is generally assumed that penile rehabilitation should be initiated early after the surgery, and therefore it is essential to discuss the option of a penile rehabilitation regimen with the patient prior to the surgery. As there is no clear benefit of one strategy over another, it is up to the discretion of the patient, supported by objective information provided by the surgeon, what rehabilitation strategy is most appropriate in each individual situation.

## Alprostadil

Montorsi and colleagues were the first to clinically test the concept of penile rehabilitation following RP. They conducted a pioneering clinical study on the effects of intracavernosal injections of alprostadil early after nerve-sparing RP. Thirty patients were randomized to alprostadil injections three times/week for 12 weeks (15 patients) or observation (15 patients). Patients were then evaluated 3 months following treatment. Twelve of fifteen men completed treatment. Of these men, eight (67 %) reported the recovery of spontaneous erection sufficient for satisfactory sexual intercourse, compared with three patients (20 %) in the observation arm [83]. The authors concluded that early use of alprostadil injections significantly increases the recovery rate of spontaneous erections after nerve-sparing RP. Notable limitations were that preoperative parameters of erectile function were not assessed and that this study was performed before the routine use of validated questionnaires. Additionally, the short duration of follow-up limits any conclusions regarding long-term impact of therapy [84]. Gontero et al. investigated the timing of alprostadil injections in non-nerve-sparing RP patients and concluded that earlier initiation of alprostadil injections resulted in a more rapid return of penile tumescence. Alprostadil injections produced valid erectile responses in a significantly higher proportion of patients when started within month 3 after the operation as tested by ultrasound evaluation [85].

Mulhall and colleagues have proposed a penile rehabilitation regimen combining PDE5i and intracavernous alprostadil. They studied 132 men who either opted or did not for penile rehabilitation post-RP. Patients were initially challenged with sildenafil. If there was efficacy of sildenafil (60 % or more rigidity), they were instructed to continue using sildenafil to obtain at least three erections/week. If an insufficient response was noted, patients were taught intracavernous injections and instructed to self-inject at least three times/week. Sildenafil failures were instructed to challenge themselves every 4 months after surgery to see if they had become responders. If this occurred, they were instructed to cease injections and start sildenafil three times/week. At 18 months postoperatively, 52 % of the rehabilitation group versus 19 % of the nonrehabilitation group were capable of having medication-unassisted intercourse. Furthermore, response to both sildenafil and intracavernous injections increased when patients followed the proposed regimen [86].

Raina and colleagues evaluated the value of early initiation of MUSE® as a penile rehabilitation strategy. In a prospective study of 91 sexually active men who had a nerve-sparing RP for PCa, 56 were treated with MUSE (125 or 250 μg three times/week for 6 months), while the remaining 35 had no erectogenic aids, except as necessary when attempting sexual activity. Self-administration of MUSE was initiated approximately 3 weeks after surgery. Of patients who completed the 6-month course of MUSE®, half were able to have successful vaginal intercourse by the end of treatment. Most of these patients reported the recovery of spontaneous erections and required no additional erectogenic aids for successful intercourse. All 56 patients who received MUSE® reported mild penile aching or urethral burning, and of these, 32 % discontinued treatment. In the untreated control group, 37 % regained erections sufficient for vaginal intercourse at the 6-month follow-up [87]. McCullough et al. directly compared the ability of alprostadil and a sildenafil to enhance penile recovery subsequent to bilateral nerve-sparing RP. They concluded that the use of nightly subtherapeutic intraurethral alprostadil was well tolerated after RP, and the benefit of return of erectile function of nightly sildenafil citrate and subtherapeutic intraurethral alprostadil appeared to be comparable within the first year of surgery [88].

## Selective Phosphodiesterase-5 Inhibitors

Padma-Nathan and colleagues reported the results of a randomized, placebo-controlled study examining the benefits of nightly administration of sildenafil during the postoperative period following bilateral nerve-sparing prostatectomy. This study included 76 men with normal preoperative erectile function. Forty-eight weeks after surgery, 27 % of patients receiving sildenafil self-reported return of spontaneous erectile function, compared with 4 % in the placebo group [89]. Although this study has been criticized for the seemingly low percentage of men considered as responders in the placebo arm, the criteria for being considered a responder were stringent. This study represents the first placebo-controlled trial suggesting benefit of oral PDE5i therapy in improving the return of spontaneous erections [84]. In a subanalysis of this study, the self-reported results were corroborated by nocturnal penile tumescence data. Postoperatively, rapid and

profound reduction in nocturnal erectile function was noted in all groups. There was a gradual dose-dependent improvement in base and tip rigidity in the sildenafil groups but little improvement in the placebo group [90].

Montorsi and collaborators initiated a trial to test the efficacy of nightly vardenafil as a mode of penile rehabilitation. This was a randomized, double-blind, double-dummy, multicentre, parallel group study conducted at 87 centers in Europe, North America, and South Africa. A total of 628 men were randomized to placebo, nightly vardenafil, or vardenafil on-demand for 9 months, followed by a 2-month washout and an optional 2-month open-label period. Following 9 months of treatment, on-demand dosing was efficacious, but nightly vardenafil for the purpose of penile rehabilitation was not efficacious [91]. This well-designed study provides a cautionary note for the present enthusiasm of PDE5i inhibitors for penile rehabilitation therapy [84].

### Vacuum Erection Device

Although application of the VED results in increased blood flow in the penis, this blood is mainly venous in origin, and it has been shown that after application of the constrictive band at the base of the penis, the penis even is in a relatively ischemic condition [92]. Thus, application of a VED goes against the generally assumed principle of penile rehabilitation which is to keep the penis oxygenized. Nevertheless, some reports have been published on the effects of VED on erectile function following RP. Raina et al. reported on 109 men post-prostatectomy who applied the device daily for 9 months starting 1-month postoperative and reported a vaginal penetration rate of 17 % and 11 % in the treatment and control groups [93]. However, they also reported a spontaneous erection rate of 32 and 37 % in the treatment and control groups, respectively; patients self-selected their arm of the study, and results were dependent on responses to mailed questionnaires [82]. Kohler and colleagues randomized 28 men to early or late initiation of VCD application [94]. They demonstrated that VED therapy is at least well tolerated, may minimize length loss, and provides patients with an active way to participate in their rehabilitation early post-prostatectomy with no systemic effects and few local side effects [82].

## Penile Rehabilitation Following Radiation Therapy

Although the mechanisms behind ED following pelvic radiation therapy have been less characterized than following RP, some studies have investigated whether (on-demand) administration of PDE5i following prostate irradiation may help to prevent the development of ED over time. Incrocci et al. have reported efficacy of sildenafil and tadalafil in randomized trials for patients complaining of ED after radiotherapy with 57 and 55 % of patients able to have successful intercourse, respectively [95, 96]. A recent open-label extension of the blinded trial with tadalafil reported improvement in erections in 84 % of patients and successful intercourse by 69 %. IIEF scores between the double-blind phase and open-label extension phase were comparable [97, 98].

## Current and Future Preclinical Research in Post-prostatectomy Erectile Dysfunction

While advancing anatomical knowledge and technology have decreased the rates of ED following RP, it remains challenging to fully preserve potency in these patients. As illustrated above, in the past decade, both clinical and preclinical research efforts have focused on stimulating nerve regeneration and prevention of corpus cavernosum fibrosis with limited success. In the latest years, preclinical researchers have mostly focused on nerve regeneration either by the use of growth factors or neuromodulatory compounds. Other promising fields of research, which are expanding very quickly, are stem cell technology and other regenerative therapies such as gene therapy. Unfortunately, due to uncertainties in pathophysiology of post-radiation ED, basic research on recovery of erectile function is lacking. It is becoming increasingly clear that preclinical pathophysiological studies need to be initiated to better understand post-irradiation ED.

### Neuromodulation

The rationale behind neuromodulatory therapies is that if CN regeneration following neuropraxia or neurotomy can be enhanced, the time frame to develop secondary penile changes narrows, and thus erectile tissue architecture is better preserved. On the one hand, various groups have shown in vitro as well as in vivo that the administration of nerve-specific or general growth factors enhances neuroregeneration and results in better recovery of erectile function following CN injury in animal models. Growth factors that have shown beneficial effects on CN regeneration and/or erectile function in animal models of post-prostatectomy include erythropoietin, growth hormone (GH) and insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), glial-cell-line-derived neurotrophic factor (GDNF), growth differentiation factor-5 (GDF-5), and neurturin [23]. On the other hand, stimulation of nerve regeneration is also seen with compounds that modulate the inflammatory reaction

following nerve injury. These compounds include neuroimmunophilin ligands and cytokine modulators. Immunophilins are a family of intracellular receptors that bind with high affinity to naturally occurring ligands produced by microbes. Initially isolated for their potent immunosuppressant activity, cyclosporine A and FK506 are among the most well-known and extensively studied immunophilin ligands. FK506 was found to protect erectile function following nerve injury. Immunohistochemical evaluation of a CN crush model treated with FK506 exhibited preserved peripheral unmyelinated axon integrity and near-normal nerve microarchitecture in a bilateral nerve crush injury rat model [99, 100]. A clinical trial has now been conducted with FK506 in patients who underwent RP, but the results have not been published at the time of writing of this textbook. Nonimmunosuppressant immunophilin ligands have recently been developed: GPI1046 by Guilford Pharmaceuticals Inc., MD, USA, and FK1706 by Astellas Pharmaceuticals Inc., IL, USA. Both compounds have been linked to preservation of erectile function, increased nerve regeneration, and preserved neural anatomy in the penises of CN-injured rats [23]. Albersen et al. investigated the effects of the anti-inflammatory cytokine-modulator pentoxifylline and found recovery of erectile function following CN injury in treated rats which was explained by preserved axonal integrity in the CN, preserved nNOS expression, and preservation of the corpus cavernosum architecture. The latter may be attributed to the inhibitory effects of pentoxifylline on TGF-β. In addition, pentoxifylline was found to exhibit direct neurotrophic effects in vitro [21]. The clinical availability and long-standing safety track record of this compound merits application in penile rehabilitation studies following RP, which have been initiated in the USA at the time of writing.

## Stem Cell Treatment

Although the number is still limited, some studies on stem cell therapy for ED have recently been conducted. The initial purpose of stem cell application was the restoration of host neurons and or penile smooth muscle cells by replacement with stem cells. Bochinski et al. used embryonic stem cells that differentiated along the neuronal cell line, which they injected into the corpus cavernosum of a rat bilateral CN crush injury model. They noted recovery of erectile function and a greater degree of neuroregeneration of nNOS-containing nerve fibers in the stem cell treatment group [101]. No incorporation or engraftment was seen in the erectile tissue, the location where the cells were transplanted. Mesenchymal stem cells are more likely making their way to clinical application due to the absence of ethical limitations. Fall et al. were the first to successfully improve erectile function using mononuclear bone-marrow-derived cells [102]. The injected cells appeared to possess both anti-apoptotic and neurotrophic effects. These results were corroborated by Kendirci et al., who transplanted p75 growth factor receptor-selected bone-marrow-derived mesenchymal stromal cells and also observed marked improvement of erectile function [103]. Both studies were not able to deliver proof of incorporation of stem cells in the host tissue. Kendirci and colleagues implied that the effects of stem cells may be mediated by paracrine signaling, and they supported this hypothesis by demonstrating a high secretory capacity of mesenchymal stem cells compared to fibroblasts [103, 104]. In our lab, we have explored the capacity of mesenchymal stem cells derived from adipose tissue which is, in contrast to bone marrow, easy to harvest, abundant, and contains many more stem cells per ml of tissue. In a study investigating the efficacy of adipose-tissue-derived stem cells (ADSC) in CN injury, we demonstrated preservation of potency which was explained by antifibrotic, cytoprotective, antiapoptotic, and neuroregenerative effects of stem cells. Smooth muscle content and nNOS expression in the penis were preserved, and fibrosis was prevented [32]. Additional experiments involving injection of ADSC lysate replicated these findings and support the hypothesis that stem cells may exert their beneficial effects on CN injury not by incorporation in diseased host tissue and replacing diseased cells but rather secrete certain molecules that interact with the host tissue. Fandel et al. completed this hypothesis by showing a time-dependent decrease of stem cells in the corpus cavernosum, while erectile function was preserved [105]. In addition, they showed a temporary increase in stem cells in the major pelvic ganglion, where the CN originates [105]. Bella et al. were able to demonstrate in vitro neurite outgrowth from the major pelvic ganglion of the rat induced by adult adipose-tissue-derived stem cells, which were not induced towards a specific neuronal cell line prior to administration [106]. Zhang et al. showed that LIX, a chemokine secreted by ADSC, may be responsible for these neurotrophic effects [107]. This body of evidence suggests that injected stem cells "home" to the injured major pelvic ganglion exert neurotrophic effects by secreting growth factors and thus preserve erectile function following CN injury. Whether there are direct protective effects on the erectile tissue, or whether this is preserved secondary to enhanced nerve regeneration, is unknown. All preclinical trials using stem cells for CN injury have shown impressive results, and therefore stem cells may hold great potential for future patients suffering from ED following PCa treatments. What the effects of these stem cells are on residual cancer cells are currently unknown and needs further clarification. Clinical trials involving the application of mesenchymal stem cells for ED following RP are being initiated at the time of writing of this textbook.

**Conclusions**

ED following treatment of PCa is a frequent problem compromising health-related quality of life in PCa survivors. Increasing insights in the pathophysiology of ED following PCa treatments have fueled the use of penile rehabilitation schedules which, although promising, have not brought the improvement that was hoped for. Novel therapeutic strategies such as neuromodulation and the use of cellular therapy are currently being investigated in various institutions worldwide and may hold great promise for those who survive PCa but are rendered impotent following treatment.

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# Immediate/Early Surgical Complications

# 82

Thomas J. Walton and Declan G. Murphy

## Complications of Radical Prostatectomy

Open radical retropubic prostatectomy (RRP) represents an effective means establishing cancer control in most men with organ-confined prostate cancer [1]. Despite an improved understanding of male pelvic anatomy [2] and advances in surgical technique and perioperative care [3], the procedure remains associated with significant morbidity. Attempts to reduce levels of intraoperative bleeding, analgesic requirement, and hospital stay have led to the introduction of laparoscopic radical prostatectomy (LRP) and more recently robot-assisted laparoscopic radical prostatectomy (RALP). Laparoscopic radical prostatectomy was first performed by Schuessler and colleagues in 1992 via a transperitoneal approach [4]. After initial enthusiasm, particularly in European centers [5, 6], it quickly became apparent that the procedure was technically demanding and associated with an extended learning curve, which has limited its widespread adoption by urologic surgeons. Robot-assisted laparoscopic prostatectomy, first reported by Binder and associates in 2001 [7], has a number of advantages over a purely laparoscopic approach, including three-dimensional vision, optical magnification, and enhanced instrument articulation, leading to its replacement of laparoscopic radical prostatectomy as the minimally invasive procedure of choice in a number of countries.

Complications of radical prostatectomy may be divided into medical and surgical, intraoperative, and postoperative. Postoperative complications may be further divided into early (occurring up to 30 days from the date of surgery), intermediate (between 31 and 90 days from the date of surgery), and late (occurring more than 90 days from the date of surgery). The degree of severity of a particular complication may also be recorded, along with an indication of the requirement for subsequent intervention. Historically, the reporting of morbidity after radical prostatectomy has been a heterogenous affair, with divergent outcome measures and differing definitions of individual complications, making it difficult to compare results between centers [8]. Very often, perioperative complications have been overlooked entirely in favor of the "trifecta" outcomes of margin status, potency, and continence [9]. In 2002, Martin et al. recommended ten essential criteria necessary for the reporting of complications after surgical procedures, including an indication of methods of data accrual, definition of complications, a minimum data set of procedure-specific complications, severity grading, morbidity and mortality rates, length of hospital stay, inclusion of outpatient data, and duration of follow-up [10]. Very few studies in the literature specific to radical prostatectomy have adhered to these principles, although a number of more recent series of laparoscopic radical prostatectomy [11–18] and robot-assisted radical prostatectomy [15, 19–23] have reported standardized complications according to the validated classification system of Clavien et al [24].

Most of the complications associated with radical prostatectomy are common to RRP, LRP, and RALP, respectively, although there are a number of unique complications specific to minimally invasive procedures which are

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**Table 82.1** Perioperative complications of radical prostatectomy

| Perioperative complications of open and minimally invasive radical prostatectomy |
|---|
| *Medical* |
| Cardiovascular |
| Myocardial infarction/ischemia |
| Arrythmia |
| Cerebrovascular accident/transient ischemic attack |
| Deep vein thrombosis |
| Pulmonary embolus |
| Pulmonary |
| Respiratory distress |
| Pneumonia |
| Gastrointestinal |
| GI bleed |
| Pancreatitis |
| Renal |
| Acute renal insufficiency[a] |
| *Surgical* |
| Urological |
| Urinoma/urine leak |
| Bladder neck contracture (anastomotic stricture) |
| Urinary tract infection |
| Urinary retention |
| Urethral stricture |
| Ureteric injury/hydronephrosis |
| Bladder calculus/suture/migrated clip |
| Catheter related (defective, inadvertent removal, retained) |
| Lymphovascular |
| Hemorrhage/hematoma |
| Lymphocele |
| Infectious |
| Infected hematoma/urinoma |
| Gastrointestinal |
| Rectal injury |
| Rectourethral fistula |
| Small bowel/colonic injury |
| Ileus |
| Neuromuscular |
| Obturator nerve injury/palsy |
| Femoral nerve injury/palsy |
| Meralgia paresthetica[b] |
| Inguinal hernia |
| Wound complication |
| Wound infection |
| Wound seroma |
| Wound dehiscence |
| Incisional hernia |
| Port-site hernia |
| Retained drain |
| Miscellaneous |
| Robot malfunction |

[a]Typically defined as postoperative serum creatinine >1.5 mg/dL
[b]Neuropraxia involving the lateral cutaneous nerve of thigh, typically due to entrapment as it passes under the inguinal ligament adjacent to the anterior superior iliac spine

**Table 82.2** Early, intermediate, and late postoperative complications of radical prostatectomy

| Timing of complication | Medical | Surgical |
|---|---|---|
| Early (≤30 days) | MI/ischemia | Urinoma/urine leak |
| | DVT/PE | Hemorrhage/ hematoma |
| | Pneumonia/respiratory distress | Rectal injury |
| | Acute renal insufficiency | Lymphocele |
| | | Urinary retention |
| | | UTI |
| Intermediate (31 to 90 days) | DVT/PE | Bladder neck contracture |
| | | Urethral stricture |
| | | Lymphocele |
| Late (>90 days) | – | Bladder neck contracture |
| | | Urethral stricture |
| | | Incisional hernia |
| | | Inguinal hernia |
| | | Erectile dysfunction |
| | | Sphincter weakness incontinence |

*MI* myocardial infarction, *DVT* deep vein thrombosis, *PE* pulmonary embolus, *UTI* urinary tract infection

discussed in the relevant sections below. Table 82.1 lists reported perioperative complications associated with open and minimally invasive prostatectomy. The list is not exhaustive but covers the majority of early and intermediate complications reported in the literature to date. Table 82.2 highlights the most commonly reported medical and surgical complications after radical prostatectomy, stratified according to time of onset after surgery. In subsequent sections of this chapter, the incidence, risk factors, and management of the most common and serious complications of ORP, LRP, and RALP will be discussed. Although undoubtedly common and serious, a discussion of the late complications of erectile dysfunction and postprostatectomy incontinence is beyond the scope of this chapter and is discussed elsewhere in the text.

## Complications of Open Radical Retropubic Prostatectomy

Various single-center [17, 25–42] and multicenter studies [43–47] have reported perioperative outcomes following open radical prostatectomy. As already discussed, the studies vary considerably in terms of reported outcomes, highlighting inherent problems with retrospective data accrual and a lack of standardization. Since Dindo reported the preeminent modification of the Clavien classification in 2004 [24], only three studies have reported standardized perioperative

outcome measures after ORP [17, 27, 42]. One notable exception is the retrospective study of 4,592 patients undergoing open and minimally invasive prostatectomy at Memorial Sloan-Kettering Cancer Center, reported by Rabbani in 2010 [17]. In this study, medical and surgical complications were identified in 8.8 and 18.7 % undergoing open radical prostatectomy. The overall mortality was reported as 0.1 %, with half attributable to cardiovascular causes.

Table 82.3 shows published RRP series with more than 250 patients for whom perioperative complications have been recorded. Weighted mean frequencies have been calculated for each parameter using patient number as the weighting factor. As befits the nature of outcomes reporting, many center have updated their results over the years, which means that cumulative analyses can be susceptible to bias introduced by "double counting"; therefore, only the most recent study from a particular institution was included unless it was irrefutable that the study contained different patients or that different outcomes were reported. As shown, the overall complication rate was 18.0 %, with a mortality of 0.13 %. These figures are very similar to the study reported by Rabbani et al. [17] and compare favorably with data obtained from published multicenter studies [43–47]. In the largest study of its type to date, Lu-Yao and associates used US Medicare claims data to report the outcomes of 93,986 patients undergoing open retropubic radical prostatectomy from 1991 to 1994 [47]. Of these, 28.8 % developed a complication within 90 days of surgery, with a 30-day mortality of 0.7 %. Similar figures have been reported in other North American multicenter studies [43–46]. The reasons for a discrepancy between multicenter and single-center studies are not clear, but notwithstanding important recording and reporting biases with undercounting and a lack of systematic measurement, the increased complication rates identified from Medicare and SEER databases may identify readmissions to local hospitals which would not necessarily appear in data from the publishing cancer center. This discrepancy is further compounded by billing practices in the United States where upcoding of nonclinically significant complications can result in higher reimbursements. Another explanation is that most multicenter studies report data from early studies which, as shown in Table 82.3, are associated with higher complication rates.

## Intraoperative Complications

The most common intraoperative complication encountered at the time of radical prostatectomy is significant bleeding. Other serious complications comprise rectal injury, ureteric, and nerve injuries. The incidence, mechanisms of injury, and risk factors along with a brief summary of the management of each are discussed below.

### Bleeding

Historically, the retropubic approach to the prostate has been associated with a formidable risk of uncontrolled hemorrhage. In 1979, Reiner and Walsh described the anatomy of Santorini's plexus and a technique for its control [3], which for the first time afforded surgeons the prospect of a relatively bloodless field in which to perform an anatomical dissection of the prostate. Widespread adoption of the technique led to reduced intraoperative blood loss, as reported by a number of early studies comparing DVC control vs. no control [48–50]. Despite this advance and further improvements in monopolar and bipolar diathermy, ultrasonic dissection, and the use of tissue sealants, bleeding at open retropubic radical prostatectomy typically remains substantial. Multiple single-site retrospective series have reported the incidence of bleeding complications during open radical prostatectomy (Table 82.3). Estimated blood loss (EBL) and transfusion rate are the most commonly reported parameters, although both are subject to significant biases [51]. EBL is influenced by a number of factors, including adequacy of suction, contamination with urine, and swab/pack weighing, whereas indications for transfusion vary widely between surgeons, anesthesiologists, and departments. In order to limit such biases, a number of studies have reported actual blood loss [51] or more commonly a fall in serum hematocrit [28, 32], although this latter parameter is also influenced by intravascular volume. Table 82.3 shows contemporary published series with more than 250 patients in which either EBL or transfusion rate have been reported. The weighted mean EBL is 943 mL, with an associated transfusion rate of 31.8 %. While appropriate correction of a low hematocrit is necessary to maintain hemodynamic status and prevent ischemic injury, it must be weighed against the risks of blood transfusion [29]. Even utilizing preoperative autologous blood donation, erythropoietin stimulation, acute normovolemic hemodilution [52], delayed intraoperative hydration [53], and intraoperative cell salvage, rates of allogenic (homologous) blood transfusion remain substantial. The weighted mean allogenic transfusion rate shown in Table 82.3 is 10.7 %. It is worth pointing out that this figure is derived from data published by major tertiary and quaternary cancer centers: it is possible that in smaller centers with reduced facilities for preoperative autologous blood donation and intraoperative cell salvage, allogenic transfusion rates are significantly higher. Contemporary factors associated with an increased risk of bleeding at open radical prostatectomy comprise large prostate size [29, 42, 54–56], high BMI [26, 42, 57], transurethral surgery [58], and the performance of pelvic lymph node dissection [42]. Low annual surgeon case volume is also a reported risk factor for increased intraoperative hemorrhage [29, 59].

**Table 82.3** Perioperative complications in open radical prostatectomy series with more than 250 patients

| | | | | Intraoperative complications (%) | | | | | | Postoperative complications (%) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference[α] | Date | Center | *n* | EBL | T/F | All. T/F | Rectal | Ureter | Nerve[β] | Bleed | Lymph | DVT/PE[γ] | Urinoma leak | BNC | Overall (%) | Mortality (%) |
| *Single-center studies* | | | | | | | | | | | | | | | | |
| McLaren et al. [60] | 1993 | Rochester, MN | 2,212 | – | – | – | 1.2 | – | – | – | – | – | – | – | – | – |
| Zincke et al. [41] | 1994 | Rochester, MN | 1,728 | 600 | 31.0 | – | 0.6 | – | – | – | – | 1.1/0.75 | – | – | – | 0.0 |
| Hautmann et al. [31] | 1994 | Ulm, Germany | 418 | 900 | – | – | 2.9 | 0.2 | – | 5.7 | 6.6 | 1.7/0.9 | 5.7 | 8.6 | 43.5 | 1.2 |
| Dillioglugil et al. [30] | 1997 | Houston, TX | 472 | – | 28.6 | 9.3 | 0.6 | 0.2 | 0.2 | – | 1.1 | 1.3/1.1 | 0.6 | – | 31.2 | 0.4 |
| Lepor et al. [35] | 2001 | New York Uni., NY | 1,000 | 813 | – | 9.7 | 0.5 | 0.1 | 0.1 | 0.5 | 0.1 | 0.2/0.4 | 0.1 | 1.0 | 6.7 | 0.1 |
| Augustin et al. [25] | 2003 | Hamburg, Germany | 1,243 | 1,284 | 29.1 | 6.1 | 0.2 | 0.3 | 0.1 | 1.1 | 0.6 | 1.2/0.2 | 12.6 | – | 19.8 | 0.0 |
| Dash et al. [29] | 2004 | Ann Arbor, MI | 1,123 | 953 | 9.3 | 3.8 | – | – | – | – | – | – | – | – | – | – |
| Chang et al. [26] | 2004 | Nashville, TN | 436 | 603 | 4.8 | 4.8 | – | – | – | – | – | – | – | – | – | – |
| Kundu et al. [34] | 2004 | Chicago, IL | 3,477 | – | – | – | – | – | 0.1 | – | 0.2 | 1.3 | – | 2.7 | 9.0 | – |
| Sacco et al. [38] | 2006 | Padova, Italy | 985 | 750 | – | – | – | – | – | 9.8 | – | – | – | 5.1 | – | – |
| Nelson et al. [36] | 2007 | Nashville, TN | 374 | – | – | – | – | – | – | – | 0.6 | 2.1/0.0 | 1.0 | – | 15.0 | – |
| Touijer et al. [40] | 2008 | MSKCC, NY | 818 | 1,267 | 49.0 | 15.5 | – | 0.3 | – | – | – | 0.7 | – | 1.4 | 6.6 | 0.1 |
| D'Alonzo et al. [28] | 2009 | Durham, NC | 280 | 1,087 | 24.0 | – | – | – | – | – | – | – | – | – | – | – |
| Krambeck et al. [33] | 2009 | Rochester, MN | 564 | – | 13.1 | – | – | 0.2 | – | 1.8 | 1.7 | 2.4/1.7 | – | 4.8 | 8.0 | 0.0 |
| [a]Constantinides et al. [27] | 2009 | Athens, Greece | 995 | – | 5.3 | – | 1.0 | – | – | 5.3 | – | 1.1/0.3 | 3.9 | 2.6 | 26.9 | 0.3 |
| Kordan et al. [32] | 2010 | Nashville, TN | 414 | 450 | 3.4 | 3.4 | – | – | – | – | – | – | – | – | – | – |
| [a]Rabbani et al. [17] | 2010 | MSKCC, NY | 3,458 | 1,100 | 55.0 | 15.6 | 0.7 | 0.5 | 0.3 | 1.4 | 3.0 | 1.4/0.9 | 2.9 | 5.5 | 18.7 | 0.1 |
| Roberts et al. [37] | 2010 | Baltimore, MD | 10,183 | – | – | – | 0.1 | – | – | – | – | – | – | – | – | – |
| Thomas et al. [39] | 2010 | Mainz, Germany | 2,447 | – | – | – | 0.5 | – | – | – | – | – | – | – | – | – |
| [a]Loppenberg et al. [42] | 2010 | Herne, Germany | 2,893 | 750 | – | 4.6 | 0.3 | 0.3 | – | – | 4.5 | – | 14.7 | – | 27.7 | 0.1 |
| | | *Weighted means* | | *905* | *31.8* | *9.2* | *0.5* | *0.3* | *0.2* | *2.9* | *2.1* | *1.3/0.7* | *6.9* | *3.8* | *18.0* | *0.1* |
| *Multicenter studies* | | | | | | | | | | | | | | | | |
| Lu-Yao et al. [47] | 1999 | Multicenter, US (Medicare) | 93,986 | – | – | – | 0.7 | – | – | – | – | 1.0 | – | – | 28.8 | 0.7 |
| Begg et al. [44] | 2002 | Multicenter, US (SEER) | 11,522 | – | – | – | – | – | – | – | – | – | – | – | 27–32 | 0.5 |
| Hu et al. [45] | 2003 | Multicenter, US (Medicare) | 12,079 | – | – | – | – | – | – | – | – | – | – | 29.1 | 35.2 | – |
| Alibhai et al. [43] | 2005 | Multicenter, Canada (OCR) | 11,010 | – | – | – | – | – | – | – | – | – | – | – | 20.4[ε] | 0.5 |
| Lowrance et al. [46] | 2010 | Multicenter, US (SEER) | 5,923 | – | – | – | – | – | – | – | – | – | – | – | 24.1 | – |

*EBL* estimated blood loss, *T/F* transfusion, *All. T/F* allogenic transfusion, *DVT* deep vein thrombosis, *PE* pulmonary embolus, *BNC* bladder neck contracture, *SEER* Surveillance, Epidemiology and End Results database, *OCR* Ontario Cancer Registry, *dashes* indicate no data provided

α – Single-center studies with >250 patients, most recent/updated results shown; β – lower limb nerve injury or neuropraxia; γ – solitary figures indicate combined values reported as "thrombosis" or "thromboembolism"; ε – reported complications limited to 30 postoperative days

[a]Indicates studies using the Clavien classification system of complications reporting

### Rectal Injury

Rectal injury is an uncommon but serious complication of open radical retropubic prostatectomy. Table 82.3 shows published series of more than 250 patients in which the rate of rectal injury is recorded. The weighted mean is 0.48 % or approximately 1 in 208 patients operated. Over 90 % are identified intraoperatively [37, 60], typically during apical dissection during attempts to develop the plane between the rectum and Denonvilliers' fascia. If a rectal injury occurs, the prostatectomy should be completed and the bladder neck reconstructed, followed by a two-layer closure of the rectum [61]. A concomitant dilatation of the anal sphincter has been advocated by some [39, 61, 62], although there is no evidence to support its role in reducing the risk of subsequent rectourethral fistula [37] and potentially risk the development of sphincter incompetence. There is however evidence to support the role of omental interposition between the rectal closure and the vesicourethral anastomosis to reduce the possibility of a rectourethral fistula. In a large single-center series of 11, 452 men who underwent open radical prostatectomy, Roberts et al. reported 18 rectal injuries, 16 of which were identified intraoperatively and repaired primarily [37]. Of these, four were bolstered with omental interposition and six with other tissues. None of these patients developed rectourethral fistulae, whereas two patients without interposition did. Where the omentum is short, mobilization of a pedicle into the pelvis may be problematic, necessitating cephalad extension of the infraumbilical incision. Even allowing for this and after mobilization of the omentum from the greater curvature of the stomach [63], adequate length may not be technically achievable. In this situation, a number of alternatives have been proposed, including local peritoneal flaps [37], fibrin glues, and collagen xenograft patches [39]. Other factors increasing the likelihood of rectourethral fistula after primary repair are size of intraoperative rectal injury [37] and prior radiation therapy [64]. In this latter circumstance, it is recommended that the primary repair is covered with a diverting colostomy.

Rectourethral fistula is a rare but severe complication of open radical prostatectomy, resulting in a protracted postoperative recovery, usually punctuated by repeated surgical intervention. It results from either an unrecognized rectal injury or a failure of a primary intraoperative repair. The incidence varies from 0.03 to 0.53 % [37, 39, 60]. Classic features are anal urinary discharge, fecaluria, and pneumaturia, typically occurring 2–3 weeks after prostatectomy. Anal urinary discharge is almost universally present and represents the hallmark of the condition [64]. Retrograde urethrography has a high sensitivity for diagnosis and is recommended as a first-line investigation, although flexible urethroscopy can detect large fistulas. While there have been a number of reports of spontaneous closure of rectourethral fistulae with prolonged urethral catheterization [39, 65], management usually comprises formal surgical repair. This typically occurs via the perineum, although transabdominal repair has been advocated by some for fistulas developing in the early postoperative period [37]. Perineal approaches may be divided into transperineal [66], transsphincteric [67], and transanal [68]. Historically, rectourethral fistula repair has been accompanied by tissue transfer (gracilis, tunica vaginalis) and a covering colostomy, necessitating a third operation to reestablish colonic continuity. Although this approach is still recommended for patients after radiation therapy and for those with coexistent inflammatory bowel disease, high success rates have been reported in patients with uncomplicated postoperative fistulae undergoing transperineal repair without a temporary colostomy [64].

### Ureteric Injury

Ureteric injuries occurring at the time of open radical prostatectomy are rare, with a reported incidence of 0.1–0.5 % (Table 82.3). The mean rate derived from various published studies is 0.36 % or approximately 1 in 275 operated cases. Injury typically occurs during dissection of the posterior bladder neck or seminal vesicles, often in men with large prostates or those with a significant median lobe encroaching into the bladder. Most ureteric injuries are identified intraoperatively. Partial injuries may be managed by primary repair and ureteric stenting, whereas more significant injuries require formal ureteroneocystostomy [69]. Very proximal ureteric injuries, occasionally reported in the context of extended pelvic lymph node dissection [70, 71], may be suitable for primary ureteroureterostomy over a double-J ureteric stent. Occasionally, ureteric injuries are identified in the postoperative period. Although immediate repair may be considered for patients in whom the diagnosis is made very early on in the postoperative period (<72 h), reoperation becomes increasingly difficult thereafter, and many surgeons advocate temporary urinary diversion via a nephrostomy tube followed by delayed repair, which may be performed by either open or laparoscopic means [15, 71].

### Nerve Injury/Neuropraxia

Peripheral nerve dysfunction affecting the lower limb is relatively uncommon after open radical prostatectomy, with a reported rate of 0.1–0.3 % in published series (see Table 82.3). Cumulative analysis produces a weighted mean rate of 0.19 %, equivalent to approximately 1 in 525 operated patients. Neuropraxia of the obturator nerve is the most commonly reported finding, typically occurring at the time of pelvic lymph node dissection, which is self-limiting and spontaneously resolves, although there have been occasional reports of obturator nerve transection [25, 30, 72] necessitating immediate open [25, 30] and laparoscopic [72] repair. Other palsies affecting the femoral nerve [17, 35] and lateral cutaneous nerve of the thigh (meralgia paresthetica) [17]

have been reported, presumably due to entrapment of the nerves as they pass under the inguinal ligament, which may be exacerbated by an excessive table break. Finally, upper limb neuropraxias involving the ulnar nerve and brachial plexus have been reported [17], emphasizing the importance of adequate padding of the elbow region and avoidance of prolonged exaggerated abduction of the shoulder.

## Postoperative Complications

Commonly reported postoperative complications, stratified for time of occurrence after surgery, are presented in Table 82.2. Bleeding, persistent urinary leak or urinoma, lymphocele formation, thromboembolism, and anastomotic stricture are discussed below. Sphincter weakness incontinence and erectile dysfunction are discussed in Chaps. 78 and 79, respectively.

### Delayed Hemorrhage/Hematoma

Bleeding after radical prostatectomy is traditionally defined as significant postoperative hemorrhage requiring the acute transfusion of blood to support blood pressure [73]. It is usually associated with a significant pelvic hematoma which increases the likelihood of anastomotic disruption, with subsequent bladder neck contracture and incontinence. It is for this reason rather than bleeding per se that some surgeons recommend immediate evacuation of the pelvic hematoma [73]. Reporting of delayed hemorrhage in the published literature is inconsistent at best; few studies provide a specific definition, indications for postoperative transfusion are unclear, and the means of determining the presence of a pelvic hematoma are usually left unstated. It is therefore not surprising that rates of delayed hemorrhage vary considerably in the literature (see Table 82.3). Reoperation rates for postoperative hemorrhage are less commonly reported but arguably more reliable, with a published range of 0.3–1.7 % [17, 25, 30, 31, 35].

### Urine Leak and Urinoma

Rates of urine leak and urinoma formation after radical prostatectomy vary considerably, with a published range of 0.1–14.7 % (see Table 82.3), reflecting a variety of definitions. Most authors have defined a postoperative urine leak as the presence of an anastomotic leak at cystography [25, 27, 31, 42]. Others have included prolonged urinary drainage via an abdominal tube drain in this definition where, in most cases, "prolonged" is defined as more than 7 days. For example, Rabbani et al. defines persistent urine leak as either evidence of extravasation on imaging (computed tomography scan or cystogram) or a drain fluid creatinine of more than 1.5 mg/dl [17]. In two studies reporting very low rates of urine leak/urinoma, the urinary catheter was left in situ for 2–3 weeks and routinely removed without a cystogram [30, 35]. In fact, the management of an anastomotic leak at postoperative cystography is simply prolonged catheter drainage, which invariably results in resolution of the defect. The definition of a urinoma is more clear-cut. It is typically defined as a collection on imaging consistent with a urinoma, usually indicated by a perianastomotic or perivesical location, as opposed to lymphoceles which are typically identified in the obturator fossae. The demonstration of fluid with high creatinine content, rather than an elevated protein level, confirms the diagnosis of a urinoma in patients undergoing therapeutic aspiration.

### Lymphorrhea/Lymphocele

The true incidence of lymphocele formation after radical prostatectomy is unknown, as cross-sectional imaging is not routinely performed in the early postoperative period. When imaging is performed for other reasons, it is not uncommon to see small fluid collections in the pelvis at the site of pelvic lymph node dissection which, unless symptomatic, require no specific treatment. Symptomatic lymphoceles are reported in 0.1–6.6 % of patients after open radical prostatectomy, with mean frequency of 2.1 % (see Table 82.3). Patients may complain of abdominal pain and distension, with occasional leg swelling. Clinical signs are usually unremarkable except for a low-grade fever. An ileus may occasionally be identified in those with very large lymphoceles. The usual cause is a failure to identify and ligate lymphatics during pelvic lymph node dissection. Risk factors for the development of lymphorrhea and lymphocele include extent of pelvic lymph node dissection, patient age, and number of lymph nodes excised [74]. Initial management comprises aspiration, with or without temporary drain insertion which usually resolves the situation. Prolonged lymphorrhea, confirmed by the finding of elevated protein (with serum levels of creatinine) in the fluid specimen, or recurrence following drain removal requires further intervention. If the drain remains in situ, one option is sclerotherapy, usually with tetracycline or povidone iodine, which is reportedly effective in 90 % of patients [75, 76], although contemporary reports are lacking, and the procedure has the potential to induce infection and loculation. Marsupialization of the lymphocele into the peritoneal cavity, increasingly performed laparoscopically [77], is usually successful.

### Thrombosis and Thromboembolism

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are serious causes of morbidity and mortality after radical prostatectomy. The incidence of symptomatic DVT in published series is 0.2–2.4 %, with a mean frequency of 1.3 % (see Table 82.3). Similarly, the rate of symptomatic pulmonary embolism is 0–1.7 %, with a mean of 0.7 %. The incidence of fatal pulmonary embolism is much lower however.

Of nine published studies reporting both mortality and rates of thromboembolism after open radical prostatectomy, with a combined total of 9,453 patients, fatal pulmonary embolism was reported in just five cases, corresponding to a rate of 0.05 % (see Table 82.3). Rates of asymptomatic thromboembolism are somewhat higher however. In a recent prospective study, 523 consecutive patients underwent Doppler compression ultrasonography immediately before and at days 8 and 21 after radical prostatectomy [78]. Even with DVT, prophylaxis in the form of graduated compression stockings and a daily standard dose low molecular weight heparin, calf vein and above-knee DVT was identified in 3.9 and 2.4 % of patients, respectively, with symptomatic pulmonary embolism in 0.9 % of cases. Of particular note is the finding that almost 80 % of cases of thrombosis developed between days 8 and 21, highlighting the importance of prolonged DVT prophylaxis, even in ambulant patients [79]. Measures to prevent venous thromboembolism include careful patient positioning on the operating table, use of intermittent compression devices, graduated compression stockings, low-dose unfractionated or low molecular weight heparin, and early mobilization. Despite a number of international guidelines supporting the use of heparinoids for prophylaxis after radical prostatectomy [80, 81], the practice remains controversial, particularly in the United States. Proponents of routine low-dose heparinoid prophylaxis cite studies identifying a clear beneficial effect for anticoagulation in patients undergoing general surgical [82, 83] and gynecological pelvic surgery [81], whereas opponents, concerned that the risk of bleeding and lymphocele formation is too high, argue that the rate of thromboembolism is naturally low and that mechanical devices are as efficient [84, 85]. A number of prospective studies have attempted to randomize patients to differing prophylactic modalities but have either been inappropriately powered [86] or have failed to show statistical significance [85]. This is hardly surprising given the low incidence of VTE after radical prostatectomy. For example, assuming an incidence of DVT after RRP of 1.3 %, a prospective randomized intervention study with a power of 80 % and a confidence level of 0.5 % would require almost 14,000 patients in each arm to detect a 25 % difference in the rate of DVT. Therefore, in the absence of a large multi-institutional trial, it is unlikely that consensus will be achieved any time soon.

### Anastomotic Stricture

Rates of anastomotic stricture or bladder neck contracture vary considerably after RRP with a reported incidence of 1.0–8.6 %, with an associated weighted mean frequency of 3.8 % (see Table 82.3). Because anastomotic stricture usually requires operative intervention in the form of either dilatation or bladder neck incision, reported rates are more objective and thus less susceptible to reporting error. Multiple dilatations are occasionally required, with occasional long-term urinary dysfunction in a small minority. Risk factors for anastomotic stricture comprise inadequate approximation at the time of surgery, distraction of the bladder neck by hematoma, or urinary extravasation. In order to limit the degree of extravasation around the urethrovesical anastomosis, a number of authors have recommended replacing conventional interrupted sutures with a continuously sewn anastomosis [87, 88], although evidence to support such an intervention in open prostatectomy is currently lacking.

## Complications of Laparoscopic Radical Prostatectomy (LRP)

Overall and specific complications after LRP are detailed in Table 82.4. The overall published complication rate in studies containing more than 150 patients is 2.9–33.2 %, with a weighted mean of 18.2 % and a mortality of 0.1 %. Higher rates of complications were generally seen in studies in which the Clavien classification was used to stratify perioperative morbidity [11–18]. The figures observed for LRP are very similar to the overall complication rate seen after open radical prostatectomy (see Table 82.3). Similar findings have been reported in a systematic review of perioperative outcomes reported by high-volume centers (>250 patients) [89], albeit with a lower overall complication rate for RRP and LRP of approximately 10 %, and also in a recent multicenter review using the Surveillance, Epidemiology and End Results (SEER) database [46]. A further review of single-center comparative studies also noted similar complication rates for each of the techniques, although statistical analyses suggested a higher overall complication rate for RRP [90]. Neither study included the large single-center study by Rabbani, however [17], which reported a significantly increased complication rate for LRP vs. RRP, a finding likely to have a bearing on the results presented herein. As most of the complications seen with RRP are also common to LRP and given that the management is broadly similar among the techniques and has been discussed at length for RRP, subsequent sections discussing perioperative complications after LRP will focus principally on differences between the techniques.

### Intraoperative Complications

LRP is without doubt a technically demanding procedure with an extended learning curve [18, 91]. Despite this, conversion rates at major centers remain low, with a reported range of 0.0–1.6 % (Table 82.3). Estimated blood loss and rates of transfusion are significantly lower than with RRP, a finding that is consistently seen in multiple single-center comparison studies [17, 40, 92, 93] and systematic reviews

**Table 82.4** Perioperative complications in laparoscopic radical prostatectomy series with more than 150 patients

| | | | | Intraoperative complications (%) | | | | | | | Postoperative complications (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference[α] | Date | Center | *n* | EBL | T/F | All. T/F | Rectal | Ureter | Nerve[β] | Open conv. | Bleed | Lymph | DVT/PE[γ] | Urinoma leak | BNC | Overall (%) | Repeat Int.[ε] (%) | Mortality (%) |
| *Single-center studies* | | | | | | | | | | | | | | | | | | |
| [a]Guillonneau et al. [13] | 2002 | Paris, France | 567 | 380 | 4.9 | 4.9 | 1.4 | 0.7 | 0.5 | 1.2 | 0.9 | – | 0.3/0.0 | 10.0 | – | 17.1 | 3.7 | 0.0 |
| Anastasiadis et al. [123] | 2003 | Creteil, France | 230 | – | 2.6 | – | – | – | – | – | – | – | – | – | – | 9.6 | – | – |
| [a]Gonzalgo et al. [12] | 2005 | Baltimore, MD | 250 | – | 2.8 | – | 0.8 | 0.4 | – | 1.6 | 2.8 | – | 0.0/0.4 | – | 1.2 | 13.8 | 4.8 | 0.0 |
| Rozet et al. [124] | 2005 | Paris, France | 600 | 380 | 1.2 | – | 0.7 | – | – | 0.2 | – | 0.7 | 0.0/0.2 | 5.2 | – | 10.5 | 1.7 | – |
| Galli et al. [125] | 2006 | Milan, Italy | 150 | 355 | 38.7 | 5.3 | 0.7 | – | – | 0.0 | 5.3 | – | – | 6.7 | 4.6 | 32.7 | 5.3 | 0.7 |
| Lein et al. [126] | 2006 | Berlin, Germany | 1,000 | – | 2.2 | – | 3.3 | 0.1 | 1.8 | 0.0 | – | – | 0.8 | 22.3 | 0.2 | 11.8 | – | 0.3 |
| [a]Hu et al. [15] | 2006 | Boston, MA | 358 | 200 | 2.2 | – | 2.5 | 0.3 | 0.6 | 0.8 | 1.1 | 0.8 | 0.0/0.0 | 13.4 | 2.2 | 33.0 | 3.1 | 0.0 |
| Goeman et al. [11] | 2006 | Creteil, France | 550 | 390 | 4.7 | – | 0.5 | – | – | 0.6 | 2.2 | 0.5 | – | – | 0.4 | 10.9 | 0.7 | – |
| [a]Permpongkosol et al. [16] | 2007 | Baltimore, MD | 468 | – | 2.2 | – | – | – | – | 1.3 | 1.9 | – | – | – | – | 15.0 | – | 0.0 |
| Jurczok et al. [92] | 2007 | Halle, Germany | 163 | 200 | 3.0 | – | 1.8 | – | – | 0.0 | – | 3.2 | – | – | – | 8.1 | – | – |
| Touijer et al. [40] | 2008 | MSKCC, New York, NY | 612 | 315 | 3.0 | – | – | 0.2 | – | – | 1.0 | – | 0.8 | – | 0.4 | 2.9 | 1.9 | 0.0 |
| Eden et al. [91] | 2009 | Guildford, UK | 1,000 | 200 | 0.4 | – | 0.7 | – | – | – | 0.4 | 0.4 | 0.4/0.3 | 0.3 | 1.1 | 4.8 | 3.3 | 0.0 |
| [a]Stolzenburg et al. [18] | 2009 | Leipzig, Germany | 2,400 | 255 | 0.7 | – | 0.5 | – | 0.2 | 0 | 0.8 | 3.8 | 0.5/– | 3.2 | 0.2 | 10.1 | 3.8 | – |
| Greco et al. [99] | 2010 | Halle, Germany | 457 | – | 0.9 | – | 0.4 | – | – | 0.0 | – | – | – | – | – | – | – | – |
| [a]Rabbani et al. [17] | 2010 | MSKCC, New York, NY | 1134[η] | 250 | 4.0 | 3.8 | 0.4 | 0.2 | 2.3 | – | 3.3 | 5.4 | 1.3/1.0 | 8.7 | 0.7 | 39.0 | 1.8 | 0.1 |
| [a]Hruza et al. [14] | 2010 | Heilbronn, Germany | 2,200 | 800 | 10.4 | – | 1.7 | 0.1 | – | 0.4 | 0.5 | 0.7 | 0.5 | 4 | 4.4 | 33.2 | 11.5 | 0.1 |
| | | *Weighted means* | | *397* | *4.1* | *4.3* | *1.2* | *0.2* | *1.0* | *0.4* | *1.0* | *2.2* | *0.5/0.4* | *6.8* | *1.5* | *18.2* | *4.8* | *0.1* |
| *Multicenter studies* | | | | | | | | | | | | | | | | | | |
| Rassweiler et al. [127] | 2006 | Multicenter Europe | 5824[θ] | – | 4.1 | – | 1.7 | – | – | 2.4 | 2.2 | – | 0.6 | 2.4 | – | 8.9 | 2.4 | – |
| Lowrance et al. [46] | 2010 | Multicenter US (SEER) | 1,006 | – | – | – | – | – | – | – | – | – | – | – | – | 21.4 | – | – |

*EBL* estimated blood loss, *T/F* transfusion, *All. T/F* allogenic transfusion, *DVT* deep vein thrombosis, *PE* pulmonary embolus, *BNC* bladder neck contracture

α – Single-center studies with ≥150 patients, most recent/updated results shown; β – lower limb nerve injury or neuropraxia; γ – solitary figures indicate combined values reported as 'thrombosis' or thromboembolism'; ε – repeat intervention, including surgical and nonsurgical; η – includes 97 robot-assisted laparoscopic prostatectomies (RALPs); θ – includes 414 RALPs

[a]Indicates studies using the Clavien classification system of complications reporting

[90, 94–96]. In studies containing more than 150 patients, the weighted mean EBL was 397 mL, compared with 905 mL for RRP. Overall and allogenic transfusion rates were also substantially lower than for RRP (Table 82.4). Because most intraoperative blood loss arises from venous sinuses, it is believed that the tamponade created by positive pressure insufflation limits bleeding. Optical magnification may aid the identification and control of small vessels, and Trendelenburg tilt may also play a role. Recognized risk factors associated with an increased risk of bleeding at LRP are prior transurethral surgery [97] and nerve-sparing procedures [98, 99]. Conflicting evidence exists regarding the role of prostate size [98, 100, 101]. The published rate of rectal injury ranges from 0.4 to 3.3 %, with an associated mean of 1.2 %, which is slightly higher than that seen with RRP (Tables 82.3 and 82.4). Analysis of the available data suggests that most rectal injuries occurred early in the LRP learning curve [11, 14, 91], which may explain the difference between the techniques. Certainly, rates of rectal injury in more contemporary series are lower than those in older studies (Table 82.4). Of 124 identified rectal injuries, 108 (87.1 %) were identified intraoperatively and managed by intracorporeal suture. In six patients, the subsequent outcome was not reported; of the remaining 102 patients, 98 (96.1 %) healed without further sequelae, comparing favorably with success rates for repair of rectal injury occurring at RRP [39]. Rates of ureteric injury in published LRP series range from 0.1 to 0.7 %, with a weighted mean of 0.2 %, which is similar to that seen for RRP (Tables 82.3 and 82.4). Injury most commonly occurs during posterior bladder neck dissection, seminal vesicle exposure, and during pelvic lymph node dissection (PLND) [71]. The type of approach (transperitoneal vs. extraperitoneal) and method of prostate dissection (antegrade vs. retrograde) do not appear to unduly influence the rate of injury. Reported risk factors include those with a previous history of prostatitis, large prostates, prominent median lobes, and extended PLND [70, 71]. A majority of injuries are identified and repaired laparoscopically. Of eight evaluable ureteric injuries identified from Table 82.4, five were identified intraoperatively and underwent immediate laparoscopic repair. An extravesical Lich-Gregoir ureteroneocystostomy was performed in three patients, with ureteroureterostomy and primary repair of a partial injury in the remaining two cases. Reported rates of lower limb nerve injury in LRP series range from 0.2 to 2.3 %, with a weighted mean of 1 %, somewhat higher than seen in a combined analysis of RRP series (Tables 82.3 and 82.4). This finding is counterintuitive, given the lower rates of PLND and better magnification with LRP, and almost certainly results from improved reporting of complications in contemporary series. Most nerve injuries involve the obturator nerve and comprise self-limiting neuropraxia, although complete transection of the nerve with intracorporeal repair has been reported [72].

## Postoperative Complications

While positive insufflation pressure has obvious advantages in terms of reduced intraoperative blood loss, its cessation at completion of LRP does not appear to be associated with increased rates of pelvic hematoma and postoperative transfusion rates. Rates of postoperative bleeding complications in published LRP series range from 0.4 to 11.8 %, with a weighted mean of 3.8 %, which is similar to rates seen for RRP (Tables 82.3 and 82.4). Rates of symptomatic lymphocele range from 0.7 to 5.4 % in published LRP series, with a weighted mean of 2.2 % which very closely approximates that seen with RRP (Tables 82.3 and 82.4). The incidence of symptomatic DVT in published LRP series is 0.0–1.3 %, with a mean frequency of 0.5 %. Similarly, the rate of symptomatic pulmonary embolism is 0.0–1.0 %, with a mean of 0.4 % (Table 82.4). The rates are slightly lower than those reported for RRP series, although studies are lacking in this regard. The frequency of symptomatic lymphocele is reportedly higher in patients in whom PLND is performed [14, 17, 18, 70] and in extraperitoneal compared with transperitoneal LRP [70]. In this latter respect, Stolzenberg et al. have described a technique for laparoscopic peritoneal fenestration at the end of extraperitoneal LRP, which appears to be associated with reduced rates of postoperative lymphocele [102]. The management of established symptomatic lymphocele is broadly similar to that described for RRP above, comprising aspiration with or without catheter drainage, or marsupialization/fenestration, which is preferentially performed laparoscopically by surgeons familiar with LRP. Published rates of urine leak/urinoma range from 4.0 to 22.3 %, with a weighted mean of 6.8 %, which is not dissimilar from that seen in a cumulative analysis of RRP series (Tables 82.3 and 82.4). As previously discussed, the degree of disparity among the studies is likely to result from differing definitions of urine leak. Despite similarities in rates of urine leak between the groups, there has been a trend toward reduced catheter duration for patients undergoing LRP compared with RRP [90, 94, 103, 104], also mirrored by rates of in-hospital stay [40, 90, 103]. While these findings are interesting, both parameters are subject to nonpatient factors such as surgeon preference and departmental management protocols. Rates of anastomotic stricture in published LRP series range from 0.2 to 4.6 %, with a weighted mean frequency of 1.5 %, which is lower than an equivalent observed rate of 3.8 % derived from RRP series (Tables 82.3 and 82.4). A similar trend has been observed in a cumulative analysis of comparative studies comparing the techniques, although the difference did not achieve statistical significance when only prospective studies were considered [90]. The reasons for such a discrepancy have not been fully elucidated however. Although follow-up data for LRP and RALP are relatively immature at present, anastomotic stricture is a relatively

early postoperative phenomenon, and as such the difference is unlikely to result from reporting bias. One theory is that urinary extravasation stimulates extraperitoneal fibrosis, which may be limited by the use of a continuous suture to create a watertight urethrovesical anastomosis. However, a study of interrupted vs. anastomotic sutures at LRP has failed to show a difference in either stricture or continence rates at 26 months [105].

## Complications of Robot-Assisted Laparoscopic Radical Prostatectomy (RALP)

Overall, published complication rates in RALP series range from 5.0 to 26.1 %, with a weighted mean frequency of 11.6 % (Table 82.5). Studies using the Clavien classification system generally report higher rates of complications, a finding also observed in RRP and LRP series (Tables 82.3 and 82.4). The figures obtained for RALP are lower than those reported for RRP, a trend observed in a number of other single-centers studies [33, 104] and systematic reviews [90, 94, 96], although in the only study to formally compare the techniques using statistical analyses, the differences were nonsignificant [90]. While RALP has a number of advantages over LRP, including three-dimensional visualization, improved articulation, and tremor-reduction algorithms, most systematic analyses have reported equivalent complication rates [90, 96]. In the systematic analyses presented herein, which includes data not hitherto analyzed, there is a reduced complication rate with RALP compared with LRP. Whether this represents a true finding is difficult to discern, particularly as only 41.6 % of patients in RALP series were evaluated for complications according to the Clavien classification, compared with 65.3 % for the LRP group. Established risk factors for complications at RALP include high BMI [106–108] and large prostate size [109, 110]. With the exception of robot malfunction, which is presented separately below, a discussion of the intraoperative and postoperative complications after RALP will focus principally on differences in complication rates between the techniques.

### Da Vinci Surgical System Failure

Robot malfunction is a relatively uncommon phenomenon, reported in 34 of 8,240 cases (0.4 %) in one multicenter study [111]. Of these, ten device failures occurred intraoperatively; eight cases were converted to open surgery, and two were managed by conversion to conventional LRP. The published rate of device failure in single-center studies is 0.1–2.6 % [19, 89, 90, 112, 113]. In a review of adverse events submitted to the Manufacturer and User Facility Device Experience (MAUDE) database of the US Food and Drug Administration (FDA), Andonian et al. estimated a device failure rate of 0.38 % based on 168 da Vinci system malfunctions reported between 2000 and 2007 [114]. Broken instrument tips or faulty electrocautery elements comprised the majority of reported mechanical issues [115]. Adverse events were associated with patient injury in 4.8 % of cases. Of 38 recorded system failures, 32 were converted to open surgery, reflecting a lack of experience with conventional LRP among surgeons in the United States.

### Intraoperative Complications

Open conversion rates reported for RALP range from 0.0 to 2.4 %, which is similar to figures obtained for LRP (Tables 82.4 and 82.5). Only a small proportion result from device failure; other causes include major intraoperative organ injury and difficulties entering the peritoneal space due to adhesions. In the latter case, extraperitoneal RALP has theoretical advantages [116] over the more conventional transperitoneal route. However, the reduced working space and concerns regarding instrument collisions have limited its widespread adoption. Estimated blood loss and rates of transfusion are significantly lower for RALP compared with RRP (Tables 82.3 and 82.5), a finding that is consistently observed in a number of single-center comparative studies [104, 117] and systematic reviews [90, 94, 96]. When LRP and RALP were evaluated, weighted mean EBL and transfusion rate were 397 mL and 4.1 %, respectively, for LRP, compared with figures of 152 mL and 1.5 % for RALP. Similar trends in EBL [118, 119] and transfusion rate [15, 118, 120] have been observed in a number of single-center comparison studies and in systematic reviews [90, 94, 96], although the differences have failed to achieve statistical significance. Weighted mean frequencies of rectal, ureteric, and nerve injuries in published RALP series are 0.4, 0.1, and 0.7 % respectively, which are similar to figures seen for LRP and RRP (Tables 82.3–82.5). Of 21 rectal injuries identified in this systematic review of RALP series, 17 (81.0 %) were identified intraoperatively and repaired robotically. Of these 16 (94.1 %) healed without further sequelae. Only one ureteric injury was identified, which was repaired by ureteroneocystostomy without the need for open conversion.

### Postoperative Complications

Published rates of postoperative bleeding complications range from 0.1 to 4.3 %, with a weighted mean of 0.7 %, substantially lower than seen in RRP series (Tables 82.3 and 82.5). The figure is also slightly lower than LRP, which has a weighted mean value of 3.8 % in published series containing

**Table 82.5** Perioperative complications in robot radical prostatectomy series with more than 150 patients

| | | | | Intraoperative complications (%) | | | | | | Postoperative complications (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference[α] | Date | Center | *n* | EBL | T/F | All. T/F | Rectal | Ureter | Nerve[β] | Open conv. | Bleed | Lymph | DVT/PE[γ] | Urinoma leak | BNC | Overall (%) | Repeat Int.[ε] (%) | Mortality (%) |
| Tewari et al. [104] | 2003 | Detroit, MI | 200 | 153 | 0.0 | 0.0 | 0.0 | – | 0.0 | 0.0 | 0.5 | 0.0 | – | – | – | 5.0 | – | 0.0 |
| Joseph et al. [116] | 2006 | Rochester, NY | 325 | 196 | 1.3 | 1.3 | 0.3 | – | – | 0.0 | – | 0.9 | 1.2/0.3 | 1.5 | 2.2 | 8.6 | 2.2 | 0.0 |
| [a]Hu et al. [15] | 2006 | Boston, MA | 322 | 250 | 1.6 | – | 0.0 | 0.3 | 0.0 | 0.0 | – | 0.9 | 0.6/0.0 | 7.5 | 0.6 | 16.2 | 2.2 | 0.0 |
| Mottrie et al. [112] | 2007 | Aalst, Belgium | 184 | 200 | 0.5 | – | – | – | 1.6 | 0.5 | 4.3 | – | – | – | – | 12.0 | – | 0.0 |
| [a]Badani et al. [19] | 2007 | Detroit, MI | 2,766 | 142 | 1.5 | – | – | – | – | 0.1 | – | – | – | – | – | 12.3 | 0.5 | 0.0 |
| Nelson et al. [36] | 2007 | Nashville, TN | 629 | – | – | – | 0.2 | – | – | – | 0.2 | 0.3 | 0.7 | – | – | 17.0 | – | – |
| Borin et al. [128] | 2007 | Orange, CA | 200 | 109 | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Zorn et al. [129] | 2007 | Chicago, IL | 300 | 273 | 1.7 | – | 0.0 | 0.0 | 1.4 | 2.3 | 1.0 | 0.6 | 0.6 | 1.4 | 1.4 | 9.0 | 1.7 | 0.0 |
| Schroeck et al. [130] | 2008 | Durham, NC | 362 | 150 | – | – | – | – | – | 1.6 | – | – | – | – | – | – | – | – |
| Chan et al. [131] | 2008 | Nashville, TN[η] | 660 | 139 | 0.9 | – | 0.9 | – | – | – | – | – | – | – | – | – | – | – |
| Krambeck et al. [33] | 2008 | Rochester, MN | 294 | – | 5.1 | – | – | – | – | – | 3.5 | 0.7 | 0.7/0.3 | 9.1 | 1.2 | 8.0 | – | 0.0 |
| [a]Fischer et al. [20] | 2008 | Zurich, Switz | 450 | – | – | 1.0 | 1.0 | 0.0 | – | – | – | 2.4 | – | 6.5 | 0.5 | 26.1 | 3.3 | 0.0 |
| Ham et al. [132] | 2009 | Seoul, Korea | 321 | – | – | – | 1.2 | – | – | 2.4 | – | 1.2 | – | 0.6 | – | 5.3 | – | – |
| [a]Murphy et al. [115] | 2009 | Melbourne, Aus | 400 | – | 2.5 | – | 1.3 | – | – | 0.3 | 0.3 | – | – | – | 3.8 | 15.8 | 4.5 | 0.0 |
| Ginzburg et al. [133] | 2010 | Farmington, CT | 839 | – | – | – | – | – | – | – | 0.4 | 1.0 | 0.1 | 0.6 | 4.6 | 16.4 | – | 0.0 |
| [a]Sharma et al. [23] | 2010 | Cambridge, UK | 500 | 200 | – | – | 0.2 | – | – | 0.0 | 0.4 | – | 0.2/0.2 | 1.0 | 0.4 | 10.6 | – | 0.2 |
| Coelho et al. [89] | 2010 | Orlando, FL | 2,500 | 100 | 0.5 | – | 0.1 | – | – | 0.0[θ] | 0.1 | 0.4 | 0.1/0.2 | 1.4 | 0.1 | 5.1 | 0.8 | 0.0 |
| [a]Novara et al. [22] | 2010 | Padua, Italy | 415 | 300 | 5.3 | – | 1.2 | – | – | 0.4 | 2.4 | 1.2 | – | 7.2[ϕ] | – | 21.6 | 2.7 | 0.0 |
| | | *Weighted Means* | | *152* | *1.5* | *0.9* | *0.4* | *0.1* | *0.7* | *0.3* | *0.7* | *0.8* | *0.3/0.2* | *2.7* | *1.4* | *11.6* | *1.3* | *0.0* |

*EBL* estimated blood loss, *T/F* transfusion, *All. T/F* allogenic transfusion, *DVT* deep vein thrombosis, *PE* pulmonary embolus, *BNC* bladder neck contracture

α – Single-center reports with ≥150 patients, most recent/updated results shown; β – lower limb nerve injury or neuropraxia; γ – solitary figures indicate combined values reported as "thrombosis" or "thromboembolism"; ε – repeat intervention, including surgical and nonsurgical; η – same cohort as Nelson 2007, different outcomes measures; θ – 2 patients converted to standard LRP due to robot malfunction; ϕ – leakage defined as >5 % contrast extravasation at cystography

[a]Indicates studies using the Clavien classification system of complications reporting

over 150 patients (Table 82.4). The reasons for this are not immediately apparent, particularly as both procedures benefit from positive pressure insufflation and have similar risks of abdominal wall bleeding associated with trocar insertion. The differences probably relate to reporting bias rather than any true effect. A similar explanation may describe differing rates of thromboembolism for LRP and RALP, respectively, but is less likely to explain a reduction incidence of symptomatic lymphocele in RALP. Weighted mean frequencies of lymphocele in LRP and RALP were 0.8 and 2.2, respectively (Tables 82.4 and 82.5), which is in keeping with the observation that lymphocele is less commonly seen after a transperitoneal approach to the prostate. Pelvic lymph node dissection is a further risk factor for lymphocele formation after RALP. Published rates of urine leak/urinoma in RALP series range from 0.6 to 9.1 %, with a mean frequency of 2.7 %, substantially lower than seen for RRP (8.1 %) and LRP (6.8 %). Again, problems with definition and reporting bias are potential reasons for the observed discrepancies. In a similar fashion to published results for LRP, RALP is associated with reduced catheterization duration and shorter hospital stay when compared with RRP [90, 96]. Finally, rates of anastomotic stricture for RALP series range from 0.1 to 4.6 %, with a weighted mean frequency of 1.4 %, compared to weighted means of 1.5 and 3.8 % for LRP and RRP series, respectively. The reduced stricture rate in RALP series compared with RRP has also been reported in a number of large single-center comparison studies [15, 33, 121]. This finding, allied to comparable results for LRP, does appear to suggest a definite advantage for the continuous "parachute"-type anastomotic suture employed during minimally invasive prostatectomy.

## Summary

Since its first description by Reiner and Walsh in 1982 [3], anatomic radical retropubic prostatectomy has evolved into a procedure associated with excellent cancer cure rates and an acceptable level of morbidity. It remains associated with a relatively high bleeding risk however. Efforts to improve perioperative morbidity and reduce inpatient stay have led to the introduction of laparoscopic prostatectomy and robot-assisted prostatectomy, which are associated with genuine reductions in estimated blood loss and transfusion rate when compared with open surgery. Catheter duration, patient stay, and rates of anastomotic stricture may also benefit from a minimally invasive approach, although quality prospective studies are lacking in this area. In this latter respect, the recent trend toward standardized reporting of complications using validated classification systems is to be encouraged, as are future efforts to enroll patients in prospective randomized comparison trials [122].

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# Population-Based Outcomes Following Treatment of Clinically Localized Prostate Cancer

83

Blake Evans and Scott M. Gilbert

## Introduction

Prostate cancer is the most common non-skin cancer in American men and accounts for greater than 200,000 new cancer cases each year in the United States [1]. Although prostate cancer is the second leading cause of cancer death, survival is favorable for most men. Currently, a number of different effective treatment modalities are used to manage prostate cancer, including surgery, external radiation therapy, interstitial radiation therapy, and ablative therapy such as cryotherapy. Outcomes following treatment vary according to disease factors (e.g., Gleason grade, pretreatment PSA levels, and disease stage) as well as treatment modality; however, most cancers are cured or controlled with local therapy. Other outcomes, such as functional outcomes, vary more substantially. Because survival is typically favorable regardless of therapy, greater focus has been placed on treatment-related morbidity and health-related quality of life (HRQOL). Several population-based studies have been used to assess these outcomes and arguably provide more accurate, real-world estimates of outcomes experienced by most patients when compared to results reported in single-surgeon or institutional case series. As a result, these population-based studies are applicable to the majority of patients treated for clinically localized prostate cancer because of the heterogeneity and community-based nature of the pooled population. This chapter will focus on several studies from three of the largest and most commonly used data sources: the Surveillance, Epidemiology, and End Results (SEER) program (and SEER-Medicare), the Prostate Cancer Outcomes Study (PCOS), and the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database.

## Surveillance, Epidemiology, and End Results (SEER) and SEER-Medicare Studies

The Surveillance, Epidemiology, and End Results (SEER) Medicare-linked database is a registry created and managed by the National Cancer Institute (NCI) that collects data on cancer patients from various regions of the country totaling approximately 28 % of the US population. SEER began collecting information on cancer cases on January 1, 1973, and has expanded on several occasions to diversify and more accurately represent the US population [2]. Most early studies utilizing SEER data to analyze outcomes for prostate cancer patients focused on results following RP. For example, several analyses have examined hospital and surgeon volume and the relationship to postsurgical morbidity. Begg et al. examined outcomes in patients undergoing RP from 1992 to 1996. The investigators found that very high hospital (>114 patients per hospital during study period) and surgeon (>33 patients per surgeon during study period) volume were related to decreased postoperative and late urinary complications. Postoperative complications were defined as life-threatening events during the first 30 days after the operation, the need for reoperation, or bleeding. Late urinary complications encompassed a wide range of problems identified by either symptomatology or procedures completed from 31 to 365 days after the prostate was removed. Ninety-four percent of late urinary events were related to bladder neck obstruction or urethral strictures. Certain high-volume surgeons (>20 patients per surgeon during study period) were found to have significantly worse rates of complications when compared to the expected rates. In addition, surgeons with high rates of complications in one outcome measure tended to have high rates of complications in other outcomes [3]. This suggested a real difference in operative ability between surgeons, even those experienced in RP.

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Using SEER-Medicare-linked data, Hu et al. studied patients who underwent RP in 1997 or 1998 and the relationship between hospital and surgeon volume and certain postoperative outcomes. Patients of high-volume urologists (>40 cases per year) experienced a lower number of in-hospital complications (cardiac, respiratory, vascular, bleeding, genitourinary, miscellaneous) and shorter lengths of stay. High-volume hospitals (>60 cases per year), although not significantly associated with the above outcomes, tended to have fewer anastomotic strictures. This outcome may be related to the fact that patients in high-volume centers in this study were younger, and age was significantly associated with stricture formation [4]. These findings suggest greater scrutiny may be necessary in analyzing hospital case volume and individual surgeon experience and outcomes when candidates for RP are considering their surgical options.

Several recent publications utilizing SEER-Medicare-linked data have investigated differences in postsurgical outcomes of patients undergoing minimally invasive (laparoscopy with or without robotic assistance) radical prostatectomy (MIRP) and open radical prostatectomy (ORP). The use of robotic-assisted MIRP increased from 9.2 to 43.2 % of all RPs from 2003 to 2007 [5]. The widespread direct-to-consumer advertising of robotic technology has increased the awareness of patients, and many are now demanding this modality even with published data suggesting early growing pains in the MIRP learning curve [6]. Some authors have estimated the learning curve to be between 150 and 250 cases in order for minimally invasive trainees to become proficient and produce outcomes comparable to the open approach [7, 8]. Hu et al. used SEER-Medicare data collected on patients undergoing MIRP or ORP between 2003 and 2007 to compare postoperative outcomes Those undergoing MIRP experienced a shorter length of stay (by approximately 1 day), were less likely to receive a blood transfusion, and were less likely to encounter respiratory complications, miscellaneous surgical complications, or anastomotic strictures. However, these patients did have a higher rate of genitourinary complications and were more often diagnosed with incontinence and erectile dysfunction (ED). A large limitation of this study, as with many population-based cohort studies, is the fact that outcomes were based on the presence of diagnosis codes. Therefore, it is not clear if men were more likely to develop incontinence or ED, possibly attributable to a lack of technical expertise given the substantial learning curve, or if they were more likely to report the adverse events to a clinician based on heightened expectations and dissatisfaction. Demographic analysis revealed Asian men, males from regions with higher high school graduation rates and household incomes, and those with organ-confined disease were more likely to undergo MIRP. Meanwhile, Black and Hispanic males and those living outside metropolitan areas were less likely to undergo MIRP [5]. In a separate analysis, Hu et al. utilized a 5 % national sample of Medicare beneficiaries who had undergone MIRP or ORP between 2003 and 2005. MIRP was associated with less perioperative complications (within 90 days of operation) and shorter lengths of stay (by approximately 3 days) which are significant considering the higher rate of multiple comorbidities and older age in the MIRP population within this study. Those undergoing MIRP were three times more likely to receive salvage therapy (ADT or EBRT) within 6 months of surgery and, in contrast to the previous analysis, experienced a higher rate of anastomotic strictures. However, an important limitation is the fact that patient and tumor characteristics, including clinical or pathological stage, lymph node examination and involvement, and preoperative PSA and Gleason score, were not adjusted for during the analysis. Although this is not likely to affect perioperative or anastomotic complication rate or length of stay, the proportion of patients receiving salvage therapy is likely to be higher in those with worse pathologic features. In addition, patients of higher volume minimally invasive urologists required salvage therapy less frequently and developed fewer anastomotic strictures, supporting the concept that increased surgeon experience may help to improve outcomes in terms of sexual and urinary function as well as cancer control [9].

## Prostate Cancer Outcomes Study (PCOS)

In 1994, the NCI initiated the Prostate Cancer Outcomes Study (PCOS) to investigate variations in the treatment of prostate cancer and the associated HRQOL outcomes in a large heterogeneous population of newly diagnosed prostate cancer patients. The PCOS was intended to be a comprehensive and generalizable source of outcomes data. Patients diagnosed with biopsy-proven adenocarcinoma of the prostate between October 1, 1994, and October 31, 1995, in six of the SEER cancer registries were eligible for the PCOS. The centerpiece of the data collection effort was a survey designed to obtain self-reported HRQOL information at different intervals following diagnosis [10]. Several of the early PCOS publications concentrated on urinary and sexual function following RP. Stanford et al. categorized 8.4 % of patients as incontinent (frequent urinary leakage or no urinary control) at 18 or more months following RP. The proportion of men bothered by the lack of urinary control was 8.7 % at 2 years. Age was related to level of urinary control, frequency of incontinence, and bother, and younger men regained function at a more rapid rate than older men. At 18 or more months following surgery, 59.9 % of patients were classified as impotent (erections not firm enough for sexual intercourse). Two years following RP, 41.9 % of patients categorized their level of impotence as a moderate-to-big problem. Sexual dysfunction was related to both age and race.

African-American men had a higher percentage of adequate erections (38.4 %) compared to Whites (21.3 %) or Hispanics (25.9 %) [11]. A PCOS analysis of both 2- and 5-year outcomes following RP was conducted by Penson et al. A slightly higher rate of 10.4 % reported incontinence at 2 years which increased significantly to 13.9 % 5 years following diagnosis. Urinary bother scores remained stable over this time period. Two years following diagnosis, 78 % reported erections not firm enough for intercourse compared to 72 % 5 years following diagnosis. The unexpected improvement in function may have been due to the introduction of sildenafil as an erection aid or a true late recovery of the neurovascular bundles. There was also a significant decline in patients reporting sexual function as a moderate-to-great problem during this interval (54 % at 24 months to 46 % at 60 months). An important finding was the fact that those patients undergoing a bilateral nerve-sparing procedure were more likely to report sufficient erections at both 2 and 5 years when compared to those undergoing a non-nerve-sparing operation. A significant limitation of studies using PCOS data is the recall bias secondary to the fact that baseline (pretreatment) urinary and sexual function scores were collected 6 months after diagnosis. This "retrospective recall" by patients was validated by the authors, but ideally, this data would have been obtained immediately following diagnosis [12]. In terms of RP, urinary and sexual function scores show an expected decline in the early stages following intervention with stabilization later in the postoperative period.

Potosky et al. utilized the PCOS questionnaire to examine functional and general health-related outcomes of patients who had undergone RP or EBRT as primary treatment for clinically localized prostate cancer. The analyses examined results 2 and 5 years following diagnosis. At baseline, patients undergoing RP tended to be younger and had fewer systemic symptoms, lower baseline PSA levels, and better disease-specific function. As expected, the RP group experienced more urinary complications. The rate of incontinence (no control or frequently leaking or dripping urine), leakage of urine more than twice per day, wearing pads to stay dry, and bother secondary to these symptoms were significantly higher in the RP group compared to the EBRT population at both 2- and 5-year intervals. It is important to note that no statistically significant differences were found between incontinence summary scores from year 2 to year 5, indicating relative functional stability between study periods. In terms of urinary bother, men who underwent EBRT indicated greater bother with slow or difficult urination as well as urgency compared to the RP subset, which may be secondary to an obstructive etiology from the retained prostate. Patients undergoing EBRT as primary therapy tended to experience more bowel dysfunction than RP patients. Specifically, bowel urgency and painful hemorrhoids remained statistically significantly worse after 5 years in the EBRT population. Although there was a pattern of less bowel bother in RP after 5 years, only passing mucus from the rectum was shown to be statistically significantly less bothersome.

In terms of sexual function, the between-treatment group difference in impotence (inability to achieve an erection sufficient for intercourse) became smaller at 5 years than it had been at 2 years following diagnosis. At 2 years, 82.1 % in RP subset vs. 50.3 % in EBRT subset reported impotence; at 5 years, 79.3 % vs. 63.5 % reported impotence, respectively. Analysis of the sexual domain summary scores demonstrated a slight improvement in RP patients and slight decline in EBRT patients at 2 years following diagnosis. However, a large statistically significant difference in the change in the summary scores was exhibited between years 2 and 5. Men who had undergone RP experienced only small declines in sexual function summary scores, while EBRT patients exhibited large declines in their scores over this interval. This corroborates the concept of slow but progressive radiation-induced fibrosis resulting in collateral involvement of the cavernous nerves and leading to a delayed decline in sexual function in EBRT patients. There were no statistically significant differences in bother due to sexual dysfunction across treatment groups. However, overall sexual function was problematic for 41–62 % of the entire cohort with the highest concerns being achieving or maintaining an erection, satisfying one's partner, and lack of sexual enjoyment.

General HRQOL outcomes were examined using the Medical Outcomes Study (MOS) short form (SF)-36 instrument which evaluates the physical role, emotional role, pain, vitality, and mental health of respondents. At both the 2- and 5-year intervals, no significant differences in general health outcomes were found between treatment groups [13, 14].

## Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE)

The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study is similar to the PCOS in that it utilizes a longitudinal, observational registry for men with biopsy-proven prostate cancer. The registry contains demographic and clinical information on patients treated at more than 30 community-based, academic, and Veterans Administration sites. Disease-specific and general HRQOL data were collected using patient-completed questionnaires including elements from the SF-36 and UCLA Prostate Cancer Index (PCI) [15]. In an analysis of urinary outcomes, Litwin et al. found that immediately after treatment, those undergoing RP had significantly worse urinary function scores than those treated with EBRT. However, the scores for surgery patients improved dramatically so that by the end of year 1, the scores between the two modalities were similar.

Over the course of year two, the slopes for urinary function remained flat and parallel, indicating very little difference between the two treatment groups. An important caveat is the fact that the PCI is designed to assess urinary leakage but not irritative symptoms which are normally experienced following EBRT. The fact that the EBRT group had a higher rate of anticholinergic use indicates the possibility of more irritative symptomatology than elucidated by the questionnaire. Patients who received EBRT acknowledge more urinary bother immediately after treatment and over the course of the following 2 years. This result is somewhat surprising given the superior urinary function experienced during the first year in the EBRT group [16].

Several studies utilizing CaPSURE data looked specifically at sexual outcomes following intervention. Le et al. analyzed sexual function and bother results out to 4 years following RP. Only 28 % of men were categorized as having high baseline overall sexual function, which is a percentage typical for the majority undergoing treatment for prostate cancer. Patients with both low and high baseline function showed partial functional recovery at 2 years but no additional improvement at 4 years following surgery. The largest declines in the specific domains of sexual function occurred in the ability to achieve erections, the quality of erections, and awakening with erections. The least significant change occurred in sexual desire, but this domain was unique in that it did not show improvement over time in contrast to the other domains [17]. Comparing outcomes following RP and EBRT, as expected, Litwin et al. found sexual function significantly better in the EBRT group immediately following treatment. Both groups showed improvement at comparable rates during the first year. However, in the second year, the EBRT population showed a statistically significant decline in function while the RP group continued to show improvement in sexual function scores. Several other key findings have also been shown to be true in a number of population-based prostate cancer studies. Older men were much less likely to regain sexual function following treatment, in part, attributable to worse baseline sexual function scores. Over time, sexual bother did not change significantly. Sexual function, age, and general health perceptions were all associated with sexual bother, with sexual function being the strongest predictor. Finally, although erectile aids enhanced sexual function, the use of them significantly worsened sexual bother, which suggests dissatisfaction among patients depending on medication for erections [18].

CaPSURE study data was utilized by Huang et al. to evaluate changes in HRQOL from baseline to 4 years after a variety of treatment modalities including RP, EBRT, BT, combination EBRT/BT, or ADT. Age at diagnosis, time from treatment, and primary treatment were all significant predictors of HRQOL in all domains except primary treatment on sexual bother. As expected, RP patients experienced the most detrimental effect on urinary function but also exhibited the most significant recovery. As seen in other studies, little change in functional results was seen in the surgery and radiotherapy groups beyond year 2. In terms of urinary bother, all groups beside ADT experienced decreases in scores during year 1 with recovery during year 2. The ADT group exhibited a subtle gradual decrease in urinary function and bother over the course of the 4-year follow-up period. Sexual function and bother trends were similar between the treatment modalities. All groups experienced significant worsening in both categories immediately following treatment. The RP subset showed the largest decline and, once again, the greatest recovery in both sexual function and bother. Each form of radiotherapy worsened bowel function and bother with recovery almost back to baseline during year 1. The majority of adverse outcomes developed immediately after treatment and recovery commonly occurred within 2 years of intervention [15]. Lubeck et al. investigated HRQOL outcomes up to 2 years following RP, EBRT, ADT, and observation. Disease-specific outcomes mirrored those reviewed previously in this report. Urinary function, sexual function, and sexual bother decreased markedly immediately after surgery. In addition, general HRQOL measures including physical functioning, role limitations because of physical health, energy/fatigue, and health change in the past year declined significantly after treatment. One year following RP, dramatic improvement was seen in these domains as well as a number of other HRQOL measures including urinary bother, bowel function, emotional well-being, and social functioning. For EBRT, ADT, and observation patients, there were no noticeable decrements in HRQOL over the course of the study [19].

## Conclusion

Population-based studies are essential in investigating diseases such as prostate cancer in which prevalence and survival are high and a diverse set of treatments affect HRQOL. The SEER-Medicare-linked database, PCOS, and CaPSURE study provide short- and long-term data regarding the functional and general HRQOL outcomes seen in 1,000 of men treated for clinically localized prostate cancer over the past two decades. The most commonly utilized and studied treatment modality is RP. Although MIRP has increased exponentially in popularity over the past few years, the only advantages consistently exhibited appear to include a shorter hospital length of stay and less perioperative complications. However, no studies have shown a distinct minimally invasive advantage in terms of surgical outcomes, and in fact, some investigations have shown higher rates of anastomotic strictures, incontinence, and erectile dysfunction in these patients, at least during the early period of disseminated use. Patients undergoing RP in a high-volume center or by

a high-volume surgeon also tended to experience fewer perioperative complications. In terms of urinary and sexual function scores, RP patients showed significant decrement immediately after the surgical intervention followed by partial recovery of function. EBRT patients tended to experience more urinary and bowel bother, as well as a delayed decline in sexual function scores. The majority of adverse outcomes developed immediately after treatment and recovery commonly occurred within 2 years of intervention. Other treatment modalities, including BT and ADT, have not been as closely examined resulting in insufficient evaluation of functional and general HRQOL outcomes following therapy.

Given the large heterogeneous nature of the data collection, several limitations are evident. First, the patients were not randomized to treatment. This introduces selection bias based largely on the practice patterns and preferences of the consenting urologist. Second, the variations in technique for each treatment modality were not controlled for and make it difficult to generalize across the different arms. Third, there are differences in the definitions of functional impairment and the extent of bother as well as the sensitivities and specificities for these domains of the questionnaires used in the studies. Finally, although most studies made an attempt to control for a number of variables, including age, extent of disease, and use of erectile aids, most investigations fell short in their multivariate analysis given the huge number of factors that influence the treatment and recovery of prostate cancer patients. Even with these shortcomings, the trends garnered from these large population-based cohorts provide clinicians with powerful insight into long-term outcomes data and the ability to effectively counsel their patients toward the treatment that best fits their functional and general HRQOL goals.

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## Suggested Reading


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# Management of Radiation Adverse Effects

84

Seth A. Strope

As outlined in other sections of this textbook, radiation therapy is very effective for treatment of prostate cancer. As with all forms of therapy, complications can occur. In this chapter, we discuss the adverse effects of radiation therapy. We address how these complications can be avoided when possible and treated when they occur. We will focus on three major themes: (1) acute complications of radiation therapy, (2) late complications of radiation therapy, and (3) management of secondary malignancies after therapy. Since the field of radiation therapy is evolving rapidly with new delivery modalities and fractionation schemes, we attempt to provide readers with insight from current literature. However, for the rare but severe long-term side effects of therapy, historical data on management is provided.

## Grading Systems for Toxicity

The Radiation Therapy Oncology Group (RTOG) has created a standardized reporting system for acute and late complications of radiation therapy. This system is widely used in studies that report on the early and late complications of radiation therapy. Acute gastrointestinal toxicity is generally considered toxicity within the first 3 months of radiation therapy and is graded on a scale from 1 to 5. Grade 1 gastrointestinal toxicity reflects increased frequency or a change in bowel habits that do not require medications. Grade 2 toxicity includes diarrhea that requires medical management, but no sanitary pads, or abdominal pain where analgesics are needed. Grade 3 toxicity includes diarrhea where adjuvant support is needed, bloody rectal discharge, or abdominal distention. Grade 4 toxicity includes bowel obstruction, fistula, perforation, bleeding requiring transfusion, or abdominal pain requiring tube decompression or bowel diversion. Grade 5 toxicity is death. Chronic radiation toxicity is also graded on a 1–5 scale. Grades 1 and 2 include diarrhea, cramping, and bloody discharge, with the separation between the grades based on the frequency and severity of the symptoms. Grade 3 toxicity is obstruction or bleeding requiring surgery. Grade 4 toxicity includes necrosis, perforation, or fistula. Grade 5 is death related to late effects of radiation.

| | GI toxicity | |
|---|---|---|
| | Acute | Chronic |
| Grade 1 | Increased frequency or a change in bowel habits that do not require medications | Diarrhea, cramping, and bloody discharge |
| Grade 2 | Diarrhea that requires medical management, but no sanitary pads, or abdominal pain where analgesics are needed | More severe diarrhea, cramping, and bloody discharge requiring medical intervention |
| Grade 3 | Diarrhea where adjuvant support is needed, bloody rectal discharge, or abdominal distention | Obstruction or bleeding requiring surgery |
| Grade 4 | Bowel obstruction, fistula, perforation, bleeding requiring transfusion, or abdominal pain requiring tube decompression or bowel diversion | Toxicity includes necrosis, perforation, or fistula |
| Grade 5 | Death | Death |

Similar scales were created for genitourinary complications. Acute urinary complications occur in the first 3 months after radiation. It is interesting to note that many authors in the assessment of brachytherapy use a longer time period, up to 1 year, for the assessment of acute urinary issues [1]. Grade 1 toxicity includes frequency of urination or nocturia not requiring medications. Grade 2 includes urinary symptoms needing local anesthetic. Grade 3 toxicity includes more severe bladder or pelvic pain where narcotic use is needed or gross hematuria. Grade 4 toxicity includes more severe hematuria, as well as

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**Table 84.1** GU Toxicity

| | Acute | Chronic |
|---|---|---|
| Grade 1 | Frequency of urination or nocturia not requiring medications | Bladder epithelial atrophy and microscopic hematuria |
| Grade 2 | Urinary symptoms needing local anesthetic or other medications | Urinary frequency and gross hematuaria |
| Grade 3 | More severe bladder or pelvic pain where narcotic use is needed or gross hematuria | Severe voiding symptoms, frequent gross hematuria, or reduced bladder capacity |
| Grade 4 | More severe hematuria requiring operative intervention, as well as ulceration or necrosis | Necrosis of tissue, contracted bladder, or severe hemorrhagic cystitis |
| Grade 5 | Death | Death |

ulceration or necrosis. Grade 5 toxicity is death. Chronic toxicity to the urinary system focuses on hematuria and voiding dysfunction as well. Grade 1 includes epithelial atrophy and microscopic hematuria. Grade 2 includes urinary frequency and gross hematuria. Grade 3 toxicity includes severe voiding symptoms, frequent gross hematuria, or reduced bladder capacity. Grade 4 toxicity includes necrosis of tissue, contracted bladder, or severe hemorrhagic cystitis. Grade 5 toxicity is death related to radiation late effects (Table 84.1).

An interesting point in the toxicity grading systems is the lack of inclusion of sexual side effects. Also, these systems have classically been assessed by the physician based on patient interviews. Many studies of acute and long term functional outcomes are beginning to use self-reported patient data. Instruments such as the expanded prostate cancer index composite (EPIC) in either long (EPIC-50) [2] or short forms (EPIC-26) [3] are validated for the assessment of patient outcomes. Another multi-domain instrument is the Prostate Cancer Symptom Index (PCSI) [4]. These instruments allow assessment of urinary incontinence, urinary irritation or obstruction, bowel, sexual, and vitality/hormonal domains. Work has been done with both instruments to translate their findings from research projects to clinical utility for decision-making [5, 6].

Alternatives to these multifaceted instruments in wide use include the American Urological Association Symptom Index (AUA-SI) which is also called the International Prostate Symptom Score (IPSS) [7, 8]. This instrument gives an assessment of urinary bother and has been widely used in the brachytherapy literature to evaluate post implantation urinary toxicity. Some authors also have reported on erectile function after radiation therapy using the Sexual Health Inventory for Men (SHIM) [9, 10]. This instrument allows assessment of erectile function based on five questions regarding erectile function over the previous 6 months.

## Acute Complications

### Rectal Toxicity

Prevention of rectal toxicity centers on safe delivery of the effective dose of radiation with sparing of the rectum. Three-dimensional conformal bean radiation therapy (3D-CRT) was a vast improvement over conventional radiotherapy since the prostate is localized by CT scan prior to treatment planning [11]. Effective doses of radiation could be delivered with relative rectal sparing. This rectal sparing is important since radiation doses to the rectum over 60 Gy are associated with Grade 2 and greater rectal toxicity [12]. IMRT represents a further advance in therapy, with the potential for even less rectal toxicity than was achieved with 3D-CRT. Sandler and colleagues compared early toxicity of IMRT-treated patients with electromagnetic tracking to 3D-CRT patients and found lower rates of rectal toxicity [13]. Furthermore, whole pelvis radiation therapy is associated with increased GI toxicity compared to prostate-only radiation therapy [14].

The time course for development of toxicity is mediated by the type of radiation therapy administered. Patients treated with conventional radiation developed toxicity between 10 and 35 days after the start of therapy. Patients treated with hypofractionated regiments developed toxicity between 9 and 65 days after the start of their therapy [15]. The time course of development of symptoms may be important for attempts at preventing toxicity or treating symptoms when they develop.

Little randomized evidence exists on how to treat the symptoms of acute rectal toxicity after radiation therapy. Minor symptoms are best treated conservatively. Diarrhea can be treated with parasympatholytic drugs such as Lomotil or Imodium. More severe diarrhea (Grade 3) could require hospitalization for fluid resuscitation. Almost uniformly, rectal bleeding should be managed conservatively without biopsy of suspicious areas in the post-radiation period. Rectal biopsy risks development of prostatourethral-rectal fistula [16]. Conservative management of severe (Grade 4) rectal bleeding involves hospitalization for blood transfusion and supportive care. Other conservative management choices include proctofoam and mesalamine enemas [17]. Other treatment options include topical anti-inflammatory medications including steroid enemas, sucralfate, and 5-ASA compounds.

Mechanisms to prevent rectal toxicity have been explored by some groups. One such method is the injection of Hyaluronan Gel between the rectum and the prostate. In a randomized study, Prada and colleagues found that use of hyaluronic acid injections decreased rectal doses from brachytherapy [18]. Additionally, in a small phase 1 study, Wilder and colleagues showed that 9 mL of hyaluronic acid

gel could be safely injected into the anterior perirectal fat prior to radiation therapy [19]. The gel increased the distance between the rectum and the prostate by 8–18 mm. All patients received high dose rate brachytherapy followed by an IMRT boost. None of the ten patients who received the injection experienced rectal toxicity versus 29.7 % in the authors' historical controls. More studies on the use of this strategy would be needed to see if it could decrease rectal toxicity in other types of radiation therapy and if the results are durable.

### GI Toxicity

In addition to direct rectal toxicity, patient can also experience nausea and emesis with radiation therapy. These symptoms are typically self-limited. Some patients may require antiemetic medications. The type of radiation therapy given can influence these symptoms. Patients who receive whole pelvis radiation therapy have more symptoms than those receiving prostate-only radiation.

### Genitourinary Toxicity

Acute genitourinary toxicity after radiation therapy for prostate cancer is often difficult to treat. Fortunately for most patients treated with external beam radiation therapy, the symptoms of frequency, urgency, and nocturia are usually short lived. At 1 month after therapy, only about 25 % of patients continue to have symptoms, and by 4 months, symptoms typically resolve completely [20]. The time of onset can vary from within a few days after starting therapy to up to 60 days after therapy began [15]. Standard therapies administered to patients while awaiting spontaneous resolution of symptoms include phenazopyridine, ibuprofen, and alpha blockers. Alpha blockers appear to have the most success with 66 % of patients experiencing symptomatic relief compared to only 16 % with NSAIDS [21]. Interestingly, patients who are on alpha blockers prior to brachytherapy may experience worse urinary toxicity than patients who are not on such therapy [22]. For refractory symptoms, sending urine for culture is reasonable and checking for retention is indicated. Depending on the study, from 0 to 0.8 % of men undergoing external beam radiation therapy develop acute urinary retention [20, 23, 24].

For men with severe voiding dysfunction, risks of genitourinary toxicity after external beam radiation therapy are increased. Indeed, severe voiding dysfunction is considered a possible contraindication to receiving radiation therapy [25]. Controversy exists as to the effects of prior TURP on urinary toxicity. Protective effects have been noted by some authors [26], while other authors note increased rates of acute toxicity [27, 28]. As for patients with urinary retention after brachytherapy, conservative management with clean intermittent catheterizations is needed. The radioactivity in the implanted seeds needs to reduce before a TURP should be contemplated. The commonly used isotopes of $^{125}$I and $^{103}$Pd have half-lives of 59.6 and 17 days, respectively. Some authors have called for avoidance of surgery for 1 year after brachytherapy implants [29]. These recommendations are related to the higher rates of urinary incontinence seen after TURP in this setting [30].

## Late Complications

### Urinary Issues

Late genitourinary toxicity is defined as problems occurring over 3 months after external beam radiation therapy and over 12 months after brachytherapy. While these complications are often minor and controlled with medications, some more severe complications such as recurrent hemorrhagic cystitis, stricture formation, and fistula can occur. We will address the management of these complications and highlight situations where these complications may be prevented.

#### Risk Factors for Development of Late Genitourinary Toxicity

Despite multiple studies, little agreement exists on what factors lead to the development of late genitourinary toxicity after external beam radiation therapy [31]. Reported factors include prior TURP [27, 32], androgen deprivation [27], presence of acute toxicity [33], prior medication for LUTS [23], and patient age [23]. These risk factors will not be easily modified. Other studies have examined the issue of preexisting LUTS on late genitourinary toxicity. For patients with urinary obstruction/irritation before therapy, Chen and colleagues noted improvement in most patients with external beam or brachytherapy by 36 months after treatment [34]. Similar results were noted by Sanda and colleagues in their assessment of external beam and brachytherapy [3]. By 24 months after therapy, most patients had returned to their baseline level of function, with prostate size and hormonal therapy associated with increased irritation or obstruction symptoms.

#### Therapy for Obstructive/Irritative Symptoms

As with acute urinary toxicity, alpha blockers are the first line therapy for obstructive and irritative symptoms in chronic urinary toxicity after radiation therapy. If this medication is not sufficient, addition of antimuscarinic medications can improve symptoms. For refractory voiding symptoms, TURP can be done [35, 36]. Care must be taken with such therapy as the risk of incontinence may be increased in the

post-radiation therapy setting [30]. Also, patients treated with brachytherapy may experience a transient symptom flare 16–24 months after seed implantation [37]. These transient symptoms should be managed conservatively.

### Therapy for Incontinence

Incontinence is a rare complication after external beam or brachytherapy for prostate cancer. Eighty-three percent of patients with no problems with incontinence prior to therapy continue to have no problems after therapy, and only 1 % develop severe problems with incontinence [34]. Also, stress incontinence is rare, with most patients experiencing incontinence from urgency symptoms [11, 23, 38]. Work-up for these men includes cystoscopy to assess for urethral necrosis (for brachytherapy patients), urinalysis and urine culture to exclude infection, and a 24-h pad test to quantify the amount of incontinence [39]. Urodynamics may be needed to fully delineate stress from urgency incontinence. As with post-prostatectomy stress incontinence, conservative management with physical therapy and biofeedback can be a first step in management. Other options include a bone anchored sling for lower levels of incontinence and an artificial urinary sphincter (AUS) for more severe incontinence. The AUS has been implanted successfully after radiation [40, 41]. Caution may be advised with bone anchored slings as some authors have found worse results with this modality in post-prostatectomy patients also treated with radiation therapy [42].

## Severe Toxicity

### Hemorrhagic Cystitis

Late hemorrhagic cystitis is a rare but often problematic complication of pelvic radiation therapy. Initial treatment involves bladder irrigation and management with blood transfusions as necessary. If symptoms do not improve quickly with this conservative management, clot evacuation in the operating room with fulguration of bleeding areas is often required. An important point to note is that all patients will need cystoscopy, even if the hematuria resolves with conservative measure, to rule out the presence of a bladder tumor. After clot evacuation, intravesical agents including alum irrigation [43], formalin instillation [44], or silver nitrate irrigation [45] can be instituted.

Alum is administered as a 1 % solution for a period of 1–4 days [46]. While anesthesia is not required, complications include suprapubic pain and bladder irritation. Serum aluminum levels may need to be monitored as increases have been seen with chronic alum irrigation [47]. Aluminum toxicity presents as encephalopathy or seizures and is related to pre-existing renal insufficiency [48].

Formalin is a painful therapy that must be administered under general or spinal anesthesia. 37.8 % formaldehyde is administered as a 1–10 % solution. Use of a preinstillation voiding cystourethrogram has been advocated to rule out reflux into the ureters since the formalin may cause ureteral obstruction if reflux exists [39]. Fatal sepsis has been reported after use of formalin irrigation [44]. Formalin irrigation is considered a last choice in therapy.

Silver nitrate provides an alternative irrigant in the treatment of radiation-induced hemorrhagic cystitis. Irrigation is typically used as a 0.25–1 % solution. Little information regarding use of this therapy is available. Good success was seen in a case series of children who had hemorrhagic cystitis after cyclophosphamide or pelvic radiation for cancer therapy [45]. Problems with this treatment have included anuria from deposition of silver salts [49]. Other case reports have shown similar problems when reflux is present and silver nitrate irrigation is used [50]. As with formalin irrigation, performance of a voiding cystourethrogram is probably warranted before using silver nitrate irrigation therapy.

Systemic therapies reported for use in refractory hemorrhagic cystitis include D-glucosamine, estrogens, and tetrachlorodecaoxide formulated for intravenous administration. A Cochrane review by Denton and colleagues found no strong evidence to support any of these systemic therapies [51]. An alternative systemic therapy is aminocaproic acid. This medication inhibits fibrinolysis and is not FDA-approved for the treatment of hemorrhagic cystitis. The oral dose in prostatic surgery has been 6 g daily in divided doses, and high concentrations of the drug are achieved in the urine. One study used a dose of 150 mg/kg/day in divided doses for up to 21 consecutive days to control gross hematuria [52]. This was an observational study of nine patients with no control group. Case reports of obstruction of the kidneys due to fibrin clot formation after use of the medication have been published [53, 54]. Aminocaproic acid has also been used as an intravesical irrigant at a dose of 20 mg/100 ml [55].

When bleeding continues despite conservative measures, cystoscopy, and irrigations, more invasive therapy may be required. Internal iliac artery embolization has been used in cases of severe life-threatening hemorrhage [56, 57]. Initially, unilateral embolization is performed. If this is not effective, a bilateral embolization can be done. Such therapy is not without risk, with gluteal pain a common side effect [57]. More severe side effects are possible including necrosis of the bladder, rectum, and gluteal muscle.

Another option for treatment of refractory hemorrhagic cystitis is urinary diversion. Diversion can be initially accomplished with percutaneous nephrostomy tubes. Although little literature exists to support this practice, such diversion makes sense from a mechanistic standpoint. Removing the urine from the bladder should decrease bladder distention and lessen the risk of rupture of friable blood vessels. A report of using cutaneous ureterostomy for a similar effect showed good results, with 11 of 16 patients completely free

of hematuria and a further three patients with only slight intermittent hematuria [58].

For truly refractory hemorrhagic cystitis, cystectomy with urinary diversion is necessary. Such surgery is highly morbid, especially after radiation therapy to the pelvis. In a review of patients treated with cystectomy after high-dose radiation therapy at the University of Southern California, 44.6 % of patients have low-grade complications, 32.4 % had high-grade complications, and the mortality rate was 6.1 % [59]. Laparoscopic cystoprostatectomy for hemorrhagic cystitis has been reported [60]. An alternative to radical cystectomy is a simple cystectomy. Such procedures avoid major vessels in men and women and avoid prostate resection in men [61]. While diversion with just an ileal conduit can be performed, leaving a defunctionalized bladder can cause complications in up to 54 % of cases [62].

### Stricture

Strictures are a rare late complication of radiation therapy for prostate cancer. Stricture formation occurs in 0–3 % of patients after external beam therapy [11, 24, 63–67] and 0–14.5 % after brachytherapy [63, 64, 68–70]. As with other stricture diseases, patients complain of decreasing urinary stream, urgency, frequency, straining, or acute urinary retention. Treatment should parallel that of non-radiation-related strictures since evidence specific to treatment of radiation-related strictures is lacking. Short strictures of the anterior urethra can be initially treated with dilation or DVIU. Recurrent or recalcitrant strictures need definitive management since success decreases with subsequent dilations [71]. Urethroplasty can be performed successfully, but prior radiation may lead to decreased success [72].

Posterior urethral (bladder neck) strictures can be treated with more dilations or incisions. These interventions can be done at least twice before moving on to other therapy. After failure of conservative measures, a TURP may be required [73]. The risk for post operative incontinence is increased in this clinical situation. Another alternative is urethroplasty, with some authors reporting good results in this challenging setting [74].

### Fistula

Rectourethral fistula after radiation therapy to the pelvis is a rare complication. It seems to be more of a risk after brachytherapy than external beam therapy [16, 75–77]. Treatment involves initial stabilization of the patient and treatment of any associated sepsis of pelvic abscess. Spontaneous closure rarely occurs [75]. Often initial fecal diversion is required [75–78]. This is combined with urinary diversion with a suprapubic catheter. Supportive care is then given for 3–6 months to allow the patient to recover for subsequent surgery and determine if the bladder and rectum are salvageable. Such repair is often challenging due to surrounding tissue damage from the radiation.

### Sexual Issues

Sexual dysfunction is often a problem after radiation therapy for prostate cancer. Only 26 % of patients with normal function before external beam therapy and 46 % with normal function before brachytherapy can be expected to have continued normal function 3-year posttreatment [34]. Hormonal therapy has a strong impact on these results, with significantly greater sexual dysfunction in men treated with neoadjuvant hormonal therapy than in those not so treated [3]. The mainstays of treatment for sexual dysfunction are the phosphodiesterase-5 inhibitors: tadalafil, sildenafil, and vardenafil. Such therapy given early in the post-radiation period may help preserve function [79]. For symptoms refractory to these medications, intraurethral preparations of alprostadil can be used. When these therapies are not sufficient, treatment with intracavernosal injections can improve erectile function. Some men also find improvement with a vacuum erection device. For men with neoadjuvant hormonal therapy, return of libido may not occur until androgen function returns. This recovery takes place over a variable time period and is often delayed in men with more than 24 months of androgen deprivation [80, 81].

## Rectal Complications

Chronic rectal bleeding can be a challenge to manage after radiation therapy. After conservative interventions have failed, endoscopic or surgical interventions may be required. Endoscopic interventions can be performed in the late setting using cauterization to control bleeding sites [82]. Argon plasma coagulation has also been advocated for the control of late rectal bleeding [83]. Instillation of formalin can control the bleeding areas [84]. Such therapy may be improved with administration of oral vitamin A [85]. Hyperbaric oxygen chambers have also been used in an attempt to control late rectal bleeding [86]. A Cochrane review also suggests a role for hyperbaric oxygen therapy in the treatment of radiation proctitis [87]. For truly refractory bleeding, a diverting colostomy may be needed.

Such complications cannot be prevented with prophylactic measures. A randomized study of rectal prostaglandin suppositories given prophylactically during radiation therapy showed no decrease in acute or late rectal toxicity [88]. Alternative methods of radiation delivery also do not prevent long term rectal complications. With long-term follow-up to a median of 9.1 years after proton beam therapy, 20 % of patients treated with proton beam therapy reported at least 1 highly bothersome bowel symptom [89].

A recent review by the Cochrane Collaboration examined the nonsurgical interventions for late radiation proctitis [90]. The authors examined the evidence for use of aminosalicylic

acid derivatives, corticosteroids, sucralfate, short chain fatty acid enemas, formalin application, coagulation therapies, analog of superoxide dismutase, hyperbaric oxygen, and pentoxifylline. Only six randomized controlled studies were available for the review. The authors conclude that rectal sucralfate or metronidazole in addition to anti-inflammatories and heater probes appears to be effective, but the evidence base to support these interventions is limited.

Another complication related to rectal toxicity is fecal incontinence. Overall, fecal incontinence occurs in about 5 % of elderly community-dwelling men. Risk of incontinence was increased by both a history of radical prostatectomy or radiation therapy for prostate cancer [91]. No therapies are available for this long term toxicity.

### GI Toxicity

Late GI toxicity is possible after radiation therapy. Problems with late development of small bowel obstruction [92, 93], fistulas [94], and short bowel syndrome [95] are possible. Treatment of these issues is usually conservative if possible. Surgery needs to be undertaken with care as the bowel is often damaged by the radiation and further complications from surgery are a definite possibility.

## Secondary Malignancy

Development of a secondary malignancy has been a concern in patients who receive radiation therapy. An early study exploring this risk using population-based registry data found the risk of bladder cancer from 5 to 8 years after radiation therapy was increased about 30 % over the expected level. For patients with over 8 years of follow-up, bladder cancer risk was elevated about 50 % [96]. Similar results were noted in an update from SEER data with increased risk of bladder cancer found only in patients receiving external beam radiation therapy [97]. This increased risk is possibly mediated by tobacco consumption, with smokers exposed to radiation therapy having a 3.5 times higher risk of bladder cancer than nonsmokers treated with radical prostatectomy [98]. Such tumors may be of higher stage and grade than cancers found in patients not previously exposed to radiation [99, 100]. Prostate radiation therapy has been associated with a small increased risk for secondary solid tumors besides bladder cancer in a few studies [97, 101, 102]; however, risk outside of the primary beams appears to be minimal [103]. Finally, proton therapy may reduce the risk of secondary malignancy compared to IMRT [104].

Despite the increased relative risk of bladder cancer seen after radiation therapy for prostate cancer, the overall incidence of such tumors is small. Thus, no screening program can be advocated. However, these risks are potentially amplified by treating younger prostate cancer patients with radiotherapy, as they will be at risk for secondary tumors longer. Following radiotherapy, all patients who are current smokers should have smoking cessation counseling [105]. Patients with hematuria, gross or microscopic, should be evaluated with cystoscopy and urine cytology. Such assessment may also be reasonable for patients with persistent dysuria or urgency. Any bladder cancer found should be treated with standard techniques. For patients requiring radical cystectomy, complications and mortality may be increased after radiation therapy [59].

### Conclusions

While radiation therapy for prostate cancer provides a minimally invasive modality for therapy, complications and toxicity after treatment can occur. Such complications can be managed successfully in most cases. Unfortunately, little randomized data exists to help guide care. Ultimately, urologists and radiation oncologists need to leverage the resources available at their institutions to take care of the patients and their complications as best as they can.

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# Management of Complications Following Minimally Invasive Prostate Cancer Therapy

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Paul Cathcart and Anthony J. Costello

## Introduction

Minimally invasive techniques such as high-intensity focused ultrasound (HIFU), cryotherapy, and photodynamic therapy are increasingly employed to treat men with both primary and radio-recurrent prostate cancer [1–7]. The use of these technologies is aimed at reducing the well documented toxicity of more traditional prostate cancer treatments, such as radical surgery or radiotherapy, and is hypothesized to result in improved perioperative outcomes and long-term "quality-of-life." The efficacy of these minimally invasive treatments is discussed in a prior chapter; however, the aim of the current chapter is to review the incidence of complications arising from such therapies and discuss their management. It must be noted however at the outset that there are limited data on the outcome of management strategies employed to treat men experiencing adverse events following minimally invasive prostate cancer treatment [8].

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## Brief Introduction to Minimally Invasive Techniques

Within the clinical setting, high-intensity focused ultrasound (HIFU) and cryotherapy are by far the two most commonly used minimally invasive technologies employed for the treatment of organ-confined prostate cancer worldwide. In contrast, alternative minimally invasive techniques, such as photodynamic therapy (PDT) and interstitial laser thermal therapy (ILTT) [9], remain confined to the research setting. All therapies aim to achieve highly controlled and directed local cancerous tissue necrosis, often referred to as tissue ablation, while preserving normal surrounding structures.

### Prostate High-Intensity Focused Ultrasound (HIFU)

Transrectal HIFU therapy was initially employed in the early 1990s as a minimally invasive alternative to transurethral resection of the prostate (TURP) for the treatment of men with symptomatic benign prostatic hyperplasia (BPH) [10]. However, the long-term efficacy and durability of HIFU was found to be inferior to that of TURP and as such, its popularity waned [11, 12]. However, about a decade later, several groups began to use the technology as a minimally invasive alternative for the treatment of localized prostate cancer [13, 14] as well as other solid organ cancers such as renal cell cancers of the kidney and primary and metastatic liver cancers [15].

HIFU therapy aims to generate thermal, mechanical, and cavitational disruption of targeted tissues by using the inherent properties of ultrasound [16, 17]. Tissue damage is achieved when an ultrasound wave is brought into a tight focus within a targeted tissue. This tight focusing is achieved either using an

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acoustic lens within the ultrasound transducer or by using a bowel-shaped transducer. Providing the energy density during the high-pressure phase of the focused ultrasound is of sufficient magnitude to achieve a local tissue temperature greater than 60 °C, coagulative necrosis is induced within the tissue causing cell death. The volume of tissue damage achieved by a single HIFU exposure is very small being about 10 mm by 1–2 mm on average. As a result, to achieve organ ablation, multiple overlapping lesions are required.

HIFU therapy for the most part is delivered transrectally and is guided using dual ultrasound transducers of varying frequency (4.0–7.55 MHz) which are built into the treatment probe itself. Given the transrectal nature of HIFU, some have argued that HIFU therapy may result in higher rectal injury rates than therapies which are performed in a transperineal manner (e.g., third-generation cryotherapy), especially in the salvage setting [18]. In this regard, work is ongoing to evaluate a new HIFU system which uses magnetic resonance imaging to guide a transurethral HIFU system which may have a safer rectal toxicity profile to the transrectal device [19].

Currently there are two commercially available HIFU devices, both of which deliver therapy transrectally. Although both devices vary considerably, especially with regard to how the therapy is monitored and controlled, neither device has been shown definitively to be safer than the other.

## Prostate Cryotherapy

Cryotherapy induces tissue damage or ablation by generating extreme cold temperatures within target tissues and has been used to treat cancers of many solid organs including the breast and cervix as well as the kidney and prostate. Such extreme low temperatures together with subsequent thawing has been demonstrated to result in a number of antineoplastic effects including direct cytolysis resulting from extracellular and intracellular ice crystal formation, intracellular dehydration, ischemic necrosis, and induction of apoptosis among others.

Cryotherapy was first employed for the treatment of prostate disease in the mid 1960s [20]. Like HIFU therapy, the first clinical application of this technology was BPH treatment with the treatment of localized prostate cancer coming almost a decade later.

Prostate cryotherapy has changed dramatically since its first inception. As a result, cryotherapy systems are often referred to as either, first, second, or third generation depending upon their level of sophistication. First-generation systems employed simple liquid nitrogen that was poured down large funnels into target structures, such as the prostate. The mode of administration for these first-generation systems was either via the urethra (transurethral) or via an open perineal approach. Later came the much improved second- and third-generation systems. These systems were able to generate extreme low temperatures by utilizing the Joule-Thomson effect which refers to the physical property of liquid gases to generate low temperatures when they rapidly change state into gaseous form. By pumping highly pressurized liquid argon gas through a specialized cryotherapy probe, the temperature at the tip of the probe can be rapidly cooled to −187 °C. This enables an area of frozen tissue to be generated at the probe tip, referred to as a cryotherapy "ice-ball." In addition, the second- and third-generation cryotherapy probes employed a second gas—helium—which was exchanged for argon when maximum "freeze" was achieved to enable a rapid thawing phase. As well as speeding the process of cryotherapy thus allowing a second freeze-thaw cycle to be performed—a process subsequently demonstrated to achieve a higher cell-kill—the use of helium allowed a faster "operator-response" to ice-ball advancement. This use of argon and helium gas, together with the use of real-time transrectal ultrasound, thermocouples, and urethral warming devices, enabled second- and third-generation cryotherapy systems proved to be markedly safer than their first-generation counterparts. As a result, reported complication rates from surgical case series that employed more contemporary second- and third-generation prostate cryotherapy systems were much lower than those reported following use of first-generation systems [21, 22].

## Vascular-Targeted Prostate Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) is a relatively new cancer therapy that is being evaluated in a number of different cancer types, including prostate cancer. PDT utilizes a light-sensitive agent—known as a photosensitizer—which when activated by light, is able to induce tissue damage by the creation of highly reactive oxygen species. The photosensitizer is essentially a drug which can be administered either via the bloodstream or by topical application. Light is subsequently delivered to the photosensitizer which has preferentially accumulated within cancerous by use of a laser fiber of a specific wavelength. Prostate PDT is often referred to as vascular-targeted photodynamic therapy as WST-09 (the photosensitizer used for prostate PDT); a bacteriochlorophyll derivative that absorbs light as 763 nm has its effects on the blood vessels supplying the cancerous tissue within the prostate, namely, by inducing thrombosis and vascular occlusion [23]. Few data exist to date on the safety and efficacy of prostate PDT. Thus, understanding the complications and their management is still in the nascent stages. Intraoperative hypotension can be a problem during the administration of WST-09 and is usually managed by intravenous fluid administration. Dysuria, urinary retention, and perineal discomfort also have been reported secondary to the perineal administration of laser fibers to the prostate. While paradoxical

cerebral emboli and thrombophlebitis have been reported rarely with WST-09, newer agents (e.g., WST-11) are water-soluble and expected to have a much lower incidence of thromboembolic complications [1–24].

### Magnetic Resonance-Guided Prostate Interstitial Laser Thermal Therapy (ILTT)

Interstitial laser thermal therapy (ILTT) is the newest minimally invasive technology being evaluated for the treatment of localized prostate cancer [10]. ILTT utilizes laser energy which is absorbed by the target tissue generating high tissue temperatures (>100 °C) resulting in thermal coagulation and thermal necrosis. Although lasers have been used extensively for the treatment of BPH, they have rarely been used for the treatment of prostate cancer. Now, lasers in the near-infrared region are being employed to ablate prostate cancer lesions using magnetic resonance imaging guidance. Data on the use of image-guided ILTT is limited to one or two case reports, and as such the complication rate and subsequent management have yet to be established and so have not been discussed in this chapter, sufficed to say that the application of any energy modality when applied to the prostate has the potential to damage the normal structures surrounding the prostate such as the rectum with the well known ensuing complications.

## Primary Versus Salvage Minimally Invasive Therapy

As mentioned in an earlier chapter, the oncological efficacy of minimally invasive therapies for the treatment of localized prostate cancer—be that primary cancer or locally recurrent cancer—is limited. However, it is well known that complication rates following all of the minimally invasive therapies which aim to cause tissue ablation are markedly higher in the salvage setting [25]. Furthermore, once a complication has occurred, e.g., a rectourethral fistula, the management of such complications is often much more demanding, needing more extensive intervention.

## Complications of Minimally Invasive Prostate Cancer Therapies and Their Management (Table 85.1)

### Impotence and Erectile Dysfunction

The rate of impotence and erectile dysfunction following both primary (47–100 %) and salvage cryotherapy (86–100 %) is very high (Table 85.1) [26–28]. While impotence rates following HIFU therapy may be slightly lower (primary 0–77 %, salvage 70–100 %) [29, 30], overall, both therapies do have a marked impact on sexual function; furthermore, when comparing different outcomes of different minimally invasive therapies, it must be noted that the quality of data available is very poor. Impotence and erectile dysfunction is due, as one would expect, to damage caused to the penile arterial blood supply and the cavernosal nerves, which are closely adherent to the prostate (Table 85.1).

The management of impotence and erectile dysfunction after minimally invasive therapy is similar to that recommended after radical surgery. Initial management with phosphodiesterase type 5 inhibitors (PDE-5) has been demonstrated to result in improved erectile scores, especially if given as part of an early aggressive penile rehabilitation program [31]. In those men in whom PDE-5 inhibitors have not been successful, potency can be restored using intracavernosal prostaglandin therapy and vacuum pump devices. For example, Robinson reporting on 38 men following prostate cryotherapy found that 34 % of men can be made to be potent if a combination of PDE-5 inhibitors, intercavernosal injection, or vacuum pump devices are employed [32]. Finally, the last report is to offer men a penile implant; however, to date, there is no data reporting outcomes of penile implants in men that have undergone prior minimally invasive prostate cancer therapy. However, one would expect outcomes to be similar to that reported following surgery.

Research is underway on how to avoid impotence altogether. For example, Onik and colleagues have proposed a tissue-preserving approach whereby the neurovascular bundles are spared [33]. Using this rationale onik has demonstrated that 90 % (36/40) of men are able to maintain satisfactory potency. Others have used integrated Doppler ultrasound to visualize the neurovascular bundles in a hope that this will result in improved erectile function rates. The future may ultimately include improved image registration systems incorporating high-resolution magnetic resonance imaging, sophisticated ultrasound mapping, and tissue characterization systems that are built into the treatment platforms [34].

### Incontinence

Rates of incontinence following minimally invasive therapy vary from as low as 1 % for primary therapy to as high as 73 % following salvage therapy [22]. With regard to cryotherapy, a number of technical modifications have been incorporated in third-generation systems in an attempt to reduce the incidence of stress incontinence, including urethral warming catheters and the use of strategically placed thermocouples [35]. For example, temperature monitoring (thermocouples) has been seen to reduce incontinence rates following two cycles (freeze/thaw) from 9 to 4 % [36], a

**Table 85.1** Studies reporting incidence of complications following prostate HIFU and cryotherapy in the primary and salvage setting

| | No. of patients | Adverse events | | | | | | Intervention rate |
|---|---|---|---|---|---|---|---|---|
| | | Incontinence | Impotence | Fistula | LUTS | Stricture | Infection | |
| *Primary cryotherapy* | | | | | | | | |
| El Hayek et al. [44] | 47 | 13 % | ■ | 0 % | ■ | ■ | ■ | ■ |
| Jones et al. [27] | 1,198 | 4.8 %<br>2.9 % pads | 75 %<br>8 % potent without PDE5 | 0.4 % | ■ | ■ | ■ | ■ |
| Shelley et al. [22] (Cochrane review) | 1,483 | 1.3–19 % | 47–100 %<br>Bladder neck – (2–55 %) | 0–2 % | ■ | 2.2–17 % | ■ | ■ |
| Creswell et al. [45] | 51 | 4 % | 86 % | 0 % | ■ | ■ | ■ | 4 % TURP |
| Anastasiadis et al. [46] | 131 | 5.9 %<br>10 % salvage | 89 %<br>90 % | ■ | ■ | ■ | ■ | ■ |
| De La Taille et al. [47, 48] (26 % rectal pain) | 16 primary<br>19 salvage | 6 %<br>11 % salvage | ■ | ■ | ■ | ■ | 3 % | ■ |
| *Salvage cryotherapy* | | | | | | | | |
| Pisters et al. [26] | 279 | 4.4 % (pads) | ■ | 1.2 % | ■ | 3.2 % | ■ | 3.2 % TURP for slough |
| Ismail et el. [28] | 100 | 13 % | 86 % | 1 % | 16 % | ■ | ■ | ■ |
| Siddiqui et al. [49] | 18 | 3 % worsening inc. (post RRP) | ■ | ■ | ■ | ■ | ■ | ■ |
| de la Taille [47, 48] BOO 5 % | 43 | 9 % | ■ | ■ | 5 % (haem) | 5 % | 5 % | ■ |
| Pisters et al. [35] | 150 | 73 % | 72 % | ■ | 67 % | ■ | ■ | ■ |
| Bales et al. [50] (100 % complication) | 23 | ■ | ■ | ■ | ■ | ■ | ■ | 55 % TURP |
| *Primary HIFU* | | | | | | | | |
| Sumitomo [51] | 129 | ■ | ■ | ■ | ■ | No TURP 16/65 (24 %)<br>TURP 7/64 (11 %) | ■ | ■ |
| Warmuth [52] | 20 articles<br>3,018 | ■ | 1–77 % | 0–15 % | ■ | ■ | 1–58 % | ■ |
| Netsch [53] | 226 | ■ | ■ | ■ | ■ | 26 % BOO<br>11 % repeated BOO | ■ | ■ |
| Ripert [29] | 65 (74 procedures)<br>55 primary<br>10 salvage | 20 % | 77 % | 0 % | 5.4 % dysuria | 9 % | 3.6 % | 7/64 (49 % complication rate) |
| Uchida [39] | 517 | ■ | 29 % | ■ | ■ | ■ | ■ | ■ |
| Ahmed [6] | 172 | 7 % no pads<br>0.6 % pads | 30 % | 0 % | ■ | 19 % SPC<br>40 % Ureth. | 24 % | ■ |
| Kock [30] | 20 | ■ | ■ | 1/20 (5 %) | ■ | ■ | ■ | ■ |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Blana | 223 single treatment<br>49 repeat | 7.6 % single<br>12 % | 50 %<br>55 % | ■ | ■ | 20 % | 0.4 % | ■ |
| Chaussy [3] | 184 | ■ | ■ | ■ | ■ | ■ | ■ | 33 % |
| *Salvage HIFU* | | | | | | | | |
| Uchida [14] | 22 | 4 (18 %) Grade 1 | ■ | 1 (4.5 %) | ■ | 1 (4.5 %) | 1 (4.5 %) | |
| Netsch [53] | 363<br>1.1 % primary<br>4.5 % salvage<br>13.6 % repeat | ■ | ■ | 8 (2.2 %) | ■ | ■ | ■ | 8/8 surgery (4/8 RRP, 3/8 Gracillis flap, 1/8 exenteration) |
| Berge [55] | 46 | 15.2 % (7) Grade 2<br>1 (2.1 %) Grade 3 | 5/7 (71 %) | 1 (2.1 %) Rectourth<br>2 (4.2 %) Urethcut | ■ | ■ | ■ | Fistula managed cons |
| Chalasani [56] (review) | ■ | 10–50 % | ■ | 0–16 % | ■ | ■ | ■ | ■ |
| Zacharakis [41] | 31 | 7 % | ■ | 7 % | ■ | 36 % | 26 % | ■ |
| Murat [57] | 167 patients<br>194 treatments | 11 % sphinter | ■ | 0 % | ■ | ■ | ■ | ■ |
| Poissonnier [58] | 72 | 44 % (12 % Grade 1, 32 % Grade 2/3) | ■ | ■ | ■ | 30 % | ■ | ■ |
| Gelet [59] | 71 | 7 % Grade 3 | ■ | 6 % | ■ | 17 % | ■ | ■ |

trend mirrored in a recent Cochrane review on outcomes of cryotherapy. Furthermore, avoidance of transurethral surgery immediately before prostate cryotherapy, a procedure performed on occasion to reduce the incidence of urethral stricture following HIFU and on occasion cryotherapy, has been demonstrated to reduce the incidence of incontinence following therapy [37].

In men that experience incontinence, minimally invasive therapy, treatment includes pelvic floor physiotherapy, urinary sphincter or sling insertion, and as a last resort urinary diversion. Use of periurethral bulking agents has been described in men that have undergone prostate cryotherapy; however, it has been reported that especially in the salvage setting, the bulking agent is hard to inject and is said to easily erode through the urethral mucosa. Erosion is also a problem for men undergoing artificial urinary sphincter insertion, although acceptable outcomes have been reported in the literature [37]. With regard use of slings for incontinence, data is sparse but many hope they may be helpful for men, not with severe urinary incontinence but for those with mild to moderate symptoms.

## Tissue Sloughing/Lower Urinary Tract Symptoms

Tissue sloughing—the passage of necrotic prostate tissue per urethra—is a complication often reported in the prostate cryotherapy literature with a reported incidence of between 14 and 85 % [36, 38], although it does not appear such a common problem following HIFU therapy [39]. Furthermore, the incidence of tissue sloughing following salvage cryotherapy is said to be higher than following primary treatment. Classically, this adverse event tends to occur between 3 and 8 weeks following therapy. Use of urethral warming devices has been demonstrated to dramatically reduce the incidence of this complication [26], which may result in urinary retention and is said to occur in about 3–4 %. Still, a significant proportion of men will have persistent lower urinary tract symptoms resulting from obstructive necrotic tissue following minimally invasive therapy, many of which (3–10 %) will require a transurethral resection of the prostate (TURP) [22].

It must however be noted that in men that have undergone transurethral resection, the rate of incontinence is high, up to 50 %, and as such the majority should undergo limited resection [37]. Furthermore, many men will benefit from urethral dilatation as opposed to a formal resection, often with the use of serial "S"-shaped urethral dilators passed over a guideline which has been passed into the bladder cystoscopically prior to dilatation. Patients should then be advised to perform intermittent self dilatation with urinary catheters in an attempt to reduce recurrent obstruction. Of those undergoing HIFU therapy using the Sonoblate device, it has been reported that roughly one-fifth of men will be required to perform some form of intermittent urethral dilatation during their follow-up [39]. Recently, it has been suggested for men undergoing HIFU therapy that using a suprapubic catheter may reduce the incidence of stricture formation by 50 %. Furthermore, certainly for the Ablatherm HIFU device, transurethral resection of the prostate prior to therapy is said to reduce the incidence of post-therapy stricture formation from 30 % to less than 10 % [6].

## Urinary Tract Infections

The incidence of following minimally invasive therapy varies drastically mainly as a result of differing study protocols which limit the ability to identify the true incidence of this complication which is often managed in the community setting. By and large, the majority of these men improve with antibiotics. Occasionally, these men will require urethral catheterization, especially if the infection is accompanied by tissue sloughing and obstructive urinary symptoms.

## Pelvic and Rectal Pain

Pelvic or rectal pain following cryotherapy and HIFU are well recognized as tenesmus. Pain may be as a result of anal dilatation during probe placement at the time of therapy or from perineal bruising following insertion of cryotherapy probes. Alternatively, pain may be a direct result of rectal wall ischemia and trauma—either through freezing or heating—damage to the pelvic side-wall musculature, or damage to other periprostatic structures such as the pubic bone. Initially, men are best managed with simple analgesics—especially nonsteriodal anti-inflammatories (NSAIDS). In addition, on occasion, nitroglycerine suppositories may be helpful. However, persistent pelvic or rectal pain is of grave concern and should be investigated—often by rigid cystoscopy and EUA (examination under anesthesia) and pelvic magnetic resonance imaging (MRI), as it is imperative to exclude a rectourethral fistula or abscess.

## Rectourethral Fistula

The incidence of this devastating complication is highly dependent on whether therapy is being performed in the primary or salvage setting varying from around 0 % to as high as 15 % [40, 41]. The incidence and management of rectourethral fistula following minimally invasive therapy is expanded on in another chapter in this book suffices to say, the majority of men should undergo delayed definitive repair approximately 4–6 months following diagnosis, a

period sufficient to enable the marked inflammatory process to resolve. In the intervening period, patients are often best managed with both urinary and fecal diversion by means of a covering colostomy and a suprapubic catheter. In addition, patients will often require intravenous antibiotic therapy for any acute episodes of sepsis. With regard to repair, depending on the degree of collateral tissue damage, surgical treatment options include a Gracilis muscle flap interposition, transrectal trans-sphincteric repair, radical prostatectomy and re-anastamosis, and pelvic exenteration, among others [42].

## Penile Numbness

Penile numbness is a well documented complaint by patients undergoing cryotherapy, said to occur in around 10 % of men. It is thought to be due to trauma to the pudendal nerve, and the majority of men report that the numbness resolves over a 2- to 3-month period following therapy. Thus, simple analgesics and reassurance should be given to men complaining of this symptom following therapy.

## Hydronephrosis and Other Complications

Hydronephrosis and small bowel injury have been reported and are due to excessive ablation, especially when treating the seminal vesicles. With regard to hydronephrosis, a percutaneus nephrostomy followed by and subsequent delayed antegrade stenting is recommended. On occasion, formal ureteric reimplantation will be required.

## Cryoshock

Finally, a condition named cryoshock can rarely occur after cryotherapy. In this disorder, patients experience a syndrome of multiorgan failure, severe coagulopathy, and disseminated intravascular coagulation. Although exceptionally rare after prostate cryotherapy (2 out of 5,432), it is associated with a high rate of perioperative death (18 %) [43]. Management of this condition should always be in the critical care setting.

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# Part VIII

# Management of Emergencies and Palliative Care

Steven A. Kaplan and Alexis E. Te

# Prostate Cancer Emergencies

86

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## Introduction

Urological emergencies of prostate cancer are increasingly becoming more common and may present to emergency departments, general physicians, and urologists. Importantly, they may result in pain and discomfort (urinary retention and skeletal fractures), loss of function (neurological complication or priapism), or in rare cases death (bone fractures, infected obstructed kidneys, and sepsis). Hence, it is mandatory to have a full understanding of the clinical presentation of these emergencies, and in addition, appreciation of rapid diagnosis and expeditious treatment is mandatory. This chapter reviews the presentation, diagnosis, and clinical treatment of acute emergencies related to prostate cancer and the complications of treatments.

The following conditions are reviewed:

- Bone-related events
  - Skeletal fractures
  - Hypercalcemia
  - Spinal cord compression
- Ureteric obstruction
- Sepsis
- Urinary retention
- Anemia
- Malignant priapism
- Hepatotoxicity

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## Bone-Related Events

Bone metastases and skeletal complications are major causes of morbidity and mortality in prostate cancer patients, typically occurring in more than 80 % of patients with advanced prostate cancer. The typical sites involved include the spine, pelvis, and rib cage. The commonest urological emergencies include skeletal fractures, spinal cord compression, and hypercalcemia.

## Clinical Manifestations

| |
|---|
| Bone pain |
| Skeletal fractures |
| Hypocalcemia |
| Hypercalcemia |
| Spinal cord compression |

## Bone Pain

Pain is the commonest symptom of bone metastases. Conventional analgesia including nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opiate and opiate medications has an important role in the care of patients in pain with cancer. Doses should be escalated as described in the well-known WHO three-step pain relief ladder. Specialist pain team should be involved, especially for patients for escalating uncontrollable pain.

Bisphosphonates have been evaluated in several meta-analyses, and evidence demonstrates that pain is altered or reduced with bisphosphonates [1].

External beam radiotherapy is widely used for the treatment of pain resulting from bone metastases at any site. It may be effective for up to 12 months. Different radiotherapy regimens ranging from a single dose of 8 Gy to fractionated regimens of 30 Gy in ten doses appear to be equally effective [1]. The rate of pathological fracture is lower with multifractionation

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regimens, but single dose radiotherapy may sometimes be repeated. Interestingly, although useful for the pain of vertebral involvement by metastatic disease, radiotherapy does not abolish mechanical pain which may progress to bony instability, vertebral collapse, and spinal cord compression.

## Skeletal Fractures

Fragility fractures are common and have an increasing incidence with increasing age. The most common causes of acquired osteoporosis in men are hypogonadism, chronic glucocorticoid therapy, and excessive alcohol intake. Androgen deprivation therapy (ADT) for men with prostate cancer causes severe hypogonadism. Lifelong ADT is a common treatment for men with prostate cancer. ADT erodes bone mineral density, accelerates bone turnover, and elevates fracture risk [2].

Vertebral bodies are the most common site of fracture, though pelvic, rib, and long-bone fractures are also seen. Fracture risk assessment tools are available. The online FRAX tool [3] has defined clinical risk factors as prior fragility fracture, family history of hip fracture, current tobacco smoking, chronic use of glucocorticoids, daily consumption of at least three units of alcohol, rheumatoid arthritis, and other causes of secondary osteoporosis such as ADT.

Clinical trials have consistently shown that bisphosphonates improve bone mineral density in men receiving ADT for prostate cancer. Alendronate, pamidronate, and zoledronic acid have all been shown to improve bone mineral density in the clinical setting.

Selective estrogen receptor modulators, such as raloxifene and toremifene, have also been shown to improve bone mineral density in men treated with ADH for prostate cancer [2]. Bone mineral density alone is an inadequate surrogate for fracture risk. Fracture prevention is used for end points in clinical trials. Denosumab and toremifene have both been shown to significantly reduce fracture risk.

Vertebroplasty and kyphoplasty are minimally invasive techniques which have been used in persistently painful spinal fractures including metastatic disease, but patient selection is crucial. The evidence for treating metastatic involvement is small. There is risk involved including cement leakage causing spinal cord compression. This should only be performed in patients with no evidence of spinal cord compression or spinal instability. It should only be performed after agreement between appropriate specialists including oncologists, interventional radiologists, and spinal surgeons. It is not commonly used in prostate cancer as bone metastases are radiosensitive, often multiple and limited availability of access to local spinal surgery facilities.

Spinal surgery can also be considered for patients with spinal metastases and imaging evidence of structural spinal failure with spinal instability. This helps to stabilize the spine and prevent metastatic spinal cord compression. It can also be considered for intractable pain even if a patient is completely paralyzed.

## Hypocalcemia

Low serum calcium can occur commonly due to its consumption, excessive bone formation, and deposition by osteoblasts, but it is usually asymptomatic. Parathyroid hormone stimulates osteoclast formation by inducing RANKL expression in bone marrow stromal cells and osteoblasts. Hypocalcemia caused by osteoblast-driven calcium phosphate deposition may stimulate PTH production. Subsequent secondary hyperparathyroidism is common. This creates a cycle of osteoclast activation, growth factor liberation from bone matrix, tumor cell proliferation in the bone, osteoblast activation, calcium phosphate deposition, and secondary hyperparathyroidism [4].

Hypocalcemia can also occur after bisphosphonate administration, most frequently following IV infusion and can occur in patients with high rates of osteoclast-mediated bone resorption (such as patients with substantial skeletal tumor burden).

## Treatment Options

The importance of assuring adequate vitamin D and calcium intake prior to starting therapies such as bisphosphonates is overlooked by many practitioners. Low vitamin D is common among elderly patients who have limited sun exposure, reduced dietary intake, and some renal impairment. Vitamin D deficiency limits dietary absorption of calcium, leading to secondary hyperparathyroidism and loss of skeletal calcium to maintain normocalcemia. National Osteoporosis Foundation suggests a calcium intake of 1,200 mg/day for men over the age of 50.

# Hypercalcemia of Malignancy

Hypercalcemia is the most common metabolic disorder in patients with cancer and occurs in up to 20 % of patients with solid tumors [5]. Hypercalcemia is defined as a corrected serum calcium ($Ca^{2+}$) concentration >2.6 mmol/L. Forty percent of plasma calcium is bond to albumin and is biologically inactive.

## Pathophysiology of Hypercalcemia

The underlying mechanisms include increased parathyroid hormone-related protein (PTHrP) production, bone-resorbing

cytokine secretion (mostly with bone metastases), tumor-mediated calcitriol production, and, rarely, ectopic parathyroid production. Humoral hypercalcemia, which results from secretion of parathyroid hormone-related protein, accounts for approximately 80 % of cases in cancer patients [6]. PTHrP is a protein similar to PTH. It binds to the PTH receptor, mimicking the physiological effects of PTH. This includes bone resorption, increased calcium resorption ion in the distal renal tubule, and inhibition of phosphate transport mechanism in the proximal renal tubule. Osteolytic bone metastases account for approximately 20 % of cases of cancer patients, but this may be a higher percentage in prostate cancer.

## Clinical Features

The clinical features are nonspecific, often leading to a delay in diagnosis and increased morbidity and mortality. They have classically been described as "bones, stones, abdominal groans, and psychic moans." Clinical presentation is influenced by rate of onset and severity of hypercalcemia.

Symptoms are as follows:

| |
|---|
| Nausea |
| Vomiting |
| Constipation |
| Anorexia |
| Weight loss |
| Bone pain |
| Polyuria |
| Polydipsia |
| Fatigue |
| Weakness |
| Bone tenderness with metastases |

Neurological symptoms tend to occur at calcium levels >3.5 mmol/L (14 mg/dL) and include:

Confusion

Lethargy

Coma

Dehydration due to concentration defects in renal tubules, nausea, vomiting, and decreased fluid intake is common. This can be further compounded by nephrogenic diabetes insipidus resulting from raised serum calcium concentrations.

## Management

A thorough history and examination is needed, remembering that malignancy accounts for two-thirds of patients requiring admission for treatment of hypercalcemia [7].

Discontinuation of oral calcium supplement and medications may induce hypercalcemia.

| *Examples of drugs that induce hypercalcemia* |
|---|
| Lithium |
| Vitamin D |
| Thiazides |
| Nonsteroidal anti-inflammatory agents |

Monitoring of fluid and urinary output should be monitored strictly. Intravenous fluid resuscitation improves renal function and inhibits calcium reabsorption in the renal tubules. It increases the glomerular filtration rate, thus increasing the load of filtered calcium passing into the renal tubule lumen. Rate of fluid administration depends on the severity of dehydration, cardiovascular status, and renal function. An infusion of isotonic saline at a rate of 200–500 mL/h is appropriate. Serum calcium should fall by 20–40 % after 6 h [5, 8]. Intravenous saline therapy alone is rarely adequate to correct anything more than mild hypercalcemia. Patients should be monitored for signs of congestive heart failure. Correction of hypophosphatemia, if detected, can minimize severity of the hypercalcemia. A loop diuretic (frusemide) should be used after adequate rehydration to increase renal excretion of calcium. A dose of 20–40 mg intravenously has been recommended. Side effects are dehydration and hypokalemia.

Following rehydration bisphosphonates are the recommended first-line medical treatment. Bisphosphonates are the most effective agents in treating hypercalcemia of malignancy. A recent systematic review showed that bisphosphonates can normalize serum calcium in >70 % of patients within 2–6 days with minimal side effects [9]. Nadir is reached within 7–10 days. A second dose of bisphosphonate can be given 7–10 days after initial dose in patients where the serum calcium does not return to normal. Evidence supports the use of intravenous pamidronate and zoledronate as the agents of choice [10]. Zoledronate is simpler to use and has shown greater efficacy than pamidronate in trials, but it is more expensive. Bisphosphonates should be given every 3–4 weeks but with care in patients with impaired renal function as detailed below. Pamidronate is given as 60–90 mg intravenously over 2 h in 100–200 mL of saline or 5 % dextrose.

Zoledronate is given as 4 mg intravenously over 15 min in 50 mL of saline or 5 % dextrose [11].

Although the majority of patients respond to rehydration and bisphosphonates, a minority are resistant to treatment, and such patients should be referred for a specialist endocrinology opinion. Further options include gallium nitrate, salmon calcitonin, and glucocorticoids. If not already initiated, consideration of anticancer therapy should also be considered. The prognosis of patients diagnosed with malignancy-associated hypercalcemia remains poor, with a median survival of <12 months.

## Bisphosphonates

Bisphosphonates are the most commonly used class of bone-targeted drugs. Their central carbon and two phosphate groups make them structurally similar to inorganic phosphate, an essential component of normal bone. They are easily incorporated into bone due to the phosphate groups' high affinity for the calcium in bone. They bind to hydroxyapatite crystals. They are preferentially incorporated into sites of active bone remodeling. Once localized to bone, they are inhibitory to osteoclast that encounter and ingest them. In addition, bisphosphonates inhibit hydroxyapatite breakdown and suppress bone resorption. Skeletal uptake and retention are dependent on host factors such as renal function, bone turnover, and binding-site availability. Bisphosphonates not retained in the skeleton are rapidly cleared from circulation by renal excretion. They are remarkably specific for bone. Maximum suppression of bone desorption occurs within 3 months of initiation of oral bisphosphonate therapy, more rapid after intravenous administration. It remains roughly constant with continuation of treatment after this time.

This makes them primary agents in such as osteoporosis, Paget's disease of bone, malignancies metastatic to bone, multiple myeloma, and hypercalcemia of malignancy. Currently available bisphosphonates, listed form lowest to highest potency, are etidronate, clodronate, pamidronate, alendronate, ibandronate, risedronate, and zoledronic acid [12].

Pamidronate gained approval as an intravenous bisphosphonate for prevention of disease-related skeletal events in patients with bone disease from multiple myeloma or bone metastases from breast cancer in 1995. Zoledronic acid gained approval in 2002 for patients with myeloma and bone metastases from prostate, breast, or lung cancer.

Zoledronic acid (4 mg every 3–4 weeks) is standard care for the prevention of skeletal-related events in men with castration-resistant prostate cancer and bone metastases. Zoledronic acid reduces skeletal-related events in men with metastatic castration-resistant prostate cancer. Skeletal-related events are generally defined as need for surgery or radiotherapy to bone and anticancer treatment for bone pain, pathological fractures, or spine cord compression. Zometa has not been shown to benefit men without bone metastases or men with hormone-sensitive bone metastases [13, 14]. The best-known paper is the Zometa 039 study [14]. This was based on 4 mg of zoledronic acid every 3 weeks for 15 months versus placebo involving 643 men with castration-resistant prostate cancer and asymptomatic or minimally symptomatic bone metastases. This showed a significant decrease in skeletal-related events and showed a trend toward improved survival. This is alongside ADH therapy. Initially, another group received higher doses of 8 mg, but this was decreased to 4 mg due to associated nephrotoxicity. Randomized controlled trials have not shown bisphosphonates to prevent bone metastases.

Clodronate and pamidronate have failed to show the same effects in trials as zoledronic acid in this clinical setting.

### Side Effects of Bisphosphonates

| *Complication* | |
|---|---|
| *Hypocalcemia* | Usually asymptomatic and can generally be prevented with calcium and vitamin D supplementation |
| Acute-phase reaction | Usually a self-limiting flu-like syndrome that usually begins within 24 h of the infusion and may include fever, nausea, and vomiting<br>Approximately 10–30 % of patients receiving their first nitrogen-containing bisphosphonate infusion will experience an acute-phase reaction. This rate declines by more than half with each infusion [15] |
| Acute renal failure | Renal toxicity consists of a spectrum from asymptomatic elevation of creatinine to dialysis dependency<br>Several recommendations attempt to minimize the risk of renal toxicity. The maximum single dose is 4 mg. All treatments should be infused over a minimum of 15 min<br>If normal baseline creatinine rises greater than 0.5 mg/100 mL or if abnormal baseline creatinine rises greater than 1 mg/100 mL, further doses should be held until the creatinine returns to within 10 % of baseline |
| Osteonecrosis of the jaw | This is an area of nonhealing, exposed or necrotic maxillofacial bone. It is a rare complication. Its incidence has been shown to be 0.8–12 % with intravenous therapies [16]<br>Associated risk factors appear to be poor oral hygiene, a history of dental procedures or denture use, and exposure to high IV bisphosphonate use<br>Several recommendations have been made to reduce the risk by the American Association of Oral and Maxillofacial Surgeons. They recommend oral examination with extraction of nonrestorable teeth before bisphosphonate treatment. If extractions are performed, 2–3 weeks delay should occur before starting bisphosphonates. Avoidance of bisphosphonates should be considered for 3 months on either side of elective dental surgery. Early lesions of osteonecrosis are treated with chlorhexidine. Antibiotics are added for intermediate lesions. More advanced lesions are managed with surgical debridement and antibiotics |

## Denosumab

Denosumab is a human monoclonal antibody that binds to and inhibits the aforementioned RANKL. It has an extremely high affinity for human RANKL. RANKL is important to the regulation of osteoclast differentiation, survival, and activation. It has been reported to be effective in reducing the risk for clinical fractures among men at elevated risk due to age and andro-

gen deprivation [17]. Denosumab reduced the 3-year incidence of new vertebral fractures by 62 % compared with placebo. Ongoing phase III trials will evaluate its ability to prevent bone metastases in men with castrate-resistant prostate cancer and to prevent skeletal-related events in men with castrate-resistant prostate cancer and existing bone metastases. Though toxicities have been comparable to placebo, ongoing investigation and follow-up are needed to further define the risks of long-term therapy. To date, nephrotoxicity and osteonecrosis of the jaw have not been observed. It does not accumulate in bone and has a long circulatory half-life (>30 days).

## Metastatic Spinal Cord Compression

Metastatic spinal cord compression (MSCC) is a well-recognized complication of cancer. The true incidence of spinal cord compression is unknown. Studies indicate it affects 5–10 % of patients with advanced cancer. This is thought to be an underestimate due to poor detection rates and incorrect coding in hospitals. It is suggested 80 % of patients diagnosed with metastatic spinal cord compression had an established diagnosis of cancer, making it an initial presentation in 20 % of patients [18].

MSCC occurs when there is vertebral body collapse or direct tumor growth causing compression of the spinal cord or cauda equina. Irreversible neurological damage ensues with resulting paraplegia. Early diagnosis and treatment are essential to prevent neurological damage, decrease morbidity, and improve quality of life for the patient. Median survival following a diagnosis of MSCC is reported as 2–3 years, but survival in prostate cancer (and hematological malignancies) has been shown to be longer, with 66 % surviving longer than 3 months [1].

### Pathophysiology

Three mechanisms are responsible for MSCC, the commonest being hematogenous spread to the vertebral spine causing collapse and compression. This accounts for 85 % of cases. Less commonly, it occurs secondary to direct tumor extension into the vertebral column or by direct deposition of tumor cells.

The cause of damage to the spinal cord from compression is complex and multifactorial. Direct compression results in edema, venous congestion, and demyelination. If the compression is gradual and of resent onset, with some preservation of neurological function, the effects are often reversible. With prolonged compression, vascular injury ensues causing infarction of the spinal cord making recovery unlikely.

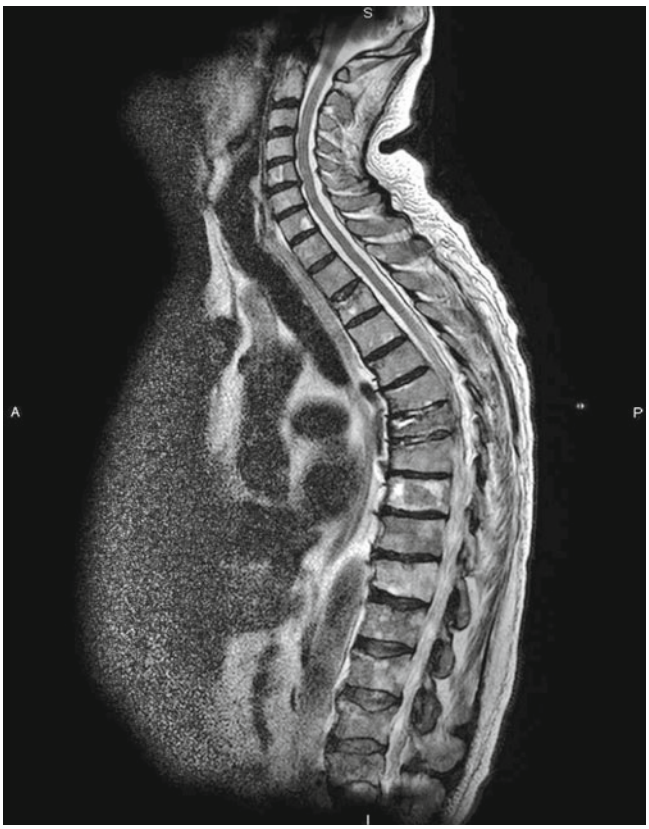
### Clinical Features

Localized back pain and tenderness are the most common and earliest features of MSCC. It is classically described as pain localized to the spinal column area which is worse on lying flat. It is typically progressively severe and may be exacerbated by coughing, sneezing, or bending. It is often present for several months before diagnosis. Back pain that awakens the patient from sleep is a sinister sign.

Weakness of the limbs is the second commonest presentation. It can present with symmetrical spastic paralysis. Only 18 % of patients can walk without help at presentation. Preambulatory function is the most important factor in determining posttreatment outcomes. Eighty percent of patients who are ambulatory at presentation continue walking after treatment. Only 10 % of nonambulatory patients regain their mobility [5, 8]. Patients who develop paraplegia have a significantly impaired quality of life and shortened survival.

Sensory symptoms are common and include paresthesia, decreased sensation, and numbness of toes. Symmetrical loss of sensation at anatomical level can be present in up to 65 % of cases, but dermatome sensory level often does not correlate well with radiological findings [7]. Increased or absent knee and ankle reflex and extensor plantar reflex are noted on examination. Autonomic functions such as distended bladder and bowel dysfunction are late presentations, affecting approximately 50 % of patients.

### Imaging: Magnetic Resonance Imaging (MRI)




MRI showing spinal cord compression due to metastatic vertebral body collapse at T7 level

Patients with suspected spinal cord compression should be referred for urgent magnetic resonance imaging of the whole spine. It is imperative to image the whole spine to exclude compression at one or more levels. Ideally, an MRI should be obtained within 24 h of the patient developing symptoms as a delay may lead to deterioration in the patient's neurological status and delayed treatment and ultimately adversely affect prognosis.

MRI has a high sensitivity for identifying metastatic disease within bone when the correct sequences are used (sagittal T1 and/or STIR (short T1 Inversion recovery)). Papers have reported 96 % sensitivity. MRI can show a soft tissue component to the mass and degree of spinal cord compression. It can also differentiate between metastatic disease and other pathologies.

PET-CT is both sensitive and specific in the diagnosis of MSCC, but it is less widely available than MRI, and there is no evidence that PET-CT provides additional clinically relevant information.

Multislice CT scanning is quick and has the ability to image the entire spine. It is less sensitive than MRI for detecting metastases. It would not replace MRI but can give additional information on bone integrity and stability for planning surgery, if appropriate.

CT myelography may still be required, for patients in whom there is a specific contraindication for MRI. Alternatives may be indicated for those who have cardiac pacemakers, mechanical valves, pacemakers, paramagnetic implants, and metal shrapnel injuries or where MRI is unavailable. However, CT myelography is an invasive procedure.

Plain radiology is not as sensitive for detecting metastatic bone disease and does not show soft tissue abnormalities.

Radioisotope bone scanning is very sensitive for the detection of metastases but does not show the extent of soft tissue compression of the cord and is not reliable in detecting the level of cord compression.

## Treatment

Treatments should improve symptoms, quality of life, and survival. It needs to take into account the degree of neurological disability, the general health of the patient, the primary site of tumor, the presence of other spinal and extraspinal metastases, and the likely response to available therapies.

### Mobilization

Immediate care includes protecting spinal alignment by avoidance of movement and maintenance of cord perfusion by lying flat. This helps prevent further damage when the cord is unstable and neurology is impaired. This involves neutral spine alignment, logrolling, and slipper pans for toileting until boney and neurological stabilities are ensured.

Severe mechanical pain is suggestive of spinal column instability, and neurological impairment suggests cord instability. These are indicative of risk of damage with inappropriate mobilization.

Currently, there is no clear evidence or guidelines for physicians to determine when to start mobilization. Mobilization usually starts following radiotherapy or after spinal stabilization or following an arbitrary period of rest. It is not possible to confirm spinal stability solely through modalities such as MRI. CT and plain radiographs can help.

Once spinal shock has settled and neurology is stable, gradual sitting from supine to 60° over 3 h should be performed with close monitoring and interval assessment [4]. If no increase in pain or change in neurology is identified, gradual continuation to unsupported sitting, transfers, then mobilization can be attempted, symptoms allowing.

### Pain

Pain can be due to neural compression due to tumor expansion and is referred to as nonmechanical pain. This could be treated by analgesia, radiotherapy, and bisphosphonates.

In others, vertebral pain may be aggravated by movement and lifting. This pain can be due to weak bone. External devices such as corsets or braces for the trunk can be used with varying responses.

Rarely, for those with intractable pain, epidural or intrathecal analgesia can be considered. A multidisciplinary approach should involve pain teams and palliative care teams.

Prostate cancer metastases tend to be radiosensitive, so surgery is not as common in these patients as in other conditions that are radioresistant.

### General Considerations

The hydration and nutritional status of patients should be assessed and appropriately managed.

Appropriate measurements should be instituted to reduce the risk of pressure sores. Pressure ulcers affect quality of life and rehabilitation outcomes. Pressure-relieving mattresses, cushions, and other devices are often not enough to prevent ulcers. They can be difficult to treat once developed and can be life-threatening. Patients on bed rest must be turned every 2–3 h by logroll technique. Patients not on bed rest should be encouraged to mobilize. Encourage those unable to mobilize independently to do pressure-relieving exercises such as forward sitting/sideways leaning at least hourly when sitting out.

Risk factors for thromboembolic events include malignancy, reduced mobility, and hospital stay for greater than 4 days, all relevant to patients with MSCC. Low molecular weight heparin subcutaneously should be given in addition to thigh-length graduated compression/anti-embolism stockings unless contraindicated.

Patients in urinary retention should be catheterized. If long-term catheterization is needed, consider intermittent self-catheterization or conversion to a suprapubic catheter.

Offer neurological bowel management programs. Take account of patient preferences when offering diet modification, fecal softeners, oral or rectal laxatives, or constipating agent.

### Corticosteroids

Corticosteroids are routinely given to patients with MSCC and should be administered without delay. They are believed to reduce tumor bulk or spinal cord swelling, thereby relieving spinal cord pressure, which should improve perfusion and improve treatment outcomes. They may result in rapid improvement of neurological function, but long-term benefit is limited. A randomized small single-blinded trial on dexamethasone as an adjunct to radiotherapy showed no difference in survival, but it did show a significant improvement in ambulatory status at 6 months [19].

High-dose, long-duration treatment with corticosteroids causes significant side effects which can be debilitating. Antacids or proton pump inhibitors should be given unless contraindicated to mitigate the gastrointestinal side effects.

Overall, there is a limited body of evidence to conclusively report an advantage of high corticosteroid dose over a lower dose. A loading dose of at least 16 mg is given as soon as possible after assessment, followed by a short course of 16 mg dexamethasone daily while treatment is planned.

After surgery or radiotherapy, the dose should be reduced gradually over 5–7 days and stopped. If neurological function deteriorates at any time, the dose should be increased temporarily.

Blood glucose should be monitored in all patients receiving corticosteroids.

### Radiotherapy

Palliative radiotherapy remains the main modality in treating spinal cord compression, but there is an increasing body of evidence for direct surgical decompression followed by radiotherapy. Unfortunately, most trials involve all causes of metastatic cord compression, as opposed to solely prostate cancer patients. Prostate cancer is responsible for 15 % of presentations of metastatic cord compression. It is known to be radiosensitive, so outcomes may be different in specific cancer subtypes. Further evidence is necessary.

Radiotherapy may be delivered as a single treatment or a number of consecutive smaller treatments (fractionation). Current clinical practice is to give fractionated radiotherapy in 5–10 fractions.

Urgent radiotherapy (within 24 h) should be offered to all patients with metastatic spinal cord compression who are unsuitable for surgery, unless they have complete paraplegia for more than 24 h and their pain is well controlled or their overall prognosis is judged to be too poor.

Occasionally, patients successfully treated with radiotherapy for MSCC or have had previous radiotherapy for spinal metastases may develop signs of recurrent or new MSCC within the previously irradiated spine. There is understandable anxiety about re-irradiating the spinal cord because of the known limits of tolerance. It is generally believed that a certain amount of recovery in the spine takes place. It is felt that for patients with a limited life expectancy, in whom a few months have elapsed since radiotherapy, re-irradiation may be safe [1]. Re-irradiation has shown to improve motor function in 31–39 % of re-treated patients [20].

### Surgery

Spinal surgery may be considered to avert or treat MSCC, stabilize spinal column to treat mechanical pain or bony instability, and perform resection/reconstruction of the spinal column in the hope of a durable surgical result providing good-quality long-term survival.

Simple decompression of the spinal cord is the least demanding. Stabilization involves rods connected to pedicle screws in healthy vertebra above and below with or without posterolateral grafts. Alternatively, the diseased vertebra can be resected and replaced with bone grafts.

Operative planning requires consideration of technical aspects, goals of surgery, general fitness of patients, site and amount of metastases, presence of comorbidities, and risk of serious life-threatening complications. Prostate cancer patients are often elderly with multiple comorbidities and multiple spinal metastases, making surgery inappropriate. The patient's motivation and wishes also need to be paramount in decision-making.

However, meta-analysis of cancer papers with metastatic epidural disease suggests that in appropriately selected patients, surgery improved ability to walk compared with conventional radiotherapy [21]. Prospective studies have also shown significant improvements in ambulation, incontinence, use of opioids, and quality of life scores [22]. These are not prostate cancer population-specific, and bias concerns are raised. Further research is needed.

### Supportive Care and Rehabilitation

Rehabilitation is integral to the promotion of independence and quality of life in patients with cancer. Patients need support with functional loss and emotional distress with advancing disease. This will involve a multidisciplinary approach.

## Obstructive Uropathy

Malignant ureteral obstruction is an ominous sign in the cancer patient. Extrinsic malignant ureteric obstruction is commonly a late manifestation of metastatic disease and can be a sign of tumor compression, retroperitoneal adenopathy, or direct tumor

invasion. Median survival for patients with malignant ureteral obstruction is less than seven months regardless of the tumor of origin [23]. Overall, survival is not significantly different in patients with unilateral and bilateral obstructions [24].

Palliative decompression of the obstructed urinary system, either by percutaneous nephrostomy, ureteric stent, or both, are recognized methods of relieving obstruction. All improve renal function and sepsis. There is currently no scientific evidence to give a reliable answer to which is the optimal management of malignant ureteral obstruction.

Recent data suggests that 53 % of patient suffer with complications in the remainder of their lifetime regardless of the method of decompression, resulting in 17 % of their remaining lifetime spent in hospital [25].

Obstructive uropathy is a common complication of advanced prostate cancer. However, prostate cancer has been shown to have better survival outcome than other pelvic malignancy with mean survival post decompression of 279 days [26]. Studies have been undertaken in prostate cancer patients specifically. In patients with bilateral ureteric obstruction and renal failure, who had not yet started androgen depletion, upper tract decompression improves survival, with a mean survival of 646 days. There was also a reduction in the length of hospital stay. However, in patients already on androgen depletion, survival was only 80 days [27]. The longest overall survival of a prostate cancer patient with obstructive uropathy reported amounted to 26 months [28].

## Percutaneous Nephrostomy

Nephrostomy tubes for palliation have been used since the 1970s. It is unusual to be unable to place a tube in a dilated obstructed system. Major complications only occur in 5 % of patients [29]. Complications include blockage, displacement, sepsis, UTI, hemorrhage, hematuria, and pain.

A number of series show that median survival after percutaneous nephrostomy, to relieve ureteric obstruction from any pelvic malignancy, ranges from 4 to 6 months [30]. Between 35 and 58 % of patient are able to have their percutaneous nephrostomies converted into internal ureteric stents. Patients spend a mean of 29 days on the ward following insertion. Seventy-nine percent of patients were successfully discharged; however, each patient was readmitted on an average of 1.6 times with stent or percutaneous nephrostomy-related events prior to their death.

## Ureteric Stents

There have been significant changes in stent materials and design through the years. At present, polyurethane and silicone are the most frequently used materials in clinical practice. Recently, longer lasting endoscopic stents have been developed such as metallic stents. Endoscopic, retrograde stent placement has a 37–47 % success rate [29]. Stent insertion can be done antegrade via a percutaneous nephrostomy or retrograde with the patient under a general anesthetic. In pelvic malignancy such as prostate cancer, insertion of stents via the retrograde approach can be technically difficult. This can be due to frozen pelvic anatomy making access difficult, and identification of the ureteric opening can be difficult due to tumor compression or invasion. Complications with stents include infection, hyperplastic reactions, encrustation, tumor ingrowth, obstruction, and migration. Stent morbidity from bladder irritation is also common.

Manufacturers recommend that stents should be replaced after 4–6 months. The usual recipients of stents for malignancy are often old and frail, suffering from terminal disease. This involves regular trip to hospital and anesthetics. Dwell times for stents without complication for 10–18 months for biocompatible copolymer ureteric stents been published [31]. Not unreasonably, clinicians are resistant to leave stents in situ beyond recommended time lengths; however, arguments could be justified for leaving functioning stents in elderly patients with advanced malignant disease, with close monitoring.

## Studies Comparing Percutaneous Nephrostomy and Stents

There is more published data about percutaneous nephrostomy than retrograde stenting. The published rates of successful decompression are higher for percutaneous nephrostomy than for retrograde stenting [32]. Most studies are not comparable due to considerable differences in patient characteristics. Also, overall survival is the most common outcome measure but is influenced by various factors other than decompression method. A number of studies are small numbers or include multiple malignant pathologies making interpretation difficult. The hormonal pretreatment status seems to be a determinant of overall survival in prostate cancer patients.

The incidence of pyelonephritis or any other complication is similar for both decompression techniques [33]. Studies show a significantly higher number of irritative urinary symptoms in stent patients but more local discomfort after percutaneous nephrostomy [32].

The majority of patients have advanced disease and short life expectancy. Factors such as diagnosis, prognosis, economy, and the patient's preference should influence the choice of urinary diversion method. However, there is currently a bigger body of evidence for percutaneous nephrostomy, and there are higher documented success rates for this procedure making this the preferred option.

When an invasive decompression has been decided, it should be initiated at the onset of clinical symptoms such as pain, fever, or when renal function deteriorates. Whenever global renal function allows for unilateral decompression, the patient should be spared a bilateral manipulation [32].

## Sepsis

Severe sepsis (acute organ dysfunction secondary to infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation) are major health-care problems.

Prostate cancer patients can get sepsis for a number of reasons: urinary tract infection due to incomplete emptying and retention or catheters, pyonephrosis due to obstructed ureters, and febrile neutropenia secondary to chemotherapy and conditions unrelated to their cancer.

There are international guidelines for the management of patients with sepsis available in hospitals as part of a Surviving Sepsis Campaign. The guidelines were last revised in 2008 [34]. Due to the implementation of a protocolized resuscitation of a patient with sepsis, the 28-day mortality has been reduced. It stipulates all patients should be assessed, cultures taken, and antibiotics given within 1 h of their pyrexia.

During the first 6 h of resuscitation, the goals include:

Central venous pressure 8–12 mmHg.

Mean arterial pressure >65 mmHg.

Urine output >0.5 $mL^{-1} \cdot h^{-1}$.

Central venous saturation >70 %.

This is achieved by IV fluid resuscitation using crystalloids or colloids and oxygen therapy as appropriate. Fluid challenges of 1,000 mL of crystalloids or 300–500 mL colloids over 30 min should be given. Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement.

Two or more blood cultures should be obtained, one being obtained from percutaneous access. Blood cultures should be taken from each vascular access device in place more greater than 48 h. Other sites should be cultured as indicated. In prostate cancer patients, this would include urine including midstream or from each nephrostomy or catheter. Antibiotic therapy should begin as early as possible and always within the first hour of recognizing sepsis. A broad spectrum should be started initially with good penetration into presumed source.

If appropriate, vasopressors such as norepinephrine or dopamine can be given during septic episodes. These have to be administered centrally. In cancer patient's disease status, prognosis and quality of life must always be considered before embarking on a route which involves intensive care transfers. Most important, patients must be included in decision-making process if possible. Decisions regarding limitation of support may need discussing with patients and families.

Intravenous hydrocortisone can be considered for adult septic shock unresponsive to adequate fluid resuscitation and vasopressors. Glucose must always be monitored in this situation. Other alternative options are recombinant human activated protein C.

In prostate cancers, ultrasonography of the renal tract should be undertaken looking for sources of infection such as obstructed ureters.

## Febrile Neutropenia

Bone marrow suppression is a dose-limiting toxicity of many chemotherapy regimens. Although all cell lines may be affected, it is generally the reduction in white cell count, specifically neutrophils, that is most profound and of clinical importance. Febrile neutropenia is one of the commonest complications associated with cancer therapy. It is a recognized complication of docetaxel used to treat prostate cancer. Febrile neutropenia is defined as a single oral temperature of greater or equal to 38.3 or a temperature over 38°C for over an hour, with a neutrophil count of less than 500 cells/$mm^3$ or a count less than 1,000 cells/$mm^3$ but predicted to fall to 500 cells/$mm^3$. The severity is inversely related to the neutrophil count. The greatest risk is with neutrophil counts less than 100 cells/$mm^3$ and prolonged duration of neutropenia. Rapid progression to septicemia can occur if untreated, and this accounts for the majority of deaths associated with chemotherapy [35]. Therefore, early recognition and prompt treatment are paramount.

Most chemotherapy regimens result in a neutrophil nadir 7–10 days after treatment, with recovery expected in 5 days [7].

The most common pathogens are gram-positive bacteria although infection with gram-negative bacteria is increasing and was more common in the 1970s. In the majority of patients, no causative organism is found.

A thorough history and examination are essential. All patients who have received chemotherapy in the preceding 4–6 weeks presenting with fever or who are unwell should be assessed for febrile neutropenia. Although fever is a sensitive sign of infection, lack of fever does not necessarily exclude it, as neutropenic patients may not be able to mount an immune response.

Laboratory investigations should include a complete blood count, renal and liver functions, blood cultures, including from any lines/cannula, urine, throat swab, sputum culture, and chest radiography.

Antibiotic therapy should be commenced without waiting the outcome of cultures.

| | |
|---|---|
| High-risk patients | Significant medical comorbidity or clinically unstable |
| | Anticipated prolonged severe neutropenia (less the 100 cells/mm$^3$ for greater than 7 days) |
| | Hepatic insufficiency |
| | Renal insufficiency |
| | Uncontrolled progressive cancer |
| | Pneumonia or other complex infections at presentation |
| | Mucositis grade 3–4 |
| Low-risk patients | No associated acute comorbidities |
| | Anticipated short duration of severe neutropenia (less than 7 days) |
| | Good performance status (ECOG 0–1) |
| | No hepatic or renal insufficiency |

Intravenous monotherapy can be used in uncomplicated high-risk patients, while duel therapy should be used in complicated cases, such as patients with hypotension or organ dysfunction. The most common regimens include aminoglycosides with antipseudomonal penicillins unless contraindicated. This empirical combination has shown an overall response rate of 60–70 % [36]. Most oncology units have locally agreed antibiotic policies in place based on local epidemiology and antibiotic sensitivity/resistance.

After 3–5 days of treatment, low-risk patients who are afebrile can be discharged on oral antibiotics. Continuation of IV antibiotics is recommended in high-risk patients until neutrophil count is greater than 500 cells/mm$^3$.

Patients who are hypotensive require intensive monitoring and treatment if appropriate depending on disease status and prognosis.

Hematopoietic colony-stimulating factors (CSF), such as granulocyte CSF and granulocyte-macrophage CSF, stimulate the survival, proliferation, differentiation, and function of progenitor and mature cells of the myeloid lineage. It shortens the duration of neutropenia and should be considered for patients with an established infection, if the patient remains febrile despite antibiotics and if the neutropenia is predicted to be long [37]. It is increasingly given as prophylaxis following chemotherapy to any patient with a risk greater than 20 % as recommended by the American Society of Clinical Oncology. Splenic rupture is a rare but life-threatening condition associated with granulocyte CSF.

Afebrile patients who are neutropenic with signs and symptoms compatible with an infection should have antibiotic therapy.

## Urinary Retention

Acute urinary retention is a common complication of a neoplastic prostate. It can also be a complication following treatment with radiotherapy or prostatectomy. Initial catheterization can be difficult following previous radiotherapy or surgery such as prostatectomy due to bladder neck stenosis. Urologist should be called for catheterization, and it may need to be done under vision with aid of a cystoscopy and a guide wire. Bladder neck dilation or incision may also be required to relieve the obstruction.

Patients need to be assessed and managed as with any patient with urinary retention. A full thorough history and examination should be undertaken to identify acute versus chronic retention, comorbidites, and previous therapies. Bloods should include renal function, liver function, screening for anemia, and glucose. Fluid status should be monitored looking for diuresis in chronic retention with daily weight and lying and standing blood pressures.

Once a catheter is in place a treatment-naive patient with acute urinary retention, endocrine therapy can be the first line of therapy. A short course of antiandrogens, followed by a delayed trial without catheter, can be performed safely in most circumstances. Success rates of 69 % have been reported in literature [38]. However, patient already on hormones who have obstructive symptoms and patients with a picture of chronic retention will likely need operative intervention or a long-term catheter.

Palliative (so-called channel) transurethral resections of prostate are used to alleviate obstructive voiding symptoms. Studies have shown that they can be performed safely in patients with advanced prostate cancer with significant improvement in urinary symptoms.

Prostate cancer is found in 15 % of patient undergoing TURP for what is thought to be benign prostatic hypertrophy [39]. Studies have been done on patients undergoing TURP with prostate cancer confirmed preoperatively and postoperatively in the two groups. There was no difference in the mean operation time, hospital stay, catheter duration, incontinence rates, or mortality [40]. Two series have been done of men with prostate cancer undergoing palliative TURP focusing on operative morbidities [41, 42]. Conclusions were that it can be performed safety.

Concerns have been raised that dissemination of locally advanced prostate cancer may be caused by TURP. It is felt that the symptomatic relief outweighs these risks on current evidence. More recent studies have looked at the long-term outcome of TURP in prostate cancer patients. Despite initial good outcomes in relation to flow rate and IPSS score at 3 months, 12-month results show a significant decline. However, patients who had had an episode of urinary retention were associated with better outcomes, and unsurprisingly, hormone refractory cancer was associated with poorer outcomes [43].

## Anemia

Anemia is defined by World Health Organization as a hemoglobin concentration less than 13 g/dL.

In longitudinal studies, even mild anemia is associated with increased mortality [44]. Anemia itself is a cause of morbidity. Solid data link anemia with frailty, functional impairment, mobility impairment, and falls. A systemic review of 60 papers found 33 % of cancer patients are diagnosed as anemic, and their median survival is decreased by 20–43 % [45]. Anemia is one of the most common incident complications occurring in the final year of life in men dying of prostate cancer, affecting 10 % of patients [46]. Anemia can be a cause of cancer-related fatigue. The association of increased hemoglobin levels with improvement of quality of life has been demonstrated by multiple randomized control trials and community-based studies.

## Pathophysiology

Anemia is a frequent complication of prostate cancer and its treatment Iatrogenic hypogonadism and age-related physiologic changes along with nutritional deficits contribute to increase prevalence of prostate cancer-related anemia.

Androgens promote erythropoiesis by increasing erythropoietin production and by direct activation of erythrocyte progenitors. GnRH agonists significantly decrease hemoglobin concentrations in men with prostate cancer. The median decrease in hemoglobin concentrations is about 1 g/dL but sufficient to cause anemia in most men [47]. Treatment-related anemia is usually mild and not associated with symptoms. It is characteristically normochromic and normocytic.

Elderly prostate cancer patients are frequently malnourished. Malnutrition and preexisting folate deficit predispose to megaloblastic anemia. Reduced food intake inhibits hematopoiesis, and a cancer or malnutrition-related depressive syndrome could heavily reduce food intake.

Hemorrhage is frequent in locally advanced prostate cancer or as a treatment side effect. Local growth in the urethra or bladder, radiation cystitis or proctitis, and intraoperative bleeding during prostatectomies can all be sources of blood loss.

Erythropoiesis dysfunction is also a possible result of bone radiotherapy. Radiotherapy-related anemia is reported in 26 % of metastatic prostate cancer patients [48]. It depends on the site and amount of bone involvement in the treatment field and delivered dose of radiation.

Chemotherapy inhibits erythropoiesis and causes chemotherapy-induced anemia. Chemotherapy myelotoxicity is more frequent and more severe among the elderly [49].

## Management

The therapeutic options for management of prostate cancer-related anemia must involve patient life expectancy, risk of complications, cost/benefit, comorbidities, patient preference, quality of life, and more importantly in elderly, functional status.

Patients need clinical assessment for possible causes such as the following:

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| Hemorrhage, hemolytic anemias |
| Liver disease, malnutrition, alcoholism, malabsorption |
| Drug exposure |
| Chronic disease, infection |
| Psychiatric assessment for depression |
| Nutritional assessment |

Laboratory test should include the following:

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|---|
| Complete blood cell count |
| Blood film |
| Folate, ferritin, B12 levels |
| Renal function |
| Liver function |
| Urinalysis |

Treatment needs to be individualized. The decision to treat the anemia has to consider the benefit to the patient. Adequate nutritional intake with necessary folate or vitamin supplementation needs to be instigated. Concomitant treatment for depression should be started if present. Intermittent androgen deprivation can be considered if recurrent symptomatic anemia occurs. There is limited available evidence for this currently. Evidence to date shows it allows 60 % of men to obtain normalization of serum testosterone levels, decreasing frequency of mild anemia and improved quality of life [50].

Red blood cell transfusions remain the standard of care. Investigations are underway regarding use of EPO-beta and EPO-alpha. Trials of EPO-alpha in the prevention of radiotherapy-related anemia have shown significant increases in hemoglobin [51].

# Malignant Priapism

Priapism is a persistent penile erection that continues hours beyond or is unrelated to sexual stimulation. Generally, it is restricted to erections greater than 4 h in trials.

Malignant priapism is rare and usually secondary to genitourinary tumors, such as bladder and prostate cancers. Prognosis is poor since it generally indicates the presence of multiorgan metastasis. Prognosis is better for single metastasis, which is an indication for radical surgery. Conservative management is generally linked with survival of 2 months [52].

## Pathophysiology

Priapism is caused by malignant infiltration of both the corpora cavernosa and spongiosum. This is thought to obstruct

venous drainage, thereby promoting stasis and thrombosis of the venous outflow from the penis.

This is a low-flow priapism. Ischemic/ low-flow priapism is an emergency. The corpora are usually rigid as a result of slow venous drainage. Pain results from tissue ischemia and smooth muscle hypoxia. By 48 h, necrosis of cavernosal smooth muscle cells has occurred resulting in fibroblast proliferation, which can result in subsequent fibrosis and calcification [53].

During veno-occlusive ischemic priapism, the entrapped pool of blood that is initially at arterial oxygenation progressively becomes hypoxic. The combined reduction in prostacyclin and nitric oxide expected under hypoxic conditions favors platelet aggregation and white cell adhesion, leading to thrombus formation and further tissue damage [54].

## Management

This condition represents a urological emergency. The goal of management of all patients with priapism is to achieve detumescence and preserve erectile function if still present. There is little literature relating to its management due to the small numbers of presentations.

A thorough history needs to be taken regarding duration of erections, degree of pain, and previous history of priapism. Drugs history must be taken, remembering a number of prostate cancer patients also use phosphodiesterase type 5 inhibitors and intracavernous injections for erectile dysfunction following treatment for their prostate cancer.

Blood gas measurements from a cavernosal sample help differentiate low- from high-flow priapism. Blood gases in ischemic, otherwise known as low-flow priapism, are hypoxic, hypercarbic, and acidotic.

Blood tests should include full blood count to investigate white cell count and platelet count. Color duplex ultrasonography can also be used in diagnosis but should not delay treatment. Patients with ischemic priapism have little or no blood flow in the cavernosal arteries.

The primary causal factor should be treated, but this is difficult in malignant priapism where there are often multiple metastases. Acute management is the same as for any priapism and is applied in a stepwise pattern with increasing invasiveness.

Initial intervention may utilize therapeutic aspiration (with or without irrigation). This involves aspiration after insertion of a 19- or 21-gauge needle into the corpus cavernosum, as part of the diagnostic purpose to obtain a blood gas. This procedure lowers intracorporeal pressure thus facilitating subsequent intracavernous injection. Priapism resolves with aspiration alone in 36 % of all cases of priapism [55].

If priapism persists, intracavernous injection of an alpha-adrenergic sympathomimetic agent should be performed. Review of literature reveals significantly higher resolution of priapism following sympathomimetic injection with or without irrigation (43–81 %) than aspiration with or without irrigation alone (24–36 %) [55]. Sympathomimetic agents are activators of adrenergic receptors. Alpha-mediated hypertensive effects occur due to actions on the peripheral vasculature. Beta-mediated effects have inotropic and chronotropic effects on the heart. Phenylephrine is an alpha-1 selective adrenergic agonist with no indirect neurotransmitter-releasing action, making it the preferred choice. This means it has the therapeutic action desired for priapism while minimizing potential adverse effects.

Phenylephrine should be diluted with normal saline to a concentration of 100–500 mcg/mL, and 1 mL injections are made every 3–5 min for approximately 1 h, before deciding that treatment has not been successful. During injection, patients must be monitored with blood pressure and electrocardiogram monitoring.

The use of surgical shunts for the treatment of ischemic priapism should be considered only when a trial of intracavernous injection of sympathomimetics has failed. Surgical shunting procedures are rarely effective in malignant priapism.

A cavernoglanular (corporoglanular) shunt is usually first choice as it is easy to perform, with fewest complications. It is performed with a large biopsy needle or scalpel inserted percutaneously through glands. It can also be performed by excising a piece of tunica albuginea at the tip of the corpus cavernosum (Al – Ghorab). More proximal shunts could be attempted if these fail (Quackels or Grayhack) [55].

Radiation therapy may be required to decrease the pain associated with malignant priapism.

## Drug-Related Hepatotoxicity

Androgen deprivation therapy has been the mainstay of treatment for men with prostate cancer. The most commonly used agents are luteinizing hormone-releasing hormone analogues (LHRH-A). Another class of drugs commonly used is antiandrogens. Two types are known: steroidal (cyproterone acetate) and nonsteroidal antiandrogens (flutamide, bicalutamide).

Abnormal liver function tests, in particular elevated transaminases, are an adverse reaction more frequently noticed during androgen deprivation with antiandrogens. In literature, several cases of fatal hepatic failure in patients treated with flutamide, nilutamide, and bicalutamide have been reported [56]. The incidence is between 6 and 10 % of patients receiving antiandrogens having elevation of liver enzymes, but the incidence of fulminant hepatic failure is unknown. Severe hepatotoxicity occurs in few patients, but it may be fatal.

Clinical features of hepatotoxicity initially include nausea, anorexia, and progressive jaundice. The diagnosis of drug-induced hepatotoxicity is usually based on exclusion of other possible causes and temporal association with the drug administration.

In the presence of symptoms, impaired hepatic function or jaundice, antiandrogens should be stopped and supportive treatment started. Discontinuation of the antiandrogen seems to cause the resolution of hepatotoxicity. A change to other antiandrogens may be an alternative long-term strategy.

Close monitoring of liver function tests is recommended during treatment, particularly if there is a preexisting liver disease.

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# Management of Bone Metastases

87

Keen-Hun Tai and Farshad Foroudi

## Introduction

Bone metastases are a common manifestation of secondary spread of prostate cancer [1]. The incidence increases with stage of the disease and factors that contribute to increased risk categories such as T-stage, level of PSA, and high Gleason score.

## Pathophysiology

Mouse models of bone metastases show that as tumor cells proliferate, there is a marked induction of osteoclastic overactivity resulting in damage to the normal architecture of the bone structure. This stimulation involves a multitude of cytokines, e.g., interleukin-1 and interleukin-6, and growth factors, e.g., epidermal growth factors and transforming growth factor [2, 3]. The acidic microenvironment resulting from this hyper-proliferation of osteoclasts is thought to directly affect the pain nociceptors that permeate the bone [4]. Bisphosphonates reduce the pain of bone metastases by causing loss of function and apoptosis of osteoclasts once taken up by these cells [5]. The recognition that activation of osteoclasts via the nuclear receptor for the κβ {kappa beta} ligand (RANKL) has led to studies looking at blocking this signaling pathway. Denosumab which is a human monoclonal antibody that inhibits RANKL is one example of targeted therapy in the management of pain from bone metastases [6]. The use of bisphosphonates and denosumab results in the reduction of skeletal-related events including osteoporotic fractures with the use of androgen ablation therapy (AAT).

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## Diagnosis

### Symptoms

Bones metastases may be asymptomatic when first detected on imaging, but the manifestations include pain, fracture, anemia, and neurological sequelae including spinal cord compression. Hypercalcemia which is a common manifestation of bone metastases in other malignancies (e.g., breast and lung cancer) is rarely seen in prostate cancer. In the asymptomatic patient, a highly elevated PSA level is an indicator of bone metastases.

### Pain

Incident pain or breakthrough pain is defined as extreme pain occurring intermittently at the time of non-noxious movement or with loading of tumor-bearing bones [7]. As a result of its severe nature occurring over many times a day, it can be debilitating with significant adverse psychological impact. It is important to distinguish between bone pain related to metastases as opposed to osteoporotic fractures (especially crush fractures of vertebrae where sclerosis seen on imaging may be confused with sclerotic metastases). Examining PSA trends and comparing image findings with serial imaging may help in distinguishing etiology of bone lesion.

### Imaging

In previously undiagnosed advanced prostate cancer, it is not uncommon to have a patient present to their physician with pain that leads to imaging confirming the diagnosis. Typically, a whole-body bone scan reveals the widespread presence of multiple bone lesions (Fig. 87.1). In an acute emergency, a patient may present with spinal cord compression from vertebral metastases (Fig. 87.2). The use of magnetic resonance imaging (MRI) has resulted in earlier diagnosis of spinal

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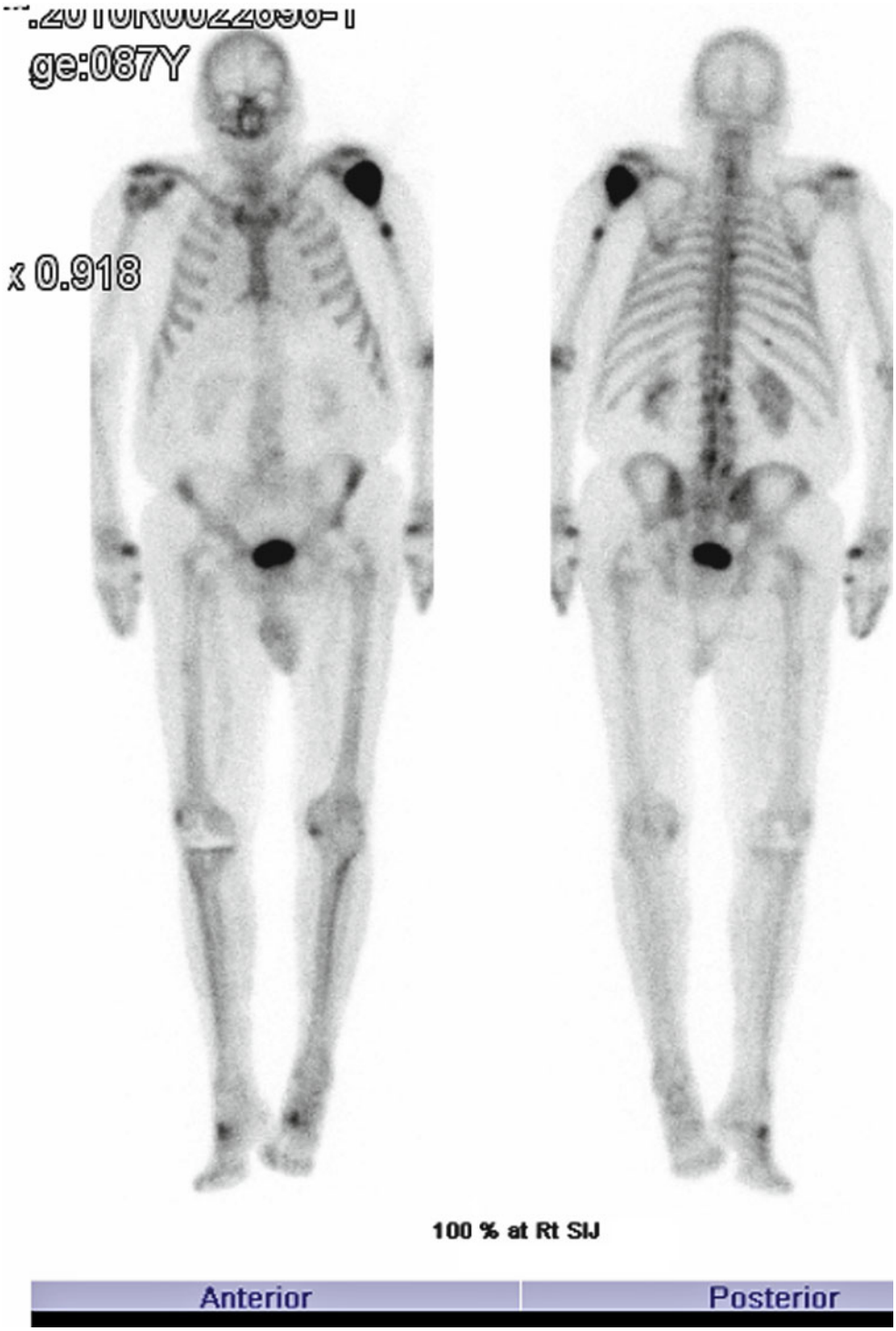


**Fig. 87.1** Typical bone scan appearance of multiple metastases arising from prostate cancer (left humerus and right 10th rib)

lesions. PET and PET-CT scans with 18F-fluorodeoxyglucose (FDG) have given variable results, although it seems to be more effective in patients with high Gleason scores [8, 9]. The use of choline (11C and 18F) as substrates with more sophisticated PET-CT scanners and multi-slice SPECT/CT is promising [10–12].

## Treatment

Metastatic prostate cancer is a fatal condition even with AAT [13]. Treatment is therefore based on palliation of symptoms. Pain from bone metastases or fractures is a major problem. Effective treatment consists of early initiation of analgesics

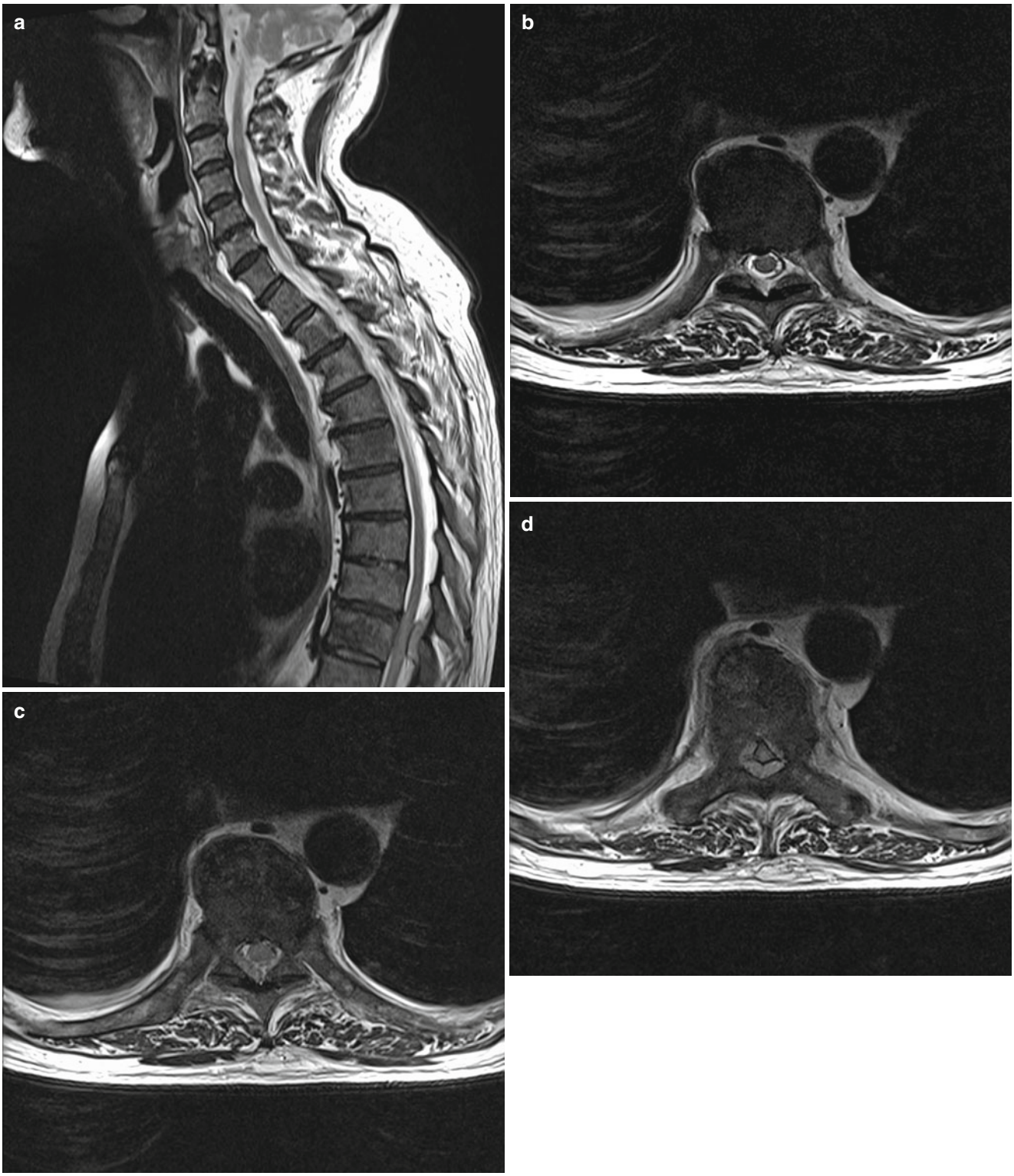


**Fig. 87.2** Spinal cord compression arising from vertebral metastasis. MRI sagittal and axial images of a lesion causing compression at the level of 9th thoracic vertebra. (**a**) Sagittal image showing spinal cord compression at T9. (**b**) Axial image showing normal CSF signal around the spinal cord at level of T8. (**c**) Axial image showing abnormal CSF signal around the spinal cord and disruption to the normal bony structure at superior aspect of T9. (**d**) Axial image showing compression of the spinal cord by tumor and disruption to the normal bony structure at the level of T9

**Table 87.1** Mirels' scoring system for risk of pathological fracture

| Variable | | | |
|---|---|---|---|
| Site | Upper limb | Lower limb | Pertrochanteric |
| Pain | Mild | Moderate | Functional impairment |
| Image of lesion | Blastic | Mixed | Lytic |
| Size (area involved) | <1/3 | 1/3 to 2/3 | >2/3 |
| Score | 1 | 2 | 3 |

With kind permission from Springer Science + Business Media, modified from Cumming et al. [17]
Each of four variables is given a score, and then the total for a particular lesion determines the risk of fracture. The higher the score, the more likely a pathological fracture will occur

and AAT, if the latter has not already been prescribed. Where spinal cord compression is suspected, emergency imaging (e.g., MRI) is mandatory, followed by appropriate steroid therapy and radiotherapy or surgical decompression as indicated [14].

## Analgesia

Management of pain is an imperative for all clinicians. While the details of this will depend on individual patients, the logical use of analgesics as per World Health Organization guidelines is a basic starting point [15]. AAT, e.g., bilateral orchidectomy, can be rapidly effective if serum testosterone levels are still normal. Patients with castrate levels of testosterone require analgesics. Often this is initially with oral medication, e.g., acetaminophen, in combination with anti-inflammatory drugs and narcotic analgesics, but transdermal medications, e.g., fentanyl and buprenorphine, can be equally effective. Oral means may allow a degree of flexibility, but all narcotic analgesics, especially sustained or prolonged methods, require strict adherence to time schedules. A combination of short-acting, e.g., 4–6 hourly, medications and sustained-acting, e.g., 12 hourly oral or 3- to 7-days, transdermal medications are often required. The physician should be experienced in the use of these narcotic analgesics and mindful of the potential pitfalls in both contraindications and side effects. Integral to this would be management of bowel complications arising from narcotic analgesics. Involvement of a palliative care physician and domiciliary nursing service within the health care team is helpful.

## Surgery

While the management of bone metastases is generally based on palliation of pain, prophylactic surgery can be an effective therapy for a lesion in a weight-bearing bone that is at risk of fracture or where other complications may arise, e.g., spinal cord compression. If a pathological fracture has occurred, internal fixation can rapidly relieve pain and allow ambulation. Minimizing the risk of fractures by vigilant assessment of osteoporosis and the use of bisphosphonates or the monoclonal antibody denosumab may help [16]. An untreated tumor at a surgically treated site will hinder repair and symptom relief. A multidisciplinary approach that includes postoperative radiation therapy and/or systemic therapy should be considered.

### Surgical Fixation of Fractures

Lesions that are considered unlikely to fracture maybe treated with radiation therapy. A scoring system can be used to distinguish these situations [17] (see Table 87.1). Osteolytic lesions, an uncommon feature in prostate cancer, are more likely to fracture. Factors to consider in offering surgical fixation include the life expectancy of the patient and his ability to tolerate such a procedure, the adequacy of adjacent bone to sustain surgical reconstruction, and the degree of benefit or improvement of performance status. On the other hand, if there has been sustained neurological impairment or poor performance status (not just related to the fracture), surgery is unlikely to help [18]. It would be common to use cemented long-stemmed prostheses for long bones, but external fixation maybe considered when there is inadequate normal bone to support a prosthesis.

### Spinal Surgery

Back and neuropathic pain unrelieved by narcotic or radiation therapy may be relieved with spinal surgery. However, emergency surgery should be considered with spinal cord decompression due to the morbidity of limb weakness, paralysis, and sphincteric dysfunction for the patients who are considered suitable for surgery. The Tomita and Tokuhashi system is a useful guide to the surgical approach [19]. Postspinal decompression radiation therapy has been demonstrated in a randomized trial to be superior to radiation therapy alone [20] (further details in "radiotherapy 3.1.2"). In a secondary analysis of data from this trial, lower age (<65 years) was a significant variable in determining the benefit of combined therapy for both functional recovery and survival time [21]. A cost-effectiveness analysis of the same collection of data has further enhanced the superiority of combined therapy with respect to savings per day of ambulation and cost per life-year gained [22].

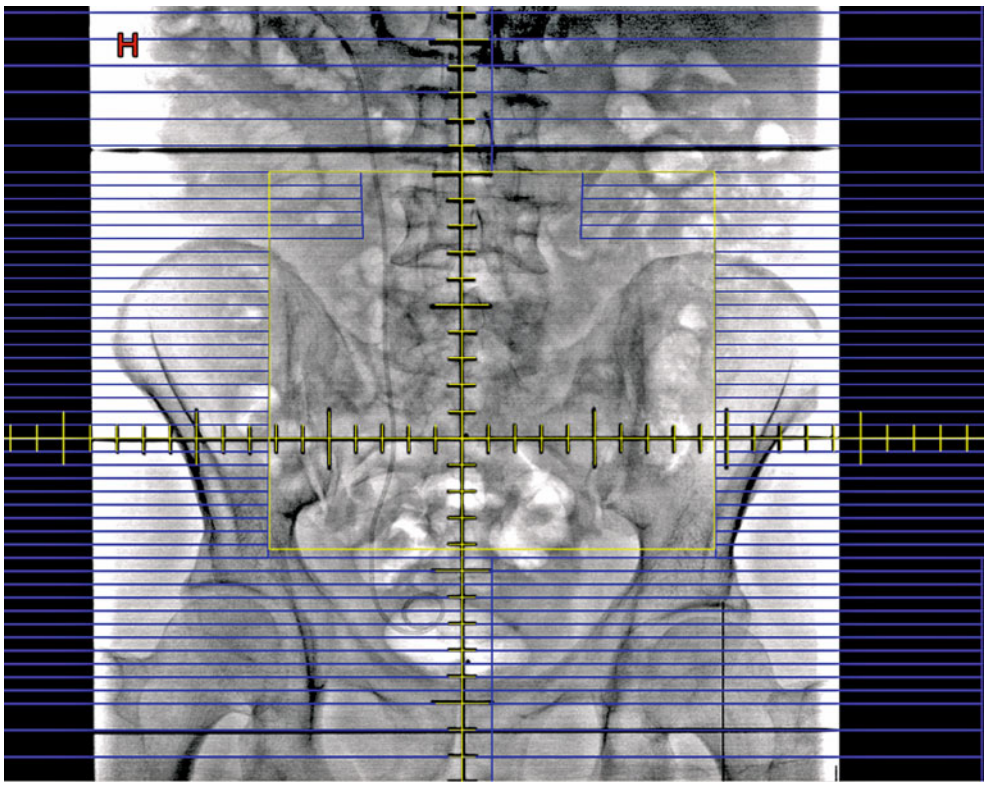

**Fig. 87.3** Radiation field coverage for prostate cancer bone metastases involving the lumbosacral and sacroiliac bones. Note the advanced disease requiring treatment with a stent in the ureter

In patients who do not have spinal cord compression, vertebroplasty and kyphoplasty are other surgical means of stabilizing the spine and to provide pain relief. However, there is a notable risk of complications that is symptomatic in 10 % and asymptomatic cement leakage in about 70 % of patients [23].

## Radiotherapy

A multitude of studies have been conducted examining the role of external beam radiotherapy in bone metastases. The majority of these studies have involved various malignancies including prostate cancer. Prostate cancer bone metastases are generally considered a favorable tumor type when considering response to radiotherapy [24].

### External Beam

#### Conventional

Conventional external beam radiotherapy encompassing the involved tumor site with a margin (Fig. 87.3) has been effective palliation for many patients. The main area of controversy with such treatment has been the number of fractions and total dose. Wu et al. [25] carried out a meta-analysis of 16 trials including 5,455 patients and found an equivalence between single and multiple fractions. Despite this evidence, there remains controversy whether single fractions are appropriate in all patients. For instance Van der Linden et al. [26] published a reanalysis of the Dutch bone metastasis study which included 1,171 patients. This study randomized patients to a single 8 or 24 Gy in 6 fractions. Van der Linden et al. [26] found re-treatment occurred in 6 % of cases with 24 Gy, while 24 % in the single 8-Gy arm ($P = 0.001$). The mean time to re-treatment was also shorter (13 weeks vs. 21 weeks) with the single 8 Gy. In a reanalysis of the Dutch bone metastasis study, it was found that a significantly higher rate of pathological fractures was observed after radiotherapy with a single 8 Gy compared with 24 Gy [27]. Similarly Sze et al. [28] found that multi-fraction radiation therapy reduced the risk of pathological fractures compared to single fractions. While most randomized trials of fractionation have not included pathological fracture or spinal cord compression, other situations such as neuropathic component have not been shown to be significant factor in determining the most appropriate dose fractionation [29].

RTOG conducted a large North American [30] randomized study comparing multiple fractionation versus shorter multiple fractions. They found 89 % of patients received minimal pain relief, 83 % received partial pain relief, and 54 % received complete analgesic relief. Initial pain score was found to be a useful predictor; patients with high scores were less likely to respond and less likely to experience a complete response [30]. While there was some pain relief within the first 4 weeks of treatment, complete relief was first reported later than 4 weeks after the start of treatment in about 40 % of patients. The median duration of pain relief was 20 weeks [30].

### Hemibody

Many patients with bone metastases from prostate cancer have multiple bone metastases causing discomfort. Hemibody radiotherapy has been used to treat such patients. Such treatment requires admission to hospital for hydration and premedication with antiemetics and steroids. The most common side effect is gastrointestinal disturbance, with rare incidence of radiation pneumonitis and significant hematological suppression. Seventy to ninety percent of patients have some relief of pain, and up to 45 % have complete relief [31]. The onset of pain relief is more rapid than that occurring with single field radiation therapy, occurring generally within 24 h of treatment.

### Postoperative Radiation Therapy

Postoperative radiotherapy is used after surgical fixation of pathological fractures or impending fractures. A systematic review of the timing of postoperative radiotherapy recommended the optimal interval should be at least 1 week to minimize wound complications [32]. Radiation fields should encompass the entire surgical field including the prosthesis in its entirety. Townsend et al. [33] found 15 % of patients treated with surgery alone developed loosening of their prosthesis or hardware requiring revision surgery, compared to 3 % treated with surgery and radiotherapy.

## Spinal Cord Compression

Spinal cord compression is an infrequent but highly morbid complication of vertebral bony metastases. A randomized trial [34] comparing laminectomy followed by radiation versus radiation therapy alone showed no difference in pain relief, ambulation, or anal sphincter function. However, in a more recent randomized trial, Patchell et al. [20] using appropriate surgical techniques found a benefit for surgery plus $10 \times 3$ Gy of radiotherapy versus $10 \times 3$ Gy alone. In this trial ($n = 101$) where the primary endpoint was the ability to walk, 84 % of the patients who had combination therapy were able to walk compared to 57 % of those who had radiotherapy alone [odds ratio 6.2 995 % CI 2.0–19.80; $P = 0.001$]. Of those who could not walk at the time of randomization, 62 % of the combined treatment group could walk after therapy versus 19 % who had radiotherapy alone ($P = 0.01$). The combined therapy group also had significantly better outcomes for durability of walking with a median duration of 122 days versus 13 days and the need of corticosteroids and narcotic analgesics. The eligibility criteria and patient characteristics in this study included expected life expectancy of ≥3 months, a Karnofsky performance score of ≥70, involvement of a single area only, and most patients had relatively high-grade compression with displacement of the spinal cord [20]. Thus the Patchell criteria regarding suitability for surgery are only applicable to 10–15 % of patients with spinal cord compression.

The earlier the diagnosis is made and treatment initiated, the better is the outcome: 94 % of patients who have the ability to walk maintain their ambulatory status after radiotherapy, where ambulation is restored in 60 % of those with motor weakness and only 11 % of those with paraplegia at presentation [35]. Generally a fractionated course of radiation therapy is used for spinal cord compression as most of the randomized trials comparing different fractionation specifically excluded cord compression. A dose of 20 Gy in 5 fractions or 30 Gy in 10 fractions is commonly used. The radiation technique often depends on the location of the cord compression, with lateral fields used in cervical levels to avoid irradiation of the upper aerodigestive tract and direct posterior fields for thoracic and lumbar lesions.

### Stereotactic Treatment

Stereotactic radiosurgery (SRS) is the delivery of megavoltage radiation to a precisely defined target. A rapid dose fall-off outside the target ensures that surrounding tissues receive a much reduced dose compared to the target. The effectiveness of conventional radiation to the spinal column has been limited by the spinal cord, which is intolerant of high-dose radiation. SRS offers the option to deliver high-dose per fraction radiation, and therefore a high biologic equivalent dose in a small number of fractions. A recent systematic literature review [36] found that SRS was safe and provided an incremental benefit over conventional radiotherapy with more durable symptomatic response and local control, even in the setting of prior fractionated radiotherapy. SRS has a particular role in patients who have a previously irradiated volume with a new, recurrent, or progressive metastatic disease [37]. A recent critical review found that local control with SRS for previously unirradiated patients was 87 %, in reirradiated patients tumors was 96 %, and in postoperative patients was 94 % [38]. While the capital costs are high and prohibitive for certain health systems, a recent cost-utility analysis found the CyberKnife stereotactic system (Accuray, Sunnyvale, California) was a superior cost-effective primary intervention for patients with metastatic spinal tumors compared to conventional external beam radiotherapy [39].

Greco et al. [40] in a study of 126 metastatic lesions treated with stereotactic image-guided intensity-modulated radiotherapy found that prostate cancer metastases responded well to lower single doses of 18–20 Gy with local control rate of 85 %. This was the highest local control of any of the histologies examined with renal cancer metastases in contrast, requiring higher single fraction doses with lower local control rates. There remains an ongoing Radiation Therapy Oncology Group (RTOG) Phase II/III study of spinal stereotactic radiotherapy versus conventional radiotherapy (RTOG 0631) [41]; until this is reported, it remains unclear which

patients may benefit most from this resource intensive and costly procedure.

## Radionuclide Therapy

Radionuclide-labeled agents are used to palliate metastatic prostate bony metastases due to preferential uptake in bone. Strontium-89 decays by beta emission with a half-life of 50.5 days. There is preferential accumulation in and around metastatic deposits, and where active bone formation takes place has been demonstrated by bone scans using $^{89}$Sr [42]. Elimination is renal, and care is required for 7–10 for disposal of urine. Ten percent of patients can have a pain flare which typically occurs at 1–2 weeks post-administration. Lewington et al. [43] in 32 patients found only patients receiving $^{89}$Sr were pain free. Porter et al. [44] in 126 patients found 40 % of patients were pain free with $^{89}$Sr compared to 23 % with placebo. Pain relief was noted in approximately 1–2 weeks, lasting for approximately 4 months. Samarium-153 is also commonly available. Sartor et al. [45] evaluated Sm-153 in a randomized double-blind trial, finding that active radioisotope had measurable reduction of pain within 1–2 weeks. Other isotopes such as rhenium-186 and rhenium-188 have been used for bone metastases for prostate cancer but are not in widespread use in North America [46]. Toxicity of $^{89}$Sr is mainly hematological with most patients having a 20–50 % drop in platelet count. In recent years, the use of $^{89}$Sr has decreased due to increasing use of systemic chemotherapy, and the hematological toxicity of $^{89}$Sr being viewed as a limiting future chemotherapy option.

The role of radionuclide therapy has been enhanced by recent studies demonstrating its benefit. The use of Alpharadin® (radium-223 chloride, alpha emitter, $t_{1/2}$ =11.4 days) in the phase III "ALSYMPCA" study has been pivotal in the rapid FDA approval of the use of this radionuclide in the treatment of bone metastases in castrate-resistant disease. This study confirmed the randomized phase II studies reported earlier [47]. With metabolic properties that are similar to that of calcium and strontium, radium-223 chloride will target the bone matrix and limit the radiation dose to the bone marrow. Further studies will determine its utility in earlier stage disease and in combination with other modalities of therapy.

## Bisphosphonates

Level 1 evidence exists that compares bisphosphonate use with placebo and shows statistically significant reduction in nonvertebral fractures, vertebral fracture, combined fractures as well as the need for radiation therapy [48]. However, many of these studies include other malignancies such as breast cancer and multiple myeloma. Saad et al. [50] randomized 643 patients with metastatic castrate-resistant prostate cancer to Zoledronic acid every 3 weeks for 15 months or placebo. They showed a reduction in skeletal-related events from 44 to 33 % ($P$=0.02); there was also a reduction in pathological fractures from 22 to 13 % ($P$=0.15). Time to disease progression or survival was similar in both groups. The need for local field radiation was not significantly different in the two groups. Median time to first skeletal event was also significantly extended to 488 days from 321 days ($P$=0.009). More recently, Saad et al. [50] reported continuing benefit of reduction of skeletal events by Zoledronic acid beyond 16 months. Randomized controlled trials have not shown a benefit of other bisphosphonates in the castrate-resistant setting, in particular intravenous clodronate [51] or Pamidronate [52]. While not showing a benefit in the castrate-resistant setting, a study of oral clodronate versus placebo found with 8 years in follow-up a significant survival benefit (22 % vs. 14 %) [53]. While hypercalcemia is rare in metastatic prostate cancer, there is level 1 evidence for the use of bisphosphonates in the treatment of hypercalcemia of malignancy [54]. Pamidronate and Zoledronic acid are the most common used agents. Most common side effects are self-limiting fever, hypocalcemia, and hyphosphosphatemia which do not require correction.

## Glucocorticoid Therapy

In a randomized trial in patients with metastatic cord compression, dexamethasone was administered in a bolus of 96 mg intravenously, followed by 96 mg orally for 3 days then tapered over 10 days. In total, 81 % of patients receiving dexamethasone and 63 % of those patients not receiving dexamethasone were ambulatory following treatment [55]. Gastrointestinal complications and psychosis were more common in patients receiving glucocorticoids compared to those receiving no steroidal treatment.

## Hormonal Therapy and Systemic Chemotherapy

Initial presentation of prostate cancer with bone metastases is increasingly rare; in these patients, up to 85 % may respond to hormonal manipulation either in form of medical or surgical castration. With two phase III trials demonstrating modest overall survival benefit, docetaxel-based chemotherapy has become the standard systemic treatment in castrate-resistant disease [56, 57]. These studies also showed significant palliative improvement in pain related to bone disease. However, it is unclear whether skeletal complications are reduced [56].

## Further Considerations

Understanding the pathophysiological and molecular bases of bone metastases in prostate cancer can help in the management of the later stages of this disease. Molecular oncology studies of bone-targeting agents like ZD4045 (an endothelin receptor antagonist), signaling and pathway agents like cadherin 11 (transmembrane protein involved in cell adhesion), cathepsin D (an aspartic protease), prosaposin (a precursor glycoprotein of the family of sphingolipid activator proteins – "saposins" – involved in migration and invasion), and cbfa1/runx2 (transcription factor associated with osteoblast differentiation) provide insights into the understanding of the mechanism of action of malignant cells as well as provide directions to therapeutic approaches. Late-phase clinical trials will test these agents and determine the indications for use. Novel imaging approaches combining current technologies of PET-CT and MRI will allow early treatment.

The discovery of the RANKL pathways and the clinical studies of denosumab is an example of this translational approach. Other approaches include dendritic-based cell therapy (sipuleucel-T), vaccines (e.g., GVAX and vaccinia virus), and novel monoclonal antibodies [59].

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# Pain Relief in Metastatic Cancer

88

Odette Spruyt and Natasha Michael

## Competent Management of Pain in Patients

> Any man's death diminishes me, because I am involved in Mankinde [1].

Not only death, but the suffering of unrelieved pain diminishes man and involves us all. The relief of pain is cited as a human right because it is now possible to manage pain well and because of the terrible impact of unrelieved pain on individuals and society and the need to challenge the indifference which leads to inadequate pain management [2].

Prostate cancer is the most frequently diagnosed cancer in men, the majority of whom live with the disease for many years. The symptoms and sequelae of prostate cancer and its treatment are therefore chronic, with physical and psychosocial implications for the patient and his family. Chronic pain, when it occurs, is a distinct disease entity in itself, with mechanisms which differ from acute or short-term pain [3].

The following case report represents the story of many men with advanced metastatic prostate cancer in whom pain management occurs within an array of other clinical challenges. These include managing disease progression, psychosocial distress, and multiple comorbidities which influence the choice and modality of analgesia, contribute to the side effect profiles, compliance, and capacity to undertake optimal analgesic strategies.

## Case Report

Mr. TR was a 77-year-old with a 13-year history of hormone-refractory prostate cancer. A recent diagnosis of metastatic bone disease heralded the beginning of severe pain. Multiple comorbidities included depression, atrial flutter, emphysema, and renal impairment. A previous laminectomy for benign disc prolapse led to continuous L5 sciatica associated with numbness in the left buttock. Recent disease staging with CT chest, abdomen, and pelvis revealed incidental findings of thrombus in the right pulmonary artery and widespread metastatic bony disease. He received palliative radiotherapy to his lumbar spine, right hip, and base of skull. The administration of zoledronic acid resulted in marked toxicity with nausea, bone aches, sweats, and weakness.

He presented with multiple symptoms of pain, dyspnea, nausea, low mood, drowsiness, and myoclonus. His main pains were bone ache following bisphosphonate administration, movement-related pain in the right rib and proximal right femur, and left buttock pain on walking. His pain remained well controlled at rest. Medications included transdermal fentanyl 50 mcg/h, gabapentin 300 mg nocte, diclofenac 50 mg bid, and oxycodone 5 mg as required and venlafaxine 150 mg daily.

## Defining Pain

Pain may be defined as a "sensory and emotional experience characterized by actual or potential tissue damage or described in terms of such damage" [4]. Pain is what the patient says it is and is a multidimensional experience not limited to a physical abnormality [5,6]. This subjective, multidimensional nature of pain contributes greatly to the clinical challenge of pain management, which calls for empathy, relationship, and attention to detail – components of clinical care which are often lacking in modern medicine.

Coping with pain in the context of advanced cancer differs from chronic pain of nonmalignant nature and also appears to vary with types of cancer. Pain intensity and quality are significantly worse in lung cancer compared to head and neck and prostate cancer. Depression levels are also greatest for individuals with lung cancer and correlate with

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**Table 88.1** Examples of cancer related pain in Prostate Cancer

| |
|---|
| *Neuropathic pain* |
| Radiculopathy from tumor compression |
| Spinal cord compression |
| Secondary to chemo, radiotherapy, and surgery |
| Related to cancer and its treatment, e.g., herpes zoster |
| *Nociceptive pain* |
| Visceral metastases |
| Ureteric obstruction |
| Lymphedema |
| Pressure areas |
| Dysuria secondary to bladder spasm and infection |
| Mucositis related to chemo or radiotherapy |
| Constipation |
| Steroid myopathy |
| Gynecomastia |
| *Bone pain* |
| Metastases |
| Fractures |
| Hypercalcemia |
| Bisphosphonate causing acute treatment-related pain and osteonecrosis |
| *Total pain* |
| Demoralization |
| Depression |
| Social isolation |
| Emasculation |

catastrophizing that influences the overall pain experience [7]. Recognizing such differences assists with developing therapeutic strategies and programs that are best suited to the characteristics of specific patient groups.

## Epidemiology of Pain

The prevalence of pain in cancer varies greatly with site, stage, and type of cancer and no single aggregate statement of prevalence can be made [8]. Up to 43 % of patients with non-metastatic prostate cancer and 66 % of patients with advanced disease have been reported to have pain, with 41 % suffering severe pain in the latter group [9,10]. A recent systematic review of the literature over the past 40 years found a prevalence of 64 % in patients with advanced cancer. Notably, this review found that pain was also prevalent in 33 % of patients following curative treatment [11]. Therefore, not all patients with advanced cancer suffer pain and much pain can be avoided.

While most cancer pain is due to direct cancer effects, not all pain is directly due to active disease [12,13] (Table 88.1). Many patients suffer multiple pains, as in prostate cancer where bone metastases are a prominent feature of disease spread [14]. Pain intensity varies greatly, does not correlate with radiological abnormality or tumor size, and shows a tendency to increase with progression of cancer.

Pain is generally of nociceptive (somatic or visceral) or neuropathic (central, peripheral, or sympathetic) mechanism or a combination of both, known as mixed pain. Nociceptive pain involves stimulation of a free nerve ending or nociceptor by physical or chemical stimuli such as tissue injury. Stimulation leads to the passage of impulses along the peripheral nerve to the dorsal horn of the spinal cord, synapsing there with spinothalamic tract neurons and on through to the brain stem, the thalamus, and terminating in various regions of the cerebral cortex. Neuropathic pain, however, results from damage of either the peripheral or central nervous system. Such damage is frequent in patients with advanced cancer. Damage may occur directly through erosive growth, compression, infiltration along neural tissue, or by cancer therapies. Chemotherapeutic agents such as vincristine and taxols may cause painful peripheral neuropathies and surgical and radiotherapy-related damage to nerves is not uncommon. A range of other cancer-related pain syndromes have been well described and are the cause of significant morbidity [15–17].

## Pain Assessment and Classification

Good pain control depends on competent assessment of pain, which is directed at diagnosis of etiology, understanding of the experience for the patient, and developing a relationship within which pain management can most successfully take place. Careful assessment includes a narrative history of pain onset, quality, and intensity; impact on function; and alleviating and aggravating factors. Characteristics of the pain assist with diagnosis. For example, visceral pain is often described as aching, dull, constant pain and neuropathic pain as burning, numb, shooting, or other terms indicative of dysesthesias.

Investigations of etiology may include diagnostic imaging, with nuclear imaging of bone of particular value in assessing the extent of bone metastases. In general, there is poor correlation between complaints of bone pain and radiological evidence, though this correlation is stronger in prostate cancer than breast cancer [18]. Urgent magnetic resonance imaging should be performed if spinal cord compression is suspected.

There is a lack of consistent validated assessment and measurement tools which hampers the evaluation of treatment effectiveness and comparative research studies [19]. The Edmonton Classification System of Cancer Pain (ECS-CP) is a validated classification tool that helps identify patients with complex pain who would benefit from early referral to specialist pain/palliative care services as well as better describe pain populations recruited to analgesic studies [20–22]. The ECS-CP identifies that patients with neuropathic pain, incident pain, history of addiction, and

psychological distress were found to be more challenging to palliate, requiring higher opioid doses, more adjuvants, and a longer time to achieve stable pain control.

### Undertreatment of Pain

There is evidence of continued undertreatment of pain in 40–50 % of patients despite the plethora of guidelines and evidence of availability of effective therapies dating back over the past 20 years [23–25]. Inadequate pain relief is not limited to resource poor countries, but the reasons for inadequate pain relief appear to vary between developed and developing countries. In the developed world, reasons include the lack of knowledge about pain relief among treating physicians, poor coordination of services across settings of care, physician indifference or poor assessment [23], and a focus on disease-based (rather than symptom-based) care. In the resource-poor world, the lack of health-care resources and infrastructure, opioid unavailability, and geography contribute greatly to undertreatment of pain [14]. Patient factors include fear of opioids and concerns about side effects and addiction leading to underreporting of pain and poor compliance with treatment [26].

## Principles of Pain Management

In general, cancer pain management approaches fall into two major categories, those which are tumor specific and those which are pain specific [19].

### Tumor-Specific Measures

To date, tumor-specific measures remain poorly evaluated in clinical trials, where the outcomes commonly focus on impact on survival rather than improvements in symptoms. Palliative radiotherapy and surgical interventions including placement of stents, relief of obstruction, and orthopedic maneuvers play an important role in optimizing pain management for many cancer patients including those with advanced disease. The benefit of radiotherapy for bone metastases is well established. External beam radiotherapy has been shown to provide at least 50 % pain relief in over 40 % of patients with just under a third experiencing complete relief after 1 month. Single fractions are as effective as multiple fractions administered for palliation [27,28]. The use of radioisotopes such as strontium-89 can reduce the number of new sites of metastases [27] and are effective for those with multiple painful metastases.

Bisphosphonates are a class of agent that act primarily by inhibiting osteoclast function and as such were assumed to have no role in prostate cancer where osteoblastic metastases predominate. However, recent studies have demonstrated high bone resorption in metastatic prostate cancer reflecting substantial osteoclastic activity [29]. The biologic rationale for its use relates both to the management of metastasis and ongoing bone loss secondary to androgen deprivation arising from treatment. Studies have shown benefit by way of reduction in bone pain and skeletal-related events particularly with the use of the more potent, new generation bisphosphonates such as zoledronic acid [30,31]. There is no evidence of influence on disease progression or survival. The reduction in pain and skeletal events with the use of bisphosphonates must be weighed against potential adverse events such as nephrotoxicity and osteonecrosis of the jaw which has a reported incidence of approximately 3 per 100 patients in prostate cancer [32].

There is little data comparing the effectiveness of differing palliative options for pain such as radiotherapy, surgery, analgesia, or interventional approaches. The burden/benefit ratio of more intensive palliative interventions must be carefully considered, ideally through a multidisciplinary approach, which is the standard for best care in oncology practice. Pain and palliative care providers experienced in cancer care bring particular expertise in the judicious selection of optimum maneuvers in the patient with advanced illness. Prognostic expertise is of particular importance. Prognostic overoptimism and reticence in truth telling lead to poor selection of palliative procedures. Developing care systems in which the experience of the whole multidisciplinary team including nursing, physiotherapists, occupational therapists, pastoral care, and psychological therapists is brought to bear, improves the quality of therapeutic decision making in advanced disease, and broadens the options available beyond the pharmaceutical or medical intervention.

### Pain-Specific Approaches

The World Health Organization cancer pain relief guidelines (1986) and analgesic ladder (Fig. 88.1) continue to provide the framework for cancer pain management today and are supported by several validation studies [33,34]. Evidence showed that significant pain reduction was achieved within the first week of treatment ($P<0.001$), strong opioids (WHO step III) were prescribed on 49 % of treatment days, administration was via the enteral route on 82 % of treatment days, good or satisfactory pain relief was reported in 88 % of patients and inadequate pain relief occurred in 12 % of patients [33]. The essential elements of this guideline can be summarized as follows: “by the mouth, by the clock, by the ladder,” that is, cancer pain is ideally treated by administration of analgesics by the oral route, at regular intervals in an

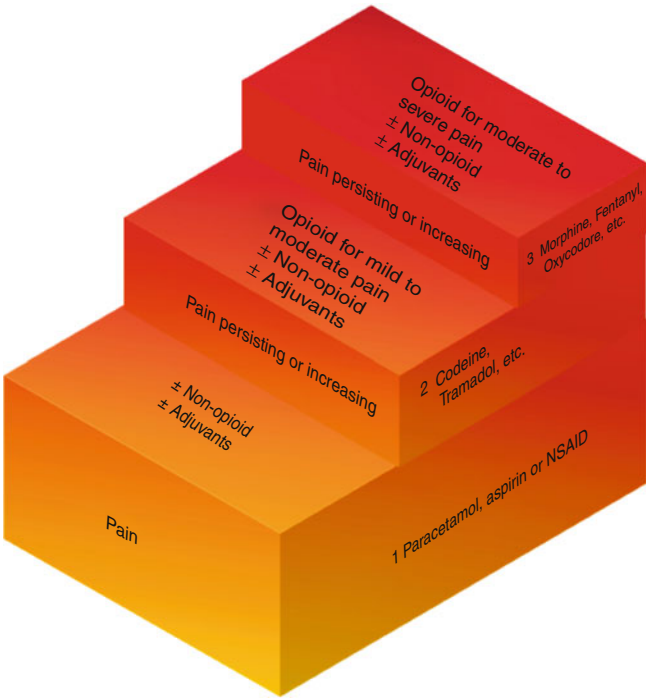


**Fig. 88.1** World Health Organization analgesic ladder

incremental manner. Frequent review and recognition of detail and difference lead to a tailored analgesic approach for each patient and avoidance of complications of analgesics used inappropriately or without due regard to their many adverse effects.

## Analgesia

### The WHO Analgesic Ladder

The WHO pain ladder is still widely utilized due to its simplicity and transferability to a variety of settings. Its three-step approach allows for the stepwise titration of opioids in an incremental manner with the concomitant use of co-analgesics and adjuvant. Mild pain requires nonsteroidal anti-inflammatory analgesics or acetaminophen/paracetamol [33–36]. Moderate pain requires commencement of so-called weak opioids. In recent years, low doses of more potent opioids have been introduced at this step in recognition of the need to titrate most patients with cancer pain onto more potent opioids in a shorter timeframe [37]. Many patients though have a resistance to commencing morphine or related potent opioids making it useful to maintain step two of the ladder.

Strong opioids are available in a range of preparations suited to chronic administration for the patient with severe pain. Initial commencement is best achieved using a short-acting formulation, replacing this with a long-acting formulation of the same opioid once acceptable pain relief and toxicity profile has been achieved [69]. When spontaneous or movement-related pain is a major component of the pain experience, potent, rapid, and short-acting opioids such as transmucosal or intranasal fentanyl and sufentanil are effective [38–40].

Adjuvant use throughout the ladder is determined by the underlying mechanism of pain. For example, anticonvulsants are used for neuropathic pain or antispasmodics for colic. Commencement of any opioid must be accompanied by the use of regular stimulant and softening laxatives as the majority of patients will develop constipation without these. The availability of new therapies for opioid-induced constipation such as methylnaltrexone or combination opioid-opioid antagonist preparations such as oxycodone-naloxone is now available for the improved management of opioid-induced constipation [41–43].

Problems with prolonged opioid use may lead to the development of opioid tolerance and opioid-induced hyperalgesia (OIH), with glial cells implicated in the development of opioid tolerance [44]. OIH is a clinical entity separate to tolerance, in which patients experience worsening of pain and abnormal symptoms such as allodynia despite increasing opioid doses. The N-methyl-d-aspartic receptor (NMDAR), a glutamate receptor, is key to the development of OIH, assisted by spinal dynorphins and descending pathway facilitators [45]. Therapeutic strategies include opioid switching which usually allows a decrease in mean equivalent daily dose of opioid and/or the addition of agents such as ketamine, an NMDAR antagonist [46].

## Cancer-Induced Bone Pain (CIBP)

Bone metastases are reported to be present in over 90 % of patients who die of prostate carcinoma [47], with the main symptom of bone pain occurring in approximately 85 % of patients [48]. Bone pain can be difficult to control and exhibit features that involve nociceptive inflammatory, neuropathic, and tumorigenic mechanisms [49]. The pattern of pain may be variable and unpredictable with both aching, dull, constant background pain and spontaneous or movement-related breakthrough pain. Breakthrough pain in particular has a profound effect on daily functioning and quality of life [50] and is associated with a poor prognosis for achieving effective pain control [22] due in part to its rapid onset, intensity, and brevity. Efforts to achieve pain control for these breakthrough episodes are often hampered by opioid toxicity that is unacceptable to the patient and reflective of the poor responsiveness of this pain to opioid analgesia.

## Molecular Biology of CIBP

In recent years, the neurobiology of CIBP has been better elucidated through the development of experimental models [48,51–54]. There is a "neurochemical signature" unique to

bone cancer pain, which is consistent with a hyperexcitable state, and which differs from persistent neuropathic or inflammatory pain [55]. Features of this include enhanced neuronal activity and enlargement of the receptive field size in lamina 1 neurons; increased responsiveness to mechanical, electrical, and thermal stimuli; and marked astrocyte hypertrophy in the spinal cord ipsilateral to the bone with cancer. These changes occur at the same time as behavioral signs of pain in rat models and do not occur in inflammatory or neuropathic pain states, making them a useful substrate for studies of new agents in CIBP [56].

## Osteobiology of CIBP and Development of Novel Therapies

In prostate cancer, osteoblastic metastases predominate with disordered proliferation and incomplete bone calcification [57,58]. The pathway of proliferation involves several neurotransmitters and receptors and commences with upregulation of an adhesion molecule, alpha 6 integrin on tumor cells, allowing them to attach to bone matrix collagen. Prostate cancer cells then produce urokinase-type plasminogen activator (uPA) which stimulates mitosis and produces growth factors resulting in osteoblast migration and differentiation. Finally, prostate cancer cells express endothelin-1 which further promotes osteoblast proliferation and other growth factors.

Increased osteoclast activity also features in CIBP of prostate cancer. Markers of increased bone turnover such as interleukin-6 and parathyroid hormone-related protein (PTHrP) are high and are thought to mediate osteoclast proliferation by triggering the receptor activator of nuclear factor-κβ ligand (RANKL)-RANK interactions [59].

Murine studies have shown that blockade of RANKL which is an essential regulator of osteoclasts attenuates sarcoma-induced bone pain, bone remodeling, and tumor growth within the bone [42]. This final common pathway is a target for novel therapies such as monoclonal antibodies to RANKL (denosumab) [60] or interrupting the ligand through use of an analog of osteoprotegerin, a decoy RANK receptor [53].

## Other Targets for Novel Therapies

In experimental models, antibodies to nerve growth factor (NGF) and antagonists to transient receptor potential vanilloid type 1 (TRPV-1) ion channel and endothelin-1 receptor have been shown to relieve CIBP [61,62] (Table 88.2). Cancer-affected bone undergoes marked sprouting and reorganization, implicating NGF activity. Nearly all nerve fibers that innervate bone also express tropomyosin kinase A and p75 receptors through which NGF sensitizes and activates nociceptors. Antibodies to NGF administered early in animal studies have shown reduction in pain-related behaviors greater than that achieved with morphine sulphate [49]. Early phase II clinical trials using tanezumab, a fully humanized monoclonal antibody to NGF, is currently underway to evaluate effects at reducing bone pain in advanced prostate and breast cancer [61].

Other strategies have included studying the action of a cannabinoid 2 receptor agonist, AM1241, on an osteolytic sarcoma murine bone cancer model. Bone loss and pain behaviors were both reduced following systemic administration both acutely and over 7 days of AM1241 [63]. Finally, increased understanding of the role of glial cells in the generation of chronic pain and hyperalgesia is leading to the exploration of their role in CIBP and the potential for human therapies in the future [3]. With the development of these and other such targeted therapies, the pursuit for better analgesia for bone metastases becomes one which is closely aligned with the pursuit for better disease therapies.

## Interventional Therapies

Increasingly, a more mechanism-based approach to managing cancer pain is advocated as opposed to the traditional WHO approach. In approximately 3–14 % of patients, cancer pain proves unresponsive to analgesics given in the more standard ways and more interventional therapies may be considered [33,34]. This may include nerve blocks, spinal infusions, vertebroplasty, and neurosurgical ablative techniques. Typically, patients are referred when there is failure to respond to pharmacological means and the pain is anatomically amenable to an intervention. However, procedures such as intraspinal administration of analgesics carry significant risk and require specialist management which may lead to prolonged inpatient care. Integrated cancer pain management programs involving palliative, anesthetic teams, and neurosurgical teams among others are required and the infrequency of utilization of interventions makes the maintenance of expertise difficult. However, with careful and early patient selection, the right intervention may dramatically transform the distressing situation of a patient in unrelieved pain.

## Non-pharmacological Methods of Cancer Pain Control

These have been defined as actions or behaviors which are not drug-based and which "come between" the pathophysiological mechanism of the cancer pain and the patient's perception of that pain [64]. Examples are summarized in Fig. 88.2. A meta-analysis of the efficacy of CBT, including pain coping skills training, suggests that systematic training in cognitive and behavioral strategies for reducing cancer

**Table 88.2** Mechanism-based therapies for the treatment of bone cancer pain

| Drug class | Target | Action | Indication | Potential complications |
|---|---|---|---|---|
| *Tumor/inflammatory products* | | | | |
| Selective COX-2 inhibitors | Prostaglandin synthesis | Peripheral and central sensitization | Prostaglandin-dependent cancers | Cardiotoxicity |
| | | | | Nephrotoxicity |
| | | | | Bone formation |
| Endothelin-receptor antagonists | Nerve fibers | Sensitization of nerve fibers | Endothelin-sensitive cancers | Hypotension |
| | Smooth muscle cells | | | Teratogenicity |
| Anti-NGF antibody | NGF receptor blocker | Analgesia | Cancers with inflammatory | ? |
| | | | Component | |
| Acid sensitive ion channels(TRPV-1; ASIC) | pH-sensitive nerve fibers | Blockade of H+through channels | Proton- or acid-producing cancers | Delayed wound healing |
| | | | | Altered taste |
| Purinergic receptor antagonists | ATP-sensitive nerve fibers | Blockade of P2Xreceptors | Cancers that invade mechanically sensitive | Altered touch perception |
| *Bone remodeling* | | | | |
| Osteoprotegerin | Osteoclast activation | Osteolysis inhibition | Lytic bone pain | Autoimmune response |
| Bisphosphonates | Osteoclast apoptosis | Analgesia | Lytic and blastic bone pain | GI toxicity |
| | | Tumor shrinkage | | Fever |
| | | Osteoclast activity | | Electrolyte abnormality |
| | | Suppression | | |
| *Nerve injury* | | | | |
| Anticonvulsants (gabapentin) | Calcium channel subunit | Aberrant neuronal discharge suppression | Neuropathic pain | Bone marrow suppression |
| | | | | Ataxia |
| | | | | Drowsiness |
| Antidepressants | NE serotonin uptake inhibition | Analgesia | Neuropathic pain | Sedation |
| | | Anxiolysis | Musculoskeletal pain | Hypotension |
| | | | Opioid enhancement | Cardiotoxicity |
| | | | | Seizures |
| GDNF-like therapy (artemin) | Growth factor receptor stimulation | Analgesia | Neuropathic pain | Stimulated tumor growth |

Adapted from Sabino and Mantyh [68]
*COX-2* cyclooxygenase-2, *NGF* nerve growth factor, *TRPV-1* transient receptor potential V-1, *ASIC* acid sensing ion channel, *P2X* purinergic receptor, *NE* norepinephrine, *GDNF* glial cell line derived neurotrophic factor

pain is effective [65]. In recognition of the psychological distress experienced by partners of patients in pain, coping skills training involving partners is being studied to evaluate benefits on both patient's pain levels and caregiver strain and self-efficacy with regard to helping patients cope with pain [66]. Much research on cancer pain and coping has focused on catastrophizing which is an overly negative appraisal of pain. Catastrophizing relates to an increased level of psychological distress which generates higher levels of concern in caregivers who report higher levels of stress and lower quality of life.

## Conclusion

"The quantity and quality of scientific evidence on cancer pain relief compare unfavorably with evidence related to treatment of other high-impact conditions, including cancer itself" [67]. From the experience over the past 20 years, there is reason to speculate that improvements in pain management in advanced cancer will need to be closely linked to improvements in disease management before real progress is to be made. This viewpoint is taken because without investment of much greater economic, scientific, and clinician resources, efforts to improve pain management will remain the concern of the few who work in the fields of palliative and anesthetic pain management rather than occupy the efforts of the many involved in the treatment of cancer. The development of new molecular targets with a translational approach in CIBP is an important link with the disease-targeted therapies which also target pain mechanisms. In the light of these developments, the pharmacological management of cancer pain, particularly CIBP, is likely to dramatically change over the coming decades. However, effective pain management will always require multimodal approaches that recognize the subjective unique experience of each patient.


**Fig. 88.2** Non-pharmacological management of pain

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# The Psychosocial Impact of Prostate Cancer

89

Addie C. Wootten and Heather M. Siddons

It is well known that the treatment of prostate cancer can result in residual symptoms post-treatment [1, 2]. These may include sexual, urinary, and bowel dysfunction [2–6] as well as cognitive difficulties, fatigue, and emotional distress [7]. Coping with these residual symptoms can be very difficult for the patient [8, 9]. This chapter will provide an overview of the psychosocial impact of prostate cancer and the residual symptoms post-treatment on the man and his partner.

## Psychological Functioning

The psychosocial implications of cancer have been documented. Depression is at least two to three times more common in patients with cancer [10], with general psychological disorders (including depression and anxiety) estimated at 25–47 % [11–13]. It is also noted that depressive symptoms are believed to be underdiagnosed and underreported among cancer patients [14].

Research investigating the impact of prostate cancer treatment on psychological well-being has revealed that among those who have had prostate cancer treatment, the prevalence of mood disorders (i.e., anxiety, depression, adjustment disorders) ranges from 9 to 38 % [13, 15–19]. The results from other studies suggest that physical side effects of prostate cancer treatment (such as incontinence and sexual dysfunction) are associated with anxiety and depression [14]. One population-based Australian study of 1,067 men diagnosed with prostate cancer found that 54 % of men expressed that they felt some level of unmet psychological support need [20]. These findings indicate the degree to which prostate cancer can have a significant impact on psychological well-being.

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The risk of suicide in men with prostate cancer has also been reported [21]. One study has found that older men with prostate cancer were more than four times more likely to complete suicide than an age- and gender-matched cohort without prostate cancer [22]. Another study conducted in Sweden found that men with advanced disease, low socioeconomic status, and receiving hormonal treatment were at an increased risk of suicide compared with the background population [23]. No increased risk was shown for men with low-grade prostate cancers [23].

## Psychological Responses to Prostate Cancer

### Diagnosis

A diagnosis of prostate cancer may be associated with a range of intense transient or long-lasting emotions. Feeling shocked is a common initial emotional reaction experienced by men following diagnosis [8]. Often, a diagnosis of prostate cancer is made despite men reporting minimal or no physical symptoms, and they therefore find it difficult to believe the diagnosis. Commonly, men perceive themselves as "strong" and "invulnerable" to illness; a self-perception that may strengthen feelings of shock at diagnosis as they never thought it would happen to them.

Fear and anxiety are an expected and appropriate response to a diagnosis of cancer. A diagnosis of cancer evokes thoughts about one's mortality, loss of control, and the impact on day-to-day life, including work, finances, and relationships. Anxiety following a diagnosis of prostate cancer may also be related to the possibility of erectile dysfunction and incontinence and threatened masculine identity. Some men experience significantly elevated levels of anxiety, which causes significant distress and impedes functioning in daily life. One in four men have been shown to report clinically elevated levels of anxiety following diagnosis of prostate cancer [15].

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**Key Concepts Underpinning Psychological Adjustment in the Context of Prostate Cancer**

Masculinity

Masculinity can be broadly defined as a core set of beliefs, attitudes, and expectations about the gender role of being a man. Masculinity is constructed within and shaped by culture in the broadest context, as well as cultures within social relationships and subgroups, including the workplace or other smaller community or social groups [24]. Commonly, men hold a belief that they should be both physically and emotionally strong, invulnerable, in control, self-reliant, powerful, and successful [25, 26]. Additionally, many men place strong emphasis on their sexual potency, which is intrinsically tied to their sense of masculine identity. For many men, the ability to have an erection serves as proof that they are a "real" man. A major illness, such as a diagnosis of prostate cancer, can pose a fundamental challenge to masculinity that results in uncertainty and a loss of sense of self [24]. In the context of prostate cancer, men are faced with the strong likelihood of erectile dysfunction following treatment. This threat to sexual function may destabilize a man's sense of masculine identity, which in turn may lead to significant distress and unhappiness and place them at greater risk of depression and other psychosocial problems [9, 26]. In this way, it may not be the degree of sexual dysfunction that directly impacts on the psychosocial outcome of the patient following prostate cancer treatment but, rather, the way in which masculine identity or the individual sexual self-concept moderates this relationship. See Fig. 89.1.

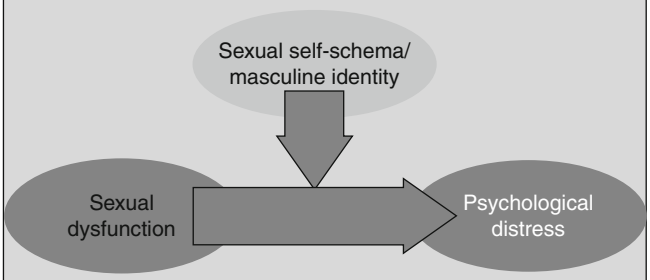


**Fig. 89.1** The moderating role of sexual self-schema between sexual dysfunction and psychological distress

Other emotional responses experienced by men during the diagnosis stage may include anger, grief and confusion, and a general feeling of being overwhelmed, particularly when faced with many treatment options.

## Treatment Decision Making

Typically, one of the first issues that many patients are confronted with is the necessity to decide between at least three treatment types, including active surveillance, radiotherapy, and radical prostatectomy. It is common for men to have difficulty deciding upon treatment [27, 28]. Learning about the various treatment options available and the respective side effects can feel overwhelming, confusing, and anxiety provoking for many patients and their families. Men experiencing heightened levels of psychological distress, such as anxiety, are likely to have impaired ability to effectively problem solve, thereby making it difficult to decide on treatment.

Cognitive appraisal of the meaning of prostate cancer and potential iatrogenic side effects, including erectile dysfunction and urinary incontinence, has been shown to influence the degree of distress experienced by patients during the treatment decision phase [29]. For example, men who view masculinity as inextricably linked to sexual potency may have particular difficulty committing to an active form of treatment.

A person's tendency toward having either an optimistic or pessimistic disposition has also been shown to influence the degree of distress during the treatment decision phase [29]. A person with an optimistic disposition is less likely to expect the worst when diagnosed with cancer, more likely to appraise the cancer as a manageable threat, and in turn, unlikely to feel overly distressed by the treatment decision process. Conversely, a person with a pessimistic dispositional style may believe the worst will happen and be limited in their ability to logically and rationally consider each treatment option [29]. Although limited, research to date suggests that men may benefit from additional support to assist in treatment decision [27, 28].

# Post-treatment

## Erectile and Sexual Functioning

It is important to draw a distinction between erectile and sexual function. Erectile function refers to the mechanics of obtaining and maintaining an erection, while sexual function encompasses broader issues including sexual identity, intimacy, broadness of sexual repertoire, level of sexual experience, sex drive, sexual fantasies, sexual attitudes, communication between partners, and relationship satisfaction [30, 31].

Sexual function must also be distinguished from sexual bother; the most commonly used quality of life scales now assess these two domains independently. Sexual function refers to an assessment of physical functioning (including an assessment of desire, arousal, and orgasm), while the sexual bother scale refers to self-reported degree of distress,

annoyance, or frustration experienced by the patient about their current level of sexual functioning [32]. Higher sexual bother would be expected to be associated with lower sexual functioning. However, sexual bother has been reported to show only low correlation with sexual functioning in some studies [33], thus highlighting the importance of an individual's perception of their disease state and the importance placed on the physical function. Age, relationship context, and role of sexuality within that relationship play an important part in determining each individual's perception of their physical functioning and consequent emotional responses. Patients under 55 years of age have been found to more commonly report a significant worsening of sexual bother than older patients [33]. Relationship status has also been implicated; men in a relationship have been reported to be less likely to have a severe worsening in sexual function but more than twice as likely to have a severe worsening of sexual bother [33]. The use of sexual aids has also been found to impact on levels of bother with those who used sexual aids being more than twice as likely as those who did not use aids to report a severe worsening sexual bother [33].

Patient expectations of treatment outcome have also been shown to significantly predict distress associated with sexual dysfunction following treatment [34, 35]. Pre-treatment expectations of sexual functioning have been reported to significantly correlate with sexual distress at 12 months post-treatment more strongly than with loss of function at 12 months post-treatment [34, 35]. This indicates that pre-treatment counseling and appropriate information provision are vital.

The research data available indicates that all treatment options will result in erectile dysfunction at some point following treatment [36]. However, the reported rates and duration of dysfunction vary widely between studies, and it appears that there are significant individual variations in erectile functioning following treatment across all treatment modalities [36]. This lack of clearly defined "recovery" milestones can be anxiety provoking and isolating for some men.

The resultant impact of erectile dysfunction on sexuality and sexual functioning can be significant. In the context of erectile dysfunction post-treatment, it is not uncommon for men to report sexual dysfunction characterized by feelings of loss of desire, lowered libido, loss of interest in sexual intimacy, and withdrawal from intimate relationships. Qualitative studies have found that sexual intimacy, everyday interactions and relationships with women, sexual imaging and fantasy life, and men's perception of their masculinity are affected by the sexual dysfunction experienced after prostate cancer treatment [37, 38].

### Incontinence

All treatment modalities also appear to have an impact on urinary continence. Post-treatment improvements in urinary function steadily occur over time, but recovery rates vary across treatment types [39]. Bowel problems have also been reported post-treatment, most commonly following radiation or androgen deprivation therapy [39]. Significant individual differences in coping with urinary incontinence or bowel problems have been observed. Patients who report a high level of distress associated with urinary incontinence report fear of loss of control and embarrassment about leakage and consequently uncertainty about engaging (and in some cases avoidance) in the social or occupational aspects of their life. Those men that have a high level of distress associated with incontinence post-treatment report the use of continence pads as demeaning, and their sense of masculinity appears to be undermined. Men who can integrate the use of pads into their life without a high level of fear of embarrassment or without it impacting on their sense of masculinity are likely to have improved psychological outcomes in relation to this challenge.

Anxiety plays an integral role in the way in which men cope with issues of incontinence post-treatment. An incontinence avoidance cycle can be perpetuated by fears of leakage and the subsequent embarrassment (see Fig. 89.2). Working with men to break this anxiety cycle can facilitate improved coping with challenges of living with incontinence issues post-treatment.

## Cancer Recurrence and Advanced Disease

Coping with a cancer recurrence or advanced disease can be very difficult. Patients and their families are faced with existential concerns, progression of disease, and impact on quality of life. Living with uncertainty about disease progression can be very destabilizing for patients and their families, and frequent PSA testing can be highly anxiety provoking. The impact of fear of recurrence on quality of life and mental health has been documented [40]; however, this impact appears to be mitigated by high levels of treatment satisfaction [41].

The impact of androgen deprivation therapy (ADT) can be significant in terms of emotional well-being, cognitive functioning, and overall quality of life [7]. Men on intermittent ADT have been reported to experience a decline in spatial reasoning, spatial abilities, and working memory during treatment as compared to baseline [7]. Significant changes in self-rated mood such as increased depression, tension, anxiety, fatigue, and irritability have also been reported during treatment compared with baseline for ADT patients [7].

## Summary

A range of emotional responses and psychological challenges can be experienced at all stages of the prostate cancer experience (see Table 89.1). Each individual will respond to the challenges at each stage in their own unique

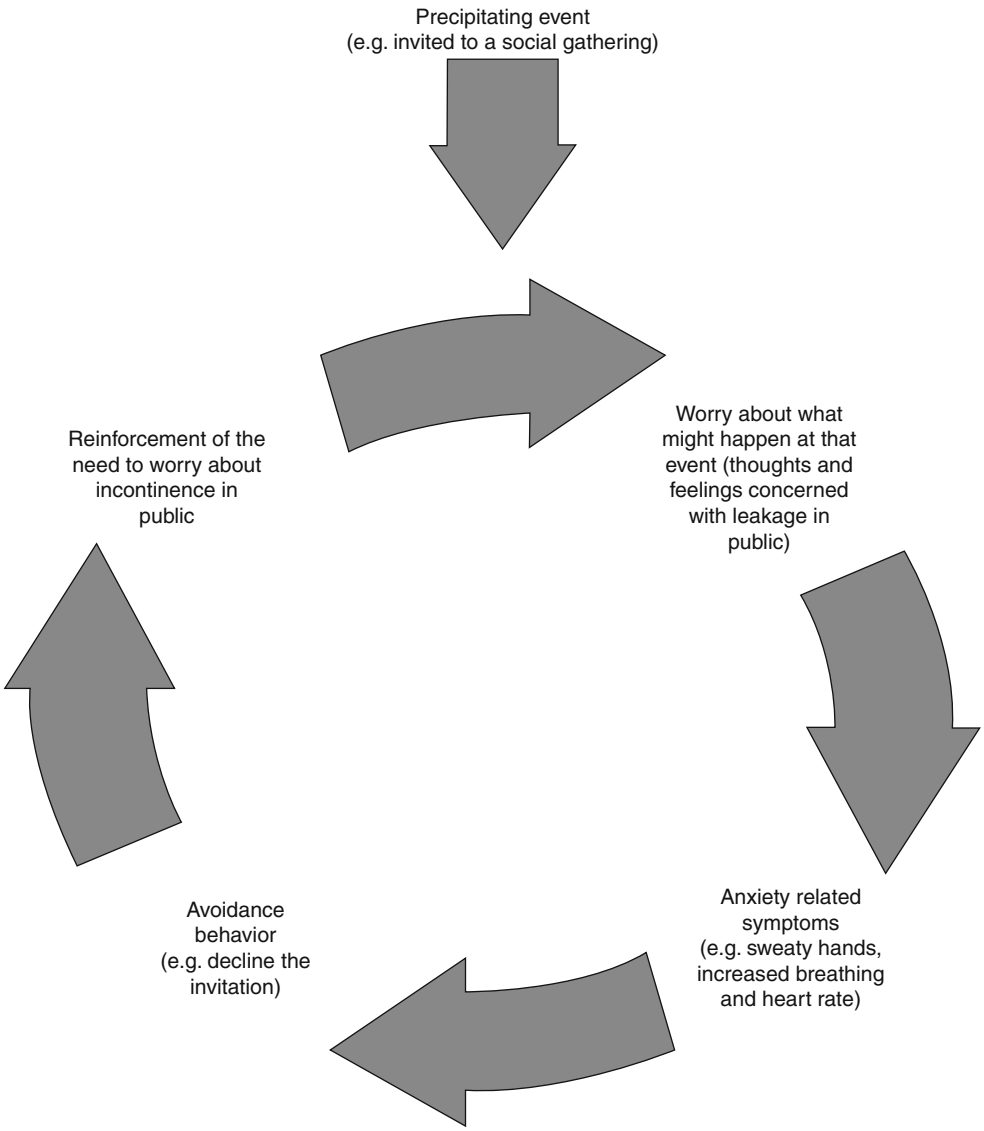


**Fig. 89.2** Continence anxiety avoidance cycle

way, and it is the responsibility of the treating clinicians to assess the level of support required by each patient. The diagnostic criteria for a generalized anxiety disorder and a major depressive disorder are also presented in Table 89.2.

## The Impact of Prostate Cancer on Partners and Relationships

Cancer may be viewed as a "family illness," and in the case of prostate cancer, partners may be particularly affected. Research has identified that partners report a considerably higher rate of depression and anxiety disorders than patients particularly at the point of diagnosis and a significant decrease in marital satisfaction over the 6-month period post-diagnosis [16]. Reduced coping skills and poorer adaptation have been linked to anxiety and depression in partners 6 months after diagnosis [42].

Given the treatment side effects, it is to be expected that prostate cancer may have a significant impact on the intimate relationship between patient and partner. Some couples adjust well to living with cancer and incurred changes to their sexual relationships, while other couples find it difficult to cope with the impact that treatment side effects may have on the relationship [43].

Partners of men with prostate cancer are often unaware of the significant impact that the treatment side effects can have on the men's sense of masculine identity, confidence, and self-esteem. Some partners may personalize the behavior of their partner with prostate cancer, such as thinking that their partner no longer finds them attractive because he does not initiate sexual intimacy, when it may be that the man feels inadequate due to not being able to have penetrative sex [44, 45].

**Table 89.1** Common psychological responses in the context of prostate cancer

| Diagnosis | Post-treatment | Advanced disease |
|---|---|---|
| Shock | Loss of identity | Fear |
| Anger | Loss of masculinity | Anger |
| Worry | Vulnerability | Worry |
| Anxiety | Loss of sexual desire and arousal | Anxiety |
| Sadness | Sadness | Sadness |
| Fear | Grief | Loss of sexual desire and arousal |
| Agitation | Agitation, irritability, or high levels of frustration | Agitation |
| Irritability | Loss of motivation | Irritability |
| Fatigue<br>Tearfulness | Withdrawal from others and communication problems, particularly intimate relationships | Loss of motivation<br>Fatigue<br>Attention, concentration, and memory difficulties<br>Fear of recurrence |

**Table 89.2** Diagnostic symptoms

| Anxiety (Generalized Anxiety Disorder) | Depression (Major Depressive Episode) |
|---|---|
| Feeling very worried | Depressed mood most of the day |
| Finding it hard to stop worrying | Loss of interest or pleasure in all activities |
| Anxiety impacting on everyday activities | Weight loss or gain (when not dieting) |
| Feeling restless or on edge | Sleeping difficulties |
| Feeling easily tired | Slowed or fastened movements |
| Difficulty concentrating | Tiredness or loss of energy |
| Irritability | Feelings of worthlessness |
| Muscle pain | Difficulty concentrating |
| Difficulty sleeping | Thoughts of death or suicidal ideation |

Undue levels of stress may be placed on the relationship especially if there is a breakdown in communication and if the patient and partner employ conflicting coping styles. Consequently, a significant impact on relationship intimacy can occur [44, 46], and patients and partners may feel isolated and as though they must cope alone. Appropriate communication styles and lower use of avoidance of cancer-related concerns can maintain a sense of closeness and intimacy which also fosters healthy adjustment for the couple and less psychological distress [46].

## Psychological and Support Interventions

### Diagnosis

Psychological therapy immediately post-diagnosis initially focuses on the assessment of the patient's psychological adjustment, with particular attention to psychological trauma, mood, and anxiety disorders. Through this process, the patient is given space to debrief and process any unresolved thoughts and feelings about the diagnosis.

Research has suggested that patients newly diagnosed with prostate cancer particularly benefit from interventions incorporating psychoeducation, problem solving, and decision support [28]. Following a structured decision-making process, in which the costs and benefits of each treatment are assessed, may help patients to gain clarity and decide on a treatment.

Throughout the treatment decision-making process, it is important to be sensitive to the patient's psychological status. Emotional states of lowered mood and anxiety are typically associated with distorted thinking, such as catastrophizing or magnifying the problem, which may hinder rational problem solving. It is therefore important to address these problems so that the patient is able to approach the treatment decision-making process with relative objectivity and clarity [29, 47].

It is equally important to be aware of the patient's sexual self-schema and their belief system with respect to masculinity. For example, a patient's anxiety about active treatment (as opposed to active surveillance) may stem from a belief that erectile dysfunction will make them "less of a man." In this situation, a process of challenging the beliefs and broadening their meaning of masculinity may enhance the decision-making process.

### Post-treatment

#### Psychological Interventions for Sexual Dysfunction

The aim of psychological interventions in the context of sexual dysfunction following treatment for prostate cancer is not to improve sexual functioning per se, but to facilitate coping with the changes to sexual functioning and exploration of ways in which the man and his partner might have an engaging and satisfying sexual relationship. Cognitive behavioral stress management (CBSM) has been found to be an effective intervention for promoting sexual functioning following radical prostatectomy [48].

Initial stages of psychological therapy often center on the emotional responses experienced at the point of diagnosis, and unresolved feelings are processed. This phase of therapy is often very important in terms of sexuality post-treatment as psychological trauma, low mood, or high levels of anxiety will have direct consequences on the man's ability to cope with sexual dysfunction post-treatment. These emotional responses can also have a significant impact on levels of sexual desire and arousal.

**Table 89.3** Common psychological interventions and target concepts

| Diagnosis | Post-treatment | Advanced disease |
|---|---|---|
| Problem solving | Cognitive behavioral therapy | Cognitive behavioral therapy |
| Cognitive behavioral therapy | Problem solving | Existential therapy |
| Supportive psychotherapy | Sensate focus interventions | Mindfulness-based therapy |
| Communication skills training | Couple-based therapy | Relaxation and stress management |
| Normalizing emotional responses | Identity-focused therapy | |
| Existential therapy | Sex therapy | |
| Relaxation and stress management | Existential therapy | |
| | Relaxation and stress management | |
| | Mindfulness-based therapy | |

Psychological therapy will then move to explore the cognitive appraisals that men might be making about their physical performance, their identity, and relationships. It is very important for men to understand the ways in which their masculine identity and belief systems may be impacting on their emotional state. This phase of therapy involves identification of patterns of thought that might be resulting in negative emotion states or withdrawal from sexual intimacy and a process of challenging these thought patterns or beliefs. For example, a man who states "My wife will only be satisfied if we can have penetrative intercourse, and I can't get an erection, so I am now no good for her" is assuming that penetrative intercourse is the only way in which his wife can have a pleasurable sexual experience and also that he is no longer a worthwhile man and husband. A process of challenging these generalized beliefs about his wife's satisfaction and his worthiness as a man may improve his self-esteem and also enable him to reengage with his wife in a sexual way (albeit without having intercourse). Expanding the beliefs about what "good sex" means to the couple is very important in this process. Exploring beliefs around engaging in other forms of sexual behavior including manual stimulation or the use of sexual aids can result in the man and his partner developing new ways of enjoying their sexual relationship.

### Coping with Incontinence

Psychological interventions to facilitate coping with incontinence take a similar approach to working with sexuality. It is important to normalize the experience of incontinence and encourage the patient to discuss the ways in which the incontinence might be troubling them. Cognitive behavior therapy can be useful when patients have fallen into the anxiety avoidance cycle detailed earlier (see Fig. 89.2). Challenging unhelpful or negative thinking patterns can facilitate improved coping.

The impact of incontinence of the man's sense of masculinity should be explored. It is common for men to feel dirty or to liken their experience of having to wear incontinence pads as turning into a woman or infant. Beliefs need to be explored and the patient supported to adjust to their experience. The impact of incontinence on sexual experiences must also be considered. Often, the fear of leakage will impact on the man's level of desire or arousal, which may result in men avoiding sexual intimacy.

## Advanced Prostate Cancer

Psychotherapy in the context of advanced disease will commonly center on issues of existential concern. Other issues such as loss of libido and coping with sexual changes or other physical complications are typically of secondary concern to the man with advanced disease; however, this cannot be taken for granted and needs to be explored with each individual.

Structured exercise programs have also shown promising results in improving cognitive, emotional, and physical complications of ADT [49]. Men who undertake this type of intervention have reported feeling physically and emotionally stronger and an increased sense of control.

## Group Therapy and Support Groups

Group therapy has been found to be a beneficial therapeutic intervention in the context of prostate cancer, both with patients with local disease and advanced disease [48, 50]. The process of sharing the prostate cancer experience within a group setting can be very powerful for men with prostate cancer as men gain insight into the shared experiences between themselves and other participants. Consequently, men feel less isolated in their prostate cancer experience.

Support groups have also been reported to be very useful to men with prostate cancer. These groups can aid in information gathering and education but also in terms of social support and normalizing of experiences [51]. Support groups, however, appear to be attractive only to certain groups of men and may not be supportive for all men with prostate cancer [52].

Table 89.3 provides an overview of the common psychological interventions across the stages of disease.

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# Nursing Issues in Prostate Cancer

# 90

Helen Crowe

## Introduction

Prostate cancer is the most commonly diagnosed male cancer and the second leading cause of cancer death in men in western countries [1]. Prior to the discovery of prostate specific antigen (PSA), the role of the nurse in prostate cancer management was limited to the care of men being palliated for symptomatic, metastatic disease in acute inpatient settings. The introduction of PSA testing has permitted the earlier diagnosis and potential cure of localized prostate cancer, with resultant developments in the treatment of advanced prostate cancer. As a result, the nursing role in prostate cancer care has now expanded significantly. There has been a shift in focus, however, with most care for this disease now being provided in an outpatient setting by advanced practice nurses. Prostate cancer nursing has developed with urology or oncology nurses providing the source of nursing expertise for this advanced practice role.

Studies have found that men living with prostate cancer report substantial unmet needs. These include a lack of information and assistance coping with urinary incontinence and erectile dysfunction and inadequate supportive psychological care [2–5]. A review of the roles of specialized prostate care nurses found that nurses may improve the experience of men with prostate cancer acting as intermediaries with medical personnel, providing information, emotional support, and clinical advice. They can also act as a patient advocate to assist patients to negotiate the care process [2, 6, 7]. Nurses are perceived to be more available than other health professionals, in particular, medical staff. Patients appreciate the amount of time nurses are able to spend with them [2, 8]. Patients also report that contact with specialist prostate care nurses is supportive and informative and an acceptable alternative to consulting with a medical practitioner [9]. The nursing role includes not only providing support for the man who has been diagnosed with prostate cancer but also for his family members, in particular, his partner. The impact of the prostate cancer diagnosis has been found to be significant for the partner as well as for the patient and to have potential implications for relationships [9–12]. To fulfill this advanced practice role, prostate care nurses need to be aware of the changing trends in prostate cancer diagnosis and treatment.

Specialist prostate care nurses have a role at all stages of the disease process. Involvement with patients from initial diagnosis through all treatment phases provides a constant for patients, providing a reliable contact for support and information. The prostate care nurse is ideally positioned to provide assistance while monitoring the patient's condition and response to treatment [8].

In pre-diagnosis, the nursing role can include provision of information to men about their risks of developing prostate cancer and appropriate testing. This is particularly important in view of the confusion that remains in the community about prostate cancer and the benefits or otherwise of diagnosis and aggressive treatment.

Specialist prostate care nurses also have an important role providing support and information at the time of prostate cancer diagnosis and during the decision-making process about treatment choice. This is often a difficult time for newly diagnosed men who need to understand the various options before they decide on treatment. Nurses are well-placed to provide men with this information and assist them through the decision-making process. Importantly, nurses then have a major role in all aspects of the recovery phase after treatment as the patients deal with treatment-related side effects. This preparation is necessary to avoid patients experiencing decisional regret.

The health problems experienced by men with advanced prostate cancer are different again, and the prostate care nurse must be aware of these needs and provide appropriate care and support. If disease progression occurs with the development of metastases, patient needs, and the nursing role, change.

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Over the course of the disease, there may be multiple medical specialties involved in an individual patient's care including urology, radiation and medical oncology, palliative care, general practitioners as well as many other allied health professionals, physiotherapists, clinical psychologists, and dieticians. It can become very difficult for patients to determine who is directing their care and who they should contact if they are experiencing problems. It has been found that the specialist nursing role can provide the link between the patient and the specialists and remove the confusion for the patient [13]. If treatment is not curative, men may now live for many years with their disease in remission. Specialist urology nurses with prostate care experience are ideally placed to meet the needs of men with prostate cancer in all but the final stages of this disease when the expert skills of oncology and palliative care physicians and hospice nurses are required.

Prostate care nurses must be responsive to the needs of men with prostate cancer, and their partners, from the time of investigation and diagnosis through to the development of metastases. The majority of this care now occurs in an outpatient setting.

## The Nursing Role Pre-diagnosis

Localized prostate cancer is usually without symptoms, and therefore, the diagnosis relies on testing for the disease. This testing initially consists of a digital rectal examination (DRE) to palpate the prostate and measurement of PSA levels [7].

While ongoing controversy surrounding prostate cancer diagnosis and treatment remains, there is confusion among the community and general practitioners about who should be tested [14]. There is no evidence to support whole-population screening, but opportunistic testing, on an individual basis, is advised by most authorities [15].

Guidelines about testing for prostate cancer from professional bodies have been inconsistent in their recommendations further adding to the confusion [16]. However, recently all major urological societies have released statements recommending opportunistic testing for prostate cancer for men from the age of 40 who have a life expectancy of 10 years and who have been appropriately informed [17]. There is agreement that appropriate testing for prostate cancer includes both PSA test and DRE. There is also agreement that men should be allowed to make an informed choice about whether or not to be tested for prostate cancer. In order to make this informed decision, they need detailed information about their personal risks of developing the disease, what testing involves, and the risks, benefits, and potential consequences of testing [17–20].

Adhering to this recommendation is neither always practical nor practiced in the general practitioner's setting due to time constraints and/or lack of knowledge. Patients report that they have had to visit several general practitioners before they could be tested or that there was no discussion about undergoing testing. Specialist nurses are able to play an active role in providing [19] and clarifying this required information [21] and conducting testing if requested [7, 22].

At the Australian Prostate Cancer Research Centre (APCRC) based in Melbourne, Australia, we have recently established a nurse-led prostate cancer risk information clinic. Men may self-refer to this clinic for information about their individual prostate cancer risks and to undergo testing by the prostate care nurses if they wish to proceed. One success of this initiative has been the portability of this clinic. Men, especially in the younger age groups, tend not to be attentive to their health and preventative health care measures. We found taking the clinic into the workplace to be more worthwhile and time-efficient than is waiting for men to come to the clinic seeking advice.

In the work setting, we conduct a group information session at an appropriate time. The style of presentation and the content are tailored to the individual workplace, with less formal presentations given by a male urologist usually being well received. Those employees attending are then given the option of having individual consultations with a prostate care nurse at a later date.

The outcomes of this clinic are still being evaluated, but initial feedback has been positive, with respondents reporting that they find the information about prostate cancer helpful and appreciating the informality and convenience of workplace testing. The majority of men attending the information sessions do then proceed with the individual consultations. It is not uncommon for these men to report they do not have a general practitioner and rarely go to a doctor. They are, therefore, not in a position to be informed about important health-related matters from that source. These workplace clinics provide a practical alternative.

If either DRE or PSA is abnormal, a transrectal ultrasound-guided biopsy (TRUS) of the prostate will provide histopathological diagnosis. Specialist prostate care nurses are also able to perform these biopsies, supported by urologists. The ability of nurses to provide this service has been found to be time-effective and to encourage continuity of care, as the prostate care nurse performing the procedure is usually a constant presence and key person throughout the course of the patient's care if prostate cancer is then diagnosed [22, 23].

## The Diagnosis of Localized Prostate Cancer

If the prostate biopsy is positive, then men are offered two forms of curative therapy: radiation therapy (external beam radiation therapy and/or brachytherapy) or surgery (open,

laparoscopic, or robot-assisted laparoscopic radical prostatectomy). There is a lack of clinical consensus about the optimal treatment for localized prostate cancer [24, 25]. Both treatments have associated side effects of urinary incontinence and erectile dysfunction, and decision-making about treatment is often a major source of stress for patients [26]. Specialist nurses have an important role in helping men throughout the decision-making process [27]. There is evidence that the intervention of specialist nurses to facilitate understanding of different treatment options for prostate cancer is valued [3]. Education, knowledge, and understanding are essential requirements for patients to make an informed decision about treatment [28]. Information about the likelihood of and management of potential treatment side effects, in particular, urinary incontinence and erectile dysfunction, is critical at this stage, as these both have a major impact on patient's quality of life, and the prostate care nurses are able to ensure patients receive appropriate information and advice.

Patients who have access to a prostate care nurse are more likely to have written information provided about treatment options and about alternative sources of help and support. Patients receiving this support were more likely to feel that they had decided on their preferred treatment themselves [2]. The availability of information via the internet can exacerbate anxiety at this time as patients sometimes feel that the next website they visit will give them all the answers they need. It is not uncommon to have these men arrive for consultations with folders brimming with downloaded material. Health professionals have a role in providing sound, reliable information sources and discouraging endless internet searches. Patients can be reassured that once they have made their treatment choice, they will feel greatly relieved.

Prostate care nurses are seen to be able to address issues other than diagnosis and treatment, including the impact that treatment may have on patient's lifestyle, and are often the health professional that patients and partners turn to for guidance [10]. The advice that prostate care nurses can provide may extend to practical concerns for patients who have to travel to specialist locations for their treatment including provision of information about local accommodation, ensuring support for patients post-discharge after surgery, or support if spending an extended period of time away from home for radiotherapy treatment.

At the time of diagnosis of prostate cancer, men are often surprised as there are usually no symptoms. They may also be angry, confused, and may become depressed [31]. It is the nurses' role to explain that all of these responses are normal and that help can be accessed if any of the emotions they are experiencing become overwhelming. It has also been our experience that depression is not uncommon even several months after treatment for prostate cancer when patients are still experiencing side effects and having to deal with the reality of having been diagnosed with cancer. The availability and accessibility of a nurse makes them ideal support persons for the men and their families to monitor these responses, and it is our experience that partners often will ring our clinic to discuss with the prostate care nurse concerns they have about their partner. In our prostate cancer practice, we routinely refer couples to a clinical psychologist prior to treatment to better prepare them for the emotional disturbances they may experience. We find that it is better to include this psychological preparation for treatment as a routine, rather than patients viewing the need to see a psychologist as a concern.

It is our practice to encourage partners to be present and involved in all of the discussions about treatment and side effects. It is well recognized that the diagnosis of prostate cancer has an emotional and physical effect on both patients and their partners, and integrating partners into the care process will assist the couple cope with the sequelae of treatment [11].

There are several reports of the economic and time benefits offered by nurse-led telephone helpline or follow-up services [8, 29, 30]. This model of information and provision of support may be particularly useful for patients in rural areas where access to specialist medical and nursing support is not readily available. Prostate care nurses need to ensure that there is a reliable contact system for patients who may need advice or responses to queries before, during, or after treatment. Individual centers will determine how this reliable contact support for patients can best be facilitated. The ability to provide this support via the internet is an area that has enormous potential for the future.

## Active Surveillance

Internationally, there are concerns about the overdiagnosis and unnecessary treatment of prostate cancer, and it is acknowledged that not all men who are diagnosed with prostate cancer require curative treatment. Watchful waiting, or active surveillance, is an alternative management option for some men with low-risk prostate cancer [32]. The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer recommend that men with very-low-risk prostate cancer and who have a life expectancy of less than 20 years and men with low-risk prostate cancer and a life expectancy of 10 years should be placed on an active surveillance program [33]. Other factors that need to be taken into consideration before deciding on this option include the patients' preferences and their willingness to comply with the surveillance program. The nursing role with these individuals includes providing education and reassurance about this option and participation in the monitoring of patients on a surveillance program including ensuring they undergo

scheduled PSA testing, prostate examinations, and repeat prostate biopsies [7, 34]. The importance of compliance with the program must be emphasized with these patients, and some centers now require informed consent from patients before enrolling them into surveillance programs. This ensures that the patients are aware of the risks of noncompliance.

## Radical Prostatectomy

The acute inpatient setting no longer offers the opportunity for education and support for men undergoing radical prostatectomy. When first performed, radical prostatectomy routinely required an inpatient stay for up to 5–7 days. Now, with the increasing popularity of minimally invasive techniques, laparoscopic and robot-assisted, overnight stay is becoming the norm, with open surgeons encouraging a similar pattern of care for their patients. Ward nurses, therefore, have little opportunity for provision of education or support for these men.

The prostate care nurse has an important role to provide comprehensive education. Prior to admission, patients need to be advised about what to expect during their inpatient stay: catheter and leg bag management, their anticipated course of recovery, advice about pain, constipation and other symptom management, and recognition and reporting of any postoperative complications [35]. Following robotic radical prostatectomy, perineal discomfort is a common occurrence, and this may persist for several weeks following surgery. We have found anti-inflammatory medication if taken regularly for a period of up to a week to be very helpful in reducing the discomfort. Pelvic floor exercises should be ceased while this discomfort is present.

Patients need to be educated about urinary incontinence following catheter removal [7]. They also need to be counseled about post-surgery erectile dysfunction [36]. Information about what measures may be taken to assist with these distressing side effects should be provided, with additional advice and support being offered at relevant times.

## Radiotherapy for Prostate Cancer

Men who choose radiotherapy to treat their localized prostate cancer have similar education and information needs as do those who undergo radical prostatectomy. Provision of this information by prostate care nurses may help patients continue their lives with less disruption while they undergo treatment [37, 38].

Radiotherapy for prostate cancer may be delivered by external beam approach (EBRT) or interstitial therapy, i.e., low- and high-dose brachytherapy. Initial side effects of EBRT include fatigue, cystitis, hematuria, and diarrhea. These most frequently occur toward the end of the treatment period and may persist for weeks after treatment, but there is the potential for them to become chronic [7, 37]. Patients undergoing brachytherapy need education about anticipated short-term side effects of treatment including dysuria, hematuria, perineal discomfort, lower urinary tract symptoms (LUTS), and the potential for urinary retention [7, 24]. If retention occurs, instruction about managing an indwelling catheter at home or intermittent self catheterization will be necessary until the treatment-related edema settles. Any increase in LUTS that occurs usually subsides within 6–12 months following brachytherapy [7].

It is the role of prostate nurse to ensure that men and their partners are aware of the potential side effects of treatment and what measures they may take to minimize these. They should also be advised about precautions they must take to avoid radiation exposure to others for the first weeks after treatment [7].

There is evidence of the success of specialist prostate care nurse-led clinics in assisting patients manage treatment-related side effects following radiotherapy [37]. Providing taped information for patients to access at specific times and the establishment of nurse-led follow-up telephone calls were found to be successful in providing support and in reducing costs when compared with conventional outpatient clinic follow-up. Advantages of the taped information include the capacity to guarantee consistency of information provided and the ability of the patient to repeat the message as often as required. Disadvantages of this form of communication include the inability to individualize the information and its impersonal nature [37]. Combining this method of follow-up with face-to face meetings with the prostate care nurse may overcome these potential drawbacks and provide a cost-efficient and cost-effective follow-up service.

Patients with positive surgical margins, extra-capsular disease, seminal vesicle involvement, or a detectable PSA reading at the first postoperative measurement are at high risk of disease progression. Adjuvant radiotherapy is an option for these men. This treatment is usually well tolerated but may produce some bladder and rectal side effects, including the development of urethral strictures [39]. Prostate care nurses need to be aware of the potential side effects of this therapy and monitor patients.

## Urinary Incontinence Following Treatment for Prostate Cancer

Urinary incontinence following prostate cancer is one of great concern for most patients. Following radical prostatectomy, urinary incontinence is experienced immediately on urethral catheter removal and varies in severity and duration

between patients. The opportunity to have an open discussion and to receive information about urinary incontinence prior to treatment was identified as being helpful by one group of post-prostatectomy patients [40]. Education targeted to the specifics of managing their urinary incontinence resulted in high levels of patient satisfaction [41].

The reported incidence of post-prostatectomy urinary incontinence varies considerably. The multiple definitions used to define incontinence make true figures difficult to assess [42]. Lack of consistency in reporting tools currently remains a difficulty in interpreting reported outcomes. There are several factors that may impact the timing of the return to continence. Any preexisting bladder pathology, e.g., overactive bladder or impaired bladder compliance may worsen the urinary incontinence experienced. The patients' age, weight, comorbidities, and physical demands of their occupation may also have an impact on their continence recovery.

There is evidence that performing pelvic floor (Kegel) exercises may accelerate the return of urinary continence following prostate cancer treatment [45, 46] and improve quality of life for these patients [47]. Prostate care nurses should educate patients about these exercises and recommend they commence them prior to their treatment [41]. Assessment by a continence physiotherapist or continence nurse who can reinforce this education, and provide feedback about the patient's ability to perform these exercises correctly, is extremely useful, and men should be referred for this assessment prior to undergoing treatment [43, 48].

All patients should be counseled to expect to experience a period of urinary incontinence following surgery and how to manage this. This education needs to include information about activities that are likely to cause urine leakage, e.g., standing, coughing, and any movement that causes downward pressure through the bladder. They should be instructed to perform and maintain a pelvic floor contraction at that time. They also need to be reassured that it is common for the incontinence to be more marked later in the day due to fatigue of the pelvic floor and advised of the benefit of having a rest in the afternoon as a means of allowing pelvic floor recovery. Pelvic floor exercises should not be overdone as this will also fatigue the pelvic floor and result in increased incontinence, and patients should also be advised not to restrict fluid intake as a means of minimizing leakage. Prostate care nurses also are able to provide valuable practical information about the availability and sources of appropriate incontinence pads and advice about when and how to change the pads [49]. Patients should also be aware of the feelings of frustration that they are likely to experience until continence returns and be advised to maintain regular contact with the prostate care nurse for feedback and reassurance. Providing this information in written form as well as having a discussion with the patient and their partner is useful.

Most men report a gradual return of continence with improvement experienced up to 1 year post-surgery [7, 40]. If incontinence remains severe and long-standing and non-responsive to pharmacologic and non-pharmacologic interventions, then surgical intervention may be warranted. Surgical options include periurethral injections to assist with urethral coaptation and insertion of an artificial urinary sphincter or a male urethral sling [43].

Urinary incontinence following radiotherapy usually has a delayed onset and may still be present 2 years after treatment [44].

It is the role of the prostate care nurse, along with the treating urologist and/or radiation oncologist, to monitor the patient's urinary incontinence and to provide support and advice until recovery occurs.

## Erectile Dysfunction Following Prostate Cancer Treatment

As with urinary incontinence, assessing erectile function outcomes following radical prostatectomy are also difficult to interpret due to the wide variety of assessment tools used [50, 51]. However, it is acknowledged that even when nerve-sparing techniques are used, it may still take up to 18–24 months for erections to return [52].

Factors that impact the recovery of erectile function include the patient's preoperative sexual function, their age, surgeon's expertise, and the nerve-sparing status of the surgery [36]. Men who are experiencing erectile difficulties prior to surgery are at increased risk of poor postoperative erectile function recovery. This may be due to existing medical comorbidities in particular, diabetes and cardiovascular disease, smoking, obesity, and medication [52]. Not surprisingly, older patients are more likely to have difficulties in the recovery of erectile function.

Treatment with radiotherapy results in a gradual decline of erectile function [53] with the average time to the development of problems being approximately 1 year. The non-surgical factors (age, comorbidity, pretreatment function, medication) that impact on patient's recovery following radical prostatectomy are also important following radiotherapy. Due to the delay in onset of potential sexual and incontinence side effects after radiotherapy, long-term follow-up and provision of support for these patients are important [54].

In 1997, it was reported that the early use of intracavernosal injections following radical prostatectomy improved long-term erectile function [55]. Current research supports instituting early erectile function rehabilitation (EFR) measures [56] to prevent corporal fibrotic changes that may occur in the absence of regular erections [57–60]. EFR may involve the regular use of phosphodiesterase-type 5 (PDE-5) inhibitors,

intracavernosal injection therapy, or use of vacuum erection devices [36]. The prostate care nurse should discuss with the patient and their partner prior to treatment the potential benefits and requirements of EFR. It is important that advice about erectile function is given to all patients and their partners as a matter of course, regardless of their age.

There are no current data available on an appropriate management to protect penile tissue following radiation therapy [60]. But patients should be advised to seek assistance if, and when, they experience sexual difficulties.

The PLISSIT model is widely used as a guide for nursing intervention for patients with sexual dysfunction [61]. There are four levels to this model: P = permission, LI = limited information, SS = specific suggestion, and IT = intervention therapy. By working through this model, the prostate care nurse can firstly set the scene for patients and their partners to discuss sexual issues then provide information about the expected impact of their treatment on their erectile function. By initiating the discussion about sexual function, the prostate care nurse gives the patients and his partner "permission" to discuss these issues. Further discussion about available treatment options for erectile dysfunction then allows the couple to determine what treatment, if any, they wish to pursue. The prostate care nurse can then provide instruction about how these treatments may be used, providing information about effective use of PDE5-inhibitors, practical instruction in intracavernosal injection technique, or the use of a vacuum erection device.

## Advanced Prostate Cancer

If prostate cancer progresses after failed curative treatment or is considered advanced at the time of diagnosis, other treatment options will be instituted.

## Androgen Deprivation Therapy (ADT)

In 1966, Dr. Charles Huggins was awarded a Nobel Prize for describing the response of prostate cancer to testosterone manipulation. The testes are responsible for approximately 90–95 % of the body's testosterone, with the adrenal glands, by producing androgens that are precursors to testosterone, contributing the remaining 5–10 % [62]. Bilateral orchidectomy is a surgical, non-reversible means of testosterone suppression, less commonly utilized these days.

Luteinizing hormone-releasing hormone (LH-RH) is the hormone primarily responsible for testosterone production. Administration of LH-RH agonists and antagonists as intramuscular or subcutaneous injections or subcutaneous pellets results in medical castration. This therapy may be continuous or intermittent and regulated by individual patients' PSA responses. Intermittent androgen deprivation therapy (ADT) offers patients some respite from the associated side effects [63].

The side effects of ADT can be quite debilitating, and a patient's ability to cope with these is dependent on how well informed they are about what to expect [63]. The most common side effect of ADT is hot flushes occurring in approximately 80 % of men and is reported as the most distressing by 27 % [64]. Other potential side effects include fatigue, lethargy, loss of muscle mass, weight gain, osteoporosis with an increased risk of fractures, hair loss, memory disturbance, mood swings, breast tenderness and gynecomastia, sexual dysfunction, loss of libido, and development of metabolic syndrome with increased risk of cardiovascular disorders [1, 65]. Testosterone levels take several weeks to reach their lowest levels after LH-RH administration, so the onset of treatment-related side effects is gradual. An initial flare in testosterone levels occurs when ADT is commenced. Antiandrogen medication may be used for a few weeks at the commencement of ADT to minimize the consequences of this testosterone flare [63]. The fall in testosterone following orchidectomy is much more dramatic with castrate levels being achieved within 24 h [66].

The nurses' role with men commencing ADT is to ensure that they understand the nature of the side effects and what measures they may take to minimize the impact of these. Explanations regarding lifestyle modifications are important, including advice regarding stopping smoking, moderating alcohol and caffeine intake, reduction in spicy foods that may minimize the hot flushes, and having regular blood pressure and serum lipid level assessments. One patient found that not wearing a tie reduced his hot flushes. The response to these lifestyle modifications is very personal. What works for some will not work for others. It is the role of the prostate care nurse to provide information about all of the possibilities and help patients work through these to achieve the best outcome. The benefits of a well-balanced diet do need to be addressed [1] and a referral to a dietician may be appropriate.

Daily supplementation with calcium and Vitamin D and regular weight bearing, resistance, and impact exercises can help prevent, and even reverse, some of the potential development of osteoporosis, muscle loss, and deterioration in physical functional performance that is associated with ADT administration [67–70]. There are clinical trials still underway examining the benefits of exercise programs for men, naive to hormone therapy, and recently in Australia, there has been the introduction of a drug company sponsored program for these men, Man Plan.

At the ACPRC, we ran a pilot study in a small group (9 men) of specific exercises twice/week for 5 weeks for men who have already been on hormone therapy for some time to determine the benefit, if any. Preliminary results of both

psychological and physiological outcomes are promising. Anecdotally, the men enjoyed mixing with others who were experiencing similar side effects of hormone therapy and became a very cohesive group in a short space of time. This program does require easy access to a gym and the expertise of an exercise physiologist.

Response to LH-RH therapy and orchidectomy is not enduring, with the disease eventually becoming castrate resistant, this being evident by a rising PSA. Second line therapy involves introduction of anti-androgen medication to suppress the remaining 5–10 % of testosterone production due to peripheral conversion of adrenal steroids to testosterone [62]. Initiation of this complete androgen blockade often produces a short-term response. Paradoxically, if there is further disease progression while the patient is on combined LH-RH and anti-androgen therapy, there may be a further treatment response with a fall in PSA occurring when the anti-androgen medication is withdrawn.

The commencement of ADT can be a time of distress for patients and their families as it signals disease progression, often without any physical symptoms. The prostate care nurse can play a role in monitoring the patient's disease status, providing emotional and practical support and suggestions about side effect management, and being alert for the development of any signs or symptoms of metastatic disease.

## Management of Bone Metastases

Prostate cancer most frequently metastasizes to bone, commonly to the axial skeleton, in particular, the spine and the pelvis. These bone metastases occur in approximately 80 % of men with advanced prostate cancer [71]. The pain associated with bone metastases may present as a dull, constant ache in a specific site. It may be worsened by movement or on weight bearing or aggravated by the patients adopting a recumbent position, thus, potentially interrupting sleep [72]. The presence of a vertebral metastasis may place the patient at risk of spinal cord compression with the potential for paraplegia. This situation is treated as a medical emergency with immediate surgical decompression often required to avoid the development of paralysis. Patients with known spinal bone metastases, and their families, should be advised of the importance to report immediately any neurological symptoms, in particular, leg weakness or abnormal sensations or any alteration in bowel or bladder function [73].

Focal, short course radiotherapy delivered to the site of painful bone metastases is very useful in relieving the pain in 60–80 % of patients [74], although some patients may experience a transient pain flare after treatment [75].

Assessing the severity and location of the patient's pain is very important, as is ensuring that analgesic requirements are met. Nurses involved in the care of these men are often required to be very proactive in assisting patients to seek appropriate management of their pain. The onset of pain is often seen as a sign of significant deterioration, and therefore some patients are reluctant to acknowledge or report this.

## Bisphosphonate Therapy

Zoledronic acid, a potent intravenous bisphosphonate, is now standard of care in the treatment of bone metastases secondary to castration-resistant prostate cancer [76, 77]. There is evidence that the administration of zoledronic acid results in a significantly prolonged time to the occurrence of the first skeletal-related event (pathological fracture, spinal cord compression, surgery, or radiotherapy to bone) and a reduction in pain in men with bone metastases [77, 78].

Zoledronic acid is administered at 3–4 weekly intervals, as a 15-min intravenous infusion [71]. Prostate care nurses have a role in monitoring and educating patients undergoing this therapy and administering these infusions. Zoledronic acid administration is usually well tolerated, but patients should be advised of the potential for experiencing an acute systemic inflammatory reaction, with flu-like symptoms and bone pain following the first administration. This response, if it occurs, is self-limiting, occurring typically within 48 h of infusion and resolving within 24–48 h [79, 80]. The symptoms may be less pronounced if this first administration is given over 30 min instead of the recommended 15 min. Symptomatic treatment with bed rest, administration of acetaminophen and NSAIDs, and heat packs for any joint discomfort experienced may be beneficial. These symptoms rarely occur after subsequent infusions.

There is evidence of acute and chronic renal impairment occurring in patients receiving zoledronic acid, with the risk of renal failure being directly related to drug infusion time and dosage [80]. Patients should be well hydrated prior to their bisphosphonate infusion and have their serum creatinine checked prior to each infusion. If mild renal impairment should occur, the dose of zoledronic acid should be reduced according to the recommended guidelines.

Osteonecrosis of the jaw (ONJ) is an uncommon side effect of bisphosphonate therapy with the incidence increasing with repeated administration [71, 80, 81], often not occurring until after the ninth treatment [78]. Prior to commencement of treatment prostate care, nurses should ensure that patients are aware of the potential for this condition [82]. Dentists should be notified about the planned treatment of their patients with bisphosphonates, and patients should undergo a thorough dental examination. Any planned or necessary dental procedures should be performed with the commencement of bisphosphonate therapy then being delayed for a significant period.

Prostate care nurses have a role providing education, encouragement, and support for men with advanced prostate cancer. In their role administering ADT and bisphosphonate therapy, they are ideally situated to identify at-risk patients and ensure timely referral and assessment [70].

## Chemotherapy for Advanced Prostate Cancer

The initial therapy for metastatic prostate cancer is ADT, but response to this is inevitably temporary, and disease progression occurs as the cancer becomes castrate resistant [83]. Historically, chemotherapy had little to offer patients at this stage of their disease until 1996 when mitoxantrone plus prednisolone provided improved pain relief and quality of life when compared to prednisolone alone [84]. In 2004, docetaxel plus prednisolone was found to offer a modest survival benefit with consistent improvement in quality of life and pain control [85] and is now standard of care.

Research efforts into the development of more effective anti-androgens and targeted and immune therapies for men with castrate-resistant prostate cancer have produced some promising findings [83]. However, many of these agents are still only available in clinical trial settings.

Once patients develop castrate-resistant disease, treatment becomes the realm of medical oncology and palliative care, but prostate care nurses need to be aware of potential treatment options and ensure patients have access to appropriate support services. The supportive relationship that the prostate care nurses develop with these patients over the years often will be still required even though the immediate care of these men has transferred into the oncology setting.

## Summary

Prostate cancer is a disease that may span several stages over a long period of time. The unique role of the prostate care nurse is such that he or she may be a constant source of support, advice, and information, not only for the patients, but also for their partner and carers. They can also ensure timely referrals for any additional care required over the course of the illness. The prostate care nurse's role may help patients navigate their way through appointments, treatments, and varying specialties and ease the burden of treatment.

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