Michel Bolla
Hendrik van Poppel
Editors

Management of Prostate Cancer

A Multidisciplinary Approach

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Editors
Prof. Michel Bolla
Department of Oncology
and Radiotherapy
University Hospital
Grenoble
France

Prof. Dr. Hendrik van Poppel
Department of Urology
University Hospital
Leuven
Belgium

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Preface

Prostate cancer remains the first ranked cancer in men in Europe. Depending on national conditions, screening or early diagnosis may be proposed to 50–75 year old men by general practitioners and urologists. They will need to take into account factors like age, family history of cancer, co-morbidity, baseline PSA, prostate volume, PSA density and velocity; moreover, they will need to give these men all possible information about biopsy modalities and side effects and about management policies with possible advantages and drawbacks. The TNM classification, the Gleason score and the baseline PSA will determine the fate of the patients found to have prostate cancer, and these risk factors will enable physicians to provide the patient with a therapeutic road map, while tomorrow, genomic signature will hopefully optimize the indications of adjuvant treatment strategies in high-risk patients. Urologists and radiation oncologists have become allies thanks to the analysis of management failures, the results of phase III clinical trials, the multidisciplinary approach and the widespread application of national and/or EAU guidelines. Medical oncologists are faced with systemic disease, more particularly castration resistant prostate cancer, with a new promising pharmacopoeia: taxanes, vaccines, bone specific targeted agents and new hormonal manipulations. This book gives a complete and updated overview from epidemiology to therapeutic algorithms in the different stages of the disease. Physicians need to keep in mind that the more science they get, the more conscientious they need to be in order to improve the relationship with their patients and to promote diagnostic and therapeutic education.

Some patients with very low risk will be allowed to choose active surveillance and can still be treated later on at pre-defined triggers. Others can be oriented towards watchful waiting or deferred treatment in case of less aggressive tumours, due to limited life expectancy or older age. Urologists are mostly the first expert to announce the diagnosis, to discuss the therapeutic possibilities and to explain the aims and the technique of radical prostatectomy, but also of external irradiation and brachytherapy, with the advantages and potential drawbacks of each approach. Patients that are candidates for radiotherapy must be proposed to see a radiation oncologist to further discuss the implications and possible toxicity of radiation treatment and eventual hormonal manipulations. Those patients who wish to quickly eradicate the cancer can prefer surgery, while those who cannot be operated on, for technical or medical reasons, or are worried about the risk of incontinence or impotence, can prefer radiotherapy. The administration of eventual concomitant

androgen deprivation therapy is based on clinical stage, prognostic factors, WHO performance status, co-morbidity and sexual health. RTOG and EORTC trials have provided us with the data in favour of short-term hormonal treatment in case of intermediate or high-risk prostate cancer. Longer term androgen deprivation therapy will be advocated in case of locally advanced prostate cancer or very high risk localized prostate cancer. The risk of relapse after local treatment of the primary must be explained as well as the available salvage modalities; indeed, salvage radiotherapy is possible in case of biochemical relapse after surgery, while salvage radical prostatectomy, high intensity focused ultrasound or cryosurgery can be done after radiotherapy. In daily practice, open or laparoscopic (robot assisted) radical prostatectomy and intensity modulated radiotherapy remain the gold standard. More recently, tomotherapy or cyberknife are proposed by medical teams that have the feasibility, the quality assurance, the human resources and the possibility of auto-evaluation. The role of the pathologists is crucial in helping to define risk factors on the surgical specimen – tumour volume, tumour stage and Gleason grade, particularly margin status – to decide about the indication for immediate post-operative or deferred salvage radiotherapy.

When a distant relapse arises, LHRH agonists, or in appropriate situations antagonists, are the standard of care, given continuously or intermittently. Maximal androgen blockade will benefit a selected group of advanced prostate cancer patients. A number of recent investigations led to approaches that can give new hope to castrate resistant patients such as vaccines, docetaxel and cabazitaxel in symptomatic patients; CYP 17 inhibitors like abiraterone acetate and more potent antiandrogens like MDV 3100; and bone targeted strategies with biphosphonates rank ligand inhibitors and radium 223.

The battle against prostate cancer is based on a public health strategy. The cure rates are increasing and mortality is decreasing. The patients have a tremendous role to play, as heroes of their own life. The cancer may give them the opportunity to participate in clinical research, a kind of joint venture which may be beneficial for them today or for others tomorrow. A lot of patients who are not cured may today have an extended survival, prostate cancer becoming more like a chronic disease, and the challenge for patients and care-givers is to give time to the time with good quality of life.

Grenoble, France — Michel Bolla
Leuven, Belgium — Hendrik van Poppel

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Epidemiology of Prostate Cancer in Europe

1

Ruben G. Cremers and Lambertus A. Kiemeney

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R.G. Cremers, M.D. • L.A. Kiemeney, Ph.D. (✉)
Radboud University Medical Centre,
Department of Epidemiology, Biostatistics and HTA (133),
P.O. Box 9101, 6500 HB Nigmegen,
The Netherlands
e-mail: r.cremers@ebh.umcn.nl, b.kiemeney@ebh.umcn.nl

1.1 Prostate Cancer

The prostate is a walnut-sized glandular organ, located beneath the urinary bladder in men. The prostate contributes to urinary flow control and produces several enzymes that play a role in the function of seminal fluid. Testosterone and its more active metabolite dihydrotestosterone serve as nourishment for prostate tissue and regulate mitosis of prostate cells. Malignant neoplasms of the prostate, further referred to as prostate cancer (ICD-10 C61), usually originate in the glandular tissue. These adenocarcinomas are most often located in the peripheral zone of the prostate. Occasionally, other morphological types of prostate cancer are diagnosed, e.g., cribriform carcinomas, acinar-cell carcinomas, or (myo)sarcomatous neoplasms. Prostate cancer can be treated with curative intent when detected early. However, one of every 4–5 men who are diagnosed with prostate cancer will succumb to the disease.

1.2 Prostate Cancer Incidence

1.2.1 Current Situation: Global Incidence in 2008

Prostate cancer is the second most common non-skin cancer neoplasm diagnosed in men worldwide, exceeded only by lung cancer. In Europe, due to the decreasing number of lung cancer

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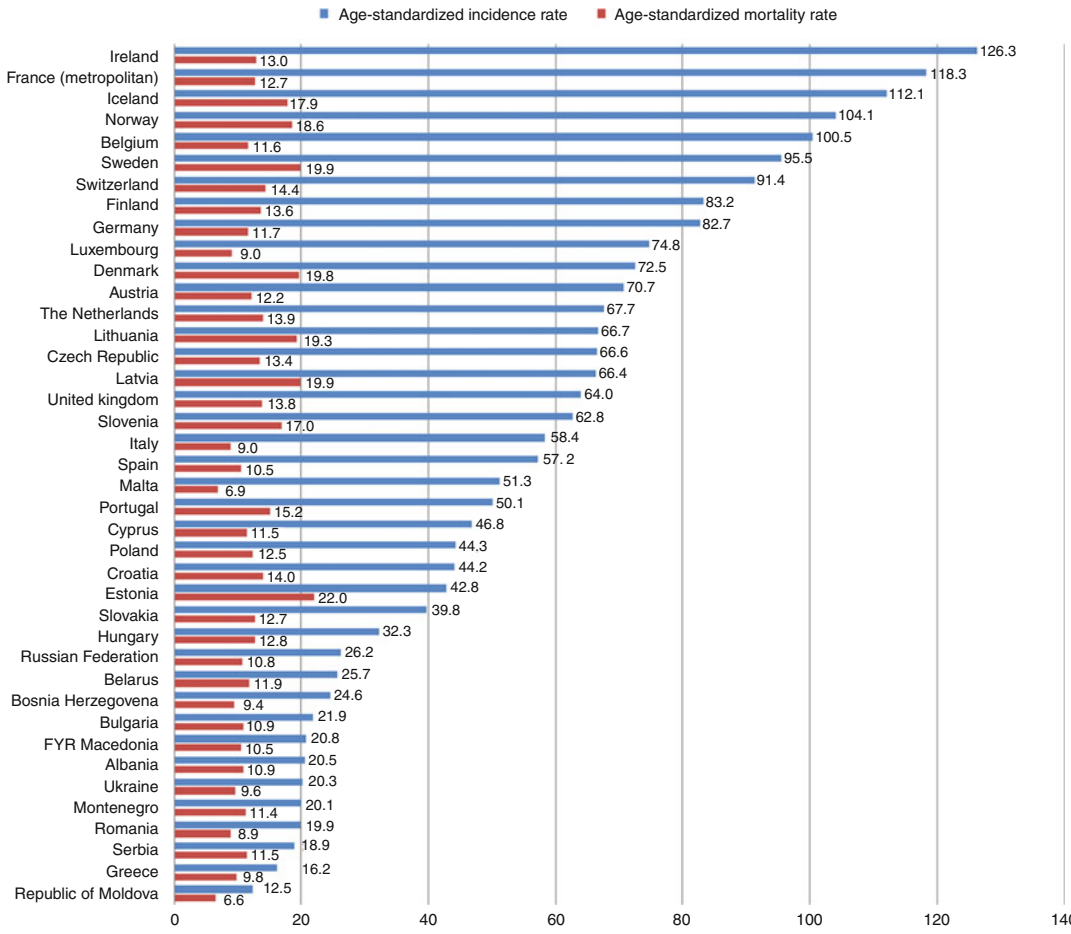

Fig. 1.1 European prostate cancer incidence and mortality rates in 2008 (age-adjusted to the World Standard Population)

cases following the decreasing trend of smoking prevalence, and an increase of prostate cancer cases, it has even been the most frequently diagnosed cancer in men for several years. In 2008,[1] 371,000 European men were newly diagnosed with prostate cancer (crude incidence rate 59/100,000 person-years[2]), accounting for 22% of all cancer diagnoses in males (excluding non-melanoma skin cancers) (Ferlay et al. 2010).

Large differences in incidence rates exist between continents. Also, between countries within continents, differences can be significant. When standardized for age distribution differences, in 2008, in Europe, the highest incidence was found in Ireland (126.3 per 100,000 person-years), France (118.3) and Iceland (112.1), where the incidence rates were 5–10 times higher than in Moldova (12.5), Greece (16.2), Serbia (18.9), Montenegro (20.1), Albania (20.5), and Macedonia (20.8) (Fig. 1.1).

Compared to other parts of the world (world total 900,000 prostate cancer diagnoses annually or 28.0 per 100,000 person-years in 2008), Northern and Western Europe are among the regions with the highest prostate cancer incidence

[1]Data on incidence and mortality were obtained from Globocan, a database maintained by the International Agency for Research on Cancer (IARC), see Ferlay et al. (2010).

[2]All reported incidence and mortality rates in this chapter were age-standardized to the world standard population.

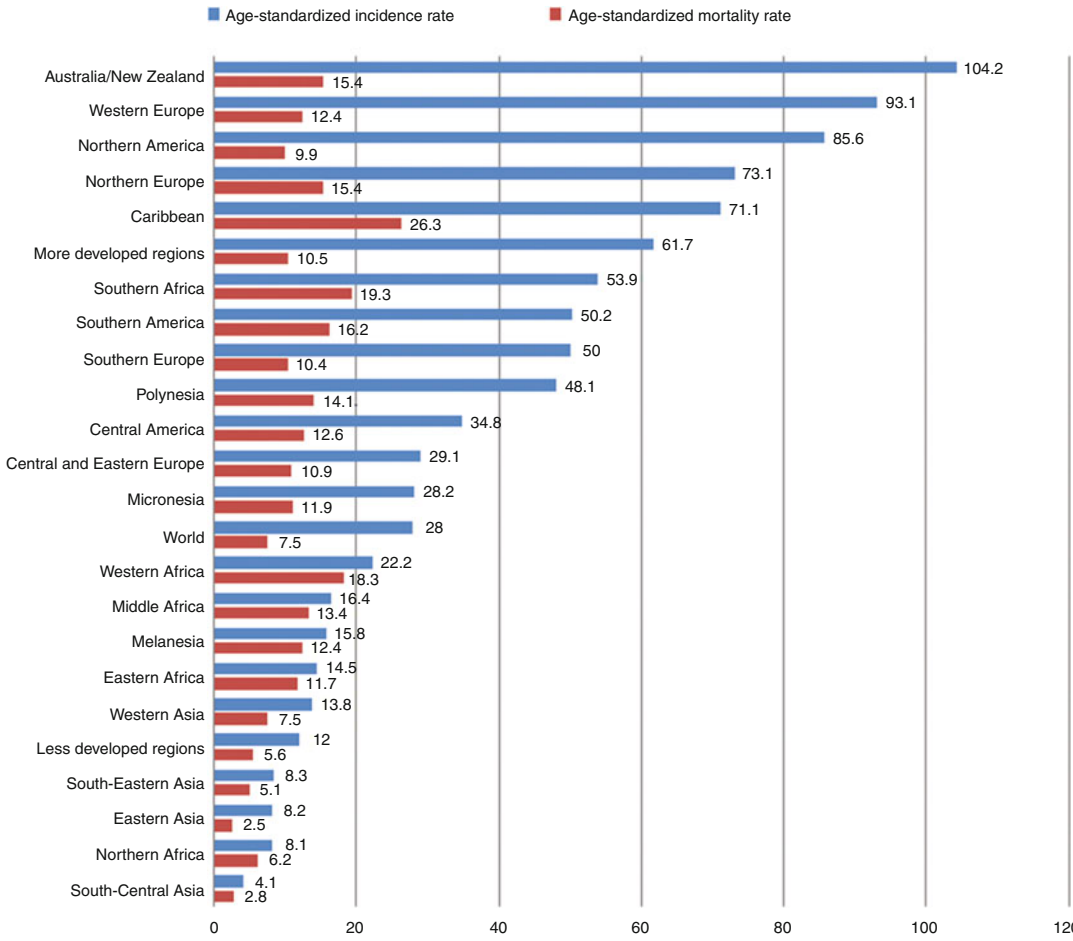

Fig. 1.2 Global prostate cancer incidence and mortality rates in 2008 (age-adjusted to the World Standard Population)

(73.1 and 93.1 per 100,000 person-years, respectively). Only the Australian region (i.e., Australia and New Zealand) reports a higher average incidence rate with 104.2 cases per 100,000 person-years (Fig. 1.2). The state with the highest reported prostate cancer incidence rate was the French oversees department of Martinique in the Caribbean with 173.7 cases per 100,000 person-years, followed at considerable distance by Barbados (140.0) and Ireland (126.3). The lowest incidence rates are found in Asia (in Asia as a whole: 7.2 per 100,000 person-years, China and India reporting 4.3 and 3.7 cases per 100,000 person-years, respectively).

Generally speaking, a decreasing polar-to-equatorial and west-to-east gradient can be observed for prostate cancer incidence. Explanations for this phenomenon might be sought in a combination of genetic (ethnic) risk differences on the one hand and environmental, dietary, and lifestyle factors on the other hand, although the specifics of these risk factors are largely unknown. For the smaller differences seen within continents, where genetic differences are probably less prominent, differences in health-seeking behavior and health-care systems might play an important role. Stage-specific data would shed more light on the reasons for these incidence differences, as an overrepresentation of localized prostate cancer in higher-income countries could be indicative of more aggressive opportunistic testing strategies. Unfortunately, the quality and methods of the cancer registries

across the world are too heterogeneous for such an evaluation.

1.2.2 Incidence Trends in Europe

Prostate cancer diagnostics changed tremendously with the identification of prostate-specific antigen (PSA) in 1987 (Stamey et al. 1987). PSA belongs to the kallikrein family (kallikrein-3, KLK3) and is produced mainly by the prostate. Other tissue types that have been described to produce PSA were almost exclusively malignant tissues (lung adenocarcinoma, breast, salivary gland, ovary), except for endometrial tissue. Given the rareness of these findings and the fact that some of these tissues are exclusively found in females, obviously, this has no serious consequences for the use of PSA in prostate cancer testing. The serum PSA level reflects how much antigen is being produced and released into the circulation. Prostate conditions, notably benign prostatic hyperplasia (BPH), prostatitis, and prostate cancer are known to elevate PSA levels. So, where PSA is *prostate specific*, it is definitely not *prostate-cancer specific*.

There are no countries that have a nationwide screening program for prostate cancer; only the Federal State of Tyrol in Austria offers PSA screening at no charge to all male inhabitants (Bartsch et al. 2001). Still, PSA is used in many developed countries as an opportunistic test for prostate cancer (Bartsch et al. 2001). Large differences exist between countries with regard to the uptake of PSA as an opportunistic screening tool. This, among other factors, has led to large variations in prostate cancer incidence trends in Europe in the last 10–20 years.

In 2010, Bray et al. (2010) published a report on trends in prostate cancer incidence (24 countries) and mortality (37 countries) in Europe. They reported increasing incidence rates since 1990 with an average of 3–4% per year in the Netherlands, Slovakia, Switzerland, and the UK. In the largest European countries (France and Germany), even stronger increases of 6–7% were observed in that period. The next section will deal with specific incidence differences and trends within different parts of Europe. When looking at these numbers, it should always be born in mind that registration differences in incidence and mortality between countries and even regions may have led to quite severe artifacts, which cannot be easily distinguished from true effects.

1.2.2.1 Northern Europe

The Nordic countries Finland, Iceland, Norway, and Sweden are among the countries with the highest incidence rates in Europe and, as such, in the world. With the exception of Sweden and Finland, which had declining incidence rates since 2005, continuous increases in incidence were seen in all countries in Northern Europe (i.e., the Nordic countries, Great Britain, Ireland, and the Baltic states) which were either already ongoing since the beginning of the registration (for some countries as far back as 1975) or showed a marked increase from 1995 onward. Sweden and Finland were the countries with the highest incidence rates. Possibly, PSA uptake in these countries was so rapid that the decline is a similar phenomenon to that seen in the USA in the early 1990s: many prevalent prostate cancers were found in a relatively short period with widespread, intensive PSA testing, leading to a temporary sharp increase in new cases followed by a temporary decrease.

1.2.2.2 Western Europe

France, Germany, and Switzerland all showed increasing incidence rates of 4–5% per year since 1990. The exception in Western Europe was the Netherlands, where a rapid increase in the early 1990s was followed by a plateau phase between 1995 and 2000. From 2000 onward, a second increase was observed until 2005, after which a second (higher) plateau seems to have been reached (Cremers et al. 2010). In 2008, due to these different trends, considerable differences in incidence rates were observed on the western part of the continent, ranging from 67.7 per 100,000 person-years in the Netherlands to 118.3 per 100,000 person-years in France. Notably, the Dutch health system, which requires a referral from a general practitioner for a visit to a urologist, may have played a role, as general practitioners are usually quite conservative in

performing opportunistic testing in the absence of a formal screening advice. As a matter of fact, PSA testing is not recommended before having extensively counseled the patient about the possible consequences of having a PSA test. By contrast, general practitioners in France are using PSA tests quite liberally (Sorum et al. 2003).

1.2.2.3 Southern Europe

Croatia, Italy, Slovenia, and Spain all had similar increases in incidence rates from the late 1980s onward. Compared to the Western European countries, this went at a slightly higher increasing rate of 5–6% per year. However, the incidence rates in these Southern European countries were still lower than in Western Europe, ranging from 44.2 per 100,000 person-years for Croatia to 62.8 per 100,000 person-years in Slovenia. As an explanation for the relatively low cancer rates, the relatively healthy Mediterranean diet (rich in fresh fruits and vegetables) has been suggested to play a role (Couto et al. 2011). But again, different health-seeking behavior between countries will also play a role.

1.2.2.4 Eastern Europe

In accordance with the rest of the continent, also in the Eastern European countries (Belarus, Czech Republic, Poland, the Russian Federation, and Slovakia), increases in incidence rates were observed, with rapid increases up to almost 10% per year in the Czech Republic and the Russian Federation. It should be noted though that the incidence rates in the Eastern European countries were still in the lower regions compared to the rest of the continent. The Russian Federation reported the lowest incidence with only 26.1 cases per 100,000 person-years in 2008.

1.3 Prostate Cancer Mortality

1.3.1 Current Situation: Global Mortality in 2008

As previously mentioned, prostate cancer can be treated with curative intent when detected in a localized stage. However, some cancers will progress to metastatic disease in spite of proper treatment of an apparently localized tumor or will already be metastasized at the time of diagnosis. The progression of metastasized prostate cancer can be slowed down for a few months to, in some cases, several years by hormonal treatment and chemotherapy, but cure is not possible if metastases have occurred. The variation in prostate cancer mortality is considerably smaller than the variation in incidence, both within the European continent as between Europe and the other continents (Figs. 1.1 and 1.2). The European countries with the highest mortality rates are the Baltic states: Estonia, Latvia, and Lithuania have mortality rates of 22.0, 19.9, and 19.3 per 100,000 person-years, respectively, followed closely by the Nordic countries such as Sweden (19.9) and Norway (18.6) (Ferlay et al. 2010). The lowest mortality rates are, similar to the incidence rates, found in the states in Eastern and Southern Europe, particularly in Moldova (6.6), Malta (6.9), Romania (8.9), and Italy (9.0). On average, the age-adjusted prostate cancer mortality in Europe in 2008 was 12.0 per 100,000 person-years. Compared to other parts of the world (world total 258,000 prostate cancer deaths annually or 7.5 deaths per 100,000 person-years in 2008), Europe is in the middle to upper league with regard to prostate cancer mortality. Along with the very low incidence rates, the Asian countries have the lowest prostate cancer mortality rates: Asia as a whole: 3.1 deaths per 100,000 person-years, China 1.8 and India 2.5 per 100,000 person-years. The highest rates are found in sub-Saharan Africa (average 15.0) and particularly the Caribbean (average 26.3). The individual country with the highest reported prostate cancer mortality was Barbados (61.7), followed at some distance by Trinidad and Tobago (46.9), Haiti (35.5), and the Bahamas (34.7).

1.3.2 Mortality Trends in Europe

In almost all European countries, prostate cancer mortality rose in the 1980s and the first part of the 1990s (Bray et al. 2010). During the 1990s, however, distinctions became apparent between different parts of Europe. Generally speaking, in the geographically more western and northern countries

in Europe, mortality stabilized or decreased from a given time in or around the 1990s. In the countries in the south and east of Europe, however, this trend change did not occur, and mortality was still increasing until the end of the registration period, well into the first decade of the twenty-first century. Differential uptake of PSA testing has been suggested to play a role in this, although it is known that the time between the intervention (PSA test) and a possible effect on the outcome (prostate cancer mortality) is long and lies between 7 and 12 years. Probably, other factors, such as improvements in surgical and radiation oncology techniques that already took place in the 1980s, may also have had an effect on the relatively early trend change in prostate cancer mortality in the western and northern part of Europe.

1.3.2.1 Northern Europe

Two distinct trends were seen for prostate cancer mortality in the northern part of Europe. Half of the countries (Denmark, Iceland, and the Baltic states) had continuously increasing mortality rates. By contrast, Great Britain, Ireland, and Finland showed increases until the middle of the 1990s, which were followed by moderate decreases thereafter. These decreases already commenced in England and Wales in 1992, followed by Scotland (1994), Northern Ireland (1996), Norway and Ireland (1997), and finally Sweden and Finland (1998). These decreases continued until the end of follow-up (typically 2006/2007) at a rate of approximately 1–2% per year. As already mentioned in Sect. 1.3.1, particularly the Baltic states have very high mortality rates. Explaining this is not straightforward, though. Incidence rates were, if anything, rather low compared to the rest of Europe. If genetics would play a strong role, one would not expect large differences between the Baltic states on the one hand and the Russian Federation and Finland on the other hand, which have mortality rates of approximately 50% of the Baltic states. Even more so, the increase in mortality rates has only gained speed since the beginning of the new millennium, with an almost 10% increase in mortality per year in Latvia since 2005. Apart from registration artifacts, this suggests that Baltic men are being diagnosed with ever-more aggressive tumors, are being diagnosed with more advanced stages of prostate cancer, or are receiving suboptimal treatment. Stage-specific data, which are not readily available, should be generated and evaluated to distinguish what exactly is causing this high mortality and the rapid increase in mortality.

1.3.2.2 Western Europe

All Western European countries (Austria, Belgium, France, Germany, Luxembourg, Switzerland, and the Netherlands) had a decreasing trend in the mortality rates at the end of the most recent reporting period (2006–2008 for all countries, except for Belgium-1999). These decreases started earlier than in the Northern European countries, i.e., between 1989 (France) and 1995 (Germany, Switzerland, and the Netherlands) and were more prominent with annual percentage changes up to 3.8% in Austria since 2000 and 4.3% in France since 2003.

1.3.2.3 Southern Europe

Markedly different mortality trends were seen between the countries in the western part of the Mediterranean (Portugal, Spain, Italy, and Malta) and the more eastern countries (Slovenia, Croatia, Albania, Greece, and Moldova). The former group had similar trends as the countries in Western Europe, with an initial increase in mortality, which switched into a decrease between 1993 (Malta) and 1998 (Spain and Portugal) of approximately 3–4% per year. The latter group, on the other hand, reported a continuously increasing mortality, with the strongest annual increase in mortality rate in Albania with 2.8% (1992–2004).

1.3.2.4 Eastern Europe

Also in Eastern Europe, two different trend patterns were observed. The two geographically most western countries in Eastern Europe, i.e., the Czech Republic and Hungary, showed trends that were similar to the Western European countries. The decreases in mortality rates observed in these

countries were actually the strongest observed for the entire continent: Hungary reported an annual decrease in prostate cancer mortality of 5.5% per year since 1999, whereas the Czech Republic even had an annual decrease in mortality of 8.0% since 2004. The other countries in this part of Europe (Belarus, Bulgaria, Poland, Romania, the Russian Federation, Slovakia, and Ukraine) had continuous annual increases in mortality rates up to 4.2% (Belarus). It should be noted though that in spite of the strongly decreasing mortality, the Czech Republic and Hungary are still the countries with the highest mortality rates of this part of Europe.

1.4 Prostate Cancer Survival

Prostate cancer survival, typically presented as 5-year relative survival (a proxy for cancer-specific survival in which the survival of newly diagnosed patients is compared to the age-matched general population), was evaluated for all European countries in the EUROCARE-3 and EUROCARE-4 studies and in many smaller studies (Sant et al. 2003; Verdecchia et al. 2007). The majority of the European countries have 5-year relative survival ratios for prostate cancer of 70–80% (measured for diagnoses in the period 2000–2002). The Czech Republic reported the lowest 5-year relative survival with 58%, where Switzerland had a 5-year relative survival of 87% (Karim-Kos et al. 2008). It needs hardly any explanation that a higher/increasing incidence due to opportunistic PSA testing will have a large influence on survival. After all, PSA testing will lead to an increase in prostate cancers with a relatively favorable prognosis. In addition to this, important improvements have been made in treatment strategies. Mainly in the field of radiation oncology, new techniques such as intensity-modulated radiation therapy have made it possible to deliver ever-higher doses to ever-smaller irradiation fields. These changes in diagnostics and therapeutics have resulted in a relative improvement in 5-year survival in Europe of 30% between the periods 1990–1994 and 2000–2002 (Verdecchia et al. 2007). To disentangle which part of this improvement can be explained by diagnostic changes vs. therapeutic changes is no easy task (de Vries et al. 2010). An evaluation of the patterns of incidence, mortality, and survival does seem to point in the direction of a larger effect of PSA testing, though. This can be explained as follows: almost all countries had increasing incidence trends, but mortality trends differed largely. However, not a single country reported a decrease in survival. So, even when the mortality rate increased in a country, this did not result in a negative effect on the average survival. This can most likely be explained by a surplus of men who must have been diagnosed at less extensive stages, thus improving the average survival.

1.5 Prostate Cancer Prevalence

Prevalence, the number of patients with prostate cancer at any point in time, is a statistic that best indicates the burden of a certain disease on public health or the society in general. As prevalence is dependent on both the number of incident cases (which is relatively high for prostate cancer in the Western world) and the mean duration of disease (which is relatively long for prostate cancer), the estimated "burden" of prostate cancer will be large. To obtain an estimate for the mean duration of disease, we used data from the USA, as reported by the Surveillance Epidemiology and End Results (SEER) program, hosted by the NCI. This program has vital status follow-up information on cancer cases in the USA since 1975, yielding a maximum of 33-years of follow-up until the reporting year of 2008. According to these data, 2,400,000 Americans with prostate cancer were alive in 2008 and diagnosed after 1975. According to the most recent GLOBOCAN data (Ferlay et al. 2010), approximately 185,000 men were newly diagnosed with prostate cancer in the USA in 2008. When ignoring the increasing trend in prostate cancer incidence of the past 15 years, this results in an estimated mean duration of disease of 2,400,000/185,000 = 13 years. Globally, with 900,000 new prostate cancer diagnoses in 2008, this would mean that, at any given

time, 13 × 900,000 = almost 12 million men are alive with prostate cancer. In Europe, this would be 13 × 370,000 = almost 5 million. It should be noted here that the duration of disease is of course greatly influenced by the moment of detection of the disease, i.e., the moment that a man becomes a prostate cancer patient. As shown previously, this differs enormously between countries. The USA is by all means one of the countries where PSA tests are used frequently and at relatively young age. So the division by 185,000 may lead to an underestimated duration of disease (before the PSA era, only about 75,000 prostate cancers were diagnosed annually in the USA) and therefore an underestimation of the global and European prevalence.

1.6 Risk Factors for Prostate Cancer

For a disease as prevalent and incident as prostate cancer, relatively little is known about its exact etiology. Convincing evidence has been produced for only a few risk factors: age, genetic predisposition, and ethnicity. Numerous scientific papers have suggested a long list of other risk factors, of which those most intensely investigated will be reported in this section.

1.6.1 Age

The most well-known risk factor for prostate cancer is increasing age. Prostate cancer is hardly ever found before the age of 45, and the mean age at diagnosis in Europe lies above 70 years of age. This has already come down significantly from an even higher age due to the increasing trend of opportunistic testing. Postmortem investigations suggest that 35–80% of European Caucasian men aged 80 harbor one or more (microscopic) foci of prostate cancer (Sakr et al. 1994; Sanchez-Chapado et al. 2003; Soos et al. 2005). This underlines one of the greatest dilemmas in prostate cancer diagnostics nowadays: most men who have prostate cancer will die WITH prostate cancer and not FROM it. So which of these prostate cancers should be detected? In absence of more discriminative tests that can accurately predict invalidating and lethal prostate cancers, this will remain the pivotal issue of investigation that has already kept prostate cancer scientists busy for many years.

1.6.2 Family History and Genetics

Besides age, a positive family history of prostate cancer is the most well-established risk factor for prostate cancer. First-degree relatives of affected man carry a two- to threefold increased risk of being diagnosed with the disease themselves. It is estimated that 5–10% of prostate cancers have a true genetic (Mendelian) cause. Yet only a few very rare high-penetrance gene mutations have been identified that cause prostate cancer (Langeberg et al. 2007). The prevalence of these mutations is so low that testing would not be useful in the general population. Even more so, testing for mutations in these genes would not even be useful in families with hereditary prostate cancer, i.e., families with three or more first-degree relatives (or two first-degree relatives of young age) with prostate cancer (Carter et al. 1993). In recent years, genome-wide association studies have added approximately 40 low-penetrance genetic polymorphisms (single nucleotide polymorphisms – SNPs) that are associated with an increased risk of prostate cancer (Varghese and Easton 2010). Some of these SNPs are in or near genes, e.g., the *HNF1B* gene, the *KLK3* gene (PSA), and the *MSMB* gene, but also in intergenic regions with unknown functions. The 8q24 region is a good example of the latter type, containing multiple SNPs that are significantly associated with prostate cancer and also with other cancer types. Because the associations of individual SNPs are relatively small (typically, odds ratios of 1.1–1.3 are found), polygenic risk scores are being developed to aid in predicting the individual risk of prostate cancer (Aly et al. 2011). But still, for only a negligible percentage of all men, the cumulative risk of these variants is expected to be high enough to be of any clinical relevance

while all men would have to be genotyped in order to identify this small group of men.

1.6.3 Ethnicity

As shown in the previous section on incidence, enormous differences in prostate cancer incidence exist between ethnic populations. The lowest incidence is found in men of Asian descent, whereas men who live in North America and Northern Europe have a relatively high prostate cancer risk. Particularly, men of African-American heritage have a very high risk of prostate cancer. Ethnic differences are most probably caused by a combination of genetic factors, exposure to environmental risk factors, and factors related to health-seeking behavior. This is illustrated most clearly by the results of migration studies, which looked at prostate cancer incidence trends in Asian men (low incidence) who migrated to the USA (high incidence); prostate cancer incidence in these men increased markedly and significantly but to a level that was intermediate between the incidence in the Japanese and the original American population (Cook et al. 1999). A similar phenomenon was found for Japanese men who emigrated to Brazil (Iwasaki et al. 2008).

1.6.4 Androgens

Androgens play an important role in prostate cancer development. Prostate cancers are usually androgen sensitive and respond to hormonal therapy with a temporary remission of disease. After some time, this remission is followed by relapse, and the disease is termed to be castration-refractory. Multiple markers for androgen status have been described and tested for an association with prostate cancer, e.g., serum testosterone and dihydrotestosterone levels, male-pattern baldness, and acne vulgaris. Nevertheless, not a single one of these markers has been consistently replicated to have any significant predictive value for prostate cancer or, more interestingly, aggressive prostate cancer. So, although hormones remain the best target of treatment in case of metastasized prostate cancer, the exact relationship between androgens and the development of prostate cancer remains to be elucidated (Bosland 2000). Another way in which hormones have more recently been targeted is the attempt to prevent prostate cancer occurrence with the use of 5-alpha reductase inhibitors (5-ARIs). Two large prospective randomized trials examined the effect of daily use of 5-ARIs: the Prostate Cancer Prevention Trial (PCPT), in which men were treated with finasteride 5 mg daily or placebo for 7 years and the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial, in which patients were treated with dutasteride 0.5 mg daily or placebo for 4 years (Thompson et al. 2003; Andriole et al. 2010). In both studies, patients underwent scheduled biopsies at the end of the study, and both reported a lower risk of prostate cancer occurrence of approximately 20–25%. This difference in prostate cancer occurrence between the two trial arms was, however, contributable to relatively low-grade tumors, which have a higher chance of being nonsignificant. In addition to this, the overall incidence of prostate cancer in these trials was approximately 25%, which is much higher than the lifetime chance of contracting prostate cancer in the general population. In Europe, the chance of being diagnosed with prostate cancer until 75 years of age is 7.4% (Ferlay et al. 2010). A similar relative reduction of 20–25% would not be clinically meaningful, as this would not outweigh the possible negative effects of 5-ARI treatment in the general population, notably increasing risk of libido loss, erectile dysfunction, and possibly cardiac failure (Bosland et al. 2010).

1.6.5 Diet

Diet is, probably, a major factor in the development and progression of prostate cancer. Dietary fats, red and processed meat, vitamin E, selenium, lycopene, cruciferous vegetables, and green tea have all been associated with prostate cancer risk. Pathways that have been suggested to play a role in this process include roles for the androgen receptor (AR) and insulin growth-factor (IGF)

signaling. Suggested chemopreventive agents (including lycopene and selenomethionine) cause the degradation of the AR via downregulation of IGF-I. Another downstream effect of downregulation of IGF-I is inhibition of the IGF-Aki pathway, which affects cellular proliferation, migration, and survival (Venkateswaran and Klotz 2010).

However, prospective population-based studies into a possible preventive effect of these dietary factors have failed to yield consistent results. A clear example of this is the SELECT trial (Selenium and Vitamin E Cancer Prevention Trial) (Lippman et al. 2009). This large prospective trial, in which 31,000 men were included, studied the effect of Vitamin E, selenium, and the combination of both vs. placebo. No effect on prostate cancer incidence was found for administering selenium, either alone or in combination. This refuted the result found in the Nutrition Prevention of Cancer (NPS) trial (Duffield-Lillico et al. 2003) that observed a 50% reduction in prostate cancer incidence in men randomized to selenium supplements. All in all, too little evidence exists to give a definitive advice on any dietary factor beyond the common or garden advice: have a versatile diet containing fruits and vegetables and use everything in moderation.

In conclusion, prostate cancer is one of the major health issues in the Western world. If the current trends continue, it will also become the most frequently diagnosed cancer in men globally, as is already the case in Europe. Many questions remain on when and how to diagnose and treat prostate cancer. Big steps will still have to be made to assure that our patients receive optimal care and support.

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Chemoprevention of Prostate Cancer

2

Bertrand Tombal

Contents

B. Tombal, M.D., Ph.D.
Service d'Urologie, Cliniques universitaires Saint Luc,
Université catholique de Louvain,
Av. Hippocrate, 10, Brussels 1200, Belgium
e-mail: bertrand.tombal@uclouvain.be

2.1 Introduction

Prostate cancer (PCa) is a very heterogeneous disease with a wide spectrum of clinical presentations and consequences. Indeed, if microscopic foci of adenocarcinoma can be found in the prostate of many men, only a minority will progress to clinically relevant, symptomatic, or potentially lethal disease. This explains the striking difference between the incidence of PCa and its mortality rate. In Europe in 2008, an estimated 382,000 cases were diagnosed while 90,000 deaths have occurred in 2008 (Ferlay et al. 2010).

The natural history of PCa is usually slow, evolving over decades from a preclinical tumour to a detectable tumour. Many low-volume/well-differentiated cancer foci never develop into clinically relevant cancer, never cause symptoms, and would probably remain undetected throughout men's lifetime if aggressive PSA screening was not advocated. Indeed, most of the deaths come from a pool of poorly undifferentiated aggressive cancer (Albertsen et al. 2005). Whether these more rapidly progressing, poorly differentiated PCa are derived from pre-existing, well-differentiated "latent" PCa or develop de novo with a much shorter preclinical phase is still unknown.

Chemoprevention implies that a disease can be prevented. Primary chemoprevention refers to reducing the risk of cancer development. Secondary chemoprevention involves reducing the risk of progression of a cancer that is already present. In the case of PCa, these two concepts overlap. The "holy grail" of prevention with respect to PCa is to avoid

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high-volume/high-grade aggressive PCa since low-volume/low-grade cancers are supposedly neither morbid nor lethal diseases. These "indolent" cancers, that for the sake of the patients should remain undiagnosed, have emerged as a major public health concern because they surface with PSA screening and are the matter of aggressive (over)treatments (Daskivich et al. 2011; Schroder et al. 2009). This poses a huge burden on the health-care system because of the costs associated with increase diagnosis and therapy. *Prevention* of PCa can thus be seen as reducing the rate of transformation of normal cells into premalignant cells but also reducing the rate of transformation from low-grade to high-grade disease. This should be kept in mind when interpreting the data of chemoprevention trials. Some author referred to risk reduction rather than true chemoprevention. Even a moderate reduction or even delay in the development of PCa accomplished through pharmacologic or dietary intervention could result in a considerable reduction in the incidence of PCa, and thus in the health and economic burden of the disease.

The genetic, epigenetic and environmental factors driving transformation from normal cells into malignant cells and then into aggressive prostate cancers remain largely unknown. Amongst the identified pathways that can be targeted by chemoprevention studies, two have been more extensively studied in large randomized trials: inflammation and hormonal stimulation of the prostate (Nelson 2007). In addition, because several epidemiological studies have suggested geographical variations in the risk of PCa potentially linked to dietary and lifestyle factors, several studies have been conducted with dietary elements and food supplements.

Here, we will review the main trials of chemoprevention for PCa trying to provide recommendations to the reader.

2.2 Anti-inflammatory and Antioxidants

Inflammation has been associated with the development of lung cancer in smokers, hepatic cancer in chronic hepatitis and bowel cancer in inflammatory bowel disease.

Prostate inflammation may contribute to prostatic carcinogenesis. Inflammation may promote carcinogenesis by causing cell and genome damage, promoting cellular turnover and creating a tissue microenvironment that can enhance cell replication, angiogenesis and tissue repair (Bardia et al. 2009). Inflammatory situations are characterized by the production of free radicals or reactive oxygen species (ROS) that damage cell membranes. ROS cause oxidative damage to LDL and damage cell membranes by means of lipid peroxidation. Interesting, one of the earlier and most ubiquitous epigenetic phenomenon identified in prostatic carcinogenesis is the somatic silencing of GSTP1, encoding a glutathione *S*-transferase capable of detoxifying ROS, and this defends against oxidant cell and genome damage (Nelson et al. 2004). Proliferative inflammatory atrophy (PIA), a lesions containing activated inflammatory cells and proliferating epithelial cells, has been identified as a precursor lesion to prostatic intraepithelial neoplasia (PIN) and PCa. Finally, epidemiological data have correlated prostatitis and sexually transmitted infections with increased PCa risk and intake of anti-inflammatory drugs and antioxidants with decreased PCa risk (Nelson et al. 2004).

2.2.1 COX-2 Inhibitors

Studies have shown that essential fatty acids, linoleic acid (LA) and arachidonic acid (AA), and their prostaglandin metabolite PGE2 stimulate tumour growth. The COX-1 and COX-2 enzymes catalyze the conversion of AA to prostaglandins and are therefore amongst the most critical key enzyme of the inflammatory process.

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) antagonize COX-2 and reduce the incidence of malignancy. High doses of COX-2 inhibitor, celecoxib, prevent precancerous adenomatous polyps from progressing to overt colon cancer (Arber et al. 2011). In vitro, COX-2 inhibitors celecoxib and rofecoxib suppress carcinogenesis by both COX-2-dependent and COX-2-independent mechanisms (Patel et al. 2005).

The *ViP study* was a double-blinded, randomized, placebo-controlled (RCT) trial evaluating the effects of rofecoxib 25 mg compared with placebo in decreasing PCa incidence in high-risk men. The initial trial plan was to recruit 15,000 men, but the trial was terminated when only 4,741 men were enrolled because rofecoxib was withdrawn from the market due to an excess of ischemic cardiac toxicity. Antonarakis et al. have investigated the effect of celecoxib administered for 4–6 weeks before radical prostatectomy (RP) in men with localized PCa (Antonarakis et al. 2009). The endpoints were tissue celecoxib concentration and difference in prostatic prostaglandin levels, COX-1 and COX-2 expressions, oxidized DNA bases, and markers of proliferation, apoptosis and angiogenesis. Unfortunately, treatment with 4–6 weeks of celecoxib had no effect on intermediate biomarkers of prostate carcinogenesis, despite the achievement of measurable tissue levels. Because of the cardiovascular toxicity of the class in chronic administration, it is unlikely that the efficacy of this approach will be tested again in the future.

2.2.2 Selenium (Se) and Vitamin E

Selenium (Se) is an essential trace element found in vegetables, grains, red meat, fish, poultry, and eggs. Se helps to make antioxidant enzymes, which play a role in preventing cell damage. Epidemiological evidence provides support for a global cancer prevention effect. Vitamin E is an essential lipid-soluble antioxidant found in plant oils such as soy, corn and olive oil. Other sources include nuts and seeds, and green leafy vegetables. It protects cells from free radicals. Several forms of vitamin E have been identified. The most active form with highest bioavailability in human tissues is α-tocopherol. The body is not capable of producing this substance, and it must be consumed in the diet or supplements for proper health.

The rationale for using Se to prevent PCa originates in the Nutritional Prevention of Cancer (NPC) trial. On secondary analysis, this RCT for skin cancer prevention trial showed that Se significantly reduced the overall incidence of PCa with a relative risk (RR) of 0.51 (95% confidence interval (CI): 0.29–0.87) (Duffield-Lillico et al. 2003). The unadjusted estimate showed a significant 65% reduction in PCa incidence with Se supplementation. The protective effect of Se supplementation (200 μg daily) was restricted to men with lower baseline PSA (≤4 ng/ml) and men with a low baseline plasma Se concentration (<123.2 ng/ml). The rationale for using α-tocopherol was based on the Alpha-Tocopherol, Beta-carotene Cancer Prevention (ATBC) study (1994). On secondary analysis, the ATBC lung cancer prevention trial found a 32% reduction in PCa incidence (95% CI: 12–47; $P=0.002$) in men receiving 50 mg/day α-tocopherol. In addition, a 41% reduction in PCa mortality (95% CI: 1–65%) was observed in the α-tocopherol group (Heinonen et al. 1998). An additional follow-up of 12 years confirmed that higher serum α-tocopherol at baseline was associated with improved PCa survival (HR: 0.67; 95% CI: 0.45–1.00) (Watters et al. 2009). The strongest survival relationship was seen for those who received α-tocopherol supplementation and were in the highest serum α-tocopherol quintile at baseline (HR: 0.51; 95% CI: 0.20–0.90) or at 3-year follow-up measurement (hazard ratio (HR): 0.26; 95% CI: 0.09–0.71).

Based on these indirect evidences, Se and vitamin E were tested separately and in combination for the prevention of PCa in a large trial, the Selenium and Vitamin E Cancer Prevention Trial (SELECT). As for today, SELECT remains the largest PCa prevention study ever performed. It randomized 35,533 men to four groups: Se (200 μg/day) + placebo, vitamin E (400 IU/day) + placebo, Se + vitamin E, or placebo + placebo. Eligibility criteria were age 50 years or older for African Americans, 55 years or older for Caucasians, a serum PSA level of 4 ng/ml or less, a digital rectal examination (DRE) not suspicious for cancer and normal blood pressure. The primary endpoint was biopsy-confirmed PCa. The first analysis of SELCT, released in 2009, had failed to show a benefit for selenium and vitamin E, alone or in combination (Lippman et al. 2009). The study was then preliminary terminated at 7 years (planned duration was 12 years). Even worse, latest results, released in 2011, demonstrated that dietary supplementation with vitamin E significantly increased the risk of PCa among healthy men. Indeed, at

this second analysis 529 men from the placebo had developed PCa, *vs.* 620 men in the vitamin E group (HR, 1.17; 99% CI, 1.004–1.36, P = .008), 575 in the selenium group (HR, 1.09; 99% CI, 0.93–1.27; P = .18), and 555 in the selenium plus vitamin E group (HR, 1.05; 99% CI, 0.89–1.22, P = .46) (Klein et al. 2011). Compared with placebo, the absolute increase in risk of prostate cancer per 1000 person-years was 1.6 for vitamin E, 0.8 for selenium, and 0.4 for the combination.

The negative results of SELECT have caused an immense disappointment, especially amongst vitamins and trace elements aficionados. PCa complementary medicines represent a multibillion over the counter market, and it was expected that "good reasons" to pursue prescription of these drug would emerge rapidly, including criticisms on the dose of vitamin E and type of Se used in SELECT. The high dose of vitamin E (400 IU/D of the alpha-tocopherol form) in SELECT may have been less effective than a lower dose such as the eightfold lower 50 IU/D of the ATBC study (Lippman et al. 2009). In SELECT, 200 μg of l-selenomethionine was chosen whereas in the NPC trial, the 200 μg of high Se yeast contained only 20% of l-selenomethionine (Duffield-Lillico et al. 2003; Lippman et al. 2009). Another drawback of SELECT is the absence of selection of patients since it is likely that personal predispositions may enhance or hinder the benefit of supplementation. For example, several studies have suggested that vitamin E is more protective against PCa in smokers, and in SELECT, less than 60% of men where current or former smokers, whereas in the ATBC study all men were smokers. As for Se, genetic susceptibilities exist may confer different benefit to Se supplementation. Chan et al. have assessed manganese superoxide dismutase (SOD2) gene variants and plasma Se in 489 patients with localized/locally advanced PCa (Chan et al. 2009). SOD2 is an endogenous mitochondrial enzyme that metabolizes reactive oxygen species and superoxide anions to oxygen and hydrogen peroxide. Several polymorphisms of SOD2 have been identified, including a single nucleotide permutation that encodes either an alanine (A) or a valine (V). SOD2 genotype alone was not associated with disease aggressiveness, whereas higher versus lower Se levels were associated with a slightly increased likelihood of presenting with aggressive disease (RR: 1.35; 95% CI: 0.99–1.84). There was evidence of an interaction between SOD2 and Se levels such that among men with the AA genotype, higher Se levels were associated with a reduced risk of presenting with aggressive disease (RR: 0.60; 95% CI: 0.32–1.12), whereas among men with a V allele, higher Se levels were associated with an increased risk of aggressive disease (for VV or VA men, RR: 1.82; 95% CI: 1.27–2.61; *P* for interaction <0.007) (Chan et al. 2009).

But clearly one of the more consistent hypotheses is that the positive effects of Se in the NPC study and of vitamin E in the ATBC trial could have been due to chance in secondary analyses. Recent results from the Prostate Cancer Prevention Trial found no significant association between vitamin E and Se and the incidence of PCa (Kristal et al. 2010). Long-term supplemental intake of vitamin E (≥400 IU/day) in the VITamins And Lifestyle (VITAL) study was not associated with PCa risk overall; however, the risk of clinically relevant advanced disease was reduced with greater long-term (10-year average intake) vitamin E supplementation (Peters et al. 2008). Currently, several prevention studies are still ongoing or have been completed. A trial by Southwest Oncology Group has evaluated the effectiveness of Se 200 (μg/day) as selenomethionine in preventing PCa in approximately 423 patients aged 40 years or older who have high-grade PIN and PSA level of ≤10 ng/ml. Three-year cancer rates were 36.6% in placebo group versus 35.6% in Se group (*P*=0.73, adjusted) (Marshall et al. 2011). The majority of patients who developed cancer on trial (70.8% Se and 75.5% placebo) had a Gleason score ≤6, and there was no difference in Gleason scores distribution between the two arms (Marshall et al. 2011).

To summarize our position regarding Se and Vitamin E supplements, the best is to literately quote P. Gann in its editorial to the publication of SELECT results:

> Epidemiology teaches that every statistical association has only 3 possible explanations: bias,

> chance, and cause. Regarding nutritional prevention of prostate cancer, first-generation phase 3 trials were too reliant on biased interpretation of prior research; second-generation trials may have been too reliant on chance; yet there is every reason to believe that the next generation will have a firmer basis for causal hypotheses. Until then, physicians should not recommend Se or vitamin E—or any other antioxidant supplements—to their patients for preventing prostate cancer.
>
> (Gann 2009)

2.3 Dietary Supplements

The incidence and mortality of PCa shows strong variations worldwide with the highest rates in North America, Australia, Western and Northern Europe and the lowest rates in Japan and other Asian countries. Interestingly, however, the incidence of latent or clinically PCa in autopsy studies among men from Japan and the USA is not substantially different. Migrant studies have shown an increase in PCa incidence in Asian men after emigration to the United States (Shimizu et al. 1991). The underlying theory is that these men adopt a western life style with a high-fat, high-protein, low-fibre diet that lacks certain substances of the Asian diet such as plant-derived antioxidants, isoflavones-containing soy, and tea polyphenols that may protect against the development of cancer. Therefore, it is hypothesized that dietary changes and pharmacological intervention could have an impact on PCa development and progression (Syed et al. 2007).

2.3.1 Isoflavones

Isoflavones, a subclass of the flavonoids, are plant-derived compounds with weak estrogenic activity and therefore classified as phytoestrogens. Phytoestrogens have been suggested to have a preventive effect against various cancers (Adlercreutz 2002). Soyfoods are a rich source of isoflavones. The main isoflavones found in most soy products are genistein, daidzein and glycitein. In vitro, genistein and daidzein inhibit the growth of PCa cells (Swami et al. 2005). The mechanism of action of the isoflavones in soy products is not entirely clear.

Epidemiological surveys have shown that serum isoflavone levels are related to the risk of PCa. Most of them have been conducted in Asian men. A case–control study, including 200 Japanese patients and 200 age-matched Japanese controls, suggested that isoflavones might be protective against PCa. The odds ratio (OR) for the highest quartile (≥89.9 mg/day) compared with the lowest quartile (<30.5 mg/day) of isoflavone intake was 0.42 ($P<0.01$) (Nagata et al. 2007). In a nested case–control study on 14,203 Japanese men in which 201 PCa were identified during a 12.8 years of follow-up, plasma genistein and equol, a metabolite of daidzein, levels were inversely associated with the risk of PCa. The ORs of PCa diagnosis in the highest group of plasma genistein and equol compared with the lowest was 0.54 (P: 0.03) and 0.43 (P: 0.02), respectively (Kurahashi et al. 2008).

A few studies have been performed on Caucasian men. Travis et al. have examined plasma concentrations of phytoestrogens in relation to risk for subsequent PCa in a case–control study nested in the European Prospective Investigation into Cancer and Nutrition (EPIC) (Travis et al. 2009). Higher plasma concentrations of genistein were associated with lower risk of PCa, OR for men in the highest versus the lowest quintiles being 0.71 (P: 0.03). A meta-analysis of 14 epidemiological studies, including eight on isoflavones, suggests that soy and isoflavone consumption is associated with a decreased risk of PCa of approximately 26% in men when highest reported intake is compared with lowest reported intake (Yan and Spitznagel 2009). The protective effect is related to the type and quantity of soy food consumed. The analysis on soy intake yielded a combined OR of 0.74 (95% CI: 0.63–0.89; $P=0.01$). The analysis of studies on non-fermented soy foods yielded an OR of 0.70 (95% CI: 0.56–0.88; $P=0.01$) and those on fermented soy foods yielded a combined OR of 1.02 (95% CI: 0.73–1.42; $P=0.92$). The analysis of studies on isoflavones yielded a combined OR of 0.88 (95% CI: 0.76–1.02; $P=0.09$). Further separate analyses showed a combined OR of 0.52

(95% CI: 0.34–0.81; $P=0.01$) from studies with Asian populations and 0.99 (95% CI: 0.85–1.16; $P=0.91$) from studies with Western populations.

However, beyond these convincing epidemiological, case–control, and in vitro/vivo studies, there are no published robust prospective RCTs with sufficient statistical power to confirm that isoflavone supplementation can reduce PCa development or delay PCa progression.

2.3.2 Lycopene

Lycopene is a carotenoid that gives the red colour to tomatoes and tomato-derived products. It is also available in other red fruits and vegetables such as red carrots, watermelons, pink grape fruit and papayas. It possesses potent antioxidant activity and appears to have anti-cancer properties (Levy et al. 1995).

One of the first observation pinpointing at a potential benefit of lycopene for PCa prevention comes from the Health Professionals Follow-Up Study, a trial initiated in 1986 with the purpose of evaluating a series of hypotheses about men's health relating nutritional factors to the incidence of serious illnesses, such as cancer, heart disease and other vascular diseases. An interim analysis of semi-quantitative food-frequency questionnaires published in 2002 suggested that high lycopene intake was associated with a reduced risk of PCa (RR for high versus low quintiles: 0.84; $P=0.003$). Intake of tomato sauce, the primary source of bioavailable lycopene, was associated with an even greater PCa risk reduction: RR for more than two servings/week versus less than one serving/month: 0.77 ($P<0.001$) (Giovannucci et al. 2002). This was confirmed by a study on plasma lycopene concentrations suggesting a statistically significant inverse association between higher lycopene plasma concentration and lower risk of PCa in younger patients (>65 years old; OR: 0.47); and in patients without a family history of PCa (OR: 0.43) (Wu et al. 2004). A meta-analysis of 11 case–control studies and 10 cohort studies or nested case–control studies showed that tomato products and lycopene may play a role in the prevention of PCa although the effect is modest and limited to high amounts of tomato products (Etminan et al. 2004). The main findings were that, compared with non-frequent users of tomato product (1st quartile of intake) the OR of PCa among consumers of high amounts of raw tomato (5th quintile of intake) was 0.89 (95% CI: 0.80–1.00). For a high intake of cooked tomato products, the corresponding OR was 0.81 (95% CI: 0.71–0.92). The OR of PCa related to an intake of one serving/day of raw tomato (200 g) was 0.97 (95% CI: 0.85–1.10) for the case–control studies and 0.78 (95% CI: 0.66–0.92) for cohort studies. For serum- or plasma-based studies, the corresponding ORs were 0.74 (95% CI: 0.59–0.92) for all studies, 0.55 (95% CI: 0.32–0.94) for case–control studies and 0.78 (95% CI: 0.61–1.00) for cohort studies. The World Cancer Research Fund (WCFR) estimates that there is a sufficient body of evidence for protective effect of lycopene-containing foods, especially tomatoes and its derivatives on PCa. This tentative health claim is based on a different meta-analysis including 5 cohort and 9 case–control studies with tomatoes, 3 cohort and 14 case–control studies with dietary lycopene and 6 cohort and 2 case studies based on serum or plasma lycopene. Most of the studies decreased risk with increased intake (www.dietandcancerreport.org) (2007). In contrast, a large nested case–control study in the prostate, lung, colorectal and ovarian cancer screening study including 692 PCa cases (Peters et al. 2007) and the recently published Prostate Cancer Prevention Trial (Kristal et al. 2010) including 9,559 participants found no correlation between lycopene and the incidence of PCa.

2.3.3 Polyphenols

Polyphenols are the largest group of constituents found in tea. Green tea contains catechins, a category of water-soluble polyphenolic substances. The four principal catechins are epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG)

(Balentine et al. 1997). EGCG, found in the highest concentration in green tea, is the most studied and most active of all green tea catechins (GTCs) for the inhibition of oncogenesis and reduction of oxidative stress. The mode of action of polyphenols is not yet fully determined. Several epidemiologic studies have focused on the lower incidence of PCa in Asian populations where green tea is consumed regularly as compared with Western populations, suggesting that green tea is protective against PCa.

In 2006, a 1-year proof-of-principle trial has been conducted to assess the safety and efficacy of GTCs for the chemoprevention of PCa in HGPIN (Bettuzzi et al. 2006). Sixty patients were randomized to 600 mg GTCs per day or placebo. After 1 year, only 1 of 30 (3%) GTCs-treated men were found to have PCa compared to 9 of 30 (30%) placebo-treated men. This is the first study showing that GTCs have potent in vivo chemoprevention activity for human PCa. GTCs treatment did not have a significant effect on PSA values throughout the study. In any case, the mean value of total PSA was always lower in patients randomized to GTCs than in patients on placebo. Secondary observations were reduction in lower urinary tract symptoms as assessed by International Prostate Symptom Score and Quality of Life scores in GTCs-treated men. No significant side or adverse effects have been reported. A 2-year follow-up was performed in a subset of patients and showed that GTCs had a long-lasting effect on PCa prevention (Brausi et al. 2008). A larger, randomized, double-blind, placebo-controlled study in 272 HGPIN patients in the United States will assess the rate of progression to PCa after treatment with either 200 mg EGCG as polyphenon E twice daily (i.e., 400 mg EGCG/day) or placebo over a 1-year period (ClinicalTrials.gov Identifier NCT00596011). Results with green tea polyphenols for PCa chemoprevention are encouraging, and patients should be encouraged to incorporate them in their daily diet. Larger clinical trials of men at risk of PCa or with early stage PCa are needed to better assess the role of green tea polyphenols in the prevention of PCa.

2.4 Hormonal Prevention of PCa

2.4.1 Rationale for Hormonal Prevention of PCa

Testosterone is critical initiator of prostate development and growth. Testosterone suppression, the standard systemic treatment of advanced PCa, induces massive apoptosis of normal and malignant prostate cells (Tombal 2007). The role of testosterone in the early development of PCa is unclear (Tombal 2011). Epidemiological surveys and prospective testosterone supplementations trials have failed to show a consistent association between low- or high-serum testosterone levels and the risk of developing cancer (Morgentaler and Traish 2009). Normal epithelial prostate cells do not express the androgen receptor (AR), and the effect of androgens is mediated by epithelial stromal interactions (Tombal 2011). In contrast to normal epithelial cells, AR expression is found in epithelial PCa cells and more importantly in its traditional precursor, high-grade PIN and PIA (Tombal 2011). This suggests that early during prostatic carcinogenesis, there is a gain-of-function that converts the AR from a growth suppressor gene to an oncogene, allowing the AR to engage the molecular signalling pathways stimulating the proliferation and survival of these initiated prostatic cells directly. In the stromal cells, normal and malignant prostate cells, the primary androgen is dihydrotestosterone (DHT), which results from the transformation of T by the 5α-reductases enzymes. 5α-reductase inhibitors (5ARIs), finasteride and dustasteride, inhibit the transformation of T into DHT. They have been used intensely in the treatment of benign prostatic hyperplasia (BPH) because they significantly reduce the prostatic volume and therefore improve urinary symptoms. In addition, 5ARIs decrease the value of PSA. Since androgen deprivation therapy (ADT) or AR direct blockade are unrealistic methods of chemoprevention because of the side effects of hypogonadism, 5ARIs became ideal chemopreventive agents to interfere with androgen regulations in the early development of PCa.

Similar to testosterone, oestrogens have been implicated in PCa carcinogenesis. Oestrogens have significant direct and indirect effects on prostate gland development and homeostasis and have been long suspected in playing a role in the aetiology of prostatic diseases (Prins and Korach 2008). Direct effects are mediated through prostatic oestrogen receptors (ER) α and β. Therefore, selective oestrogen receptor modulators (SERMs) that interfere with ER have been seen as potential chemoprevention agents.

2.4.2 Randomized Controlled Trials with Chemo "Hormono" Prevention

2.4.2.1 SERMS

The SERM toremifene has been tested in a multicentre, double-blind study on 514 men with HGPIN and no cancer that were re-biopsied at 6 and 12 months(Price et al. 2006). After 12 months, there was a 21.8% reduction in the cumulative risk of PCa in favour of toremifene, PCa being diagnosed in 24.4% of patients receiving 20 mg of toremifene and 31.2% of those taking placebo ($P<0.05$). Based on this observation, a larger trial was initiated in 1,590 men with high-grade PIN and no cancer on biopsy to compare 20 mg toremifene to placebo daily for 3 years, with yearly repeat biopsies (NCT00106691). The sponsor GTx issue a press release on May 24, 2010, announcing that toremifene reduced the incidence of prostate cancer by a non-significant 10.2% ($P=0.385$) and that the trial was stopped.

2.4.2.2 5ARIs Finasteride and Dutasteride

The Prostate Cancer Prevention Trial (*PCPT*) has tested the benefit of 5 mg finasteride per day versus placebo for a period of 7 years. In total, 18,882 men ≥55 years old with a PSA ≤ 3.0 ng/ml, a normal digital rectal examination (DRE) and no suspicion of PCa were included (Thompson et al. 2003). There were no baseline biopsies. Patients were followed by PSA and DRE. In the finasteride group, PSA was corrected to adjust for finasteride effect (×2 for year 1–2 and ×2, 3 thereafter) and "for-cause" biopsy with ≥6 cores was recommended in case of PSA >4.0 ng/ml or a suspicious DRE. An end-of-study prostate biopsy was recommended at year 7 for patients remaining undiagnosed with PCa. The final analysis, published in July 2003, included 9,060 men (48%) who had for-cause and/or an end-of-study biopsy. Finasteride reduced by 24.8% the prevalence of PCa during the 7-year period (18.4% in finasteride group vs. 24.4% in placebo group; $P<0.001$). For-cause biopsies were done in 39% of the participants, and 52% of the cancers were diagnosed on for-cause biopsies. There were 15% fewer for-cause biopsies and 10% fewer PCa in the finasteride group. Noteworthy, the reduction in overall PCa detection was entirely due to a reduction in Gleason ≤6 cancers, and there was an increase in Gleason ≥7 cancers: 280 (6.4%) in the finasteride group versus 237 (5.1%) in the placebo group ($P=0.005$).

There have many attempts to provide explanation for that increase in high-grade cancer and to answer whether finasteride improves the detection of high-grade PCa or negatively impacts the natural history and behaviour of PCA. Interestingly indeed, the increase in Gleason ≥7 cancers concerns for-cause biopsies. In "end-of-study" biopsies, there were 92 and 89 Gleason 7–10 cancers in the finasteride and placebo groups, respectively. The fact that there was fewer for-cause and end-of-study biopsies in the finasteride arm suggests that finasteride most likely influenced the decision to biopsy. Additional analyses have suggested that finasteride improves the sensitivity of both PSA and DRE to detect PCa, including high-grade cancers (Thompson et al. 2006, 2007). This might be partially explained by the decrease in prostate volume resulting from 5AR inhibition, on average 24% lower in the finasteride arm at the time of biopsy (Serfling et al. 2007). Finally, Lucia et al. have reported extended analysis on biopsies and radical prostatectomies (RP) specimens from 222 patients receiving finasteride and 306 receiving placebo (Lucia et al. 2007). Mean percentage of positive cores was lower in men receiving finasteride (34% vs. 38%, $P=0.016$), as well as mean tumour linear extent (greatest

[4.4 vs. 4.8 mm, $P=0.19$] and aggregate [7.6 vs. 9.2 mm, $P=0.13$]), bilaterality (22.8% vs. 30.6%, $P=0.046$) and perineural invasion (14.2% vs. 20.3%, $P=0.07$). More interestingly, the finasteride-associated increase in Gleason ≥7 PCa at biopsy (42.7% finasteride vs. 25.4% placebo, $P<0.001$) was reduced and not significant anymore on the RP specimens (46.4% finasteride vs. 38.6% placebo, $P=0.10$). Biopsy identified a greater proportion of patients with high-grade disease present at prostatectomy in the finasteride group than in the placebo group (69.7% vs. 50.5%, $P=.01$). The rate of upgrading (from low-grade cancer at biopsy to high-grade cancer at prostatectomy) and pathologic stage at prostatectomy were similar in both groups.

Several post hoc analyses have been conducted to attempt to account for these factors in determining the true effect of finasteride on overall and Gleason ≥7 cancers (Cohen et al. 2007; Kaplan et al. 2009; Pinsky et al. 2008; Redman et al. 2008). All these analyses seem to confirm the hypothesis that finasteride increases the detection of high-grade cancer and rule out a negative impact on its natural history.

The Reduction by DUtasteride of prostate Cancer Events (*REDUCE*) trial has tested the benefit of 0.5 mg dustateride versus placebo daily in 8,122 men to reduce the risk of biopsy-detectable PCa over a period of 4 years (Andriole). Men were aged 50–75 years old, had a PSA between 2.5 and 10.0 g/ml, a prostate volume <80 ml and, in contrast to PCPT, a single, negative previous biopsy of 6–12 cores within 6 months prior to study enrolment. Repeat, study-mandated prostate biopsies were taken after 2 and 4 years; for-cause biopsies could be done at any time. Overall, PCa was diagnosed in 858 men in the placebo group (25.1%) and 659 men in the dutasteride group (19.9%) with a relative risk reduction of 23% ($P<0.0001$) (Andriole). Gleason 7–10 cancers were diagnosed in 220 men in the dutasteride group (6.7%) and 233 men in the placebo group (6.8%) ($P=0.81$). In the subset of Gleason ≥8 cancers, there were 29 cancers in the dutasteride group and 19 cancers in the placebo group ($P=0.15$). During the first 24 months, there were 17 and 18 Gleason ≥8 cancers in the dutasteride and placebo groups, respectively. Subsequently, during years 3 and 4, there were 12 Gleason ≥8 cancers in the dutasteride group and only one in the placebo group, out of 2,343 biopsies.

Similar to PCPT, several hypotheses were generated to explain that apparent small but disturbing increase in high-grade cancers. The low number of Gleason ≥8 cancers in the placebo arm at year 3–4 could be explained by 141 more Gleason ≤7 cancers being diagnosed in the placebo arm during years 1 and 2 and subsequently removed from treatment. There was therefore no opportunity for those cancers to be reclassified or upgraded during years 3 and 4. Another argument against dutasteride increasing the rate of high-grade cancers is the result of CombAT, a 4-year BPH trial comparing dutasteride and tamsulosin monotherapies with the combination of the two in 4,800 patients with lower urinary tract symptoms (Roehrborn et al. 2008). In that trial, prostate biopsies were done by investigators in case of PSA elevation or DRE abnormality, and there was no evidence of an increase in high-grade cancers in the two dutasteride arms compared to the tamsulosin monotherapy arm.

Side effects of dutasteride and finasteride are similar, the most common being related to sexual function. In the PCPT, erectile dysfunction (ED) occurred in 67% of the finasteride group and 61% of the placebo group. Decreased libido occurred in 65% of the finasteride group and 60% of the placebo group (Thompson et al. 2003). In REDUCE, new instances of decreased libido occurred in 5.1% of the dutasteride group and 2.9% of the placebo group (Andriole). New instances of ED occurred in 9.0% of the dutasteride group and 5.7% of the placebo group; 4.3% of the dutasteride group and 2.0% of the placebo group dropped out due to drug-related side effects. Gynecomastia occurred in 4.5% of the finasteride arm of the PCPT and 1.9% of the dutasteride arm of REDUCE, double the incidence of gynecomastia in the placebo group (Andriole et al. 2010; Thompson et al. 2003). There have been no life-threatening or serious side effects proven to be related to either finasteride or dutasteride. Both can occasionally be associated with allergic-type skin reactions.

2.4.3 Balancing the Benefits and Risks of 5ARIs for Prostate Cancer Risk Reduction

In December, 2010, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted against recommending dutasteride and finasteride for the indication to reduce PCa risk because in the view of the ODAC members, the risk for more aggressive tumours outweighed the potential for chemoprevention. ODAC recommended against PCa chemoprevention labelling for both 5α-reductase inhibitors—dutasteride (vote 14 (no) to 2 (yes), with 2 abstentions) and finasteride (vote 17 (no) to 0 (yes), with 1 abstention). Currently so far, neither of these drugs is approved for the indication of chemoprevention, and no trials are planned. As for know, we have to live with the fact that registration authorities refuse to rule out that either dutasteride or finasteride induces the growth of high-grade cancer.

This creates an interesting, although schizophrenic, registration paradigm. Indeed, both finasteride and dutasteride are effective treatments for men with symptomatic BPH. They not only improve urinary symptoms related to an enlarged prostate but also reduce the risk of acute urinary retention and the need for BPH-related surgery. What should we say to these men regarding their subsequent risk of developing PCa? Most of these patients could in theory receive 5ARI for BPH or PCa prevention because they have a moderately enlarged prostate with a moderately elevated PSA and BPH symptoms. Is it for them like choosing between the plague and cholera, balancing a demonstrated risk of reducing urinary retention and surgery and an increased risk of being diagnosed with high-grade Gleason. Very important questions on which, interestingly, the industry has been extremely quiet regarding that issue and most guidelines have avoided tackling the issue.

Finally, one should notice that the long-term effect of 5ARI on the responsiveness to further hormonal manipulation in men needing ADT for advanced cancer is not known. Neither the PCPT nor REDUCE were designed to measure the impact of 5ARIs on PCa survival. One may question if a cancer that progresses under 5ARIs will respond effectively to more aggressive androgen ablation. 5ARIs may or may not induce adaptation mechanisms similar to those observed during castration resistance and therefore decrease the sensitivity to ADT. This should be taken into account when evaluating the benefit of chemoprevention not in terms of reduction of incidence but of PCa mortality. For example, Koivisto et al. have studied six PCa diagnosed during finasteride treatment. Comparative genomic hybridization detected genetic alterations in four tumours, including Xq gains and 6q losses. Some of these abnormalities, including AR amplification and mutation, were consistent with what has previously been shown for PCa progressing under ADT (Koivisto et al. 1999).

2.5 Conclusions and Future Perspectives

So far, neither attempts to claim PCa chemoprevention has been very successful. Randomized phase III with nutrients have been overall negative or difficult to interpret. Differences in study design, sample size, doses administered and/or concentrations achieved in the body may be the reason for the many observed inconsistencies. Therefore, no recommendation can be made beyond a healthy diet, Mediterranean style and a correct load of physical activity. Chemo "hormone" prevention with 5ARIs can be quoted "effective" in reducing PCa incidence, but that effectiveness result largely from reducing the rate of Gleason ≤6 cancer. Today, it is widely accepted by most guidelines that these cancers pose little threat to men with life expectancy of less than 20–10 years. We agree that these cancers are nowadays overtreated and that effective strategies are required to reduce the rate of overtreatment. Overtreatment should be avoided with counselling and education and presently not with 5ARI as long as the controversy on the increase risk of high-grade cancer is not resolved.

Is it then the dusk of chemoprevention? We believe not, but smart adaptation and expectation, especially regarding the definition of risk categories

will be needed. It seems reasonable to believe that chemoprevention strategies are more effective in high-risk groups, which, at this moment, are still very difficult to identify. Patients with isolated HGPIN on prostate biopsies constitute a unique and well-demarcated risk group for PCa. Prospective, randomized data on chemopreventive strategies in HGPIN are scarce but seem promising. Other high-risk groups include those above 40 years of age, with elevated PSA levels, rapid PSA velocity, sub-Saharan African ethnicity, with a family history of PCa or with specific genes, obese men with insulin resistance and those who would benefit from early diagnosis and treatment with at least 10–15 years of life expectancy.

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Individual and Mass Screening

3

Chris H. Bangma, Pim J. van Leeuwen,
and Monique J. Roobol

Contents

C.H. Bangma, M.D., Ph.D. (✉)
Department of Urology, Erasmus MC,
H-1093, Rotterdam, The Netherlands
e-mail: h.j.vanalphen@erasmusmc.nl

P.J. van Leeuwen • M.J. Roobol
Department of Urology, Erasmus MC,
University Medical Centre, Rotterdam,
The Netherlands
e-mail: m.roobol@erasmusmc.nl

3.1 Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the sixth leading cause of cancer death among men worldwide, with 914,000 new cases and 258,000 deaths were predicted to occur in 2008 (Ferlay et al. 2010). The lifetime risk of a PCa diagnosis is 15.8% for an individual man in the United States and approximately 9% for a man in Western Europe (Jemal et al. 2010; Collin et al. 2008; Bray et al. 2010). The lifetime risk of dying from PCa is lower, i.e. 2.8% in the United States and 3.1% in Western Europe (Jemal et al. 2010; Collin et al. 2008; Bray et al. 2010). Overall, these incidence and mortality rates give PCa an important public health relevance (Dixon et al. 2009).

The introduction and widespread use of prostate-specific antigen (PSA) testing for the early detection of PCa have led to major changes in PCa incidence (see Chap. 1), the tumour grade and stage at diagnosis, treatment, and the mortality from PCa over the past two decades. This has lead to the diagnosis of cancers that rather should not have been diagnosed, as their detection and subsequent treatment is unlikely to benefit patients, or even might harm them. These cancers are referred to as ‘overdiagnosis’, and their treatment as ‘overtreatment’.

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Table 3.1 The continuum of prostate cancer risk for different PSA ranges

Authors	Methods	Results							Notes
		PSA, ng/ml	PC, any grade			PC, Gleason grade ≥8			
			Sen (%)	Spec (%)	LR	Sen (%)	Spec (%)	LR	
Thompson et al. (2004), PCPT	Among 5,587 men, a PSA determination and a sextant prostate biopsy were performed to assess the sensitivity and specificity of PC detection for all PSA ranges in relation to Gleason grade.	1.1	83.4	38.9	1.4	94.7	35.9	1.5	*N*=1,225 (21.9%) were diagnosed with prostate cancer
		2.1	52.6	72.5	1.9	86.0	65.9	2.5	
		2.6	40.5	81.1	2.1	78.9	75.1	3.2	
		3.1	32.2	86.7	2.4	68.4	81.0	3.6	
		4.1	20.5	93.8	3.3	50.9	89.1	4.7	
		6.1	4.6	98.5	3.1	26.3	97.5	10.5	
		10.1	0.9	99.7	3.0	5.3	99.5	10.6	

PCPT Prostate Cancer Prevention Trial, *PC* prostate cancer, *PSA* prostate-specific antigen, *DRE* digital rectal examination, *TRUS* transrectal ultrasound, *Sen* sensitivity, *Spec* specificity, *LR* likelihood ratio

3.2 Screening Instruments: PSA, DRE, TRUS and the Prostate Biopsy

PSA (prostate-specific antigen), DRE (digital rectal examination), and transrectal ultrasound (TRUS) are the three main modalities for the early detection of PCa, of which serum PSA is the main tool. All serve as an indicator for diagnostic prostatic biopsies. The PSA test seems to be acceptable to the population as a screening procedure since the participation and adherence to mass screening in subsequent screening rounds is overall high (Schroder et al. 2003). PSA is a specific organ marker, but not strictly a tumour marker, since prostatitis and benign prostate hyperplasia (BPH) can also increase the serum PSA (Sindhwani and Wilson 2005; Rao et al. 2008). Due to this, no clear PSA threshold level exists as an indicator for diagnostic prostatic biopsies. The continuum of PCa risk for different PSA ranges is presented as a result of the Prostate Cancer Prevention Trial (PCPT) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) (Thompson et al. 2004; Schroder et al. 2008) (Table 3.1). According to these study results, a physician who would like an 80% confidence in not missing a PCa should apply a PSA cut-off value of 1.1 ng/ml as indication for biopsy (sensitivity), which would result in 60% unnecessary (negative) biopsies (specificity) (Thompson and Ankerst 2007) (sensitivity = those who test positive divided by all those who have cancer, specificity = those who test negative divided by all those who do not have cancer).

Sensitivity decreases with the increasing PSA level, while specificity increases with the increasing PSA level. Consequently, lowering PSA cut-off levels leads to a higher detection rate of PCa, but also leads to an increase of negative (unnecessary) biopsies and of the overdiagnosis of harmless cancers (Postma et al. 2007). Currently, therefore, the suggested PSA cut-off to biopsy a man for screening differs between 2.6 and 4.0 ng/ml (Gohagan et al. 2000; Krumholtz et al. 2002; Schroder et al. 2003). Future data that include the comparison of the different studies with long follow-up might show the difference in mortality and morbidity outcomes using these different PSA thresholds.

3.2.1 PSA Velocity

The changes of PSA over time were analysed for their predictive value in follow-up rounds of population-based studies with intervals ranging between 1 and 4 years. PSA velocity (the increase of the absolute level of PSA during 1 year) showed in various studies a statistically difference between men with versus without cancer (in the ERSPC 0.62 ng/ml/year for PCa, versus 0.46 ng/ml/year for non-cancer Roobol et al. 2004; Loeb et al. 2007), and also in mean PSA doubling time (5.1 vs. 6.1 years). A threshold of 0.4 ng/ml/year discriminated between significant and insignificant

disease (Loeb et al. 2010). However, the variability of these parameters for individual decisions would be too high for practical application. In a multivariate analysis of a comparable cohort, the odds ratio for the PSA velocity was 0.73 (95% CI: 0.20–2.6; $P=0.64$) (Vickers et al. 2009). In another study, doubling of the PSA concentration within the 4 years, or any other increase of PSA (PSA velocity), did not contribute to the prediction of a detectable cancer (Raaijmakers et al. 2004). PSA velocity as indication for prostate biopsy is, however, included in some US guidelines. An empirical evaluation of the additional value of PSA velocity next to age, PSA, DRE, and family history showed, however, no evidence to support the recommendation that men with high PSA velocity should be biopsied in the absence of other indications (Vickers et al. 2011).

3.2.2 DRE

DRE is the classical method for PCa detection. However, DRE findings are only moderately reproducible, even amongst experienced urologists (Smith and Catalona 1995; Gosselaar et al. 2008). Further, DRE tends to diagnose the tumours when they are pathologically advanced and therefore less likely to be curable by radical prostatectomy (Thompson et al. 1987; Epstein et al. 1994). DRE has a low sensitivity and predictive value in men with low PSA levels (Crawford et al. 1996; Schroder et al. 1998; Yamamoto et al. 2001; Andriole et al. 2005; Bozeman et al. 2005). The positive predictive value of DRE is limited to 4–19% at serum PSA levels below 3.0 ng/ml. Therefore, several researchers suggest that with the use of DRE men will be screened more selectively, as men with a positive DRE are more likely to have high grade PCa than men with non-palpable tumours (Ghavamian et al. 1999; Borden et al. 2007). For this reason, the risk of omitting DRE, and therefore of biopsies at low PSA levels, might be that potentially aggressive tumours remain initially undetected. Still, screening without DRE at low PSA levels (PSA < 3.0 ng/ml) did not lead to the detection of significantly more (poorly differentiated) carcinomas 4 years later in a mass screening program (Gosselaar et al. 2006).

3.2.3 TRUS

TRUS has remained the standard investigation tool for systematic diagnostic prostate needle biopsy since the mid-1980s. TRUS has the advantage of facilitating more accurate measurements of prostate size, which may help interpretation of PSA results (Benson et al. 1992a, b). As serum PSA is closely related to prostatic volume, the PSA density can improve the diagnostic specificity, reducing the number of unnecessary biopsies.

3.2.4 Diagnosis by Biopsy

PCa is diagnosed by histology of prostatic biopsies. For many years, a lateralized sextant biopsy technique was in use (Eskew et al. 1997). An additional biopsy was often performed from any suspicious area on TRUS. Approximately one fifth of biopsy detectable PCas are missed with a sextant biopsy (Schroder et al. 2010). Currently, a volume-adjusted number of biopsy cores is standard (Vashi et al. 1998; Ficarra et al. 2005; Djavan and Margreiter 2007). However, although men with a smaller prostate volume and an initially high PSA level are at greater risk of cancer detection and of an aggressive cancer, this does not mean that in a mass screening program, volume-adjusted biopsy schemes should not be implemented automatically. Relevant cancers will be detected due to regular repeated screening (van Leeuwen et al. 2009). Side effects of biopsy procedures, such as haematuria, haemospermia, infection, and urine retention are well described and have a limited clinical impact even when volume-adjusted biopsy schemes are used (Paul et al. 2004). A recently published Cochrane review of randomized trials on antibiotic prophylaxis for transrectal prostate biopsy showed that antibiotic prophylaxis is effective in preventing infectious complications following prostate biopsy. There were no data to confirm that antibiotics for long-course (3 days) were

superior to short-course treatments (1 day) or that multiple-dose treatment is superior to single-dose (Zani et al. 2011).

3.3 Mass Screening for Prostate Cancer

The objective of screening is to identify a disease at a stage in its natural history where treatment can be applied to prevent death or suffering (Habbema et al. 1982). Screening aims to avoid deaths from cancer by preventing the development of advanced disease. Therefore, effective treatment of early staged disease is essential to attain the aims of screening. Although screening may lead to an earlier diagnosis, screening tests will not always benefit the person being screened; overdetection with the potential result of overtreatment, increased costs, side effects, and complications are potential adverse effects of screening (Habbema et al. 1982; Pienta 2009).

The final endpoint of a cancer screening trial is cancer-specific mortality. However, there are more criteria that have to be fulfilled before screening can be adopted in a public health program. A total of ten WHO criteria for appraising the validity of a screening program were developed by Wilson and Jungner in 1968 (Wilson and Jungner 1968). Medical practice afterwards has resulted in several modifications of the classic criteria, resulting in ten new criteria, Table 3.2. For PCa screening, criteria 3 and 6 are currently not met, while criteria 9 and 10 are at least object of intense discussion.

Table 3.2 The ten updated criteria by Andermann et al. 2008

1. The screening programme should respond to a recognized need.
2. The objectives of screening should be defined at the outset.
3. There should be a defined target population.
4. There should be scientific evidence of screening programme effectiveness.
5. The programme should integrate education, testing, clinical services and programme management.
6. There should be quality assurance, with mechanisms to minimize potential risks of screening.
7. The programme should ensure informed choice, confidentially and respect for autonomy.
8. The programme should promote equity and access to screening for the entire target population.
9. Programme evaluation should be planned from the outset.
10. The overall benefits of screening should overweight the harm.

3.3.1 Randomized Control Trials for Prostate Cancer Screening

A small number of population-based studies have illustrated the grade and stage shift occurring by PSA based early detection of the population, and a significant reduction of prostate cancer mortality compared to geographic or historical controls (Oberaigner et al. 2011). There are, however, five randomized control studies (RCT) that are evaluating the effectives of mass screening, primarily the effect on prostate cancer mortality (Labrie et al. 2004; Sandblom et al. 2004; Andriole et al. 2009a; Kjellman et al. 2009; Schroder et al. 2009). They have been reviewed in the Cochrane systematic review 2010 (Ilic et al. 2011), in which it is stated that only the ERSPC and the PLCO trial provide unbiased data that live up to the Cochrane criteria for meta-analysis. The European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO trial) were designed to analyse whether population-based screening reduces the mortality from PCa, with an acceptable level of quality-of-life aspects and the associated costs(Gohagan et al. 2000; Schroder et al. 2003). The third randomized trial that reported recently independently on the mortality results after 14-year follow-up is the Swedish study from Gothenburg that participates in the ERSPC (Hugosson et al. 2010).

The ERSPC is conducted in eight European countries (Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden, Switzerland) and enrolled 267,994 men 55–74 years of age. All men with a prior diagnosis of PCa were excluded. In the ERSPC, men were screened in most countries with an interval of 4 years; however, in Sweden, men were screened with an interval of 2 years. The screening algorithm differed among the study centres (Berenguer et al. 2003; Ciatto et al. 2003a; Finne et al. 2003; Hugosson et al.

2003; Kwiatkowski et al. 2003; Roobol and Schroder 2003; Villers et al. 2003).

The PLCO is a trial in the United States that enrolled 155,000 women and men, 55–74 years of age, in ten screening centres. All men with a prior diagnosis of PCa, but not with previous PSA screening, were excluded. In the PLCO, men in the intervention arm received screening once each year by DRE and PSA for a period of 4 years and by PSA alone for 2 years more. A sextant biopsy was recommended for PSA values more than 4.0 ng/ml and/or an abnormal DRE. The regional health-care providers made final decisions on whether to take a biopsy and on the biopsy technique used (Gohagan et al. 2000).

3.3.2 Results of RCTs in Mass Screening

The ERSPC trial reported that PSA screening without digital rectal examination was associated with a 20% relative reduction in the death rate from PCa at a median follow-up of 9 years, the cumulative incidence of PCa was 8.2% and 4.8% for the intervention and control group, respectively (Schroder et al. 2009). The absolute reduction in the screening population was 7 PCa deaths per 10,000 men that were screened. The results were associated with a number of 1,410 men that needed to be screened (NNS) and 48 men that needed treatment (NNT) to save one death from PCa death. The treatment distributions were slightly different between the two groups, however, unlikely to play a major role in interpretation of the final results (Wolters et al. 2010a). Data analysis of the ERSPC with adjustment for the diluting effect of nonattendance and contamination showed that the mortality effect among men was increased to 30% (Roobol et al. 2009; van Leeuwen et al. 2010). In the ERSPC, 82.2% of the men in the screening group were screened at least once, and the average rate of compliance with biopsy recommendations was 85.8% (range, 65.4–90.3). The level of contamination by PSA testing in the control group was estimated in the order of 20–31% (Ciatto et al. 2003b; Otto et al. 2003; Roobol et al. 2009). The ERSPC is constructing their final study report as we write in 2011, demonstrating a relative mortality reduction of 21% in favour of population-based PSA screening after a median follow-up of 11 years in an intention to screen analysis (Schröder et al. 2011). This is only a marginal increase compared to the 2009 figure of 20%, and longer follow-up will be performed as only 19% of participants have reached the mortality endpoint.

The Gothenburg screening trial published their own mortality outcomes independently in 2010 (Hugosson et al. 2010). The Gothenburg trial was initiated as an independent study in 1994 as an effectiveness trial (without upfront informed) but joined the ERSPC trial shortly thereafter. Data up to 2008, after a median follow-up of 14 years, showed a RR for PCa death of 0.56 (95% CI: 0.39–0.82; $P=0.002$). This resulted in a NNS of 234 and NNT of 15. The main differences with the ERSPC as a whole are the type of randomization, younger age, a shorter screen interval, and, most importantly, a longer follow-up due to the simultaneous randomization of all participants in 1994.

The PLCO trial found no mortality benefit from combined screening with PSA testing and DRE during a median follow-up of 7–10 years comparing those screened to those that were not (Andriole et al. 2009b). The incidence of PCa death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (rate ratio, 1.13; 95% CI: 0.75–1.70) after a median of 7 years follow-up. The data at 10 years were 67% complete and consistent with these overall findings. The treatment distributions were similar in the two groups within each tumour stage. In the PLCO trial, the compliance with the screening protocol overall was 85% for PSA testing and 86% for DRE. The average rate of compliance with the biopsy recommendations was only 40% since the final decision to actually perform the biopsy was left to urologist. The level of contamination is well established, i.e. the rate of PSA testing was 40–52%, and the rate of screening by DRE ranged from 41% to 46% in the control group. Approximately 44% of the men in each study group had undergone one or more PSA tests before randomization, which would have eliminated some cancers detectable on screening from the randomized population, especially in health-conscious men (who tend to be screened more often, a form of selection bias). No

results are available for the effect of screening after the adjustment for the contamination; however, the PCa specific mortality was 25% lower among the men who were screened prior to randomization in the PLCO. Whereas the ERSPC found a statistically significant reduction in PCa mortality with screening, the PLCO trial did not. In the PLCO trial, the contamination in the control group and compliance with the screening protocol in the intervention group is of major influence. This is highlighted in the stage distribution among the men in the control arm of the PLCO study. In comparison to the 96% of men diagnosed with a stage ≤ II tumour in the intervention arm, there were 94.3% of men with a stage ≤ II tumour diagnosed in the control arm of the PLCO. Consequently, the PLCO trial is more a trial comparing two screening strategies of a different intensity and is inadequate in establishing if PCa screening has the potential to reduce the PCa specific mortality. Therefore, we can conclude that systematic PCa screening is not effective in terms of reducing the PCa specific mortality in comparison to widespread opportunistic screening and early detection.

3.3.3 Potential Harms of Prostate Cancer Screening: Overdiagnosis, Overtreatment, Quality of Life

Screening increases the PCa incidence. Approximately 50% of PCa diagnosed in population-based studies are overdiagnosed, as they show the pathological features of the incidental cancers found at autopsy (Gosselaar et al. 2005). With repeat screening sessions, this percentage increases even more (Boevee et al. 2010).

This implies that a subset of men diagnosed with PCa do not require any active, invasive treatment during life. In the ERSPC, over 600 men with these clinically and pathologically defined low-risk PCa features were observed without primary treatment over a period of 10 years (Roemeling et al. 2007). Overall survival was 70%, while none died of PCa.

The excess incidence and overtreatment by radiotherapy or surgery are associated with a distinct pattern of change in quality of life (Sanda et al. 2008; White et al. 2008). Quality-of-life (QoL) parameters that are affected are a change pattern in the urinary, bowel, and erectile functions, as well as the emotional distress and anxiety (Korfage et al. 2005; Mols et al. 2009).

Decisions on whether screening for prostate cancer should become a health-care policy require next to a reduction in the mortality from prostate cancer information on health-related quality of life and cost-effectiveness. A framework within both can be assessed was developed during the course of the two randomized trials (Miller et al. 2001). A first cost-effectiveness analysis on the basis of the ERSPC screening results revealed that introduction of PSA screening will double the total health-care costs for prostate cancer, mostly due to costs related to over detection (Heijnsdijk et al. 2009).

One QoL analysis is presented by the ERSPC study group, none by the PLCO. The QoL analysis have estimated the ratio between the benefits (PCa specific mortality reduction, life years gained, and reduction in advanced disease) and the harms (screening, overdiagnosis, overtreatment, and the additional life years that a man will live with cancer) of screening. To estimate the impact of screening in a large group of asymptomatic men, PCa incidence was compared with a non-screening situation using incidence data in the general population in a period in which not much opportunistic screening was taking place. For screening from age 55 to 70 years at 4-year interval, the predicted benefits per 1,000 men of all ages were 7 PCa deaths prevented and 60 life years gained over the lifetime of the population. The harms were overdiagnosis and overtreatment of 28 men and the loss of 716 PCa-free life years. The QALYs gained were 25 which is only 42% of the life years gained (De Koning et al. submitted 2012).

3.3.4 Interval Cancers

Screening does not detect all cancers, and cancers may emerge in between scheduled screening activities. They are called interval cancers. Therefore, interval cancers are either cancers that have developed after the previous screen or

cancers that were "missed" at the last screen. The reported interval cancers in the ERSPC and PLCO trial were infrequent and in general had favourable characteristics. The ERSPC-Rotterdam reported in the first 4 years after initial screening 25 interval cancers. All were classified as stage T1A–C or T2A, none were poorly differentiated or in a metastatic stage (van der Cruijsen-Koeter et al. 2006). In the PLCO, 204 interval cancers were diagnosed. Of these cancers, 96.1% were classified as stage T1A–C or T2A, and 2.0% were classified as stage IV disease (Grubb et al. 2008).

In ERSPC section Gothenburg, men were screened biennially in contrast to the rest of the ERSPC. Although it was reported in 2004 that the number of interval cancers was favourable and 20% of the number of cancers detected in the control group (Hugosson et al. 2003), a comparison of the rate of interval cancers between the Rotterdam and the Gothenburg group in 2007 did not reveal a difference between screening with the 4- and with the 2-year interval, while also the tumour characteristics were similar in both centres (Roobol et al. 2007). A very recent ERSPC study compared the long-term disease-specific survival of interval cancers to cancers in the control arm and concluded that these were similar (Zhu et al. 2011).

So far, no results from randomized controlled trials are reported on cost-effectiveness, cost utility, or cost benefit of screening for PCa.

3.4 Risk Factors in Mass Screening Studies

As a result of the population-based studies or cohorts, also incorporating limited side studies on biological data like family history, serum markers like PSA-isoforms (Bangma et al. 2010), and tissue analysis (genomics, proteomics), a large number of candidate risk factors have been analysed in order to assess diagnostic or prognostic value. The information should be incorporated into the design of prospective population trials that need to answer questions when to start (and stop) screening, how to do this, with which rescreen interval, and how to deal with men diagnosed with cancer. So far, multivariate analysis on ERSPC data has provided the prostate cancer risk calculators that is a decision support at various levels (www.uroweb.org, www.erspc.org, www.prostatecancer-riskcalculator.com), and can be used to stratify men for initial screening and biopsy (Roobol et al. 2010a). Such studies are being initiated in Sweden and the UK. Early initiation of screening at the age of 40 years and beyond has been advocated based on longitudinal serum PSA data (Lilja et al. 2007), in which, amongst other factors, only a PSA value of less than 0.6 ng/ml at the age between 44 and 50 years would predict the near absence of prostate cancer for 25 years. Men between 50 and 74 with a serum PSA < 1.0 ng/ml (36% of all men) or men with PSA < 2.0 ng/ml (67% of all men) can be reassured that even if they harbour a biopsy detectable cancer, it is unlikely to become life-threatening during their lifetime (Roobol et al. 2005). Such risk stratification measures may lead to an increased acceptance of screening among men and might increase the compliance among those at high risk, if they are informed of their risk status and their individualized harm-benefit trade-offs.

'Hereditary' prostate cancer is a term applied to a specific subset of patients with prostate cancer. This form of prostate cancer accounts for an estimated 43% of early onset disease (affecting men less than 55 years of age) but only 9% of all prostate cancer in men up to 85 years of age. A greater number of affected family members and early onset among family members are the most significant predictors of risk (McLellan and Norman 1995). Two meta-analyses, both published in 2003, have shown the association between family history and risk of prostate cancer. Based on 23 studies, the first meta-analysis showed a pooled RR estimate of 1.93 for men with a history of prostate cancer in any relative. A second meta-analysis based on 13 studies showed a pooled relative risk of 2.5 for men with affected first-degree relatives (Bruner et al. 2003; Johns and Houlston 2003).

3.5 Individual Screening

As the public awareness on prostate cancer and early detection by PSA started at the same time as the design for studies on population-based

screening was made, individual screening (or 'wild' screening) took place from around 1990 onwards. This resulted not only in some contamination of the RCTs but especially in a significant increase of overall prostate cancer incidence. The amount of overdiagnosis of indolent cancer started to be quantified after several years from the intermediate results of RCT analyses. Extrapolation of these data was used to improve clinical decisions for individual screening. As it was seen that risk stratification based on baseline PSA appeared an option in order to optimize the harm-benefit trade-off in a PCa screening program [van Leeuwen], this was transferred to risk calculators for individual men that wanted to be screened.

3.5.1 Risk Assessment Strategies

Men with low initial PSA values are unlikely to benefit from early detection. This observation allows making specific individualized risk stratifications after measuring men's PSA baseline. As a result, men at high risk can be informed about their more favourable harm-benefit trade-off in respect to the overall NNS and NNT presented by the randomized controlled trials. Men may present at the outpatient clinic of physicians and urologists at any age and with any previous history of screening. Therefore, relevant risk factors need to be addressed, such as previous PSA and negative biopsies in order to analyse their current risk. Based on their individual and objective assessment, they should obtain an advice and decide how to continue. For example, the relation between concentrations of PSA at age 60 and subsequent diagnosis of clinically relevant PCa in an unscreened population showed that men aged 60 with PSA concentrations below the median (≤1 ng/ml) were unlikely to have clinically relevant PCa (0.5% risk of metastasis by the age 85 and 0.2% risk of death from PCa). The risk of dying from PCa for men with PSA lower than 1.0 ng/ml after 9 years follow-up was 0.1% (Vickers et al. 2010a).

Figure 3.1 shows the various levels of the ERSPC risk calculator, and a screenshot from the free accessible website (www.prostatecancer-riskcalculator.com).

3.5.2 Nomograms

Risk-based strategies for biopsy, as provided by the ERSPC PCa risk calculator (www.uroweb.org; www.prostatecancer-riskcalculator.com), or the PTCP risk calculator (www.ptcp.org) are based on study cohorts that are biased by the upfront selection of men that undergo prostate biopsies. It is likely best to use the set of ERSPC calculators as a whole, in the geographical area in which they have been validated (Northern Europe), while using the PTCP calculator, which also includes information on black Americans, in the USA. Nevertheless, for white Americans, the ERSPC risk calculator performed better in white Americans compared to the PTCP calculator, as the ERSPC instrument includes prostate volume in its calculation of probability (Bergh et al. 2008). Direct head to head comparisons of the two risk calculators have been published recently and show that overall, the ERSPC risk calculator has better discriminatory capability (Cavadas et al. 2010; Trottier et al. 2010; Oliveira et al. 2011). It has to be realized that actors not measured by current models are, for example, baseline quality of life, comorbidity, life expectancy, and treatment preference, and this may form a limitation to (Cooperberg 2008).

The importance of comorbidity for PCa treatment decisions, or even for screening, was recently highlighted by Albertsen et al. (2011), illustrating the influence of the Charlson score (Charlson et al. 1994) on overall and tumour-specific survival. For example, for men aged 66–75 diagnosed with a PCa staged T1c with a Gleason sum of 7 or less, a Charlson score of 2 or more increases overall mortality by approximately threefold over a period of 20 years (10-year mortality rate per 100 from 28.8 to 83.1) compared to a Charlson score of 0. This while the tumour-specific mortality rate remained stable with 4.8–5.3%. Using this comorbidity information for individual predictions is preferable to overall statistics of life expectancy on a population level that provide a robust but only very general impression.

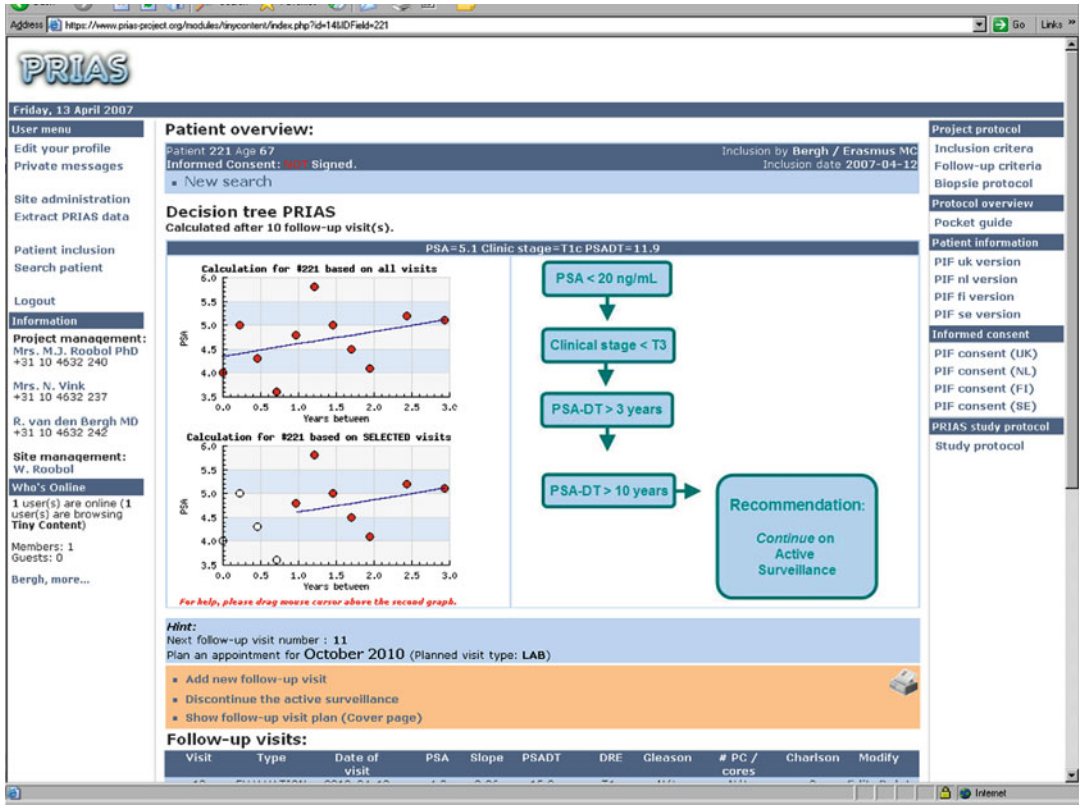

Fig. 3.1 Various levels of the ERSPC risk calculator, and screenshots (From the free accessible website [www.prostate-cancer-riskcalculator.com])

In order to implement nomograms into the daily urological routine, a series of validations needs to be followed after the initial construction phase. Traditionally, a nomogram would be tested on an independent but relevant population set. Next, an evaluation of the implementation should take place to analyse the impact of the instrument as a decision tool on the actions taken by patients and physicians. The compliance with biopsy recommendations provided by the ERSPC prostate cancer risk calculator was evaluated by Van Vugt (Van Vugt et al. *abstract*, *2011 EAU*, *article submitted accepted BJUI*). In a setting in which 291 men with a request for PCa screening agreed to submit themselves to the use of this risk assessment instrument, 84% were compliant with the advice to biopsy or to refrain from it. Remarkably, the most important reason for non-compliance of the 31 of 119 men that were advised not to be biopsied was the reluctance of the physicians due to the PSA level as a single parameter. It showed that the traditional biopsy threshold of PSA over 3 ng/ml overruled the advice given by the nomogram. Analysis of the compliance to a risk calculator on the probability of low-risk, or indolent, PCa with subsequent active surveillance was also performed by Van Vugt and showed similar results (in preparation 2011).

3.5.2.1 Improving Nomograms

Candidate markers at presence are the kallikreins (Vickers et al. 2010b) proPSA (Bangma et al. 2010), PCA3 (Ankerst et al. 2008), or histologic markers (Wolters et al. 2010b). However, readers of manuscripts describing the additional the value of a new biomarker in an existing nomogram should be aware of the fact that this new marker should be judged by its impact on the accuracy of a prognostic model, which is best measured by multiple criteria such as change in concordance index, calibration, impact on predictions, and

decision curve analysis (Nguyen and Kattan 2011). Next to biomarkers, imaging is expected to play a larger role in the initial assessment of risk, as it is to be in the monitoring of men on active surveillance (Sciarra et al. 2011).

3.6 Conclusions and Way to Go

Obviously, two of the most important negative side effects of individual and mass screening for PCa are unnecessary invasive testing (prostate biopsy) and overdiagnosis with the related overtreatment. Individual detection and mass screening protocols differ primarily in their way how information about early detection is presented, whether on an individual way by a personal health professional (nurse practitioner, physician), or by public information generated by the health authorities by the public media. The latter may prevent an individual bias but might also not be efficient to identify men at higher risks. Risk-based strategies might be applied in both situations by means of risk calculators derived from population-based studies. Algorithms will offer possibilities to increase specificity at every decisional step during screening, rescreening, diagnosis, and initial treatment, but studies need to be continued in order to decrease the confidence intervals around every step. Algorithms incorporating other variables next to PSA (from genomic, proteomic, or metabolomic analysis of serum, urine, or tissue biopsies) to make accurate risk assessments and predict the chance of having PCa with the possibility to differentiate between indolent and potentially aggressive disease are warranted.

It is obvious that future mass screening protocols have to be adjusted to the currently available information. Mass screening becomes more individualized, while the methods for individualized screening will be closely related to screening protocols of the population. For example, if population-based screening is considered not to be a reasonable option to reduce a 0.2% risk of cancer-specific death after 25 years, systematic repeated screening should not be applied to men with low baseline serum PSA values. Screening algorithms have already been developed and validated (Ankerst et al. 2008; Chun et al. 2009; Roobol et al. 2010b). Nevertheless, future studies must further develop an accurate individualized screening algorithm.

Harm-benefit trade-offs are likely to differ between populations in Europe. The PCa deaths rates in the Nordic European countries (Norway, Sweden, Denmark, Iceland, and Estonia) are five times higher than those seen in several Central and Eastern European countries. National authorities will have to link up with regional study results in order to decide on their national screening policies and the design of guidelines.

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Anatomo-Pathology

4

Theodorus H. Van der Kwast

Contents

T.H. Van der Kwast, M.D., Ph.D., FRCPC
Department of Pathology, University Health Network and University of Toronto, Toronto, Canada
e-mail: theodorus.vanderkwast@uhn.on.ca

4.1 Gross Anatomy of the Prostate: Clinical Importance

For several reasons, interest in the anatomy of the prostate gland has been increasing during the last decade. The site of origin of a prostate cancer and its localization within the prostate gland may affect the diagnostic process and influence treatment considerations. Also the recent advent of focal therapy makes it more imperative to establish the exact localization and extent of the prostate cancer or cancers. For adequate pathological staging, it is important to have an understanding of the boundaries of the prostate, particular at its anterior border, at its apex where the prostate borders the skeletal muscle constituting the striated or urethral sphincter and its proximal (bladder neck) border where the prostate merges with the detrusor muscle of the urinary bladder (Hammerich et al. 2009). Finally, ongoing improvements in imaging of the prostate also have led to a more thorough analysis of the gross anatomy of the prostate gland. The official anatomic terminology of the prostate and its contiguous structures has been revised several times in the past, and current recommendations try to accommodate clinical concepts within an updated terminology (Myers et al. 2010) as highlighted in a recent authoritative and well-illustrated review of the topic (Walz et al. 2010).

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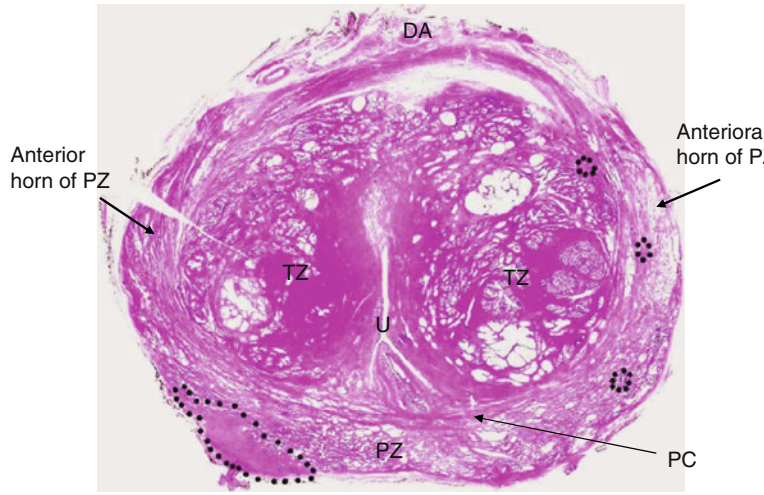

Fig. 4.1 Wholemount section of radical prostatectomy specimen, with multifocal prostate cancer (marked by *dotted line*). *DA* detrusor apron, *PC* posterior commissure, *PZ* peripheral zone, *TZ* transition zone, *U* urethra. The index tumor is located in the posterior peripheral zone, and one small cancer is located in the transition zone of the anterior prostate

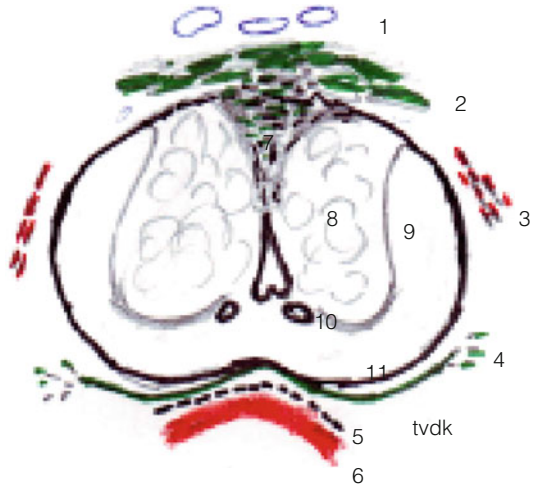

Fig. 4.2 Schematic drawing of the main structures of the mid prostate and its surroundings. The rectal fascia (*5*) is separated from Denonvilliers fascia (*4*) by the mesorectal plane. Legend: *1*=dorsal vascular complex, *2*=detrusor apron, *3*=levator ani skeletal muscle, *4*=Denonvilliers fascia, *5*=rectal fascia, *6*=rectal wall, *7*=anterior fibromuscular stroma, *8*=transition zone, *9*=anterior horn of peripheral zone, *10*=ejaculatory duct, and *11*=peripheral zone (posterior)

4.1.1 The Boundaries of the Prostate

The prostate is situated between the rectum at the posterior surface and smooth muscle fibers originating from the outer, longitudinal detrusor muscle of the bladder (detrusor apron) at its anterior surface (Figs. 4.1 and 4.2).

4.1.1.1 Denonvillier's or Posterior Prostatic Fascia

The posterior surface of the prostate is demarcated by Denonvillier's fascia, a continuous fibromuscular layer that covers the posterior surface of the prostate enveloping the seminal vesicles. Its superior (cranial) part merges with the subperitoneal connective tissue of the urinary bladder. Denonvillier's fascia has previously been referred to as rectovesical septum, although this fascia is not really a septum and it is also not belonging to the rectum or bladder wall. More recently, Denonvillier's fascia has been coined posterior prostatic and seminal vesicle fascia (Walz et al. 2010). Current consensus is that Denonvillier's fascia originates from the fusion of the two walls of the embryological peritoneal cul-de-sac, analogous to the female rectovaginal septum, but these two layers cannot be distinguished during surgery (Lindsey et al. 2000). Denonvillier's fascia consists of a single layer of fibrous tissue, loose connective tissue, and smooth muscle of variable caliber (Fig. 4.3). More laterally, the fascia becomes fragmented and disappears. The thickness of the fascia is highly variable, becoming thinner at advancing age. When a surgeon performs an interfascial or extrafascial dissection during prostatectomy, the Denonvillier's fascia will be visible in the pathology specimen. The latter dissections

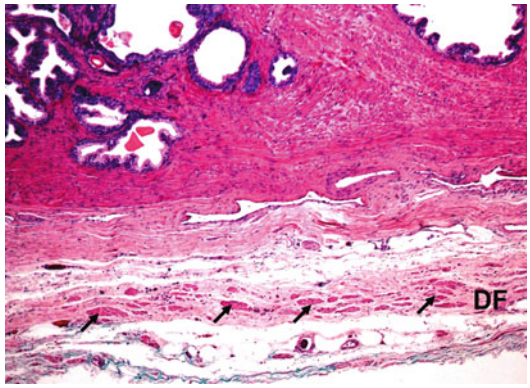

Fig. 4.3 Section of posterior margin of the prostate, displaying Denonvilliers fascia (*DF*) with small bundles of smooth muscle (*arrows*) embedded in fibrous tissue of low cellularity. Here, Denonvilliers fascia is separated from the outer prostate by a thin layer of loose connective tissue

have an optimal oncological outcome, because Denonvillier's fascia is adherent to the prostate at its mid portion. Further, prostate cancers rarely if at all extend beyond Denonvillier's fascia (Villers et al. 1993). To preserve the neurovascular bundle as good as possible, an intrafascial dissection may be chosen, obviously with an increased risk of prostate incision (Walz et al. 2010).

4.1.1.2 The Endopelvic Fascia and Pubovesical Ligaments

On the anterior (ventral) aspect of the prostate is the "endopelvic fascia," representing a sheet of tissue of variable thickness covering the prostate from its base to the apex, while extending laterally and inferiorly toward the pubic bones of the symphysis, where it connects with and is reinforced by the fibers of the puboprostatic or pubovesical ligaments (Myers et al. 2010). The latter contains fibrous tissue but also smooth muscle of longitudinal detrusor muscle origin. The composition and structure of the endopelvic fascia can display much individual variation.

Cross sections of a prostatectomy at the mid prostate at the site of the verumontanum (seminal colliculus), harboring the orificium of the ejaculatory ducts show at its anterior surface a mixture of bundles of smooth muscle (detrusor apron), skeletal muscle, likely an extension of the levator ani and fibroadipose tissue, adhered to the prostate at the midline to the anterior fibromuscular septum or anterior commissure (Fig. 4.2). More anterior, adipose tissue may be present, containing the veins and arteries of the dorsal vascular complex (Fine et al. 2007; Myers et al. 2010). The anterior fibromuscular septum, separating the left and right halves of the prostate varies in thickness and merges imperceptibly with the extraprostatic tissue in the midline (Fig. 4.2). As a consequence, it may be challenging for the pathologist to determine the presence of extraprostatic extension of an anterior localized adenocarcinoma (Fine et al. 2007; Magi-Galluzzi et al. 2011). More lateral, adipose tissue may occasionally be present between the prostate and the endopelvic fascia, facilitating the identification of extraprostatic extension of an anterior carcinoma.

4.1.1.3 The Inferior Boundary of the Prostate

The prostate apex represents the site where the intermediate or membranous part of the urethra exits the prostate. This part of the urethra is surrounded by the external urethral sphincter composed of thin caliber skeletal muscle fibers. The external urethral sphincter is a distinct muscular structure, separated from the pelvic floor musculature by a thin fibrous layer (Stolzenburg et al. 2007). The sphincter is horseshoe-shaped, with only collagenous and elastic fibrous tissue posteriorly. Historically, the terminology of urogenital diaphragm was used to describe the external striated urethral sphincter, but this was shown to be an artifact of cadaveric dissection (Myers et al. 2010). Cross sections of the prostate apex of a radical prostatectomy specimen show an intermixture of benign prostatic glandular tissue with skeletal muscle fibers at the anterior part of the specimen, obfuscating a clear demarcation between prostate and sphincter tissue. For this reason, extension of a carcinoma between skeletal muscle fibers of the apex is not considered a manifestation of extraprostatic extension.

4.1.2 Prostate Lobes

Clinically, during digital rectal examination, a lobulation of the prostate may be noted. This lobulation of the prostate may be the consequence of (1) an anatomic phenomenon, that is, the indentation of the rectal surface, and (2) the preferential growth of the transition zone in elder men, commonly referred to as benign prostatic hyperplasia (Myers et al. 2010). The degree of the furrow of the rectal surface of the prostate was found to be dependent on the closeness of the ejaculatory ducts to the posterior surface of the prostate. Thus, anatomic variations of the localization of the ejaculatory ducts may contribute to the outside appearance of the prostate. In the mid-posterior urethral position, benign prostate hyperplasia may result into median lobe hyperplasia, also known as Home's lobe, protruding as a ball valve into the bladder lumen just inferior to the trigone. Rarely, a discrete midline anterior benign prostate hyperplastic lobule may be seen mid anterior at the bladder neck. Another cause of a lobular appearance may be the development of a nodule as the consequence of a carcinoma. Although the vast majority of contemporary carcinomas do not present themselves as a nodule, prostate cancers identified by positive digital rectal examination are pathologically advanced in over 50% of men (Gosselaar et al. 2008).

4.1.3 McNeal's Four Prostate Regions

In 1988, McNeal proposed a model of zonal anatomy of the prostate gland, abolishing the previous concept of a lobular organization of the gland structure (McNeal 1988). In his model, the prostate is divided into four regions, that is, (1) the anterior fibromuscular stroma, (2) the central, (3) the transition, and (4) the peripheral zone (Figs. 4.1 and 4.2).

4.1.3.1 The Anterior Fibromuscular Stroma

The anterior fibromuscular stroma represents dense fibromuscular tissue, stretching between the anterior part of the urethra to the outer anterior margin of the prostate, merging with the internal sphincter of the bladder neck and with the striated muscle of the external sphincter at the apex. The distal (apex) portion of the anterior fibromuscular stroma is rich in striated muscle and is important in voluntary sphincter function, whereas in its more superior end, smooth muscle becomes a dominant feature with an important role in involuntary sphincter functions (Hammerich et al. 2009). The anterior fibromuscular stroma contains few if any prostatic glands. Maintenance of its integrity may be important for the outflow resistance of urine.

4.1.3.2 The Central Zone

The central zone is a cone-shaped area between the ejaculatory ducts and the bladder neck, situated posterior to the ascending prostatic urethra. Histologically, the prostatic glands in the central zone have a distinct and more complex architecture often with cribriform and papillary features as compared to those in the other zones. For pathologists, it is important to recognize central zone glands, because their nuclear features may resemble high-grade prostatic intraepithelial neoplasia (H-PIN), a precursor lesion of prostate cancer (Bostwick et al. 2004). Confusingly, radiologists may occasionally refer to "central gland" when actually describing the combined periurethral transition and central zone, while they usually do not separately report on the "central zone."

4.1.3.3 The Transition and Peripheral Zone

The transition zone is mainly located lateral and anterior of the urethra (Figs. 4.1 and 4.2) and may be separated from the peripheral zone by a band of denser fibromuscular stroma, that is, the posterior commissure (Myers et al. 2010). The largest amount of peripheral zone tissue is at the inferior (apex) and posterior part of the prostate, but it extends as the lateral horn of the peripheral zone to the anterior part of the prostate. Thus, the anterior prostate comprises both a peripheral zone (lateral) and transition zone (mediolateral) component, as well as the midline anterior fibromuscular stroma (Fine et al. 2007). It should be noted

that the definition of the anterior region, e.g., anterior to the urethra (Bott et al. 2002), varies among authors.

4.1.4 Prostate Zones and Cancer

About 70% of prostate cancers originate in the peripheral zone, most of them at a posterior or posterolateral localization (McNeal 1988). This coincides with the frequent occurrence of the cancer precursor H-PIN in the peripheral zone and its much rarer occurrence in the transition zone (Bostwick et al. 2004). In several patient series, it was shown that, in spite of significantly higher PSA levels as well as greater tumor volume when compared with those of peripheral zone cancers, tumors from the transition zone showed similar biochemical cure rates following radical prostatectomy (Van der Kwast et al. 2011). This would suggest a less aggressive phenotype for transition zone cancers when compared to tumors from the peripheral zone, but contradictory findings have also been reported. Augustin et al. (2003) reported that the zonal location was not an independent prognostic factor on multivariate analysis.

The determination of the zonal origin of prostate carcinoma by the pathologist is more challenging on standard quadrant sections of prostatectomy specimens when compared to whole-mount sections (Fine et al. 2007). Often a prostate cancer involves both the peripheral and transition zone, and presence of histological features typical for some of the transition zone cancers and/or the presence of the largest proportion of a carcinoma in the transition zone might occasionally provide an argument that the tumor has arisen within the transition zone.

4.2 Microscopic Anatomy of the Prostate

Histologically, the prostate glands and ducts in all zones share a similar cellular composition; they are lined by an inner layer of luminal or secretory cells and an outer rim of basal cells. Each of the three anatomically distinct zones of the prostate has its own set of periurethral main prostatic ducts. Their lining often displays a hyperplasia of basal cells, and here the luminal cells may display a more columnar (ductal) appearance (Pickup and Van der Kwast 2007). The periurethral ducts give off branches, with tributaries adopting the epithelial morphology of prostatic acini as they progress upstream from the urethra. Here, the ducts and acini are no longer distinguishable. Interspersed within the glandular lining of the ducts and acini are the neuroendocrine cells which secrete regulatory neuropeptides. Only the luminal cells express prostate-specific antigen, which is under androgen regulation. Androgen receptors can be found in the nuclei of luminal cells and fibromuscular stromal cells (Fig. 4.4), whereas the neuroendocrine cells and most of the basal cells lack androgen receptors (Krijnen et al. 1993).

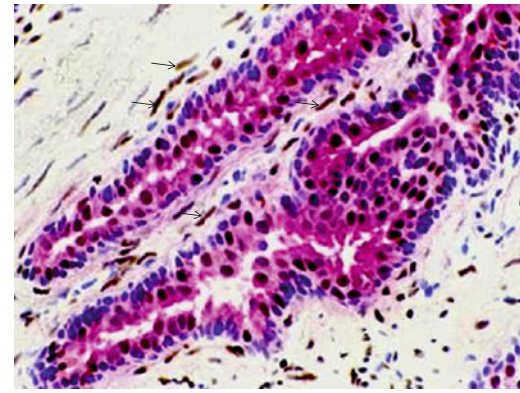

Fig. 4.4 Microscopic image of prostate tissue immunostained for PSA (*red*) and androgen receptor (*brown*). *Blue* nuclei are unstained. Both stromal cells (*arrows*) and PSA-positive luminal cells are positive for androgen receptor, while basal cells are negative for androgen receptor

4.2.1 Prostate Zones: Age-Related Microscopic Changes

Although morphologically the peripheral and transition zone show a strong resemblance, expression array studies have shown consistent differences in expression patterns (Van der Heul-Nieuwenhuijsen et al. 2006). There are also physiological differences, which become manifest during aging and under conditions of androgen deprivation

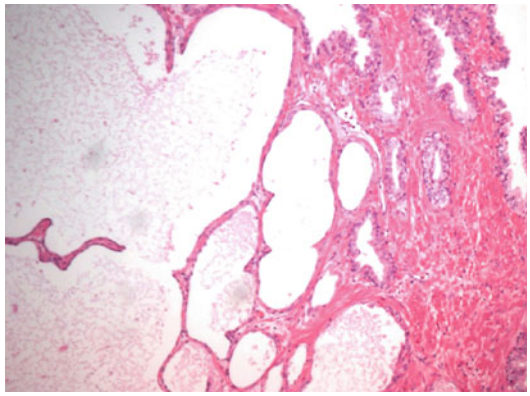

Fig. 4.5 Microscopic image of prostate glands showing cystic atrophy, adjacent to normal prostate glands at the *right*

(see Sect. 4.2.2). In aging men, hyperplasia of both the glandular and/or fibromuscular component occurs almost uniquely in the transition zone. Infarctions do also occur more frequently in the transition zone of the prostate, particularly in enlarged prostates due to benign prostate hyperplasia (Brawn et al. 1994). In comparison with the transition zone, the peripheral zone is more often subject to glandular atrophy. Aging-related atrophy as seen in the peripheral zone mostly has a focal distribution. Various histological forms of atrophy may coexist, including partial atrophy, cystic atrophy (Fig. 4.5), sclerotic atrophy, and hyperplastic atrophy or postatrophic hyperplasia. It was recently shown that partial atrophy and focal atrophy are generally not associated with chronic inflammation (Billis et al. 2010). Some postulated mainly on the basis of circumstantial evidence that chronic inflammation associated with glandular atrophy, that is, postinflammatory atrophy, is a condition underlying the subsequent development of cancer (De Marzo et al. 2004), but evidence for this view is inconclusive.

4.2.2 Androgen Deprivation-Induced Changes

It is well-established that long-term use of aromatase inhibitors, such as Dutasteride, leads to an average reduction in prostate gland volume by 17.5% after 2 years, mainly attributed to its effect on BPH (Andriole et al. 2010). Microscopic changes of the normal tissues during long-term administration of aromatase inhibitors have not been described. This is in contrast to the pronounced effects of antiandrogens and lutein hormone releasing hormone agonists. After androgen deprivation to castration levels, the entire prostate will shrink in size to about 80% of the original size within 3 months of treatment. This reduction in volume is associated with a profound remodeling of the prostate tissue (Têtu et al. 1991). This remodeling is different for the peripheral and transition zone of the normal prostate: in the peripheral zone, a general atrophy of prostatic glands is noted, that is, flattening of the luminal cells resting on a single conspicuous layer of cuboid basal cells, while the glands lose their infoldings and they have a more flattened appearance. In contrast, the transition zone glands display more prominent basal cell hyperplasia, and the glands become smaller and more rounded. Castration-level androgen deprivation is also causing periprostatic fibrosis, which may impact surgery in case of the now obsolete neoadjuvant therapy for more advanced prostate cancer (Têtu et al. 1991).

4.3 Precursor Lesions of Prostate Cancer (H-PIN)

A few histopathologically distinct glandular proliferations have in the past been proposed as a precursor lesion for prostate cancer. They include H-PIN, atypical adenomatous hyperplasia (adenosis), and intraductal carcinoma of the prostate (IDC-P). Only H-PIN is now commonly recognized as a true prostate cancer precursor lesion, while the jury is still out for IDC-P and adenosis is now considered an unlikely prostate cancer precursor.

4.3.1 High-Grade Prostatic Intraepithelial Neoplasia

H-PIN is the term used to denote the presence of dysplastic features in the luminal cells lining prostatic glands or ducts, while retaining the antecedent

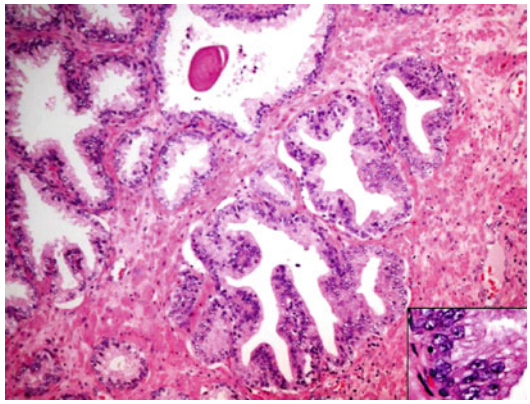

Fig. 4.6 Micrograph showing H-PIN at the *right* and benign glands *upper left*. H-PIN maintains the normal glandular architecture, but its cytoplasm is more basophilic. The *inset* illustrates the prominent nucleoli which are a hallmark of H-PIN

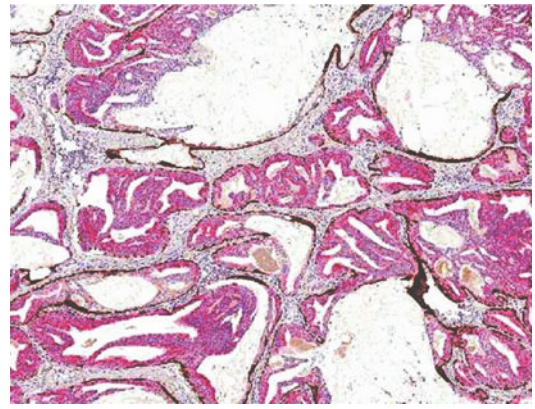

Fig. 4.7 Low-power micrograph of an extensive intraductal carcinoma of the prostate immunostained for alpha-methyl coenzyme A (*red*) racemase and the basal-cell marker high-molecular weight keratin (*brown*). Glands and ducts are distended by large numbers of neoplastic cells (*red*), but remain lined by basal cells (*brown*)

architecture of benign glands (Fig. 4.6). The hallmark of H-PIN is the presence of prominent nucleoli in cells lining prostatic glands or ducts with a luminal (but not basal) cell morphology and location (Bostwick et al. 2004). Montironi et al. (2005) reported that H-PIN was found in association with invasive carcinoma in 70% of cystoprostatectomy specimens with an incidental prostate cancer and in 50% of specimens without prostate cancer. Because of this association of H-PIN with carcinoma, their similarity in cytonuclear features, their close spatial association in the prostate, and shared specific genetic changes, H-PIN is considered as precursor for prostate cancer (Epstein 2009). It remains, however, unclear which proportion of H-PIN actually progresses over time to invasive prostate cancer.

4.3.2 Intraductal Carcinoma

Intraductal carcinoma of the prostate (IDC-P) is a histopathologically distinctive entity characterized by malignant cells expanding the lumen of prostatic ducts and acini, while at least a partial rim of basal cells continues to be present (Guo and Epstein 2006; Pickup and Van der Kwast 2007). IDC-P is commonly associated with conventional acinar prostatic adenocarcinoma, but in rare cases, IDC-P may be predominant (Fig. 4.7) or even lacking an invasive component (Robinson and Epstein 2010). Originally, it was considered most likely that IDC-P represents the intraductal spread of frankly invasive carcinoma, but the possibility that it could represent a prostate cancer precursor was also entertained (Kovi et al. 1985; McNeal and Yemoto 1996). Particularly, the occasional finding of an extensive IDC-P with no or limited invasive carcinoma would be in line with the view that IDC-P could represent a precursor lesion, developing from a subset of H-PIN. Mostly, IDC-P can be reliably distinguished by pure morphological criteria from H-PIN, mainly based on the filling up and distension of the lumen by the dysplastic cells in IDC-P (Guo and Epstein 2006).

Several studies have reported that IDC-P represents an independent prognosticator for early biochemical recurrence after radical prostatectomy (McNeal and Yemoto 1996; O'Brien et al. 2011).

4.4 Prostate Cancer

Prostate cancer is a very common finding in elder men, and its clinical course is highly variable with most cancers running an indolent course. The histopathological features of prostate cancer and its spatial extension have been shown to

be the strongest predictors of their behavior, as well as surgical margin status after radical prostatectomy.

4.4.1 Types and Variants of Adenocarcinoma

Apart from the vast majority of conventional acinar adenocarcinomas, separate types of prostate cancer may occasionally be identified as well. The latter may reveal a different behavior, or they may occur as a consequence of earlier treatment for prostate cancer. Variants of prostate cancer belong to the group of conventional acinar adenocarcinoma, and their description is of diagnostic help for the pathologist, and they also may have a distinct clinical behavior. As of yet, molecular typing has not led to the identification of distinct genotypes of prostate cancer with a clearly distinct morphologic counterpart. This stands in contrast to findings in, e.g., breast cancer.

4.4.1.1 Conventional Acinar Adenocarcinomas and Its Variants

Conventional acinar adenocarcinoma is the most common type of prostate cancer, representing over 95% of cancers. This type of adenocarcinoma displays a remarkable morphologic heterogeneity, which may coexist within the same tumor focus. Most common is the formation of small-to-medium-sized glands, but these glands may fuse or form cribriform or ragged sheets of cells. These architectural patterns are reflected in the histopathological grading of the conventional acinar adenocarcinomas. Variants of conventional acinar adenocarcinoma are mucinous or colloid carcinoma, the more rare signet ring cell carcinoma, lymphoepithelioma-like carcinoma, and the sarcomatoid variant (carcinosarcoma), as well as the pseudohyperplastic and atrophic variants (Grignon 2004). The latter two may be a diagnostic pitfall, particularly when encountered isolated in a prostate biopsy. Most of these variants occur in the context of a conventional acinar adenocarcinoma. The mucinous variant requires that at least 25% of the carcinoma displays a mucinous morphology (Epstein et al. 2004). All variants follow essentially the same Gleason grading rules (see Sect. 4.2) as the conventional acinar adenocarcinomas.

4.4.1.2 Ductal Adenocarcinoma

Although in the current WHO classification of prostate cancer, ductal adenocarcinoma is coined as a distinct type of prostate adenocarcinoma, some would consider it as a variant of the conventional adenocarcinoma. Ductal adenocarcinoma as a dominant pattern accounts for a mere 0.2–0.8% of all prostate cancers (Grignon 2004; Yang et al. 2004). They typically involve the large periurethral ducts and may become clinically manifest as an exophytic papillary mass in the prostatic urethra. Ductal adenocarcinoma is, however, more frequently (in up to 3% of prostate cancer diagnoses) found as a minor component of conventional-type (acinar) adenocarcinoma. In >80% of prostatic ductal adenocarcinomas, an associated acinar adenocarcinoma is found, usually in close proximity to the ductal component. Consistent with the features of large periurethral duct epithelium (see Sect. 4.2), the columnar neoplastic cells form a pseudostratified epithelium, often lining papillary structures with true fibrovascular cores and their nuclei are mostly elongated or oval with often a single macronucleolus. Ductal adenocarcinoma can often be found extensively growing within prostatic ducts with the morphology of intraductal carcinoma or even comedocarcinoma (Pickup and Van der Kwast 2007).

4.4.1.3 Neuroendocrine Carcinoma

Poorly differentiated neuroendocrine carcinomas of the prostate may also be referred to as small cell or large cell (undifferentiated) carcinomas (Evans et al. 2006), but the first terminology is now preferred. Notably, neuroendocrine differentiation of scattered cells and small foci of neuroendocrine cells is a common phenomenon in conventional acinar adenocarcinoma (Krijnen et al. 1993). In poorly differentiated neuroendocrine carcinoma,

large sheets of tumor cells, lacking glandular differentiation, with large nuclear/cytoplasm ratio and hyperchromatic nuclei give the tumor a basophilic appearance. In about 50% of the cases, they are admixed with a conventional adenocarcinoma (Grignon 2004). Although still rare, they are more common in patients who have been treated with androgen deprivation. A metastatic origin from another body site must be excluded when the tumor occurs in its pure form. Immunohistochemistry is helpful to demonstrate its neuroendocrine differentiation, using antibodies, e.g., against synaptophysin and chromogranin A. They generally lack androgen receptors or PSA, whereas the lung/thyroid cancer marker TTF-1 is commonly positive (Evans et al. 2006), but about 50% of them may overexpress the prostate-specific marker ERG (Williamson et al. 2011). Their clinical behavior is as aggressive as poorly differentiated neuroendocrine cancers from any other body site, whether in its pure form or admixed with conventional adenocarcinoma, and treatment is the same.

4.4.1.4 Other Rare Prostate Cancer Types

Other rare types of prostate cancer include a.o. basal cell carcinoma, squamous cell carcinoma, and adenosquamous carcinoma of the prostate (Grignon 2004). Basal cell carcinomas also referred to as adenoid cystic carcinomas are extremely rare. Some of them show features such as comedonecrosis typical of the aggressive basaloid carcinomas, and others have a more bland morphology.

Primary squamous cell carcinoma originating in the prostate is very rare, and propagation of a urothelial or squamous cell carcinoma derived from the urinary bladder or urethra should be excluded. By definition, squamous cell carcinomas do not contain glandular or urothelial components, and they may originate from the periurethral glands or from the basal cells of prostatic glandular acini differentiating into squamous cells. Adenosquamous carcinoma of the prostate is a carcinoma, composed of a blend of conventional adenocarcinoma and squamous cell carcinoma. About 50% of the reported adenosquamous carcinomas occur in prostate cancer patients subsequent to androgen deprivation therapy and/or radiotherapy. Both squamous and adenosquamous carcinomas tend to metastasize rapidly with a predilection for the bones.

4.4.2 Gleason Grading of Prostatectomy Specimens

The Gleason grading system, based on architectural and not on cytonuclear features, continues to be the strongest prognosticator of prostate cancer (Eggener et al. 2011). This system accounts for the heterogeneity of prostate cancer by identifying five grades on the basis of the tumor architecture, ranging from 1 (most differentiated) to 5 (least differentiated). Grades 1 and 2 are typical of the transition zone with grade 1 now virtually obsolete (Epstein et al. 2005). By adding the most dominant growth pattern (the primary Gleason pattern) to the next most dominant growth pattern (the secondary Gleason pattern), a nine-tiered total score of ascending aggressiveness from 2 to 10 is obtained. Figure 4.8 displays the four frequent, but distinct patterns of cancer constituting a grade 4 prostate cancer. When the high-grade (Gleason grades 4 or 5) component constitutes less than 5% of the cancer volume, it is not incorporated in the Gleason score (5% rule), but it will be reported as a tertiary grade. A meta-analysis by Harnden et al. (2007) has shown convincingly that presence of a tertiary grade 5 has an unfavorable prognostic impact. On the other hand, most studies have shown that a <5% grade 4 component in an otherwise Gleason score 6 (3+3), carcinoma does not adversely affect the prognosis. The biological behavior of a tumor is more related to the proportion of poorly differentiated (grade 4/5) components within the tumor (Vis et al. 2007; Cheng et al. 2005) than the Gleason score itself, even if by current convention the very heterogeneous Gleason score 7 category is subdivided in those with a dominant pattern 3, that is, Gleason score 7 (3+4), and those with a dominant pattern 4, that is, Gleason score 7 (4+3). Table 4.1 gives an overview of the Gleason grades for the various types and variants of prostate cancer.

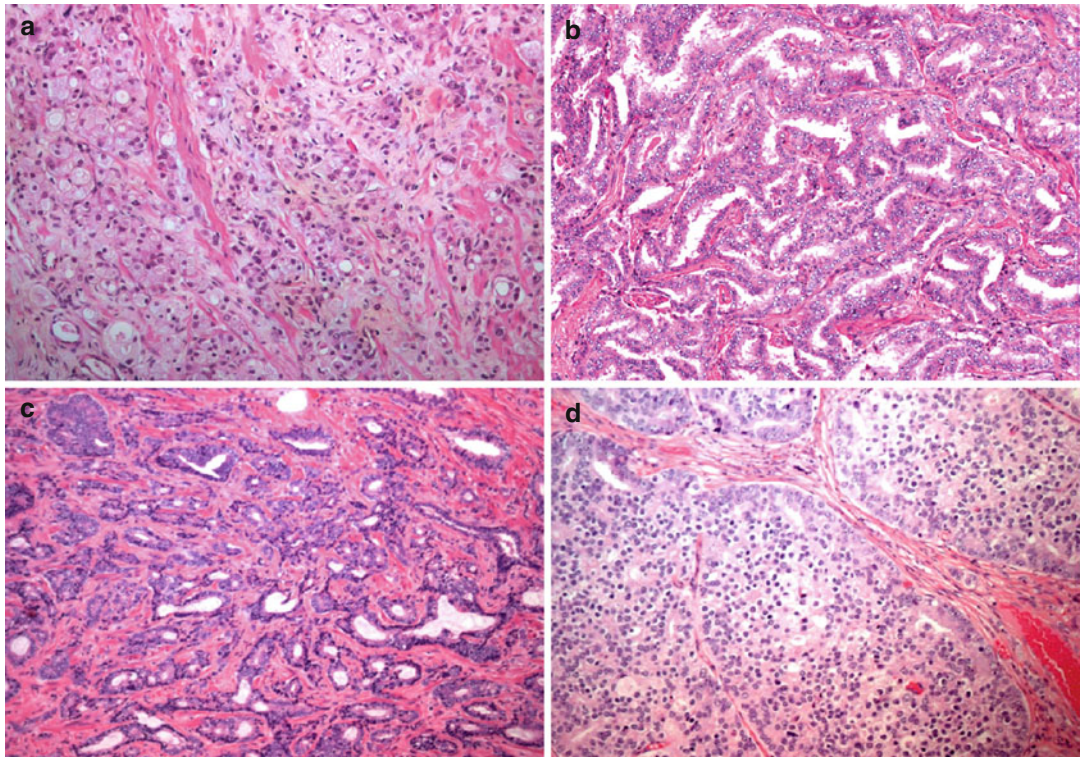

Fig. 4.8 The heterogeneity of Gleason grade 4 prostate cancer is displayed in these four micrographs: small glandular nests and strands (**a**), large fused glands (**b**), small fused glands (**c**), and large cribriform structures (**d**)

Table 4.1 Types and variants of prostate cancer and Gleason grade

	Type or variant	Gleason grade
Type	Ductal adenocarcinoma	Grade 4, if comedonecrosis grade 5
	Basal cell or adenoid cystic	Not applicable
	Squamous or adenosquamous	Not applicable
	Poorly differentiated neuroendocrine	Not applicable
Variant	Mucinous[a]	Often grade 4
	Pseudohyperplastic[a]	Mostly grade 3
	Foamy gland[a]	Mostly grade 3
	Atrophic	Grade 3
	Sarcomatoid	Grade 5
	Signet ring cell	Grade 5

[a]For these variants, the Gleason grade is determined by the architecture of the glandular neoplastic cells

4.4.3 Staging of Prostatectomy Specimens

The objective of staging is to (1) group malignancies which have an apparently similar prognosis so as to inform a uniform therapeutic approach, (2) assist clinical trials and research studies by defining homogeneous patient populations, and (3) promote the comparability of clinicopathologic data from multiple hospitals and research groups.

In general, pathologic (sub)staging of tumors should maintain symmetry with clinical (sub) staging, thus allowing direct comparison of

cases. The 2010 TNM system distinguishes organ-confined (pT2) and non-organ-confined prostate cancers (pT3a,b/pT4) to describe the extent of prostate cancer in a radical prostatectomy specimen (International Union Against Cancer (IUCC) 2009).

4.4.3.1 Stage pT2 Prostate Cancer

Organ-confined prostate cancers are stage pT2, which means they are within the confines of the prostate, including its outer fibromuscular border. Substaging of pT2 cancers is now optional, given its lack of clinical and academic value (Van der Kwast et al. 2011). Although clinical substaging of cT2 prostate cancer has clinical value, they do not correspond with the pathological substages.

4.4.3.2 Stage pT3a Prostate Cancer

Extraprostatic extension can be diagnosed unequivocally when tumor is in contact with adipose tissue, but also in the posterolateral area extraprostatic extension can be determined when tumor is within loose connective tissue or perineural spaces of the neurovascular bundles even in the absence of adipocytes. Extraprostatic extension may also be recognized as a distinct tumor nodule within desmoplastic stroma that bulges beyond the normal contour of the gland (Magi-Galluzzi et al. 2011). In the apex, benign glands are frequently admixed with striated muscle in the apex, and as a consequence, the finding of malignant glands within striated muscle does not represent extraprostatic extension. Further, in the current era of bladder-preserving prostatectomy, invasion into the bladder neck is no longer considered as stage pT4, but instead pT3a (Aydin et al. 2004).

At the anterior fibromuscular stroma, the prostate blends in with extraprostatic smooth muscle, and here, extension beyond the prostate contour or adipose tissue at the sides (Bouyé et al. 2009) should help determine the presence of extraprostatic extension (Figs. 4.9 and 4.10). Since in contemporary series, at least 50% of patients with extraprostatic extension at radical prostatectomy do not show tumor progression over a 10-year follow-up period, ways to improve the prognostication of extraprostatic extension were examined (Magi-Galluzzi et al. 2011). Accordingly, focal

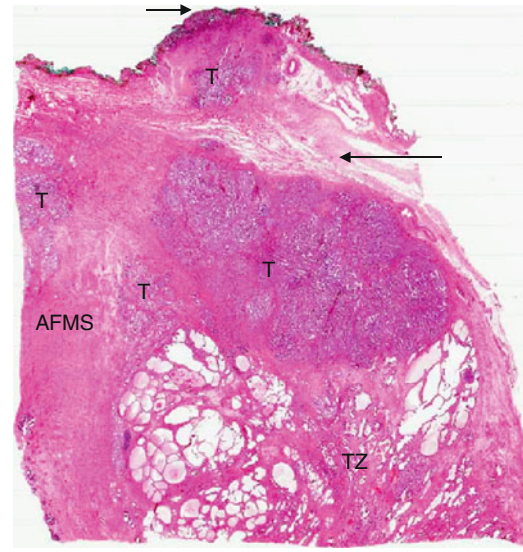

Fig. 4.9 Upper right quadrant section of prostatectomy specimen with a larger anterior cancer (*T*) of the transition zone (*TZ*), penetrating the anterior surgical margin (*short arrow*). The *long arrow* indicates the plane separating the prostate from the anterior extraprostatic tissue. The tumor is adjacent to and infiltrates the anterior fibromuscular stroma (*AFMS*)

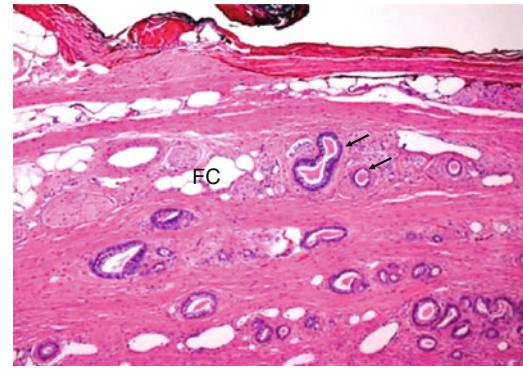

Fig. 4.10 A few tumor glands (*arrows*) are found at the level of fat cells (*FC*), indicating focal extraprostatic extension

extraprostatic extension as opposite to established or extensive extraprostatic extension has been defined as the presence of a few extraprostatic glands or 1 or 2 high-power fields in one or maximum two levels (Fig. 4.10). Each of these categorizations has prognostic significance, to the effect that focal extraprostatic extension has the same risk of progression as organ-confined prostate cancer.

4.4.3.3 Stage pT3b Prostate Cancer

Seminal vesicle invasion as defined by the invasion of the muscular wall of the extraprostatic seminal vesicles (stage pT3b) conveys a highly unfavorable prognosis. The carcinoma can invade the seminal vesicles by (1) spreading along the ejaculatory duct and/or by direct invasion at the base of the prostate and/or (2) by extending into periseminal vesicle soft tissue and then into the wall of the seminal vesicle. Rarely, discontinuous metastases in blood vessels can here be found as an isolated finding (Berney et al. 2011). As for the latter, there is no consensus whether to consider this as pT3b stage.

4.4.3.4 Stage pT4 Prostate Cancer

The designation of stage pT4 in a prostatectomy specimen is highly restricted now: pT4 urinary bladder neck involvement by prostatic carcinoma includes only prostate cancer with gross or radiographic extension into the bladder neck. It is allowable to assign a pT4 stage associated with radical prostatectomy if an associated biopsy of urinary bladder, rectum, or pelvic side wall is positive for prostatic carcinoma that is directly invading these structures, as assessed by clinical and/or radiological means (Magi-Galluzzi et al. 2011). Positive surgical margin at the bladder neck does not constitute stage pT4 cancer, but is reported as pT3a margin positive cancer (Buschemeyer et al. 2008).

4.4.4 Surgical Margins

Approximately 10–35% of radical prostatectomy specimens are reported to have positive surgical margins on pathologic evaluation. Biochemical progression free survival for men with surgical margin positivity on radical prostatectomy is about 60% as compared to 80% in patients with negative surgical margin (Ohori et al. 1995; Cheng et al. 1999). Most investigators have been able to confirm the independent prognostic impact of this parameter in multivariable analyses (Tan et al. 2011).

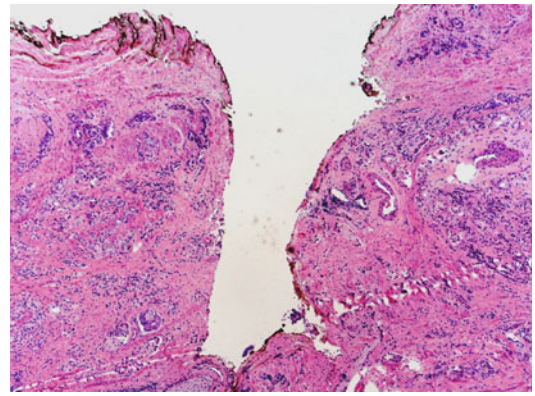

Fig. 4.11 A laceration into the prostatic tissue. Although tumor cells are here in contact with the ink, this may not be considered as a true positive margin

4.4.4.1 Definition of Positive Margins

As for surgical margins, tumor cells should really be in contact with ink in order to consider the margin positive. In a study of 278 margin-negative radical prostatectomy cases, Emerson et al. (2005) found that the closest distance between tumor and resection margin, which ranged from 0.02 to 5 mm, did not significantly predict PSA recurrence in univariate or multivariate logistic regression analysis and concluded that routine pathologic reporting of this distance was not required. This is in line with the finding of Epstein (1990) that a close margin (i.e., <0.1 mm) should not be designated as positive surgical margin since this would not impact the prognosis. Also, lacerations in the capsule should be accounted for as they may cause a false-positive diagnosis of positive margins (Chuang and Epstein 2008), even though tumor cells may be covered by ink at these sites due to leakage (Fig. 4.11). Similarly, presence of tumor cells in the outer surface of the specimen, *not* covered by ink should in general not be considered as evidence for a positive margin.

4.4.4.2 Location and Extent of Positive Surgical Margin

Published reports on the impact of location of positive surgical margins on outcome have been

conflicting (Tan et al. 2011). Several studies have shown that the extent of tumor at the surgical margin correlates with postoperative disease recurrence, but a large study by Stephenson et al. (2009) demonstrated that neither location nor extent of positive margin improved the predictive accuracy of a nomogram compared to one in which surgical margin status was modeled as positive versus negative.

4.4.5 Anterior Prostate Cancers

Transition zone cancers particularly when in an anterior location tend to be detected late, since they are generally not targeted by the standard biopsy scheme which focuses mainly on the cancers in the posterior location (Bott et al. 2002). Often, they have reached a large size and/or transformed into an aggressive higher-grade cancer before their detection, and under these circumstances, there is a greater risk of a positive margin and biochemical failure when prostatectomy is performed (Fig. 4.9). Anterior prostate cancers are not uncommon, with about 35% of the anterior prostate cancers originating from the anterior horn of the peripheral zone, thus representing peripheral zone carcinomas (Al-Ahmadie et al. 2008).

The recently proposed term acronym PEATS (i.e., prostatic evasive anterior tumor syndrome) alludes to the phenomenon of anterior cancers detected at a stage too advanced to be cured (Lawrentschuk et al. 2010). It is obvious that in patients enrolled in an active surveillance program, it remains a challenge to identify the presence of these hidden aggressive anterior tumors. Magnetic resonance imaging guided biopsies targeting anterior zone abnormalities play an increasing role in this clinical setting.

4.4.6 Multifocality and Index Tumor

Multifocality of prostate cancer (Fig. 4.1) is very common, with 2–5 tumors of variable size found in 80% of prostatectomy specimens (Wise et al. 2002). The concept of an index or dominant tumor was derived from the Stanford group who measured the volume of the largest tumor nodule in wholemount sections and demonstrated its independent clinical significance (Stamey et al. 1999). The advancement of focal therapy for treatment of prostate cancer has made this concept more relevant, but it has been challenged in the past on two grounds. Firstly, several subsequent studies have failed to demonstrate the independent prognostic significance of the tumor volume (Wolters et al. 2010) and secondly because the dominant nodule does not always represent the component of tumor having the highest Gleason score or the most advanced pathological stage (Andreoiu and Cheng 2010). Conversely, other features may influence the clinical importance of the individual tumor foci, and in particular, pT category and Gleason grade/score may need to be included in the defining characteristics. Thus, in a clinical setting in case of a multifocal cancer, the index tumor would represent the tumor with the worst prognostic features.

4.4.7 Tumor Volume and Insignificant Cancer

Although the prognostic significance of quantitation of prostate cancer volume and the proportion of prostate gland tissue involved by carcinoma is not disputed, few studies were able to provide evidence that parameters reflecting prostate cancer volume are of significance independent of Gleason score, pathological stage, and surgical margin status (Van der Kwast et al. 2011). Nevertheless, a cutoff of the index tumor volume of 0.5 ml is included in the current definition of a clinically significant prostate cancer, that is stage pT2, Gleason score 6 (3 + 3) and volume of index tumor <0.5 ml (Epstein et al. 1994). This <0.5 ml TV threshold is based on incidentally detected PC in a single radical cystoprostatectomy series, published by Stamey et al. (1993) based on a 8% lifetime risk to be diagnosed with clinically significant PC. It was recently validated on an independent

dataset, yielding the same volume threshold, if Gleason score and pathological stage were not taken into account (Wolters et al. 2011).

Imaging technology is now making such progress that visualization of most prostate cancers of a volume in the order of 0.5 ml is possible. It should be noted, however, that a potential limitation of imaging is the failure to identify "sparse" tumors, which contain less than 50% of cancer glands in their cross-sectional areas (Langer et al. 2008). This may cause an underestimation by magnetic resonance imaging of the actual tumor volume of some cancers. On the other hand, it remains unclear, whether these sparse tumor areas are clinically relevant (Ayala et al. 2011). It is envisaged that, in the future, further advances in imaging techniques will result in more accurate clinical estimations of the volume of the index tumor. This might reinforce the clinical rationale for incorporating a size-related staging parameter into pathological reporting of prostate cancers.

4.5 Concluding Remarks

As reflected in this chapter, much progress has been made in recent years in the understanding of the complex anatomy of the prostate and the appreciation of its considerable individual variation particularly with regard to its anterior and posterior boundaries. It is also becoming clearer that continuous efforts in the past to reconcile anatomic and clinical terminology are now resulting into a more uniform terminology based on increasing consensus on the composition and origin of the various fascias and muscular structures bordering the prostate. This improved knowledge has led to more detailed pathological staging criteria for prostate cancers. Consensus meetings of the International Society of Urologic Pathology held during the past few years have further led to a more standardized approach to grading, staging, and determination of margin status in prostatectomy specimens, while resolving several staging-related issues of cancers extending into the bladder neck, the apex, and at the anterior boundary. Some molecular-pathologic evidence suggests that prostate cancers of the peripheral and transition zone are different, but for pathologists an accurate zonal assignation of a prostate cancer can be challenging. As a consequence of the advancement of imaging in prostate cancer management, including active surveillance and the application of focal therapy for low-risk prostate cancer patients, more attention is currently being paid to the clinicopathologic features of prostate cancers located in the anterior region of the prostate. Finally, awareness of the potential for overdiagnosis and overtreatment of prostate cancer continues to drive the search for improved pathological, molecular-genetic, and imaging parameters for diagnostic and prognostic purpose. In this respect, recognition of the histological heterogeneity of prostate cancer and its stromal composition, even within one Gleason grade might benefit the development of imaging tools distinguishing aggressive from favorable prostate cancer. Clearly, the possibility to accurately distinguish clinically low-risk from high-risk prostate cancers continues to be an important field of research in the years to come.

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Biomarkers for Prostate Cancer

5

Gisele H.J.M. Leyten, Peter F.A. Mulders,
and Jack A. Schalken

Contents

G.H.J.M. Leyten, M.D. • P.F.A. Mulders, M.D., Ph.D.
J.A. Schalken, Ph.D. (✉)
Department of Urology,
Radboud University Nijmegen Medical Center,
Nijmegen, NL
e-mail: j.schalken@uro.umcn.nl

5.1 Introduction

Traditionally, clinical diagnosis and management of the individual patient are based on clinical cohort based studies. The heterogeneity within "risk cohorts" can still be considerable which impairs decision-making for an individual patient. Therefore, we urgently need improved methods to accurately predict the biological behavior and therapy response for well-stratified/homogeneous groups of patients. In the last decade, revolutionary advancements in molecular profiling technologies have been made resulting in new diagnostic algorithms. It is noteworthy that it is just 60 years ago that the double-helix model for the structure of DNA was first described. Molecular biology developed quickly, and with nucleic acid amplification technologies, whole genome gene and expression profiling became feasible. The field expanded beyond the traditional/core genes that follow Francis Crick's dogma (gene → RNA → protein) by the discovery of noncoding RNAs, including microRNAs. This enables us to identify the individual in a different way from the way we did before. These advances have marked the beginning of a new era for modern medicine: individualized medicine. This is an approach that strives for a "customized" health care: patient-specific strategies instead of the standard "one-size-fits-all" approach.

Biomarkers are important tools in individualized medicine. A biomarker can be defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological

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processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working Group 2001). This includes physiological measurements and clinical imaging, but also specific cells, molecules, genes, gene products, enzymes, or hormones.

Biomarkers in cancer (can) have several valuable applications:

- Improve diagnosis
- Improve staging
- Indicate disease prognosis (e.g., indolent vs. clinical significant prostate cancer)
- Monitor response to treatment
- Select patients for different treatment options
- Surrogate end point in trials
- Therapeutic target

In prostate cancer, prostatic acid phosphatase (PAP) is considered the first known biomarker. This enzyme was discovered to be increased in men with metastasized prostate cancer in 1938 (Gutman and Gutman 1938). The use of PAP was not useful for diagnosis and was only used to monitor prostate cancer patients after diagnosis. In the 1980s, prostate-specific antigen (PSA) was introduced into clinical practice. This is to date the only widely used biomarker in prostate cancer. The introduction of PSA has resulted in earlier detection of the disease, but also has important limitations. Its use in screening and prognosis remains controversial. Novel biomarkers are needed to differentiate indolent from aggressive disease to minimize overtreatment of clinically insignificant prostate cancer.

The ideal characteristics of a biomarker for prostate cancer are:

- Only produced by tumor tissue
- Noninvasive test, easy to manage
- As inexpensive as possible
- Ability to detect prostate cancer at an early stage
- Differentiate between indolent and clinically significant tumors
- High sensitivity and specificity

Given the heterogeneous character of prostate cancer, it is most likely that in the future, a panel of (novel) biomarkers will be used to optimize predictive value. Prostate cancer biomarkers can be detected in different diagnostic substrates, each aiding different clinical decisions (Table 5.1).

Table 5.1 Different diagnostic substrates for prostate cancer biomarkers

Diagnostic substrates	Invasive	Clinical decision
Urine	–	Biopsy
Blood	–	Biopsy
Biopsy specimen	+	Treatment
Prostatectomy specimen (Gleason score + pTNM)	++	Adjuvant treatment

Novel biomarkers can be identified through genetic epidemiological studies (evaluating inherited genetic predispositions in large cohorts, Genome-Wide Association Studies, GWAS) or molecular profiling studies, evaluating the molecular profile of the tumor. The GWAS studies have revealed at least thirty genetic loci that are associated with an increased chance to develop prostate cancer. The observed relative risks are insufficient to individualize diagnosis (Ioannidis et al. 2010), yet may be of use for preselection. This chapter will focus on established biomarkers and promising novel biomarkers identified by molecular profiling studies, arranged by tissue markers, blood markers, and urine markers.

5.2 Tissue Markers

Once tissue is available, important decisions have already been made, either a biopsy has been taken or the gland was surgically removed. Thus, the main clinical need is to accurately predict the biological behavior of the malignant process. In case the pathologist is not sure about the diagnosis of invasive prostate cancer, immunohistochemistry using antibodies against the basal cell specific high molecular weight keratins (34β E12) and AMACR has proven to be helpful (Kumaresan et al. 2010). It is striking that this is the only molecular pathological application that has been widely accepted and used in prostate cancer. Numerous studies report on the potential of biomarkers detected by immunohistochemistry, yet none is routinely used for a better assessment of prognosis. Whereas, for other malignancies, biomarkers that predict progression of the disease in

patients that were treated with curative intend are routinely used (e.g., breast and colon cancer); so far, there has not been a great interest in adjuvant treatment of patients with high-risk localized prostate cancer. The most significant study in this respect was the EPC initiative, in which a stratification on standard clinical and pathological risk factors was used. Now, better treatment modalities become available, adjuvant strategies are likely to be considered again; and biomarkers indicative for biological behavior determined in tissue will be needed. In this part, we will focus on high potential biomarkers for which standardized methods are or can be developed.

5.2.1 Gene Fusions: TMPRSS2-ERG

The classic example of a gene fusion implicated in cancer development is the BCR:ABL fusion in patients with chronic myelogenous leukemia. This fusion results from a reciprocal translocation T(9;22), first recognized as the Philadelphia chromosome. This discovery has been revolutionary as it has lead to the development of imatinib (Deininger et al. 2005). This is an inhibitor of the BCR:ABL gene fusion product which transformed the previously fatal leukemia into a manageable chronic disease for many patients.

In prostate cancer, recurrent gene rearrangements were discovered in 2005: a fusion of the 5′ untranslated region of TMPRSS2 (androgen-regulated transmembrane protease, serine 2) to Ets family genes (oncogenic transcription factors) (Tomlins et al. 2005). Oncogene ERG (v-ets erythroblastosis virus E26 oncogene homolog (avian)) is the most commonly involved Ets family member in gene fusion. TMPRSS2-ERG has been detected in approximately 50% of Caucasian prostate cancer patients. This gene fusion is less frequently seen in men from other ethnic background. A recent study reported fusion-positive prostate cancers in 31% of African American men and only in 16% of Japanese men (Magi-Galluzzi et al. 2011). Rearrangements with other Ets transcription factors have been identified in approximately 5–10% of PSA-screened prostate cancers: ETV1 (ETS variant 1 gene), ETV4, and ETV5 (Attard et al. 2008; Han et al. 2008; Tomlins et al. 2006). In addition to TMPRSS2, other fusion partners involved in ETS fusions have been identified. Their possible clinical relevance is not clear.

As a result of gene fusion with TMPRSS2, the expression of ERG becomes androgen-regulated and thus overexpressed. ERG expression can be detected in prostate cancer patients by immunohistochemistry with a high specificity of >95% and is not seen in benign prostate epithelium (Park et al. 2010; Minner et al. 2011). This suggests ERG immunostaining could be a solid diagnostic biomarker, albeit in approximately half of the prostate cancer patients. The clinical relevance of Ets gene fusions is currently under investigation. Results on a potential prognostic value are conflicting. A worse prognosis of fusion-positive cancers has been reported by several studies (Demichelis et al. 2007; Nam et al. 2007; Wang et al. 2006). Other studies could not validate these results (FitzGerald et al. 2008; Gopalan et al. 2009) or found a favorable prognostic association (Saramaki et al. 2008; Winnes et al. 2007). A recent large study showed that ERG status had no influence on the risk of PSA recurrence after radical prostatectomy (Minner et al. 2011). In addition, they report a strong association between ERG positivity and high androgen receptor expression levels. This suggests that ERG status might have predictive value for response to antiandrogen therapy. However, this requires further investigation, before implementation into clinical practice can be realized.

5.2.2 Ki-67-/MIB1-Labeling Index

Expression of the Ki-67 protein is strictly associated with cell proliferation. Ki-67 has therefore been extensively studied for its potential use as a proliferation marker in different types of cancer, including prostate cancer. Its name is derived from the city of origin (Kiel) and the number of the original clone in the 96-well plate (Scholzen and Gerdes 2000). Ki-67 can be determined by immunohistochemistry using the monoclonal antibody MIB1 (Cattoretti et al.

1992). The proportion of tumor cells staining positive for Ki-67 is known as the Ki-67-labeling index. This proved to be an independent and significant prognostic biomarker for prostate-cancer-specific survival (Aaltomaa et al. 1997; Borre et al. 1998). Furthermore, the Ki-67-labeling index has repeatedly shown to be a predictive marker for disease recurrence and progression after radical prostatectomy and radiotherapy (Bettencourt et al. 1996; Bubendorf et al. 1996; Scalzo et al. 1998). Although its usefulness has been well established, the Ki-67-labeling index is currently not used in daily practice.

5.2.3 PTEN

PTEN (phosphatase and tensin homologue) is a tumor-suppressor gene, located on chromosome 10q23 (Li et al. 1997). This gene plays a key role in carcinogenesis. PTEN antagonizes the PI-3K/Akt pathway and thereby modulating cell growth/survival and cell migration/adhesion (Uzoh et al. 2009). In prostate cancer, PTEN loss has been associated with proliferation and survival of cancer cells, resistance to castration (Shen and Abate-Shen 2007), chemotherapy (Huang et al. 2001; Priulla et al. 2007) and radiotherapy (Anai et al. 2006), bone metastasis (Wu et al. 2007), and recurrence after radical prostatectomy (Bedolla et al. 2007). Thus, PTEN is assumed to be a potent prognostic marker and a clear target for novel (gene) therapies. However, this requires further research.

5.2.4 E-cadherin

Cadherins are a family of epithelial cell-cell adhesion molecules that play a key role in preserving epithelial integrity (Takeichi 1988). Their function is dependent on calcium, hence, their name ("calcium-dependent adhesion"). E-cadherin is the most extensively studied member of the cadherin family. During cancer progression to an invasive state, intercellular adhesions between tumor cells are disrupted. Thus, aggressive tumor cells were hypothesized to have loss of E-cadherin. And indeed, decreased E-cadherin expression has repeatedly been shown to correlate with a loss of tumor differentiation and a poor prognosis (Umbas et al. 1992, 1997; Birchmeier and Behrens 1994). This correlation has been shown for several tumor types, including prostate cancer. However, large prospective studies will have to define its potential clinical relevance in prostate cancer, as a prognostic biomarker or as a molecular target for therapy.

5.2.5 EZH2

The EZH2 gene (enhancer of zeste homolog 2), encoding a polycomb-group (PcG) protein, is responsible for maintaining the silent state of genes. EZH2 mediates trimethylation of histone H3 lysine 27 (H3K27), leading to repression of transcription and thereby silencing of gene expression (Chen et al. 2005; Koyanagi et al. 2005). EZH2 is upregulated in various aggressive tumors, including prostate cancer (Varambally et al. 2002; Kleer et al. 2003; Breuer et al. 2004). Furthermore, it mediates transcriptional silencing of the tumor-suppressor gene E-cadherin (Cao et al. 2008). This demonstrates an inverse correlation between dysregulation of EZH2 and repression of E-cadherin during cancer progression. In conclusion, EZH2 upregulation might play a key role in oncogenesis and progression of cancer. This makes it a promising biomarker of disease progression and a viable target for therapeutic interventions in aggressive cancers.

5.2.6 The Neuroendocrine Phenotype

The expression of a neuroendocrine phenotype in prostate cancer has been reported almost 25 years ago (di Sant'Agnese and de Mesy Jensen 1987). There is in good agreement that the relative fraction of cells with a NE phenotype increases in advanced prostate cancer, yet the use to predict biological behavior in localized prostate cancer remains controversial. Only in case of a "pure" NE phenotype, in small cell prostate cancer, a rare entity (<1% of all prostate cancer), the biology of the disease is markedly different from

adenocarcinoma of the prostate, and therefore, treatment of this type of prostate cancer is different.

In summary, we can conclude that a robust set of candidate prognostic biomarkers is available that can be measured by immunohistochemistry. Stratification of patients based on these markers is well within reach provided the methods and scoring systems are standardized.

5.3 Blood Markers

5.3.1 Kallikreins

5.3.1.1 Total PSA

In 1986, PSA was approved by the Food and Drug Administration as a marker to monitor treatment in patients with prostate cancer, and in 1994 as a diagnostic marker. It is currently the only widely used marker for prostate cancer.

PSA, also known as kallikrein 3 or hK3, is a serine protease that is a member of the family of glandular kallikrein-related peptidases. The genes for the glandular kallikreins are clustered at chromosome 19q133-4, and transcription of PSA is regulated by androgens (Lundwall et al. 2006). The function of PSA is to liquefy seminal fluid through its action on the gel-forming proteins semenogelin and fibronectin (Lilja 1985).

PSA is not a *cancer*-specific marker, as it is produced by both benign and malign prostate epithelial cells. Normally, PSA blood levels are low. A healthy prostate is surrounded by a continuous layer of basal cells and a basement membrane which prevent the high concentrations of PSA in the prostate to leak into blood. High-PSA blood levels can be caused by an elevated synthesis or an increased release of PSA into blood. An elevated PSA synthesis can be a result of benign prostatic hypertrophy (BPH) and prostate manipulation (Herrala et al. 2001; Lintula et al. 2005). PSA expression, ergo PSA synthesis, is slightly decreased in the development and progression of prostate cancer (Qiu et al. 1990). Therefore, as is seen in prostatitis, the increased PSA blood levels in prostate cancer are assumed to be a result of an increased release of PSA into blood through the disrupted architecture of the prostate.

Despite extensive research, difficulty persists in defining the optimal cutoff value for PSA. Traditionally, it was set at 4.0 ng/ml. Using this PSA cutoff provides a sensitive test, with a positive predictive value of 37% and a negative predictive value of 91% (Bradford et al. 2006). In other words, 75% of men with PSA 4.0–10.0 ng/ml who undergo biopsy do not have cancer (Barry 2001). In addition, several studies showed a substantial probability of prostate cancer within the PSA interval 0–4.0 ng/ml (Thompson et al. 2004, 2005; Efstathiou et al. 2006). The Prostate Cancer Prevention Trial (PCPT), for example, reported that 27% of men with normal DRE and a serum total PSA between 3.1 and 4.0 ng/ml have prostate cancer (Thompson et al. 2004). On the other hand, it has never been demonstrated that lowering the PSA cutoff affects the long-term survival in men with prostate cancer. Furthermore, this will most likely lead to a higher number of unnecessary biopsies and an increased detection of clinical insignificant prostate cancer. Other factors of influence on PSA blood level is ethnic background and the use of medication. Men from African descent have higher PSA levels than Caucasian men, even after adjusting for prostate volume (Morgan et al. 1996; Fowler et al. 1999). And men using 5α-reductase inhibitors for treatment of BPH (such as dutasteride and finasteride) will have lower PSA levels by an average of 50% after 6 months of treatment (Marks et al. 2006; D'Amico and Roehrborn 2007).

Several studies report that PSA measured before age 50 might be indicative for the risk of developing prostate cancer years or even decades later (Loeb et al. 2006; Lilja et al. 2007). It is also suggested that total PSA level at age 44–50 might also predict the likelihood of developing advanced prostate cancer, defined as clinical T3 or higher or metastatic disease at time of diagnosis (Ulmert et al. 2008). This, however, needs further validation before possible implementation into clinical practice.

5.3.1.2 Risk Calculators

Risk calculators including several predictive factors to stratify patients for prostate biopsy have been developed. Two well-known calculators that are available online are the PCPT and the ERSPC

risk calculator (Thompson et al. 2006; van den Bergh et al. 2008). The first includes serum PSA, DRE results, age, family history of prostate cancer, ethnicity, and prior biopsy. The latter includes serum PSA, DRE results, TRUS findings, prior biopsy, and prostate volume. The use of risk calculators allows a more individual assessment of prostate cancer risk and provides a better predictive accuracy compared to PSA alone (Schroder and Kattan 2008).

5.3.1.3 PSA Derivatives

PSA derivates have been evaluated in the attempt to enhance the diagnostic accuracy of total PSA: age-specific total PSA cutoffs, total PSA density, total PSA velocity, and total PSA doubling time. Age-specific PSA cutoff values were suggested to enhance the predictive value of PSA. The suggested cutoff values were: 40–49 years old: 2.5 ng/ml, 50–59: 3.5 ng/ml, 60–69: 4.5 ng/ml, and 70–79: 6.5 ng/ml. However, the use of an age-specific total PSA cutoff is not validated and criticized for missing clinically significant cancers in older men (Borer et al. 1998).

PSA density is defined as the total serum PSA level divided by the volume of the prostate (in grams). A PSA density of 0.15 ng/nl/g or higher has been considered abnormal and suspicious for cancer. However, the value of this test remains controversial (Lilja et al. 2008). PSA density correlated with biopsy outcome, tumor aggressiveness, and unfavorable pathological features in several studies (Benson et al. 1992; Rommel et al. 1994; Karazanashvili and Abrahamsson 2003). However, other studies could not validate these results (Brawer et al. 1993; Ohori et al. 1995). In addition, PSA density requires transrectal ultrasound, which is time consuming, expensive, and causes patient discomfort. All together, PSA density is not widely used in clinical practice.

PSA dynamics have been extensively studied for their assumed predictive value to discriminate between benign and malign conditions of the prostate. This includes PSA velocity, the change in PSA over time, and PSA doubling time, the number of months for a certain level of PSA to increase by a factor of two. PSA dynamics are indisputably correlated with the diagnosis of prostate cancer on biopsy. However, there is no sufficient evidence that PSA velocity or PSA doubling time has *additional* diagnostic value beyond the use of total PSA. Thus, there is no justification for the use of PSA dynamics in clinical decision-making before treatment in early-stage prostate cancer (Vickers et al. 2009). PSA dynamics are however valuable to monitor treatment. Recurrence after radical prostatectomy can be monitored with high sensitivity using PSA doubling time. Although currently widely used, PSA response to chemotherapy in castrate-resistant prostate cancer patients does not predict long-term benefit adequately.

5.3.1.4 PSA Molecular Forms

PSA circulates in blood either in a stable complexed form or in an unbound "free" form. Complexed PSA is bound to proteins: α1-antichymotrypsin (ACT), α2-macroglobulin (A2M), and α1-protease inhibitor (API). A lower percent-free PSA (free PSA/total PSA × 100) is correlated with a higher probability of finding prostate cancer on biopsy (Catalona et al. 1998; Woodrum et al. 1998). The use of percent-free PSA has been approved as a diagnostic marker by the Food and Drug Administration in men with PSA levels 4.0–10.0 ng/ml. A cutoff value of 25% is generally used. Note that free PSA is less stable than complexed PSA, causing greater analytic variability. Suboptimal blood sample handling can considerably influence free PSA levels (Ulmert et al. 2006).

Free PSA exists in different molecular isoforms, including pro-PSA, BPH-associated BPSA, and intact-free PSA (Mikolajczyk et al. 1997; Linton et al. 2003). Several studies report significantly higher levels of pro-PSA in patients with prostate cancer and decreased levels of BPSA and intact-free PSA (Mikolajczyk et al. 2000; Catalona et al. 2003; Mikolajczyk et al. 2004). This implies that pro-PSA might be a purer biomarker for prostate cancer that free PSA. Pro-PSA has also been suggested to selectively identify patients with more aggressive prostate cancer. Its suggested additional diagnostic and prognostic value has yet to be validated.

Human kallikrein 2 (hK2) and urokinase plasminogen activation (uPA) are potential future prostate cancer biomarkers that are thus far not validated. HK2 is from the same gene family as PSA, but differ in their enzymatic activity (Yousef and Diamandis 2001). Several studies have shown that the use of a combination of hK2 with free and total PSA might improve the predictive value for prostate cancer (Becker et al. 2000; Nam et al. 2000). HK2 might also have prognostic value (Recker et al. 1998; Haese et al. 2001). The serum protease uPA might be involved in tumor development and progression through degradation of the extracellular matrix (Duffy 2002). The potential role of uPA as a biomarker of metastatic prostate cancer needs to be validated in large multicenter studies.

5.3.2 MicroRNAs

The discovery of microRNAs (miRNA) in 2004 was a revolutionary step in understanding the mechanisms regulating gene expression and function (He and Hannon 2004; Chen and Rajewsky 2007). Subsequently, it was reported that miRNAs play an important role in cancer by initiating carcinogenesis and driving progression (Croce 2009).

MiRNAs are small endogenous noncoding RNAs, up to 22 nucleotides long, that regulate gene expression posttranscriptionally. MiRNAs bind to complementary sequences within messenger RNAs (mRNA) to alter their translation by inhibiting their translation or inducing the cleavage of specific target mRNAs (Bartel 2004). In most cases, miRNAs "fine-tune" protein expression (only a modest reduction of the target mRNA concentration) (Bartel 2009). Occasionally, it causes upregulation or complete destruction of the target mRNA (Calin et al. 2004; Bartel 2009; Guo et al. 2010).

MiRNAs are known to regulate common cellular targeted pathways (intracellular signaling, DNA repair, and cellular adhesion/migration) (Galardi et al. 2007; Bonci et al. 2008; Josson et al. 2008), androgen signaling (Lin et al. 2008; Ribas et al. 2009; Waltering et al. 2011), and apoptosis avoidance (Papagiannakopoulos et al. 2008; Sylvestre et al. 2007). The exact role of miRNAs in the development and progression of prostate cancer is still being investigated. Yet, miRNAs are promising potential biomarkers and novel therapeutic targets for prostate cancer.

5.3.3 Circulating Tumor Cells

The importance of circulating tumor cells (CTC) was already acknowledged in 1869 by Thomas Ashworth, an Australian physician who observed CTCs microscopically (Miller et al. 2010). Only recent advances in technology facilitate a reliable method for the detection of CTC in blood. The presence of CTCs in blood proved to be associated with overall survival in patients with metastatic breast (Cristofanilli et al. 2004, 2005), colorectal (Cohen et al. 2008, 2009), and prostate cancer (de Bono et al. 2008; Scher et al. 2009).

In castrate-resistant prostate cancer (CRPC), CTC number before and after treatment is an independent predictor of survival. This is a strong predictor both as a continuous variable and when using discrete cutoff values (≥5 CTC/7.5 ml of blood vs. <5 CTC) (Danila et al. 2007; de Bono et al. 2008; Scher et al. 2009). Posttreatment CTC number showed to be a stronger prognostic factor for survival than a 50% decline in PSA (AUC 0.87 vs. 0.62). CTCs are approved by the Food and Drug Administration as a prognostic biomarker to monitor disease status in patients with metastatic breast, colorectal, and prostate cancer. To further explore the potential link to survival, CTCs have been incorporated as an exploratory end point in several phase II and III trials (Ang et al. 2009).

5.4 Urine Markers

5.4.1 PCA3

In 1999, Bussemakers et al. first identified and characterized the differential display clone 3 (DD3, later called PCA3) gene, to date, one of the most prostate-cancer-specific genes (Bussemakers et al. 1999). PCA3 is noncoding RNA

and located on chromosome 9q21–22. Its function is unknown. PCA3 is highly overexpressed in prostate tumors compared to adjacent benign prostate tissues, on average between 70- and 80-fold. An upregulation is seen in 95% of the primary prostate tumors, and no PCA3 expression is found in nonprostate tissue (i.e., benign and malign tissue from breast, cervix, endometrium, ovary, and testis; cell lines originating from bladder, kidney, and ovarian cancer) (Bussemakers et al. 1999).

In the initial PCA3 studies, a real-time RT-PCR analysis was used for the quantification of PCA3 messenger RNA (mRNA) in prostate tissue. Later, Hessels et al. developed a dual time-resolved fluorescence (TRF)-based RT-PCR assay to detect PCA3 mRNA in urinary sediments after digital rectal examination (DRE) (Hessels et al. 2003). A urine test provides a noninvasive method to obtain prostate (cancer) cells, which makes it suitable for clinical purposes. A DRE is performed to mobilize prostatic cells toward the prostatic urethra, which are flushed out with the first-voided urine. A prostate massage is obsolete and causes needless patient discomfort, as a regular DRE sheds enough cells into urine for analysis. In 2006, the Progensa PCA3 test was introduced, a transcription-mediated amplification (TMA) assay (Groskopf et al. 2006). This assay is also performed on first-voided urine samples after DRE, but it is a simpler, faster, and sensitive enough method compared to the initial RT-PCR-based assay, therefore, more viable for widespread clinical implementation. The PCA3 score is the ratio of PCA3/PSA mRNAs multiplied by 1,000. The Progensa PCA3 test is commercially available and Conformité Européenne (CE)-approved since November 2006 to aid in the decision to take initial or repeat biopsies. The Food and Drug Administration approval process is currently ongoing.

The clinical utility of PCA3 and its additional predictive value beyond PSA has been extensively studied. PCA3 has been validated as a reliable predictor of prostate cancer at initial or repeat biopsy (Hessels et al. 2003; Marks et al. 2007; Haese et al. 2008; Deras et al. 2008; de la Taille et al. 2011). Currently, a cutoff value of 35 is used, resulting in a sensitivity of 47–69% and a specificity of 72–79% (Groskopf et al. 2006; Marks et al. 2007; Haese et al. 2008; Deras et al. 2008). However, the optimal cutoff value is subject to debate. Several studies indicate that a cutoff value of 20 or 25 might be preferable, missing less prostate cancers and still preventing a considerable amount of prostate biopsies (de la Taille et al. 2011). Future studies will have to clarify this issue. Furthermore, PCA3 showed to be an independent predictor of prostate cancer in *addition* to established prostate cancer risk factors (age, PSA, DRE, prostate volume, and biopsy history) (Ankerst et al. 2008; Chun et al. 2009). The use of PCA3-based nomograms has recently been validated (Auprich et al. 2010), providing a novel tool for clinical decision-making.

It was hypothesized that PCA3 might be associated with more aggressive cancer. This was based on the theory that aggressive prostate cancer cells are more invasive and would therefore more easily shed into the prostatic ductal system after DRE (van Gils et al. 2008). However, to date, the prognostic value of PCA3 is considered to be limited. Some studies found a correlation of PCA3 with Gleason score (Haese et al. 2008; Nakanishi et al. 2008; de la Taille et al. 2011), but this is contradicted by a range of other studies that show no (additional) predictive value for Gleason score (van Gils et al. 2008; Hessels et al. 2010; Auprich et al. 2011; Ploussard et al. 2011). As concluded by Auprich et al., the clinical value of PCA3 to predict aggressive prostate cancer at radical prostatectomy seems to be marginal at best (Auprich et al. 2011). PCA3 has been shown, however, as a valuable predictor of tumor volume and insignificance of prostate cancer (Haese et al. 2008; Auprich et al. 2011; Ploussard et al. 2011). Data on predictive value for extracapsular extension are conflicting (Haese et al. 2008; Whitman et al. 2008; Auprich et al. 2011). Furthermore, PCA3 currently has no role in risk assessment during active surveillance protocols, though this requires further investigation in larger studies (Tosoian et al. 2010; Ploussard et al. 2011).

5.4.2 TMPRSS2-ERG

For a complete description of the gene fusion TMPRSS2-ERG, see Sect. 5.2.1. In summary,

TMPRSS2-ERG is a fusion of TMPRSS2 (the androgen-regulated transmembrane protease, serine 2) to Ets family genes (oncogenic transcription factors). Oncogene ERG is the most commonly involved Ets family member in gene fusion. It occurs in approximately half of Caucasian prostate cancer patients.

A publication in 2006 showed the feasibility to detect TMPRSS2-ERG fusion transcripts noninvasively in urinary sediments obtained after DRE using an RT-PCR-based research assay (Laxman et al. 2006). Since then, extensive research has been performed on the clinical applicability of this urine test. A sensitivity of 37% and specificity of 93% to predict prostate cancer was reported, resulting in a positive predictive value of 94% (Hessels et al. 2007). Although not (yet) validated, this test is assumed to improve the specificity of established prostate cancer risk calculators.

5.4.3 Urine Marker Panel

Given the tumor heterogeneity in prostate cancer, the use of a panel of biomarkers may provide the best diagnostic accuracy. Hessels et al. evaluated the combination of PCA3 with TMPRSS2-ERG fusion transcripts detected in the urine, showing an improved sensitivity of 73%, compared to 62% for PCA3 alone, without compromising the specificity for detecting prostate cancer (Hessels et al. 2007). A recent study confirmed an enhanced predictive value of PCA3 combined with TMPRSS2-ERG (Tomlins et al. 2011). In conclusion, these preliminary results on the combined use of PCA3 and TMPRSS2-ERG seem promising but require further validation. Future studies will have to assess the use of other (novel) biomarker panels.

5.5 Future Perspectives

In the worldwide search for novel diagnostic and prognostic biomarkers for prostate cancer, many tumor markers have been proposed. The number of articles published on this subject has increased substantially in the last decade. However, PSA, PCA3, and CTCs are still the only ones used in clinical practice. Many published results on novel prostate cancer biomarkers appear not reproducible in subsequent studies and thus will never attain the FDA-approved status (Table 5.2). Where a double-blind, randomized, placebo-controlled trial is the gold standard for therapeutic studies, biomarker studies are not regulated by clear guidelines. These studies often suffer poor study design, lack methodological quality and standardized assays, and information on key elements of design and analysis are often not reported. To improve the quality of diagnostic studies, the STARD (standards for reporting of diagnostic accuracy) statement was developed by a group of scientists and editors in 2003 (Bossuyt et al. 2003). It consists of a checklist of 25 items and flow diagram that authors can use to ensure that all relevant information is present. In addition, the REMARK guidelines (reporting recommendations for tumor marker prognostic studies) were published in 2005 (McShane et al. 2005). These are guidelines for transparent and complete reporting of studies, so that poor studies can be better identified. These initiatives are important steps forward in improving the quality of tumor marker studies, but further improvement of future studies is warranted.

Table 5.2 Different stages of biomarker research

Stages of biomarker research	Examples of markers in prostate cancer
1. Exploratory, no intended use cohort	microRNA, uPA, EPCA-1, etc.
2. Research use only assay, evaluated retrospectively	hK2, PTEN, Ki-67, EZH2, E-cadherin
3. Research use only assay, evaluated prospectively	TMPRSS2-ERG
4. CE/FDA approved	PSA, PCA3, circulating tumor cells

Other future improvement includes the use of a secured database with audit trail, so that results cannot be manipulated after analysis. Validation of a potential novel biomarker should only be approved after multiple prospective studies with an "intended use" cohort. Furthermore, it should be kept in mind that it is not sufficient to show that a potential novel biomarker is statistically significant in multivariate analysis, it should improve the predictive accuracy of the multivariate model. In conclusion, future biomarker

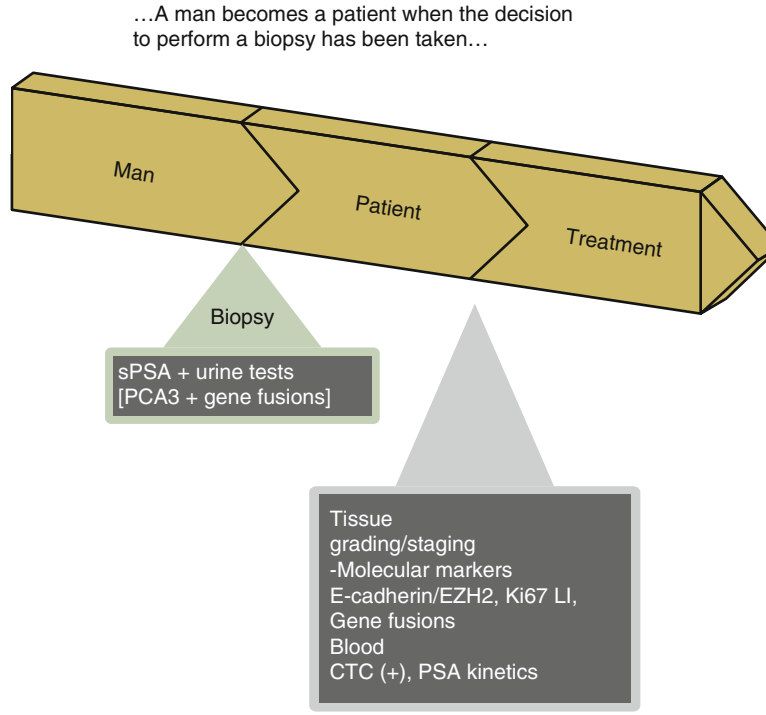

Fig. 5.1 The two main themes in the clinical arena of prostate cancer: to predict biopsy outcome and to predict the prognosis and therapy need/response

studies should meet the STARD criteria and should be reported in compliance with the REMARK guidelines.

So, many new biomarkers are ready for "prime time," yet it needs carefully designed studies to test the exact clinical positioning. In the clinical arena two main themes can be discriminated (Fig. 5.1). Develop methods to better predict biopsy outcome; once the decision to take a biopsy has been taken, the man is a patient, a patient with or without prostate cancer. This is a tough challenge since the man with indolent cancer should not be bothered with a biopsy, yet the ones in the low PSA ranges with aggressive disease should be identified. Once the cancer is diagnosed, we should better predict the prognosis and therapy need/response. This will require significant efforts from molecular pathology.

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Diagnosis, Clinical Work Up, TNM Classification, Markers

6

Jean-Luc Descotes and Anne-Sophie Gauchez

Contents

J.-L. Descotes, Ph.D., D.Sc. (✉)
Department of Urology and Renal Transplant, CHU GRENOBLE, Grenoble, France
e-mail: jldescotes@chu-grenoble.fr

A.-S. Gauchez, Ph.D., D. Ph. (✉)
Department of Biology, CHU GRENOBLE, Grenoble, France
e-mail: asgauchez@chu-grenoble.fr

6.1 Diagnosis of Prostate Cancer (PCa): Clinical Work Up

6.1.1 Localized Prostate Cancer

Prostate cancer, usually affecting elderly, is now recognized as a health problem as it became in developed countries the first cancer of men over their 50 years.

Today, the diagnosis of prostate cancer results more on the realization of digital rectal examination (DRE) and PSA blood test leading to randomized transrectal ultrasonography (TRUS) biopsy than on other clinical symptoms (Parekh et al. 2007).

Usually an elevated level of PSA evokes a diagnosis of prostate cancer, especially if the rectal examination (DRE) is suspect. The level of PSA is a continuous parameter: the higher the value, the most likely the existence of prostate cancer.

Initially, most guidelines for early detection of prostate cancer used cut-off values of PSA to indicate a biopsy, with recommendations varying between PSA values of 2.5 and 4.0 ng/ml.

However, according to the Prostate Cancer Prevention Trial (PCPT) study summarized in the Table 6.1, prostate cancer may occur even with a PSA level below the upper level of 4 ng/ml, suggesting that there is no cut-off point to eliminate prostate cancer (Parekh et al. 2006).

For example, in the European Randomized Study of Screening for Prostate Cancer (ERSPC), a PSA cut-off ≥3 ng/ml was, for the Rotterdam

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Table 6.1 Incidence of PCa according to the level of PSA (Hamdy and Roupret 2008)

PSA level ng/ml	Patients number (n=2,950)	Positive predictive value for cancer (%)	Positive predictive value for aggressive cancer (%)
0–0.5	486	32 (6.6)	4 (12.5)
0.6–1	791	80 (10.1)	10 (8)
1.1–2	998	170 (17)	20 (11.8)
2.1–3	482	115 (23.9)	22 (19.1)
3.1–4	193	52 (26.9)	13 (25)

PSA level ng/ml	Positive predictive value for cancer (%)
0–1	2.8–5
1–2,5	10.5–14
2.5–4	22–30
4–10	40
>10	70

section, an indication for prostate biopsy, and the author justifies this low threshold because the overall risk or prostate cancer death is low in this cohort (Roobol 2011).

These results also showed that the value of PSA was not correlated with the tumoral aggressiveness currently identified by a Gleason score >7 on the biopsies (Teillac and Abrahamsson 2006).

At least, when a rectal examination is carried out, either on a systematic way or because of functional non-specific voiding disorders like dysuria or frequency, or minimal clinical modifications like asymmetry and irregularities of one lobe, prostate biopsy is justified, irrespectively of the PSA level, especially in young patients to eliminate the diagnosis of prostate cancer (Heidenreich et al. 2011).

While rectal examination and PSA results are fundamental because they work out the local extension of the tumor and allow the repartition of the patients according to d'Amico's Classification (Table 6.3), prostate biopsy decision must take account of other risk factors (increasing age, ethnicity, and heredity), and therapeutic choices are argued after a complete medical check-up of the patient. At least, the clinician must imperatively evaluate different functional data and take care of:

- Voiding function: it is best evaluated by an auto questionnaire which integrates question on irritative and obstructive symptoms.
- Several questionnaires are accessible and were validated in the literature, the most frequently used being score IPSS (Appendix A) (Barry et al. 1992).
- Erectile function: just as for the voiding disorders, a precise evaluation of the erectile score before any treatment and after treatment is essential for a better evaluation of the morbidity frequency, or minimal clinical modifications of the treatments. Questionnaires are accessible as IIEF5 score (Appendix B).
- Intestinal disorders that may compromise radiotherapy.

Assessment of the patient is also focused on evaluation of co-morbidities, which can be analyzed by a general score like the Charlson score (Appendix C). Complementary information as measurement of the body mass index (BMI) and explanation of toxicities of treatments will allow a clear discussion of different therapeutic choices adapted to the individual risks of the patient and his priorities during a multidisciplinary medical team discussion.

6.1.2 Advanced and Metastatic Cancer

By screening, the clinician can discover prostate cancer early, before the appearance of the clinical signs, and it is now rare to discover this tumor with inaugural metastasis.

It is nevertheless important to eliminate prostate cancer in front of any osseous pain when the

diagnosis is reluctant or in front of a neurological complication as para- or quadriplegia by spinal cord compression which represents the most dramatic entity and the most pejorative form of initial diagnosis of prostate cancer.

Therefore, any biological syndrome in relation with a tumoral extension like acute renal insufficiency or hypercalcemia is suspicious for locally advanced or metastatic prostate cancer and justifies clinical and biological evaluation for prostate cancer.

6.1.3 In Summary

Today, the dilemma is probably to find an accurate test (biological and/or radiological) to define when we really need to perform biopsy in order to limit unnecessary biopsy on asymptomatic men.

Thus, the indication of prostate biopsies leans on interpretation of PSA, urinary markers like PCA3, and the results of imaging studies especially multimodal MRI which has been developed for 10 years and nomograms combining all these results.

A better knowledge of family factors and genetic profiles will probably allow, in the near future, a better identification of the patients with an aggressive tumor, leading to improvement of screening diagnosis and adapted treatments.

6.2 Diagnosis of Prostate Cancer (PCa): Biological Evaluation

6.2.1 Blood Markers

6.2.1.1 PSA

PSA remains one of the cornerstones of biological markers of prostate cancer but due to the lack of cancer specificity, interpretation may be influenced by many factors.

For example, PSA is increased with benign prostate hypertrophy, urethral trauma, bacterial acute or chronic prostatitis, or endoscopic bladder exploration.

On the other hand, obesity, or different medications like hormonotherapy, finastéride, or dutasteride decrease the value of PSA (Payne et al. 2011).

Despite these limits, PSA remains nevertheless the marker of reference.

As there is no real threshold of PSA value below which the clinician is allowed to eliminate the back thought of prostate cancer prostate, it is advisable to interpret the value of PSA in order to limit the negative and the false-positives of the test and to optimize the indication of prostate biopsies.

This is more and more important, considering the potential morbidity of the biopsies such as infectious risk, which increases with the number of biopsies carried out, and hemorrhagic complications (hematuria, rectal hemorrhage), themselves facilitated by anticoagulant treatments started for cardiovascular diseases.

To increase PSA accuracy and interpretation, the clinician can use:

- *PSA density* (*PSA d*), described by Oesterling (Beduschi and Oesterling 2007), is interesting while adjusting with prostatic volume, in particular, with the volume of the zone of transition.
- The use of the PSA density improving specificity could avoid between 25 and 37% of biopsy. The limiting value is of 0.10 ng/ml/cm^3 of prostate.
- Multivariate analysis showed that PSA transitional zone was more powerful in prediction of prostate cancer however, we must keep in mind that PSA density measurement requires transrectal ultrasound and it is unlikely that it will replace PSA for prostate cancer screening (Benson et al. 1992).
- *PSA velocity* (*PSA v*) *or PSA doubling time* (*PSA DT*) analyses variations of PSA *measurements with time*.
- *The accurate measurement of* PSA v or PSA DT requires longitudinal checking over many years and can be calculated easily on the net (www.mskcc.org/mskcc).
- While PSA DT can be interesting for prostate cancer detection with a threshold >0.65 ng/ml, PSAv >0.75 ng/ml/year or with a threshold of 2 ng/ml the year before, prostatectomy is now recognized as a specific factor of death

(Carter et al. 1992); PSA v could be helpful in detecting aggressive cancer and in determining patients to be rescreened for early detection (Schroder et al. 2008).

- *Different thresholds, while adjusting PSA value with age*
- Interpretation of PSA according to the age would make it possible to increase the detection of cancer among young patients with a variable threshold between 40 and 80 years.
- (Steuber et al. 2008) suggests the realization of the first PSA blood test at 40 years old which must be lower than 0.7 ng/ml; interestingly, an early result would limit the number of blood controls later.
- However, all these modifications tend to correlate highly with PSA, and the few studies that appropriately evaluated their independent diagnostic contribution to PSA showed no incremental value above PSA (Steuber et al. 2008).
- *Others blood markers*, combining PSA with the result of molecular isoforms: ratio of free PSA/total PSA, pro PSA, or complexed PSA values, PHI, etc. All these biomarkers are under evaluation and discussed further.
- *Nomograms*
- Many authors also recommend determining for their patients their personal risk by using a risk calculator based on different data in order to decide with the clinician whether or not to undergo a biopsy (www.uroweb.org; http://www.prostatecancer-riskcalculator.com/via.html). We must keep in mind that these nomograms are based on different databases and that they are not completely adapted to our own patients but they are undoubtedly helpful (Ngo et al. 2011; Parekh et al. 2006).

6.2.1.2 PSA Isoforms

As t PSA has a limited specificity and sensibility in determining the presence of prostate cancer especially in the range between 2 and 10 ng/ml, several derivatives have been described (Fig. 6.1) and their performance studied (Jolivet-Reynaud et al. 2008).

- *% Free PSA* [*(f PSA/t PSA) × 100*]:
- The f PSA/tPSA ratio is suspected of cancer when this report is lower than 10 or 15%, and this was an important predictor of prostate cancer if the volume of the gland was <30 ml (Djavan et al. 2011).
- Free PSA levels below 15–25% are classically associated with an increased risk of prostate cancer, but it is estimated that only 30–50% of men with free PSA less than 15% have a positive biopsy (Catalona and Partin 1998).
- In a large review, Roddam (Roddam et al. 2005) has shown that the diagnostic performance of f/t PSA and c PSA was equivalent in both the 2–4 and 4–10 ng/ml t PSA ranges, while the performance of the f/t PSA tests in the 4–10 ng/ml range was significantly superior to that in the 2–4 ng/ml range.
- So, % free PSA can be used to increase the sensitivity when t PSA has lower values than 4 ng/ml or to increase the specificity of t PSA when it is between 4 and 10 ng/ml.
- This meta-analysis showed that the specificity of % free PSA remains low, 18% at a sensibility of 95% in the 4–10 ng/ml t PSA range, and 6% in the 2–4 ng/ml range (Guazzoni et al. 2011), thus limiting the interpretation of this blood test which can vary with kits of different manufacturers.
- *Complexed PSA*
- Complexed PSA is PSA bound to protease inhibitor.
- Complexed PSA to α_1 antichymotrypsin is augmented in patients with prostate cancer. This blood test requires immunoassay and was shown to moderately improve specificity by 6.2–7.9% compared to t PSA in the range 2.0–10.0 ng/ml, but because of the limited amount of data, diagnosis performance of c PSA is difficult to investigate (Partin et al. 2003).
- *B PSA*
- Milolacyk has found that B PSA was augmented in the transitional zone of patients with benign prostatic hyperplasia (BPH) (Mikolajczyk et al. 2000; Mikolajczyk et al. 2004), suggesting that assays could discriminate patients with BPH from those with early prostate cancer (Canto et al. 2004).
- To our knowledge, this has not been confirmed by multicentric studies.
- *p2 PSA* ([*−2*] *pro PSA*)

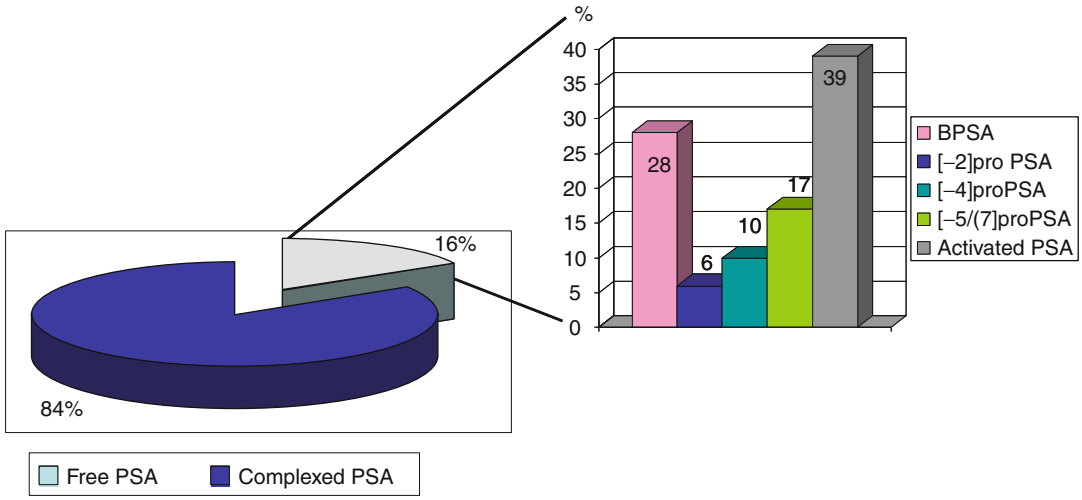

Fig. 6.1 Repartition of PSA isoforms

- Pro PSA is one of several distinct isoforms of free PSA found in serum. The primary form in PCa tissue is p2 PSA; p2 PSA is a PSA isoform, namely, % p2 PSA.
- Prostate health index (PHI) is a mathematical formula combining % p2 PSA with f PSA and PSA [p2 PSA/f PSA × t PSA $^{1/2}$]. This mathematical combination of f PSA, t PSA, and p2 PSA was recently described, and an immunoassay system (Jansen et al. 2010) seems promising because p2 PSA and PHI were significantly higher in patients with prostate cancer than in controls (Catalona et al. 2011; Sokoll et al. 2008).
- p2 PSA may improve the accuracy of t PSA and f PSA in predicting prostate cancer on biopsy of men when t PSA ranges between 4 and 10 ng/ml (Guazzoni et al. 2011), and % p2 PSA and PHI were 23% more accurate than t PSA in detecting patients with prostate cancer with sensibilities of 42.9% for PHI and 38.8% for % p2 PSA, higher than those of t PSA (5.1%), % f PSA (20%), and PSA d (26.5%) at 90% specificity.
- The usefulness of p2 PSA and its relationship with prostate cancer aggressiveness are in debate, and PHI may have a relationship with biopsy Gleason score (Catalona et al. 2011). However, due to the small number of patients included in these studies, multicentric confirmatory studies are mandatory.

- *Early prostate cancer antigen 2* (*EPCA-2*)
- Early prostate cancer antigen (EPCA) is a nuclear matrix protein that has shown promise as a diagnostic marker for PCa. A recently developed blood-based assay showed a 92% diagnostic sensitivity and a 94% diagnostic specificity in a small cohort of 12 PCa and 34 healthy patients (Paul et al. 2005). It was confirmed in a larger cohort of 385 men in which specificity and sensibility of EPCA2 blood test to detect prostate cancer were, respectively, 94% and 92% while PSA sensitivity was 65%, differentiated localized tumor from extracapsular tumor ($p < 0.0001$), and confirmed that EPCA-2 was able to differentiate localized PCa from metastatic PCa with an AUC of 0.89 (Leman et al. 2007). However, methodologic deficiencies with this marker have been identified, casting doubt on its actual validity (Diamandis 2007).
- Recently, two studies on Chinese populations were published, confirming the interest to EPCA-2. In the first one, serum EPCA-2, with a cut-off of 10 ng/ml, was measured on 449 patients with symptomatic BPH and 112 healthy men: 100% specificity for healthy men. And 98% specificity and 100% sensitivity in separating men with PCa from those without were found (Zhigang et al. 2010). In the second one, 40 healthy controls, 77 patients with localized PCa who underwent

radical prostatectomy, and 51 patients with locally advanced or metastatic disease who received androgen deprivation therapy were enrolled in a prospective study. Serum EPCA level, cut-off 15.2 ng/ml, was significantly correlated with a poor prognosis (Zhigang et al. 2011).

- In summary, EPCA-2 seems to be a specific diagnostic marker for prostate cancer, an aggressive marker of prostate cancer, but larger studies are needed to confirm these promising data.
- *Other blood markers*
- Many markers are discussed in the literature including insulin-like growth factor 1, human glandular kallikrein 2, molecular subfraction of f PSA, somatic cytochrome C, glutamate decarboxylase 1, etc.

Today, none of them is useful in clinical practice, and further prospective studies are required to evaluate their efficacy against other markers and all require specialized laboratory (Djavan et al. 2011).

6.2.2 Urinary Markers

6.2.2.1 PCA3

PCA3 measurement in urine specimens is a prostate-specific marker associated with the likelihood of biopsy prostate cancer detection, considered as a promising new biomarker under development because PCA3 codes for a messenger RNA highly overexpressed by prostate cancer cells.

Performance of PCA3 compared to or associated with other markers (PSA, free PSA) is always under evaluation, but many results suggest that there is a significant potential to combine PCA3 with other risk factors to predict biopsy outcome (Steuber et al. 2008).

Usually, PCA3 measurement is proposed as a second-line diagnostic test after a previous negative biopsy result. In this group, PCA3 score can help the decision of whether or not to rebiopsy regarding the high specificity of the test around 70%.

Different cut-offs of PCA3 score have been studied in the literature in order to predict prostate cancer in men with one or two previous negative biopsy (Haese et al. 2008; Remzi et al. 2010).

Table 6.2 Performance of PCA3 score according to different cut-offs

PCA3 score cut-off	Sensitivity (%)	Specificity (%)
>20	73	51
>35	47	72
>50	35	82
% f PSA cut-off 25%	83	23

In a multicentric European prospective study of 463 men candidate for a second or third repeat biopsy, Haese showed that with a cut-off 35, PCA3 score was significantly higher in men with significant cancer; PCA3 score was superior to % free PSA for predicting biopsy outcome. Sensibility and specificity of PCA3 assay were reported according to different cut-offs (Table 6.2).

The sensibility and specificity of the PCA3 score at a cut-off of 35 was comparable in men with one or two previous negative biopsy with an area under the receiver operating curve (ROC) of 0.66–0.87.

PCA3 score was not affected by age, prostate volume, chronic prostatitis, or total PSA (t PSA) value and confirming that PCA3 score was promised in guiding repeat biopsy decisions (Deras et al. 2008; Vlaeminck-Guillem et al. 2011).

PCA3 performance in combination with PSA was validated in the REDUCE trial (Aubin et al. 2010); in this study, PCA3 was increased in cancer with significant Gleason score greater than 6; the result was predicting biopsy outcome at 2 years and could give additional information to evaluate the cancer risk and help the clinician in biopsy decision.

PCA3 was studied as a first-line diagnostic test and compared to PSA value >3 ng/ml during rescreening of 721 men biopsied within the ERSPC trial (Roobol et al. 2010). In this study, the cut-off score of PCA3 was very low (>10) and also compared with the recommended cut-off value of 35. Based on the ROC analyses, PCA3 performs marginally better than PSA ($p = 0.143$), suggesting that in the low PSA ranges, PCA3 score was not useful in identifying aggressive cancer. Contradicting results were recently published in another study of 516 men enrolled with a total PSA of 2.5–10 ng/ml before initial biopsy decision. With a biopsy detection rate of

40%, ROC curve analysis showed a significant AUC of >0.761 for PCA3 score (>35) versus 0.577 for t PSA, 0.689 for PSA d and 0.606 for free PSA, suggesting a clinical utility for initial diagnosis especially when the result is included in a risk calculator (PCPT risk calculator available at: http://deb.uthscsa.edu/URORiskCalc/Pages/calcsPCA3.jsp).

In parallel, PCA3 score may have a clinical utility identifying patient with low-volume and low-grade tumor. PCA3 was correlated with tumor volume on 72 prostatectomy specimens and prediction of extracapsular extension (Whitman et al. 2008). Correlation with multifocality was also reported in a study of 102 patients treated by radical prostatectomy (Vlaeminck-Guillem et al. 2011) with a median PCA3 score of 96 when more than 4 cancer foci were identified compared to 32 when only one tumor foci is present.

In summary, despite heterogeneous results of the studies in terms of sensibility and specificity caused by the differences in the optimum cut-off point of the PCA3, PCA3 assay is helpful as a diagnostic tool in the decision of which men need repeat biopsy; PCA3 score may be useful as a diagnostic tool for initial biopsy, and future studies will clarify its position as a prognostic marker (Auprich et al. 2010; Chun and De la Taille 2009; De la Taille et al. 2011; Ficarra et al. 2010; Auprich et al. 2011.

6.2.2.2 Annexin A3; Sarcosine

Annexin A3 (ANXA3) belongs to a family of calcium and phospholipid binding protein that is implicated in cell differentiation, migration, and immunomodulation. Five hundred ninety-one patients from 4 European urological clinics were prospectively recruited. Urine was obtained directly after digital rectal examination and Annexin A3 was evaluated. Annexin A3 has an inverse relationship to cancer, and therefore its specificity was much better than that of prostate specific antigen (Schostak et al. 2009).

Sarcosine is an *N*-methyl derivative of the amino acid glycine. Androgen receptor and the ERG gene fusion product coordinately regulate components of the sarcosine pathway. Sarcosine was identified as a differential metabolite that was highly increased during prostate cancer progression to metastasis and can be detected non-invasively in urine. Sarcosine is considered as a potentially important metabolic intermediary of cancer cell invasion and aggressively (Sreekumar et al. 2009).

6.2.3 Fusion Genes: TMPRSS2-ERG

The recent identification of fusion gene provides new insights into the initial mechanisms of molecular events implicated in the prostate carcinogenesis (Beuzeboc et al. 2009; Perner et al. 2006). The gene TMPRSS2 was demonstrated to be upregulated by androgenic hormones in prostate cancer cells and downregulated in androgen-independent prostate cancer tissue. TMPRSS2 protein's function in prostate carcinogenesis relies on overexpression of ETS transcription factors, such as ERG (estrogen-regulated gene). ERG overexpression contributes to development of androgen independence in prostate cancer through disruption of androgen receptor signaling. The presence of TMPRSS2-ERG fusion gene in up to half of all human prostate cancer makes it one of the most common genetic rearrangements in human epithelial tumors (Demichelis et al. 2007).

A significant association was observed between TMPRSS2-ERG, identified in fluorescence *in situ* hybridization (FISH), rearranged tumors through deletions and higher tumor stage and the presence of metastatic disease involving pelvic lymph node. The deletion as cause of TMPRSS2-ERG fusion is associated with clinical features for prostate cancer progression compared with tumors that lack TMPRSS2-ERG rearrangement. The TMPRSS2-ERG fusion may contribute to a more aggressive prostate cancer phenotype and perhaps account in part to higher grade prostate cancer and support the critical role of ERG as an oncogene in prostate cancer (Perner et al. 2006).

Recently, combining urinary detection of TMPRSS2-ERG and PCA3 with serum PSA has been described as performing better than the individual biomarkers alone in predicting prostate cancer (Salami et al. 2011).

Urinary TMPRSS2-ERG in combination with PCA3 improved the performance of the

multivariate Prostate Cancer Prevention Trial (PCPT) risk calculator in predicting cancer on biopsy. Tomlins et al.'s study demonstrates that urine TMPRSS2-ERG, in combination with PCA3, enhances the utility of serum PSA for predicting prostate cancer risk and clinically relevant cancer on biopsy. The two limitations of this study are that more than 85% of patients were Caucasian and only PSA-screened cohort had been retained. Studies with other geographic cohorts of men and non-PSA-screened population will be required to determine the potential utility of these biomarkers (Tomlins et al. 2011).

In summary, the fusion gene TMPRSS2-ERG is a promising new biomarker predicting aggressive prostate cancer phenotype. Recently, a panel of urinary TMPRSS2-ERG associated with urinary PCA3 and serum PSA seems to be interesting for predicting prostate cancer risk and clinically relevant cancer on biopsy.

Evidence is pointing to the use of a multiple markers to fully characterize the heterogeneity of prostate tumor. Multiplex models PCA3, TMPRSS2, ERG, Annexin A3, and sarcosine seem to add more to the diagnostic performance for predicting PCa (Cao et al. 2010).

6.3 Classification and Prognostic Groups

6.3.1 The 2009 TNM Classification (Tumor Node Metastasis)

TNM 2009 is used throughout different guidelines for diagnosis and treatments and must be used systematically.

T – Primary tumor

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Clinically unapparent tumor not palpable or visible by imaging

T1a Tumor incidental histological finding in 5% or less of tissue resected

T1b Tumor incidental histological finding in more than 5% of tissue resected

T1c Tumor identified by needle biopsy (e.g., because of elevated PSA level)

T2 Tumor confined within the prostate

T2a Tumor involves one half of one lobe or less

T2b Tumor involves more than half of one lobe, but not both lobes.

T2c Tumor involves both lobes

T3 Tumor extends through the prostatic capsule

T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement

T3b Tumor invades seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

M – Distant metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

M1a Non-regional lymph node(s)

M1b Bone(s)

M1c Other site(s)

Remarks:

1. Tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.
2. Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.
3. Metastasis no larger than 0.2 cm can be designated pN1 mi.
4. When more than one site of metastasis is present, the most advanced category should be used.

6.3.2 Classifications

Using the TNM classification, different prognostic groups are useful to stratify patients and discuss treatments.

According to d'Amico, three different groups are described:

Table 6.3 Staging and risk stratification of PCa

	Low risk	Intermediate risk	High risk
Clinical stage	T1a–c N0 M0 T2a N0 M0	T2b–c N0 M0	T3 – T4 N0 M0
PSA	And <10 ng/ml	Or 10–20 ng/ml	Or >20 ng/ml
Gleason score	And ≤6	Or =7	Or >7

Table 6.4 Staging of PCa according to EAU guidelines 2011

Prognostic group	Clinical stage			PSA	Gleason score
Group I	T1a–c T2a	N0 M0		<10 <10	≤6 ≤6
Group II a	T1a–c T2a,b	N0 M0 N0 M0		<20 ≥10<20 <20	7 ≤6 ≤7
Group II b	T2c T1 – 2	N0 M0		Any PSA ≥20 Any PSA	Any Gleason Any Gleason ≥8
Group III	T3a,b	N0	M0	Any PSA	Any Gleason
Group IV	T4 Any T	N0 N1 Any N	M0 M0 M0	Any PSA	Any Gleason

In the EAU guidelines, four prognostic groups have been published (Table 6.4).

Note: When either PSA or Gleason is not available, grouping should be determined by cT category and whichever of either PSA of Gleason is available. When neither is available prognostic grouping is not possible, use stage grouping.

6.4 Diagnosis and Local Evaluation of Prostate Cancer: The Place of MRI

While MRI provides the best images of prostate, there is no definite consensus about the role of MRI in prostate cancer either for early detection or for local staging.

Traditionally, MRI for prostate cancer has been performed with an endorectal coil and a 1.5 T machine to predict the local extension of the tumor. With the introduction of higher field strength (3 T) and the development of new MR techniques, detection and characterization of prostate cancer imaging is improving.

6.4.1 MR and Early Cancer Detection

Multiparametric MRI has shown a potential value in prostate detection, and its role is now increasing.

Multiparametric MRI includes standard T2-weighted sequences, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and diffusion-weighted imaging sequences (DWI sequences). Each of these sequences has his own interest and their combination is necessary, many data suggesting that these sequences have the potential to guide biopsy (Scherra et al. 2010).

Obviously, a radiological expertise in prostate imaging is mandatory to define tumor localization and volume. A pelvic phased array coil is commonly used; this does not require bowel preparation like endorectal coils, but a bowel relaxant is recommended.

3 T equipment is under evaluation and could improve the sensibility of the technique in cancer detection to 92% when using DW sequences (Roy et al. 2010).

However, in the literature, the reported accuracy of prostate cancer detection with MRI varies widely between 54% and 93% according to technical issues, patient groups or the experience of the reader.

The relative high specificity of multiparametric MR seems remarkable when combining more than one functional MR technique like DW + prostate spectroscopy which analyses the concentration of different metabolites (citrate, creatine, choline) within prostate voxels could reduce indications for non-useful biopsy (Sciarra et al. 2011). However, controversies are still reported because of limited data on spectroscopy.

At least, accuracy of MR for identification of cancer remains tumor volume dependant:

- Considering any tumor volume, sensibility of MR for detection of cancer foci remains low at 32% with a specificity of 95%.
- When tumor volume is >0.5 ml, for an expert radiologist, sensibility approaches 85% without any significant change of specificity.

MRI may also contribute to depict anterior cancer especially when adding DW imaging and dynamic sequences (Sciarra et al. 2011).

In a recent publication, 16 European prostate experts discussed different items related to imaging parameters for tumor detection, localization, imaging interpretation, and reporting. For disease detection, T2W, DW, and DCE sequences were appropriated for any cancer in the peripheral zone. No clear benefit of proton spectroscopy was reported for prostate localization, but combination of the different metabolite ratios was used, with promising discrimination among different aggressiveness cancers results (Kobus et al. 2011).

Different "guidelines" for prostate cancer imaging were reported (Dickinson and Ahmed 2011):

- All individual lesions and areas of prostate should be separately scored for probability of malignancy with and ADC measurement, and the maximum diameter of largest abnormal lesion should be recorded because different information are possible to be gained from each sequence in isolation.
- DW sequence should always be associated: it is the most appropriate to exclude clinically significant disease as defined neither by a lesion size <0.5 or <0.2 cm^3 nor by a peripheral lesion Gleason 7 (4 + 3).
- At least, clinical results (DRE, PSA, history of previous surgical or medical prostate treatments, time scale, and results of previous biopsy) should be transmitted to the radiologist as these informations may influence the overall score for probability of cancer given on the report (Figs. 6.2a, b, 6.3 and 6.4).

A recent study compared diagnostic accuracy of diffusion tension imaging, Dynamic Contrast Enhanced magnetic resonance imaging and their combination in diagnosing prostate cancer on 25 patients with clinical suspicion of prostate cancer with 3 T MRI before TRUS biopsies. The analysis showed that the combination of both techniques improved the accuracy in prostate cancer diagnostic with a specificity of 77% (69–83%) and a sensitivity of 100% (97–100%), but the cohort is small (Kozlowskia et al. 2010).

In summary, MRI, delivered with these standards, could be helpful for cancer localization and targeted biopsy (Dickinson and Ahmed 2011), but today, MRI cannot be routinely incorporated into clinical care before a first set of biopsy. Multimodal MRI can help the clinician to identify patients at risk for clinically significant cancer and reduce the number of non-useful biopsy. Targeted biopsy using fusion of 3D transrectal ultrasound and MRI images can optimize detection of significant cancer and different equipments are already available in order to improve biopsy strategy (Urostation®, Targetscan®). MR-targeted cores will probably play a major role in the future (Pondman et al. 2008).

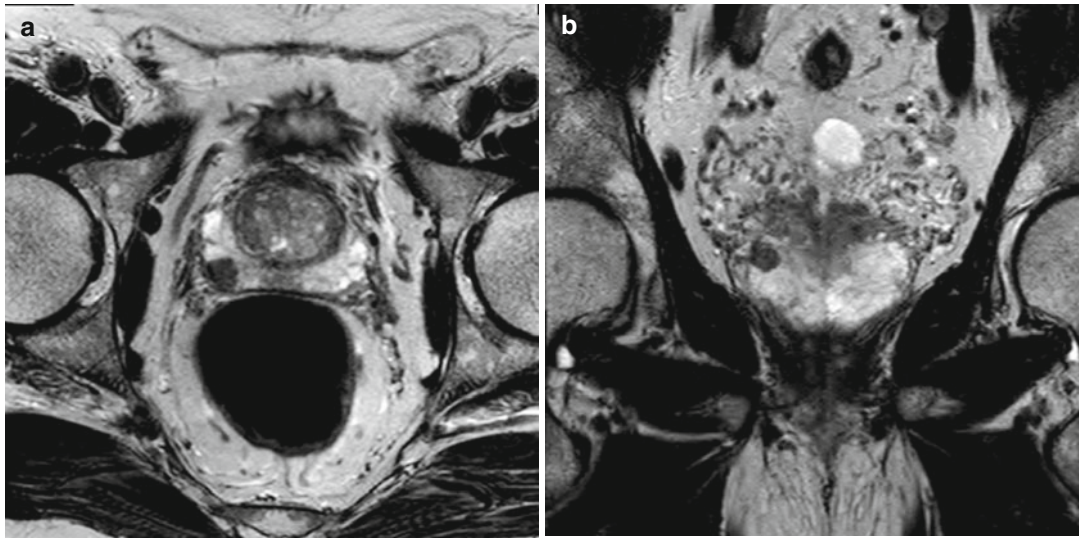

Fig. 6.2 (**a** and **b**) Axial T2-weighted and coronal images show low signal intensity in the base of the left peripheral zone

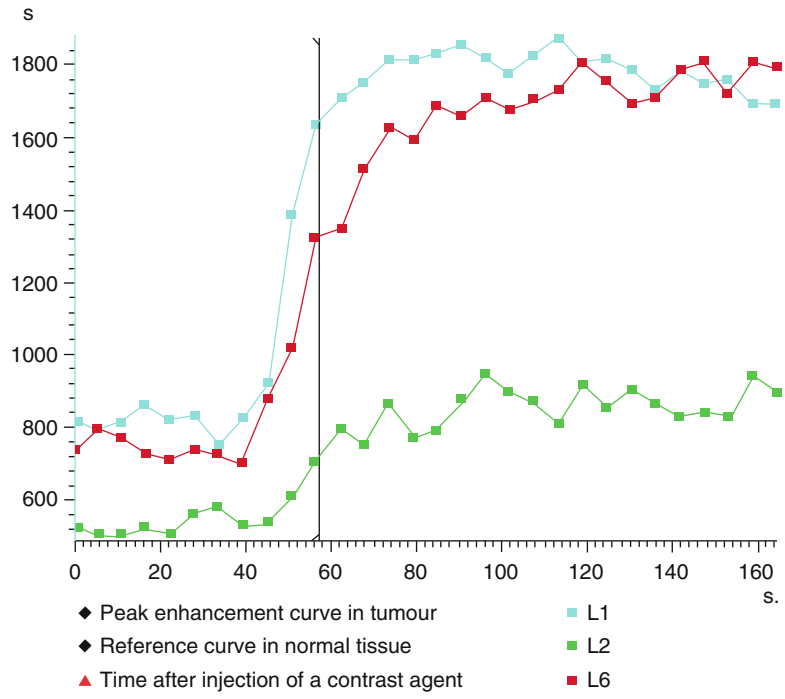

Fig. 6.3 Dynamic sequences show early enhancement in the suspected area

6.4.2 Ultrasonography, Doppler, and Elastography

Detection and localization of prostate tumors using grayscale ultrasound are poor, and transrectal ultrasound is mainly used to guide systematic biopsy. However, TRUS has several limitations for prostate detection: it is subjective, operator-dependent, and prostate echogenicity changes are often non-cancer-specific (hypo 60–70%; iso 25%; hyper less than 5%) (Gomella et al. 2001).

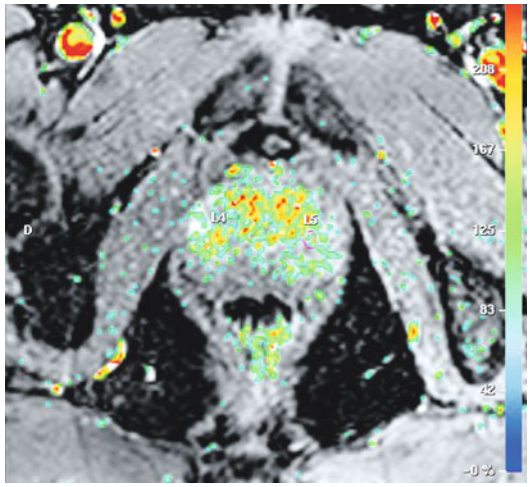

Fig. 6.4 DWI sequences show lower ADC in the suspected area, resulting in restricted water movement in PCa zone where cellular density is higher than in normal glandular tissue

As tumor growth induces neovascularization, enhanced ultrasound techniques have been investigated, such as color flow Doppler (CDI) and power Doppler studies. Although studies suggest that CDI has potential prognostic significance, CDI still has two major pitfalls: overlap with prostatitis and low sensitivity in detection of tumor blood flow within prostate cancer. Contrast-enhanced ultrasound was developed in prostate; different contrast agents were then administered intravenously because they add reflectors into the bloodstream and, as these microbubbles remain intravascular, this technique could increase the sensibility of color and power Doppler imaging (Gomella et al. 2001). Routine use of CEUS was analyzed as a first-step research program by four European centers in the period 2002–2006; additional value of contrast-enhanced ultrasound was not established in this study (Wink et al. 2008). Utilization of phosphodiesterase-5 inhibitor to increase microvascularization during power Doppler ultrasound is another approach which could increase cancer detection (Morelli et al. 2011), but today, diffusion of CEUS techniques remains limited by the availability of contrast agent, cost and a lack of prospective randomized trial demonstrating a clear benefit over standard biopsy techniques.

At least real-time elastography is also a promising tool for prostate cancer detection and targeted biopsy. This technique was analyzed for patients scheduled for radical prostatectomy, and identification of the lesions was compared with radical prostatectomy specimen; the positive predictive value, negative predictive value and accuracy were 87%, 5%, 59%, and 76%, respectively. Elastography findings correlated best with tumor lesions in the apical region, and detection rate increased with higher Gleason score, and results were reproducible on more recent study. However, more objective and reliable parameters are needed to limit the subjective estimation of electrographic colors and the inter-observer variability of elastography for systematic biopsy (Aigner et al. 2010; Salomon et al. 2008; Walz et al. 2011).

6.5 Conclusion

Research on prostate cancer markers is concerning most of developed countries.

Despite various and promising new blood, and urine biomarkers, today, PSA remains the gold standard, and guidelines to improve its utilization are frequently proposed and discussed. Other markers are always under investigation and still have to be validated to improve prostate cancer detection and limit the number of prostate biopsy on asymptomatic men.

The use of multiple markers in combination with clinical data will probably aid in predicting patients who are at risk for developing PCa, but cost will limit their utilization.

Furthermore, better visibility of malignant tissue with new imaging techniques is also improving. In the future it is likely to be able to better select patient for indications of prostate biopsies, and then to define aggressiveness of the tumour using a combination of radiological images and more specific biological tests.

6.6 Appendix A

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month, how often have you had to urinate again less than 2 h after you finished urinating?	0	1	2	3	4	5
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month, how often have you had to push or strain to begin urination?	None	1 time	2 times	3 times	4 times	5 times or more
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

Total Symptom Score

The International Prostate Symptom Score uses the same seven questions as the AUA Symptom Index (presented above) with the addition of the following Disease Specific Quality of Life Question (bother score) scored on a scale from 0 to 6 points (delighted to terrible):

> If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?

6.7 Individual Items of International Index of Erectile Function Questionnaire and Response Options (US Version)

Question/Response Options

Q1: How often were you able to get an erection during sexual activity?
0 = No sexual activity
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

Q2: When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
0 = No sexual activity
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

Q3: When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
0 = Did not attempt intercourse
I = Almost never/never

2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

Q4: During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
0 = Did not attempt intercourse
I = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

Q5: During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
0 = Did not attempt intercourse
1 = Extremely difficult
2 = Very difficult
3 = Difficult
4 = Slightly difficult
5 = Not difficult

Q6 How many times have you attempted sexual intercourse?
0 = No attempts
1 = One to two attempts
2 = Three to four attempts
3 = Five to six attempts
4 = Seven to ten attempts
5 = Eleven + attempts

Q7: When you attempted sexual intercourse, how often was it satisfactory for you?
0 = Did not attempt intercourse
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

(Raymond et al. 1997)

6.8 Appendix C

Category	Weights of the comorbid conditions
Myocardial infarct	1
Congestive heart failure	1
Peripherical vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes + end organ damage	2
Any tumor	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
AIDS	6

The 19 conditions contributing to conventional Charlson score

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Active Surveillance for Favorable Risk Prostate Cancer: Background, Patient Selection, Triggers for Intervention, and Outcomes

7

Laurence Klotz

Contents

7.1 Introduction

Modern medicine, with its emphasis on early detection of disease, has enhanced the health of men and women throughout the world. However, early detection of disease carries with it a significant risk of overdetection of conditions that, although they fulfill pathological or clinical criteria for disease, pose little or no threat to the patient.

With the advent of increasingly sensitive and widely used diagnostic testing, cancer overdiagnosis in particular has emerged as a problem in multiple organ sites. Welch and Black (2010) recently estimated that the "overdiagnosis" rates for prostate, thyroid, and breast cancer, if the entire reservoir of disease were being detected, are 87–94%, 99.7–99.9%, and 43–90%, respectively. Those estimates reflect the high prevalence of microfocal disease in the healthy population (30–70% for prostate, 36–100% for thyroid, and 7–39% for breast cancer).

Because of the very high incidence of latent prostate cancer in aging men, the availability of the PSA test, and the long-term effects of definitive therapy, this has the greatest ramifications in the case of prostate cancer.

Screening for prostate cancer with prostate-specific antigen (PSA) is widely used in North America and Europe. Compared to clinical diagnosis, it results in the identification of potentially lethal prostate cancer at a much more curable stage. The widespread use of PSA has been associated with significant falls in prostate cancer mortality (Bray et al. 2010). The cost, however, is

L. Klotz, M.D.
Department of Surgery, Sunnybrook Health Sciences Centre, University of Toronto,
2075 Bayview Ave.#MG408, Toronto,
ON M4N 3M5, Canada
e-mail: laurence.klotz@sunnybrook.ca

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a very high rate of diagnosis—and treatment—of prostate cancer.

The recently published European Randomized Trial of Screening for Prostate Cancer (ERSPC) reported that, in 180,000 men randomized either to PSA screening every 4 years or to usual care, prostate cancer mortality was reduced by 20% (Schroder et al. 2009). A more recent randomized screening study from Goteborg (Hugosson et al. 2010) estimated the mortality reduction with screening at 50%. The number needed to treat for each prostate cancer death avoided in ERSPC was 48. It is widely anticipated that this NNT figure will fall with longer follow-up. Indeed, the NNT in the Goteborg study was 12. However, most patients dying of prostate cancer had intermediate- or high-grade disease (Van den Bergh et al. 2010a and 2010b). The number needed to treat with low-grade, small-volume prostate cancer for each death avoided is almost certainly higher.

Despite randomized controlled trials demonstrating survival benefits for prostate cancer screening among men with good life expectancy, the "harms of detection," primarily those related to overtreatment, underlie the negative assessments of screening promulgated by the U.S. Preventive Services Task Force (http://www.uspreventiveservicestaskforce.org/uspstf12/prostate/prostateart.htm) and others. Although the new recommendation by the American Urological Association to begin screening at age 40 for most men (Greene et al. 2009) might be expected to identify a higher proportion of lethal tumors at an earlier, curable stage, it will likely be associated with risks of further overdiagnosis of indolent tumors among men at even younger ages. The implication is that treatment must be applied selectively, and the timing and aggressiveness of treatment should reflect disease and patient characteristics.

Much recent evidence suggests that patients diagnosed with low-grade cancer who go on to die of disease have been undergraded at the original biopsy and in fact harbored higher grade cancer (Klotz et al. 2010). The likelihood of "true" microfocal low-grade disease actually progressing to metastatic disease appears to be extremely low (Eggener et al. 2011).

The condition of most men with favorable-risk prostate cancer is far removed from the consequences of a rampaging, aggressive disease. The majority of these men are not destined to die of their disease, even in the absence of treatment. Unfortunately, most of these patients are treated radically and are exposed to the risk of significant side effects. A selective approach to treatment is therefore appealing. The concept is to identify the subset that harbors more aggressive disease early enough that curative therapy is still a possibility, thereby allowing the others to enjoy improved quality of life, free from the side effects of treatment.

This review article summarizes the evidence supporting active surveillance and the current approach to this management strategy, including the roles of serial biopsy, PSA kinetics, and MR imaging.

7.2 Definitions

A key concept is the pathologic definition of clinically insignificant prostate cancer. For 30 years, this has been defined as Gleason 6 or less prostate cancer with a volume <0.5 cc, based on work by T. Stamey on cystoprostatectomy specimens (Kabalin et al. 1989). There is much evidence that this is an overly stringent definition. Recently, the ERSPC group performed a similar analysis based on the ERSPC patients (Wolters et al. 2011). Their conclusion was that the threshold for clinically insignificant disease was a cancer volume <1.3 cc. This has major implications for the use of MRI and other imaging modalities.

An emerging consensus therefore supports deferring treatment initially for a growing proportion of men diagnosed with low-risk (i.e., low volume, stage, and grade) prostate cancer. Under the management strategy of active surveillance, men are followed carefully with serial PSA assessments, repeat biopsies, and other tests intended to identify early signs of progression. The term "active surveillance" has supplanted "watchful waiting," but the two are not synonymous. The latter term generally applied to older men with significant comorbidity; they were advised to defer treatment unless symptoms developed, at which point palliative androgen deprivation could be offered. Active surveillance, on the other hand, rests on the presumptions that

Table 7.1 Summary of prospective active surveillance Cohorts

Author (Year)	*N*	Median F/U months	pT3 in RP pts	OS	CSS
Van As 2007	326	22	8/18 (44%)	98	100
Carter 2007	407	41	10/49 (20%)	98	100
Van den Bergh 2009	533–1,000	48	4/24 (17%)	90	99
Soloway 2008	99	45	0/2	100	100
Roemeling 2007	278	41		89	100
Khatami 2006	270	63		Not stated	100
Klotz 2010	452	73	14/24 (58%)	82	97@10 year
Total	2,130–3,000	43		90	99.7

the lead time from diagnosis to clinical progression is usually long for low-risk disease (Draisma et al. 2009) and that at the first signs of higher risk disease, the cancer can be treated, very likely well within the window of opportunity for cure. The distinction is particularly important in that neither oncologic nor quality of life outcomes from patients assigned to observation in older randomized trials (Bill-Axelson et al. 2011; Klotz and Thompson 2011), nor those identified in population-based registries as receiving conservative management (Johansson et al. 1997), can be considered representative of those expected with contemporary active surveillance.

Definition: Active surveillance in the context of localized prostate cancer is defined as initial expectant management, with close follow-up, and selective delayed intervention for the subset of patients reclassified over time as at higher risk for progression, based on clinical, pathological, or molecular parameters.

7.3 Experience with active surveillance

Table 7.1 summarizes the published experience with active surveillance, comprising more than 2,900 patients (Van As and Parker 2007; Carter et al. 2007; van den Bergh et al. 2009; Soloway et al. 2008; Roemeling et al. 2007; Khatami and Hugusson 2006; Klotz et al. 2010). Certain observations emerge from these data.

Over time, approximately one third of patients will be reclassified as higher risk for progression and will be treated. This proportion depends on how stringently patients are evaluated at baseline, how "liberal" the inclusion criteria for surveillance are, and how quick the clinician is to pull the trigger for treatment. A very stringent approach, restricting surveillance to men who have had extended biopsies with only one or two positive cores with minimal disease on those cores, will likely identify a cohort more likely to remain untreated. This will also mean that many men with indolent disease will not be offered surveillance.

In most cases that are reclassified as higher risk, the reclassification is due to upgrading at the time of repeat biopsy. This upgrading is not time dependent, suggesting strongly that it is due to more accurate sampling rather than true biologic progression. After an initial extended biopsy (10–14 cores), approximately 25% of patients will be found to have higher grade cancer on repeat biopsy. More than 90% of these are Gleason 3+4.

In the intermediate time frame (5–15 years), prostate cancer mortality is exceptionally low. To date, in the collected series, approximately 250 patients have been followed for between 10 and 15 years. The prostate cancer mortality in this group is also low. To date, none of the prostate cancer deaths in men on surveillance have occurred after the 10-year time point. The Toronto group has reported outcomes in the 30% of patients in that cohort treated radically. In that group, the PSA recurrence rate was 50%, representing 15% of the total cohort. Among the 453 patients in the cohort, the actuarial 10-year prostate cancer survival is 97%.

In most men on prostate cancer surveillance, mortality comes from other causes. In the most mature cohort (Toronto) (Klotz et al. 2010), with a median follow-up of 8 years, the relative risk for non-prostate-cancer death was 19 times that for

prostate-cancer mortality. Although prostate cancer mortality is likely to increase as the surveillance cohorts mature, so will non-prostate-cancer mortality. It is very plausible that the foregoing ratio will remain relatively constant.

The relative risk of prostate cancer in comparison with other-cause mortality is directly correlated with the age of the patients at diagnosis—insofar as the risk of other-cause mortality is a function of age. In men under 70 years of age, the cumulative hazard ratio for non-prostate to prostate cancer death was 9:1.

The limitation of these studies is the length of follow-up relative to the natural history of prostate cancer. It will require another 5–7 years before the most mature of these studies will have a median 15 years of follow-up. Nonetheless, the results to date are extremely encouraging.

Recently, the critically important Scandinavian trial of radical prostatectomy vs. watchful waiting reported their third update of overall and disease specific survival (Bill-Axelson et al. 2011). The magnitude of reduction in the rate of metastases and mortality in the "low-risk" group in this study is surprising, given the favorable outcomes reported above. These "low-risk" patients were clearly a heterogeneous group with many aggressive cancers. We have superimposed the data on prostate-cancer mortality in this study over those from the Toronto active surveillance cohort (Fig. 7.1) (Klotz and Thompson 2011). The differences are striking. The 10-year actuarial mortality from prostate cancer in the surveillance cohort is 3%, as compared with 8% in the watchful waiting group and 5% in the radical-prostatectomy group in the Scandinavian study. The favorable risk patients in the study by Bill-Axelson et al. differ from those in the Toronto surveillance cohort. Only 12% of the patients in the Scandinavian trial were diagnosed by means of PSA screening (stage T1c). Fine-needle aspiration or sextant biopsies, which can miss substantial cancers, were performed in the Scandinavian trial. Sampling with 10–12 cores, with confirmatory biopsies within 1 year, was performed in the Toronto cohort. Delayed curative therapy was available only in the surveillance cohort. The benefit of radical prostatectomy in low-risk patients should be extrapolated with caution to current low-risk screening-detected patients.

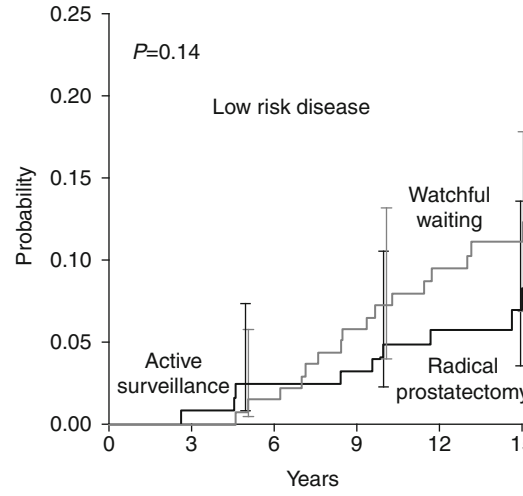

Fig. 7.1 Superimposition of Toronto active surveillance mortality over Scandinavian radical prostatectomy vs. watchful waiting mortality

7.4 Follow-up strategies

A number of recent publications have compared the pathologic findings at radical prostatectomy in men who fulfilled the D'Amico criteria for favorable risk prostate cancer (Oliveira et al. 2010; Kane et al. 2010; Raventós et al. 2010; Ploussard et al. 2010; Thaxton et al. 2010; Smaldone et al. 2010; Davis et al. 2010; Duffield et al. 2009; Mufarrij et al. 2010). Between 6% and 28% percent of men are upgraded to Gleason 3+4 or higher, and 15–20% have extracapsular extension. Several recent studies have indicated that, in most of the favorable risk patients with microfocal disease on biopsy harboring large-volume cancers, the occult cancers were anterior. This is logical given the posterior approach to biopsy taken with TRUS. This upgrading is thus primarily due to sampling error on the original biopsy rather than true grade progression over time. The implication is that the prostate must be characterized as carefully as possible after a diagnosis of favorable risk prostate cancer in order to identify the subset with adverse features early. How to do this most effectively is a matter of debate.

Biopsy: All patients contemplating surveillance must have a confirmatory biopsy within 12 months of the original biopsy. This biopsy should specifically target the anterior prostate

Table 7.2 Triggers for Intervention in surveillance series

	Klotz et al. (2010)	Van As et al. (2007)	Van den Bergh et al. (2009)	Soloway et al. (2008)	Carter et al. (2007)	Cooperberg et al. (2011)
PSA kinetics	DT < 3 years	PSA velocity <1 ng/ml/year	PSA DT < 3 years			<0.75 ng/ml/year
Grade progression		≥4 + 3 or >50% core	≥3 + 4 or >2 cores	≥3 + 4 or >2 cores	≥3 + 4 or >2 cores or >50% core	
Clinical progression	>50% increase in mass		>T2			

and anterolateral horn, as well as the traditional posterior peripheral zone.

If the confirmatory biopsy is negative or shows microfocal Gleason 6 disease, subsequent biopsies should be performed every 3–4 years, depending on PSA kinetics and/or clinical examination of the prostate. At age 80, biopsies may be discontinued (due to diminishing benefit of treatment of early prostate cancer) unless there are striking changes in PSA or prostate examination.

PSA should be performed every 3 months for 2 years and then every 6 months indefinitely. PSA doubling time or velocity should be calculated based, preferably, on 8–9 data points over a 2-year period. A PSA doubling time of >3 years is considered "stable," and such patients should be managed with ongoing surveillance unless there is a change in Gleason grade on biopsy.

In several of the published series, PSA doubling time or velocity has been used as a trigger for definitive intervention Table 7.2 (Klotz et al. 2010; Van As and Parker 2007; Carter et al. 2007; van den Bergh et al. 2009; Soloway et al. 2008; Cooperberg et al. 2011). A short doubling time and/or a PSA velocity >2.0 ng/ml/year is associated with a worse prognosis in many prostate cancer states. In men with an intact androgen axis, progression to metastatic disease is almost always accompanied by a substantial increase in PSA. In the Toronto cohort, 100% of patients who have progressed to metastatic disease have had a PSA doubling time <2 years (Loblaw et al. 2010). However, some recent studies have questioned the correlation between PSA kinetics and adverse disease characteristics (Ross et al. 2010). A recent overview of this subject concluded that PSA kinetics, although predictive, did not add predictive value to absolute PSA and should not be used for decision making in localized prostate cancer (Vickers 2008). Thus, our current approach is to use PSA kinetics as a guide for further evaluation rather than a trigger for intervention on its own.

Nonetheless, a common dilemma in managing surveillance patients occurs when the biopsy shows only minimal Gleason 6 disease, but the PSA is rising rapidly. MRI represents a way out of this dilemma.

Thus, the current recommendation is to use PSA kinetics as a trigger for further diagnostic tests, including MRI and/or repeat biopsy. The absence of a lesion has a negative predictive value of 94–97% for absence of high-grade cancer (Delongchamps et al. 2011), and these patients should remain on surveillance. The finding of a large lesion on MRI with definitive cancer characteristics in a patient with proven prostate cancer has had a very high predictive value for clinically significant prostate cancer (Villeirs et al. 2011; Fütterer et al. 2009). Thus, this finding in a patient on surveillance should trigger either a targeted biopsy or definitive intervention. An equivocal lesion should trigger a repeat biopsy of the lesion.

7.5 Summary and Conclusion

Active surveillance for localized prostate cancer entails initial expectant management rather than immediate therapy, with curative-intent treatment deferred until there is evidence that the patient is at increased risk for disease progression. This approach is a rational response to the clearly documented risks of overdiagnosis and overtreatment of favorable risk prostate cancer, which in most cases

poses little or no threat to the patient. It is based upon the prolonged natural history of prostate cancer and is an attempt to balance the risks and side effects of overtreatment against the possibility of disease progression and a lost opportunity for cure. Favorable risk prostate cancer is more accurately viewed as one of multiple risk factors for the presence of higher grade prostate cancer. Like PIN and ASAP, it should be managed with close follow-up but without radical intervention unless there is clear evidence of more aggressive disease.

For men who place a high premium on avoiding the side effects of definitive treatment and who accept the slight increased risk of late metastasis or death, active surveillance is recommended. The optimal criteria for patient selection have not been defined but include the clinical stage, serum PSA, and Gleason score from the diagnostic biopsy.

Eligibility criteria consist of clinical stage T1c or T2a prostate cancer, a Gleason score ≤ 6, and a serum PSA ≤ 10 ng/ml. For patients over age 70 years, less stringent criteria can be applied (Gleason score ≤ 7 [3 + 4] and/or PSA ≤ 15 ng/ml). An important corollary is that young patients who have microfocal disease only can be managed with an initial surveillance approach. The quality of life benefits of maintaining normal erectile and voiding function are enhanced in young men. The risk of progression of low-grade disease is low.

The optimal schedule for monitoring includes measurement of the serum PSA at 3-month intervals to calculate the PSA doubling time. We use a doubling time of 3 years or less as a flag for higher risk disease. In the past, these patients were offered radical intervention. Currently, a short PSA doubling time mandates multiparametric MRI, with further management depending on the imaging results. This approach requires further validation.

A repeat prostate biopsy is performed at 1 year to rule out higher grade disease that may have been missed on the original biopsy. Following this, biopsies are repeated every 3–4 years (until age 80) to look for evidence of biologic progression to Gleason 4 + 3 or higher.

This approach is associated with an extremely small risk of prostate cancer mortality, currently estimated at 3% at 10 years. Recognizing that not all prostate cancer deaths are preventable even with aggressive treatment of all patients, it is likely that the number of patients who will succumb "unnecessarily" is smaller, likely one in several hundred. Further, these "preventable" deaths occur many years after diagnosis, in many cases close to the end of the patient's natural life. Compared to the morbidity associated with treating all such patients radically, this is a small price to pay and makes active surveillance an easy choice for well-informed patients.

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Open Radical Prostatectomy

8

Hein van Poppel and Steven Joniau

Contents

Abbreviations

BPFS	Biochemical progression-free survival
CSS	Cancer-specific survival
DVC	Dorsal venous complex
HT	Hormone therapy
NVB	Neurovascular bundle
PCa	Prostate cancer
PCSM	Prostate cancer-specific mortality
PSA	Prostate-specific antigen
RP	Radical prostatectomy
RRP	Retropubic radical prostatectomy
RT	Radiation therapy
TRUS	Transrectal ultrasound
TURP	Transurethral resection of the prostate

8.1 Introduction

The surgical treatment of prostate cancer has been introduced more than a century ago. The first important series of radical prostatectomies (RPs) were performed through a perineal approach. The retropubic approach to RP was adopted in the 1940s and is now the most commonly used operative technique for the treatment of clinically localized prostate cancer (PCa). Reiner and Walsh defined the anatomy of the dorsal vein complex and the neurovascular bundles (NVBs) which led to improvement of the morbidity (Reiner and Walsh 1979). In 1983, Walsh described the technique for anatomic nerve-sparing RP (Walsh and Donker 1982; Walsh et al. 1983). Since the initial report of anatomic RP by

H.van Poppel (✉) • S. Joniau
Department of Urology,
University Hospital, K.U. Leuven,
Leuven B-3000, Belgium
e-mail: hendrik.vanpoppel@uz.kuleuven.ac.be

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Walsh et al. in 1998 (Walsh 1998) and refinements in the understanding of the surgical anatomy of the prostate, open retropubic radical prostatectomy (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 gold standard surgical procedure attempting to control localized and selected cases of locally advanced prostate cancer. The goal of RP is to eradicate cancer while preserving continence and, whenever possible, potency (Bianco et al. 2005). Currently, RP is the only treatment for localized PCa to show a benefit for cancer-specific survival (CSS) compared with watchful waiting, as shown in a prospective, randomized study (Bill-Axelson et al. 2008; Bill-Axelson et al. 2011). In the past decade, several centres have acquired experience with laparoscopic RP, and more recently, robot-assisted laparoscopic RP has been developed. At present, the available data are not sufficient to prove superiority of any surgical approach in terms of functional and oncological outcomes. Further prospective studies are warranted (Ficarra et al. 2009; Barocas et al. 2010). In this chapter, we will focus on the indications of RP, our institutional experience with RRP and the surgery-related complications and review the oncological and functional results based on the available literature.

8.2 Indications

RP is a common treatment for patients with low- and intermediate-risk localized PCa (cT1a-cT2b and Gleason score 2–7 and PSA ≤ 20 ng/mL) and life expectancy >10 years (Heidenreich et al. 2011). RP is also an option for patients with T1a disease and a life expectancy >15 years or Gleason score 7 and for selected patients with low-volume high-risk localized PCa (cT3a or Gleason score 8–10 or PSA > 20 ng/mL) (Heidenreich et al. 2011). The patient's performance status and the assessment of the individual's life expectancy will be important factors when advising a patient the most appropriate treatment option. Obese patients should be carefully selected and counselled about the risk of their physical condition since the RRP technique is more difficult in obese patients. Older patients should also be cautiously selected because of possible comorbidities and complications such as urinary incontinence. RP is also a possible choice in selected patients with very high-risk localized PCa (cT3b-T4 N0 or any T N1) in the frame of a multimodality treatment strategy (Heidenreich et al. 2011). A recent paper reveals that even in selected patients with PSA > 100 ng/mL, RP may be an option as part of a multimodality treatment (Gontero et al. 2011).

8.3 Surgical Technique

8.3.1 Preoperative Measures

Before performing an 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 increase the risk of surgical complications such as rectal injury. They also render the preservation of the neurovascular bundle (NVB) difficult or complicate the intraoperative evaluation of possible extraprostatic extension. The period between TRUS biopsy and RP permits inflammatory adhesions or hematoma to resolve and gives time for further tumour staging, surgical risk assessment and patient counselling. Whether or not to perform a nerve-sparing RP should be decided preoperatively, taking into consideration the location, grade and size of the tumour and the results of the digital rectal examination (DRE), TRUS and/or magnetic resonance imaging (MRI). The evening before surgery, patients receive a classical bowel preparation with Fleet Oral 45 mL for 1 L of water to be ingested twice to ensure a clean and empty colon which is important for surgical access and in case of a rectal injury. Before being transferred to the operating room, patients receive subcutaneous low-molecular-weight heparin. Today, most centres favour a combined spinal-epidural anaesthesia, which is associated with a reduced intraoperative blood loss (Peters and

Walsh 1985; Shir et al. 1995), a faster recovery and a reduction in the use of opioid analgesics (Salonia et al. 2004). Other advantages are a lower incidence of pulmonary embolism and deep venous thrombosis, and optimal pain management through the epidural catheter. The latter may be used for patient-controlled analgesia for the first 24–48 h postoperatively.

8.3.2 Surgical Procedure

The patient is placed in supine position with slight hyperextension of the chest. The skin is prepared and draped in the usual way. A latex Foley catheter, at least 20 French, is placed. Following an 8–10-cm, midline, extraperitoneal, lower abdominal incision between the umbilicus and the pubis, the preperitoneal space of Retzius can be opened. By gentle cephalad retraction of the bladder and sweeping of fatty tissue, the anterior aspect of the prostate and the endopelvic fascia are exposed. If needed, a limited or extended lymph node dissection is performed at this stage of the procedure. The risk of lymph node involvement is low in men with low-risk PCa and <50% positive biopsy cores (Heidenreich et al. 2011). In men with intermediate- and high-risk PCa, an extended lymph node dissection should be performed if the estimated risk of lymph node invasion exceeds 7% (Briganti et al. 2006; Heidenreich et al. 2011). The endopelvic fascia is incised over the levator ani muscle laterally, taking care not to damage the dorsal venous complex (DVC). Before starting the same manoeuvre on the left side, the lateral dissection is accomplished. Dissection of the levator muscle allows full exposure of the NVBs dorsolateral to the prostate and anterior to the rectum. When the endopelvic fascia is opened, the puboprostatic ligaments are divided to get access to the apex of the prostate and the overlying DVC. An important step in RRP is to divide the DVC with minimal blood loss. The DVC is controlled in a standardized way by passing a right-angled clamp just anterior to the urethra. After transection of the DVC, a 2-0 backbleeding stitch is placed through the anterior commissure of the prostate to avoid backbleeding. Any bleeding from the DVC is oversewn at this stage. The urethra is now in complete view in its anterior aspect. By gentle blunt dissection, very close to the urethra, the NVBs are separated from the prostatic apex. 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. At this stage, some urologists place one or more stitches to facilitate finding the urethral stump at the time of anastomosis. The apical dissection is a critical manoeuvre in the procedure because of the need for a complete resection to avoid apical positive margins and the close relation with the NVB. After division of the rectourethralis muscle, the posterior aspect of the prostate is bluntly dissected with the index finger. At this point of the procedure, depending on the indication of a nerve-sparing or non-nerve-sparing procedure, the NVB is either resected along with the prostate, or the lateral dissection is done closely to the prostate, without touching the NVB. Nerve-sparing surgery has a significant impact on sexual function and urinary continence and should be performed in all patients provided that complete tumour excision is not compromised. 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 (Walsh 2001). The next step is the transection of the prostatic pedicles. 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. 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 vessels at the apex of the seminal vesicles are clipped and divided. The same procedure is then repeated at the contralateral side. At this stage, the prostate is completely mobilized posteriorly and laterally up to the bladder neck. Once the prostate is fully resected, 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 (Walsh and Partin 2007; Graefen et al. 2006). The bladder neck must be considered for either resection or preservation. The so-called bladder-neck-preserving RP is actually more an intraprostatic-urethral-preserving resection, enabling the reconstruction of a neobladder neck. The bladder neck can also be resected and be restored with a classical "tennis racket" closure and meticulous eversion of the bladder mucosa. Some surgeons have proposed a bladder neck "intussusception," with buttressing sutures lateral and posterior to the reconstructed bladder neck to hasten the early return of urinary control that would prevent passive opening of the bladder neck with filling (Walsh and Marschke 2002). An intravenous diuretic may be administrated to help identifying the ureteral orifices. Once the bladder neck has been reconstructed, the ureteral catheters are removed just before completing the vesico-urethral anastomosis. Meticulous hemostasis is done, avoiding the use of electrocautery in the case of a nerve-sparing procedure because this could definitely damage the NVBs. The last step of the procedure is the vesico-urethral anastomosis. A Ch 14-16 Foley (silicon) catheter is brought into the new bladder neck, and four anastomotic sutures are placed at 2, 5, 7 and 11 o'clock. 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 and the wound is closed.

The surgical technique of an RP for locally advanced T3 cancer is different from that applied in locally confined tumours. RP of locally advanced T3 PCa must include a more radical extirpation including an extensive lymph node dissection, a clean apical dissection, a broad NVB resection at least at the tumour bearing site, a complete resection of the seminal vesicles and, in some cases, a resection of the bladder neck. The bladder neck or intraprostatic urethra can usually be preserved in apical T3 tumours (Van Poppel 2005; Hsu et al. 2005). In patients with small unilateral and non-apical T3a prostate cancer, the contralateral NVB can be spared. Absolute contraindications of the nerve-sparing procedure are the T3b tumours and the palpable lesions at the apex (Sokoloff and Brendler 2001). A limited number of authors have reported their experience with RP in clinical locally advanced T3 PCa (Morgan et al. 1993; Van den Ouden et al. 1994; Lerner et al. 1995; Gerber et al. 1997; Van Poppel et al. 2006; Martinez de la Riva et al. 2004; Ward et al. 2005).

8.3.3 Postoperative Care

For the first 48 h after surgery, a patient controlled analgesia (PCA) pump is used for pain control. Postoperatively, attention should be given to general status, wound control, drain volume and bowel movements. On the second postoperative day, a regular diet is offered provided that peristalsis is restored. Drains are taken out when daily drainage is less than 10 mL. Low molecular weight heparin that has already started the day before surgery is continued up to 1 month after the operation to prevent thromboembolism. Five or six days after the operation, the patients are discharged from the hospital with a Foley catheter in place. Ten to fourteen days after the operation, they return for removal of the catheter. A cystogram before withdrawal of the catheter is only carried out if any postoperative problem has arisen that might have caused leakage. Directly after removal of the Foley catheter, pelvic floor physiotherapy is started to improve incontinence.

8.3.4 Complications and Functional Results

8.3.4.1 Intraoperative Complications

The acute side effects of RRP are haemorrhage, rectal injury and ureteral injury. The most common intraoperative complication is haemorrhage that can occur because of a blunt lateral dissection of the lateral aspect of the prostate, because

of insufficient control of the DVC, because of the presence of veins that perforate the pelvic floor or because of the nerve-sparing procedure. Bleeding is usually sufficiently managed once the dorsal vein has been divided and ligated (Walsh and Partin 2007) and will only rarely exceed 1,000 mL. Rectal laceration is an uncommon (once in every 100–300 patients) but serious complication. It occurs during apical dissection while attempting to develop the plane between rectum and the recto-urethralis muscle or the Denonvilliers' fascia. In some cases, 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 before restoring the bladder neck with a tennis racket closure.

8.3.4.2 Postoperative Complications

General postoperative complications after RP are deep venous thrombosis and pulmonary embolism. These complications should be prevented by low molecular weight heparin started the day before surgery and continued up to 1 month after the operation. Early postoperative complications include anastomotic leak, prolonged lymphatic drainage, premature accidental catheter withdrawal and recto-urethral 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 drain should not be taken out until they drain less than 10 mL per 24 h. The incidence of urinary fistula that is clinically important is very rare in open RRP. We almost always place four anastomotic stitches only, and some patients indeed have a temporary urine leak in the suction drains, but when the catheter is correctly inserted in the bladder, this will spontaneously stop in all cases. Urinary fistula can occur after catheter blockage (e.g. in case of haemorrhage that must be avoided by proper bladder neck reconstruction and eversion of the bladder neck mucosa). A ureteral damage can cause a urine leak. Accidental early catheter withdrawal is a rare but embarrassing complication that most often is caused by inadequate postoperative fixation of the catheter. Recto-urethral fistula is uncommon and actually only occurs when rectal injury has not been recognized during surgery. When it occurs, immediate colostomy is mandatory.

The late complications of RP are anastomotic strictures, urinary incontinence and erectile dysfunction. To avoid anastomotic strictures, surgeons should perform a good bladder neck reconstruction with eversion of the mucosa and avoid making a too narrow bladder neck. Anastomotic strictures, predominantly in patients who had a previous TURP, excessive bleeding or an anastomotic leak, can often be successfully treated with a urethral dilatation. Incision of the stricture must be avoided as this may compromise urinary continence.

Urinary continence and potency are among the key concerns that men have with respect to the complications of RRP. Urinary incontinence is for most men the most disabling complication and is very difficult to predict. The reason is invariable damage to the urethral sphincter or its innervation. Pelvic floor muscle exercises, before and after RP, may improve early urinary continence (Van Kampen et al. 2000; Overgärd et al. 2008; Centemero et al. 2010). Erectile dysfunction is associated with age, preoperative erectile function and the oncologic required degree of resection of one or two NVBs (Albersen et al. 2009). Recovery of potency also depends on the proper selection of patients and the experience of the surgeon with performing nerve-sparing operations. The result of an open RP in most patients will be a temporary reduced erectile function. Even if the NVB is spared, reinnervation will take about 8–9 months. A recent placebo-controlled prospective study showed no statistically significant difference among patients with erectile dysfunction following bilateral nerve-sparing RP receiving nightly vardenafil and those receiving on-demand vardenafil in the postoperative period. On-demand vardenafil treatment resulted in significantly greater International Index of

Erectile Function–erectile function domain (IIEF-EF) score of ≥22 and better response rates on the Sexual Encounter Profile (SEP) questions 2 and 3 than placebo over the entire treatment period (Montorsi et al. 2008). In another placebo-controlled prospective study, nightly sildenafil administration increased the return of normal spontaneous erections (Padma-Nathan et al. 2008). Men who fail phosphodiesterase-5-inhibitors treatment for their post-RRP erectile dysfunction are excellent candidates for intracavernous injection therapy. The need for penile implants in RP patients is very limited.

8.3.5 Surgical Modifications to Standard Anatomic RP

During the last decades, surgical modifications to standard anatomic RP have been proposed in order to improve early return of urinary continence, erectile function or both. This became possible because of a better understanding of the surgical anatomy of the prostate. These modifications focus 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 (Walsh and Partin 2007). It has been suggested that bladder neck preservation may help in an early return of continence, although its role in recovering urinary continence after RRP is controversial. Although in many studies bladder neck preservation was associated with earlier continence (Klein 1992; Braslis et al. 1995; Shelfo et al. 1998; Soloway and Neulander 2000; Deliveliotis et al. 2002; Abou-Elela et al. 2007; Arroua et al. 2008; Razi et al. 2009), the randomized study of Srougi et al. (2001) found no difference in urinary continence rates in patients in the bladder neck resection and preservation group (Srougi et al. 2001). Whether the seminal vesicle should be spared to avoid potential damage of the surrounding structures and maintain urinary continence (John and Hauri 2000) or should be removed completely to ensure cancer control (Theodorescu et al. 1998) remains also controversial and should ideally be tested in a double-blind randomized study. In addition, 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 (Kim et al. 1999, 2001; Kim and Seo 2001). However, this still remains to be proved in the randomized setting. The advantages of the more common unilateral nerve graft are difficult to verify, since for some men the preservation of a single nerve is sufficient to recover erectile function. A randomized phase II trial showed that the addition of sural nerve grafting to a unilateral nerve-sparing RRP did not improve potency at 2 years following surgery (Davis et al. 2009). Singh et al. (2004) investigated the recovery of urinary function with respect to unilateral sural nerve grafting after RRP with unilateral nerve resection. They found a greater rate of urinary function recovery, suggesting that the cavernous nerves may play a role in return of continence (Singh et al. 2004). These results should be validated in larger, multicenter, prospective, randomized studies.

8.4 Results

8.4.1 Surgical Margins and Oncological Results

A study evaluating the outcome of RP in patients with unilateral T3a PCa showed that increased overall surgical experience results in improved positive surgical margin rates over time (75% in 1987–1994, 42% in 1995–1999 and 10.4% in 2000–2004) (Hsu et al. 2007b). When used in well-selected patients, the nerve-sparing procedure does not increase the risk of developing positive surgical margins or biochemical recurrence following RP (Nelles et al. 2009). Surgical experience influences the occurrence of surgical margins and cancer control. Further research should focus on specific careful techniques used by experienced surgeons that will further reduce positive margin rates and improve outcomes (Cookson and Chang 2010).

Open RRP provides excellent long-term oncological outcomes for the majority of patients with clinically localized PCa. Studies showed 10-year PSA-free survival rates of >60% and

10-year CSS rates of >94% (Isbarn et al. 2009; Roehl et al. 2004; Han et al. 2001; Hull et al. 2002; Porter et al. 2006). At present, the first externally validated nomogram predicting PCa-specific mortality (PCSM) after RP for patients treated in the PSA era can be used in patient counselling and clinical trial design (Stephenson et al. 2009). Although still controversial, it is increasingly evident that surgery has an important role as initial treatment for locally advanced disease (cT3a). Several retrospective case series including patients with cT3 disease that underwent RP monotherapy showed 5- and 10-year overall survival (OS) rates of >75% and >60%, respectively. The CSS after RP at 5- and 10-year follow-up varied between 85–100% and 57–91.6%, respectively (Yamada et al. 1994; Gerber et al. 1997; Van den Ouden et al. 1998; Martinez de la Riva et al. 2004; Ward et al. 2005; Hsu et al. 2007a). In a recent study, Hsu et al. evaluated the long-term outcome of 164 patients with locally advanced PCa after RP and reported a 15-year CSS of 66.3%. Mean follow-up was 100 months (Hsu et al. 2010). Nomograms can be used for recognizing patients with locally advanced or high-grade PCa most likely to benefit from surgical treatment (Joniau et al. 2007; Gallina et al. 2007). Patients with cT3 disease are overstaged 9–44% of the time (Van Poppel et al. 2006; Carver et al. 2006; Ward et al. 2005; Freedland et al. 2007; Loeb et al. 2007; Hsu et al. 2007a). For these patients who have organ-confined disease, but also for those who actually have pT3 disease, RP alone might result in a definite cure. In patients with high-grade PCa, Donohue and colleagues examined the outcome of RP monotherapy and found a 5- and 10-year biochemical progression-free survival (BPFS) of 51% and 39%, respectively (Donohue et al. 2006). This is in agreement with rates reported in other series (Lau et al. 2002; Oefelein et al. 1995; Tefilli et al. 1999). Up to one third of patients with high-grade PCa are subsequently downgraded and have better BPFS probability after RP (Manoharan et al. 2003; Grossfeld et al. 2003; Bastian et al. 2006). In a substantial number of patients with locally advanced or high-grade PCa, RP monotherapy will not be sufficient. Therefore, multimodality treatment consisting of RP with radiation (RT) or hormone treatment (HT), combination of both or newer treatment combinations should be considered.

A study evaluating the outcome of locally advanced PCa after RP showed that pathological tumour grade and node status were significant predictor factors in biochemical progression-free survival (BPFS), clinical progression-free survival (CPFS) and CSS after 100 months follow-up (Hsu et al. 2010). Another recent study showed that biopsy Gleason score is the strongest predictor of progression and mortality. PSA > 20 ng/mL associated with biopsy Gleason score ≤ 7 resulted in 10-year PCa-specific mortality (PCSM) of 5%; when associated with biopsy Gleason score ≥ 8, PCSM was 35% (Spahn et al. 2010).

8.4.2 Functional Results

The complications associated with RP are described in an earlier section (see Sect. 3.4). Even using a standardized technique for the nerve-sparing procedure, a learning curve exists, giving better functional results for the more experienced surgeon. Short retraining in specialized centres can have a positive effect on the surgical quality. Urinary continence and erectile dysfunction rates vary among different studies. The incontinence rate after open RRP is low and is highly associated with the nerve-sparing technique (Burkhard et al. 2006). Kundu et al. evaluated urinary incontinence, potency and postoperative complications in preoperatively potent men treated with RRP from 1983 to 2003 with a minimum follow-up of 18 months. They concluded that when RRP is performed by an experienced surgeon, the rate of long-term incontinence after RRP is only 2–7%. The potency rate was 76% after bilateral nerve-sparing RRP ($n=1,770$) and 53% after unilateral or partial nerve-sparing ($n=64$) RRP. Potency rates following bilateral versus unilateral nerve-sparing RRP were better for men <70 years (78% vs. 53%; $P=0.001$) compared with those in men ≥70 years (52% vs. 56%; $P=0.6$). The postoperative complication rate was 9% (Kundu et al. 2004). Another large study has reported similar rates after

18 months of follow-up (Loeb et al. 2008). One study (Ayyathurai et al. 2008) reported the return of erectile function in 1,620 consecutive preoperatively potent men treated from 1992 to 2006 with nerve-sparing RP where feasible. Follow-up was a minimum 6 months. Of 619 men who had a bilateral and of 178 who had a unilateral nerve-sparing RRP, 72% and 53%, respectively, were potent. When stratifying by age group (≤49, 50–59, 60–69 and ≥70 years), potency rates were 86%, 76%, 58% and 37%, respectively. In line with other large studies (Loeb et al. 2008; Kundu et al. 2004), the authors concluded that potency rates after RRP were better in younger men (Ayyathurai et al. 2008). Recently, Löppenberg et al. has evaluated complication rates after RP at a single centre between 2003 and 2009. All ten Martin criteria for a high-quality report of complications were fulfilled. All complications that occurred within a 30-day postoperative period were graded retrospectively according to the Clavien-Dindo classification. Complications after patient discharge were captured using a non-validated questionnaire. The authors observed an acceptable overall complication rate of 27.7% (801 of 2,893 patients). Of these complications, 596 were grade I (63.2%), 183 grade II (19.5%), 142 grade III (15.1%) and 15 grade IV (1.8%). The mortality rate (grade IV) was 0.1% (4 of 2,893). Patients of older age, those with greater prostate volume and those who had undergone simultaneous lymphadenectomy were at risk for higher grade complications (grade III or greater) (Löppenberg et al. 2010).

For patients with cT3 disease, the morbidity is similar to that previously reported for patient with cT2 disease (Ward et al. 2005). In a study evaluating the outcome of RP in patients with locally advanced or high-risk PCa, potency and continence rates were preserved in 60% and 92%, respectively. Median follow-up was 88 months (Loeb et al. 2007).

8.5 Conclusion

Contemporary nerve-sparing open RRP remains the gold standard 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 has resulted in excellent oncological outcomes, decreased positive surgical margins, significantly reduced operative complications and better functional results. Most of the complications are low grade. In the hands of an experienced surgeon, incontinence rates are low. Nerve-sparing RP performed with sufficient expertise and additional phosphodiesterase-5-inhibitors or intracavernous injection therapy provide acceptable potency rates. RRP can also be recommended as initial treatment for locally advanced and high-grade PCa when used in combination with multimodality treatment, including RT, HT, combination of both or newer treatment combinations.

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Robot-Assisted Radical Prostatectomy

9

Stefan Carlsson and Nils Peter Wiklund

Contents

S. Carlsson, M.D., Ph.D. • N.P. Wiklund, M.D., Ph.D. (✉)
Department of Surgical Science, Section of Urology,
Karolinska Institutet,
Box 171 77, Stockholm, Sweden
e-mail: stefan.carlsson@ki.se;
peter.wiklund@karolinska.se

9.1 Introduction

Since the world's first robot-assisted radical prostatectomy (RARP) was performed by Binder and Kramer in Germany about 10 years ago, there has been a rapid transition from this first pioneering operation to what has become the most common treatment modality for organ-confined prostate cancer in the USA, where approximately 80% of all prostatectomies are performed using robotic assistance (Binder and Kramer 2001; Su 2010). There is unequivocal evidence of lower bleeding rates for RARP (Tewari et al. 2003; Eden et al. 2002) but no good evidence of the overall superiority of one modality over another, and it is uncertain whether robotics can yet be justified, given the resulting increase in cost and training requirements (Dasgupta and Kirby 2009). The most important outcomes to assess when comparing open prostatectomy (ORP), and RARP, are cancer control, complications, urinary continence, and sexual potency. Unfortunately, progress in doing randomized controlled studies (RCTs) has been notoriously poor (Tewari et al. 2003) with only one such trial reported, comparing ORP and conventional laparoscopic technique (LRP) (Guazzoni et al. 2006). In addition, out of the thousands of papers published on the surgical treatment of prostate cancer with radical prostatectomy, there have been very few comparative studies. A recent review found 37 comparative studies: 23 ORP and LRP, 10 ORP and RARP, and four LRP and RARP (Ficarra et al. 2009).

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The term robot-assisted surgery in prostate cancer treatment usually refers to the use of the da Vinci (Intuitive Surgical™, Inc, Sunnyvale, CA, USA) robot. The original telesurgery robotic system was developed with intention to facilitate remote surgery close to the battlefield. The name "robot-assisted" may be misleading since a true robot is an enslaved device under human control that accomplishes its assignment without human assistance. This is not the case with the da Vinci robot since it requires that the surgeon guides every movement performed by the robot. Nevertheless, the term robotic or robot-assisted surgery is used in this chapter to describe the procedure used by surgeons who perform radical prostatectomy with computer-enhanced master–slave telemanipulators (Guillonneau 2003).

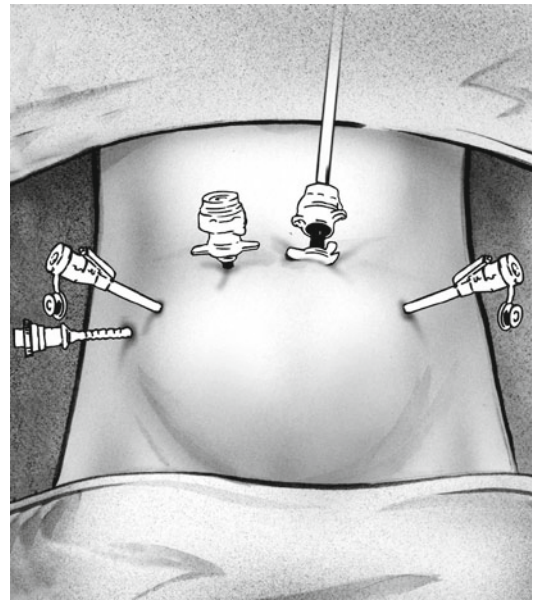

Fig. 9.1 Port placement for robot-assisted laparoscopic radical prostatectomy at Karolinska University Hospital. From the patient's right side the ports are as follows: 5-mm assistant port, 8-mm robot instrument port, 12-mm assistant port, 12-mm camera port, and 8-mm robot instrument port (Published with permission from *Scandinavian Journal of Urology*)

9.2 Surgical Technique

Although da Vinci is not a true robot, there are some important technical advantages for the surgeon using this minimally invasive technique. The three dimensional (3D) vision with up to 15 times magnification and the seven degree of freedom in the movement of the instruments combined with lack of tremor provides important technical help for the surgeon. Furthermore, the wristed (Endowrist™) instruments enable the surgeons to dissect around corners and make the suturing easier. The good eye–hand coordination enabled by the robotic system is also an advantage for the surgeon who is learning the technique of minimally invasive prostatectomy. It seems clear that surgeons with extensive experience in open radical prostatectomy surgery will benefit from these features (Ahlering et al. 2003). A potential disadvantage of robot technology is the lack of tactile sensation.

The operating surgeon (console surgeon) is seated at the console and does not scrub. One of the robotic arms controls the binocular endoscope and the other arms control the robotic instruments. Two finger-controlled handles (masters) control the robotic arms and camera. Manipulation of the masters is transmitted to a computer that filters, scales, and relays the surgeon's movements to the robotic arms and instruments. This scaling allows for finer and precise execution of the surgeons movements.

The surgical technique utilized at Karolinska Hospital in Stockholm has previously been described in detail (Nilsson et al. 2006). Briefly, the patient is placed in a Trendelenburg, and pneumoperitoneum is ensured with the Hasson technique (Hasson et al. 2000). Four additional ports are placed under camera vision; two 8-mm ports are used for the robotic instrument arms placed 10–11 cm on both sides of the midline on a line joining the anterosuperior iliac spine to the umbilicus (Fig. 9.1). A robot is docked to the robotic ports. The assisting surgeon uses two ports. The lateral one is a 5-mm port, and the medial one is a 10-mm port. Conventional laparoscopic instruments are used by the assistant surgeon and include atraumatic grasper, scissors, intracorporeal clips, and suction. The console

surgeon performs the dissection using two robotic instruments: bipolar forceps (left hand) and round-tipped scissors (right hand). A needle driver is used during the anastomosis.

A posterior dissection of the vases and seminal vesicles is performed. When sparing of the erectile nerves is planned, the tips of the seminal vesicles are left intact in the patient. The fascia of Denonvilliers is incised and the prostate is freed from prerectal fat leaving the fascia of Denonvillier on the specimen. The urinary bladder is freed from the abdominal wall to gain access to the anterior part of the prostate. Bladder neck dissection is performed, and the prostatic pedicles are clipped and transected. The neurovascular bundles are dissected either intra-fascialy, inter-fascialy, or extra-fascialy depending on preoperative potency scores and tumor characteristics. The dorsal venous plexus is incised and bleeding is controlled by continuous suture and the distal urethra is transected. The anastomosis is performed with a double needle continuous suture and the specimen is retrieved through the umbilical incision.

9.3 Clinical Outcome

9.3.1 Operative Time

The weighted means for operative time were 163 min (130–236) for RARP and 165 min (131–204) for ORP in the review from Coelho et al. when series at high-volume centers were analyzed (Coelho et al. 2010). However, other studies (Krambeck et al. 2009; Fracalanza et al. 2008) have shown shorter operative time for ORP compared with RARP, which probably reflects differences in surgeon's experience and the different hospitals' surgical volume. Studies commonly compare the operative time for an existing method (ORP) with the operative time of a new method (RARP), including the patients in the early learning curve for the new method. Our experience of RARP at the Urology Department Karolinska University Hospital beginning in 2002, illustrates the effects of surgical experience on operative time (Fig. 9.2).

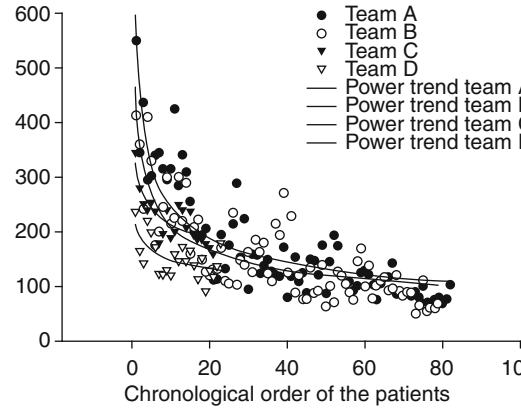

Fig. 9.2 Operative times (minutes) for four surgeons performing robot-assisted prostatectomy at the Karolinska Hospital Stockholm, Sweden. The surgeons in teams one and two have extensive experience from open surgery, whereas the surgeons in team three and four have limited experience but started robotic training under the supervision of the experienced surgeons

9.3.2 Blood Loss

RALP has been associated with decreased blood loss (mean estimated blood loss 164.2 mL) compared with ORP (951 mL) (Coelho et al. 2010). The reason is likely a combination of the tamponade effect of the pneumoperitoneum, the Trendelenburg position, and the improved visualization. Men undergoing RARP are less likely to need blood transfusions compared to those undergoing ORP with transfusion rates of 1.4% and 20.1%, respectively, in a systemic review and cumulative analysis of comparative studies (Ficarra et al. 2009). This finding corresponds well with our experience at the Urology Department Karolinska Hospital (2002–2007) with blood transfusion rates of 4.6% and 23%, respectively (Carlsson et al. 2010).

9.3.3 Length of Hospital Stay and Sick Leave

RARP has a mean shorter hospital stay (1.43) compared to ORP (3.48) as shown by analyses using the weighted mean hospital stay in a review of outcomes reported by high-volume centers (Coelho et al. 2010). This shorter hospital stay is

probably associated with lower postoperative pain after RARP as compared to ORP (Menon et al. 2002a). It is not possible, however, to rule out that part of the difference in length of hospital stay might be influenced by patients' expectations. The median numbers of days on sick leave was 11 in the RARP group and 49 in the ORP group in a multicenter cohort study of 127 RARP and 147 ORP patients from Scandinavia (Hohwu et al. 2009). These data indicate that RARP shortens the convalescence after a radical prostatectomy.

9.4 Cancer Control

It is unclear if the 3-D and 10× magnification visual system and the improved eye–hand coordination enabled by the robot system will improve cancer control, but cumulative analysis of all comparative studies reporting data on margin status in the review by Ficarra et al. showed a statistically significant difference in favor of RARP (Ficarra et al. 2009). It has been shown that positive surgical margins (PSM) do have an impact on both biochemical cancer recurrence (BCR) and clinical progression, but due to various definitions used, it is problematic to use this surrogate marker for cancer control, when comparing ORP with RARP (Pfitzenmaier et al. 2008). Recently, medium-term data on BCR and disease-free survival after robot-assisted radical prostatectomy have been published showing only 13.6% BCR at 5 year median follow-up, suggesting that cancer control is not likely to be inferior in RARP patients compared to patients subjected to ORP (Menon et al. 2010).

9.5 Quality of Life After a Radical Prostatectomy

It has been reported that after curative treatment, prostate cancer survivors have on average 5.1 new symptoms caused by the therapy (Bellizzi et al. 2008). The quality of life for a prostate cancer patient after radical therapy is of extra importance due to the high number of patients that must be treated to prevent one death from prostate cancer (Bill-Axelson et al. 2011) and because of the possible negative consequences on basic functions such as sexual, urinary, and bowel functions resulting from treatment (Steineck et al. 2002; Sanda et al. 2008). No randomized studies exist that compare outcomes between ORP and RARP so comparisons concerning symptoms and self-assessed quality of life between these treatment modalities are based on observational data. In Sweden, the LAPPRO study is ongoing. The study is a prospective, multicenter (12 hospitals), non-randomized study ($n=2{,}100$) comparing the results of ORP with RARP regarding morbidity such as urinary incontinence, erectile dysfunction, oncological result, self-assessed quality of life, and health economics (http://www.controlled-trials.com/ISRCTN06393679/06393679).

9.5.1 Urinary Function

Estimated rates of urinary incontinence after radical prostatectomy vary widely in different published studies, ranging from 8% to 77% (Klingler and Marberger 2006). One of several explanations for the variation is the lack of consensus on the definition of postoperative incontinence and how to quantify postoperative incontinence. The risk of incontinence following ORP has been shown to range from 5% to 10% when reported by surgeons from large series and from 20% to 30% when patients were evaluated by questionnaires (Klingler and Marberger 2006). Menon's group reports excellent results on urinary continence rate and found that patients achieved continence much quicker after robot-assisted prostatectomy than after open surgery (Tewari et al. 2003). In the study by Coelho et al. comparing outcome in high-volume centers, the weighted mean continence rates at 12 months for ORP, LRP, and RARP were 80%, 85%, and 92%, respectively (Coelho et al. 2010). In our first series at the Karolinska Hospital, we have evaluated continence by use of a questionnaire. We found that 1.5% of the patients used more than one pad per 24 h in our series (Carlsson et al. 2006).

Toijer et al. at Memorial Sloan-Kettering, New York, have shown that after conventional laparoscopy (LRP), patients had a twofold higher risk of being incontinent (2b level) compared with ORP (Touijer et al. 2008). However, in the review by Ficarra et al., cumulative analysis of the available data suggests no difference in incontinence rate (2b) between LRP and ORP (Ficarra et al. 2009).

It has been suggested that the anastomosis between the urethra and bladder neck and the dissection of the apex may be performed more easily with a robot-assisted technique compared with conventional laparoscopy due to the improved vision and wristed instruments. Whether this improved technique will result in better urinary function postoperatively is still unclear. Tewari et al. showed that median time to continence was significantly shorter after RARP compared to ORP (2b) (Tewari et al. 2003). The main endpoint in the Swedish LAPPRO study is incontinence at 1 year. Thus, the LAPPRO result may contribute to the answer to this question in 2013, but up till now, there is no proven difference in urinary continence outcome between ORP and RARP.

9.5.2 Sexual Function

One of the most important factors in reducing the morbidity of radical prostatectomy is to increase the number of patients that recover their sexual function after surgery. However, potency is one of the most difficult outcomes to compare after a radical prostatectomy. In a study by Montorsi, only 43% of the men who verbally self-reported preoperative full potency showed a baseline normal erectile function using the erectile function domain of the IIEF score (Salonia et al. 2006). Menon's group has reported that robot-assisted prostatectomy enhances the return of erections and the ability to have intercourse compared to open surgery (Tewari et al. 2003). In the study by Coelho et al. comparing outcomes in high-volume centers, the weighted mean potency rates at 12 months for ORP, LRP, and RARP were 61%, 54%, and 93%, respectively (Coelho et al. 2010). Longer follow-up is needed to evaluate if robot-assisted prostatectomy will show better results regarding sexual side effects compared to open surgery and conventional laparoscopy. The bother from erectile function should probably be considered more clinically important than the grade of erectile function alone. In the future, it will be important to focus not only on the erectile function but also on patients' sexual health including orgasm satisfaction, painful orgasm, climacturia, and bother from erectile dysfunction.

9.6 Complications

In a cumulative analysis of comparative reports on the overall complication rate after radical prostatectomy, Ficarra et al. showed significantly higher complication rates for ORP compared with RARP (Ficarra et al. 2009). However, in the review by Coelho, where only studies with a sample size more than 250 patients were included, no such difference was seen (Coelho et al. 2010). When we studied complication rate in 1,738 patients that had undergone a radical prostatectomy at Karolinska University Hospital between 2002 and 2007, we found that ORP was associated with significantly increased risk of rectal injury, pulmonary embolism, pneumonia, bladder neck contractures, blood transfusions, and wound infection compared with RARP (Carlsson et al. 2010). When stratified by Clavien grade, the incidence of Clavien IIb-V complications was significantly lower in the RARP (3.7%) group compared with the ORP group (12.9%) (Carlsson et al. 2010). The bladder neck contracture rate for ORP was 4.1% which was about 20 times as high as for the contracture rate for RARP group.

9.7 Future Aspects of Robot-Assisted Surgery

It is unclear if the next generation of robots will further improve the surgical results after RARP. It is likely that they will be less expensive as compared to the current systems, and new instruments that will allow more exact dissection are

likely to be developed. This may enhance the possibility to perform nerve-sparing surgery and reduce the morbidity inflicted by prostate cancer surgery. An exciting improvement in the future will be incorporation of imaging techniques into the robotic device; these will enable the surgeon to have an improved view of the localization of the tumor as well as the neurovascular bundles during surgery and also be able to actually view the prostate cancer localization during surgery.

9.8 Conclusion

Unlike LRP, which is difficult and time-consuming to learn (Menon et al. 2002b), RARP can be learned more easily by surgeons skilled in open prostatectomy. The greater availability of surgical robots with 3-D vision and wristed instruments with higher degrees of freedom have resulted in greatly increasing numbers of RARP and decreased numbers of LRP performed today. However, it remains to be scientifically evaluated whether these technical improvements will translate into better results regarding continence rate, erectile function, and cancer control. There is growing evidence of the importance of surgeons surgical experience for gaining optimal oncological and functional outcome after LRP, ORP, and RARP (Hong et al. 2010), and therefore it is even more troublesome to make any reliable comparison regarding oncological and functional outcome between these different techniques. There is evidence in the literature for less postoperative pain, decreased bleeding, a shorter hospital stay, and shorter convalescence for RARP compared to ORP. This may in fact be enough for the prostate cancer patient to choose RARP over ORP.

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Permanent Prostate Brachytherapy 10

Jan J. Battermann

Contents

J.J. Battermann, M.D., Ph.D.
Department of Radiation Oncology,
University Hospital Utrecht,
Utrecht, The Netherlands
e-mail: j.j.battermann@umcutrecht.nl

10.1 Introduction

Prostate cancer is the most frequent male malignant tumour in the Western world and affects about 10% of all men. In localised prostate cancer, various treatment options are available such as surgery, either by open, laparoscopic or robot-guided surgery, external beam irradiation, brachytherapy with low dose Iodine-125 seeds or an HDR Iridium-192 source, cryotherapy, HIFU and active surveillance.

Brachytherapy for the treatment of prostate cancer is already mentioned in 1913 by Pasteau and Degrais using radium in a silver tube in the urethra (Pasteau and Degrais 1914). Other techniques were executed as well, such as radium needles inserted into the prostate through the rectum, via the perineum or bladder. These techniques with radium resulted in severe rectal and bladder complications including ulceration and fistulae. Flocks used radioactive gold (Au-198) colloidal solution injections (Flocks et al. 1954). Au-198 has a short half-life of 2.7 days and emits short-range beta radiation plus gamma radiation. Due to difficulties with the use of colloidal gold, Au-198 gold seeds were developed for insertion into the prostate, either alone or in combination with EBRT. The radiation exposure hazard associated with the high energy of Au-198, however, made these techniques unpopular. The high morbidity rate of early brachytherapy techniques and the advent of megavoltage radiation with Cobalt and somewhat later linear accelerators reduced interest in brachytherapy in the 1960s.

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Hilaris and Whitmore at the Memorial Sloane Kettering Cancer Centre in New York introduced Iodine-125 seeds in 1970 (Whitmore et al. 1972). I-125 has a half-life of 60 days and emits low energy photons (28 keV). Due to the low energy, there are nearly any radiation exposure problems. The seeds were implanted in the prostate by a retropubic approach in combination with bilateral regional lymph node dissection. They found a 5-year survival of 79% in a population of 606 patients treated from 1970 to 1980, strongly related to T stage (T1 96%, T2 76%, T3 69% and T4 13%). Recurrence rate was highly related to tumour grade (Fuks et al. 1991). A small series from the Netherlands Cancer Institute showed similar results with 52% versus 48% local recurrences for the Whitmore series (Roeleveld et al. 1996). We know now that the retropubic approach is inadequate for a proper implant due to the poor guidance of the needles by the index finger in the rectum.

In 1980, Charyulu already described a perineal technique where patients received EBRT and a boost dose with Radon-222 (Charyulu 1980). The position of the needles was guided by a template, and the tip of the needle was checked with radiography of the Foley balloon. Kumar improved this technique, using C-arm fluoroscopy to guide the needles (Kumar and Bartone 1981).

A breakthrough was the introduction of the transrectal ultrasound (TRUS)–guided perineal technique by Holm et al. (1983). A perspex template was attached to the ultrasound probe to guide the needles into the prostate. This technique was refined by the Seattle group and is still the most common way to perform permanent prostate brachytherapy (Blasko et al. 1987).

Because of better staging modalities such as TRUS and magnetic resonance imaging (MRI) and the awareness by men of prostate cancer, the majority of patients are nowadays diagnosed with a low-risk prostate cancer, resulting in a high cure rate for most patients.

10.2 Patient Selection

Guidelines for permanent prostate brachytherapy (PPB) are published by ASTRO (Nag et al. 1999, 2000) and by ESTRO (Ash et al. 2000). According to T stage, Gleason sum and PSA value patients can be categorised in three risk groups (Table 10.1). Besides tumour characteristics, also functional characteristics are taken into account. International prostate symptom score (IPSS), urodynamic parameters such as bladder volume, maximum flow rate and residue are considered to be also important. In the low risk group patients are included with T1c–T2b tumours, Gleason sum < 7 and PSA < 10 ng/ml. These are excellent patients for PPB, with cure rates of over 90% at 10 years (see results). The opposite is the high-risk group with T3, or Gleason > 7, or PSA > 20, or Gleason =7 and PSA 10–20 ng/ml. These patients in general are not treated by PPB, although it is not clear whether other modalities show better outcome. The intermediate group consists of T2c, or Gleason 7, or PSA 10–20 ng/ml. These patients in general are still candidates for PPB, with somewhat lower cure rate than low-risk patients as will be described in the results.

Preoperative work-up includes PSA, digital rectal examination, TRUS of the prostate, CT or (preferably) MRI of the pelvis. Bone scan and other imaging modalities are not recommended for low-risk and (low tier) intermediate-risk patients. A previous TURP is a relative contraindication since a large TURP defect will result in the loss of seeds while urinating. Furthermore, these patients are at higher risk for urethral necrosis, strictures and incontinence (McElveen et al. 2004). It is advised to wait for 6–12 months after TURP to perform PPB. Even so, TURP after PPB should be postponed for several months to reduce complications.

Patients with prostate volumes more than 50 cc are not good candidates for PPB. Pubic arch interference may hinder the placing of the needles close to the bony structures. Further, the contour may not fit in the template and the TRUS image quality is worse than in smaller prostates. Also, a large number of seeds are needed, resulting in more complications such as acute retention. Androgen ablation therapy (ADT) may reduce the prostate volume with approximately 30% and can be used to downsize the prostate (Lee 2002). However, in volumes over 80 cc, the volume reduction still will be insufficient for PPB in most of these patients.

Table 10.1 Risk groups according to the ESTRO/EAU/EORTC recommendations (Ash et al. 2000)

	Recommended, do well	Optional, do fair	Study, do poor
PSA (ng/ml)	<10	10–20	>20
Gleason sum	<7	=7	>7
Stage	T_{1c-2a}	T_{2b-c}	T_3
IPSS	0–8	9–20	>20
Volume (cc)	<40	40–50	>50
Q max (ml/s)	>15	15–10	<10
TURP	–	–	+

In Europe mainly iodine seeds are used for PPB. In the USA, still a substantial number of patients are treated with Palladium-103. The energy is similar, but the half-life is 17 days in place of 60 days and therefore delivers a much higher dose rate than iodine. Although palladium is advocated for fast growing tumours (Gleason > 7), there is no clinical confirmation of this hypothesis.

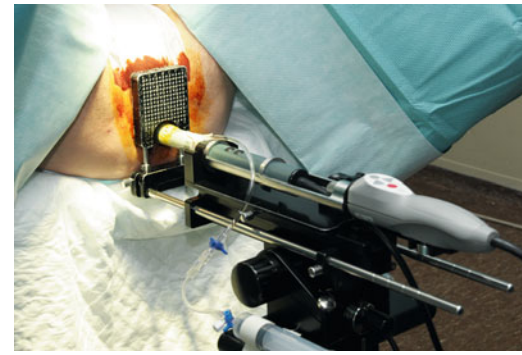

Fig. 10.1 Support frame with stepping unit. The stepping unit can make steps of 5 mm through the prostate for contouring of the prostate gland. The grid is placed on the stepping unit. Also the motor for rotation of the probe is visible at the probe

10.3 Treatment Planning

10.3.1 Preplanning

Preplanning is performed to measure the size of the prostate to order the number of seeds and making a preplan for seed implantation. This is in general done by TRUS. With the stepping unit of the support frame (Fig. 10.1), transversal slices are made at increments of 5 mm through the prostate from base to apex. In general, the prostate volume will be larger with this method than with routine transaxial measurement using the equation $L \times W \times H \times 0.52$. The prostate should be in the middle of the template; this means that the urethra is not always in the middle of the gland in case of hyperplasia.

From this volume study, the contour of the prostate is depicted on each slice (Fig. 10.2). The images are digitised and fed into a dedicated planning computer. The planning treatment volume is routinely with a margin of 5 mm outside the depicted contour in lateral and ventral direction. However, for the dorsal side close to the rectum, often, a smaller margin is used to avoid rectal damage as stated in the update of the GEC-ESTRO guidelines (Salembier et al. 2007).

Teh (Table 10.2) found in prostatectomy material of 712 patients that the majority of extracapsular extension is within a few millimetres from the capsule (Teh et al. 2003). Schwartz describes the association of extraprostatic extension with preoperative PSA, percentage of cancer in biopsy cores, and clinical tumour stage (Schwartz et al. 2007).

10.3.2 Needle Loading

Per definition the dose in brachytherapy is inhomogeneous. To exploit this inhomogeneity further, differential loading of the needles can avoid high dose to the prostatic urethra and rectum. With differential loading (that is not filling a needle with seeds at a fixed distance from each other, but placing less seeds and extra spacers to reduce dose, or place extra seeds without spacers to increase the dose), one can more or less paint the dose over the

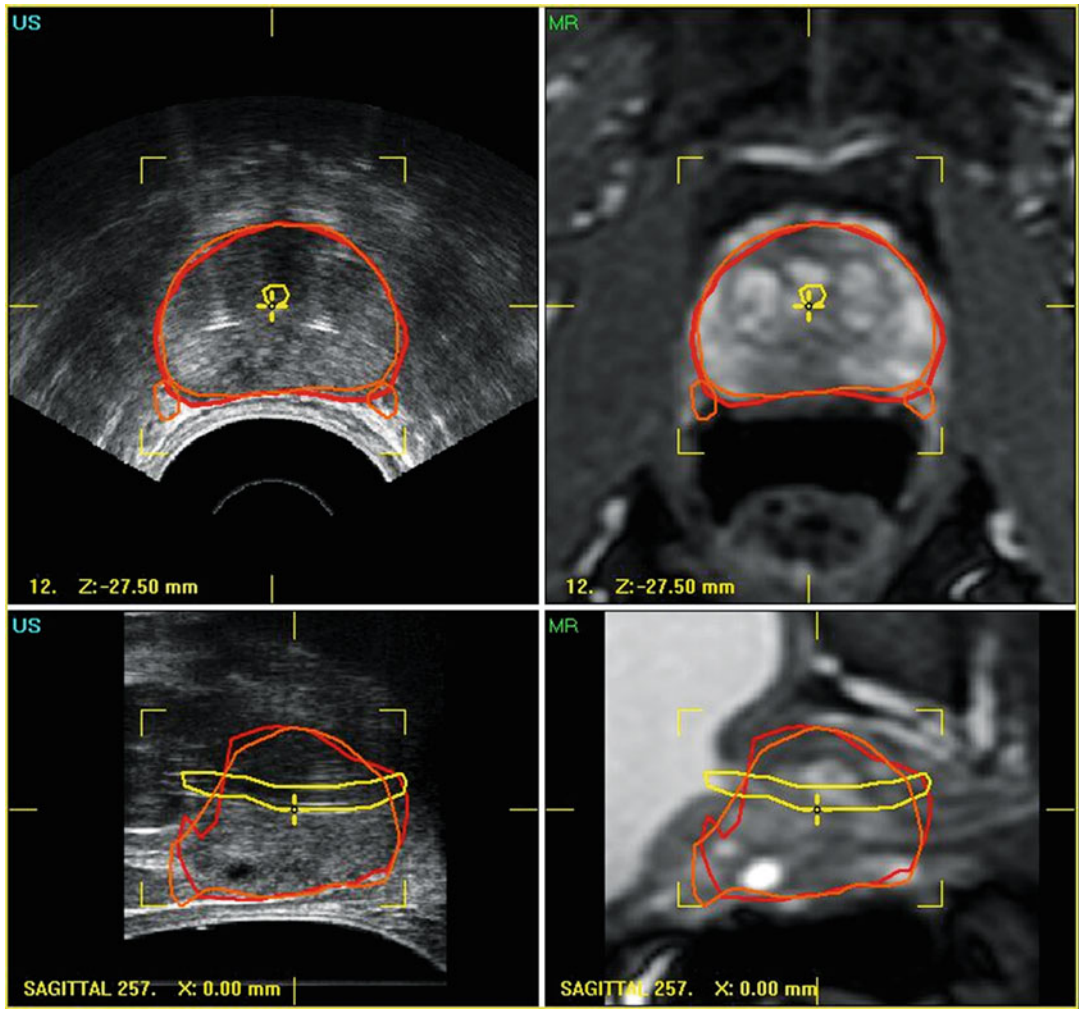

Fig. 10.2 Slice with contour of the prostate with TRUS in transversal and sagital direction. Similar for MRI (*right side*). *Red line* is contour obtained from TRUS, *orange line* is contour from MRI with also neurovascular bundle

Table 10.2 Extracapsular extension (ECE) in prostatectomy specimen of 712 patients (Teh et al. 2003)

ECE depth (mm)	Number (%)	Cumulative percent
0	527 (74)	74
<2	57 (8)	82
2–5	108 (15.2)	97.2
>5	20 (2.8)	100

prostate volume. Typically, the highest dose will be in the peripheral zone with areas of 200% and more of the prescription dose. For the urethra dose, 100–150% of the reference dose is acceptable and will not lead to severe urethral complications. For the rectum dose, 100% should be the limit to avoid rectal injury. The planning system will also give dose volume histograms (DVH), a very helpful tool in determining the best configuration of the seed placement and the quality of the implant, avoiding overdoses in critical parts.

The prescription dose for iodine seeds is 145 and 120 Gy for palladium for monotherapy. In combination with EBRT the doses are reduced with 25–40%. The required number of seeds depends on the volume of the prostate and the activity of the seeds. In general, the activity is

0.4–0.5 mCurie and the number of seeds lower with higher active seeds.

10.3.3 Other Planning Strategies

In place of preplanning, several other planning strategies can be performed. One can use intraoperative planning. In this situation, a preplan is made before the implant procedure with the patient already anaesthetised on the treatment table in lithotomy position and immediately execution of the plan. Also one can perform interactive planning, that is, stepwise refining the plan using computerised dose calculations according to the actual needle positions. With this planning technique variation in patient set-up, swelling and gland movement can be accounted for. Even more accurate would be dynamic dose calculation using continuous seed position feedback. However, this is still not available because the seeds are difficult to identify on TRUS. Several centres perform inverse planning, using constrains for critical tissues in and around the prostate (Martin et al. 2007).

10.4 Treatment Techniques

10.4.1 Patient Preparation

The procedure is performed on an outdoor basis or with one night of hospitalisation. Patients should have an empty rectum to optimise TRUS. This means a diet and laxative for 1 week and a rectal enema about 1 hour before the procedure will start. The treatment can be done with spinal/saddle block or general anaesthesia. Most centres give prophylactic antibiotics, either for several days or in one bolus before the implant. Since the needles are placed transperinealy, in contrast to the transrectal route for biopsies, there is hardly any infection.

The patient is placed in lithotomy position on the edge of the table in the same position as during the preplanning. A Foley catheter is introduced to visualise the urethra. Aerated gel (lubricating gel plus air to make small bubbles) can help to visualise the urethra. The scrotum is displaced from the operating field and fixed with adhesive dressing, and the perineum is washed with antiseptic solution.

The ultrasound probe is inserted and positioned under the prostate. A new volume study is performed and verified with the preplan (if done earlier). A volume study can also be done with a rotating probe in the rectum, making a 3D scan of the prostate.

10.4.2 Implant Procedure

Although there are several techniques for prostate implantation, in essence, the technique is the same, viz. the insertion of needles in the prostate guided by TRUS and the placing of the sources at the right position.

Needles can be preloaded according to the preplanning or can be afterloaded when the configuration for each needle is established. With the Mick applicator (see Fig. 10.3), single seeds are placed in the prostate according to the dose plan. One can also use strands, with seeds connected at a distance of 5 mm and embedded in a stiff polyglactin suture. In both situations, the seeds are inserted manually into the prostate.

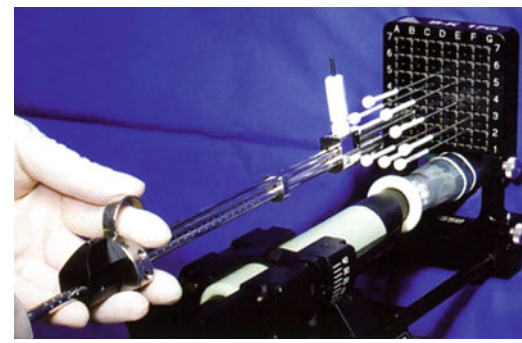

Fig. 10.3 Mick applicator. The foot of the applicator is placed against the grid. Inserted needles are visible, as well as the cartridge on the applicator

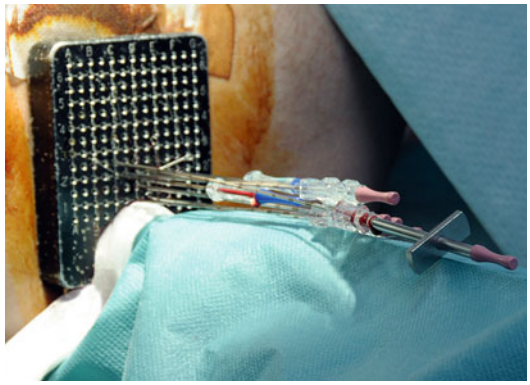

Fig. 10.4 Utrecht strand holder is placed on the hub of the needle. With the needle obturator the train of seeds and spacers will be placed in the prostate

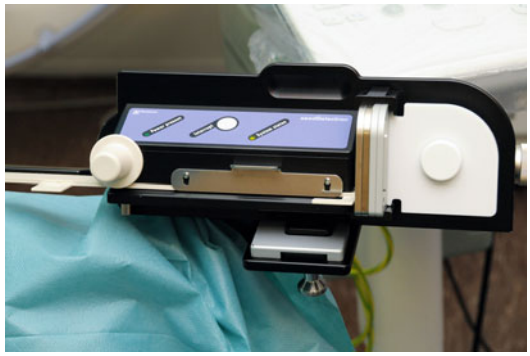

Fig. 10.5 FIRST system. The seedSelectron shows the two cartridges, the glossy one for active seeds, the second one for spacers. The two are connected with the drive wire. Further, we see the compose element, protected with the steel plate

In Utrecht, we developed strand holders to facilitate the insertion of a strand into the needle and subsequently into the prostate using the obturator of the needle (Fig. 10.4). Also, the holder gives radiation protection while inserting the seeds. With the Fully Integrated Radiotherapy Seed Treatment (FIRST) system (Fig. 10.5) single seed configurations are composed by a computer and inserted automatically into the prostate. With all systems differential loading can be performed. The Bard company created a special system to link seeds with spacers according to the plan (Fig. 10.6). In literature, there are publications that single seeds may result in a better dose distribution and even a better clinical outcome. Moerland found a significant larger decline of post-implant D90 (dose received by 90% of prostate volume) for stranded seeds as opposed to loose seeds (Moerland et al. 2009). Saibishkumar described a greater loss of seeds with strands compared with loose seeds (Saibishkumar et al. 2009). However, prostate dosimetry on days 7 and 30 was similar between both types of seeds. Reed found in the only two data-randomised comparison a higher post-implant D90 and V100 value for loose seeds. The results were based on only 62 men. In some cases, loose seeds were added to the stranded seed treatment (Reed et al. 2007). Hinnen assessed the clinical outcome in terms of biochemical no evidence of disease (bNED) from PPB for loose seeds (358 patients) and stranded seeds (538 patients) (Hinnen et al. 2010b). He found 5-year bNED of 86% and 90% (95% confidence interval) for strands and loose seeds, respectively, and an associated biochemical failure reduction of 43% for loose seeds.

Stabilising needles are helpful to reduce movement of the gland during the insertion of the needles. One can introduce all needles first, afterloading the needles with the appropriate number of seeds or one can insert a needle and insert the seeds, or use preloaded needles prepared by the vendor according to the configuration of the preplan. During the procedure, the planning can be adjusted to the exact position of the needle, taking into account a different route of the needle than planned (interactive planning). When all seeds are placed in the prostate, fluoroscopy can be done to verify the number of seeds in the prostate (Fig. 10.7). Also a C-arm with CT option can be used, to get a better insight of the position of the seeds over the prostate volume. If necessary, extra seeds might be placed (Westendorp et al. 2011).

After recovering from the anaesthesia, the Foley catheter can be removed. When the patient urinates spontaneously, he can return back home. Patients receive an alpha blocker to increase the urinary flow. Pain medication is seldom required. Physical exercise is allowed, but the patient should refrain from bicycling for one or more months depending on the urinary symptoms because this gives extra irritation of the prostatic urethra.

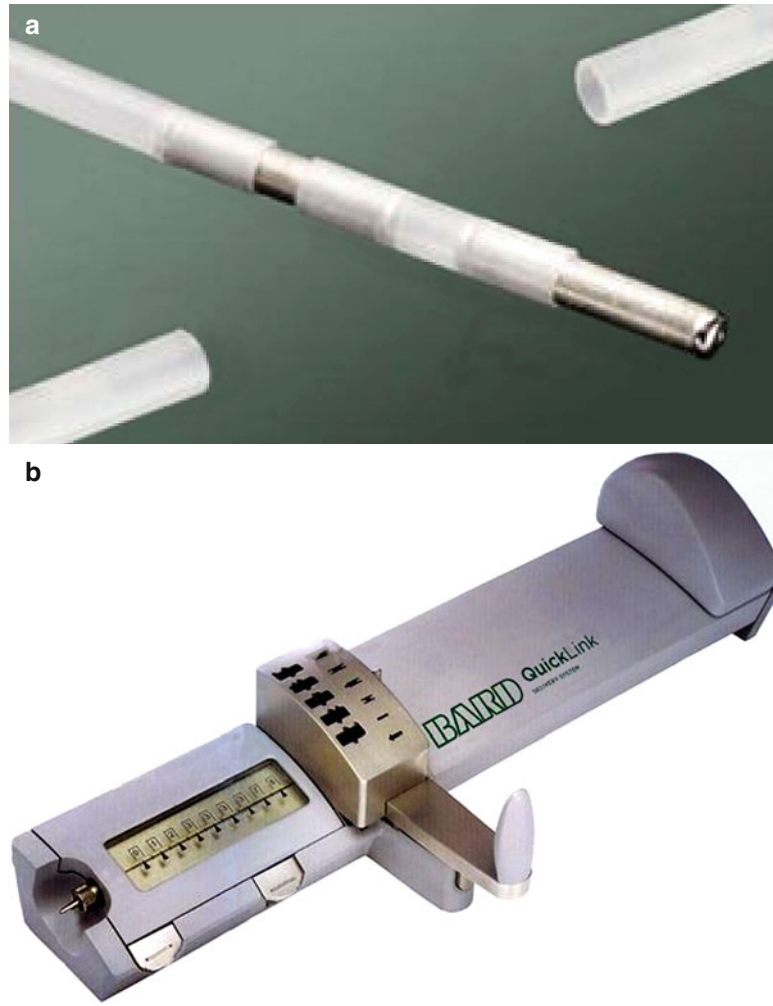

Fig. 10.6 (**a**) Shows the tool to prepare strands from loose seeds and spacers. (**b**) The tubes are depicted to make a strand of desired lengths with irregular spacing between the seeds

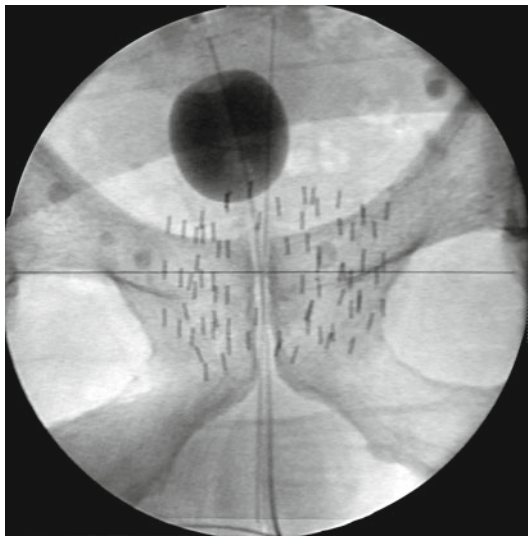

Fig. 10.7 X-ray at the end of prostate seed implantation to count the number of inserted seeds

10.4.3 Postplanning

It is recommended to do a postplanning approximately 1 month after the brachytherapy procedure. Swelling as result of the insertion of all needles will have disappeared by that time. CT or MRI can be used for imaging of the prostate and the seeds, with CT the seeds are better visualised, with MRI the prostate is better imaged and fusion of both modalities is the most appropriate (Villeirs et al. 2005). From the post planning the dosimetric parameters can be calculated by the planning computer. DVHs are useful indices considering the implant quality. What exactly is a good implant is still under debate. A D90 (dose of 90% of the prostate) value of more than 140Gy is recommended (Stock et al. 1998). Kao evaluated 643 patients after PPB with D90s of

180 Gy or greater and found excellent 5-year bNED of 96.5% for the whole group with 97.3% for low-risk patients and 92.8% for intermediate-/high-risk patients (Kao et al. 2008). However, Ash showed also good results with lower D90s (Ash et al. 2006).

10.4.4 Radiation Safety

Safety procedures include exposure measurement before discharge, information to the general practitioner and information for the patient and his relatives. Although the radiation exposure to other persons is very limited, it is advised that patients should not have close contact with young children and pregnant women for 2 months. The wife of the patient can sleep in the same bed with the patient. Measurements from South Africa with radiation monitors for the family and pets did not show any radiation, except for the wife sleeping in the same bed. However, still the radiation exposure was well below the International Commission on Radiological Protection (ICRP) limits with a lifelong dose of 0.1 mSv for iodine-125 and 0.02 mSv for palladium-103 (Michalski et al. 2003). Sexual intercourse is permitted, but a condom should be used during the first ejaculations since an iodine seed may be lost through this way. Seeds might disappear with the urine or can migrate within the body, mainly into the lung or regional lymph nodes. Although second primary cancer (SPC) such as bladder cancer may appear, the incidence is very low and should not be used as an excuse to refrain from brachytherapy (Singh et al. 2010). The ICRP considers the risk of SPCs after PPB negligible (Cosset et al. 2004).

Safety monitors in shops and warehouses are not triggered by the seeds. However, at some airports in the USA and in Russia, radiation monitors are used, and patients might be stopped up till 6 months after seed implantation. These patients should have a declaration from the hospital to enter the country.

10.5 Combined Treatment

Combination of PPB and EBRT is advocated for intermediate-risk patients with a higher chance for extracapsular extension (Blasko et al. 2000). The same group from Seattle reported on the 15-year bNED in clinical T_1–T_3 following combined EBRT and PPB. At 15 years, the bNED results were 88% for low-risk, 80% for intermediate-risk and 53% for high-risk patients (Sylvester et al. 2007). Critz shows also good results with the combined approach, but results are not better than with seeds alone, both in clinical outcome and side effects (Critz and Levinson 2004). However, there are no randomised studies to prove this. Several arguments are mentioned in favour for combined treatment. A higher dose outside the prostate capsule can be achieved to eradicate tumour cells outside the prostate. It also may eradicate tumour in lymph nodes and it results in a higher total dose to the prostate. Contra-arguments are that a dose of 40–55Gy with EBRT is too low to eradicate significant tumour, especially more than 5 mm outside the prostate contour. According to Teh, the majority of extracapsular growth is within 2 mm from the capsule, and if more it should be visible on MRI and TRUS, making the patient not suitable for PPB (Teh et al. 2003). In general, PPB will give such a high dose to prostate and margin that extra dose is not necessary. Finally the combined approach is more expensive and may result in more side effects. Blasko stated that combined therapy is perhaps indicated in centres with limited experience, to homogenise the total dose within the prostate (Blasko et al. 2000).

10.6 Results

According to a combination of PSA value, Gleason score and sum, and T-stage patients can be categorised in three risk groups, low, intermediate and high risk (Table 10.1), although systems in use in Europe and the USA may differ in criteria (Table 10.3). In general, only low- and intermediate-risk patients are considered candidates for PPB.

Table 10.3 Different criteria for the three risk groups

Centre	Low risk	Intermediate risk	High risk
Seattle	T_{1c}–T_{2b} and Gleason 2–6 and PSA ≤ 10	>T_{2b} or Gleason ≥ 7 or PSA > 10	2 or 3 factors
Mount Sinai	T_1–T_{2a} and Gleason 2–6 and PSA ≤ 10	T_{2b} or Gleason = 7 or PSA 10≤20	2 or 3 factors and/or Gleason 8–10 and/or PSA > 20 and/ or ≥T_{2c}
Boston	T_1–T_{2a} and Gleason 2–6 and PSA ≤ 10	T_{2b} and/or Gleason = 7 and/or PSA 10–20	2 or 3 factors and/or ≥T_{2c}, Gleason 8–10, PSA > 20

It is recommended to use the classification as published by GEC-ESTRO (Ash et al. 2000).

10.6.1 Low-Risk Patients

Low-risk patients are defined as T1c-2b, PSA < 10 ng/ml and Gleason sum ≤6. Because randomised studies are not available, data of clinical outcome are results from single institutions or combined from several centres. Follow-up time in large series is often more than 5 and even 10 years. Table 10.4 is showing excellent outcomes with percentages from 82% to 89% for bNED and around 95% for disease-specific survival (Beyer and Brachman 2000; Grimm et al. 2001; Battermann et al. 2004; Sharkey et al. 2005; Potters et al. 2005; Zelefsky et al. 2007; Hinnen et al. 2010a; Henry et al. 2010; Taira et al. 2011). In some articles, PPB is compared with other treatment modalities such as prostatectomy and EBRT (Pickels et al. 2010; Kupelian et al. 2004; Tward et al. 2006; Colberg et al. 2007; Jabbari et al. 2010). From these data, it is clear there is no significant difference in tumour control after PPB and prostatectomy. Only in the Kupelian paper, there is a significant lower outcome for patients irradiated with and insufficient external beam dose of < 72 Gy (Kupelian et al. 2004). Pickles and Morris describe a match-pair analysis of 601 patients treated with PPB or 3D conformal EBRT. The 5-year results of bNED were 95% for PPB and 85% for EBRT and after 7 years, still 95% for PPB, but only 75% for EBRT. Higher late toxicity was found for PPB for urinary symptoms and worse for bowel symptoms after EBRT. Colberg reported on 741 patients from one institution treated with prostatectomy (391 patients) or PPB (350 patients, 35% with 125-I and 65% with 103Pd). Only 8% were treated with combined PPB plus EBRT; 25 patients received ADT to downsize the prostate. At a median follow-up of 42 months, bNED was identical for the favourable group (93% vs. 92%), the intermediate group (70% vs. 70%) and poor group (50% vs. 52%) (Colberg et al. 2007). Tward looked at 60,290 patients from the SEER program with low and intermediate prostate cancer for prostate-cancer specific mortality (PCSM) and any-cause mortality (ACM). Median follow-up was 46 months. For patients age <60, PCSM at 10 years was 1.3% for surgery, 0.5% for PPB and 3.75% for no definitive treatment. Men over 60 had PCSM of 3.8%, 5.3% and 8.4%, respectively. On univariate and multivariate analysis, both prostatectomy and PPB had statistically equivalent PCSM and CSM (Tward et al. 2006). In the paper by Jabbari, also proton boost was included, but the conclusion of the paper was the finding of excellent results for PPB, suggesting at least equivalent 5-year bNED rates and a greater proportion of men achieving lower PSA nadirs compared with 3D-CRT or CPBRTB (Jabbari et al. 2010).

Table 10.4 Results of low risk patients

Author	Number of patients	Median f-up (months)	% bNED/ year rate
Beyer (2000)	128	84	85/7
Grimm (2001)	125	81	87
Battermann (2004)	114	48	91/7
Sharkey (2005)	528	72	87
Potters (2005)	481	82	89/12
Zelefsky (2007)		63	82/8
Hinnen (2010a)	232	72	88/10
Henry (2010)	575	57	86/10
Taira (2011)	319	74	97/12

Table 10.5 Results of intermediate risk patients

Author	Number of patients	ADT (%)	Median f-up (months)	% bNED/ year rate
Beyer (2000)	345	0	84	66/7
Cosset (2008)	276	68	43	94/5
Morris (2009)	419	100	54	96/5
Taira (2011)	144	0	74	96/10
Hinnen (2010a)	369	18	69	61/10
Henry (2010)	430		57	86/10

10.6.2 Intermediate-Risk Patients

Intermediate-risk patients (T1c-2c; Gleason 7; PSA 10–20 ng/ml) show good results as well, as can be seen in Table 10.5. Definitions of intermediate-risk cases and selection criteria may be different from series to series, and PPB may be combined with external beam radiotherapy and/or androgen deprivation therapy (Kupelian et al. 2004; Merrick et al. 2005a; Datolli et al. 2007; Morris et al. 2009; Munro et al. 2010). Both for the combination of EBRT plus seeds and the use of seeds plus ADT, it is not proven to be better than PPB alone (Merrick et al. 2005a). Henry described 1,298 patients, of whom 44.2% received ADT and found an association with poorer overall biochemical control rates, particularly in the intermediate risk group. She explained this difference that in patients with higher percent positive biopsy scores, the presence of perineural invasion, or Gleason 4+3 histology received ADT (Henry et al. 2010).

Hinnen reported an improvement in outcome for patients in the past decade compared with earlier experience in Utrecht for intermediate-risk patients since the use of intraoperative planning. This might not only be attributed to intraoperative planning but also to better patient selection by better (MRI) imaging, improved guidelines for implantation or greater consistency in biopsy Gleason score. However, for low-risk patients, there was no improvement, probably because the results for these patients already are very favourable (Hinnen et al. 2010a).

As was discussed earlier, outcome after PPB was found related to the D90 (dose to 90% of the prostate) over or under 180Gy and implantation technique using stranded or loose seeds (Ash et al. 2006; Piña et al. 2010; Hinnen et al. 2010b).

10.6.3 Gleason Sum 3+4 or 4+3, Does It Matter?

Results from literature concerning results in Gleason 3+4 and 4+3 give either a poorer prognosis for 4+3 tumours or not for all treatment modalities. Wright looked at prostate cancer–specific mortality for these groups of patients after surgery and radiotherapy and found an increased risk of recurrence or progression and specific mortality in those with Gleason 4+3 versus 3+4 (Wright et al. 2009). Merrick described a series of 530 patients with Gleason 3+4 (300 patients) or 4+3 (230 patients). At 10 years, primary Gleason score did not impact survival, while deaths from cardiovascular disease or second malignancies were 9.6 times more common than death from prostate cancer (Merrick et al. 2007).

10.6.4 High-Risk Patients

A significant lower cure rate is found in high-risk patients (≥T2c; Gleason > 7; PSA > 20 ng/ml) after all treatment options. This may be due to the fact that a substantial number of them will have microscopic metastases. In the treatment of patients without traceable metastases brachytherapy can be used, either as monotherapy or in combination with EBRT and/or ADT. Many of these combined treatments are performed successfully using HDR brachytherapy (Galalae et al. 2002; Martinez et al. 2010). For patients categorised as high risk due to a PSA value over 20 ng/ml and/or Gleason sum higher than 7, PPB might still be an option. Stone reports good results for these patients with PPB at a D90 of more than 200 Gy (Stone et al. 2010).

10.6.5 Does Age Matter?

Patients before 60 years of age should not withhold PPB according to data in literature (Merrick et al. 2006; Shapiro et al. 2009; Burri et al.

2010a, b). Shapiro found freedom from progression at 10 years after PPB, in patients with low, intermediate and high risk of 91.3%, 80.0% and 70.2% compared to 91.8%, 83.4% and 72.1%, respectively, for men before 60 years versus men of 60 years or older. Interestingly, high rates of cause-specific and biochemical progression- free survival after PPB in 145 consecutive men over 74 years of age were reported. Overall survival and non-cancer deaths were best predicted by tobacco status (Merrick et al. 2008).

Second primary tumours do occur, but still the number is negligible as mentioned earlier in this chapter (Liauw et al. 2006). Hinnen found in a series of 136 PPB patients, compared with 87 patients after prostatectomy with a median follow-up of 5 years for both a low incidence of second primary cancers. However, in patients under 60, there was a higher chance for bladder cancer after PPB (Hinnen et al. 2011b). Moon looked at the SEER registry for men with incident prostate cancer and evaluated type of treatment, tumour stage and grade, and age at diagnosis. Data were evaluated for second primary cancers beginning 5 years after treatment. Patients after EBRT had significantly higher odds of developing second cancers compared with men without radiation therapy, both in the treated area (bladder, rectum) but also in areas not potentially related to radiation. Lowest odds of developing cancers were found with men after PPB (Moon et al. 2006).

10.7 Morbidity

The majority of patients will experience some degree of urinary irritation with complaints of higher frequency, reduced flow, urge and burning while urinating. These symptoms are the result of swelling of the prostate because of the needles that have been placed. After a few weeks prostate radiation inflammation will take over the symptoms. Although many men will recover in weeks or months, in a small number of men, symptoms become worse and may result in urinary obstruction. The incidence rate varies in literature from 5% to 20% and is related to prostate volume and initial voiding problems with high IPSS (Terk et al. 1998; Blasko et al. 2002; Crook et al. 2002; Martens et al. 2006). Also after combined treatment, a similar rate of obstruction is found. The majority of obstructed patients can be helped with a Foley catheter for some weeks. Occasionally, the problems remain and a suprapubic catheter should be placed to drain the bladder. This is more comfortable and the patient himself can monitor his voiding pattern. It is advised to wait at least 6 months and better 12 months before surgical procedures are performed to reduce the chance for incontinence. If surgery is performed, the procedure should be as minimal as possible (median incision, bladder neck incision, or mini TURP). Incontinence rate is less than 1%, only patients who had previous TURP have a higher chance for incontinence (Blasko et al. 2002; Stone and Stock 2002; McElveen et al. 2004). Keyes presented a paper on predictive factors for acute and late urinary toxicity in 712 patients. IPSS returned to baseline at a median of 12.6 months. On multivariate analysis, higher baseline IPSS resulted in a quicker resolution of their IPSS. Higher D90, maximal post-implant IPSS, and urinary retention slowed IPSS resolution time. Actuarial 5-year late urinary toxicity Grade 3 and 4 was reported 6.2% and 0.1% (Keyes et al. 2009a). The same group also report on urinary flare in the same group of patients. Typically, this is found 16–24 months after implant with an incidence of 52% (flare definition of an IPSS increase ≥5) and 30% (flare ≥8). Patients with symptoms had a resolution of these symptoms within 6 months of 65% and at 12 months of 91% (Keyes et al. 2009b).

Late complications are pain in the perineum, urethra strictures and rectal bleeding. Since the use of intraoperative dose planning, the rate of these complications is reduced considerably (Salembier et al. 2007). All these complications are rare nowadays and recover often spontaneously with pain medication, alpha blockers or in severe and persisting situations a treatment session of hyperbaric oxygen. Fistulae and other grade 4 toxicity are reported 0–2% in experienced hands (Stone and Stock 2002).

Erectile dysfunction is found in 20–50% of men, depending on age, sexual activity, smoking, diabetes and use of medication, e.g. β-blockers (Robinson et al. 2002; Merrick et al. 2005b). Sildenafil and other stimulating drugs can help to

improve erections. Especially in younger patients, a decrease of erection may appear a few months after seed implantation and in general will recover spontaneously.

From a study in Utrecht, it was shown that patients after 6 years had the same quality of life score as before iodine implantation (Roeloffzen et al. 2010). Malcolm found after 2 years from open or RALP prostatectomy, cryosurgery or PPB in all domains (bother score, urinary and sexual function) higher scores after PPB (Malcolm et al. 2010). Crook reported on the outcome of the SPIRIT study on the comparison of health-related quality of life 5 years after treatment. Of 168 survey responders 60.7% had PPB and 39.3% surgery. Median follow-up was 5.2 years. There was no difference in bowel or hormonal domains, but patients after PPB scored better in urinary and sexual domain, and in patient satisfaction (Crook et al. 2011).

10.8 Management of Recurrences

After PPB, patients are followed by both the radiation-oncologist and the urologist. PSA levels are closely monitored. If PSA levels are rising, this indicates local recurrence, distant recurrence, local plus distant recurrence and most common PSA bounce. In the last case, it means there is a temporary PSA increase about 1.5 years after seed implantation. PSA can increase with up to 2 ng/ml. Kirilova examined patients with a bounce after iodine seed implantation with 3D MRI spectroscopy and found diffuse metabolic activity during an ordinary bounce, whereas in case of recurrence, there was more focal activity (Kirilova et al. 2011). This rise is most likely caused by death of many normal prostate cells due to hypoxia. It was found that this phenomenon is related to a better outcome than in patients without this rise (Crook et al. 2007; Hinnen et al. 2012). PSA levels should come down to non-measurable levels, but this might take several years. Grimm observed a period of 6 years before 80% of the patients had reached their nadir of <0.2 ng/ml (Grimm et al. 2001). If PSA remains to increase, further diagnostic examination is mandatory to differentiate between distant or local recurrence. However, in many cases, it is not possible to find either a local or distant tumour recurrence. MRI, especially dynamic contrast-enhanced (DCE) MRI can help to locate local recurrence by showing a higher blood perfusion (Futterer et al. 2006). Of course, histological proof is needed before calling the finding a local recurrence. Although the possibilities are limited, still some options are open for the patient. This is highly related to the initial risk group and the delay between the first implantation and the onset of recurrence. In general, PSA increases soon after brachytherapy indicates distant spread, especially when the PSA doubling time is less than 6 months. Second brachytherapy is an option as described by (Moman et al. 2010). She advocates only doing this second treatment if the recurrence is located in one lobe. Then a seed implant of that lobe is performed with much lower toxicity than with a full implant. In a previous paper, Moman found in a series of 31 local recurrences after initial brachytherapy (11 patients) or EBRT (20 patients) freedom for biochemical recurrence of 51% after 1 year and 20% after 5 years. Toxicity was high with genito-urinary tract grades 1, 2, and 3 of 29%, 58% and 3% in the acute phase and 16%, 39% and 19% in the late phase, respectively. For gastrointestinal toxicity, this was 45%, 10% and 0% in the acute phase and 48%, 3% and 6% in the late phase, respectively (Moman et al. 2009). Nguyen showed a similar major toxicity of 30% versus 29% but with a much better tumour outcome with 70% failure free after 4 years. However, in this series only low-risk patients were candidates for salvage brachytherapy (Nguyen et al. 2007). Burri published the results from the Mount Sinai group on 37 patients (32 EBRT and 5 PPB) with a median follow-up of 86 months. Salvage brachytherapy was associated with a 10-year bNED of 54% and cause-specific survival of 96%. Presalvage PSA < 6 ng/ml was significantly associated with improved bNED. Toxicity was low, but with three Grade 3 toxicities and one Grade 4. Toxicity was correlated with pelvic lymph node dissection (Burri et al. 2010b). Another option is salvage surgery. In case of

prostatectomy, the same criteria can be used to consider a patient candidate for salvage surgery and might be successful in well-selected patients. Bianco reports on 100 consecutive patients with local recurrence after EBRT (58 patients) and after PPB (42 patients). The overall 5-year progression-free probability was 55%. Preoperative PSA was the only significant predictor of disease progression with probability of 86%, 55% and 37% for PSA level of <4, 4–10, and >10, respectively (Bianco et al. 2005). In an earlier paper by the same group, toxicity was described. In patients operated after 1993, the major complication rate was 13%, significantly less than the 33% from previous experience. Urinary incontinence was reported in 68% of patients, requiring one pad a day or less, while 23 patients needed an artificial urinary sphincter (Stephenson et al. 2004). External beam irradiation with IMRT can be a possibility, although there is not much literature available. Salvage seed implantation after failure of EBRT is an option, again with the same criteria as mentioned above (Beyer 2004; Lee et al. 2008).

10.9 Discussion and Conclusions

Early experience with permanent prostate brachytherapy was rather dismal. However, the rationale to deliver a high local dose with sparing of normal tissues remained appealing. With the introduction of the perineal technique, using TRUS for guidance of the needles, much better results were obtained and gave PPB a solid place in the armamentarium for the treatment of localised prostate cancer. Long-term results are available and show outcomes equivalent to radical prostatectomy and beam irradiation.

With modern imaging techniques such as MRI with or without endorectal coil, multi-slice CT, choline-PET-CT a further improvement in staging will result in better patient selection and hence better outcome for all treatment modalities. But we should remember the phrase from Whitmore on patient selection: 'Is prostate brachytherapy necessary for those who want it and is prostate brachytherapy possible for those who need it'.

Prostate brachytherapy appears to be the treatment of choice for low and intermediate cancers and can be used in combined therapy as a boost with or without androgen deprivation for patients with less favourable criteria. Whether HDR monotherapy will be used routinely for early-stage lesions is not clear but has a major advantage in the costs of treatments due to the high price of iodine seeds in Europe. Also, the radiobiology with low α/β ratio for prostate cancer could be in favour of HDR.

Urologists are considering using focal therapy in selected patients. In place of cryosurgery and HIFU, prostate brachytherapy with seeds or HDR can be a more appropriate technique in these cases. However, Isban published up to 60% multifocal tumour apart from the diagnosed unilateral tumour in biopsies (Isban et al. 2010).

Finally, we have to keep in mind that more men after permanent prostate brachytherapy will not die of their cancer but of other causes (Bittner et al. 2008).

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High-Dose-Rate Brachytherapy: Indications, Technique, and Results

11

Alberto Bossi, Rodolfe Verstraet, Lucie Calmels, and Pierre Blanchard

Contents

A. Bossi, M.D. (✉) • R. Verstraet, D.Sc.
L. Calmels, D.Sc. • P. Blanchard, M.D.
Department of Radiation Oncology and Medical Physics, Institut Gustave Roussy, Villejuif, France
e-mail: alberto.bossi@igr.fr

11.1 Background and Rationale

11.1.1 Dose–Response Relationship for Prostate Cancer

Convincing experimental and clinical data have been published in recent years, clearly demonstrating that high doses are needed in order to optimize clinical and biochemical outcomes when irradiating men with localized prostate cancer (Cahlon et al. 2008; Dearnaley et al. 2007; Peeters et al. 2006). It is widely accepted that a dose–response relationship exists for prostate cancer, and conformal and intensity-modulated external beam radiotherapy techniques have been developed to achieve dose escalation and to allow a better sparing of radiosensitive dose-limiting adjacent normal structures such as rectum and bladder. However, inter- and intrafractions organ motion together with variations in daily setup represent a serious challenge to external beam radiotherapy even when image-guided technology is employed (De Crevoisier et al. 2005). Brachytherapy on the contrary is not limited by positioning uncertainties as the target is immobilized by the implanted needles (or catheters) and treated within very short treatment times; therefore there is no need for an extramargin expanding the clinical target volume (CTV) to the planning target (PTV).

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11.1.2 Radiobiology

Extensive literature supports the concept of a low *a*/*b* ratio describing the radiobiological response of prostate cancer cells to irradiation. Although this value is still debated, a general consensus estimate it around 1.5–3, well below 5 (Brenner et al. 2002). This implies that an enhanced cell kill is to be expected when larger than standard dose per fraction is used, and furthermore, assuming that the *a*/*b* ratio for prostate cell is lower than the one for the rectal mucosa, an increase in the therapeutic ratio regarding rectal toxicity is also to be expected, and in this respect, HDR brachytherapy may be considered as an extreme form of hypofractionated irradiation. HDR brachytherapy thus combines the advantages of being one of the most efficient methods to perform dose escalation by means of the most favorable fractionation schedule. In fact, when comparing HDR brachytherapy regimens to standard external beam radiotherapy regimens (2–3 Gy per fraction), equivalent dose in 2 Gy fractions (EQD2) or biologically equivalent dose (BED) formula is often used, indicating invariably that HDR regimens deliver 25–50% higher doses in the prostate as compared to conventional fractionated EBRT (Joiner and Bentzen 2009; Hoskin 2008). Interestingly, several authors have compared different radiotherapy techniques (HDR brachytherapy, IMRT, TomoTherapy, CyberKnife) in terms of their capabilities of obtaining the best dose distribution both for target coverage and of organs at risk sparing (Hermesse et al. 2009; Nickers et al. 2006). Invariably, HDR has been associated to the highest dosimetric selectivity.

11.1.3 HDR Versus LDR Brachytherapy

Moreover, high dose rate presents several advantages as compared to LDR brachytherapy (Kovacs et al. 2005; Martinez et al. 2005a; Hoskin 2008). By implanting at first nonactive afterloading guide needles or catheters, the spatial source position may be accurately modulated and the source dwell time efficiently adapted according to a three-dimensional-imaging-based individual dose prescription, and only once the most suitable dose distribution is obtained the irradiation is started. This means that small inaccuracies in needles/catheters placement can be corrected by adjustments of treatment parameters before irradiation while accurate seeds implant within the gland is technically challenging with limited possibility for live adjustments. In addition, HDR needles/catheters may be placed not only inside the prostatic capsule but also in the extraprostatic tissue or even in the seminal vesicles, making it possible to treat more advanced cases as compared to a strictly intraprostatic technique as LDR brachytherapy. No source preparation is necessary before or during HDR treatment, and no free radioactive materials are used during the implant, thus minimizing the risk of source loss and the need for radioprotection procedures. Finally, costs of temporary HDR brachytherapy are limited as many radiotherapy centers are equipped with an afterloading unit for other brachytherapy treatments.

11.2 Indications and Patients Selection

Originally, HDR brachytherapy has been reserved for patients with locally advanced prostate cancers in the intermediate-to-high-risk groups (Gleason Score >6, PSA at diagnosis >10 ng/ml) as a boost to the prostatic volume combined with external beam RT. Recently, HDR monotherapy schedules have been proposed for patients having favorable risk cancers with HDR brachytherapy delivering the entire radiation treatment. The GEC/ESTRO-EAU group has published guidelines for patients selection for HDR brachytherapy (Kovacs et al. 2005): classical exclusion criteria for any transrectal-ultrasound (TRUS)-guided transperineal implant technique are suggested also for HDR (Table 11.1), but it should be emphasized that large gland size (>60 cc) should not be regarded as an absolute contraindication when considering the potential for geometrical downsizing of 3–6 months of androgen deprivation therapy (ADT). Probably, no absolute cutoff

Table 11.1 Patient selection criteria for temporary high-dose-rate (HDR) brachytherapy

Absolute contraindications	Pubic arc interference (even after ADT)
	Significant low urinary tract symptoms (LUTS)
	Lithotomic position/anesthesia not possible
	Tumor invasion of the bladder neck
Relative contraindications	Prostate volume >60 cc
	Prior transurethral resection of the prostate (TURP)
	Rectum-prostate distance at transrectal ultra sound (TRUS) <5 mm

volume exists since what really matters is the relationship between the gland volume and the pelvic anatomy of the patient with hip positioning and TRUS-probe angle adjustments, playing a major role in making the implant feasible even for large glands. When a pubic arch interference (PAI) is suspected on digital rectal examination or on imaging, it is preferable to check it with a TRUS with the patient in the implant position in order to decide on the need for hormonal cytoreduction knowing that preimplantation ADT reduces prostate size by about 30% (Stone et al. 2010) to the price, at least for some authors, of a higher postimplant retention rate (Crook et al. 2002). Likewise, a prior history of transurethral resection of the prostate (TURP) is clearly associated with a somewhat higher risk of developing postimplant grades 2–3 late genitourinary toxicity (mostly incontinence), but this probably holds true only when a large central defect is present in the gland, and in general, a lower dose to the urethra may be administered without compromising the peripheral zone dose coverage. Again a preimplant TRUS may help in evaluating the TURP central defect. Low urinary tract obstructive symptoms (LUTS) should be carefully investigated prior to the implant using a validated scoring scale such as the International Prostate Symptom Score (1991) or the American Urological Association (AUA) criteria (Barry et al. 1992), and preferably, a voiding study by uroflowmetry should be carried on to evaluate the urinary flow rate and the postvoiding residual volume (Martens et al. 2006) knowing that a substantial urinary obstruction represents a possible exclusion criteria due to the accrued risk of developing postimplant bladder retention. The GEC/ESTRO-EAU recommendations also mention tumor invasion of bladder neck and a rectum-prostate distance at TRUS inferior to 5 mm as exclusion criteria. Finally, the role of imaging in the local staging of prostate cancer for patient's selection for HDR brachytherapy should be emphasized. Magnetic resonance (MR) is the single most sensitive imaging investigation in assessing the local extent of prostatic adenocarcinoma. The precise knowledge of the extent and the location of extracapsular disease and/or seminal vesicles infiltration may guide the brachytherapist for further treatment decision (Cornud et al. 2002). Independently, of the technique adopted for needles/catheters placement and for treatment planning (TRUS, CT, or MR based), it is thus advisable to perform a staging MR before planning the implant (Fuchsjager et al. 2008; Heidenreich et al. 2011; Kovacs et al. 2005).

11.3 Technique

11.3.1 Procedure

The technique of HDR brachytherapy is similar to LDR one, and the equipment needed is not very different. Obviously, a treatment room with adequate shielding is necessary (where, if possible, also the needles implantation should take place in order to avoid additional patient transportation and potential needles displacement) together with an afterloading HDR unit with a 192Iridium stepping source and a camera system to monitor the patient during the irradiation (Kovacs et al. 2005). Slightly different methods are proposed by the teams performing HDR brachytherapy, depending on the adoption of a two-step procedure (preplanning a few days before implantation) or an intraoperative online planning, on the imaging used for needles guidance and for dose planning (TRUS, CT, or MR based), and on the clinical protocol adopted (single fraction versus multifractionated HDR), but some general steps are common. (1) The

procedure requires general or spinal anesthesia with the patient in the dorsal lithotomy position: particular care should be reserved to patient positioning especially when a PAI is suspected (= more acute spine-hip angle). (2) Modern brachytherapy implants are performed transperineally, and needles placement is generally made under TRUS control. The TRUS device is secured to a stepper unit, and adequate fixation (to the floor or to the patient table) is needed in order to avoid movements during the procedure. (3) A Foley catheter is placed in the bladder in order to better visualize the transprostatic urethra and the bladder neck during the entire procedure, and the gland is localized by TRUS on the axial, coronal, and sagittal planes and positioned as symmetrical as possible in relation to the urethra by adequate probe inclination. If the treatment planning is performed using three-dimensional TRUS reconstructed volumes, a set of images using the stepper unit is acquired in 3–5 mm steps from 1 cm above the base to 1 cm below the apex of the prostate and recorded in the treatment planning unit. (4) TRUS-based contouring of the prostate (CTV), rectum adjacent to the gland, urethra (following the Foley catheter images and eventually using aerated gel to better visualize it), and bladder neck is performed, and commercially available software will integrate ultrasound images to provide a three-dimensional reconstruction of the CTV and organs at risk for intraoperative online planning purposes (see Sect. 3.2). Alternatively, when CT and/or MR images are used for contouring and treatment planning, the patient should be transferred *after* the implant in the supine position with a Foley catheter in place to the CT-MR scan unit for the acquisition of the set of images needed for organ contouring. Generally, no margins are added to the CTV to obtain a PTV (= the CTV and the PTV are identical), but some authors advocate the need to contour, beside a whole gland CTV (= CTV1), a CTV2 encompassing the peripheral posterior zone of the prostate (where a highest tumor load is presumed) and even a CTV3 if tumor infiltration areas are detectable by classical imaging techniques or by functional ones (Kovacs et al. 2005). (5) A template with a detachable perineal portion and holes with 0.5 cm spacing is used for needles guidance. It is fixed to the stepper unit and positioned parallel and close to the perineal skin plane. Needles are implanted under direct TRUS control as parallel as possible to each other and to the probe with the largest prostate cross section seen on sonography used as reference view for needle distribution (Fig. 11.1). Different philosophies exist in the literature about the best needles implant distribution strategy. Some authors prefer a homogenous intraprostatic needle distribution with fixed interneedle spacing, while others start by implanting peripheral needles at 8–10 mm spacing (Fig. 11.2): in this case, the central needles are implanted at a later stage according to the actualized dosimetry, and for eventual real time, better tuning of the final dose distribution (Edmundson et al. 1995; Slessinger 2010). The prostatic base-plane is regarded as the planned position of the needles tips which are all inserted at the same depth, but if needed and especially in the posterior aspect of the gland when seminal vesicles infiltration is suspected, a few needles may be pushed at different depths to better adapt to the prostate shape. It is important to remember that the first source position available for treatment is some millimeters backward from the tip of the needle/catheters: this implies that, using the sagittal TRUS view, all needles should be inserted deep enough in order to obtain an optimal dose coverage particularly at the level of the prostate base without piercing the bladder and/or the urethral wall. The tenting of the bladder mucosa by needles' tips may be checked by a

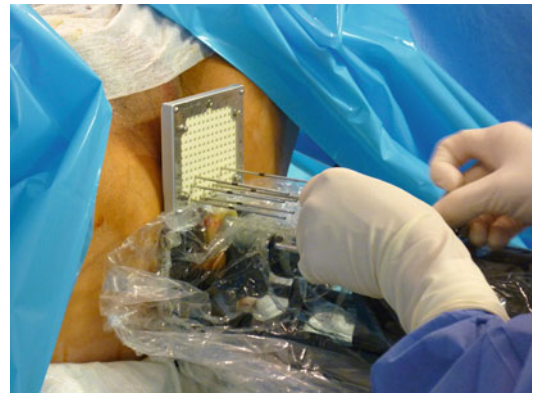

Fig. 11.1 Needles implant using the high-dose-rate template

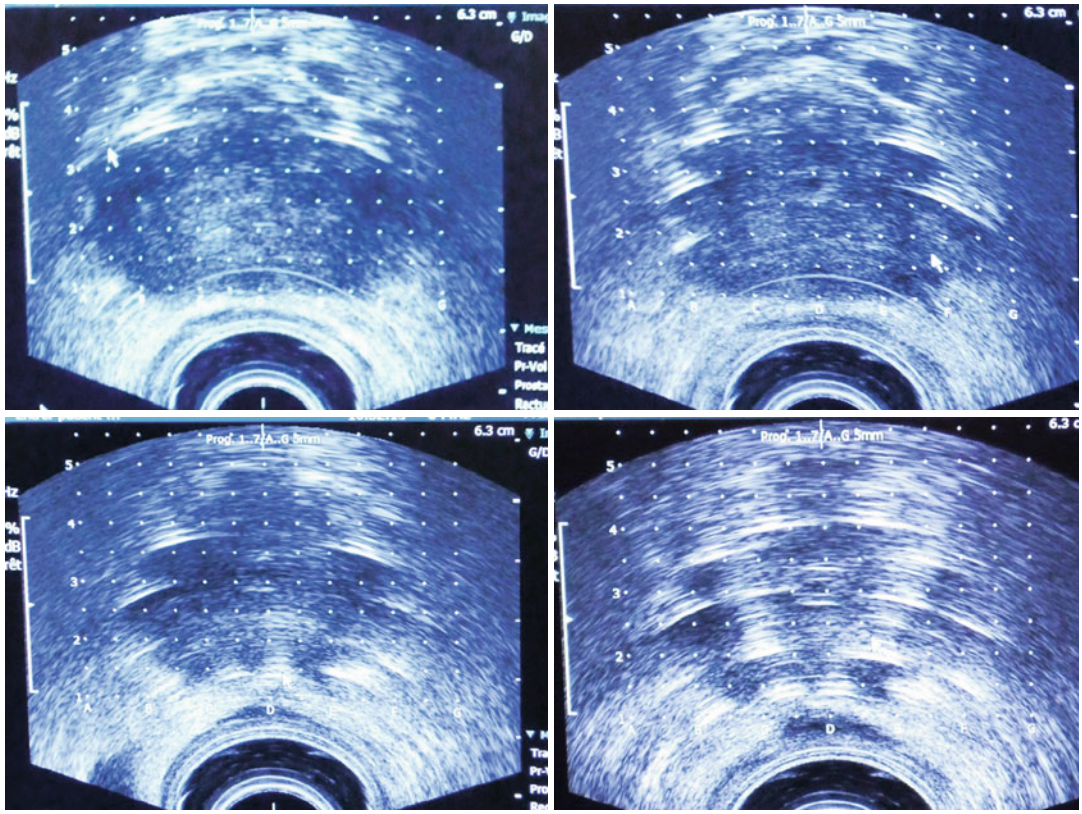

Fig. 11.2 At first, peripheral anterior needles are implanted (*top left*) followed by the central ones

flexible cystoscopy if available once the implant is completed. On average, 12–22 needles/catheters are needed for whole prostate coverage depending on the volume and shape of the prostate. (6) Finally, when several fractions are planned and/or when CT-/MR-based treatment planning is performed, the detachable perineal part of the template is unscrewed and sutured to the skin, and the patient is transferred to the CT/MR unit for treatment planning scan. Transferring the patient from the operating room table to the CT/MR table and then to the treatment one, or when several fractions are planned, implies that a nonnegligible source of error is introduced in the procedure due to needle retraction in the craniocaudal direction associated with repositioning (Foster et al. 2011; Simnor et al. 2009). The needles/catheters shift has been reported in the range of 5–7 mm and may translate into suboptimal dose coverage especially at the base of the prostate but also into a higher than planned urethral dose. As a consequence, the regular control of needle geometry is strictly recommended (by visual inspection and catheters measurements, by fluoroscopy, and by repeated scanning before each fraction), and any displacement of more than 3 mm should be corrected (Seppenwoolde et al. 2008; Tiong et al. 2010).

11.3.2 Treatment Planning and Delivery

As already mentioned, treatment planning can be based on three-dimensional TRUS, CT, or MR imaging: in this latter case, flexible plastic catheters will have to replace metallic needles to allow for CT planning. Intraoperative, TRUS-based, real-time planning is time sparing and certainly advantageous for patient comfort while CT- and/or MR-based postimplant procedures will benefit from a better visibility of prostate and catheters contours as compared to sonography. Once the contouring is completed,

planning of the treatment can start: intraoperative real-time treatment planning optimization software's are available to perform multiple iteration of the 192Iridium source position (= dwell positions, every 2.5–5 mm) and the duration (= dwell time) that the source will remain in any particular position within each single needle/catheter in order to provide the requested dose distribution to the target and organs at risk. Once the optimized treatment plan is approved by the brachytherapist, each catheter/needle is connected by means of transfer tubes to the HDR afterloading apparatus and dose delivery begins (Fig. 11.3). Large variations in terms of number of implants and/or fractions, planning parameters (= dose constraints for the target and the organs at risk), dose per fraction, and timing of the implant, both for HDR as a boost combined to EBRT or as a monotherapy, are reported in the literature with patterns of practice having undergone significant evolution across institutions. Tables 11.2 and 11.3 report the HDR brachytherapy schedules adopted in some of the series recently published for, respectively, combined HDR + EBRT treatment and HDR alone. For combined HDR-EBRT, the prescribed brachytherapy dose to the prostate varies from 5.5 to 15 Gy per fraction for a total dose of 15–21 Gy in 1–4 fractions (1–3 implants), while the total EBRT dose is reported between 37.5 and 55 Gy in 1.8–2.75 Gy/fr. When HDR brachytherapy is employed alone, 3–6 fractions of 6–10.5 Gy each are used in 1–2 implants (total dose of 31.5–54 Gy). Due to differences in protocols (HDR given before, after, or during EBRT) and techniques (a new implant for each fraction or one implant with several loadings), the reported interfraction times vary from a few hours to 21 days. The clinical relevance of these differences (timing of HDR, overall treatment time, interfraction gap) is not clearly understood. For comparison with full EBRT course at standard fractionation, Tables 11.2 and 11.3 also report the EQD at 2 Gy for *a*/*b* values of 1.5 and 3 knowing the limits of applicability of

Fig. 11.3 Needles/catheters are connected to the afterloading 192Iridium source projector for treatment

Table 11.2 High-dose-rate (HDR) brachytherapy combined with external beam radiotherapy (EBRT): treatment schedules and corresponding equivalent dose in 2 Gy fractions (EQD2) for different *a*/*b* values

Reference	No. of pts	ADT (%)	HDR Gy/fr	No. of implant	EBRT Gy tot/fr	EQD2, *a*/*b* = 1.5	EQD2, *a*/*b* = 3
Deutsch (2010)	160	45	7/3	1	45–50.4/1.8	93–98.5	85–90
Hoskin et al. (2007)	109	76	8.5/2	1	35.75/2.75	115	102
Martinez (2005a, b)	934	44	7.5/2 5.5/3 10.5/2 6/4	2–3	40/2 46/1.8–2 36/1.8	78.6–118	71.5–103
Hsu (2010)	125	40	9.5/2	1	45/1.8	102	91
Morton (2010)	125	0	15/1	1	37.5/2.5	114	95
Demanes et al. (2005)	209	0	5.5–6/4	2	36/1.8	78–85	72–78
Galalae et al. (2006)	324	0	5.5–11.5/2–3	2–3	45–50/1.8–2	75–128	71–110

Table 11.3 High-dose-rate (HDR) brachytherapy alone: treatment schedules and corresponding equivalent dose in 2 Gy fractions (EQD2) for different *a/b* values

Reference	No. of pts	Gy/fr	No. of fr	Gy tot	No. of implant	EQD2, $a/b = 1.5$	EQD2, $a/b = 3$
Corner et al. (2008)	110	8.5	4	34	1	97	78
		9	4	36	1	108	86
		10.5	3	31.5	1	108	86
Ghadjar et al. (2009)	36	9.5	4	38	1	119	95
Rogers (2012)	284	6	6	36	1	77	65
Mark et al. (2010)	301	7.5	6	45	1	116	94.5
Demanes et al. (2011)	157	7	6	42	2	102	84
	141	9.5	4	38	1	119	95
Yoshioka et al. (2011)	112	6	8–9	48–54	1	116	97

Table 11.4 High-dose-rate (HDR) brachytherapy combined with external beam radiotherapy (EBRT): dose constraints

Reference	HDR Gy/fr	No. of implant	EBRT Gy tot/fr	Prostate	Urethra	Rectum	Bladder
Crook 2011	–	–	–	V100 > 95% V150 < 35% V125 < 60%	D_{max} < 125% D10 < 120%	D_{max} < 75% V80 < 0.75%	–
Hoskin et al. (2007)	8.5/2	1	35.75/2.75	V100 = 100%	D10 < 10 Gy	D2 cc < 6.7 Gy	–
Martinez et al. (2011)	7.5/2 5.5/3 10.5/2 6/4	2–3	46/2	V100 > 96% V125 < 60% V150 < 30%	V115 < 5%	D_{max} < 75%	–
Hsu (2010)	9.5/2	1	45/1.8	V100 ≥90%	V125 < 1 cc	V75 < 1 cc	V75 < 1 cc
Morton (2010)	15/1	1	37.5/2.5	V100 > 95%	D_{max} < 118%	D_{max} < 80%	D_{max} < 80%

the linear-quadratic model for dose per fraction beyond 5–6 Gy (Joiner and Bentzen 2009).

11.3.3 Dose Constraints

The optimization process for treatment planning is based on dose prescription to the prostate volume and on dose constraints for organs at risk. It has correctly been pointed out that, in contrast to EBRT, the exclusive use of dose-volume histograms (DVH) is of limited value in brachytherapy when evaluating a treatment plan due to the nonhomogenous dose distribution obtained within the target by temporary (or permanent) implants (Kovacs et al. 2005). Tables 11.4 and 11.5 report the dose constraints suggested in the literature for HDR brachytherapy combined with EBRT or when used alone. There is no general agreement on which parameters to use and which dose level to recommend: it is in general advisable to adopt maximum dose (D_{max}), dose to fixed volume levels (D2 cc, D0.1 cc,…), or volumes in cc receiving certain dose levels (V100, V125,…) since dose to percent of the organ (D10, D30,…) depends on contouring protocols (typically for rectum and bladder). Urethral D_{max} should not be higher than 120–125% of the prostate prescribed dose, while rectum (and bladder) D_{max} should be kept lower than 75–80%. The volume of the CTV-PTV receiving 100%, 125%, and/or 150% of the prescribed dose (V100, V125, V150) should be respectively >90–95%, <60%, and <35–40%. When using HDR combined to EBRT,

Table 11.5 High-dose-rate (HDR) brachytherapy alone: dose constraints

Reference	Gy/fr	No. of fr	Gy tot	Prostate	Urethra	Rectum	Bladder
Corner et al. (2008)	8.5	4	34	–	D30 <125%	D2 ml <100%	–
	9	4	36				
	10.5	3	31.5				
Martinez et al. (2011)	9.5	4	38	V100 > 90%	D_{max} <120%	D_{max} <75%	D_{max} <80%
				D90 > 100%	V120 <1 cc	V80 <1 cc	V80 <1 cc
Yoshioka et al. (2011)	6	9	54	–	D_{max} <150%	D_{max} <100%	–
Demanes et al. (2011)	7	6	42	V100 > 97%	D_{max} <110%	D_{max} <80%	D_{max} <80%
				D90 > 100%			

no predetermined dose constraints are suggested for the external irradiation part of the treatment. Finally, for reporting purposes, it is suitable to "translate" the dose limits adopted into *absolute* dose levels in Gray in order to make the comparisons with other treatment schedules easier.

11.4 Clinical Results

11.4.1 Efficacy

The greatest clinical experience with HDR for prostate cancer involves its *combination with EBRT*. A recent systematic review of available literature has compared EBRT alone (at doses >75 Gy), EBRT combined with HDR brachytherapy boost, and EBRT combined with LDR permanent seeds boost in terms of efficacy endpoints (Pieters et al. 2009). More than 180 papers published from 1980 to 2007 have been analyzed, and despite the fact that patients treated with EBRT + HDR boost had more advanced disease, both biochemical-disease-free survival (biochemical Not Evidence of Disease, bNED) and overall survival rates were significantly better with this combination. Moreover, Hoskin et al. have published the early results of the only phase III randomized trial available in this field comparing EBRT alone (55 Gy in 20 fractions) versus a combined EBRT (35.75 Gy in 13 fractions) + an HDR boost of 2 fractions of 8.5 Gy (Hoskin et al. 2007). A significant advantage in bNED is reported favoring the combined arm (mean bNED at a median follow-up of 30 months is 5.1 years in the HDR arm versus 4.3 years in the EBRT arm), but not in overall survival. The principal limitations of this study pertain to the control arm of EBRT alone: the hypofractionated regime chosen cannot be considered as standard practice today, and furthermore, the EQD2 of this regimen is clearly lower than the one of the EBRT + HDR boost arm (66.8 vs. 92 Gy for an a/b of 1.5): not surprisingly, the bNED results of the EBRT alone arm are suboptimal as compared to other series. Table 11.6 reports the efficacy results of the most relevant published series of combined HDR brachytherapy and EBRT. Comparisons between series and with other therapeutic options for the same patients risk groups are complicated by inherent methodological difficulties in terms of dissimilar HDR and EBRT schedules, varying risk categories treated, use of different irradiated volumes and dose, use of ADT, reported endpoints and biochemical-relapse-free survival definitions adopted, and length of follow-up. Since intermediate- to high-risk patients are often well represented in HDR + EBRT series, the use of ADT in association to irradiation is frequently considered. Interestingly, ADT has not always been shown to improve outcomes in this setting with some authors even reporting a detrimental effect of ADT on overall survival and metastatic failure rates (Krauss et al. 2011; Martinez et al. 2005a, b). *HDR as monotherapy* for patients diagnosed with low-to-intermediate prostate cancer is not yet widely established, and few series with mature survival data have been published so far (Table 11.7). It is worthwhile mentioning that the phenomena of *PSA bounce* after HDR monotherapy or combined HDR-brachytherapy-EBRT has been described. In a comparative,

Table 11.6 High-dose-rate (HDR) brachytherapy combined with external beam radiotherapy (EBRT): efficacy results

Reference	No. of pts	Risk group	HDR Gy/fr	EBRT Gy tot/fr	ADT (%)	Median FU (year)	OS%	bNED%	
Hoskin et al. (2007)	110	Low: 2 Int: 48 High: 60	8.5/2	35.75/2.75	77	7.1	88	66 P	Random
Martinez et al. (2011)	167 305	Int/high	5.5–9.5/2–3 9.5–11.5/2	46/2	–	8.2	–	57 P 81 P	Prospective
Arruda-Viani et al. (2009)	131	Int: 65 High: 66	20–24	45–50/2	55	5.2	91	81 P	Retrospective
Astrom et al. (2005)	214	Low: 80 Int: 87 High: 47	10/2	50/2	70 neo	4	89	82 A	Retrospective
Demanes et al. (2005)	209	Low: 70 Int: 92 High: 47	5.5–6/4	36/1.8	No	7.3	–	85 P	Consecutive
Galalae et al. (2002)	144	High	9/2	40/2	38	8.2	80	69 A	Consecutive
Neviani et al. (2011)	403	Low: 179 Int: 120 High: 104	5.5–7/3	45/1.8	64 neo	4		92 88 85	Retrospective

Overall survival (*OS*) and biochemical not evidence of disease (*bNED*) according to the ASTRO definition, A, or the Phoenix definition, P

Table 11.7 High-dose-rate (HDR) brachytherapy alone: efficacy results

Reference	No. of pts	Gy/fr	No. of fr	Gy tot	ADT (%)	Median F UP (year)	bNED (%)	OS (%)
Demanes et al. (2011)	298	7 9.5	6 4	42 38	24	5.2	97	95
Yoshioka et al. (2011)	112	9	6	54	89	5.4	83	96
Martinez et al. (2010)	221	9.5	4	38	30	4.8	91	–

Overall survival (*OS*) and biochemical not evidence of disease (*bNED*) according to the Phoenix definition

nonrandomized study, patients treated with HDR monotherapy showed higher rates of PSA bounce as compared to patients irradiated with EBRT alone or with combined protocols with significant differences identified for bounce definitions ≥0.3 and >0.5 ng/ml (McGrath et al. 2010).

11.4.2 Toxicity and Quality of Life

11.4.2.1 Combined HDR-Brachytherapy-EBRT

The only phase III randomized clinical trial published so far and comparing EBRT to EBRT combined with a HDR boost has also reported treatment toxicities and quality of life data according to the FACT-P summary score, a validated patient-reported questionnaire (Hoskin et al. 2007). The RTOG acute and grade 2 and greater late toxicity scores were similar in the two arms of the study while a significant difference favoring the combined HDR-EBRT arm was present at 12 weeks after irradiation as far as quality of life was concerned. In all published series, *acute toxicity* primarily consists of mild LUTS (dysuria, urinary frequency, urgency) in 40–60% of patients, but grade 3 genitourinary (GU) symptoms are only presents in 1–5%. Morton has prospectively measured in a cohort of 125 patients treated with EBRT (45 Gy in 25 fractions) with an HDR brachytherapy boost of 15 Gy in a single fraction without ADT, the

Table 11.8 High-dose-rate (HDR) brachytherapy combined with external beam radiotherapy (EBRT): late genitourinary (*GU*), gastrointestinal (*GI*) toxicity, and erectile dysfunction (*ED*) rates

Reference	No. of pts	HDR Gy/fr	EBRT Gy tot/fr	Median FU (year)	Scales	Grade	GU%	GI%	ED%
Galalae et al. (2002)	144	9/2	40/2	8.2	RTOG/EORTC	3 >3	2 0	4 0	–
Demanes et al. (2005)	209	5.5–6/4	36/2	7.3	RTOG	2 3 4	8 7 1	2 0 0	61
Astrom et al. (2005)	214	10/2	50/2	4	ns	Mild Mod Sev	45 26 10	24 17 0	55 41 14
Hoskin et al. (2007)	110	8.5/2	35.75/2.75	7.1	Dische	Sev	26	7	–
Kalkner et al. (2007)	154	10/2	50/2	6	RTOG	2 3 4	13 4 1	8 1 0	–
Martinez et al. (2011)	472	5.5–9.5/2–3 9.5–11.5/2	46/2	8.2	RTOG	3	2.5	0.5	
Mohammed et al. (2011)	447	9.5/2	46/2	5.2	CTC v3	≥2 ≥3 Strict	28 12 10	9 1 0	–
Neviani et al. (2011)	403	5.5–7/3	45/1.8	4	RTOG	3 4 Strict	8 0.3 9	0.6 0.3	–

evolution of acute GU toxicity by means of the IPS-Score: the return to baseline values was obtained at the third month postimplant, much earlier than after LDR brachytherapy (Morton et al. 2010). In the immediate postimplant hours, hematuria is also relatively common but resolves rapidly without special intervention. Urethral stricture is the most frequent nontrivial *late toxicity* reported after combined HDR and EBRT (Table 11.8) occurring in the bulbomembranous urethra in more than 90% of the cases (Sullivan et al. 2009). Overall, urethral strictures develop in 5–15% of patients with several patient-related predictors being identified such as a prior history of TURP, an elevated preimplant IPS-Score, older age, prostate volume (and use of neoadjuvant ADT for preimplant downsizing), and hypertension but also with a number of treatment-related ones (HDR dose per fraction, number of midline needles implanted, a long Z-axis of the CTV). Incontinence is less common and typically related to postimplant need of a TURP. *Gastrointestinal* (GI) toxicity is frequently dependent on EBRT protocol adopted (irradiated volumes, prostate alone versus pelvis +/− prostate CTV, dose/fraction to the pelvis) with grade 3 toxicity reported occasionally and proctitis, anal pain, and rectal bleeding occurring in less than 5% of patients in all published papers. Data on *erectile dysfunction* after combined HDR-brachytherapy-EBRT irradiation have been rarely reported with a variety of scales at different time frame from implant which makes it extremely difficult to derive a meaningful global picture. Duchesne et al. have prospectively evaluated the erectile function in 55 patients irradiated with combined EBRT (46 Gy in 23 fractions) and HDR boost (16–20 Gy in 4 fractions) without ADT and potent before treatment with an "in-house" scale (Duchesne et al. 2007). The 5-year actual incidence of insufficient erection for intercourse (grade 2) or no erection at all (grade 3) was 77%. The International Index of Erectile Function (IIEF) (Rosen et al. 1997) has been prospectively used by Morton: the median baseline IIEF Score (=19) decreased to 6 one-year posttreatment and among patients reporting good baseline erectile function

Table 11.9 High-dose-rate (HDR) brachytherapy alone: late genitourinary (*GU*), gastrointestinal (*GI*) toxicity, and erectile dysfunction (*ED*) rates

Reference	No. of pts	HDR Gy/fr	Gy tot	Median FU (year)	Scales	Grade	GU%	GI%	ED%
Corner et al. (2008)	110	8.5–10.5/3–4	31.5/36	1–1.5	RTOG CTC v3	≥1 3	28 2	15 1	–
Martinez et al. (2010)	221	9.5/4	38	4.8	CTC v2	2 3	13 6	1.5 0.5	20
Yoshioka et al. (2011)	112	9/6	54	5.4	CTC v3	2 3	5 2	7 1	–
Demanes et al. (2011)	156	7/6	42	5.2	CTC v3	2 3	20 3	<1	–

(IIEF >21), 35% developed moderate-to-severe erectile dysfunction (Morton et al. 2010).

11.4.2.2 HDR Monotherapy (Table 11.9)

It has been correctly observed that the pattern of toxicity after HDR monotherapy is different from that after LDR brachytherapy (Hoskin 2008; Crook 2011). *GU symptoms* after HDR alone peak in the first 2 weeks after the implant with IPS-Score increasing at that time but rapidly falling to baseline in 2–3 months. As already mentioned, hematuria may be present in the immediate postimplant hours due to bruising of the bladder wall during the procedure but generally resolves spontaneously within 2 days. So far, no randomized trial has ever compared the two techniques, but nonrandom evaluations have confirmed that both acute (dysuria, urinary frequency, and urgency) and late toxicity are significantly less frequent after HDR than LDR monotherapy (Martinez et al. 2010). In contrast, the rates of urinary retention or incontinence and of erectile dysfunction do not seem to be different between HDR and LDR monotherapies.

11.5 Future Directions

Current data have established HDR brachytherapy, both as a boost combined with EBRT or alone for patients with low-to-intermediate-risk disease, as an effective form of local treatment for prostate cancer. However, several areas remain for further investigations and should be explored in future trials. (1)The optimal dosing regimens is still unclear: the first published series (both for HDR as a boost and as monotherapy) adopted HDR schedules of two or more fractions, while recently, protocols proposing a single fraction/implant have been developed with encouraging early results, thus minimizing the risk of potential needles/catheters displacement between fractions. (2) Therapeutic options for local salvage (re)treatment after biopsy-proven intraprostatic relapse of irradiated prostate cancers are currently limited to ADT (continuous or intermittent), salvage prostatectomy, cryotherapy, or high-intensity-focused ultrasound. HDR (together with LDR) brachytherapy has also been proposed in this setting with encouraging results both in terms of efficacy and of toxicity, but larger series with longer follow-up are needed to fully validate this strategy (Lee et al. 2007; Tharp et al. 2008). (3) The typical inhomogeneous dose distribution obtained with brachytherapy techniques can be exploited in view of a "focal irradiation" of the prostate for carefully selected patients harboring limited unilateral cancers at the diagnostic biopsy confirmed by imaging techniques such as functional MRI. HDR is probably the best technique to create intraprostatic dose gradients that will give the opportunity to target limited regions of the gland to very high doses, while treating to more conventional doses the biopsy-negative subvolumes of the CTV (Ares et al. 2009; Zaider et al. 2000). (4) We have already mentioned that costs of temporary HDR brachytherapy are limited. Rigorous cost analysis and comparisons between therapeutic alternatives have so far never been attempted, but if HDR brachytherapy techniques are able to

convincingly demonstrate a cost-effective advantage as compared to other therapeutic options for localized prostate cancer, the procedure is likely to be offered in the near future to increasing numbers of patients and to gain popularity even in developing countries.

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Intensity Modulated Radiotherapy for Prostate Cancer

12

Olivier Chapet, Corina Udrescu, and Ciprian Enachescu

Contents

O. Chapet, M.D., Ph.D. (✉) • C. Udrescu
C. Enachescu, M.D.
Department of Radiation Oncology, Centre Hospitalier Lyon Sud, University Claude Bernard Lyon 1, EA3738, Pierre Benite, France
e-mail: olivier.chapet@chu-lyon.fr

12.1 Concept of Intensity Modulated Radiotherapy (IMRT)

IMRT is a highly conformal radiotherapy technique able to optimize the shape of the dose distribution and to *generate a concave isodose profile* by intensity modulated beams, which can deliver more than two intensity levels for a single beam direction and a single source position in space. IMRT is designed using *inverse planning method* (computer optimization) based on dose–volume criteria, in which above all the radiation oncologist prescribe the target volume dose coverage "objectives" and normal tissue protection "objectives," and then, the computer creates a custom intensity modulation plan to satisfy the prescribed objectives (Intensity Modulated Radiation Therapy Collaborative Working Group 2001).

The major IMRT advantage is the better sparing of close-proximity organs at risk (OAR) for an identical tumor dose and consecutively the reduction of adverse event rates with no difference in disease-related outcomes. Moreover, IMRT can allow theoretically dose escalation to the primary tumor, keeping safe dose–volume constraints to organs at risk. Because of the close relation between the prostate and the rectum and the bladder, IMRT seems particularly adapted for prostate irradiation (Martin et al. 2010) (Fig. 12.1).

In a systematic review, Veldeman et al. (2008) analyze the toxicity events reported in comparative (IMRT against non-IMRT) studies on head

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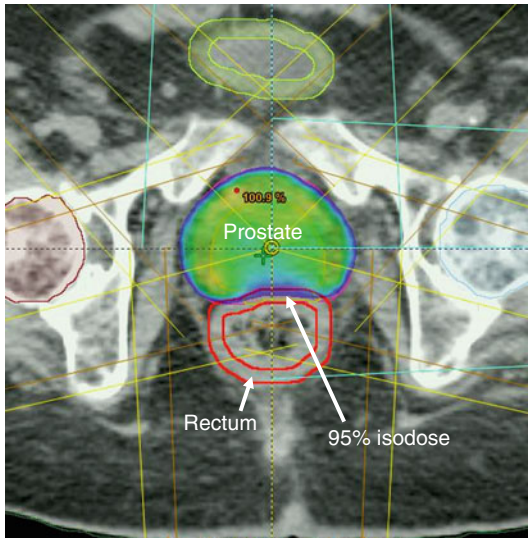

Fig. 12.1 Intensity modulated radiation therapy for prostate cancer with 95% isodose avoiding the rectum wall

and neck, prostate, gynecological, CNS, breast, and lung cancer and in noncomparative studies on mesothelioma and gastrointestinal malignancies. It demonstrated that compared with classical 3D irradiation, IMRT is not inferior in terms of local tumor control and survival and results in a decrease in toxic effects. Regarding the possibility of safe total-dose or fractionated-dose escalation to improve cancer control, future randomized clinical trials (RCT) to directly compare standard dose with total or fraction-dose escalation should be performed.

To summarize, IMRT generates concave isodoses which can bypass some organs at risk of toxicities. Thus, the interest of IMRT in prostate cancer could be important by reducing the doses received by the rectum and the bladder. A reduction of toxicities could be expected, allowing new approaches of doses escalation.

12.2 3D Conformal Radiation Therapy (3DCRT) Versus IMRT

12.2.1 Irradiation of Prostate and Seminal Vesicles Only

To date, no randomized study has compared the 3DCRT with IMRT. In several publications, the authors proposed to compare the two irradiation techniques. Thus, Kupelian has compared 166 patients treated with IMRT with 116 patients treated with 3DCRT (Kupelian et al. 2002). The results are in favor of a significant reduction ($p=0.002$) of acute rectal toxicity and nonsignificant of late toxicities of grade ≥2 (5% vs. 12%, $p=0.24$) with IMRT. However, a hypofractionated schema was used for IMRT and normofractionated for 3DCRT, making it difficult to distinguish between fractionation and intensity modulated in the differences of the obtained results between the two groups. In the study of Vora et al., 145 patients were treated on prostate and seminal vesicles with IMRT at dose of 76.5 Gy and 271 patients with 3DCRT at dose of 68.4 Gy (Vora et al. 2007). Despite a difference in total dose irradiation of 8 Gy, there was no significant difference found between groups for acute and late urinary and rectal toxicities. A benefit found in terms of biochemical-recurrence-free survival at 5 years (74.1% vs. 60.4%, $p<0.0001$) suggested that IMRT would increase the control rates of the disease by increasing the delivered dose without increasing the toxicities. In another publication, Lips et al. also concluded that IMRT allows an irradiation dose escalation without increasing the toxicities (Lips et al. 2007). In this study, the 78 patients treated with conformal radiotherapy had received a dose of 70 Gy, and 92 patients treated with IMRT had received a dose of 76 Gy. In a series of 1,571 patients treated for a T1–T3 prostate cancer by radiotherapy alone Zelefsky et al. (2008a, b), found a significant reduction in gastrointestinal toxicities when IMRT is used (5% vs. 13% $p<0.001$). Finally in 2011, Sharma et al. assessed the IMRT contribution when the irradiation is associated with hormone therapy (Sharma et al. 2011). Data from two groups of 123 patients treated with IMRT and 170 patients treated with IMRT were analyzed. Again, the benefit of the IMRT was found in terms of reduced acute and late gastrointestinal toxicities.

12.2.2 Prostate and Pelvic Irradiation

Ashman et al. compared 13 patients treated with IMRT at a dose of 81 Gy with 14 patients

treated with 3DCRT at a dose of 75.6 Gy (Ashman et al. 2005). The volumes of irradiation included initially the pelvis. Despite an escalated total dose irradiation, IMRT appeared to give less acute rectal toxicities (7% vs. 36%) and intestinal disorders (0% vs. 43%) of grade 2 than 3DCRT. In another study, Sanguineti et al. (2006) also evaluated the IMRT contribution when a pelvic irradiation (54 Gy) was associated with prostate irradiation (76 Gy). Using the RTOG criteria, the toxicities were evaluated in a group treated with IMRT (45 patients) and a group treated with 3DCRT (68 patients). At 2 years, the cumulative rates for grade 2 rectal toxicities were 4% with IMRT and 21.2% without IMRT. No grade 3 toxicity was observed.

To summarize, compared to 3DCRT, IMRT reduces acute and late rectal and urinary grade ≥2 toxicities. A dose escalation can be achieved without increasing toxicities. This could result in improved biochemical-relapse-free survival. This benefit is found in case of localized prostate and seminal vesicles irradiation, but also when a pelvic irradiation and/or a hormone therapy are associated. However, mainly retrospective studies have been published, and no randomized trial is available.

12.3 Dose Escalation in Prostate Cancer

12.3.1 Interests of Dose Escalation in Prostate Cancer

Several randomized studies (Sathya et al. 2005; Peeters et al. 2006; Dearnaley et al. 2007; Kuban et al. 2008; Zerini et al. 2010; Zietman et al. 2005; Beckendorf et al. 2011) evaluated the impact of a dose escalation on disease control. Doses of 66–70 Gy were compared to doses of 74–80 Gy. In none of these studies, a hormone therapy was associated with radiotherapy. The increase in total dose of about 10 Gy was associated with an improved rates of biochemical-recurrence-free survival at 5 years from 50–60% to 70–85%, all stages of the disease combined. Of these studies, three proposed an irradiation dose of 78–80 Gy in the experimental arm. Thus, in the M.D. Anderson study, a dose of 78 Gy was compared to a dose of 70 Gy (Kuban et al. 2008). In total, 301 patients were included, having an intermediate-to-high-risk cancer. The main objective was to assess the impact of this increase dose on the clinical and/or biological-disease-free survival using the Phoenix definition (nadir + 2 ng/ml). At 5, 8, and 10 years, respectively, it increased from 78% to 85%, 59% to 78%, and 50% to 73% in the 78 Gy arm compared to 70 Gy arm. The increase in irradiation dose was though associated with an increase of late grade ≥2 rectal toxicities (26% vs. 13%) and urinary toxicities (13% vs. 8%). In the Dutch study (Peeters et al. 2006), 669 patients with intermediate-to-high-risk cancers were randomized between two doses of irradiation: 68 and 78 Gy. At 7 years, the biochemical-recurrence-free survival increased with the dose, from 45% to 56%. The cumulative incidence of gastrointestinal toxicity was also increased by 25–35%. The subgroup analysis showed a greater benefit for the intermediate-risk group. Finally, in the GETUG 06 (Beckendorf et al. 2011), a dose of 80 Gy was compared to a dose of 70 Gy in patients having mainly intermediate-risk prostate cancer. At 5 years, the survival rates without biochemical recurrence were respectively 68% and 76.5% in the 70 and 80 Gy arms, using the Phoenix definition. The benefit seemed greater when the PSA rate was higher than 15 ng/ml. In this study, the increase in radiation dose was also associated with an increase of acute and late rectal and urinary toxicities.

All these data support the benefit of an irradiation dose escalation mainly for the intermediate-risk cancer. However, the dose augmentation may also be a benefit for the high-risk cancer patients. In fact, in the study of MD Anderson, if a majority of patients have had low-to-intermediate-risk prostate cancers, 30% (70 Gy) to 35% (78 Gy) of patients had a high-risk prostate cancer. Specific analysis in this group of patients shows a benefit at 5 years in biochemical-recurrence-free survival, local-progression-free, and without metastasis, in favor of dose increasing. In the Dutch study, half of the patients had high-risk prostate cancers. This benefit of increasing the radiation dose in high-risk patients had already been suspected in most retrospective studies. Thus, in the study of Zelefsky et al., on 752 patients irradiated

for a high-risk cancer, increasing the radiation dose from 70.2 to 86.4 Gy improved the survival without metastatic evolution from 77% to 82% (Zelefsky et al. 2008a, b). The question remains whether this benefit persists when a 3-year hormone therapy is associated with radiotherapy. The GETUG 18 study aims to answer this question by randomizing patients into two levels of dose (70 vs. 80 Gy) in combination with 3 years of hormone therapy in both arms.

12.3.2 IMRT in Dose Escalation

The first IMRT experiences for prostate cancer treatment were described by Memorial Sloan-Kettering Cancer Center (MSKCC). In the early 2000s, Zelefsky et al. reported the results of a series of 171 patients treated at a dose of 81 Gy with IMRT, between 1992 and 1998 (Zelefsky et al. 2000). A dosimetric study to compare, for the same patient, two treatment plans, with and without IMRT, was also performed on 20 patients. This study showed that the intensity modulation provides a benefit in terms of target volume coverage and rectum and bladder preservation. A comparison of clinical outcomes in the two groups of patients treated with and without IMRT confirmed a reduced actuarial risk of late rectal toxicity of grade 2 at 2 years, from 10% to 2% when using IMRT. The toxicity grades were defined using the radiation therapy oncology group (RTOG) criteria. In 2002, the same author (Zelefsky et al. 2002) published the results of a series of 772 patients treated with IMRT for a prostate cancer at doses between 81 (90% of patients) and 86.4 Gy (10% of patients). The rates of rectal and urinary acute toxicities of grade 2 were respectively 4.5% (0% of grade 3) and 28% (1 toxicity of grade 3). In total, 15% of patients developed a late rectal toxicity of grade 2 and 0.1% a rectal toxicity of grade 3. The probability of developing a rectal toxicity of grade ≥2 was of 4% at 3 years. In terms of urinary toxicity, 9% of patients presented a late toxicity of grade 2 and 0.5% of grade 3. The probability of developing a late urinary toxicity of grade ≥2 was estimated at 15% at 3 years. In 2011, data at 10 years were published for the 170 patients treated with IMRT, at doses of 81 Gy (Alicikus et al. 2011). The actuarial biochemical-recurrence-free survival at 10 years was of 81%, 78%, and 62% respectively for patients with low-, intermediate-, or high-risk prostate cancer. Using the CTC AE V3 criteria, the probabilities at 10 years of developing a rectal toxicity of grades 2 and 3 were respectively 2% and 1%. The 10-year probabilities of grades 2 and 3 urinary toxicities were 11% and 5%. Finally, Cahlon et al. reported the results for 478 patients treated at a dose of 86.4 Gy (Cahlon et al. 2008). With a median follow-up of 53 months, the rates for rectal toxicities of grade 2 were 8%, and no higher grade toxicity was observed. Using the Phoenix definition of biochemical recurrences (nadir + 2 ng/ml), the actuarial rate of biochemical-recurrence-free survival at 5 years was respectively 98%, 85%, and 70% for low, intermediate, and high risks. Other IMRT experiences were published for prostate irradiation with at least 80 Gy. Thus, Ghadjar et al. analyzed the data from 102 patients treated with IMRT at 80 Gy and with IMRT and daily image-guided radiotherapy (IGRT) of the prostate (Ghadjar et al. 2010). A total of 5% late rectal toxicities of grade 2 were observed, and no grade 3 toxicity. The rates of late urinary toxicities of grades 2 and 3 were respectively 21% and 1%. Azria et al. reported a French series of 373 patients treated at a total dose of 80 Gy with IMRT (Azria et al. 2009). The rates of late rectal and urinary toxicities ≥2 are respectively 5.3% and 5.9%.

To summarize, several randomized trials demonstrated the benefit of a dose escalation in prostate cancer with an increased rate of biochemical relapse free survival. Using IMRT, a dose escalation above 80 Gy can be performed with a low rate of grade ≥2 late rectal toxicities (<10%). The impact of IMRT on the urinary tract seems smaller with rates of late grade ≥2 toxicities, often above 10–20%.

12.4 Optimal IMRT Approach for Prostate Cancer

If currently, IMRT appears as the optimal technique of irradiation of prostate cancer, the preservation of healthy tissues in IMRT could be

optimized by the contribution of imaging (fusion CT/MRI) and a systematic association with a daily repositioning using the image-guided radiotherapy (IGRT).

12.4.1 CT/MRI Fusion (Fig. 12.2)

Prostate definition on the CT scan is associated with high interphysician and interscan variations (Mitchell et al. 2009; Valicenti et al. 1999; Gao et al. 2007) and an overestimation of the clinical target volume (CTV), with CT images was confirmed (Sannazzari et al. 2002). However, these differences are significantly reduced when an MRI is used (Smith et al. 2007; Rasch et al. 1999; Jackson et al. 2004; Freedman et al. 2001; Roach et al. 1996; Usmani et al. 2011). MRI allows a better definition and delineation of the apex and base of the prostate (Milosevic et al. 1998; Jackson et al. 2004).

Excepting the prostate contouring, the importance of using a CT/MRI fusion method or an MRI exam for prostate radiotherapy was also demonstrated for:

- Reducing the dose to the rectum, penile bulb, and the erectile arteries in order to improve the patient's posttherapy sexual functioning and quality of life (Perna et al. 2009; Steenbakkers et al. 2003; Meirovitz et al. 2003)
- A better visualization of the prostate for patients with bilateral hip prostheses (Rosewall et al. 2009)
- For the tumor localization into the prostate using different MRI sequences (Groenendaal et al. 2010a, b; Franiel et al. 2009; Kajihara et al. 2009)

Most of the studies, that evaluated the interest of a CT/MRI combination, used registrations based on the bony landmarks (Milosevic et al. 1998; Roach et al. 1996; Acher et al. 2010; Chen et al. 2004; Petersch et al. 2004). Intraprostatic gold markers are recommended to be implanted for a better daily repositioning before and/or during the irradiation, improving the prostate localization, but the interest in using intraprostatic markers, rather than bony structures for the CT/MRI registration, was also presented (Parker et al. 2003).

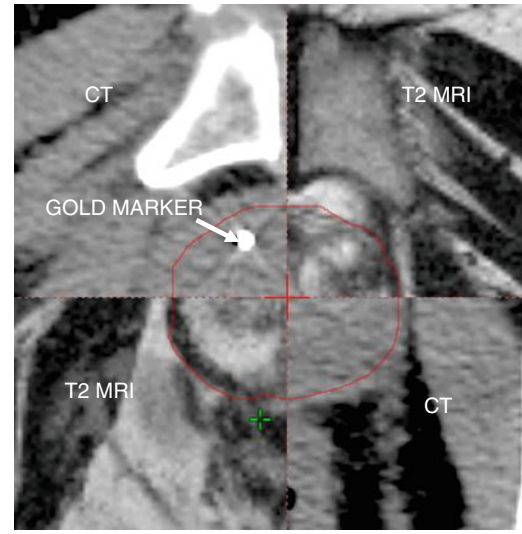

Fig. 12.2 CT/MRI T2 fusion on gold markers

Contouring protocols were published in order to improve the radiation therapists' technique (McLaughlin et al. 2010; Villeirs et al. 2005), but still, it is important that the physician has a good experience in prostate MRI description when using a CT/MRI fusion (Tanaka et al. 2006).

12.4.2 Image Guidance Radiation Therapy IGRT

IGRT means that imaging is used at each fraction of irradiation for high precision of repositioning of the target volume. In prostate cancers, the interfraction variation of the prostate position within the pelvis makes IGRT particularly interesting. In fact, as there is a dose-effect relation on the local control, a precise prostate positioning at each session of irradiation might have an important clinical impact by insuring that the dose of irradiation is well delivered into the prostate. Several studies demonstrated that the variation of prostate position according to the rectal volume and the rectal distension on the planning CT scan significantly increases the risk of local recurrence in multivariate analysis (de Crevoisier et al. 2005; Heemsbergen et al. 2007; Pinkawa et al. 2006). When daily IGRT is used for registration, the overall outcomes appear to be very favorable

(Kupelian et al. 2008). A recent study of Haverkort et al. evaluated, using electronic portal images (EPIs), the effect of gold markers-based position correction on the cumulative dose in the rectal wall, when changes in the rectum anatomy and position appear (Haverkort et al. 2011). Compared to bony anatomy-based correction, the rectal wall $D_{50\%}$ and $D_{70\%}$ and the mean anal wall dose were significantly lower when using gold markers.

In the last years, the literature demonstrates the effort in finding the easiest and best method of prostate tracking and repositioning: ultrasound-based (BAT) tracking (Boda-Heggemann et al. 2008; Scarbrough et al. 2006), real-time tumor tracking (Kitamura et al. 2002; Langen et al. 2008; Kupelian et al. 2005), portal images on implanted markers (Balter et al. 1995a, b), cone-beam CT (CBCT) (Pouliot et al. 2006; Sorcini and Tilikidis 2006), etc. Several studies have attempted to compare the different techniques together. Definitive conclusions are difficult to make but however, it seems that a prostate repositioning, using a CBCT or the detection of intraprostatic gold markers (KV/KV) offers the greatest precision (Barney et al. 2011; Clancy et al. 2009; Neicu et al. 2009; Owen et al. 2010).

To summarize, CT/MRI fusion allows a higher precision in the prostate contours delineation especially when fiducial markers are used. By correcting the interfraction motion of the prostate, IGRT should allow a reduction of the margin of the planning tumor volume. A combination of these two approaches with IMRT could improve the prostate coverage and reduce the volume of rectum and bladder irradiated.

12.5 Perspective of Evolution of Prostate Irradiation

12.5.1 Hypofractionated Radiotherapy (HR)

In radiotherapy, the daily dose of reference or standard fractionation (normofractionation) is of 1.8–2 Gy per fraction. The HR is an increase of the radiation dose delivered per fraction and a decrease in total number of irradiation fraction compared to a conventional fractionation.

Three reasons justify the development of HR for prostate cancers:

1. *Prostate cancer would have a particular sensitivity to the dose delivered in each session*. This sensitivity is defined in radiobiology by the *a/b* ratio. The closer this ratio is to 0, the cells are more susceptible to the dose per fraction; the more this ratio is greater, the impact of fractionation is low. Many studies consistently show that this ratio would be between 1.5 and 3 Gy for prostate cancer (Leborgne et al. 2012; Miralbell et al. 2012; Carlson et al. 2004; Wang et al. 2003; Brenner and Hall 1999; Brenner et al. 2002).
2. *The treatment with external beam radiotherapy of prostate cancer requires between 35 and 40 fractions of irradiation or 8 weeks of treatment with a standard dose per fraction of 1.8–2 Gy per fraction*. A reduction of this irradiation time to 4–5 weeks or less would definitely represent an amelioration of the patients' quality of life.
3. A reduction of several weeks of the radiotherapy treatment duration due to the development of HR would significantly reduce the costs and improve the treatment processing of patients in radiotherapy.

12.5.2 Experiences of Hypofractionated Radiotherapy

Many studies have described the feasibility of the HR using different doses per fraction. Only recent studies using 3D conformal radiotherapy techniques with or without intensity modulation are described below.

12.5.2.1 HR with a Dose per Fraction Inferior to 3 Gy

The study of Kupelian et al. (2007) is probably the reference in the development of HR. The dose per fraction was 2.5 Gy for a total dose of 70 Gy, or 28 fractions. A technique of irradiation with a daily repositioning of the prostate and intensity modulated radiotherapy has been used to treat a

total of 770 patients. The biological equivalent dose for a 2 Gy fractionation was estimated at 80 Gy. According to the Phoenix definition (nadir + 2 ng/ml), the biochemical recurrence-free survival at 5 years was 94%, 83%, and 72%, respectively, for patients with low-, intermediate-, and high-risk cancers. These rates are particularly high especially for intermediate-to-high-risk patients. A fractionation close to 72 Gy in 30 fractions of 2.4 Gy was used in an Italian study of 25 patients (Zerini et al. 2010). A 3D conformal radiotherapy with a daily ultrasound repositioning was performed. With a mean follow-up of 45 months, only late rectal (16%) and urinary (32%) grade 1 toxicities were described. Only one biochemical recurrence was reported.

A dose per fraction of 2.64 Gy was evaluated in the study of Junius et al. (2007). The delivered dose to the seminal vesicles was 50 Gy in 25 fractions, while the delivered dose to the prostate during the 25 fractions was 66 Gy. With a median follow-up of 20 months, three biochemical recurrences are described in a population of 38 patients consisting primarily of intermediate stages to high according to D'Amico classification. The limit of these two studies is the use of moderately increased doses per fraction that probably not allows an optimal hypofractionation effect on prostate cancers.

12.5.2.2 HR with a Dose per Fraction Superior or Equal to 3 Gy

Several studies have evaluated a dose per fraction of 3–3.15 Gy. In the study of Leborgne and Fowler (2009), 89 patients with prostate cancer were treated with 20 fractions of 3 ($n=52$) or 3.15 Gy ($n=37$). The biochemical recurrence-free survival at 5 years was 96%, 84%, and 85% respectively for low-, intermediate-, and high-risk stages. Thirty percent of patients had late rectal toxicity, with 6% of grades 2–3. In the study by Yassa et al. (2008), 19 fractions of 3 Gy were delivered to 42 patients. With a mean follow-up of 46 months, 79% of patients had no biochemical recurrence. Acute rectal toxicity of grade ≥2 was observed in 36% of patients while 12% of them had late rectal toxicity, bleeding symptoms of grades 1–2. In the Canadian study of Faria et al. (2008), 72 patients were treated with a dose of 66 Gy in 22 fractions of 3 Gy. The technique of radiotherapy was 3D conformation without intensity modulation. The margins defining the target volume were limited to 7 mm. In total, 39% of patients experienced late rectal toxicity. In 18% of patients, it was grades 2–3 toxicity. In a more recent publication (Rene et al. 2010) of 129 patients, using the same technique of irradiation and the same fractionation, the rates of late urinary and rectal toxicities of grade ≥2 are respectively 32% and 25% but do not persist in time (only 2% and 1.5%). Akimoto et al. (2004) reported the results of a phase II study in which 52 patients were treated with a hypofractionation schema of 69 Gy in 23 fractions of 3 Gy. The rate of late rectal toxicity of grade ≥2 was 25% and a late rectal toxicity of grade 3 was observed.

12.5.3 Experiences of HR with IMRT

In 2007, Martin et al. (2007) reported the results of radiotherapy of 60 Gy in 20 fractions of 3 Gy delivered with IMRT and daily repositioning of the prostate on gold markers. In total, 36% of 92 enrolled patients showed a gastrointestinal acute toxicity of grades 2–3 in 12% of cases. The late rectal toxicities were less frequent with only 6% of grades 1–2. At 3 years, the rate of biochemical control was 76% as defined by ASTRO (3 successive of PSA increase). More recently, Coote el al. (2009) reported the results in terms of tolerance to an irradiation of 3 Gy per fraction for a total dose of 57–60 Gy. The irradiation technique was based on conformal radiotherapy with modulated intensity. In total, 57% of patients treated with 57 Gy and 70% of patients treated with 60 Gy showed an acute rectal toxicity. This toxicity was grade 2 in 20% and 10% of patients respectively treated with 57 and 60 Gy. No acute rectal toxicity of grade 3 was observed. In the group treated with 57 Gy, 27% of patients presented a late rectal toxicity of grade 1, whereas at 60 Gy, 19% of patients presented a late rectal toxicity of grades 1 or 2 (50% of grade 2). No grade 3 late toxicity was reported. Vesprini et al. reported a series of 121 patients

treated with IMRT to a dose of 60–66 Gy using the same fractionation of 3 Gy per fraction (Vesprini et al. 2011). With a follow-up of 47 months, the rates of urinary and rectal late toxicities of grade 2 and more were respectively of 15% and 16%. Finally, the results of a phase II study (Lock et al. 2011) on 66 patients have been published in which the treatment associated an intensity modulated irradiation at a dose of 63.2 Gy in 20 fractions with a daily repositioning on gold markers or using ultrasound. With a median follow-up of 30 months, the rates of late rectal toxicities of grades 2 and 3 were respectively of 25% and 3%. The rates of late urinary toxicities of grades 2 and 3 were respectively 14% and 5%.

12.5.4 Comparison HR and Conventional Fractionation Radiotherapy

In a recent randomized study, Arcangeli et al. compared the efficacy and tolerance of a normofractionation radiotherapy (80 Gy in 40 fractions) and of a hypofractionated radiotherapy (62 Gy in 20 fractions of 3.1 Gy) on 160 patients (Arcangeli et al. 2010). The main quality of this study was to propose in both arms biological equivalent doses by taking an $a/b = 1.5$ Gy. The first results, with a follow-up of 3 years, were in a favor of an increase in biochemical-recurrence-free survival in the hypofractionated arm (87% vs. 79%). This difference was observed even for the high-risk stages (88% vs. 76%). The rates of late rectal toxicities of grade 2 and more at 3 years were similar in both arms (17% and 16%).

Previously, an Australian randomized study (Yeoh et al. 2010) compared an irradiation of 64 Gy in 32 fractions ($n = 109$) with and irradiation of 55 Gy in 20 fractions ($n = 108$). The irradiation was in 2D for the majority of patients. At 90 months, the HR gave a better biochemical-recurrence-free survival (53% vs. 34%) without improvement of toxicity. The results of this study are difficult to interpret because of the low doses delivered in the normofractionated arm. Four randomized studies are underway to compare hypofractionated radiotherapy to conventional radiotherapy (RTOG 0415, MRC trial, NCIC trial, and Fox Chase trial).

To summarize, hypofractionated radiotherapy gives encouraging results in terms of biological control. When the dose per fraction is superior or equal to 3 Gy, the rate of late rectal toxicity grade ≥2 appears to be between 15% and 25%. When IMRT is used, this rate seems closer to 10–15%. Several randomized studies are underway to compare this radiation technique to conventional radiotherapy.

12.5.5 Stereotactic Body Radiotherapy (SBRT)

12.5.5.1 Concept of SBRT

The principle of stereotactic radiotherapy is to deliver a high-radiation dose highly conformed on a small tumor. The result is a "removal" of the tumor while ensuring the preservation of the surrounding tissue. This technique requires great precision in the localization of the tumor and, therefore, was first developed in the treatment of brain metastases. In fact, by immobilizing the skull (and thus the brain), it was possible to pinpoint an intracerebral lesion. More recently, the use of new technologies in the spatial location of tumors (integrated scanner to an accelerator, detection of intratumoral implants, etc.) permits the visualization with a high precision (order of mm), the tumor position, even in the soft tissues (lung, liver, etc.). Stereotactic radiotherapy has been thus developed in the irradiation of tumor sites outside the brain as some small-cell lung cancer (T1 and T2N0). For these tumors, although considered radioresistant, the local control rate passed from 30% to 40%, after conventional radiotherapy, to 80–90% after stereotactic radiotherapy. The prostate, due to its limited volume and easy location (intraprostatic implants), represents a well-suited organ for developing such technique.

12.5.5.2 Stereotactic Radiotherapy and Prostate Cancer

The experiences of various radiotherapy centers, having developed stereotactic radiotherapy in

prostate cancer, have been reported. The first experience is the one of Seattle (Madsen et al. 2007). Forty patients were enrolled in a phase I/II study and treated at a dose of 33.5 Gy in 5 fractions of 6.7 Gy with an equivalent dose of 78 Gy using a conventional fractionation of 2 Gy per fraction. With a median follow-up of 41 months, one urinary toxicity of grade 3 was reported. The rate of actuarial survival without biochemical recurrence was 90% at 48 months using the Phoenix definition for local recurrences. A repositioning based on intraprostatic implants was used at each fraction. The irradiation dose was delivered with a linear accelerator. At Stanford University (King et al. 2009), 41 patients were included in a phase I/II study and received a dose of 36.25 Gy in 5 fractions of 7.25 Gy. With a median follow-up of 33 months, no toxicity of grade 4 or more was observed. Two urinary toxicities of grade 3 were reported, but no grade 3 rectal toxicity. At the time of publication, no patient had presented biochemical recurrence. In a more recent publication on 67 patients (King et al. 2012), but with a median follow-up of 27 months, rates of urinary toxicities of grades 1, 2, and 3 were respectively 23%, 5%, and 3% and the rectal toxicities of grades 1, 2, and 3 respectively of 12.5%, 2%, and 0%. Two recurrences proven by biopsy were reported. In Toronto (Tang et al. 2008), 30 patients were treated at dose of 35 Gy in 5 fractions of 7 Gy with IMRT and under a conventional accelerator. At 6 months for all patients, no toxicity superior to grade 2 was observed. At Naples (Friedland et al. 2009), 112 patients with prostate cancer of favorable stage were treated at a dose of 35–36 Gy in 5 fractions. With a median follow-up of 24 months, two patients experienced a local recurrence, histologically proven. The average PSA value was 0.78 ng/ml. Only one patient presented a rectal toxicity of grade 3. At Dallas, a phase I study of dose escalation per fraction in 3 levels of 45, 47.5, and 50 Gy in 5 fractions was conducted (Boike et al. 2011). The irradiation technique combined an image-guided radiotherapy, an IMRT technique, and an endorectal balloon. In total, 45 patients were included (15 to different dose levels) without reaching the limiting toxicity dose. With a median follow-up of 30 months, only 18% of patients had a late rectal toxicity of grade ≥2 and 2% grade 3 toxicity. The rates of late urinary toxicities of grades ≥2 and ≥3 were respectively 31% and 4%. The PSA control was 100%. A phase II study is currently undergoing at a dose of 50 Gy in 5 fractions of 10 Gy. Finally in 2010, Katz et al. reported a series of 304 patients treated in 5 fractions of 7–7.25 Gy (Katz et al. 2010). After 17 months, only one urinary toxicity of grade 3 was described, but four biochemical recurrences were reported.

To summarize, four important informations can be taken from these studies: (1) stereotactic radiotherapy is technically feasible in prostate cancer; (2) with an experience still low, the rectal and urinary toxicities of grade 3 or greater are less frequent; (3) with the same experience, the local control is excellent (between 90% and 100%); and (4) in many of these studies, conventional accelerators were used, suggesting the possibility of development in a greater number of radiotherapy departments. However, to date, the literature data are not sufficient to allow the development of stereotactic irradiation outside studies. Phase III studies are needed to compare this new approach to conventional irradiation.

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13 Combination of Androgen Deprivation Therapy and Radiation Therapy for Locally Advanced and Localized Prostate Cancer

Michel Bolla and Camille Verry

Contents

Abbreviations

ADT	Androgen deprivation therapy
CTV	Clinical target volume
CADT	Combined androgen deprivation therapy
DVH	Dose volume histogram
EORTC	European Organization on Treatment and Research of Cancer
GETUG	Genitourinary tumor group
HT	Hormone therapy
IMRT	Intensity-modulated radiotherapy
LTADT	Long-term androgen deprivation therapy
LHRH	Luteinizing-hormone-releasing hormone
MRC	Medical Research Council
MSKCC	Memorial Sloan-Kettering Cancer Center
NCIC	National Cancer Institute Canada
NCADT	Neoadjuvant concurrent androgen deprivation therapy
PFS	Progression-free survival
PCa	Prostate cancer
PORT	Prostate only radiotherapy
PSA	Prostate-specific antigen
RTOG	Radiation therapy oncology group
RT	Radiotherapy
STADT	Short-term androgen deprivation therapy
TCD 50	Dose which controls 50% of tumors
3D-CRT	Three-dimensional conformal radiotherapy
WPRT	Whole-pelvis radiotherapy
WHO	World Health Organization

M. Bolla (✉) • C. Verry
Clinique Universitaire de Cancérologie-Radiothérapie, Centre Hospitalier Universitaire Albert Michallon, BP 217 38043, Cedex 9, Grenoble, France
e-mail: mbolla@chu-grenoble.fr; cverry@chu-grenoble.fr

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13.1 Introduction

To better control the growth of high-risk prostate cancer (PCa), the combination of a local treatment with a systemic treatment has become mandatory, due to the limited curative potential of definitive conventional irradiation (Bagshaw et al. 1988; Hanks et al. 1995). High-risk PCa includes men with locally advanced PCa (T3-4 N0-X M0) or localized PCa (T1-2 N0-X M0) with either a Gleason score 8–10 and/or a baseline PSA > 20 ng/ml (Scardino et al. 2003). Huggins and Hodges introduced androgen deprivation therapy (ADT) in the 1940s (Huggins et al. 1941), with surgical castration or estrogens, based on the dependence of prostatic epithelial and adenocarcinoma cells on androgenic hormones, which explains that more than 80% of the patients respond to orchiectomy or estrogens (Schröder 1990). Their side effects obliged clinicians to replace them by agonists of the luteinizing-hormone-releasing hormone (LHRH) which had the same efficacy (Parmar et al. 1985) with reversibility. As a result of screening (Schroder et al. 2009), the incidence of locally advanced PCa is decreasing, while the incidence of localized PCa is increasing, but ADT remains an important part of the therapeutic panoply.

The positive results of phase III randomized trials have promoted long-term adjuvant ADT (≥2 years) as a standard of care for locally advanced PCa, while short-term AD (4–6 months) is proposed to patients with intermediate- or poor-risk localized PCa. Far from compensating a nonoptimal radiotherapy (RT), ADT has to be combined with optimal modalities of RT because local control remains of paramount importance, all the more as intensified modulated radiotherapy has replaced conventional irradiation and enables radiation oncologists to increase the dose without increasing morbidity (Zelefsky et al. 2008). The role of surgery in high-risk PCa being treated in Chap. 8, we would like to consider in this article (1) the rationale of this approach, (2) the results of phase III randomized controlled trials focusing on the duration and the chronology of HT with respect to RT, (3) the new options linked to the breakthrough of radiation techniques and/or drugs, and (4) the morbidity and quality of life referring to ADT.

13.2 Rationale for Combining Androgen Deprivation Therapy and Radiation Therapy

The objectives of combining androgen deprivation with external beam radiotherapy are (1) to decrease both prostate gland volume and prostate cancerous tissue, thereby decreasing the clinical target volume (CTV) and improving bladder and/or rectum dose volume histograms, (2) to reduce the risk of local relapse within the planning target volume by inhibiting repopulation during irradiation, (3) to decrease, thanks to a spatial cooperation, the occurrence of distant metastases due to the presence of an infraclinical disease at the time of diagnosis, as for breast cancer (Early Breast Cancer Trialists Collaboration Group (EBCTCG) 2005) and, (4) to improve the effectiveness of radiation by an additive or supra-additive effect. To assess the effect of sequencing of ADT by means of castration and radiotherapy on PCa growth, animal studies have been done on transplantable androgen-dependent tumor, treated by radiation alone, radiation preceded by orchiectomy, radiation followed by orchiectomy +/− androgen restoration. Zietman et al. (1997) at the Massachusetts General Hospital have used a transplantable murine mammary androgen-dependent tumor (Shionogi tumor model) as allografts in the hind limbs of athymic nude mice and have shown that neoadjuvant ADT (given 12 days before RT) provides the greatest effect according to TCD 50. Joon et al. (1997) used Dunning R3327-G rat prostate tumors transplanted in the flanks of Copenhagen rats, and a supra-additive apoptotic response was obtained when castration was initiated 3 days prior to radiation. Kaminski et al. (2003) have used R3327-G rat prostate tumors implanted in the flanks of Copenhagen rats and have calculated the tumor volume doubling time: the results suggest that neoadjuvant ADT may result in prolonged suppression of tumor growth, even after testosterone

replacement. All these results were obtained from animal models under experimental conditions that do not allow hormonal treatment during and after irradiation to be delivered in a more protracted way.

13.3 Combined Androgen Deprivation Therapy and Radiation Therapy: Results of Randomized Controlled Trials (Table 13.1)

13.3.1 Locally Advanced Prostate Cancer

The main trials showing a benefit on overall survival were launched by the radiation therapy oncology group (RTOG) and the radiotherapy oncology group of the European Organization on Treatment and Research on Cancer (EORTC). Devoted to T3-4 N0-X M0 patients and sometimes bulky T2 patients, these trials deal with an agonist analogue of LHRH. Two trials were done before with conventional modalities of castration. One, conducted at the MD Anderson Cancer Center on a cohort of T3 NX M0 patients ($n=78$) treated by pelvic radiotherapy +/– DES (5 mg), has shown a striking difference in 15-year disease-free survival in favor of the combined treatment, not translated in improvement of overall survival (Zagars et al. 1988). The other, launched by the Medical Research Council (Fellows et al. 1992), focused on 277 T2-4 NX M0 cases treated by castration ($n=90$), radiotherapy ($n=88$), or combined treatment ($n=99$): irradiation was left to the discretion of each center; it resulted that orchiectomy delayed the onset of distant metastases, and radiotherapy or orchiectomy proved equally effective in controlling local disease.

13.3.1.1 Concomitant and Long-Term LHRH Adjuvant Androgen Deprivation Therapy

The EORTC trial 22863 was the first to show a gain in overall survival (Bolla et al. 1997). It recruited 415 patients classified as T1-2 N0 histological grade 3 WHO or T3-4 N0 M0 to compare RT with concomitant and adjuvant ADT to RT alone and a deferred ADT in case of relapse; 82% of patients were T3, 10% were T4, and 89%, N0. The hormone treatment was oral cyproterone acetate, 50 mg three times daily for 1 month, beginning 1 week before the start of radiotherapy and subcutaneous injection of Zoladex® 3.6 mg every 4 weeks for 3 years starting on the first day of RT. The pelvic target volume received 50 Gy and the prostatic target volume 70 Gy. With a median follow-up of 66 months, there was a significant difference in overall survival, 78% in favor of the combination versus 62% for RT alone ($p=0.001$) (Bolla et al. 2002).The 10-year results (median follow-up of 9.1 years) confirm that the addition of HT increased the clinical-disease-free survival from 22.7% to 47.7% ($p<0.0001$), distant progression-free survival (PFS) from 30.2% to 51.0% ($p<0.0001$), and overall survival from 39.8% to 58.1% ($p=0.0004$). The 10-year prostate-cancer mortality was 30.4% with RT alone and 10.3% with long-term ADT combined with radiotherapy ($p<0.001$) (Bolla et al. 2010a), and no significant difference in cardiovascular mortality was noted between treatment groups.

13.3.1.2 Long-Term LHRH Adjuvant Androgen Deprivation Therapy

The RTOG trial 85-31 was designed to evaluate the effectiveness of indefinite Zoladex® alone after radiotherapy; 977 patients with stages T3-T4 M0 with or without lymph node involvement or pT3 after radical prostatectomy in the event of capsule invasion, positive margins, or seminal vesicle involvement were included. Monthly administration of Zoladex® was started during the last week of RT and was continued indefinitely or until relapse (arm 1) or started at relapse (arm 2); no antiandrogen was given at the very start of Zoladex® to inhibit the initial rise of LH and then of testosterone. Fifteen percent of patients had undergone radical prostatectomy in arm 1 and 14% in arm 2, and 29% and 26% had lymph node involvement, respectively. The pelvic target volume received 45 Gy and the prostate target volume 65–70 Gy. Patients with a pT3 tumor received 60–65 Gy to the postoperative target volume. The combined approach has been

Table 13.1 Phase III studies addressing use/duration of androgen deprivation and/or irradiation dose as combined modality adjuvant treatment for prostate cancer

Study	Year of publication	TNM 2002	Number of patients	Androgen suppression therapy	External irradiation	Effect on overall survival
Androgen suppression + radiotherapy versus radiotherapy alone						
(a) *Adjuvant (+/− concomittant) androgen suppression*						
EORTC 22863 (Bolla et al. 2002)	2002	T1-2 poorly differentiated M0 or T3-4N0-1 M0	415	LHRHa for 3 years	70 Gy RT	Significant benefit for combined treatment (HR = 0.51, 95%CI:0.36–0.73, $p = 0.0002$)
RTOG 85-31 (Pilepich et al. 2005)	2005	T3 or N1M0	977	Orchiectomy or LHRHa	65–70 Gy RT	Significant benefit for combined treatment ($p = 0.002$) seems mostly caused by patients with Gleason score 7–10
Granfors et al. 2006	2006	T3N0-1M0	91	Orchiectomy	65 Gy RT	Significant benefit ($p = 0.02$), mainly caused by lymph node positive tumors
D'Amico et al. 2008a	2008	T2N0M0 (localized unfavorable risk)	206	LHRHa + flut. 6 months	70 Gy 3D-CRT	Significant benefit (HR = 0.55, 95%CI: 0.34–0.90, $p = 0.01$)that may pertain only to men with no or minimal comorbidity
(b) *Neoadjuvant and concomittant androgen suppression*						
TROG 96-01 (Denham et al. 2005)	2005	T2b-T4N0M0	802	Goserelin + flutamide 3 or 6 months before + concomitant	66 Gy	No significant difference in overall survival reported. Benefit in prostate-cancer-specific survival (HR = 0.56 [0.32–0.98], $p = 0.04$)
RTOG 94-13 (Lawton et al. 2007)	2007	T1c-T4N0-1M0	1,292	2 months neoadjuvant + concomitant versus 4 months adjuvant	Whole pelvic RT versus prostate only 70.2 Gy	No significant difference in neoadjuvant + concomitant versus adjuvant ADT groups (interaction suspected)
RTOG 86-10 (Roach et al. 2008)	2008	T2-4N0-1	456	Goserelin + flutamide 2 months before + concomitant	65–70 Gy	No significant difference at 10 year
Short- versus long-term androgen suppression adjuvant (+/– concomittant) to radiotherapy						
RTOG 92-02 (Horwitz et al. 2008)	2008	T2c-4N0-1M0	1,554	LHRHa 2 year adjuvant after 4 months neoadjuvant	65–70 Gy RT	$p = 0.73$ overall. Significant benefit ($p = 0.044$) in subset with Gleason 8–10
EORTC 22961 (Bolla et al. 2009)	2009	T1c-T2abN1M0 T2c-4N0-1M0	970	LHRHa 6 months versus 3 years	70 Gy 3D-CRT	Better result with 3-year treatment than with 6 months (+3.8% survival at 5 year)
Androgen suppression therapy + radiotherapy versus androgen suppression alone						
SPCGF-7/SFUO-3 (Widmark et al. 2009)	2009	T1b-T2 Grade 2–3 T3N0M0	880	LHRHa 3 months + continuous flutamide	70 Gy RT versus no RT	Significantly better survival with combined treatment (HR = 0.68, 95%CI: 0.52–0.89, $p = 0.004$)
NCIC CTG PR.3 MRC PRO7/SWOG (Warde et al. 2010)	2010 ASCO	T3-4 N0M0	1,205	Continuous LHRHa	60–65 Gy RT versus no RT	Significant benefit in favor of combined treatment (HR = 0.77, 95% CI 0.61–0.98, $p = 0.033$)
French study (Mottet et al. 2010)	2010 ASCO	T3-4N0M0	273	LHRHa for 3 years	70 Gy 3D-RT versus no RT	Significant reduction of clinical progression. Effect on overall survival not reported

Table 3 from Bolla et al. (2010a), *Lancet Oncology*; page 1071, authorization given

associated with all 8-year efficacy endpoints except overall survival (49% versus 47% ($p=0.36$)); subset analysis by Gleason score revealed a significant overall survival ($p=0.036$) in favor of the adjuvant HT arm for centrally reviewed Gleason 8–10 patients who had not previously undergone prostatectomy (Lawton et al. 2001). With a median follow-up time of 7.6 years, statistical significances were reached in favor of the adjuvant HT arm for 10-year overall survival (49% versus 39%, $p<0.002$), 10-year incidence of distant metastases (24% versus 39%, $p<0.001$), and disease-specific mortality (16% versus 22%, $p=0.005$) (Pilepich et al. 2005).

In this trial, 173 patients had biopsy-proven pN1 lymph nodes, and 98 of these received RT plus adjuvant HT; with a median follow-up of 6.5 years, multivariate analysis revealed that the combined approach had a statistical impact on all endpoints: overall survival ($p=0.03$), disease-specific failure ($p=0.014$), metastatic failure ($p<0.0005$), and biochemical control ($p<0.0001$) (Lawton et al. 1997). These data are in keeping with those of Granfors et al. (1998) who compared for T1-4 pN0–3 M0 patients, the combination of orchiectomy, and RT ($n=45$) to RT alone and androgen ablation deferred at clinical disease progression ($n=46$). The study was prematurely closed due to an insufficient accrual, and after a median follow-up of 9.3 years, there was a significant difference in overall survival ($p=0.02$) and progression-free survival ($p=0.005$) in favor of the combined arm; this difference was mainly caused by lymph node positive tumors. In conclusion, patients with pathologically or clinically involved pelvic lymph nodes should be considered for RT plus immediate long-term HT (level of evidence 2b).

13.3.1.3 Long-Term Antiandrogen Adjuvant Monotherapy

The early prostate-cancer program consisting of three randomized, double-blind placebo-controlled trials included 1,370 patients with T1-4, any N M0 PCa. A nonsteroidal antiandrogen – bicalutamide (Casodex®) 150 mg/day orally – was given as immediate adjuvant to RT during 2 years (trial 23), 5 years (trial 24), or until progression (trial 25), as an alternative to castration due to the potential benefits in terms of sexual interest, physical capacity, and maintenance of bone mineral density. At a median follow-up of 5.3 years (Tyrell et al. 2005), bicalutamide 150 mg significantly reduced the risk of disease progression ($p=0.003$) in patients with locally advanced PCa ($n=305$).

13.3.1.4 Neoadjuvant and Concomitant Short-Term Androgen Deprivation Therapy

The RTOG trial 86–10 was designed to test the potential value of a combined ADT prior (2 months) and during RT (2 months) with respect to RT alone or at relapse: 471 patients with bulky (5×5 cm) tumors (T2-4) with or without regional lymph node involvement were included: 7% had a positive nodal status in the combined treatment arm versus 9% in the RT alone arm. Thirty percent of patients had a T2 tumor, and 70% were classified as T3-4. Hormonal treatment consisted of oral flutamide (250 mg 3× day) and a subcutaneous injection of Zoladex® 3.6 mg every 4 weeks (Pilepich et al. 2001). The pelvis received 45 Gy and the prostate target volume 65–70 Gy. At 8 years, ADT has been associated with all efficacy endpoints except overall survival, but subset analysis demonstrated that a significant enhancement in overall survival was seen in patients with Gleason score 2–6: 70% versus 52%; $p=0.015$. These results were maintained at 10 years with a significant difference in disease-specific mortality (23% versus 36%; $p=0.01$), distant metastases (35% versus 47%; $p=0.006$), disease-free survival (11% versus 3%; $p<0.0001$), but no difference in 10-year overall survival (43% versus 34%; $p=0.12$) (Roach et al. 2008).

The Trans-Tasman Radiation Oncology Group 96.01 trial has included 818 men randomly assigned to RT alone (66 Gy/33 fractions) (Denham et al. 2005), 3 months' androgen deprivation with goserelin and flutamide starting 2 months before radiotherapy or 6 months' ADT with the same regimen starting 5 months before radiotherapy. After a median follow-up of 10.6 years, compared with patients assigned RT alone, those assigned 3 months' ADT had a

decrease cumulative incidence of PSA progression ($p=0.003$), and local progression ($p=0.0005$), and event-free survival ($p=0.0001$). Six months' ADT reduced PSA progression ($p<0.0001$) and local progression ($p=0.0001$) and led to a greater improvement in event-free survival ($p<0.0001$); moreover 6 months' ADT decreased distant progression ($p=0.001$), cancer-specific mortality ($p=0.0008$), and all-cause mortality ($p=0.0008$) compared with RT alone (Denham et al. 2011).

These two trials suggest that the significant impact of HT on disease-specific survival is certainly due to the concomitant component of HT during RT. In the trial reported by Crook's et al. (2004), 378 patients were randomized between 3 and 8 months neoadjuvant combined ADT with flutamide and goserelin before RT (66 Gy): with a median follow-up of 44 months, there was no impact on biochemical control or survival.

Nevertheless, starting ADT 2 or 3 months before radiotherapy may be useful to decrease the tumor volume of high-risk prostate cancer and improve DVH, while treating the patient immediately instead of delaying the onset of irradiation.

13.3.1.5 Short-Term Neoadjuvant Versus Short-Term Adjuvant Combined Androgen Deprivation Therapy with Whole-Pelvis or Prostate-Only Radiotherapy

RTOG 94-13 study is a four-arm trial devoted to 1,323 patients T1c-4 N0 M0 PSA < 100 ng with an estimated risk of lymph node involvement >15% based on the equation: risk of positive nodes = ((2/3) PSA + ((GS) − 6) × 10). The first randomization is done between neoadjuvant concurrent ADT (NCADT) – 2 months before and 2 months during RT – and 4-month adjuvant hormone therapy (AADT) after RT; the second randomization took place between whole-pelvis radiotherapy (WPRT) followed by a boost to the prostate or prostate-only radiotherapy (PORT). WPRT plus NCADT improved the 4-year progression-free survival (61%) compared with PORT + NCADT (45%), PORT + AADT (49%), and WPRT + AADT (47%) ($p=0.008$), and there was no advantage to WPRT over PORT without neoadjuvant ADT (Roach et al. 2003). With longer follow-up, progression-free survival and biochemical failure (Phoenix definition) continue to favor the WPRT arm ($p=0.034$ and 0.0098, respectively), but we await the major secondary endpoints, cause-specific, and overall survival, since not enough events had occurred (Lawton et al. 2007).

13.3.1.6 Long-Term Androgen Deprivation Therapy Alone Is Inferior to Long-Term Androgen Deprivation Therapy Plus Radiation Therapy

The abovementioned studies have shown the efficacy of hormonal treatment combined with RT, but the impact of LTADT alone was not assessed so far. The SPCG-7/SFUO-3 trial has included 875 patients T1b-T2, G2-G3, or T3 any WHO histological grade (1–3) (78% of T3) with baseline PSA < 70 ng/ml; patients were randomly allocated to endocrine treatment alone with 3 months of total androgen blockade followed by continuous flutamide ($n=439$ patients) or to the same endocrine treatment combined with RT ($n=436$ patients). After a median follow-up of 7.6 years, the cumulative incidence at 10 years for PCa-specific mortality was 23.9% in the endocrine alone group and 11.9% in the endocrine plus RT group for a relative risk of 0.44 (0.30–0.66); the cumulative incidence for overall mortality was 39.4% and 29.6% with a relative risk of 0.68 (0.52–0.89) (Widmark et al. 2009). In conclusion, in patients with locally advanced or high-risk localized PCa, the combination of RT to HT halved the 10-year prostate-cancer-specific mortality and decreased overall mortality with fully acceptable risk of side effects, compared to HT alone.

Protocol NCIC CTG PR-3/MRC PR07/SWOG included 1,205 patients with T3-4 ($n=1,057$) or T2, PSA > 40 ng/ml ($n=119$), or T2, PSA > 20 ng and Gleason > 8 ($n=25$) and N0-X M0 PCa who were randomized to lifelong ADT (bilateral orchiectomy or LHRH agonist) with or without RT (65–70 Gy to prostate ±45 Gy to pelvic lymph nodes). With a median follow-up of 6 years, the addition of RT to ADT significantly reduced the risk of death ($p=0.033$) and the risk of specific death ($p=0.001$) (Warde et al. 2010).

The Mottet trial included 273 patients with locally advanced PCa T3-4 or pT3 N0 M0 randomly assigned to lifelong ADT by LHRH agonist

(leuprorelin) with or without RT (70 Gy to prostate plus 48±2 Gy to pelvic lymph nodes). With a median follow-up of 67 months, there was a significant improvement of the 5-year disease-free survival ($p<0.001$), metastatic-disease-free survival ($p<0.018$), and loco-regional-progression-free survival ($p<0.0002$), but the effect on overall survival was not reported (Mottet et al. 2010).

13.3.1.7 Short-Term Androgen Deprivation Therapy Is Inferior to Long-Term Androgen Deprivation

The aim of RTOG protocol 92-02 devoted to 1,554 patients classified T2c-4 N0 was to investigate the value of a long-term adjuvant ADT (LTADT) after a short-term ADT (STADT). All patients received 2 months of CADT with Zoladex® and flutamide before RT, followed during RT; a radiation dose of 65–70 Gy was given to the prostate. Patients were randomly assigned to receive no additional therapy or 24 months of Zoladex®. Compared with the STADT, the LTADT arm showed significant improvement in all efficacy endpoints except 5-year overall survival; in a subset of patients Gleason scores 8–10, the LTADT arm had significantly better overall survival: 81% versus 70.7%, ($p=0.04$) (Hanks et al. 2003). The 10-year results confirmed significant benefits in all 10-year efficacy endpoint terms except overall survival ($p=0.35$); in a subset analysis, the overall survival benefit was limited to patients with Gleason score 8–10 ($p=0.006$) (Horwitz et al. 2008).

EORTC (22863) and RTOG (85-31) trials have demonstrated that LTADT (>2 years) is recommended for high-risk PCa (level I evidence), but they do not determine the optimal duration of hormonal treatment combined with external beam RT. That is why the EORTC equivalence trial 22961 randomly assigned patients who had received 3D-CRT plus 6 months of ADT in two groups: one to receive no further treatment (STADT) and the other to receive 2.5 years of further treatment (LTADT) with a LHRH agonist, triptorelin, Decapeptyl 11.25 mg®. An outcome of noninferiority of STADT as compared to LTADT required a hazard ratio of more than 1.35 for overall survival, with a one-sided alpha level of 0.05. An interim analysis showed futility, and the results are presented with an adjusted one-sided alpha level of 0.0429. Nine hundred seventy patients were randomized: 483 STADT and 487 LTADT. At a median follow-up of 6.4 years, the 5-year overall survival shows 84.8% for the LTADT arm and 81% for the STADT arm with an estimated hazard ratio of 1.42 ($p=0.008$). The 5-year clinical-progression-free survival was 80.5% for the LTADT arm and 68.7% for STADT arm ($p<0.0001$). The 5-year biochemical-progression-free survival was 77.7% on the LTADT arm versus 56.8% on the STAD arm $p<0.0001$. In conclusion, the combination of RT plus 6 months of ADT provides inferior survival as compared with radiotherapy plus 3 years of ADT (Bolla et al. 2009).

Additional support can be found in a retrospective analysis assessing combined HT with RT (median follow-up >45 months) which showed that long-term ADT (median duration 25.6 months) improves 5-year overall survival (87.5%) with respect to short-term ADT (75%) ($p=0.009$) in patients with a PSA level >20 ng/ml, irrespective of Gleason score and T-stage (Berthelet et al. 2005).

13.3.2 Intermediate and High-Risk Localized Prostate Cancer

13.3.2.1 Six-Month Neoadjuvant and Concomitant Short-Term Androgen Deprivation Therapy

The Boston group published a trial concerning 206 men with localized (T1b-T2b N0-X M0), but unfavorable-risk PCa (baseline PSA ≥ 10 ng/ml and ≤40 ng or a Gleason score of at least 7); patients were randomized to receive RT alone (70 Gy 3D-CRT) or RT plus 6 months of ADT; low-risk patients were ineligible unless they had radiologic evidence of extracapsular extension or seminal vesicle invasion. After a median follow-up of 4.5 years, patients who received 3D-CRT plus ADT had a higher survival ($p=0.04$) and a lower cancer-specific mortality ($p=0.02$) (D'Amico et al. 2004). With a median follow-up of 7.6 years, overall survival was higher for men who were randomized RT and ADT compared

with RT: 74% versus 61% ($p=0.01$), but the survival benefit varies according comorbidity: among the 49 patients with moderate or severe comorbidity, the 8-year overall survival was 25% for those randomized to RT and ADT as compared to 54% for those with RT ($p=0.08$) (D'Amico et al. 2008a).

13.3.2.2 Four-Month Neoadjuvant and Concomitant Short-Term Androgen Deprivation Therapy

In RTOG trial 94-08 (Jones et al. 2011) which has accrued 1,979 patients with T1b-T2b localized PCa, a stratification was done with PSA (≤20 ng/ml), histological grade, and nodal status. Patients were randomized between neoadjuvant CADT, 2 months before conventional RT and 2 months during RT versus RT alone. The 10-year overall survival was 62% for the combined approach as compared with 57% ($p=0.03$) among patients receiving RT alone. Biochemical failure, distant metastases, and the rate of positive findings on repeat prostate biopsy at 2 years were significantly improved with RT plus STADT, but the gains in overall survival and reductions in disease-specific mortality were mainly limited to men in the intermediate-risk subgroup.

In conclusion, 6 months of neoadjuvant and concomitant CADT combined with 3D-CRT (70 Gy) improved overall survival in men with intermediate- or poor-risk localized PCa without moderate or severe comorbidity; meanwhile, a conventional RT (66.6 Gy) plus 4-month of CADT improves overall survival only in men with intermediate localized PCa.

13.4 New Trends

13.4.1 Four to Six-Month Combined Androgen Deprivation Therapy Versus Six-Month LHRH Analogue

The rationale of using an antiandrogen in association with an LHRH agonist is: (1) to block the androgens of adrenal origin, which are left free to continue to stimulate prostate cancer (Labrie et al. 1993), (2) to block the androgen receptors (AR) to prevent the so-called flare that can result due to the surge in testosterone resulting from the use of LHRH agonist, and (3) to contribute independent antitumor activity. To know the optimal duration of combined androgen blockade in high-risk patients would require a large phase III randomized trial. Since a meta-analysis of 27 randomized trials devoted to advanced prostate cancer has shown that the addition of an antiandrogen to androgen deprivation, improved the 5-year survival by about 2% or 3%, with a range of uncertainty between 0% and 5%, it is unlikely that the effect would be very large but a small effect in patients with metastatic disease might be larger in men with high-risk localized PCa analogous to the benefits of adjuvant 5-Fu chemotherapy for regional as compared to metastatic disease (Bauer and Spitz 1998; Colucci et al. 1999; Focan et al. 2000). Considering the positive impact of 4-month (Jones et al. 2011) or 6-month (D'Amico et al. 2008a) CADT on the overall survival of intermediate- and high-risk localized prostate cancer and the positive impact of 6-month CADT on locally advanced PCa (Denham et al. 2011), CADT has to be preferred to LHRH agonists alone. Moreover, it has been shown that men with localized but unfavorable-risk PCa who were treated with RT and 6-month of planned combined ADT appear to have an increased risk of recurrence when treated with less than as compared with 6 months of the antiandrogen; recurrence risk was significantly decreased ($p=0.001$) with each additional month of antiandrogen use after analysis adjustment for prognostic factors (D'Amico et al. 2008b).

13.4.2 Androgen Deprivation Therapy Plus Dose Escalation

IMRT and image-guided radiotherapy allow dose escalation without increasing acute or late toxicity; a meta-analysis of seven randomized controlled trials accruing 2,812 patients showed a significant reduction in the incidence of biochemical failure in those patients treated with high-dose radiotherapy ($p<0.0001$) (Viani et al.

2009). The MD Anderson Cancer Center phase III trial (Kuban et al. 2008) which accrued 301 patients with stage T1b to T3 was the first to show an improvement in freedom from biochemical failure or clinical failure in favor of the 78 Gy arm: 78% as compared with 59% for the 70 Gy arm ($p=0.004$) with an even greater benefit in patients with initial PSA > 10 ng/ml: 78% versus 39% ($p=0.0014$). Dose escalation will be more developed in Chap. 12.

13.4.2.1 Intermediate-Risk Localized PCa

Two phase III trials have shown the gain in overall survival linked to the combination of conventional RT with ADT (D'Amico et al. 2008a; Jones et al. 2011). A retrospective analysis on a cohort of 1,044 patients with intermediate ($n=782$) or high-risk ($n=262$) PCa treated with dose-escalated external beam RT alone, brachytherapy, or high-dose-rate brachytherapy plus pelvic external beam RT has shown – with a 5-year median follow-up – that no advantages in any clinical endpoints at 8 years were associated with ADT administration: the loco-regional failure rate was 5% with or without ADT, and the 8-year cause-specific survival was 97% with ADT versus 99% without ($p=0.20$) (Krauss et al. 2011). Another retrospective study concerning 919 stage T1-T3 N0M0 patients – with a median follow-up of 97 months – treated with RT alone supports such an approach: the 7-year local failure rate stratified by dose group (<72 Gy, >72 but <82 Gy, and >82 Gy was 6%, 2%, and 2%, respectively ($p=0.012$)) and the 7-year distant metastases rate 9%, 6%, and 1%, respectively ($p=0.008$) (Kupelian et al. 2008). The GETUG 14 randomized trial has addressed this question about 377 patients with localized intermediate-risk PCa; lymphadenectomy was mandatory when the risk of node involvement was >10%. Patients were randomly assigned to high-dose RT (prostate 80 Gy; seminal vesicles 46 Gy) either alone or in combination with 4-month CADT (flutamide + Decapeptyl® starting 2 months before RT). With 37 months median follow-up, the 3-year biochemical or clinical control probabilities were 86% and 92% in RT and CADT-RT groups, respectively, ($p=0.09$) and the 3-year biochemical control probabilities 91% and 97% ($p=0.04$) (Dubray et al. 2011).

Dose escalation alone may be proposed to patients who are reticent to short-term ADT due to comorbidities or because they want to preserve their sexual health, provided the prostate dose delivered by image-guided IMRT is around 80 Gy.

13.4.2.2 High-Risk Localized PCa

We do not have data comparing high-dose RT alone (78/80 Gy) versus 70 Gy plus ADT; the combined approach has to remain with a dose escalation. Dearnaley et al. reported the findings of the MRC trial RT01 with 843 men with localized PCa randomly assigned to standard dose (64 Gy) or escalated dose (74 Gy); both delivered with conformal RT with neoadjuvant CADT. The freedom from PSA failure was better ($p=0.0007$) for the dose-escalated arm, and the 5-year control rate was 71% for the dose-escalated arm compared to 60% for conventional dose arm ($p=0.16$). Of note, there was also a trend for improved freedom from salvage ADT ($p=0.12$) and metastases-free survival ($p=0.21$) (Dearnaley et al. 2007).

13.4.2.3 Locally Advanced PCa

Dose escalation will certainly have an impact on survival outcomes, as suggested by the Zapatero trial (Zapatero et al. 2005) based on a cohort of 416 patients: low risk treated by 3D-CRT alone ($n=181$), intermediate risk allocated to receive neoadjuvant 4–6 months before and during 3D-CRT ($n=160$), and high risk receiving neoadjuvant and adjuvant 3D-CRT 2 years after RT ($n=75$). With a stratification for treatment groups, the 5-year biochemical-disease-free survival for high-risk patients with ADT was 63% for dose <72 Gy and 84% for dose ≥72 Gy ($p=0.003$). In a MSKCC retrospective analysis (Zelefsky et al. 2008), 296 T3 patients were treated with dose escalation and 189 patients (43%) were treated with STAS prior to RT. They noted that 3D-CRT +/− IMRT was associated with excellent tumor control and survival outcomes with a 10-year local control rates of 88% and a 10-year cause-specific survival of 83%, respectively 88% for

T3a and 79% for T3b. The incidence of late grade 3 urinary and rectal toxicities was remarkable at only 4% and 1%.

In conclusion, in the management of locally advanced prostate cancer treated by a combined approach – despite the absence of level I evidence for a significant impact on overall survival – dose escalation with IMRT is recommended up to 76–78 Gy.

13.4.3 Pelvic Lymph Node Irradiation

This topic remains controversial. The RTOG 94-13 trial (Roach et al. 2003; Lawton et al. 2007) has shown a positive impact of neoadjuvant ADT on progression-free survival with whole pelvic RT, not confirmed by the GETUG-01 trial (Pommier et al. 2007): (1) the GETUG trial included 444 T1b-T3 N0-pNX M0 patients and more than 1,200 for RTOG 94-13; (2) the GETUG trial allowed a STADT, but not required for patients in the high-risk group, and 56.8% of the patients had a lymph node risk lower than 15% according to the Roach formula (thus the number of patients at risk for positive nodes was much smaller) (Roach et al. 2006); (3) no patients received whole pelvic RT using the RTOG cutoff at L5 S1 interspace, considered by RTOG investigators to be a critical determinant of outcome (Pommier et al. 2007); and (4) no difference in 5-year PFS between the pelvic (46 Gy) and prostate RT (66–70 Gy) arm, with a 42-month median follow-up. The definition of the limit of the pelvic fields is of paramount importance, and Shih et al. (2005) have shown that by using lymphotropic-nanoparticle-enhanced magnetic resonance imaging, 80% of the metastatic nodes were located only in the pelvis with a superior border of 2 cm above the common iliac bifurcation; moreover, lateral rectal shielding to reduce the rectal dose contribution resulted in an underdosage of the presacral lymph nodes (Sanguineti et al. 2006).

In daily practice, pelvic irradiation is not considered for localized or intermediate-risk localized PCa; conversely, high-risk and locally advanced PCa required pelvic irradiation all the more as an RTOG consensus on pelvic lymph node CTVs was reached available as web-based computed tomography images allowing to choose an optimal IMRT technique to cover the correct lymph node volume and to prescribe an appropriate dose (Lawton et al. 2009a, b).

13.4.4 Adjuvant Chemotherapy

Taxanes are radiosensitizer agents, which block the cell cycle during the G2/M phase, inhibit the antiapoptotic effect of *bcl-2*, and induce apoptosis (Milas et al. 1999; Schiff et al. 1979). Moreover, docetaxel has been shown to produce a cytotoxic effect during the S-phase, known to be radioresistant (Hennequin et al. 1995). In androgen-dependent and independent human prostate-cancer xenografts, docetaxel showed a significant antitumoral effect in hormone-sensitive tumors compared with mitoxantrone and estramustine (Oudard et al. 2003). In patients with castration-resistant prostate cancer, the results of randomized trials showed a significant improvement in biological response and survival in favor of docetaxel-containing regimens compared with the reference treatment (Petrylak et al. 2004; Tannock et al. 2004). These results have prompted testing the drug in locally advanced PCa within the frame of phase II trials assessing the feasibility of concomitant (Kumar et al. 2004) or concomitant and adjuvant docetaxel (Bolla et al. 2010b) with radiotherapy and phase III randomized trials assessing the role of adjuvant docetaxel with ADT and RT. The GETUG 12 trial has addressed the role of neoadjuvant chemotherapy with docetaxel on PFS about a cohort of 413 high-risk patients defined as ≥1 of the following criteria: T3-4, Gleason score ≥ 8, PSA ≥ 20 ng/ml, pN+; patients were randomly assigned to either goserelin 10.8 mg every 3 months for 3 years and four cycles of docetaxel 70 mg/m^2 q3w plus estramustine 10 mg/kg/d d1–5 (arm 1) or goserelin alone (arm 2). Local therapy was administered at 3 months which consisted of RT in 358 patients (87%). Toxicity included grades 3–4 neutropenia (27%) with neutropenic fever in 2%, but no toxicity-related death

and no secondary leukemia. With a median follow-up of 4.6 years, the 4-year PFS was 85% in arm 1 versus 81% in arm 2 ($p=0.26$) (Fizazi et al. 2011), but data need to mature.

13.5 Health-Related Quality of Life Related to Androgen Deprivation Therapy

ADT with LHRH agonists is known to adversely affect quality of life, leading to hot flushes, fatigue, impact on cognitive function, sexual side effects, anemia, weight gain, insulin resistance, bone mineral density loss (Israeli et al. 2008; Shahinian et al. 2005), increased diagnoses of cardiac disease (D'Amico et al. 2007), and metabolic side effects (Smith et al. 2008a). These side effects assessed by a self-administered questionnaire (Potosky et al. 2001) are in relation with the prevalent comorbidities of the patients and the duration of the treatment. As regard cardiovascular mortality, the retrospective analysis made on the data of the EORTC and RTOG trials by taking into account all deaths linked to cardiovascular disease has shown that LTADT did not increase the cumulative incidence estimates of cardiovascular mortality as compared with short-term or no ADT (Bolla et al. 2010a, 2009; Efstathiou et al. 2008, 2009). Using data of the 92-02 RTOG trial, Smith et al. (2008b) have found that weight, but not prevalent diabetes, is associated with prostate-cancer mortality in men undergoing combined treatment, but prevalent diabetes was associated with greater all-cause and non-PCa mortality. Many studies have demonstrated that chronic ADT was associated with an increased risk of fractures: Shahinian et al. (2005) studying records from the surveillance, epidemiology, and end results database and Medicare mention that of men surviving at least 5 years, 19.4% of those who received ADT had a fracture versus 12.6% of those not receiving this treatment ($p<0.001$). After radiotherapy and 6 months of androgen blockade, fatigue, hot flushes, and sexual problems increased significantly both statistically ($p<0.001$) and clinically (Bolla et al. 2009); for patients continuing ADT after 6 months for 2.5 years more, there were statistically significant differences between the groups in terms of insomnia ($p=0.006$), hot flushes ($p<0.001$), and sexual interest and activity ($p<0.001$), but overall quality of life did not differ significantly between the two groups ($p=0.37$) (Bolla et al. 2009). In the phase III bicalutamide trial, the adverse events among patients receiving 150 mg plus RT ($n=694$) were breast pain (74.8%), gynecomastia (66.6%), diarrhea (15.4%), asthenia (13.4%), impotence (12.7%), and hot flushes (9.8%), which were mild to moderate in >90% of cases.

All these potential side effects have to be discussed in depth with the patients, taking into account age, WHO performance status, comorbidities, blood count, and the recommendations of a multidisciplinary approach. They must not dissuade radiation oncologists from prescribing LHRH agonists after obtaining an informed consent; they must advise patients to observe regular physical exercise and modification of diet to prevent or minimize these side effects and to pay attention to a careful monitoring of blood pressure, lipid, and glucose levels according to the status of the patient with the help of the general practitioner. In case of long-term ADT, an adequate timing for the measurement of bone mineral density by dual-energy X-ray absorptiometry is also recommended to enable a pharmacological treatment by bisphosphonate in case of osteoporosis when the T-score is <2.5 (Diamond et al. 2004).

13.6 Conclusions (Table 13.2)

In high-risk PCa, the aim of ADT is to potentiate irradiation whatever its technique and to destroy the infraclinical disease outside the irradiated volume. Many phase III randomized trials have paved the way for establishing the indications of the combination of ADT with external irradiation. For locally advanced PCa, long-term ADT (≥2 years) with LHRH agonists combined with external irradiation is a gold standard (level 1a of evidence); should there be a significant comorbidity, a reticence of the patient and/or a poor tolerance, a 6-month duration may be proposed. For high-risk localized PCa a 4–6-month complete ADT is

Table 13.2 Guidelines regarding sequencing of androgen deprivation therapy according to risk groups (2002 TNM classification)

Risk	IMRT	Neoadjuvant/ concomitant	Adjuvant+/– concomitant
Low T1c-2a, Gleason ≤ 6, PSA ≤ 10 ng/ml	+	–	–
Intermediate T2b, or 10 < PSA ≤ 20, or Gleason 7	+[a]	+	–
High (T2c, PSA > 20) Gleason > 7	+	+	+[b]
Very high T3–4, N1	+	+[c]	+

[a]Consider high dose (80 Gy) as alternative to ADT
[b]Long-term ADT (2–3 years) for T2c
[c]RTOG 9202 starts with neoadjuvant androgen deprivation therapy followed by concomitant and adjuvant

recommended (level 2a evidence). For intermediate-risk localized PCa, patients may benefit from a combined approach with a short-term ADT. Image-guided IMRT allows a dose escalation for high-risk PCa and may offer the opportunity to treat intermediate-risk localized PCa without ADT. Nobody has the monopoly of the knowledge, and the right way to find an adequate compromise is the multidisciplinary approach based on guidelines (Heidenreich et al. 2011). Patients have to be fully informed of the potential morbidity of ADT, and a close cooperation is needed with general practitioners and specialists to prevent as much as possible harmful side effects.

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Postoperative Irradiation: Immediate or Early Delayed?

14

Dirk Bottke and Thomas Wiegel

Contents

D. Bottke • T. Wiegel (✉)
Department of Radiation Oncology and Radiotherapy, University Hospital Ulm, Albert-Einstein-Allee 23, Ulm 89081, Germany
e-mail: dirk.bottke@uniklinik-ulm.de; thomas.wiegel@uniklinik-ulm.de

14.1 Introduction

Radical prostatectomy (RP) and radiation therapy are the two major first-line therapeutic options for patients with prostate cancer, with best results achieved in patients with organ-confined disease. Recurrence of prostate cancer after RP has been associated with multiple factors including Gleason score, prostate-specific antigen (PSA) level before surgery, tumor stage, infiltration of the seminal vesicles, or positive surgical margins (Chun et al. 2006; Swindle et al. 2005; Salomon et al. 2003; Pinto et al. 2006). However, biochemical recurrence is a common event even in patients with favorable prognostic factors.

Following RP, PSA should become undetectable within 4–6 weeks, as serum half-life of PSA is approximately 2–3 days (Stamey et al. 1987). Persistent serum PSA levels after RP indicate residual prostatic tissue, either malignant or benign (BPH). In the former case, such levels predate clinically evident disease and do correlate well with disease progression.

A PSA increase of ≥0.2 ng/ml is a common definition of progression of disease following RP (Heidenreich et al. 2011; Wenz et al. 2010). It occurs in up to 50% of patients with pT3/4 tumors, and this value ranges up to 70% in case of pT3 tumors with positive surgical margins and/or positive pelvic lymph nodes (Roehl et al. 2004; Stephenson et al. 2009). The rate of biochemical progression after 7 years for patients with organ-confined tumors (pT2) and positive surgical margins is about 25% (Stephenson et al. 2009).

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Vital tumor tissue was histopathologically proven by biopsies from the urethrovesical anastomosis in 35–55% of all patients, with rising PSA after RP without clinical correlates suggestive of recurrent tumor (Shekarriz et al. 1999).

The optimal management of patients with clinical and pathologic features of increased risk for developing a biochemical recurrence continues to be a source of controversy. Two treatment approaches for the postoperative management of these patients are adjuvant radiation therapy in men with an undetectable PSA or observation followed by early salvage radiation therapy in men with persisting or rising PSA after initially postoperative undetectable values.

The purpose of this chapter is to review the rationale, results, and possible side effects for the different treatment approaches ART and SRT.

14.2 Adjuvant Radiation Therapy

14.2.1 Randomized Clinical Trials

Three randomized phase III trials demonstrated a nearly 20% absolute benefit for biochemical progression-free survival (bNED) after adjuvant radiation therapy (60–64 Gy) compared with a "wait and see" policy, mostly for pT3 cN0 or pN0 tumors (Table 14.1). The greatest benefit (30% bNED after 5 years) has been demonstrated in patients with positive margins and pT3 tumors (Bolla et al. 2005; Thompson et al. 2006; Van der Kwast et al. 2007; Wiegel et al. 2009a). In the meantime, 10-year follow-up data of the EORTC trial were reported and confirmed these results (Bolla et al. 2010).

In the prospective study of the South Western Oncology Group (SWOG), overall survival was improved from 13.5 years without to 15.2 years with adjuvant radiation therapy (Thompson et al. 2009). Notably, central pathologic review on the outcome at 5 years in the EORTC trial showed that only surgical margin status caused a statistically significant interaction with the treatment effect, to such an extent that the treatment benefit in patients with negative margins did not remain significant. The hazard ratio for the treatment benefit in the group with negative surgical margins was 0.87 ($P=0.601$) compared to 0.38 ($P<0.0001$) in the group with positive surgical margins according to the review pathology. Excluding the patients with a PSA of >0.2 ng/ml after prostatectomy, the hazard ratio for postoperative irradiation was 1.11 ($P=0.740$) and 0.29 ($P<0.0001$) for the patients with negative and positive margins, respectively (Van der Kwast et al. 2007). This benefit was also seen in the real adjuvant situation, when the PSA was undetectable before the start of radiation therapy (Wiegel et al. 2009a and 2009b). In the trial of the German Cancer Society, 159 patients were randomized into the observation and 148 into the adjuvant irradiation arm (60 Gy in 30 fractions over 6 weeks). After a median follow-up of nearly 5 years, there was a significant benefit from adjuvant radiation therapy for bNED: 72% versus 54% ($P<0.03$). In the subgroup of pT3 R1 tumors, this benefit increased from 18% to 28% (Wiegel et al. 2009a).

It is notable that the three randomized studies have used different definitions of biochemical progression: SWOG: PSA > 0.4 ng/ml, EORTC: PSA > 0.2 ng/ml, ARO: PSA > 0.05 ng/ml.

Consequently, biochemical recurrences (as an increase of the PSA out of the undetectable range) were detected earlier in the EORTC and the ARO study. In the light of that, the apparently worse results of the ARO study could be explained (Table 14.1).

It is well known that the location, the extent, and the number of positive surgical margins after radical prostatectomy are significant predictors of biochemical progression after radical prostatectomy. The investigators of the Cleveland Clinic/Ohio found in their retrospective series of 7,160 patients treated with radical prostatectomy 1,540 patients with positive margins. The 7-year progression-free probability was 60% in those patients, resulting in an hazard ratio for biochemical recurrence of 2.3 in the case of positive surgical margins compared with negative margins. There was also an increased risk of biochemical recurrence in patients with multiple versus solitary positive surgical margins (HR 1.4) and extensive versus focal positive surgical margins (adjusted HR 1.3) (Stephenson et al. 2009). From the data of the randomized trials mentioned above, these patients with positive margins and

Table 14.1 Overview of all three randomized trials for adjuvant radiation therapy after radical prostatectomy

Reference	*n*	Inclusion criteria	Randomization	Definition of biochemical recurrence PSA (ng/ml)	Median follow-up	Biochemical progression-free survival (bNED)	Overall survival
Thompson et al. (2009), SWOG 8794	431	pT3 cN0 ± involved SM	60–64 Gy vs. "wait and see"	>0.4	152 months	10 years: 53% vs. 30% ($P<0.05$) 5 years data not given	10 years: 74% vs. 66% Median time: 15.2 vs. 13.3 years $P=0.023$
Bolla et al. (2005), EORTC 22911	1,005	pT3 ± involved SM cN0 pT2 involved SM	60 Gy vs. "wait and see"	>0.2	60 months	5 years: 79% vs. 56%	91.5 vs. 90.8 n.s.
Wiegel et al. (2009a), ARO 96-02	388	pT3 (± involved SM) pN0 PSA post-RP undetectable		>0.05 + confirmation	54 months	5 years: 72% vs. 54%	Not given

n.s. not significant, *PSA* prostate-specific antigen, *SM* surgical margins

pT3-tumors do stand to profit mostly from postoperative radiation therapy.

In the EORTC trial, when the data of patients with pT2 tumors and positive surgical margins were analyzed, there was a significant benefit of 5-year biochemical progression-free survival rate in the irradiated group (76.4% vs. 52.2% in the wait-and-see group) (Bolla et al. 2005). However, these data come from a subgroup analysis, and biochemical progression-free survival was not the primary end point of this study. Therefore, the results must be interpreted with caution. The possible benefit of radiotherapy must be weighed out carefully in consideration of potential late effects as erectile dysfunction.

14.2.2 Definition of Clinical Target Volume (CTV)

In the EORTC and SWOG trials radiation was based on 2D treatment planning, where the prostatic fossa was targeted by using large treatment portals. Obviously, precise definition of target volumes was not essential, which is in great contrast to modern radiation treatment techniques such as IMRT. Compared to 2D-based planning, IMRT provides significant normal tissue sparing but also demands exact definition of target volume.

Consideration of the local failure patterns in the post-RP setting is essential for optimal definition of CTV. The most common sites of local relapse proven by biopsy are the vesicourethral anastomosis (VUA) (66%) followed by the bladder neck (16%) and retrotrigone area (13%) (Connolly et al. 1996). Recently, endorectal magnetic resonance imaging (MRI) was used to detect local relapse patterns following RP in order to further define the optimal CTV (Miralbell et al. 2007). Based on the results of this study, the authors recommended a cylindrical-shaped CTV centered 5 mm posterior and 3 mm inferior to the VUA, concordant with the previously mentioned pathologic studies.

To address any uncertainties in definition of CTV, the Radiation Therapy Oncology Group (RTOG) (Michalski et al. 2010), the EORTC Radiation Oncology Group (Poortmans et al. 2007), and other cooperative groups (Wiltshire et al. 2007) have created consensus guidelines for delineation of target volumes for postprostatectomy patients. In the RTOG recommendations, the CTV should extend superiorly from the level of the caudal vas deferens remnant (or 3–4 cm superior to the pubic symphysis, whichever is higher) and inferiorly 8–12 mm inferior to VUA. The VUA is defined as the retropubic region that can be visualized one slice below the most inferior urine-containing image of the bladder (often best seen on a sagittal reconstruction). Below the superior border of the pubic symphysis, the anterior border is at the posterior aspect of the pubis and extends posteriorly to the rectum. At this level, the lateral border extends to the levator ani muscles. Above the pubic symphysis, the anterior border should encompass the posterior 1–2 cm of the bladder wall and should extend posteriorly to the mesorectal fascia.

14.2.3 Use of Image Guidance to Improve Postprostatectomy Prostatic Fossa Localization

In recent years, several innovative methods have been developed to improve localization of the prostatic fossa and minimize daily internal setup error. Techniques currently utilized in most practices include daily portal imaging with implanted gold fiducial markers (Schiffner et al. 2007), daily cone-beam or kilovoltage imaging (Nath et al. 2010), and the use of electromagnetic transponders (Canter et al. 2010). Such image-guidance techniques allow for a minimal (7–10 mm) expansion from a CTV to a planning target volume, thereby providing further normal tissue sparing by minimizing RT dose to the rectum and bladder (Showalter et al. 2008).

14.2.4 Adjuvant RT of Pelvic Lymph Nodes?

The three randomized trials included only patients with cN0 or pN0 disease. The effect of adjuvant RT in node-positive prostate cancer has not yet

been prospectively assessed. However, there are interesting retrospective data raising the question whether men with nodal involvement confirmed during prostatectomy could benefit from adjuvant RT. A recent retrospective study reported a significant positive impact of RT in combination with hormonal therapy in patients with nodal metastases treated with RP and pelvic lymph node dissection (Da Pozzo et al. 2009). However, this study was limited by a potential patient selection bias mainly due to its retrospective and unmatched design. In fact, patients treated with adjuvant RT were those affected by more aggressive disease. For this reason, no effect of adjuvant RT on cancer-specific survival was demonstrated on univariate survival analyses. There was significant gain in predictive accuracy when adjuvant RT was included in multivariable models predicting biochemical recurrence-free and cancer-specific survival (gain: 3.3% and 3%, respectively; all $P<0.001$).

In a huge retrospective series, Briganti et al. assessed the effect of adjuvant RT in node-positive prostate cancer including two homogeneous matched patient cohorts exposed to either adjuvant RT plus HT or adjuvant HT alone after surgery. In this series from Milan and Jacksonville, a total of 703 patients were treated, with a median follow-up of 95 months. Patients were matched for age at surgery, pathologic T stage and Gleason score, number of nodes removed, surgical margin status, and length of follow-up. The overall survival advantage was 19% in favor of adjuvant radiation therapy plus hormonal treatment compared with hormonal treatment alone. Similarly, higher survival rates associated with the combination of HT plus RT were found when patients were stratified according to the extent of nodal invasion (namely, ≤2 vs. >2 positive nodes; all $P\leq0.006$) (Briganti et al. 2011). Because of the retrospective nature of this series with no standardized definition of target volumes, radiation dose, and duration of hormonal treatment, these results should be interpreted with caution. However, it provides support for this treatment in selected cases, whereas it should be validated in prospective clinical trials.

14.2.5 Additional Use of Hormone Therapy to ART

It is now clearly established that the standard nonoperative management for patients with locally advanced prostate adenocarcinoma includes long-term ADT. Two previous cooperative group trials have demonstrated an overall survival advantage for high-risk patients with an intact prostate treated with 2–3 years of ADT (Bolla et al. 2009; Horwitz et al. 2008). It remains unknown if there is a benefit to the addition of adjuvant ADT for men with high-risk, node-negative prostate adenocarcinoma initially treated with RP and pelvic lymph node dissection. The primary rationale for use of ADT post-RP is to (1) improve local control by eradicating disease in a hypoxic scar that may be radioresistant, (2) address micrometastatic disease which may have spread to the lymph nodes or distant sites, and (3) alter PSA kinetics in patients who will eventually relapse (Hanlon et al. 2004. Kaminski et al. 2003; Rossi et al. 2011).

Previous studies have indicated a potential benefit for men at high risk of recurrence treated with combination therapy. A secondary analysis of patients' status post RP enrolled on Radiation Therapy Oncology Group (RTOG) 85-31 (Corn et al. 1999), a phase III trial comparing standard external beam RT plus immediate ADT versus RT alone for patients with non bulky prostate cancer, found a biochemical control advantage for patients who received combination therapy as compared to men treated with RT alone. With a median follow-up of 5 years, the progression-free survival for men treated with combination therapy was estimated to be 65% as compared to 42% for men treated with RT alone ($P=0.002$). Similar results were seen in a retrospective study performed at Stanford University (King et al. 2004). A subsequent RTOG study (P-0011) was designed to determine the benefit of combination therapy for man with unfavorable prognostic factors and an undetectable PSA treated with ART. This trial was unfortunately closed due to poor accrual (Elshaikh et al. 2011).

Table 14.2 Results for salvage radiotherapy after biochemical recurrence from selected studies

Investigator	Patients (*n*)	Median PSA (ng/ml)	Median dose (Gy)	bNED
Anscher et al. (2000)	89	1.4	66	50% at 4 years
Buskirk et al. (2006)	368	0.7	64.8	35% at 8 years
Cadeddu et al. (1998)	82	4.1	64	10% at 5 years
Chawla et al. (2002)	54	1.3	64.8	35% at 5 years
Garg et al. (1998)	78	1.2	66	65% at 3 years
Hagan et al. (2004)	91	4.5	64	55% at 5 years
Neuhof et al. (2007)	171	1.1	60–66	35% at 5 years
Pazona et al. (2005)	307	0.8	64	40% at 5 years; 25% at 10 years
Peyromaure et al. (2003)	62	2.5	65	42% at 5 years
Pisansky et al. (2000)	166	0.9	64	46% at 5 years
Siegmann et al. (2011)	301	0.28	66.6	74% at 2 years
Stephenson et al. (2007)	1,540	1.1	65	32% at 6 years
Taylor et al. (2003)	71	0.8	70	66% at 5 years
Tsien et al. (2003)	57	1.2	65	30% at 8 years
Ward et al. (2004)	211	0.6	64	34% at 10 years
Wiegel et al. (2009b)	162	0.33	66.6	54% at 3.5 years

In ongoing EORTC trial 22043, patients with Gleason score 5–10, undetectable PSA, and pathologic stage pT2R1 or pT3a–b will be randomized within 3 months after radical prostatectomy between postoperative irradiation alone and postoperative irradiation and short-term adjuvant androgen deprivation for 6 months. The primary trial end point is 5-year biochemical progression-free survival.

14.3 Salvage Radiation Therapy

As an alternative, salvage radiation therapy should be considered for men presenting with persistent PSA after prostatectomy or showing an increase of PSA levels after initially postoperative undetectable values (Stephenson et al. 2007; Wiegel et al. 2009b; Neuhof et al. 2007; Trock et al. 2008; Bottke et al. 2009; Swanson et al. 2011) (Table 14.2).

It remains uncertain whether a PSA increase after RP indicates isolated local disease, distant metastatic progression, or both (Shekarriz et al. 1999). Therefore, the best treatment for recurrent prostate cancer in patients with increasing or persisting PSA without clinical evidence of disease still remains controversial. On the other hand, only RT can offer the chance of cure to patients with truly localized malignant disease after RP.

There are indicators for a higher likelihood of local recurrence, e.g., slow PSA rise (PSA doubling time ≥12 months), more than 1 year between RP and the demonstration of PSA in the serum, Gleason score <7, and negative surgical margins (Pisansky et al. 2000). On the other hand, there are also indicators suggesting metastatic disease such as short PSA doubling time (<12 months) or Gleason score at RP from 8 to 10 (Pazona et al. 2005; Ward et al. 2004). Some authors tried to define combinations of risk factors. For example, patients with a combination of PSA < 1 ng/ml before RT, pre-RP Gleason score < 7, and a long PSA doubling time after progression have a high risk of local disease (Stephenson et al. 2004). Recently, a predictive model for the outcome of RT for PSA progression after RP has been established (Stephenson et al. 2007). Assuming a local nature of the underlying disease, salvage radiotherapy (SRT) of the prostatic bed has widely been used to treat patients in the absence of biopsy-proven local recurrence. An established standard is conformal radiotherapy to the prostatic fossa with a dose of about 66 Gy, aiming to irradiate the presumed local recurrence and hence to reduce the risk of a "second wave of metastasis" leading to clinical progression of disease (Coen et al. 2002; Heidenreich et al. 2011; Wenz

et al. 2010). In the light of these well-known problems in detecting local recurrence in the prostatic bed, radiotherapy to the prostatic fossa is one of the rare therapies in which most radiation oncologists irradiate without a histologic proof of tumor recurrence.

14.3.1 Role of Investigations in Case of Persisting/Rising PSA

A local recurrence is more likely to be confirmed with biopsy when abnormal tissue in the post-radical prostatectomy bed is detected with either digital rectal exam (DRE) or imaging (Stephenson et al. 2004). Imaging modalities that can detect post-radical prostatectomy recurrence and potentially guide biopsy include TRUS, MRI, and nuclear medicine methods; these modalities can also aid in monitoring disease progression or planning salvage radiation therapy.

TRUS is the most available and most commonly performed imaging technique used in post-radical prostatectomy patients with suspected recurrence. The main role of TRUS is in detecting sites of suspected recurrence and directing biopsies. The sensitivity of TRUS-guided biopsies (66–75%) has been shown to be greater than that of DRE-guided biopsies (29–50%) in the post-radical prostatectomy patient (Scattoni et al. 2003; Deliveliotis et al. 2007). The sensitivity of TRUS-guided biopsies increases with higher PSA levels at the time of recurrence (Shekarriz et al. 1999), obviously related to larger tumor volume. A recent study showed that only 25% of patients with PSA < 1 ng/ml had biopsy-proven recurrence compared with 53% of patients with PSA levels >2 ng/ml (Deliveliotis et al. 2007). More recent advances in TRUS of post-radical prostatectomy patients include the use of color and power Doppler to detect areas with increased vascularity. Both techniques have been shown to improve sensitivity and specificity (Tamsel et al. 2006).

The advantages of MRI over TRUS are its superior soft-tissue resolution and its ability to cover the entire postprostatectomy fossa and reveal recurrences that are located beyond the region routinely imaged on ultrasound. The combination of an external and an endorectal coil improves the ability to detect local recurrence of prostate cancer (Huch Boni et al. 1996). The anatomic detail and wide coverage of the pelvis by MRI facilitates its increasing use in directing salvage radiation therapy when a recurrence is demonstrated (Miralbell et al. 2007). Additionally, pelvic lymphadenopathy and osseous metastases, the most common early metastatic sites from prostate cancer, are routinely evaluated on MRI.

The reported sensitivity and the specificity of MRI for depicting local recurrences by experienced investigators in 82 patients who underwent prostatectomy are 87% and 78%, respectively. PSA levels at MR imaging in patients with clinically proved recurrences ranged from undetectable to 10 ng/ml (mean, 2.18 ng/ml) (Sella et al. 2004).

Advancements in MRI technique, including magnetic resonance spectroscopy and DCE-MRI, have not yet been systematically evaluated for detection of post-radical prostatectomy recurrence.

A variety of nuclear medicine techniques are currently being evaluated in post-radical prostatectomy patients with a PSA relapse. These studies include evaluation for local recurrence and for metastatic disease in the pelvis with combined PET/CT, utilizing various tracers. Older studies using the radiotracer ^{18}F-FDG, which is commonly used in cancer imaging, showed a low sensitivity and specificity (Hofer et al. 1999). With the clinical introduction of newer image reconstruction algorithms, however, newer generations of PET scanners with higher spatial resolution, and the use of combined PET/CT, this has changed. Although ^{18}F-FDG continues to be a suboptimal radiotracer for the detection of local recurrence, disease can be detected in selected patients, with the probability of detection depending on PSA level and PSA doubling time (Schoder et al. 2005). New radiotracers, including ^{11}C or ^{18}F choline, ^{11}C or ^{18}F acetate, or anti-1-amino-3–^{18}F-fluorocyclobutane-1-carboxylic acid, appear more promising for the detection of both local and metastatic recurrent prostate cancer (Cimitan et al. 2006; Scattoni et al. 2007).

The diagnostic accuracy of choline PET in detecting sites of prostate cancer relapse has been investigated by several authors, the overall reported sensitivity ranges between 38% and 98%. It has been demonstrated that choline PET technology's positive detection rate improves with increasing PSA values. The routine use of choline PET/CT cannot be recommended for PSA values <1 ng/ml (Rinnab et al. 2007; Picchio et al. 2011).

14.3.2 Results of Salvage Radiotherapy/Prognostic Factors

The level of PSA at the time of salvage radiation therapy is one of the most important predictors for response. Stevenson et al. reported the results of 1,540 patients from 16 contributors. These patients received salvage radiation therapy with a median dose of 66 Gy and had a median follow-up of 53 months. A 6-year biochemical progression-free survival rate of 48% could be achieved when the PSA was <0.5 ng/ml compared with only 18% when the pre-radiation therapy PSA was >1.5 ng/ml. In the whole series, the 6-year progression-free survival rate was 32% (Stephenson et al. 2007). The authors identified several prognostic factors that were associated with a poor response to radiation therapy including Gleason score of 8–10, preradiation PSA > 2 ng/ml, negative surgical margins, postoperative PSA doubling time <10 months, and seminal vesicle invasion. Patients without these adverse features had a 6-year progression-free survival of 69%. Also, some subsets of patients with Gleason score 8–10 would benefit from salvage radiation therapy if the pretreatment PSA was <2.0 ng/ml, surgical margins were positive, and PSA doubling time was >10 months. In this situation, the 6-year bNED was 33% (Stephenson et al. 2007).

It is important to point out that achieving an undetectable PSA after salvage radiation therapy offers a second chance of cure. Wiegel et al. reported the results of a homogenously treated group of 162 patients, all pN0, treated with a median dose of 66 Gy in fractions of 1.8 Gy. In the multivariate analysis, the most important predictor for biochemical progression-free survival was the achieving of an undetectable PSA after salvage radiation therapy (Wiegel et al. 2009b). These results were confirmed by others (Neuhof et al. 2007).

14.3.3 Total Dose of Salvage Radiotherapy

There remains, however, a controversy about the best irradiation dose for those patients. In the guidelines, total doses of "at least 66 Gy" are recommended (Heidenreich et al. 2011; Wenz et al. 2010). However, some recently published series demonstrated a better outcome with higher total doses (Bernard et al. 2010; Siegmann et al. 2011; King and Kapp 2008). Bernard and coworkers from the Mayo Clinic, Jacksonville, investigated 364 men with salvage radiation therapy after radical prostatectomy after a median follow-up of 6.0 years. They used three dose groups (low: <64.8 Gy, moderate: 64.8–66.6 Gy, high: >66.6 Gy). In multivariate analysis, they found that compared with the high-dose level, there was a decreased bNED for patients treated with the low-dose level (HR 0.60) (Bernard et al. 2010). This was similar to the results published by Siegmann et al. from the group in Berlin and Ulm. In their retrospective series including 301 patients, 234 received 66.6 Gy, while 67 patients with a PSA decrease during salvage radiation therapy were selected and irradiated up to 70.2 Gy. In the multivariate analysis, the total dose was a significant predictor of reduced risk of biochemical progression ($P=0.017$) (Siegmann et al. 2011).

The need for a higher irradiation dose remains uncertain, nevertheless, seems justified especially in patients with histologically confirmed local recurrence after radical prostatectomy. Some data suggest a better outcome with a total dose of more than 66 Gy in these patients (Roscigno et al. 2007).

14.3.4 RT of Pelvic Lymph Nodes?

An important, but unsolved, question is the value of an additional whole pelvic irradiation compared

with prostate bed irradiation alone. Spioto from the Stanford University reported on 160 patients who underwent adjuvant or salvage radiation therapy, out of which 87 had short-course total androgen suppression. One hundred fourteen patients were considered at high risk of lymph node involvement although cN0 (Gleason Score > 8, preoperative PSA level >20 ng/ml, seminal vesicle involvement). Seventy-two underwent whole pelvic radiation therapy, and 42 underwent prostate bed radiation therapy. The median follow-up was >5 years. Limited to high-risk patients, there was a superior bNED of whole pelvic radiation therapy compared with prostate bed radiation therapy (5-year rate 47% vs. 21%, $P<0.05$). Whereas these data have to be confirmed in a prospective trial, whole pelvic radiation therapy combined with modern delivery techniques like IMRT can be offered as an attractive option for high-risk patients (Heidenreich et al. 2011; Wenz et al. 2010; Spiotto et al. 2007).

14.3.5 Additional Use of Hormone Therapy to SRT

Interesting retrospective data have been reported from the Mayo Clinic and from the University of Michigan (Choo et al. 2009; Soto et al. 2011). They raise the question of the efficacy of an additional androgen deprivation during and after salvage radiation therapy. Choo and coworkers reported on 75 patients treated with salvage radiation therapy + 2-year androgen deprivation treated in a pilot prospective study. With a median follow-up from salvage radiation therapy of 6.5 years, all patients achieved an initially complete PSA response (<0.2 ng/ml). Relapse-free survival rate at 7 years was 78% of the whole population (Choo et al. 2009). A group of the University of Michigan treated all together 630 men for salvage indications after radical prostatectomy. Out of this group, 66% had high risk factors and the mean radiation therapy dose was 68 Gy. Twenty-four percent of all patients received concurrent androgen deprivation. The median ADT duration for these patients was 11 months. With a median follow-up of 3 years, the concurrent androgen deprivation was shown to be a significant independent predictor of progression-free survival in the high-risk group ($P<0.05$) (Soto et al. 2011). Therefore, it seems attractive to treat high-risk patients with salvage radiation therapy and an additional androgen deprivation. The optimal duration of this androgen deprivation therapy remains uncertain.

RTOG 96-01 is a randomized, multicenter phase III trial designed to compare antiandrogen therapy (bicalutamide monotherapy 150 mg/day) plus salvage radiation therapy ($n=387$) to a placebo plus salvage radiation alone ($n=383$) in men with pT3 ($n=518$)/pT2 R1 ($n=252$) N0 M0 prostate cancer who have an elevated PSA after surgery. Median follow-up in surviving patients was 7.1 years. The primary end point is overall survival. The addition of 24 months of peripheral androgen blockade during and after RT significantly improved freedom from PSA progression (FFP) 57% vs. 40% ($P<0.0001$) and reduced the incidence of metastatic prostate cancer (7.4% vs. 12.6%, $P<0.04$) without adding significantly to radiation toxicity. The significance of benefit in overall survival, as well analysis of risk-stratified subsets, must await longer follow-up (Shipley et al. 2010). Therefore, there are currently no clear conclusions from these data. Possibly, high-risk patients profit from additional antiandrogen therapy.

A current RTOG trial (0534) is investigating the benefit of short-term ADT, as well as pelvic nodal irradiation, in the SRT setting. In this trial, patients will be randomized to one of three treatment arms: (1) prostatic fossa irradiation alone, (2) prostatic fossa + whole pelvic irradiation alone, or (3) prostatic fossa + whole pelvic irradiation with short-term ADT. The primary end points of this study are to determine (1) whether the addition of short-term androgen deprivation therapy to prostatic fossa irradiation improves freedom from progression for 5 years over that of prostatic fossa irradiation therapy alone and (2) whether short-term ADT and whole pelvic RT improves freedom from progression over that of short-term ADT and prostatic fossa irradiation alone for men treated with SRT. The target of accrual for this trial is 1,764 patients and, to date, nearly 40% of the target accrual goal has been met.

14.4 Radiation Therapy Techniques

Traditionally, a 4-field technique has been used. The conventional treatment volumes were typically very generous, being approximately 10 × 10 cm in the anterior-posterior fields with the inferior border at the ischial tuberosities. The lateral fields extended from the anterior aspect of the pubic symphysis and split the rectum posteriorly.

After introduction of modern 3D CRT techniques, a major controversy about the target volumes of postoperative radiation therapy started. Critical evaluation of target volume delineation by different authors and participation of experienced radiation oncologist showed that variations up to 65% maybe present even in cases of adjuvant or salvage radiation to the prostatic fossa (Michalski et al. 2009). These differences have been presented despite the presence of guidelines published on behalf of the EORTC Radiation Oncology Group two years earlier (Poortmans et al. 2007).

In 3D CRT, the target volume should include the bladder neck (pulled into the prostate bed), the periprostatic tissue and surgical clips, and the seminal vesicle bed (including any seminal vesicle remnants if present) if initially involved or as a confirmed site of recurrence. There are some anatomic landmarks that are useful in maximizing coverage of the surgical bed. Inferiorly, the vesical-urethral anastomosis should be included. This anastomosis is the most frequent area of positive prostate bed biopsies. By placing the inferior field edge at the top of the bulb of the penis (best seen on magnetic resonance imaging) and adding a margin for uncertainties, there should be adequate coverage. Laterally, the field should extend to about the medial aspect of each obturator internus muscle. Although the rectum is a landmark posteriorly, the relative position of the rectum appears to shift after the prostate is removed as well as during radiation therapy (Naya et al. 2005; Fiorino et al. 2005). For this reason, a generous margin from CTV to pTV posteriorly is recommended, such as setting an 8-mm margin with image guidance (Paskalev et al. 2005). The superior margin is more subjective. The former prostate can extend above the pubic symphysis, but it is recommended that the anterior part of the bladder be avoided at this level because this is the least likely area for extracapsular extension and involved margins. Treatment of the seminal vesicle bed, lying behind the bladder, is advised for pT3b tumors. If vascular clips were used at prostatectomy, they are likely to be seen in this region. The level of the posterior-superior clinical target volume is somewhat subjective and should be guided by the extent of disease at the prostate base and whether the seminal vesicles were involved.

For all these reasons, the recommendations of the RTOG (Michalski et al. 2009) and of the EORTC (Poortmans et al. 2007) should be considered as being very helpful in delineation of the target volume for irradiation of the prostatic fossa.

However, the definition of the target volumes remains difficult. Recently, a study assessed the interobserver agreement of prostate bed delineation after radical prostatectomy as proposed by the EORTC guidelines. Six observers delineated the prostate bed (PB) and the original seminal vesicle position (SV) of 10 patients. Contours were then compared for agreement between observers. The mean volume of 100% agreement was only 5.0 (±3.3) ml for the PB and 0.9 (±1.5) ml for the SV, whereas the mean union of all contours (±1 SD) was 41.1 (±11.8) ml and 25.3 (±13.4) ml, respectively. The overall standard deviation of the outer margins of the PB ranged from 4.6 to 7.0 mm (Ost et al. 2011b).

Given the potential for late toxicity after postoperative radiation therapy, the use of IMRT is appealing (Bastasch et al. 2002). As with 3D CRT, a generous definition of the prostate bed target volume and adequate margins to account for target motion (especially due to the variation in rectal and bladder filling) and setup uncertainties are critical. The theoretical advantages of IMRT are that dose falloff is more geometrically rapid than for 3D CRT and the better conformation of the dose to irregularly shaped targets (e.g., the superior-posterior aspect of the postoperative field). A greater sparing of the superior-anterior part of the bladder, the posterior part of the rectum, and the penile bulb can be achieved using IMRT, despite using the same target volume definition (Pinkawa et al. 2007). The comparison

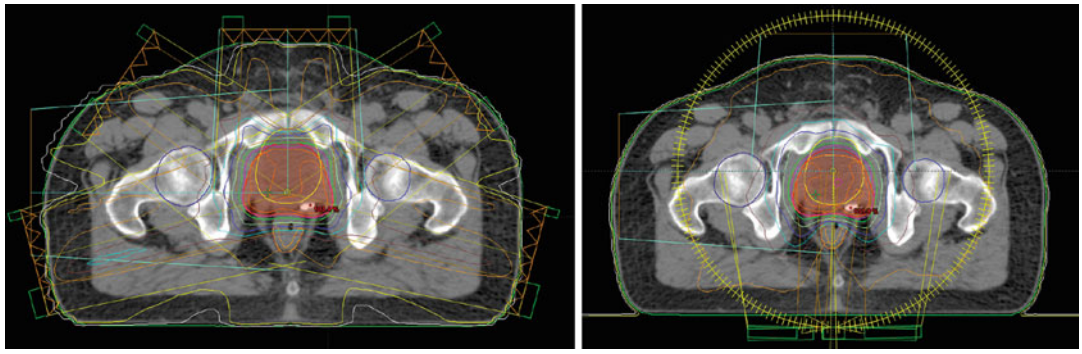

Fig. 14.1 5-Field IMRT treatment plan (*left*) compared with rotational IMRT (*right*) for prostatic bed irradiation

of a 5-field IMRT and a rotational IMRT (e.g., "Rapid Arc") technique is displayed in Fig. 14.1.

For optimization of the margins needed for delivery of IMRT, IGRT remains a helpful tool. Ost and coworkers from Gent University demonstrated a significant reduction of acute toxicity using patient positioning with cone beam CT (Ost et al. 2011a). Sandhu et al. from the University of California used IGRT in patients undergoing post-prostatectomy irradiation. Prostate bed localization was done using image guidance based on surgical clips, relative to the reference isocenter on the digitally reconstructed radiographs made during radiation therapy planning. They assumed that surgical clips are a useful surrogate for the prostate bed and measured daily shifts of the position of the surgical clips in 3 dimensions. With an average (standard deviation) prostate bed motion in anterior-posterior, superior-inferior, and left-right directions of 2.7 mm (2.1), 2.4 mm (2.1), and 1.0 mm (1.7), the majority of the patients experienced only grade 1 side effects. They recommended daily IGRT for accurate target localization (Sandhu et al. 2008). However, the most efficient approach for IGRT during the 6–8 weeks of irradiation remains controversial (Kupelian et al. 2006; Schiffner et al. 2007).

When indicated, like in patients at a high risk for lymph node involvement or confirmed pelvic lymph node involvement, the pelvic lymphatics should be irradiated (Heidenreich et al. 2011; Wenz et al. 2010). For this case, the recommendations from the RTOG, published by Lawton et al. following a consensus reached by a group of specialized uro-oncologic radiation oncologists, can be used (Lawton et al. 2009). The typical dose recommended for pelvic irradiation is 1.8 Gy per fraction up to a total dose of 45–50.4 Gy. The value of IMRT for irradiation of the pelvic lymphatics has been proven by reducing acute and late gastrointestinal and genitourinary toxicity (Lawton et al. 2009; Alongi et al. 2009).

14.5 Side Effects and Toxicity

The three randomized clinical trials discussed above included prospective collection of data on gastrointestinal or genitourinary toxicity in the two cohorts (ART vs. observation). However, it should be mentioned that in the EORTC and SWOG trials, radiation was based on 2D treatment planning which did not enable to significant normal tissue sparing. In contrast, modern 3D-based radiation treatment techniques such as IMRT allow for minimization of dose to the rectum and bladder.

In the SWOG 8794 study, 3.3% of postoperative irradiated patients developed grade 3 or higher adverse events such as rectal bleeding or proctitis as compared to 0% of patients in the observation group ($P = 0.002$). The incidence of urethral strictures was significantly higher in the immediate postoperative RT group (17.8% vs. 9.5%, RR 1.9, $P = 0.02$). Total urinary incontinence occurred in 6.5% of men in the RT group as compared to 2.8% of men in the observation group (RR 2.3, $P = 0.11$) (Thompson et al. 2006).

In the EORTC trial, there was no significant difference in high-grade (grade 3 or higher) toxicity between both arms, ART, and observation. At 5 years, the cumulative incidence of late grade 3 events was 4.3% versus 2.6% ($P=0.0726$). Though, in the ART cohort all late grade 2 and 3 toxicity events combined were more prominent ($P=0.0005$). Unlike the SWOG trial, the EORTC trial did not assess total urinary incontinence; however, in an interim analysis, there was no significant difference concerning urinary incontinence between the two treatment arms (Bolla et al. 2005).

In the German study, which utilized 3D-based radiation treatment planning, the incidence of late grade 3 or higher adverse events was only 0.3% (Wiegel et al. 2009a). One patient developed a urethral stricture in the observation arm compared to two patients in the ART arm. Urinary incontinence was not assessed in this trial.

In the EORTC study, 100 randomized patients were evaluated concerning the continence situation. There was no difference in the number of fully continent patients after 24 months between the group receiving 60 Gy and the group under observation (Van Cangh et al. 1998).

SRT with a dose of 66.6 Gy is generally associated with a low rate of severe acute and late side effects. Urinary incontinence in 0–5% of the cases, moderate proctitis in 0–10%, and mild to moderate cystitis in up to 10% may result from this procedure (Stephenson et al. 2004; Neuhof et al. 2007; Do et al. 1998). Severe late effects are rare events affecting 3–6% or fewer of the patients (Do et al. 1998). In our study, SRT was well tolerated, with only a few severe effects: Only 4 patients (2.4%) had grade 3 cystitis, and 4 of 162 patients (2.4%) had urethral strictures after SRT after radical prostatectomy (Wiegel et al. 2009b).

A low rate of side effects is of particular importance for a therapy without histologic confirmation. As literature data attest, doses up to 66 Gy given in the frame of three-dimensional RT treatment planning are rarely associated with serious long-term side effects (grade 3/4 according to the RTOG-EORTC grading system) involving the rectum and bladder. Although in general, side effects tend to be underreported in retrospective analyses, a proportion of <3% seems to be a realistic estimate. Fairly higher rates of 10% genitourinary grade 3 complications, namely anastomotic strictures and bladder neck contractures requiring dilatation, reported in a series of 115 patients from the Memorial Sloan-Kettering Cancer Center, need to be interpreted with caution (Katz et al. 2003). It may be difficult to differentiate side effects of RT from preexisting disabilities and sequelae of RP. At least equivalent rates of severe genitourinary complications following RP alone have been reported in a SEER database analysis of 11,522 patients published by the same institution (Begg et al. 2002). Formenti et al. investigated the rate and degree of incontinence and erectile dysfunction after nerve-sparing RP with or without adjuvant RT. Unfortunately, follow-up examinations only comprised a questionnaire with inherent weaknesses. No difference was found between 72 patients who underwent both RP and RT and 138 patients who underwent RP only when total doses of 45–54 Gy were applied (Formenti et al. 1996).

14.6 Adjuvant Versus Salvage Radiation Therapy

Multiple prospective and retrospective studies dealt with the clinical question whether adjuvant radiation therapy or salvage radiation therapy is preferable in terms of local control and freedom from biochemical failure (FFBF) (Thompson et al. 2006; Bolla et al. 2005; Wiegel et al. 2009a, b; Stephenson et al. 2007; Neuhof et al. 2007; Trock et al. 2008; Loeb et al. 2008; Bernard et al. 2010; Siegmann et al. 2011; King and Kapp 2008). A consistently higher improvement in local control and FFBF has been observed in adjuvant radiation therapy compared with salvage radiation therapy patients. The 5-year FFBF rates are approximately 69–89% after adjuvant radiation therapy. Local control is 96–100% after adjuvant radiation therapy and 79–93% after salvage radiation therapy (Bottke et al. 2007). Recently, Trabulsi and colleagues studied a group of patients undergoing adjuvant radiation therapy with a matched control group undergoing salvage radiation therapy after biochemical failure. Using a multi-institutional database of

2,299 patients, 449 patients with pT3–4 N0 disease were eligible, including 211 patients receiving adjuvant radiation therapy and 238 patients receiving salvage radiation therapy. Adjuvant radiation therapy significantly reduced the risk of long-term biochemical progression after radical prostatectomy compared with salvage radiation therapy (5-year FFBF was 73% after adjuvant radiation therapy compared with 50% after salvage radiation therapy; $P = 0.007$). Gleason score 8 was a significant predictor of FFBF (Trabulsi et al. 2008). These results were confirmed by others (Budiharto et al. 2010), but Ost et al. reported a better outcome after salvage radiation therapy compared with after adjuvant radiation therapy (Ost et al. 2011c). For all of these reasons, the best choice for treatment (adjuvant radiation therapy vs. salvage radiation therapy) has to be discussed individually with each patient, taking into account the possible risk for overtreatment with immediate postoperative irradiation.

In 2007, a prospective randomized study was initiated to address this question as well as the potential role of concomitant androgen deprivation (Parker et al. 2007). The RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery) trial is an effort to evaluate adjuvant versus salvage radiation therapy. Patients are randomized after surgery to early or delayed radiation. Delayed radiation will be given when there are either two consecutive PSA rises and a final PSA > 0.1 ng/ml or three consecutive PSA rises. The planned accrual is 2,600 patients with cause-specific survival being the primary outcome. There is a second randomization regarding androgen deprivation therapy.

14.7 Conclusions

Adjuvant radiation therapy (ART) provides improved biochemical relapse-free survival and, potentially, overall survival for patients at high-risk following prostatectomy compared to observation. Therefore, ART is really indicated for selected patients. However, it remains unknown if early salvage radiation therapy (SRT) initiated after a PSA failure is equivalent to ART. At the present time, there are no published randomized trials to compare ART versus SRT. When SRT is indicated, it should be initiated as early as possible (with PSA < 0.5 ng/ml). In this situation, SRT is the only curative therapy option.

Modern radiation therapy techniques like IMRT and IGRT should be used. Serious side effects are apparently low, thus confirming the suitability of this therapeutic approach. The role of AD after adjuvant or salvage RT remains poorly defined. But in the RTOG 96-01 trial, the addition of 24 months of peripheral androgen blockade during and after RT significantly improved freedom from PSA progression and reduced the incidence of metastatic prostate cancer. The analysis of risk-stratified subsets must await longer follow-up.

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High-Intensity Focused Ultrasound (HIFU) for Prostate Cancer

15

Albert Gelet, Sebastien Crouzet, Olivier Rouviere, and Jean-Yves Chapelon

Contents

A. Gelet, M.D. (✉) • S. Crouzet
Department of Urology and Transplantation, Edouard Herriot Hospital, 5 place d'Arsonval, 69437, Cedex 03, Lyon, France and
Therapeutic Ultrasound Research Laboratory, Université de Lyon, Inserm, U1032, Lyon, F-69003, France
e-mail: albert.gelet@chu-lyon.fr

O. Rouviere
Therapeutic Ultrasound Research Laboratory, Université de Lyon, Inserm, U1032, Lyon, F-69003, France and
Department of Radiology, Edouard Herriot Hospital, Lyon, France

J.-Y. Chapelon
Therapeutic Ultrasound Research Laboratory, Université de Lyon, Inserm, U1032, Lyon, F-69003, France

15.1 Introduction

The incidence of prostate cancer is increasing worldwide. In Europe, the mortality rate declined from 15 per 100,000 in 1995 to 12.5 per 100,000 in 2006 (Bosetti et al. 2011). This decline of mortality can be attributed to two factors: Firstly, since the use of screening with prostate-specific antigen, 70% of these newly diagnosed prostate cancers are organ-confined and therefore suitable for a local, potentially curative therapy; secondly, better control of the disease was secured from a

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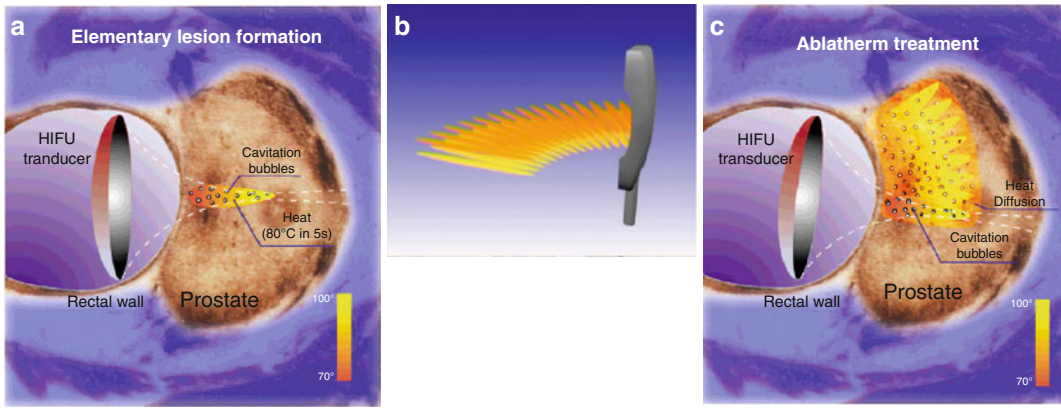


Fig. 15.1 To treat the prostate, the HIFU transducer is previously covered with a balloon filled with coupling liquid. Then, it is inserted into the patient's rectum and positioned close to the rectum wall in such a way that the base of the lesion will stop close to the prostate capsula (**a**). This precise positioning prevents from any rectal wall damage. Prostate treatment is performed by the repetition and juxtaposition of several elementary lesions (**b**). The sum of these elementary lesions creates a continuous volume where tissue is entire destroyed (**c**)

main sonication parameters are acoustic intensity, duration of exposure, on/off ratio, the distance between two elementary lesions, and the displacement path when multiple lesions are made. This technique has the advantage of a transrectal treatment with prostate destruction while sparing the rectum itself. By combining a precise control of the position of the transducer within the rectum and an active cooling of the rectal mucosa, the risk of rectal injury is minimized. HIFU induced-lesions are visible using standard ultrasound as hyperechoic areas, but their extent is not always accurately defined. MRI is the gold-standard technique used for HIFU treatment efficacy assessment. Gadolinium-enhanced T1-weighted images can show very clearly the extent of necrosis (Rouviere et al. 2001). MRI has also been used to guide HIFU treatment as well as to monitor temperature changes during HIFU, but it must be noted that this technology is experimental for transrectal prostate cancer treatment.

15.4 Prostate Modern Imaging: A Critical Key for Improving HIFU Outcomes

Imaging plays a critical role in the management of patients treated with HIFU ablation (Rouviere et al. 2007). Recent progress in modern imaging should improve the outcome of HIFU ablation in the near future. However, additional improvement is still needed at least in three different fields: patient selection and treatment planning, assessment of HIFU ablation in the operating room, and detection of local recurrences.

15.4.1 Patient Selection and Treatment Planning: The Need for a Better Prostate Cancer Mapping

A precise knowledge of the size and location of tumor foci could improve treatment outcome by identifying poor candidates for HIFU ablation (e.g., patients with anterior tumors that might be beyond the focal point of the transducer, or apical tumors close to the urethral sphincter). It could also allow better targeting of the treatment (e.g., the operator could slightly extend the treated volume into the periprostatic tissue around the tumors in order to treat potential microscopic extracapsular extensions).

The need for a precise preoperative mapping of tumor foci is even more important in the perspective of focal HIFU ablation, the success of which will depend not only on the accurate localization of the tumor targets but also on the correct identification of sectors free of cancer.

Unfortunately, for many years, prostate imaging has yielded suboptimal results in prostate cancer detection and localization, and the results

wider adoption of radical prostatectomies and the use of combines androgen deprivation and radiotherapy for patients with locally advanced disease. But the morbidity associated with the radical treatment of either surgery or radiotherapy is significant, suggesting that radical surgery and/or radiation therapy should only be offered to men who are likely to survive more than 10 years. In the randomized study radical prostatectomy versus watchful waiting of the Scandinavian prostate Cancer Group Study, the incidence of death from prostate at 15 years was 14.6 in the surgery group as opposed to 20.7 in the watchful waiting group (Bill-Axelson et al. 2011). However, among men 65 years or older, there was no significant reduction of deaths or metastatic incidences. Albertsten et al. recently reported the Impact of Comorbidity on Survival Among Men With Localized Prostate Cancer. The results suggest that relatively few men diagnosed with moderately differentiated localized prostate cancer older than 65 years will die as a result of prostate cancer within 10 years of diagnosis (Albertsen et al. 2011). Most men with either no comorbidity or only one will survive at least 10 years, whereas men with two or more comorbidities have a high risk of dying as a result of a competing medical hazard within this time frame. Thus, the quest continues for a reliable alternative to open surgery or radiation therapy and one whose chief objective is to find a procedure as minimally invasive as possible.

Klotz et al. published the results of a large series of patients treated with active surveillance (watchful waiting protocol with selective delayed intervention) in 2010 (Klotz et al. 2010a). Focal therapy is an alternative to active surveillance of low-risk prostate cancer with the aim of achieving local control of the cancer without the associated morbidity of radical therapies: HIFU is also a very promising technology for focal therapy of prostate cancer.

15.2 HIFU in Prostate Cancers Models and First Clinical Trials

The first description of HIFU was made in 1942 and the ability to destroy tissue established in 1944 (Lynn et al. 1942; Lynn and Putnam 1944). In 1992, Chapelon et al. established the ultrasound parameters required to induce irreversible tissue lesions in animals. With the experimental adenocarcinoma of a prostate implanted in rats (R 3327 AT2 Dunning tumor), they demonstrated that HIFU could be used to ablate the tumor and cure cancer without causing metastasis (Chapelon et al. 1992). In 1993, Gelet et al. established that it was possible to induce irreversible coagulation necrosis lesions in dog's prostates through a transrectal route without damaging the rectal wall (Gelet et al. 1993a). An ethics committee approved the evaluation of the use of HIFU for the treatment of localized prostate cancer in humans. The results of a pilot study were published in 1996 and the preliminary results of the first 50 patients in 1999 (Gelet et al. 1996, 1999).

15.3 Principles

HIFU produces ultrasound waves that are generated by a spherical transducer. The ultrasound energy is focused on a fixed point. The first experiments on the prostate were made on dogs and on men with benign prostate hypertrophy (Gelet et al. 1993a, b; Madersbacher et al. 1993). Ultrasound waves deposit energy as they travel through tissues. For imaging purposes, this deposited energy is insignificant. By increasing the intensity of the waves and focusing them on a single point, HIFU allows the deposit of a large amount of energy into the tissue, resulting in its destruction through cellular disruption and coagulative necrosis (Beerlage et al. 1999). There are two mechanisms involved in the destruction of the tissue: thermal effects and cavitation (Kennedy et al. 2003). The thermal effect relies on the absorption of ultrasound energy by the tissue and its conversion into heat. In the right conditions, the temperature within sonicated tissue will rise to a level sufficient to induce irreversible damage. Cavitation is the result of the interaction between ultrasound and microbubbles in the sonicated tissue. This interaction may lead to oscillation of these microbubbles, violent collapses, and dispersion of energy, enhancing tissue ablation. The aim is to treat the entire gland by a juxtaposition of elementary lesions (Fig. 15.1). The

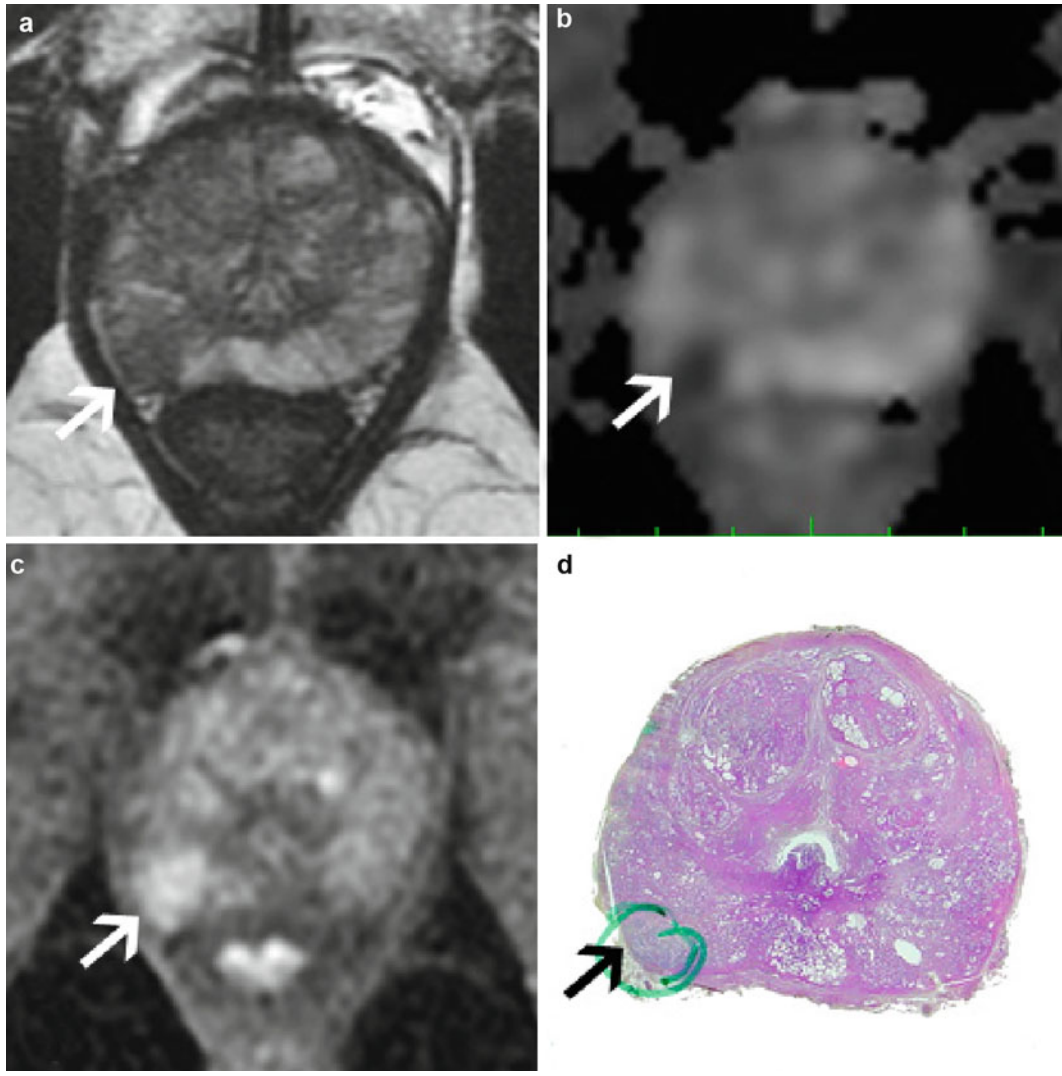


Fig. 15.2 Multiparametric axial MR images (**a** – T2-weighted image; **b –** apparent diffusion coefficient (*ADC*) map computed from diffusion-weighted images (*b* values: 0 and 2,000 s/mm²); **c –** dynamic contrast-enhanced image) and **d –** axial section of the prostatectomy specimen obtained in a 66-year-old patient with a Gleason 8 prostate cancer of the right midgland and base at biopsy. MR images showed a highly suspicious lesion located in the posterolateral part of the peripheral zone of the right midgland, with hyposignal on T2-weighted image (**a**, *arrow*), decreased ADC values (**b**, *arrow*), and early and intense enhancement (**c**, *arrow*). **d –** The analysis of the prostatectomy specimen was confirmative and showed in that area a Gleason 8 cancer. The rest of the gland did not contain cancer

in the US-based techniques have been particularly disappointing (Rouviere et al. 2007).

Nonetheless, excellent results have been recently published with MRI, especially since dynamic contrast-enhanced (DCE) and diffusion-weighted sequences have been used in addition to the classical T2-weighted imaging. There is now a large and concordant body of literature showing that this so-called prostate multiparametric MRI allows a good detection of high-grade prostate cancers (Gleason score ≥ 7), with an excellent negative predictive value, in candidates to radical prostatectomy (Girouin et al. 2007; Villers et al. 2006; Turkbey et al. 2010) but also in the more challenging population of patient candidates for biopsies (Cheikh et al. 2009) (Fig. 15.2). The

detection of anterior tumors, which are usually missed by random biopsies, is also excellent (Lemaitre et al. 2009).

In 2008, we started a database in order to collect information on the precise correlation between MR and pathological specimen findings in patients who received a radical prostatectomy at our institution (CLARA-P database). To date, 127 patients imaged either at 1.5 T ($n=65$) or 3 T ($n=62$) have been included. The MR images were reviewed by 2 independent readers and compared to histological findings. Both readers detected all Gleason ≥8 tumors. The detection rates for Gleason ≤ 6 tumors with a volume of 0.05–0.5, 0.5–2, and >2 cc were 27–37%, 42–51%, and 67–83%, respectively. For Gleason 7 tumors, the detection rates were respectively 61–64%, 80–83%, and 96%. There was no difference between 1.5 T and 3 T results (Bratan et al. 2011).

These results suggest that MRI is an excellent screening tool, with a good negative predictive value, for Gleason ≥ 7 tumors.

MRI does, however, still have some weaknesses that need to be corrected.

First, its sensitivity for Gleason ≤ 6 cancers remains suboptimal, and even when the tumor volume is >0.5 cc. Second, its specificity needs to be improved: approximately 40% of suspicious areas noted in the CLARA-P database were benign. However, the two readers were able to stratify the risk of malignancy by attributing a suspicion score to each suspicious MR abnormalities. Thus, at 1.5 T, 12–37% of score 1 (likely benign), 30–52% of score 2 (indeterminate), 78–82% of score 3 (likely malignant), and 97–100% of score 4 (definitely malignant) abnormal MR areas were cancers. These figures were 5–22%, 22–45%, 45–62%, and 93–96% at 3 T (Bratan et al. 2011). Third, the reproducibility of multiparametric MRI needs to be improved. The good results obtained in specialized university centers are not always reproduced in daily practice. Intensive research is ongoing in order to validate simple suspicion scores aimed at helping nonspecialized radiologists identify abnormal areas seen at MRI. But promising results have also been obtained with computer-aided diagnosis software (Niaf et al. 2011; Puech et al. 2009).

After radiation therapy, MRI, and especially DCE MRI, has also shown promising results in detecting and localizing local recurrences (Rouviere et al. 2004; Haider et al. 2008). It seems that postradiation local recurrences are even easier to localize than untreated prostate cancer because of the favorable contrast between poorly enhancing postradiation fibrosis and recurrent cancer (Fig. 15.3). Besides, MRI also provides prognostic information: In a series of 46 patients with postradiotherapy local recurrences treated with HIFU at our institution, the position of the recurrence anterior to the urethra (as determined by DCE MRI) was shown to be an independent negative predictive factor along with the pre-HIFU PSA value (unpublished results).

15.4.2 Postoperative Evaluation of the Ablated Area

Ideally, imaging should show the amount of prostate volume destroyed at the end of the HIFU ablation session so that in the event of unsatisfactory results, another HIFU ablation can be performed immediately. Unfortunately, transrectal ultrasound, used to guide HIFU treatment, cannot show the ablated area with the necessary accuracy (Rouviere et al. 2007).

Gadolinium-enhanced (nondynamic) MRI clearly reveals the treated volume as a devascularized zone (corresponding to the central core of the coagulation necrosis) surrounded by a peripheral rim of enhancement (corresponding to edema), but MRI cannot be obtained in the operating room (Rouviere et al. 2001; Kirkham et al. 2008).

We have recently shown that contrast-enhanced ultrasound (CEUS), using Sonovue™ as a contrast agent, can show the ablated volume immediately at the end of the treatment with an excellent correlation with MR and biopsy findings. All prostate sectors showing no enhancement at CEUS at the end of HIFU ablation can be safely considered to have been entirely destroyed. On the other hand, prostate sectors showing any degree of enhancement can be considered to contain living (benign or malignant) tissue (Rouvière et al. 2011) (Fig. 15.4). These results should

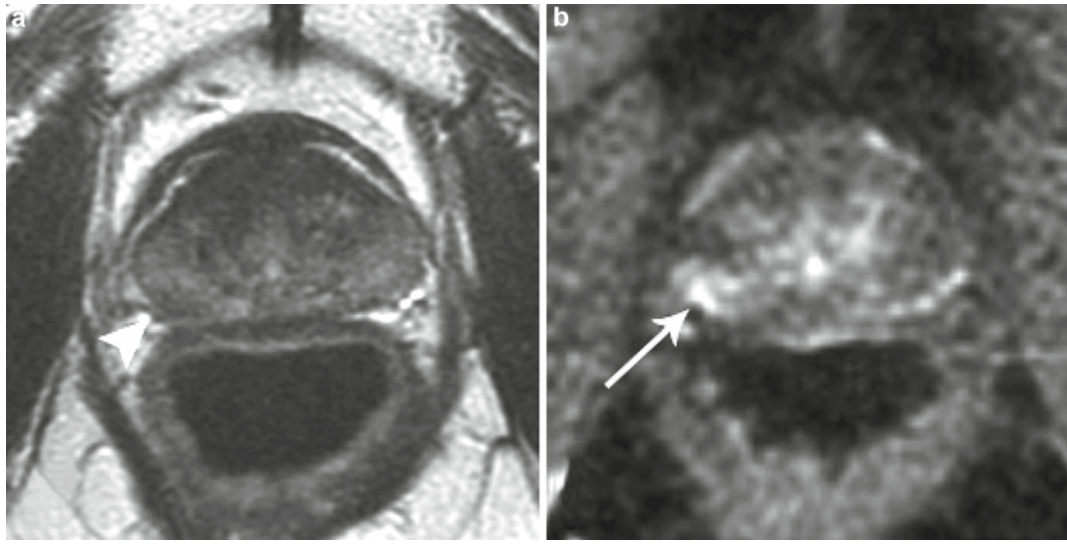


Fig. 15.3 Multiparametric MR images (**a –** T2-weighted image; **b –** dynamic contrast-enhanced image) obtained in a 69-year-old patient with history of radiation therapy for prostate cancer 10 years before. The nadir of the PSA level after radiation therapy was 0.8 ng/ml. The PSA level had slowly increased to 3.21 ng/ml at the time of MRI. MR images showed a suspicious lesion of the right midgland, with mild hyposignal on T2-weighted imaging (**a**, *arrowhead*) and marked enhancement on dynamic imaging (**b**, *arrow*). Biopsy showed Gleason 6 recurrent cancer in the right midgland

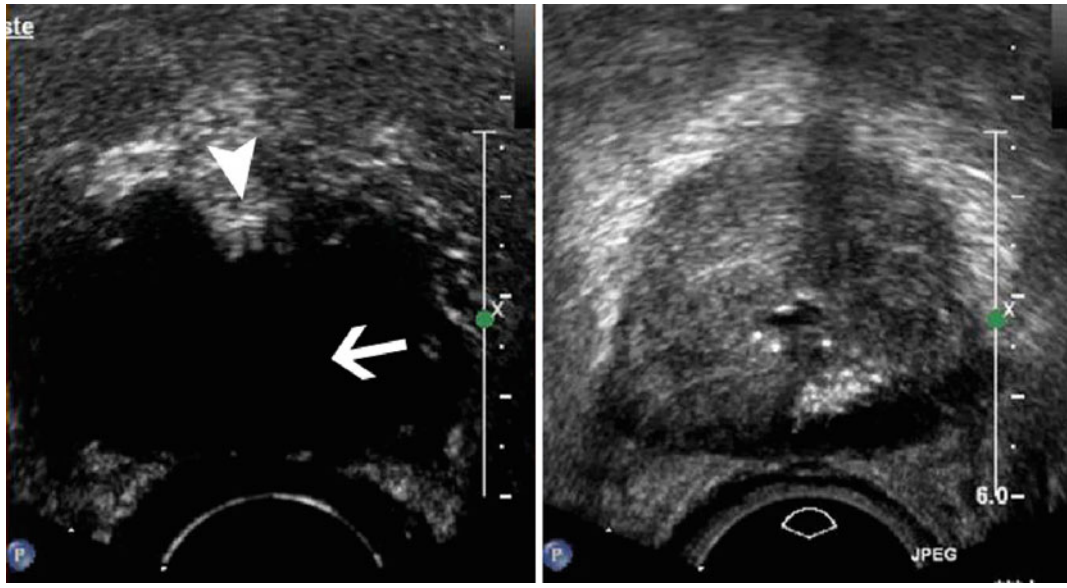


Fig. 15.4 Contrast-enhanced ultrasound (CEUS) axial image (*left part* of the figure), with corresponding low mechanical index gray-scale image (dual mode; *right part* of the figure), obtained after HIFU ablation of a local recurrence of prostate cancer after radiation therapy in a 68-year-old patient. CEUS image showed the nearly complete devascularization of the gland (*large arrow*), with a small strip of anterior and median residual parenchyma that still enhanced (*arrowhead*). Note that tissue destruction is not visible on the gray-scale image

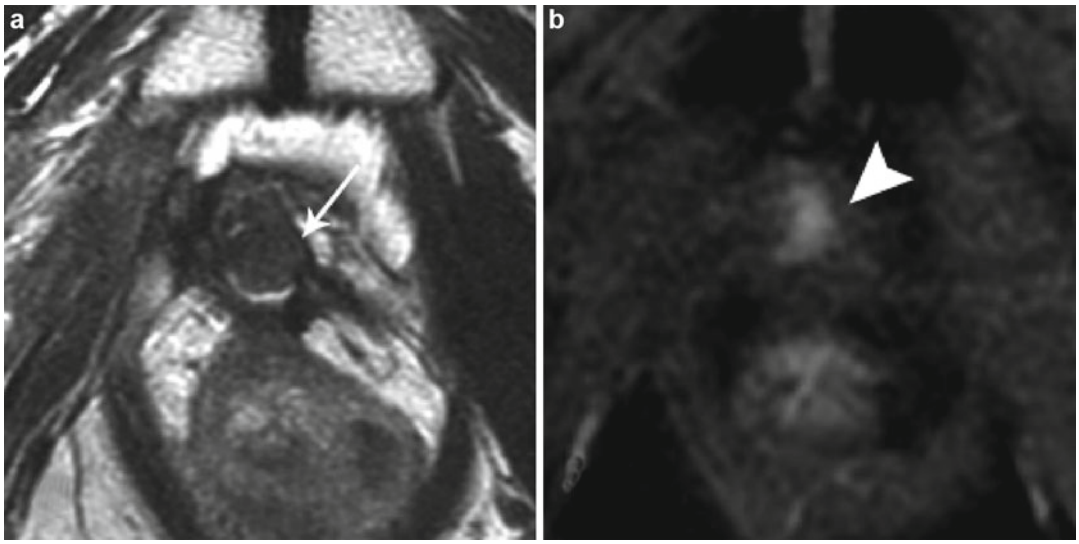


Fig. 15.5 Multiparametric MR images (**a –** T2-weighted image; **b –** dynamic contrast-enhanced image) obtained in a 76-year-old patient with history of HIFU ablation for prostate cancer 5 years before. The nadir of the PSA level after HIFU ablation was 0.03 ng/ml. The PSA level had slowly increased to 1.47 ng/ml at the time of MRI. MR images showed an atrophic residual prostate (approximately 4 cc; **a**, *arrow*) with a marked enhancement of its anterior and central part (**b**, *arrowhead*). Targeted biopsy showed recurrent Gleason 6 cancer in this area

allow immediate re-treatment of the parts of the gland showing residual enhancement and that are within the range of the transducer.

15.4.3 Detection of Post-HIFU Local Recurrences

After HIFU ablation, the residual prostate is composed of scarred fibrosis and benign prostate hyperplastic (BPH) tissue that, because of its anterior position, has not been destroyed.

Because local recurrences (or residual cancers) after HIFU ablation can be treated by a second session of HIFU ablation or by radiation therapy (Pasticier et al. 2008); it is imperative that they be detected early. The precise location of these recurrences can also help in selecting the salvage treatment (e.g., anterior recurrences may be better treated by radiation therapy).

Even if color Doppler can sensitize TRUS (Rouviere et al. 2006), US-based techniques are not accurate enough to detect early local recurrences and guide the biopsy.

MRI, and particularly DCE MRI, seems to provide early detection and accurate localization of recurrent cancers that enhance earlier and more than post-HIFU fibrosis (Ben Cheikh et al. 2008; Rouviere et al. 2010) (Fig. 15.5). However, DCE MRI does lack specificity. It is indeed difficult to distinguish recurrent cancer from residual BPH tissue. In a retrospective study of 65 patients with biochemical recurrence after HIFU ablation performed at our institution, neither the enhancement pattern nor the apparent diffusion coefficient (ADC) was able to significantly distinguish BPH nodules from recurrent cancers, even if the latter had, on average, higher wash-in rates, lower washout rates, and lower ADCs (unpublished results).

Thus, to date, all patients with rising PSA after HIFU ablation should undergo prostate MRI, and all areas with early and intense enhancement should be biopsied to distinguish cancers from BPH residual tissue.

15.4.4 Toward an Increased Integration of Imaging and Therapy

Imaging has become so essential for patient selection, treatment planning and guidance,

Fig. 15.6 Ablatherm® device

assessment of tissue destruction, and detection of local recurrences that it is likely that imaging and therapy will become increasingly integrated in the future.

Two possible technological strategies can be foreseen.

The first one is the development of prostate cancer HIFU ablation under MR guidance. This approach would directly benefit of MR cancer detection/location capabilities. It can also provide real-time temperature monitoring during treatment (Salomir et al. 2006). Contrast-enhanced MRI could immediately assess the volume of tissue ablated, and re-treatment would be quite easy in cases of incomplete tissue destruction. This MR-guided integrated approach is probably the ideal solution, but it will be expensive and will require dedicated scanners.

Another approach, much less expensive, will be to keep the traditional US guidance but after taking into account preoperative MR cancer mapping by using US/MR fusion software. The assessment of the ablated volume at the end of the treatment will be obtained using CEUS, and thus immediate re-treatment will be possible.

It is too early to know which approach will prevail in the future.

15.5 HIFU Devices and Techniques

Two devices are currently available for the treatment of prostate cancer: Sonablate® (Focus surgery Inc., Indianapolis IN, USA) and Ablatherm® (EDAP-TMS SA, Vaulx en Velin, France).

The Ablatherm has both the imaging (7.5 MHz) and therapeutic (3 MHz) transducers included in a unique endorectal probe focused at 40 mm. Ablatherm requires a specific bed with a patient on a lateral position (Fig. 15.6). Lateral position treatment allows gas bubbles produced through the heating of the prostate tissue to rise with gravity to a position lateral to the prostate, which will reduce the risk of acoustic interference with the HIFU waves. The Ablatherm includes three treatment protocols with specifically designed

treatment parameters depending on the clinical use (standard, HIFU re-treatment, and radiation failure). The size of the HIFU-induced lesion can be precisely controlled by adjusting the power and the duration of the ultrasound pulse. The size of the elementary lesion may vary from 19 to 26 mm in length (1.7 mm in diameter). HIFU efficacy was mathematically modeled (Chavrier et al. 2000). This allows the calculation of the optimal acoustic intensity necessary to achieve an irreversible necrosis lesion in several clinical situations, particularly for an irradiated prostate. The last Ablatherm device (integrated imaging) offers a real-time ultrasonic monitoring of the treatment. In the Ablatherm system, the HIFU probe is robotically adjusted with a permanent control of the distance between the transducer and the rectal wall. By repeating the shots and moving the transducer, a precise volume can be treated, defined by the operator (planning phase). The treatment is made in transversal layers (Fig. 15.1). The prostate is usually divided into 4–6 volume boundaries and treated from the apex to the base, slice by slice, by an entirely computer-driven probe. The risk of urethrorectal fistula has been reduced to almost zero thanks to the refinement of the acoustic parameters and many safety features (control of the distance transducer/rectal wall, cooling system, patient motion detector). The standard treatment parameters used 100% of the acoustic power with a 6-s pulse of energy to create each discrete HIFU lesion with a 4-s delay between each shot. For HIFU re-treatment, the shot duration was reduced to 5 s with the acoustic power of 100% and a 4-s delay between each shot. Starting in March 2002, specific postradiation treatment parameters were adopted (5-s pulse, 5-s waiting period, 90% of the acoustic power). These were developed because of the decreased vascularity of the previously irradiated tissue. The goal was to optimize the thermal dose delivered within the gland while minimizing the damage probability to the surrounding tissues, and particularly the rectal wall, caused by the conductive heat transfer. Finally, postbrachytherapy parameters have been developed with 85% of the acoustic powers with 4-s of energy and 5-s waiting period. In contemporary series, the incidence of urethra-rectal fistula was reported between 0% and 0.6% for primary procedures.

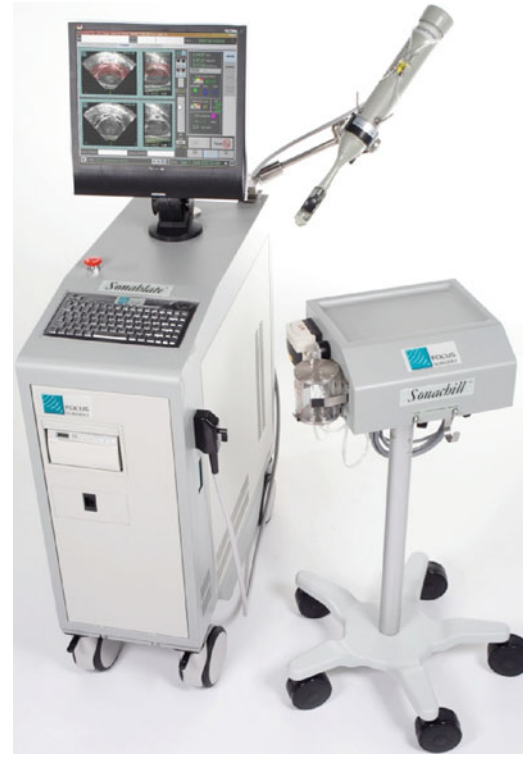


Fig. 15.7 Sonablate® device

The Sonablate uses a single transducer (4 MHz) for both imaging and treatment. Several probes are available with many focal lengths (from 25 to 45 mm) (Fig. 15.7). The size of elementary lesion is 10 mm in length and 2 mm in diameter. The Sonablate procedure is conducted in a dorsal position with a patient lying on a regular operating table. Sonablate uses a single treatment protocol in which the power has to be adapted manually by the operator. The treatment is usually made in three consecutive coronal layers, starting from the anterior part of the prostate and moving to the posterior part, with at least one probe switch during the procedure (Uchida et al. 2006a). The probe chosen depends on the prostate size, with larger glands requiring longer focal length probes.

The size of the prostate is one drawback of HIFU technology: Due to the limitation of the focal lengths of therapy transducers, it is not yet possible to treat a prostate gland greater than 35 cc.

In order to reduce the size of the prostate, and in particular the distance between the rectal wall and the prostate's anterior part, a TURP could be carried out 2 months before the HIFU session. Moreover, the TURP dramatically reduces the catheter duration after the HIFU session (Vallancien et al. 2004; Chaussy and Thuroff 2003; Thuroff and Chaussy 2000) and reduces the risk of bladder outlet obstruction, which is one of the main side effects observed after HIFU. Most of the team performed a TURP at the time of the HIFU treatment in order to reduce the duration of catheterization. The TURP can be performed before the HIFU treatment (Vallancien et al. 2004; Chaussy and Thuroff 2003; Thuroff and Chaussy 2000; Netsch et al. 2010) or after (Sumitomo et al. 2010).

15.6 HIFU Outcomes

In most cases, the PSA nadir was reached 3–4 months after the HIFU treatment and was ≤0.05 ng/ml in 55–91% of the cases. The most commonly reported adverse event was prolonged urinary retention, but this has been dramatically reduced by performing a TURP at the time of the HIFU treatment. The urinary catheter is generally removed at post-op day 2 or 3. Incontinence after HIFU as a primary therapy is low: grade I 4–6% and grade II 0–2%. The rate of incontinence increases in cases of HIFU re-treatment or salvage HIFU. Other infrequently reported side effects are urinary tract infection, urethral stricture, and chronic pain. Urethral rectal fistula has been reported in the early experience but is now a very rare occurrence, particularly when safety margins and contraindications are respected.

The HIFU contraindications included a rectal wall thickness >6 mm, a rectal stenosis, chronic inflammatory disease of the intestines, and intense prostate calcifications not removed by the TURP.

15.7 HIFU as Primary Care Treatment

The recommendations and updated guidelines on the use of HIFU for prostate cancer as a primary treatment concern patients with localized prostate cancer (clinical T1–T2 stage Nx/0 M0 prostate cancer) for whom radical prostatectomies are not an option for one the following reasons: age >70 year old, life expectancy ≤10 years, major comorbidities which preclude surgery etc., or the simple refusal on the part of the patient to undergo one (Rebillard et al. 2003; AURO 2009). Among publications on HIFU as a primary therapy for prostate cancer, 16 studies report a series of at least 50 patients (Uchida et al. 2006a, b, 2009; Crouzet et al. 2010a; Lee et al. 2006; Poissonnier et al. 2007; Ahmed et al. 2009; Blana et al. 2008a, b, 2009; Mearini et al. 2009; Misrai et al. 2008; Ganzer et al. 2008; Thuroff et al. 2003; Chaussy and Thuroff 2001; Gelet et al. 2000), while the others report on fewer patients (Ficarra et al. 2006; Challacombe et al. 2009; Maestroni et al. 2008; Koch et al. 2007). Follow-up varies significantly between series (range: 6 months to 6.4 years). In most cases, the PSA nadir was reached 3–4 months after the HIFU treatment and was = 0.05 ng/ml in 55–91% of the cases. Many studies have demonstrated that the PSA nadir was a significant predictor of HIFU failure. Patients with a PSA nadir over 0.5 ng/ml must be carefully monitored (Lee et al. 2006; Ganzer et al. 2008). A PSA nadir >0.2 ng/ml after HIFU has been associated with a four times greater risk of treatment failure (as defined by cancer on biopsy after HIFU) (Uchida et al. 2006c).

The 7 years disease-free survival rate in the longest follow-up multicenter studies was 75%, 63%, and 62% for low-, intermediate-, and high-risk patients, respectively, and the 8 years cancer-specific survival rate was 99% (Crouzet et al. 2010a). Complication rates are low, with sloughing occurring in 0.3–8.6%. Impotence occurs in 20–77% of patients and bladder outlet obstruction in 12–22%. Incontinence rates reported in a recent study were grade I (4–17.5%) and grade II and III (0–5%) (Chaussy et al. 2005; Crouzet et al. 2011). In our institution, we have recently reviewed the results of 880 patients. Mean age was 70 years. Stratification according to D'Amico's risk group was low, intermediate, and high in 36%, 48%, and 16%, respectively. Median follow-up was 41 months. Median PSA nadir was 0.1 ng/ml. The overall and cancer-specific survival

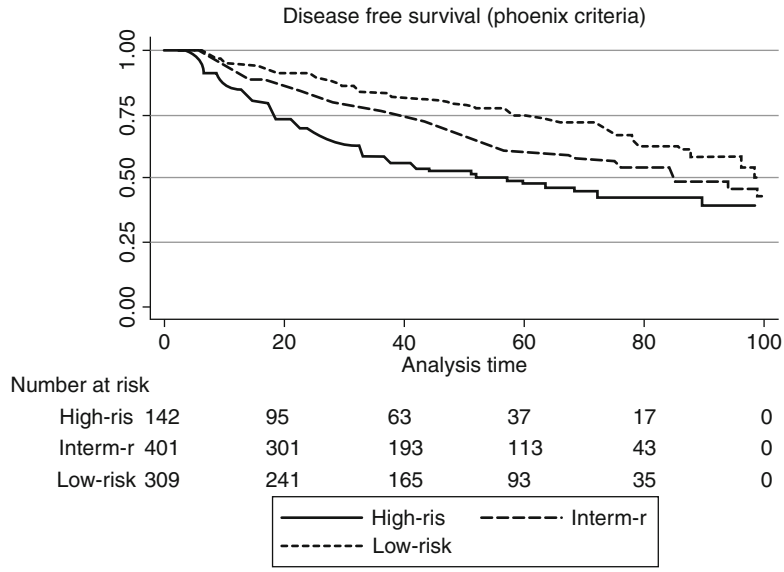


Fig. 15.8 Biochemical survival rates for low-, intermediate-, and high-risk patient after HIFU

rate at 7 years was 90% and 98%, respectively. The metastasis-free survival rate at 7 years was 96%. The 5- and 7-year disease-free survival rates were 75–62%, 59–50%, and 45–39% for low-, intermediate-, and high-risk patients, respectively ($P=0.0001$) (Fig. 15.8) (Crouzet et al. 2010b).

In a study from a prospective database, Shoji et al. included 326 patients who filled self-administered questionnaires on urinary function, QOL, and sexual assessment (Shoji et al. 2010). The FACT G, FACT-prostate, and IIEF 5 were used. Maximum flow rate and residual urine volume were significantly impaired at 6 months ($P=0.010$) after HIFU, even if they returned to baseline values at 12 or 24 months after HIFU. The total FACT-G score significantly improved at 24 months ($P=0.027$) after HIFU. At 6, 12, and 24 months after HIFU, 52%, 63%, and 78%, respectively, of the patients who had not received neoadjuvant hormonal therapy were potent.

In a prospective study, Li et al. compared the IIEF score, penile color Doppler ultrasound, and penile length and circumference on patients treated for prostate cancer with HIFU or cryoablation (Li et al. 2010). A total of 55 patients in the HIFU group and 47 in the cryoablation group were included. At 36 months, cryoablation patients experienced a lower erectile function recovery rate compared to HIFU patients (cryoablation = 46.8%; HIFU = 65.5%; $P=0.021$). No significant decreases in penile length and circumference were found in the two groups (all P values ≥ 0.05).

Finally, HIFU treatment seems to be standardized with similar outcomes between centers (Rebillard et al. 2003).

15.8 HIFU Re-treatment

In case of incomplete treatment or treatment failure, HIFU does not result in a therapeutic impasse. Unlike radiation, there is no dose limitation and no limited number of sessions. The re-treatment rate is estimated in the literature to be between 1.2% and 1.47% (Uchida et al. 2006a; Crouzet et al. 2010a; Thuroff et al. 2003; Blana et al. 2006). The morbidity related to repeat HIFU treatment for localized prostate cancer has been studied on 223 patients with a re-treatment rate of 22%. While urinary infection, bladder outlet obstruction, and chronic pelvic pain did not significantly differ after one or more sessions, a significant increase was observed for urinary incontinence and impotence in the group which required re-treatment (Blana et al. 2006).

15.9 Salvage EBRT After HIFU Failure

EBRT is feasible after HIFU. In a retrospective study, Pasticier et al. included patients treated with salvage radiation after HIFU (Pasticier et al. 2010). A total of 100 patients were included, with a median follow-up of 33 months. Mean doses of radiation were 71.9 ± 2.38 Gys; 83 patients underwent only radiation treatment, and 17 patients underwent radio-hormonal treatment. The mean delay between HIFU and EBRT was 14.9 ± 11.8 months. Mean PSA before salvage EBRT was 2.1 ± 1.8 ng/ml, and the nadir PSA after EBRT was 0.28 ± 0.76 ng/ml, with 17.4 ± 10.8 months to reach nadir. The incontinence rate was the same both before and 1 year after salvage EBRT. The progression-free survival rate was 76.6% at 5 years, and was 93%, 70%, and 57.5% for low-, intermediate-, and high-risk group, respectively. The predicting factors of failure were the PSA nadir after salvage EBRT and the time to reach nadir after EBRT. Recently, similar results were published by Ripert et al. which reported the disease-free survival rate after salvage radiotherapy after HIFU was 83.3% at 36.5 months (Phoenix criteria) and there was no major EBRT-related toxicity at 12 or 24 months (Ripert et al. 2011).

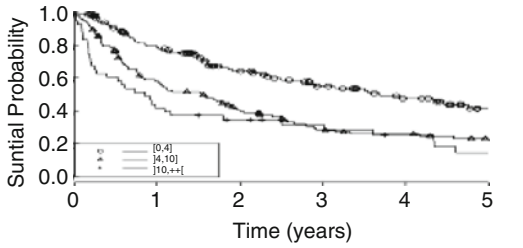
15.10 Salvage Surgery After HIFU Failure

Salvage surgery is feasible after HIFU but with a higher morbidity than after primary surgery. Lawrentschuk et al. reported the results in 15 men with a rising PSA and biopsy-verified prostate cancer after HIFU treatment (Lawrentschuk et al. 2011). Perioperative morbidity was limited to one transfusion in a patient with a rectal injury. Pathological extensive periprostatic fibrosis was found in all patients. Postoperative PSA value was undetectable in 14 patients (93.3%). Six of ten patients experienced no postoperative incontinence at 12 months but with uniformly poor erectile function. Salvage surgery after HIFU is difficult to perform due to fibrotic reaction. In selected patients with a long life expectancy, experienced surgeons alone should perform the salvage surgery after HIFU.

15.11 Salvage HIFU After EBRT or Brachytherapy

15.11.1 EBRT Failure

The rate of positive biopsy after external beam radiotherapy (EBRT) for prostate cancer in the literature is between 25% and 32% (Borghede et al. 1997; Zelefsky et al. 2001). There appears to be a role for salvage HIFU therapy with curative intents for patients with a locally proven recurrence after external beam radiation therapy and no metastasis that are usually treated with androgen deprivation (AD). Local control was achieved with negative biopsies in 73% of the cases, with a median PSA nadir of 0.19 ng/ml (Murat et al. 2009). With a mean follow-up of 18.1 (3–122) months, the overall actual 5-year specific survival rate was 84%. The actual 3-year progression-free survival rate (PSA greater than nadir + 2 ng/ml, positive biopsy, or salvage treatment requirement) was 53%, 43%, and 25%, respectively, for low- and intermediate-risk patients according to D'Amico's risk groups. Disease progression was inversely related to the pre-HIFU PSA and the use of (AD) during PCa management. In a recent study, we examined the outcomes of salvage HIFU in 290 consecutive patients (nonpublished, submitted data). The mean PSA nadir post-HIFU was 1.54 ± 3.38 ng/ml (median 0.14). The estimated cancer-specific and metastasis-free survival rates at 5 and 7 years were 80% (95% CI 72.7–88.5%) and 79.6% (95% CI 73.5–86.2%), respectively. In the multivariate analysis, three factors were significantly linked to disease progression. The increase of the progression-free survival rate (PFSR) with the pre-HIFU PSA level was statistically significant ($P = 0.0002$) (Fig. 15.9). A previous AD treatment increased the PFSR by a factor of 1.3 ($P = 0.01$), and a Gleason score over or equal to 8 increased it by a factor of 1.2 ($P = 0.01$) compared to a Gleason score less than or equal to 6. While the technique offers promising results, it has to be



At risk						
[0,4]	129	90	61	42	29	15
]4,10]	119	63	39	24	20	14
]10,++[	40	18	13	10	7	4
Events						
]0,4]	-	25	40	48	53	56
]4,10]	-	48	67	77	79	81
]10,++[	-	25	20	29	31	34

Fig. 15.9 Progression-free survival rate according to the pre-HIFU PSA value

weighed against the side effects. Since 2002, the Ablatherm® device included specific acoustic parameters for salvage HIFU. The acoustic dose was adapted to the low blood flow inside the gland fibrosis induced by radiation. For incontinence, 54% of the patients had no incontinence after salvage HIFU, and 25% had a grade I incontinence (no pads + grade I = 79%). The risk of URF was only 0.4% with the introduction of a specific treatment algorithm designed for radiation failure. The impotence rate increased from 36.9% before salvage HIFU to 58.7% after treatment (Berge et al. 2010). With the Sonablate, the biochemical survival rate was 71% at 9 months (Zacharakis et al. 2008) and 52% at 5 years (Uchida et al. 2010).Nevertheless, the risk–benefit ratio of salvage HIFU compares favorably with those of the other available techniques and with less morbidity and similar oncological outcomes. In this context, HIFU appears to be an effective curative treatment option for local recurrence after radiation failure.

15.11.2 Brachytherapy Failure

Sylvester et al. reported 15-year biochemical relapse-free survival rate and cause-specific survival following I (125) prostate brachytherapy in 215 patients: 15 years BRFS for the entire cohort was 80.4%, and the cancer-specific survival rate was 84% (Sylvester et al. 2011). There was no significant difference between the low- and intermediate-risk group. Salvage surgery is a challenging procedure after Brachytherapy (Heidenreich et al. 2010). A study with the Ablatherm® device is being conducted presently in Lyon which includes 26 patients (mean age 67 years) with MRI and biopsy-proven recurrence after brachytherapy (nonpublished data). Nineteen of them underwent a whole gland ablation, and 7 underwent a focal therapy (hemiablation). The mean follow-up was 19 months. The mean PSA before HIFU was 5.02 ± 4.8 ng/ml (median PSA 0.35ngml). Nine patients have undetectable PSA with no hormonal deprivation treatment; 8 needed hormonal deprivation treatment for a rising PSA, and 9 are recent cases with a very short follow-up. The complication rate was high in the first nine cases with three urinary incontinences (grade 3) and one urethrorectal fistula. For those first patients, we used the treatment acoustic parameters defined for radiation failure. Because of the high rates of rectal injury and sever incontinence, new specifically designed treatment parameters for brachytherapy failure were developed, with a decrease in the acoustic dose according to the intense prostate fibrosis. Since the introduction of those new parameters, no urethrorectal fistula occurred, and no rectal lesion was seen on control MRI and without any reduction of the treatment's efficacy.

15.12 Focal Therapy

HIFU focal therapy is another pathway that must be explored when considering the accuracy and reliability for PCa mapping techniques. HIFU would be particularly suitable for such a therapy since it is clear that HIFU results and toxicity are relative to treated prostate volume.

15.12.1 Focal Therapy as Primary Care Treatment

The ERSPC trial indicates that we need to treat 48 men for prostate cancer in order to save one

life. Active surveillance has been adopted as an option for men who have a low-risk prostate cancer. The advantages of active surveillance must be weighed against the very real possibility of missing the "window" to cure some cancers because of delayed treatment. In the Canadian trial, overall, 30% of patients have been reclassified as higher risk and have been offered definitive therapy (Klotz et al. 2010b). Of 117 patients treated radically, the PSA failure rate was 50%, which was 13% of the total cohort. As is the case with breast cancer and kidney cancer, improvements in screening meant that many men with early-stage prostate cancer are amenable to organ-sparing procedures. Focal therapy is emerging as an alternative to active surveillance in the management of low risk, low grade, and selected patients. In patient candidates for active surveillance, the risk of extracapsular extension was found to range from 7% to 19% and seminal vesicle invasion ranged from 2% to 9%, depending on the inclusion of patients with Gleason 7 disease (Conti et al. 2009). Mouraviev et al. identified unilateral cancers in 19.5% of 1,186 radical prostatectomy specimens (Mouraviev et al. 2007). This study suggests that almost 20% of the patients who are candidates for radical surgery could be amenable to hemiablation using thermal therapy targeting one lobe of prostate. A careful selection of patients is needed. The literature showed a direct correlation between the Gleason score and the outcomes after radical surgery (Blute et al. 2001). Stamey et al. demonstrated that tumor volume was associated with biochemical relapse: Recurrence occurs in only 14% of men with a tumor volume of less than 2.0 ml (Stamey et al. 1999). Focal therapy (hemiablation) must be used only in carefully selected patients (Gleason 6, small unilateral cancer foci) included in prospective trials. The main problem is to identify appropriate patients using MRI and biopsies (transrectal or transperineal). Accurate characterization of the spatial distribution of cancer foci within the gland will be the key to the success of focal therapy. The concept of an index tumor does, however, potentially allow for the use of focal therapy on patients with bilateral tumors. Some evidence exists which shows that the largest tumor (the index lesion) is the main driver of progression, outcome, and prognosis; small secondary cancers might be clinically irrelevant (Wise et al. 2002; Noguchi et al. 2003). Focal therapy can be performed using several techniques: cryotherapy, HIFU, brachytherapy, and interstitial laser therapy with or without photodynamic therapy (PDT). HIFU might be one of the best techniques for focal therapy because it is performed under real-time control using ultrasound or MRI. An immediate control of the boundaries of the necrosis area is possible using contrast agents (either with ultrasound and MRI). HIFU procedures can also be repeated if necessary. Finally, salvage standard curative therapies are feasible after HIFU (EBRT, surgery, or cryoablation).

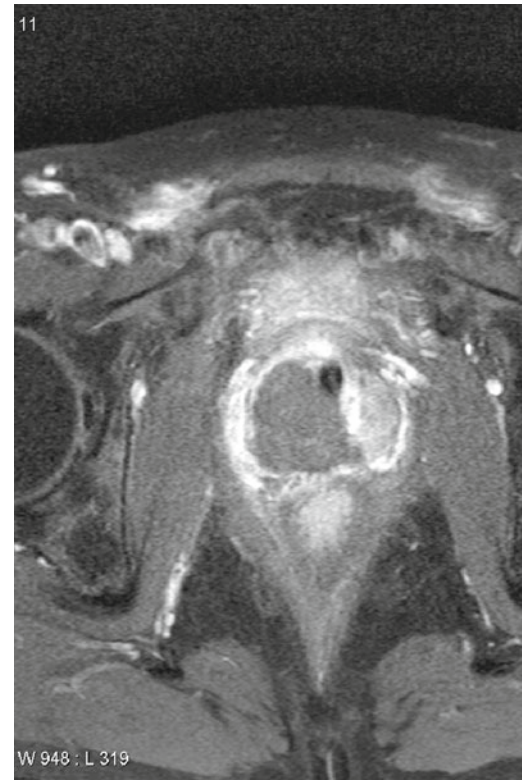
In 2008, Muto et al. reported the outcomes of 29 patients treated with Sonablate™ device (Muto et al. 2008). In selected patients whose cancer was confined to only one lobe by multiregional biopsies, the total peripheral zone and a half portion of the transitional zone were ablated. The prostate volume decreased from 35.8 c to 30.3 cc, and the PSA level decreased from 5.36 ± 5.89 ng/ml to 1.52 ± 0.92 at 36 months. Twenty-eight patients underwent control biopsies 6 months after the procedure: A residual cancer foci was found in 3 patients (10.7%). Seventeen patients underwent control biopsies 12 months after the procedure: A residual cancer foci was found in four patients (23.5%); only one patient had a urethral stricture. No significant differences were noted in the 2-year disease-free survival rates for low- and intermediate-risk patient treated with between whole (90.9% and 49.9%, respectively) and focal therapy (83.3% and 53.6%, respectively). The period of the indwelling urethral catheter after HIFU session was 15 ± 4 days. The frequency of urethral stricture and symptomatic tract infection was 4% in both cases. No significant change was found on IPSS score and maximal flow rate before and 12 months after the procedure. No information was provided about the potency.

More recently, a short series of prostate hemiablation with HIFU was published (Ahmed et al. 2011). Inclusion criteria were men with

low-moderate risk (Gleason = 7, PSA = 15 μg/ml), unilateral PCa (=T2bN0M0) on TRUS biopsy, and underwent multisequence MRI (T2, DCE, diffusion) and 5 mm-spaced transperineal template biopsies to localize disease. All were treated using transrectal HIFU incorporating the entire positive hemiprostate up to urethra. A total of 20 patients (mean age 60.4 years) were treated. Of the men, 25% had low-risk and 75% intermediate-risk cancer. The mean PSA pre-HIFU was 7.3 ng/ml. Ninety-five percent were pad free. An erection sufficient for penetrative sex occurred in 95% of the patients. Mean PSA decreased to 1.5 ng/ml ± 1.3 at 12 months. A total of 89% of the patients had no histological evidence of any cancer. Two patients (11.1%) had positive protocol biopsy at 6 months, with residual 1-mm Gleason 3 + 3: one elected for re-treatment and the other active surveillance. Eighty-nine percent achieved the trifecta status.

The French Urological Association (AFU) has started a multi-institutional study to evaluate hemiablation with HIFU as a primary treatment for patients >50 years, T1C or T2A, PSA < 10 ng/ml, Gleason 6, and with no more than 2 contiguous biopsies in no more than one lobe after MRI and random and targeted biopsies. To be included the tumor must be >6 mm from apex and >5 mm from the midline. Only one prostatic lobe is treated (Picture 15.1). The study is in progress.

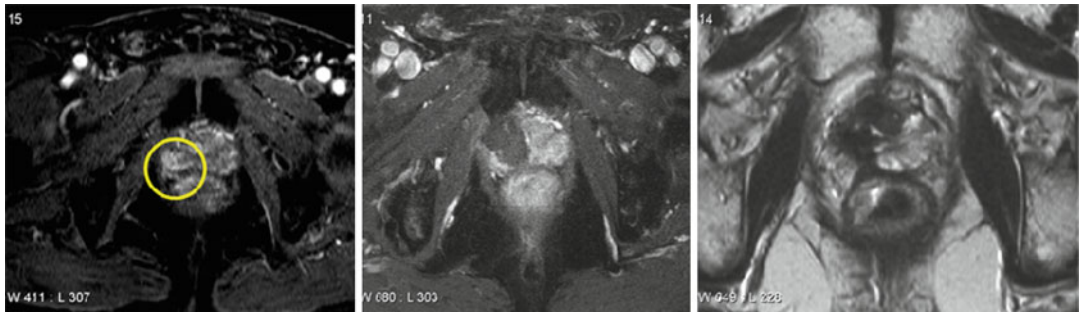
Exciting developments are pending that will make HIFU an even more effective treatment option for focal therapy: Dynamic focusing using annular or phase array transducers will create HIFU lesions able to precisely follow the shape of the targeted cancer foci. The key point will be to achieve an accurate mapping of the cancer foci.



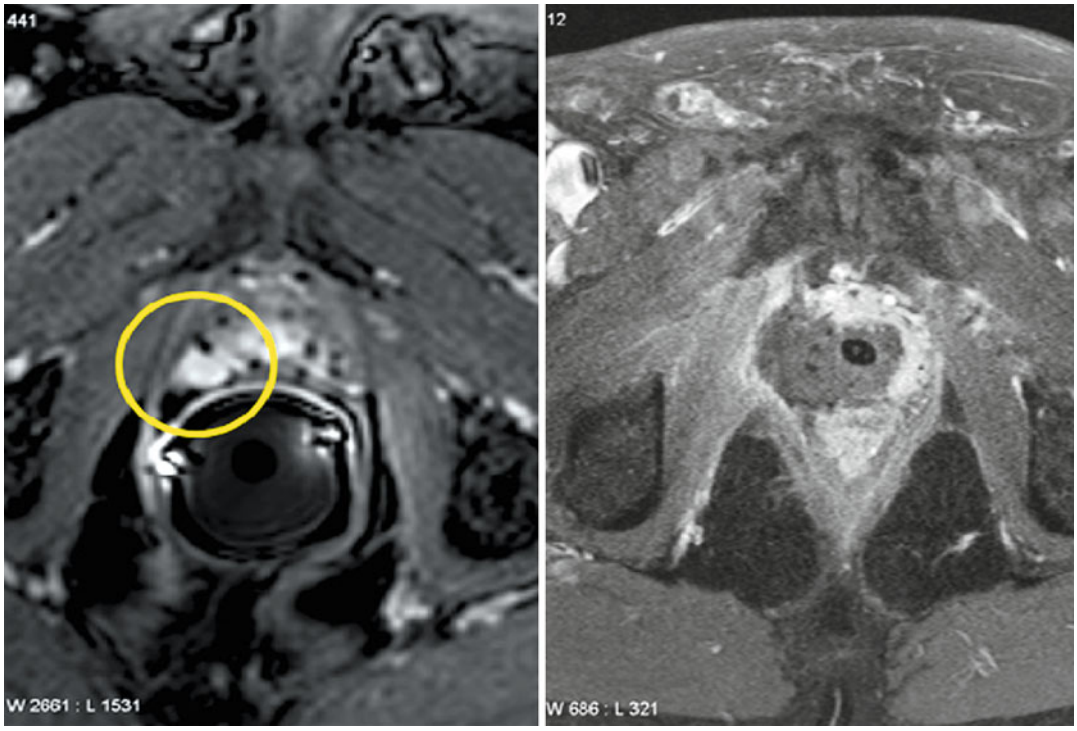
Picture 15.1 Hemiablation as primary treatment

15.12.2 Focal Therapy as Salvage Treatment (Focal Salvage HIFU)

Early identification of a local relapse after radiation therapy failure is feasible using MRI and targeted biopsies performed soon after the biochemical failure (Phoenix criteria). Focal salvage HIFU is a new therapeutic option. The aim of focal salvage HIFU (FSH) is to destroy the recurrent cancer with a minimal risk of severe side effects. A study designed for EBRT failure with MRI and biopsy-verified unilateral local recurrence is currently being conducted in Lyon (AFU 2011). Only one prostatic lobe is treated. Systematic control MRI is performed one week and one year after the HIFU session (Picture 15.2). All patients underwent control biopsies at least 12 months after the procedure. Twenty-one patients were included (mean age 65 years). The mean PSA value falls from 3.06 to 0.34 ng/ml after FSH. Control biopsies were negatives in the treated lobe in 9 of 10 patients who underwent biopsies. Severe incontinence only occurred in one patient. FSH seems to offer similar results with the other focal thermal therapy options. Eisenberg et al. reported the results of partial salvage cryoablation (Eisenberg and Shinohara 2008). Nineteen patients were included. The BFSR (ASTRO) at 3 years was



Picture 15.2 Focal salvage HIFU after EBRT



Picture 15.3 Focal salvage HIFU after brachytherapy

50%. Complications included incontinence (1), urethral stricture (1), and urethral ulcer (1). In patients with unilateral relapse after EBRT, focal therapy with HIFU or cryotherapy can achieve a local control of the disease with minimal morbidity. This focal salvage treatment can also be used for brachytherapy failure (Picture 15.3, Uchida et al. 2010). The results are promising, but longer follow-up is required.

15.13 Androgen Deprivation and Chemotherapy Associated with HIFU for High-Risk Prostate Cancer

15.13.1 Androgen Deprivation

Promising preliminary results on HIFU and hormonal deprivation in patients with locally advanced disease and/or high-risk PCa have been

published (Ficarra et al. 2006). At 12 months after the procedure, 28 patients (93%) were continent. Seven of the thirty men (23%) had a positive prostate biopsy. At the 1-year follow-up, only 3 of the 30 patients with high-risk prostate cancer had a PSA level of >0.3 ng/ml.

15.13.2 Chemotherapy

Experimental studies have demonstrated the potential of chemotherapy associated with HIFU. Paparel et al. evaluated in a rat model the therapeutic effect of HIFU combined with docetaxel on AT2 Dunning adenocarcinoma (Paparel et al. 2005, 2008). They showed a synergistic inhibitory effect of the HIFU + docetaxel association.

In an ethical-committee approved study, 24 high-risk patients (Gleason≥4+3 and/or PSA > 15 ng/ml and/or >2/3 of positive biopsy) underwent HIFU associated with docetaxel. Chemotherapy was delivered 30 min before the HIFU treatment. The protocol included a dose escalation starting at 30 mg/ml. Fifteen patients received 30 mg/m^2 of docetaxel with no adverse effects; two patients received 50 mg/m^2 with one febrile neutropenia and one transient alopecia grade 1, and seven patients received 40 ml/m^2 with adverse effects. The follow up was 15.8 ±9.9 months. A complete response with undetectable PSA was observed in 13 patients (54%). An AD was used in seven cases for rising PSA. The results for four patients are too early to be conclusive.

15.14 MRI-Guided HIFU

15.14.1 Principle

Magnetic resonance imaging (MRI) is an imaging technique based on the magnetic moment (spin) of hydrogen particles present in the water (H_2O) of a living body. It provides an excellent soft tissue contrast and is often considered to be the "gold standard" for tumor detection (Leach 2009). It is, therefore, an excellent choice for soft tissue target definition. MRI also has two other benefits: temperature monitoring and tissue coagulation detection. These resulted in the combination of ultrasound transducers with MRI (Hynynen et al. 1993, 1996) that have been proposed for interventional therapies such as HIFU. The sensitivity of MRI signals, the resonance frequency of protons at a temperature in the human body, is of particular interest in achieving the guidance of these therapies. The possibility of measuring the temperature rise is to ensure the adequate deposited thermal dose and thus prevent damage to adjacent tissues and treatment effectiveness in the target area. MRI-compatible methods to deliver these exposures have undergone such rapid development over the past 10 years such that clinical treatments are now routinely performed.

Most methods used for temperature mapping by MRI (Quesson et al. 2000; McDannold 2005; Rieke and Butts Pauly 2008) use temperature-dependent proton resonance frequency shift (Ishihara et al. 1995) as a measure of temperature elevation that has been shown to be linear even above the thermal coagulation threshold (Peters et al. 1998). A phase image is obtained just prior to the ultrasound exposure, and then a series of images is acquired during and after HIFU sonication. By subtracting the phase of each voxel from the baseline, a phase difference image is obtained that is proportional to the temperature elevations. This method provides thermometry with high spatial and temporal resolution but does not work in fat where the proton screening coefficient is not temperature dependent (Peters et al. 1998; Kuroda et al. 1998). The temperature history obtained from the serial images is used to calculate thermal dose in order to determine tissue damage (McDannold et al. 2000).

15.14.2 Works in Progress

Several devices have been developed on this principle combining HIFU and MRI, and a significant number of applications have been explored, especially for the treatment of uterine fibroids (Okada et al. 2009) or tumors of the brain (Larrat et al. 2010), the esophagus (Melodelima et al. 2004), the liver, the kidney (Quesson et al. 2011),

and the prostate (Fig. 15.10). Manufacturers have, in turn, developed probes therapy compatible with their own MRI devices such as the Sonalleve (Philips) or compatible with commercially available MRI devices such the ExAblate (InSightec).

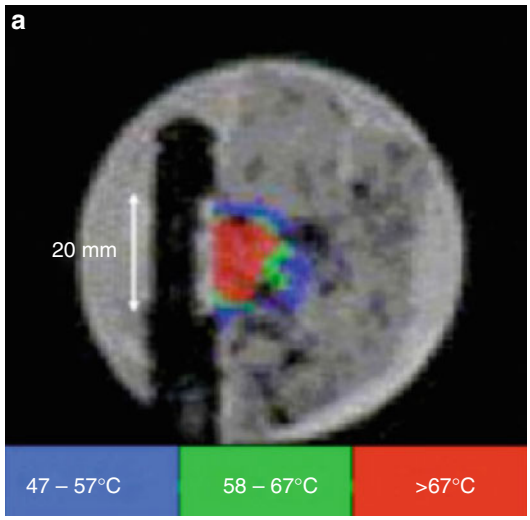


Fig. 15.10 Examples of HIFU guided by MRI: (*a*) temperature measurement to control the treatment of esophagus tumors (Beerlage et al. 1999)

All of the current clinical results of HIFU are based on an open-loop concept where thermometry is obtained during prior sonications. With MRI, an alternative method is to use thermometry to control the power during the sonication (Salomir et al. 2000) so that the desired exposure is induced without wasting energy, as it is the case with the open-loop concept (Fig. 15.11). Feedback control may allow reduced treatment times for thermal coagulation of prostate with intraurethral applicators that slowly rotate to sweep the whole gland (Chopra et al. 2005). These closed-loop feedback systems reduce the complexity of operating the systems and can make the energy delivery optimal and thus minimize the treatment times.

15.15 Conclusion

The outcomes achieved for primary care patients seem close to those obtained by radiation therapy. HIFU does not represent a therapeutic impasse: EBRT is a safe salvage option after HIFU failure, and salvage surgery is possible in young and motivated patients. On the other hand,

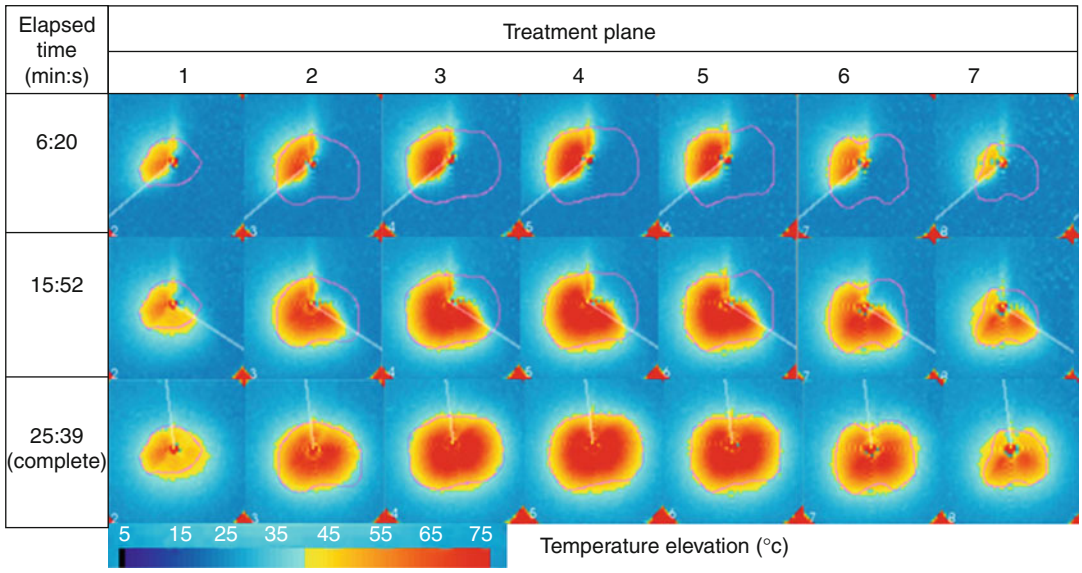


Fig. 15.11 Toward 3D conformal prostate treatments (3 T). Simultaneous treatment with seven planar transducers (5 mm long) using active MR temperature feedback from nine planes (After Chopra et al. 2005). Prostate shape is taken from a clinical patient

HIFU has a considerable potential for local recurrence after radiation failure. Recently, some early experiences on focal therapy suggest that HIFU provides an excellent opportunity to achieve a local control of the disease in low-risk prostate cancer and in early identified local relapse after EBRT.

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Cryotherapy

16

Matvey Tsivian and Thomas J. Polascik

Contents

16.1 Introduction

Cryosurgery has been applied in oncologic treatments for over 150 years (Arnott 1850), constantly evolving into the modern minimally invasive approach for the treatment of prostate cancer (PCa). Today, modern cryosurgery is an accepted option for both the primary and salvage treatment of localized PCa recognized by the international guidelines (Babaian et al. 2008; Heidenreich et al. 2011). Herein, we review the indications, procedure details, as well as contemporary results of cryotherapy for PCa.

16.2 Elements of Cryobiology

The basis of cryogenic injury is tissue destruction by subtraction of energy and achievement of nonvitally low temperatures. There are two main mechanisms that can be considered as the principal pathways of cryoinjury, and these consist of vascular-related injury on one hand and direct cellular damage on the other (Hoffmann and Bischof 2002).

Extreme temperatures mainly affect the small vessels, damaging the endothelium whereby vessel cell lining sloughs and blocks blood flow, thereby inducing a typical inflammatory response with permeability of the vessels, distention of vessel walls, thrombosis, ischemia, and necrosis of the supplied tissue (Hoffmann and Bischof 2002). Moreover, during the thawing phase of cryotherapy, reperfusion injury enhances endothelial

M. Tsivian, M.D. • T.J. Polascik, M.D., F.A.C.S. (✉)
Division of Urology, Department of Surgery,
Duke University Medical Center,
Yellow Zone, DUMC Box 2804, Durham,
NC 27710, USA
e-mail: polas001@mc.duke.edu

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damage stimulating the inflammatory response with release of oxygen radicals and augmenting tissue damage.

Direct cell injury relies on tissue water biophysics. The complex cryoinjury process can be summarized by two topographically distinct processes: intracellular and extracellular ice formation. Intracellular ice crystal formation occurs at high freezing rates typically seen in cryosurgery. These ice crystals mechanically disrupt and damage vital cell structures such as organelles and the membrane. Extracellular ice formation subtracts water from the extracellular environment and, aside from its mechanical damage, induces extracellular hypertonicity that in turn draws water from within the cells, dehydrating them and disrupting normal enzymatic processes and membranes properties (Mazur 1984; Theodorescu 2008). Achieving temperatures below −40°C as well as maintaining the exposure for longer times enhances tissue destruction as virtually all water is transformed to ice at these extreme conditions (Gage and Baust 2007; Klossner et al. 2007). Extracellular ice formation is likely the predominant injury mechanism during cryoablation; however, using high freezing rates as typically seen with modern devices, intracellular ice formation, and the associated mechanisms of cell damage certainly come into play potentiating the overall effect.

Moreover, during the thawing phase, additional injury mechanisms come into play. Specifically, when frozen tissue temperature rises above −40°C, smaller ice crystals fuse to form larger structures in a process known as recrystallization, and additional structural damage is inflicted upon cell structures. As thawing proceeds, extracellular ice melts and a hypotonic environment is created driving overloading water shifts into the cells (Theodorescu 2008).

Despite the same injury mechanisms coming into play, different cell types and cell lines respond differently to cryoinjury. PCa cells' response to cryoinjury has been extensively studied. Cryoinjury is a time-dependent process as cryoinjury progresses with freezing. Reaching temperatures below a −40°C threshold ensures effective PCa cell destruction (Tatsutani et al. 1996), although at the periphery of the ice ball, where temperatures are not as cold, cryoinjury may only be reversible (at temperatures −20°C to 0°C) or induce apoptosis (Gage et al. 2009). Apoptosis plays an important role in cryoablation of prostate cancer. It has been shown that cryoablation sensitizes cancer, but normal prostate cells, to pathways of apoptosis suggesting a potential role for combination strategies in PCa cryosurgery (Clarke et al. 2007; Kimura et al. 2010a; Santucci et al. 2011) to enhance targeted damage to cancerous tissue.

Along with local mechanisms of destruction, cryotherapy offers an additional perspective to cancer control. Since cancerous tissue is not removed by the procedure and cancer-specific antigens are left in situ, these can be recognized by the immune system and stimulate a cancer-specific immune response towards them. However, there is controversy regarding the nature of such immunologic response with conflicting data reported in the literature. While some studies support an anticancer response after cryoablation, others indicate that immunosuppression or tolerance to these antigens may be induced (Ablin 1974; Urano et al. 2003; Udagawa et al. 2006; Yamashita et al. 1982; Miya et al. 1987). It appears that the nature of the immune response depends on local and systemic factors such as cytokines, antigen-presenting cells, as well as the type of antigen presented that build up the immune system response (Sabel 2009).

16.3 Indications for Cryosurgery

Cryosurgery for PCa is a recognized treatment option (Babaian et al. 2008; Heidenreich et al. 2011); however, there is no agreement to date upon the indications and contraindications for this approach, and international guidelines remain cautious in this regard.

In the setting of primary cryotherapy for localized PCa, both the European Association of Urology (EAU) and the American Urological Association (AUA) guidelines agree that cryosurgery is an option for patients who do not desire or are not good candidates for conventional surgery

(Babaian et al. 2008; Heidenreich et al. 2011). The AUA statement on cryosurgery recognized cryosurgery as an option for low, intermediate, and high-risk PCa (Babaian et al. 2008), albeit high-risk PCa patients may require multimodality treatment. The EAU guidelines identify the ideal candidates for cryosurgery as these patients having minimal extension beyond the prostate, gland size ≤40 cc (larger glands may present technical difficulties with probe placement and can be downsized with hormonal treatment prior to intervention), PSA < 20 ng/mL, and biopsy Gleason score < 7 (Heidenreich et al. 2011).

Without a doubt, patient and disease characteristics need to be taken into account when considering cryotherapy as an option for prostate cancer. The lack of homogeneous data in the literature, specific to low, intermediate, and high-risk disease, however, is translated into almost conflicting recommendations from the major guidelines. As long-term outcomes of primary cryosurgery become available, we are likely to see a refinement of the guidelines with stronger and more precise recommendations made.

There are several technical contraindications to cryosurgery that apply both in the primary and salvage settings. As large defects in the prostatic fossa may impair the effectiveness of the urethral warmer coaptation used during the procedure to safeguard the urethral lining and increase the chance of mucosal sloughing, a history of transurethral resection of the prostate or similar procedures should be considered relative contraindications. Additionally, major rectal pathology may be considered a contraindication. Moreover, extensive counseling is needed for potent patients expecting to maintain erectile function as potency is typically impaired following whole-gland cryoablation. Large prostate glands (>40 cc) may be difficult to treat due to sheer size alone or interference of the pubic arch. The latter obstacle can be overcome with either manual positioning of the probes that is void of transperineal grid constraints or extended lithotomy position of the patient. For larger prostates, gland downsizing using hormonal agents can be utilized prior to intervention.

Cryotherapy in the salvage setting represents an attractive alternative to salvage prostatectomy offering reduced morbidity and technical challenge (Kimura et al. 2010b). Salvage cryosurgery has been used both after external beam radiation and interstitial radiotherapy, along with other failed primary therapies such as cryoablation, high-intensity focused ultrasound, etc. Therefore, patients with local biopsy-proven recurrence of prostate cancer after radiation or other primary therapy with no evidence of metastatic disease represent potential candidates for salvage cryotherapy. Due to a higher chance of seminal vesicle invasion, we recommend considering seminal vesicle biopsies and lymph node sampling in the evaluation of potential high-risk candidates.

Several studies have suggested factors associated with greater success of salvage cryotherapy, and these can be summarized as favorable disease characteristics: low PSA nadir after primary treatment, low PSA presalvage cryotherapy (<4 ng/mL), PSA doubling time >16 months, as well as the Gleason grade of the recurrent disease (Ng et al. 2007; Spiess et al. 2006; Ismail et al. 2007).

In summary, although cryoablation is a recognized option both in the primary and salvage settings for the treatment of localized prostate cancer, there is difficulty in reaching a consensus on selection criteria and to define ideal candidates for this approach. This is mainly due to the paucity of data in the literature and is likely to resolve in the near future as more studies on cryoablation add their results to the pool of available information. There is agreement that currently cryoablation should be considered as a treatment option for patients that are not willing or are not good candidates for conventional surgery.

16.4 Cryoablation Procedure

Herein, we describe the general steps of the procedure using third-generation cryotechnology that utilizes the Joule–Thompson principle of gas expansion and therefore heat delivery and subtraction by means of ultrathin needle-like cryoprobes. Translating the physical principle into

practice, as compressed gas is delivered to the tip of the cryoprobe in a closed circuit and allowed to expand through a minute opening, gas pressure falls, and it changes its physical properties (internal state). For argon gas, the change of state subtracts energy resulting in reduction of the temperature and freezing. The opposite is true regarding the properties of helium gas that upon expansion releases energy to the environment, thereby generating heat that translates into active thawing. The opposite effects of helium and argon derive from differences in attractive and repulsive forces of the molecules (internal energy) of these gasses. A newer cryotechnology that has been introduced relies on argon gas as the sole cryogen, whereby both freezing and thawing phases are achieved by regulating the properties of this gas, since Joule–Thompson coefficients of gasses vary with pressure and temperature. At pressures of 3,500 PSI, expansion of argon gas results in temperature drop and thus freezing. Allowing this gas to expand under lower pressures (200–500 PSI), when Joule–Thompson coefficient of argon is very low and only negligible cooling takes place, the gas is used to heat the needle shaft by spreading the heat generated by an electrical heating source embedded in the needle. This technical modification allows for the use of a single gas (argon) for both freezing and thawing during cryoablation.

Several cryoablation platforms are commercially available, and these consist of a console for treatment planning and monitoring that receives information from the probes and regulates the freezing/thawing phases. The console is connected to peripherals such as a urethral-warming catheter, a transrectal ultrasound mounted on a stepper, cryoprobes, and temperature sensors. Gas tanks (argon with or without helium) are connected to the system. On the console monitor, the information from the treatment planning is integrated with ultrasound imaging in real time which allows for precise monitoring of the procedure as well as input from temperature sensors and cryoprobes. For treatment planning, the desired ice coverage can be precisely sculptured by varying the configuration of the probes as well as by using different probes generating different shapes and sizes of ice balls. The probes are positioned in the gland through a transperineal grid template under ultrasonographic guidance to produce a series of overlapping ice balls that cover the entire gland.

Typically, cryoablation is performed as an outpatient procedure under spinal, locoregional, or general anesthesia. With the patient in lithotomy position, cryoprobes are positioned under transrectal ultrasonographic guidance using both sagittal and transverse views. In addition to cryoprobes, temperature sensor probes are placed to allow for precise monitoring of ice ball development. These thermocouples can be positioned in Denonvillier's fascia, the urethral sphincter, and/or the neurovascular bundles to monitor the freezing process and avoid injury to adjacent structures. Once the probes are in place, flexible cystoscopy is used to verify the integrity of the urethra and bladder and to place a superstiff guidewire for the introduction of the urethral-warming catheter. A dual freeze/thaw cycle is performed and monitored by ultrasonography and readings from the temperature probes. At the end of the procedure, the urethral-warming device is replaced with a urethral catheter, although some prefer placing a suprapubic cystostomy to ensure adequate bladder drainage in the postoperative period. Acute swelling and inflammatory processes following cryoablation typically resolve within 1–2 weeks. In our experience, most patients are able to void spontaneously by 1 week after treatment.

16.5 Primary Cryotherapy: Complications

Cryoablation of the prostate is a minimally invasive surgical technique, and its morbidity profile has been extensively studied. Table 16.1 provides a summary of the reported complications. The majority of the postoperative events reported in the literature are self-limiting. Transient penile and scrotal swelling and paresthesia have been reported to occur within 2–3 weeks in up to 10% of patients and typically resolve in 2–6 months (Wake et al. 1996; Ghafar et al. 2001). Major

Table 16.1 Complication rates after primary cryoablation of the prostate using third-generation technology

Reference	Number of patients	Complication rates (%)							
		Slough	Perineal pain	Urinary retention	UTI/sepsis	Urethral stricture	Fistula	Incontinence	ED
Bahn et al. (2002)	210	NR	NR	3	NR	NR	2.4	9	41
Shinohara et al. (1996)	102	NR	3	23	3/3	NR	1	4 (15[a])	86
Han et al. (2003)	106	5	2.6	3.3	0	NR	0	3	87
Wake et al. (1996)	100	1	NR	20	NR	2	0	8	NR
DiBlasio et al. (2008)	78	NR	NR	NR	NR	1	NR	7.7	84.6
Cohen (2004)	98	2	NR	NR	NR	NR	0	0	NR
Prepelica et al. (2005)[b]	65	NR	0	3.1	NR	NR	0	3.1	NR
Hubosky et al. (2007)	89	2	6	4	1/0	NR	1	2	NR
Donnelly et al. (2010b)	117	NR	NR	15.4	NR	NR	NR	32.5	70.9
Chin et al. (2008)[c]	33	NR	32	NR	NR	NR	NR	7	29
Lian et al. (2011)	102	4.9	NR	0	NR	0	0	4	64.1

UTI urinary tract infection, *ED* erectile dysfunction, *NR* not reported
[a]Including patients who underwent transurethral resection of prostate following cryoablation
[b]High-risk patients
[c]Locally advanced disease

complications are rare with a reported incidence of rectourethral fistula ranging from 0% to 2.4%, urethral sloughing occurring in <5% with the use of urethral-warming devices, and incontinence requiring pads being reported in less than 10% with most cases resolving spontaneously. It remains unclear whether urge or stress incontinence is the predominant type, since most studies did not distinguish between the types of incontinence. Similarly, episodes of urinary retention have been reported in <5% of patients following cryoablation (Hubosky et al. 2007; Han et al. 2003), albeit the definitions of urinary retention vary and most of retention episodes are transitory and resolve within several weeks of surgery. Urethral stricture rates are approximately 2.5% (compared to 8.4% with radical prostatectomy) (Elliott et al. 2007).

Incontinence and erectile dysfunction are among the most widely used measures of functional outcomes following treatments for localized PCa. For cryoablation, erectile dysfunction occurs in most patients treated with whole-gland ablation although some studies report that a majority of patients remained potent (Table 16.1). A recent study using the Surveillance Epidemiology End Results (SEER) database reported on complications of primary cryotherapy derived from Medicare claims (Roberts et al. 2011); the authors estimate 20.1% of erectile dysfunction following cryotherapy, along with 9.8% incontinence.

An accurate assessment of the rates of erectile dysfunction and urinary incontinence is hampered by the varying definitions of these outcome measures and only scattered use of validated instruments to adequately identify these conditions. For future studies, it is of paramount importance to use validated tools (e.g., questionnaires) to evaluate both erectile function and continence.

Kimura et al. used validated tools to assess urinary function after cryoablation and found that while urinary function and bother scores dropped immediately following cryoablation, they recovered steadily and persistently in a 12-month period (Kimura et al. 2010c). Another study reported excellent voiding function outcomes with no apparent change in urinary function scores after primary cryoablation (DiBlasio et al. 2008). Malcolm and colleagues reviewed quality of life outcomes comparing brachytherapy, robotic and open radical prostatectomy, and cryotherapy (Malcolm et al. 2010). These authors have shown that cryotherapy, as well as brachytherapy, were associated with a better health-related quality of life, especially that related to the urinary function and bother along with sexual bother as assessed by validated tools. When directly compared to brachytherapy,

Table 16.2 Complication rates after salvage cryoablation using third-generation cryotechnology

Reference	Number of patients	Complication rates (%)							
		Slough	Perineal pain	Urinary retention	UTI/sepsis	Urethral stricture	Fistula	Incontinence	ED
Ng et al. (2007)	187	NR	14	21	10	2.1	2	40	NR
Han and Belldegrun (2004)	29	NR	NR	NR	NR	NR	0	7	NR
Ismail et al. (2007)	100	2	4	2	NR	NR	1	13	86
Pisters et al. (2008)[a]	279	NR	NR	NR	NR	NR	1.2	4.7	69.2
Ghafar et al. (2001)	38	0	39.5	0	2.6	NR	0	7.9	NR
Cresswell et al. (2006)	20	NR	NR	4	NR	NR	0	4	86
Bahn et al. (2003)	59	NR	NR	NR	NR	NR	3.4	8	NR

UTI urinary tract infection, *ED* erectile dysfunction, *NR* not reported
[a]Series includes a portion of cases treated using second-generation technology

cryoablation resulted in worse sexual function scores for up to 12 months while urinary scores were similar; however, after 18 and 24 months, cryoablation has shown consistently better urinary domain scores compared to brachytherapy (Hubosky et al. 2007).

Kimura and colleagues (2011) assessed erectile function outcomes using validated questionnaires and found that 77.4% of patients had moderate to severe erectile dysfunction following cryoablation and suggested that the use of erectile aids may assist in recovery of potency to preoperative levels. Similarly, Ellis et al. (2007a) have suggested that penile rehabilitation strategies (regular use of vacuum devices and oral agents) after cryoablation may increase potency rates. In fact, the authors report steady recovery of erectile function over time with over 50% of preoperatively potent patients regaining erections sufficient for intercourse over a 4-year follow-up (Ellis et al. 2007a). Despite encouraging reports, more studies are needed to determine the appropriate strategies to enhance both urinary and sexual function in men undergoing cryoablation.

16.6 Salvage Cryotherapy: Complications

Complications profile of salvage cryotherapy for radiorecurrent prostate cancer appears to be similar to that in the primary setting with higher rates of events (Table 16.2). Urethral mucosal sloughing remains a rare event using third-generation technology and has been reported in <2% of patients. Specifically, fistula rates appear to be higher, up to 3.4%, as well as incontinence rates that remain in most series under 10%. In the few series reporting erectile function outcomes, only a minority of patients regain potency. These results favorably compare to conventional salvage radical prostatectomy series (Kimura et al. 2010b), suggesting that salvage treatment with cryosurgery may be considered as a relatively low morbidity option.

16.7 Primary Cryotherapy: Oncological Outcomes

Oncological outcomes reported in the literature are summarized in Table 16.3. The various definitions of biochemical recurrence make it very challenging to adequately compare the different series emphasizing the need for a consensus on the matter. Conventional criteria of biochemical failure adopted for radical prostatectomy are most likely not suitable for cryoablation since a portion of PSA-producing tissue is spared periurethrally due to the use of urethral-warming devices, and therefore undetectable PSA levels are not always achievable. Similarly, biochemical failure criteria used in radiation oncology are likely not suitable as well, since an effective ablation of the entire gland is carried out and most of PSA-producing tissue is destroyed. Despite the obvious difficulties with diverse definitions of failure, the currently

Table 16.3 Oncologic outcomes of primary cryoablation

Reference	Number of patients	Definition	bDFS 1 year	bDFS 3 years	bDFS 5 years	bDFS 7 years
Hubosky et al. (2007)	89	ASTRO	94%	–	–	–
		≤0.4	70%	–	–	–
DiBlasio et al. (2008)	78	ASTRO	97.9%	95.7%	71.1%	–
Prepelica et al. (2005)[a]	65	ASTRO	83.3%[b]	–	–	–
Cresswell et al. (2006)	31	≤0.5	60%	–	–	–
Donnelly et al. (2010b)	117	Nadir+2	–	82.9%	75%	–
Bahn et al. (2002)[c]	590	ASTRO	–	–	–	89.5%
Jones et al. (2008)[c]	1,198	ASTRO	–	–	77.1%	–
Lian et al. (2011)	102	<0.5	92.2%[b]	–	–	–

bDFS biochemical disease-free survival
[a]High-risk patients
[b]Median follow-up of 30–35 months
[c]Contains a proportion of patients treated with earlier-generation technology

available literature shows that in most series over 80% of patients remain disease free at 1 year. Biochemical disease-free survival has been reported at 5 years in three studies, showing consistent results of approximately 75% of patients using similar definitions borrowed from radiation oncology (DiBlasio et al. 2008; Donnelly et al. 2010a; Jones et al. 2008).

Oncological outcomes of primary cryoablation are strongly dependent on disease characteristics. Favorable disease characteristics translate to better bDFS rates. Clinically low-risk patients have better outcomes compared with intermediate and high-risk ones (Hubosky et al. 2007; Bahn et al. 2002). Caso et al. (2010) have evaluated predictors of biopsy-proven recurrence after primary cryotherapy and found that, on multivariate analysis, only time of undetectable PSA (TUPSA) was associated with both biochemical and biopsy-proven disease-free survival, suggesting that TUPSA may be used as a potential informative tool during follow-up. As the experience with primary cryotherapy matures, we are likely to be able to identify additional factors associated with oncologic outcomes and produce predictive models as well as more accurate recommendations on patient selection for this approach.

It is also important to compare cryotherapy to other well-standardized approaches for the treatment of localized PCa. Two randomized clinical trials comparing cryosurgery to radiation were published yielding conflicting results. Chin et al. (2008) found cryoablation to be inferior to external beam radiation in bDFS. However, a similar trial by Donnelly et al. (2010a) concluded that the two approaches have comparable oncological efficacy. This discrepancy may be due to differences in study designs; in fact, while Chin et al. included only patients with locally advanced PCa and had small sample size, Donnelly and colleagues excluded bulky disease from their study and benefited from a larger sample size.

To date, only two studies reported long-term oncological outcomes following primary cryoablation (Cohen et al. 2008; Cheetham et al. 2010). Both studies are based on early cohorts of patients (1990s) and therefore may not represent accurately the outcomes of third-generation technology. Cohen et al. (2008) reported on biochemical disease-free survival with in 370 men treated with primary cryosurgery before 1999. The authors have found that in low, intermediate, and high-risk groups, bDFS at 10 years were 80.5%, 74.2%, and 45.5%, respectively. Cheetham et al. (2010) focused on overall and cancer-specific survival. They report on 25 patients treated between 1994 and 1999 with 10 years of follow-up where only two patients died of prostate cancer compared to eight deaths attributed to other causes. This is clearly preliminary data, and conclusions should not be hasted, but it establishes the basis for future reports on long-term outcomes.

Table 16.4 Oncologic outcomes of salvage cryoablation

Reference	Number of patients	Definition	bDFS 1 year	bDFS 3 years	bDFS 5 years	bDFS 7 years
Ng et al. (2007)	187	Nadir + 2	–	–	56%	–
Ghafar et al. (2001)	38	Nadir + 0.3	86%	74%	–	–
Ismail et al. (2007)	100	ASTRO	83%	59%	–	–
Cresswell et al. (2006)	20	≤0.5	66.7%	–	–	–
Bahn et al. (2003)[a]	59	≤0.5	–	–	–	59%
Pisters et al. (2008)[a]	279	ASTRO	–	–	59%	–

bDFS biochemical disease-free survival
[a]Includes earlier-generation technology

It appears from the available data that the oncological outcomes of primary cryotherapy are acceptable and competitive with other primary treatments for PCa. Yet, it is paramount to emphasize the need for agreement on the definition of biochemical failure and encourage further outcome data to be evaluated.

16.8 Salvage Cryotherapy: Oncological Outcomes

The data on oncological outcomes following salvage cryotherapy for radiorecurrent PCa is affected by the same difficulties of lack of consistency in the definition of biochemical failure and therefore inability to perform an effective comparison between the published results. The summary of the literature is provided in Table 16.4.

Despite various definitions of biochemical failure, it is apparent that bDFS at 1 year can be as high as 86%. Long-term data suggests that with a strict definition of PSA, ≤0.5 ng/mL following salvage cryosurgery, 59% of patients are disease free at 7 years (Bahn et al. 2003), and these results are comparable to >55% bDFS at 5 years from other studies (Ng et al. 2007; Pisters et al. 2008). Recently, Cheetham et al. (2010) reported on 10-year data regarding outcomes after salvage cryoablation focusing on overall and cancer-specific survival. In their report, 8 out of 51 patients (15.7%) who underwent salvage cryotherapy died of PCa over 10 years. Williams et al. (2011) reported on 176 men undergoing salvage cryotherapy with long-term follow-up; the authors found that 47%, 39%, and 39% of patients were disease free at 5, 8, and 10 years, respectively. This study has also evaluated metastasis-free survival, indicating 87% at 5 and 82% at 10 years.

Several studies attempted to identify prognostic factors associated with the outcome of salvage cryoablation. A report from the COLD (Cryo On-Line Data) registry analyzed 455 patients and found that PSA nadir levels <0.6 ng/mL after salvage cryotherapy were associated with better cancer control outcomes offering 80% bDFS at 1 year and 67% bDFS at 3 years, whereas higher PSA nadirs were associated with progressively worsening outcomes (Levy et al. 2010a). In this study, it was also determined that Gleason scores of the recurrent cancer correlated with the outcome. The same group found that disease burden (the ratio of positive cores to prostate volume) is of prognostic value following salvage cryoablation (Levy et al. 2010b). Another study showed that preradiation PSA, Gleason score, as well as presalvage PSA level and postsalvage PSA nadir were associated with biochemical disease-free survival (Williams et al. 2011). The authors showed that patients with presalvage Gleason score of ≤6 had a 54% bDFS at 10 years, underlining the importance of disease characteristics in defining cancer control outcomes.

Spiess and colleagues (2010) developed a nomogram that quantifies the risk of biochemical failure after salvage cryotherapy based on initial PSA level, Gleason score, and clinical stage. This tool may be useful to generate realistic expectations with regards to the probability of biochemical failure in candidates for salvage

cryoablation. However, this nomogram's performance is not optimal, and it requires external validation.

16.9 Future Directions: Focal Therapy

Technological advances, specifically those that brought cryotherapy to be recognized as an option in the treatment of prostate cancer, have enabled physicians to rethink treatment schemes and potentially move away from whole-gland treatments towards a targeted, partial ablation of the gland (Polascik and Mouraviev 2009; Polascik et al. 2009). The concept of focal therapy relies on a selective, targeted destruction of known cancer while sparing the uninvolved tissue, thereby potentially reducing morbidity and improving quality of life. The concept of focal therapy for prostate cancer has gained interest and popularity, especially in the era of growing evidence that overdiagnosis and overtreatment of prostate cancer is becoming a pressing public concern (Welch and Black 2010).

Advances in imaging of the prostate, namely, magnetic resonance and novel ultrasound techniques, are permitting the physician to visualize PCa foci within the prostate and characterize those with a guided, targeted biopsy. The same imaging technology can then potentially be used, in appropriate candidates to guide the targeted ablation of these lesions while leaving intact the remainder of the prostate.

Early results of focal therapy are promising, albeit based on a small number of single-institution, small-sized studies. Biochemical disease-free survival reported in the literature ranges between 84% and 96% at 2–5 years while potency is preserved in the vast majority (72–89%) of patients (Ellis et al. 2007b; Bahn et al. 2006; Lambert et al. 2007; Onik et al. 2008, 2007). There remains a lack of consensus on the appropriate candidates and selection methods for focal therapy, as well as tools to be used in postablation follow-up. Despite the hurdles, the focal therapy approach is being investigated intensively and followed with great interest. Randomized trials are under way to set stage for the introduction of this intriguing therapeutic option.

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Follow-up After Radical Treatments and Relapse

17

Nicolas Mottet

Contents

N. Mottet, M.D., Ph.D.
Urology department, University hospital,
CHU St Etienne, 42055 St Etienne Cedex 2, France
e-mail: nicolas.mottet@chu-st-etienne.fr

Whatever the curative treatment modality, failure is not uncommon. Curative treatment is defined as radical prostatectomy or radiotherapy (either external or interstitial) alone, or in combination. We will also cover the nonfully established procedures, such as HIFU or cryotherapy. Between 27% and 53% of all patients undergoing a "curative treatment" will develop local or distant recurrences within 10 years of initial therapy, and 16–35% of patients will receive second-line treatment within 5 years of initial therapy (Lu-Yao et al. 1996; Grossfeld et al. 1998). Some failures might have an impact on patient's survival, leading to second-line treatments with curative intent again or to palliation, sometimes for years. The balance between second-line treatment side effects and the expected benefits must always be considered. The primary aim of a follow-up policy is to find a situation before advanced disease is present in order to be curative again or as effective as possible in term of palliation. Usually, this is based on an early diagnosis.

17.1 How to Follow-up?

Only PSA level, and eventually DRE, needs to be carried out routinely. During each visit, a disease-specific history is mandatory including signs of disease progression and treatment-related complications (beyond the scope of this chapter).

DRE is performed to follow the gland and assess whether or not there is a suspicion of local recurrence. After radiotherapy, the DRE findings

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are usually difficult to interpret. A newly detected nodule should be considered as suspicious. Although discussed a local recurrence is possible without any PSA rise (Oefelein et al. 1995; Leibman et al. 1995). But this has only been proven in patients with undifferentiated tumors. The measurement of PSA level is the cornerstone in the follow-up strategy. PSA recurrence nearly always precedes clinical recurrence, in some cases by many years (Horwitz et al. 2005; Stephenson et al. 2006). Usually, a single PSA suggesting a recurrence must be confirmed by another measurement.

Thus, PSA measurement and DRE comprise the most useful combination of tests as first-line examination in follow-up after radiotherapy or radical prostatectomy, but PSA measurement may well be the only test in cases with favorable pathology (Chaplin et al. 2005).

Other modalities such as transrectal sonography, bone scan, computed tomography, or MRI have no place in asymptomatic men. In new developing bone symptoms, a bone scan is mandatory as metastatic disease may occur even at undetectable PSA level (Oefelein et al. 1995; Leibman et al. 1995).

17.2 When to Follow-up?

Most recurrence occurs during the first 2 or 3 years. A closer follow-up is therefore useful during the first 3 years, with a proposed interval of 3, 6, and 12 months initially, every 6 months for 2 years thereafter, followed by a yearly interval later on (Mottet et al. 2011). This regimen must be adapted based on tumor and patient characteristics: nodal disease, positive margins, or Gleason > 8 might shorten the intervals, while advanced age or significant comorbidities might expend the intervals.

17.3 PSA Definition of Recurrence

The level of PSA at which to define treatment failure differs between treatment modalities. If a consensus exists regarding surgery or radiotherapy, none exists for HIFU or cryotherapy. The PSA recurrence is defined based on the PSA nadir after treatment.

After surgery, PSA is expected to be undetectable (i.e., <0.1 ng/ml) within 6 weeks after the procedure (Stamey et al. 1889). After radiotherapy (external beam or brachytherapy), the time to nadir is prolonged, sometimes as long as 3 years. The optimal value remain controversial, a nadir below 0.5 ng/ml being possibly associated with a better outcome (Ray et al. 2006).

Recurrence following surgery is usually defined by two consecutive values of 0.2 ng/ml increasing (Boccon-Gibod et al. 2004; Mottet et al. 2011). Other authors have argued for an even higher cut-off of 0.4 ng/ml (Scher et al. 2004) as this threshold was the best predictor of secondary metastases (Stephenson et al. 2006). A single PSA value above a threshold is inappropriate: only 49% of patients had a second PSA increase if above 0.2 ng/ml, compared to 62% and 72% if above 0.3 or 0.4 ng/ml, respectively (Amling et al. 2001). So far, the use of an ultrasensitive PSA assay is not justified for routine follow-up (Taylor et al. 2006); also, preliminary results suggest that this might change in the future (Hong et al. 2010). Values between the nadir and the defined threshold are controversial in term of prognosis significance.

Following radiation therapy, the previous ASTRO definition of relapse was three consecutive increases (ASTRO 1997). The new ASTRO-RTOG definition of failure (also known as the Phoenix definition) is a rise of 2 ng/ml above the PSA nadir (Roach et al. 2006). It is valid for patients treated with radiotherapy alone or combined with hormonotherapy.

After HIFU or cryotherapy, a variety of definitions for PSA relapse have been used (Aus 2006), with a cut-off around 1 ng/ml. No accepted definition is available, as none have been validated against clinical progression or survival.

17.4 PSA Relapse and Survival

Nowadays, PSA relapse by itself is not a surrogate marker for survival. And only recently was the relation between PSA relapse and survival observed. In a retrospective analysis of 3,071

Table 17.1 Prostate-cancer-specific mortality based on PSA-DT at relapse (D'Amico et al. 2003)

		PSA-DT < 12 months (%)	PSA-DT < 6 months (%)	PSA-DT < 3 months (%)
Surgery	Year 5	7.6	13.9	31.2
	Year 10	17.5	34.1	67.8
Radiotherapy	Year 5	15.9	27	38.4
	Year 10	39.6	60.6	76.6

Table 17.2 Major findings to discriminate between a probable local or systemic relapse after a local treatment

	Relapse definition (PSA based)	Favoring local relapse	Favoring systemic relapse
After surgery	PSA > 0.2 ng/ml and increasing	pN0, ≤pT3a	Postoperative detectable PSA (>0.1 ng/ml) and Gleason > 7
		Delay to recurrence >2 years (discussed)	pN1, pT3b
		PSA-DT at relapse >12 months	PSA-DT (relapse) <6 months
		Other possible parameters: Gleason ≤ 6, positive margins	Other possible parameters: Gleason > 7
After radiotherapy	PSA > nadir + 2 ng/ml	PSA nadir <0.5 ng/ml	PSA at 1 year >2 ng/ml
		PSA at 1 year <2 ng/ml	PSA-DT at relapse <6 months
		PSA-DT at relapse >12 months	

men treated with surgery, biochemical relapse occurred after a median 7.4 years in 546 men. In a multivariate analysis, PSA failure was associated with overall survival (hazard ratio 1.03, $p=0.025$) (Choueiri et al. 2010). Similar results regarding prostate-specific survival have also been observed in another retrospective cohort of 1,270 men after either surgery or radiotherapy (Uchio et al. 2010).

PSA-relapsing patients represent a heterogeneous cohort of patients. The PSA evolution is one of the most important prognostic parameter. In 2003, based on 5,918 patients with surgery and 27,851 with external beam treatment, D'Amico demonstrated a direct relationship between the PSA-doubling time (PSA-DT) and the specific mortality (Table 17.1). A PSA-DT below 3 months was associated with specific mortality (hazard ratio 19.6 [12.5–30.9]) (D'Amico et al. 2003).

17.5 Relapse: Local or Systemic?

To determine whether the recurrence is local or systemic is of paramount importance and will change the treatment modality. About 50% of patients after surgery will have a local failure (ASTRO 1997). Major findings are summarized in Table 17.2.

17.5.1 Surgery

A persistently elevated PSA (i.e., >0.1 ng/ml) equals persistence of prostatic tissue. This is generally thought to be residual cancer due to either micrometastases that were not detected or undetectable beforehand, or residual disease in the pelvis possibly due to positive surgical margins. The benign origin of this PSA is unlikely. The prognosis of these patients is worse compared to those with an undetectable PSA, but again is inhomogeneous: PSA nadir, margin status, and specimen Gleason score are independent predictors for recurrence, while PSA nadir and pT3b predict overall mortality (Moreira et al. 2009).

In patients with an undetectable PSA, its evolution is the key factor. A high PSA velocity (above 0.75 ng/ml/year) or a low PSA-DT are strong predictors of systemic relapses (threshold mainly <6 months) (Pound et al. 1999; Roberts et al. 2001; Rosenbaum et al. 2004; Freedland

et al. 2007), or specific survival (threshold <3 or 12 months) (Albertsen et al. 2004; Zhou et al. 2005). For some authors, this parameter is the only predictor for systemic relapse in multivariate analysis including Gleason and recurrence delay. To obtain a reliable value for the PDA-DT, at least three values above 0.1 ng/ml are mandatory (Svatek et al. 2006). The MSKCC website might also be helpful (http://nomograms.mskcc.org/prostate/PsaDoublingTime.aspx).

Clinical parameters have also been suggested to predict local or systemic recurrence, such as pT status (pT3b, pN1, Gleason ≥ 7) being associated with an increased risk of systemic relapse (Pound et al. 1999). The margin status is not a predictive factor for the type of relapse (Pound et al. 1999). The time to PSA recurrence is more controversial. Initially considered as a predictive factor of systemic relapse if less than 2 years, this finding has been recently discussed in a retrospective cohort of 14,632 patients followed for a median 11.5 years after surgery (Boorjian et al. 2011).

17.5.2 Radiation Therapy

Achieving a PSA nadir of less than 0.5 ng/ml seems to be associated with a favorable outcome (Ray 2006). The PSA at 1 year after radiotherapy alone is also proposed as a predictor of metastasis and death if above 2 ng/ml (Alcantara et al. 2007). As after surgery, a low PSA-DT is associated with secondary metastases (Maffezzini et al. 2007) with less clear thresholds: <3 months, 6 months, or 12 months (Zelefsky et al. 2005; D'Amico et al. 2006).

17.6 Clinical Workout at Relapse (Table 17.3)

Table 17.3 Proposed workout in PSA-relapsing patients

Bone scintigraphy and *CT scans*: no additional diagnostic value unless PSA above 20 ng/ml or PSA velocity above 2 ng/ml/year
MRI after surgery has no place in routine practice. After radiotherapy, if a local salvage curative treatment is considered, biopsies and endorectal MRI should be considered. 11C-PET might play a role in the future, for PSA above 1–2 ng/ml

17.6.1 Biopsies

They have no place after surgery as the results of salvage radiotherapy did not differ based on the biopsy results (Koppie et al. 2001; Leventis et al. 2001). They might be considered after radiotherapy in some cases.

17.6.2 Images

Bone scan and abdominal CT scan might be safely omitted in the routine workup of relapsing patients based on their low sensitivity and specificity (Scher et al. 2004). Only 4.1% and 27% of the bone scan were positive out of 144 scans in 93 patients (Cher et al. 1998); the lowest PSA associated with positive findings was 46 ng/ml in the absence of adjuvant hormonal therapy, and 15.47 ng/ml in patients who had received hormonal therapy. The likelihood of a positive bone scan remains ≤5% as long as PSA remains below 40 ng/ml. Similar data have been achieved by another (Gomez et al. 2004), the PSA predicting the finding on bone scan, while the PSA velocity predicted the finding of bone and CT scan. Recently, 239 relapsing patients were analyzed regarding the probability of having a positive bone scan after surgery (Dotan et al. 2005). Based on 60 positive scans, 4%, 36%, 50%, and 79% had a positive scan for a PSA level of respectively 0–10, 10–20, 20–50, or above 50 ng/ml. In multivariate analysis, PSA slope, PSA velocity, and total PSA were predictors of positive scan, total PSA being the highest predictive factor.

Endorectal MRI has been considered as a useful technique after surgery (D'Amico AV et al. 2006). In a cohort of 48 patients, its sensitivity was as high as 81%, with the mean PSA of 2 ng/ml at the time of diagnosis. Another series of

72 men obtained the following results (Cirillo et al. 2009): Sensitivity, specificity, predictive positive value, negative predictive value, and accuracy were respectively 61.4%, 82.1%, 84.4%, 57.5%, and 69.4% for unenhanced endorectal MRI and 84.1%, 89.3%, 92.5%, 78.1%, and 86.1% for enhanced endorectal MRI, with a statistical difference favoring the enhanced MRI. The mean total PSA was 1.23% ± 1.3 ng/ml. In practice, relapse after surgery is considered for PSA levels below 0.5 ng/ml where endorectal MRI is still too insensitive and inaccurate. Therefore, endorectal MRI has no place in routine practice for relapses after surgery.

Positron emission tomography (PET) published data suggest that this modality might be useful in relapsing patients. Only PET choline must be considered, and it must be remembered that the uptake of 11C-choline is not specific for prostate cancer. Its overall detection rate varies between 38% and 98% (Picchio et al. 2011). There is a link between the positive rate and the PSA level: if below 1 ng/ml, the detection rate is inacceptable (5–36%), a cut-off value of 1.4 ng/ml being considered as the lowest acceptable value (Giovacchini et al. 2010a) and others considering 2–2.4 ng/ml as optimal (Castellucci et al. 2009). Apart from PSA level, there is also a link between the PSA-DT and the positivity rate (Castellucci et al. 2009; Giovacchini et al. 2010b), suggesting that for PSA-DT <3 months, this imaging modality might have a place. Immunoscintigraphy using Prostacint (a radiolabelled monoclonal antibody based on prostate-specific membrane antigen for messenger RNA (PSMA), known as 111-indium capromab pendetide) has no role, based on high false-positive and negative rates (Scher et al. 2004).

17.6.3 PSA Relapse Following Radiation Therapy: Local Staging

This local staging plays a major role if a local salvage procedure is considered. According to an ASTRO consensus recommendation (Cox et al. 1999), systematic prostate biopsy at PSA relapse has no place. But when considering a local salvage treatment, especially radical prostatectomy, they have a major role (Heidenreich et al. 2008). They are best performed after 1.5–2 years following radiation therapy or brachytherapy seeds and 3 months after cryotherapy or high-intensity focused ultrasound (HIFU): a local relapse is confirmed if positive (viable cancer cells) beyond 2 years after radiation therapy. In those situations, endorectal MRI, MRI spectroscopy, and dynamic contrast-enhanced MRI might have a major role (Rouvière et al. 2004; Pucar et al. 2005; Sala et al. 2006) based on a clear differentiation of active and fibrous tissue on T2-weighted signal, with a sensitivity and a specificity of 86% and 96%, respectively, for extracapsular extension and seminal vesicle invasion. They appear to be more sensitive than TRUS or TRUS-guided prostate biopsies to detect viable tumor.

17.7 Treatment of Biochemical Failure After Treatment with Curative Intent

The timing and treatment modality of PSA-only recurrence remain controversial. The decision to undergo a salvage treatment must be evidence-based with answers on several parameters: what is the patient's expected survival, what is the natural history of his recurrence, is it a local or a systemic one, and what is to be expected from the treatment: overall survival benefit, symptom benefit, symptom-free duration benefit, and at which side-effects cost?

17.7.1 Evaluation of the Expected Survival

This point is the cornerstone of any decision. A patient with a local relapse and a 3-year PSA-DT will be offered different modalities: if he is 55 years old, ECOG 0, or 78 years old, ECOG 3. Above 70 years of age, the expected

survival is really heterogeneous as shown by Walter et al. (2001). A 14-year life expectancy is expected at 75 years of age if healthy (25% of the population), 9 years if vulnerable, while it is only 5 years if frail (25% of the population). This highlights the importance of an individual evaluation. Many tools are available, none being perfect and really simple, the ASA, ECOG, or Karnovsky being too vague to really discriminate. The most often used is the Charlson, and the most predictive and simple might be the chronic disease score (CDS) (Boulos et al. 2006), or even simpler such as the gait speed (Studenski et al. 2011). For older patients, guidelines are available (Droz et al. 2010). A detailed analysis of these tools is far beyond the scope of this article, but considering this point before any decision is all the more important since the patient is having comorbidities. They will lead the survival in the vast majority of the situations (Lu-Yao et al. 2011).

17.7.2 Natural History After Relapse

The overall median time from recurrence to metastasis is 8 and 5 years from metastasis to death (Pound et al. 1999). Different results have been published regarding long-term metastasis-free survival or specific survival in relapsing patients after surgery. At 15 years, Pound et al. (1999) reported a 25% metastases-free survival, while Boorjian et al. (2011) observed a 76% metastases-free survival. The same discrepancy was observed regarding 15-year specific survival: from 53% (Freedland et al. 2006) to 84% (Boorjian et al. 2011). Not surprisingly, major factors associated with survival were those previously discussed: low PSA-DT, high Gleason score, pN+, or pT3b status. The differences in the long-term survival reported might be associated with different populations, different adjuvant, or salvage policies (early or symptom differed). However, these results highlight the fact that apart from very aggressive situations (Gleason > 7, pN+, pT3b, PSA-DT < 6 months at relapse), the clinical impact of relapse is usually differed to a very long term. This might question the systematic use of salvage treatment with these associated side effects (Pinover et al. 2003; Guillonneau and Fizazi 2011).

17.8 Salvage After Surgery

17.8.1 Salvage Radiation Therapy

The place of adjuvant or salvage radiotherapy is discussed elsewhere (Chap. 13, Wiegel). Available data on salvage radiotherapy suggest some points to be clear predictors of efficacy. Clinical stage (pT < pT3b, pN0, Gleason) (Stephenson et al. 2004b) appears to be predictive, while margin status remains controversial (Leventis et al. 2001), the negative status being often considered to increase the risk of a second failure (Katz et al. 2003; Stephenson et al. 2004b). The most powerful factor appears again to be the PSA, either its doubling time or its preradiation status. A normalized postoperative PSA is a strong predictor of efficacy compared to a PSA > 0.1 ng/ml (Cox et al. 1999). A PSA-DT above 10 or 12 months is also associated with a better response to salvage radiotherapy (Leventis et al. 2001; Stephenson et al. 2004b). Finally, the PSA at the time of radiotherapy is the one of the strongest predictor. In a retrospective multicenter cohort of 1,540 patients with a salvage radiotherapy (Stephenson et al. 2007), the 6-year biochemical-free survival was 48% in men with PSA <0.5 ng/ml, whereas it was only 40%, 28%, and 18% in men with PSA levels of respectively 0.51–1 ng/ml, 1.01–1.5 ng/ml, and >1.5 ng/ml, respectively. Even if highest in patients with the lowest PSA, a metastasis-free survival benefit was observed in all PSA categories (<0.2, 0.2–1.0, >1.0 ng/ml), from a subgroup analysis of the SWOG S8974 trial (Swanson et al. 2007). All these parameters have been combined in prediction tools either segmented (Buskirk et al. 2006) or continuous (Stephenson 2007), none being externally validated. The survival impact of this salvage procedure has only recently been observed (Trock et al. 2008). In a retrospective cohort of 635 relapsing patients, with a median follow-up of 6 years after recurrence, the benefit of salvage radiation for prostate-cancer-specific mortality was seen (threefold increase in prostate-cancer-specific survival) if

delivered less than 2 years after relapse. In a multivariate analysis, the benefit however was only seen in those with the most aggressive relapse: in those with a PSA-DT below 6 months, the 10-year specific survival was 82% compared to 30% without salvage radiotherapy, while it was 86% and 75% for those with a PSA-DT above 6 months. No apparent benefit was observed in those with a long PSA-DT. Based on a retrospective study, these results must be externally confirmed, ideally in a prospective trial.

The most frequently used dose for adjuvant and salvage radiation is less than 66 Gy. However, as with primary treatment, an increased dose in the salvage setting may improve the biochemical response (Swanson et al. 2007) without worsening local toxicity (King and Kapp 2008; King and Spiotto 2008). Dosages up to 70 Gy showed better biochemical recurrence-free rates at higher doses, with 66.8 Gy found to be the dose required for 50% biochemical recurrence-free survival (TCD50).

Target volume delineation is another conflicting issue, even if guidelines are available (Poortmans et al. 2007). They have been found to vary by up to 65% between different radiotherapists (Wiltshire et al. 2007; Mitchell et al. 2009). The place of whole pelvis salvage radiation remains unclear, even if suggested to be beneficial in high-risk patients only (Spiotto et al. 2007). In the EORTC 22911 study, 3.1% of men had to interrupt adjuvant radiation because of local complaints, mainly diarrhea. Although grade 3 or 4 toxicity is rare for adjuvant or salvage radiation, it was almost doubled in the adjuvant arm of the EORTC 22911 study (2.6% vs. 4.2%) (Bolla et al. 2005) and the SWOG S8794 (Thompson et al. 2009) study, particularly urethral stricture and incontinence.

17.8.2 Salvage Hormonal Therapy

Compared to salvage radiotherapy, no randomized trial is available using salvage androgen deprivation therapy (ADT), and we must rely on retrospective cohorts only. Two large cohorts are available. In the first one (Moul et al. 2004) including 1,352 patients with postoperative PSA recurrence, no significant difference was observed in the time to clinical metastases with early ADT (at PSA recurrence, using different PSA thresholds) compared to delayed ADT (at the time of clinical metastases) ($p=0.66$). However, early ADT (either when PSA was below 5 or 10 ng/ml) delays the time to clinical metastases in high-risk patients (Gleason >7 and/or a PSA-DT ≤12 months). But ADT had no impact on specific survival. The second large cohort (Siddiqui et al. 2008) is based on 6,401 pN0 patients with postoperative ADT, including 265 with salvage ADT at relapse and a median 10 years of follow-up. Using a matched-paired comparison, no specific survival benefit was observed if salvage was used whatever the considered PSA threshold (0.4, 1, or 2 ng/ml), and even a possible decreased specific survival in some subgroups. Lastly, a highly selected group of 91 relapsing patients were treated with ADT at the time of metastasis (Makarov et al. 2008). In this cohort, the median time from surgery to failure was 24 months, 36 months from failure to metastasis, and 84 months from metastasis to death, representing a median 168 months between surgery to death. PSA-DT below 3 months again was a highly significant predictor of death. Once the salvage ADT is instituted, the obtained PSA nadir is predictive of specific survival, the threshold being a PSA below 0.2 ng/ml, even with a PSA-DT that is below 3 months (Stewart et al. 2005).

All these data have been obtained using a continuous medical castration, mainly surgical or with an LHRH analogue. Results using other medical ADT (nonsteroidal antiandrogen as monotherapy, or minimal androgen blockade) are even more scarce and unreliable.

Intermittent androgen deprivation (IAD) might be an elegant way to overcome the long-term side effects and costs of ADT (Abrahamsson 2010). The trial reported by Tunn et al. (2003) on 218 relapsing patients comparing continuous versus IAD did not show any difference in terms of hormone-refractory status at 48 months. The recently presented SWOG-JPR7 trial (Klotz et al. 2011) in relapsing patients after radiotherapy is a strong plea favoring IAD in relapsing patients, as long as ADT is considered. It will be discussed in the next paragraph.

Compared to the locally advanced situation, the salvage combination of ADT to external beam has been analyzed. No survival benefit was seen in a retrospective cohort (Trock et al. 2008). Last year, the results of the RTOG-9061 trial comparing salvage radiotherapy combined with either placebo or bicalutamide (150 mg daily for 24 months) were reported (Shipley et al. 2011). A benefit in terms of progression-free survival at 7 years (57% compared to 40%, $p < 0.0001$) and metastasis-free survival (92.6% vs. 87.4%, $p = 0.0107$) was observed. But without any overall survival difference, ongoing trials will clarify the effectiveness of such a combination, using more conventional ADT (French GETUG 16) and MRC RADICALS trials. Currently, there is no place for chemotherapy in patients with PSA recurrence only based on available preliminary negative results (Oudard et al. 2011).

17.9 Salvage After Radiotherapy

In a recent review from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) comprising 2,336 patients (Grossfeld et al. 2002) demonstrated that 92% of patients initially irradiated received secondary ADT for PSA progression. In the absence of salvage procedures, the mean time interval from biochemical to clinical progression is approximately 3 years.

Therapeutic options in these patients are ADT or local procedures, such as salvage radical prostatectomy, cryotherapy, and interstitial radiation therapy (Stephenson et al. 2004a; Heidenreich et al. 2010). Salvage surgery has not gained widespread acceptance because of its associated morbidity, namely, incontinence, local recurrences, and rectal injuries. However, in well-selected patients, the procedure may result in long-term disease-free survival.

17.9.1 Salvage Surgery

Salvage radical prostatectomy is a rarely performed procedure based on its poor reputation: difficult procedure with a high associated complication rate, and a poor efficacy. Up to this year, mainly single-center retrospective cohorts were reported. Recently, a large international retrospective cohort of 404 patients has been published (Chade et al. 2011). All had biopsy-proven recurrence; median age was 65 years, and the median presurgery PSA, 4.5 ng/ml (range 0.1–105). None received any form of ADT. After a median 4.4 years of follow-up, the 10-year relapse-free was 37% (31–43%); metastasis-free survival, 77% (71–82%); and specific survival, 83% (76–88%). On multivariate analysis, presalvage PSA, biopsy, and specimen Gleason score predicted relapse-free and metastasis-free survival. Nodal involvement was also predictive of metastasis-free survival. The best outcome was observed with a presalvage PSA below 4 ng/ml and a presalvage biopsy Gleason ≤7. Predictors of organ-confined disease have been clarified (Heidenreich et al. 2010): biopsy Gleason at salvage below 7, less than 50% positive cores at salvage, PSA-DT > 12 months at relapse, and previous brachytherapy.

The toxicity of this difficult procedure is acceptable in tertiary centers with an overall perioperative complication rate ranging from 9% to 27%, a transfusion rate from 4.5% to 29%, a rectal injury from 2% to 3%, and a social continence from 50% to 81% (also, it must be acknowledge that no standard definition has ever been used). The initial radiotherapy modality appears to lead to different preoperative difficulties and postoperative continence results (Heidenreich et al. 2010).

17.9.2 Salvage Brachytherapy

The experience with salvage brachytherapy for radiation failures is very limited (less than 300 cases reported). A systematic review has been recently published (Kimura et al. 2009). Most series are limited (17–49 patients) and have a short follow-up (median 19–64 months). The overall results are at best moderate, with a disease-free survival at 5 years between 34% and 87%. But the use of different failure definition and the unknown use of combined or salvage ADT preclude any clear conclusion. Recently,

Burri reported an extended 86 months median follow-up for 37 patients (Burri et al. 2010), achieving a 10-year biochemical disease-free survival, and CSS were 54% and 96%, respectively. Presalvage PSA below 6 ng/ml was the only associated factor for long-term disease-free survival. Salvage brachytherapy after a combination of external beam and brachytherapy has also been reported with poor results: 20% relapse-free survival at 5 years in 31 patients after 9-year mean follow-up (Moman et al. 2010). All these modalities have been associated with significant grade 3–4 toxicity (GU ranging from 14% to 47%, GI from 6% to 24%).

17.9.3 Salvage High-Intensity Focused Ultrasound (HIFU)

The experience of salvage HIFU after radiation therapy is very limited, based on less than 400 patients reported in retrospective studies (Zacharakis et al. 2008; Murat et al. 2009). Based on the largest series of 167 patients followed for a mean 18 months (Murat et al. 2009), the 3-year relapse-free survival is only 53% (Phoenix definition). The overall oncological control rate after a short median follow-up of near 2 years is in the range of 30–40%. Factors associated with a short relapse-free survival are a high pre-HIFU PSA, a high preradiotherapy D'Amico risk group, and the use of ADT during the treatment. Side effects are significant with 49% incontinence rate (leading to 11% artificial urinary sphincter implantation), 8.5–36% obstruction rate, and 17–20% urethral or bladder neck stricture rate, difficult to manage. Up to 3% of patients also developed a urethrorectal fistula.

17.9.4 Salvage Cryosurgical Ablation

Salvage cryosurgery might be an alternative to local salvage using surgery or HIFU. The device improvement with the argon/helium-gas-based cryotherapy is the standard technology. Most available data are single-center based, with less than 1,000 reported patients (Kimura et al. 2009). The median follow-up ranges from 12 to 39 months, leading to 5-year disease-free survival between 44% and 73%. As with salvage brachytherapy, the failure definition was not uniform, limiting the interpretation. Pretreatment D'Amico risk classification is an important predictive factor of efficacy (Ismail et al. 2007), as are the pretreatment PSA (<10 ng/ml) and biopsy Gleason score (<7) (Chin et al. 2001; Pisters et al. 2008). This modality is associated with significant side effects, especially urinary incontinence (ranging from 4% to 40%, with 2–4% severe incontinence), obstruction, or retention (from 0% to 21%). With the use of thermocouples and the third-generation device, the recto-urethral fistula incidence is around 1–2% and still decreasing.

17.9.5 Local Salvage: How to Choose?

The most effective local salvage modality appears to be salvage radical prostatectomy. However, its use is limited with its technical difficulties and high complication rate. Less-invasive procedures are appealing. It must be recognized that even if less toxic, they are not associated with long-term results and large multicenter cohorts. The most studied minimally invasive procedure so far appears to be the third-generation cryotherapy; also, this does not mean that it is the most effective. Large prospective trials with universally accepted failure definition are urgently awaited.

Finally, if local salvage is considered, these minimally invasive modalities could be used as focal salvage, provided an effective imaging of the intraprostatic recurrence (Rouviere et al. 2010).

17.9.6 Salvage ADT After Radiotherapy

Clear data regarding the effectiveness of salvage ADT after radiotherapy are lacking. One of the largest cohorts is retrospective, based on 248 patients (ASTRO definition) (Pinover et al. 2003). The use of salvage ADT was associated with a clear benefit in terms of metastasis-free survival at 5 years (57% compared to 78%, $p = 0.0026$),

but only for those having a PSA-DT < 12 months. No survival benefit was seen in any group.

Long-term ADT is associated with significant side effects. Using an intermittent modality might be beneficial. The recently presented SWOG-JPR7 trial answers this specific question (Klotz et al. 2011). This large cohort of 1,340 patients relapsing after radiotherapy (either primary of following radical prostatectomy), was able to show a noninferiority of IAD compared to continuous ADT (median overall survival of 9.1 years in the continuous compared to 8.8 years in the intermittent arm) ($p = 0.009$ for noninferiority). After an 8-month induction period using an LHRH analogue combined with a nonsteroidal antiandrogen for 1 month, patients were randomized between IAD and continuous ADT in the absence of clinical progression, and the PSA was below 4 ng/ml. In the IAD arm, the ADT was stopped and resumed when the PSA went above 10 ng/ml for fixed 8-month periods. Other benefits apart from less drug were observed, such as an improved quality of life in the intermittent arm. The full paper is awaited.

17.10 Salvage After First-Line HIFU

Although, first-line HIFU is still a matter of intense debate, and salvage radiotherapy after failed HIFU seems to be effective. The largest cohort (Riviere et al. 2010) of 100 patients (83 patients without any form of ADT) after a median 33 months of follow-up showed an overall 72.5% relapse-free survival at 5 years without ADT. The D'Amico classification was predictive of relapse-free survival, as were the PSA nadir and time to nadir postsalvage. The toxicity was acceptable (7.1% GU grade 3 or above).

17.11 Conclusion

Any form of salvage treatment must be balanced by the natural history of the individual relapse, the expected benefit (PSA relapse-free survival, metastasis-free survival, or cancer-specific survival), and the individual overall life expectancy. Apart from treating patients and sometimes doctor's anxiety, treating the PSA only is no longer acceptable. A clear and real benefit must be expected and accepted by the patient before embarking into any form of treatment.

Following surgery, even if effective at relapse, the optimal timing of postoperative radiotherapy remains unclear. If considered at salvage, it should be used as early as possible. Based on the recognized importance of local control to decrease the metastasis rate and increase the overall survival, it must be systematically considered in patients with a low PSA-DT, as long as survival is the main objective. For slow-growing PSA, its survival impact is as best questionable. The clinical benefit of salvage ADT remains questionable except in the most aggressive situations (Gleason > 7 and/or PSA-DT < 12 months), as long as metastasis-free survival is the main objective. No survival benefit has ever been observed. And the PSA response must be balanced against the long-term side effects of ADT. IAD should be considered as the new standard. In 2011, the combination of ADT and external beam at salvage remains experimental.

Following radiotherapy, salvage prostatectomy is a surgically challenging but effective secondary treatment with curative intent. It must be restricted to those young patients with the highest probability of long-term cure, i.e., as soon as possible after relapse, with a PSA < 4 ng/ml, a PSA-DT > 12 months, and a postradiotherapy Gleason score < 8. Other local salvage modalities (brachytherapy, cryotherapy, or HIFU) must still be considered as experimental. Systemic salvage after radiotherapy is based on ADT, even if convincing data are lacking. As for surgery, only those with a PSA-DT < 12 months might benefit from early use. No survival benefit has ever been observed. IAD should be considered as the new standard.

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First-Line Hormonal Manipulation of Prostate Cancer

18

Suresh Venugopal and John Anderson

Contents

S. Venugopal, M.S., MRCS • J. Anderson, ChM, FRCS (✉)
Department of Urology, Royal Hallamshire Hospital, Sheffield, UK
e-mail: john.anderson@sth.nhs.uk; johnanderson@clara.co.uk

18.1 History of Hormone Manipulation

Little did the Flemish anatomist Andreas Vesalius know that the prostate gland he had illustrated for the first time in 1543 in De humani corporis fabrica would assume such importance. In 1853, the British surgeon John Adams described 'A case of scirrhus of the prostate gland with a corresponding affection of the lymphatic glands in the lumbar region and in the pelvis' and had judged this to be a rare disease (Denmeade and Isaacs 2002). Prostate cancer is now recognised to be the most common cancer in men with 258,000 men dying worldwide from the disease in 2008 (Ferlay et al. 2010).

The dependence of the prostate gland on testosterone had been first recognised in 1786 by John Hunter who found removing the testicles from young male animals prevented growth of the prostate (Hunter 1786). In 1941, Charles Huggins and Clarence Hodges confirmed that prostatic cancer is dependent for its growth on androgen activity in the body and that disseminated carcinoma of the prostate could be inhibited by eliminating androgens, either through surgical castration or neutralisation of their activity by oestrogen injection (Huggins and Hodges 1941). It was not until 1971, however, that Andrew Schally identified the complete peptide sequence of endogenous leutinising hormone-releasing hormone (LHRH) which is produced in the hypothalamus (Schally et al. 1971) and responsible for luteinising hormone (LH) secretion in the anterior pituitary which prompts the Leydig cells in the testis to produce testosterone.

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From there, he went on to develop synthetic analogues which formed the basis for medical castration therapies. Achieving these two important milestones resulted in Charles Huggins and Andrew Schally each being awarded the Nobel Prize for Medicine and Physiology in 1966 and in 1977, respectively, and, to date, they remain the only Nobel Prizes awarded in the field of urological practice. Today, in 2012, hormone manipulation remains the first line and mainstay of treatment for men with metastatic prostate cancer (Baker et al. 2008; Heidenreich et al. 2011).

18.2 Physiology of Hormone Manipulation

A full understanding of the hypothalamic–pituitary–gonadal axis has allowed different means of testosterone suppression or control to be developed for the treatment of prostate cancer. LHRH is produced by the neuroendocrine cells in the hypothalamus and stimulates the anterior pituitary gland to release LH. This in turn stimulates the Leydig cells in the testis resulting in the secretion of testosterone. Testosterone production acts as negative feedback on the hypothalamus to maintain normal testosterone levels in the body. Thus, manipulation of testosterone levels to control prostate cancer growth can be achieved in one of the three ways (Fig. 18.1) (Anderson 2003):

1. Surgical removal of the testes where the testosterone is produced
2. Disruption of the hypothalamic–pituitary–gonadal axis to reduce testosterone secretion by the testis
3. Direct block of the androgen receptors in the prostate itself to counteract the effects of circulating testosterone

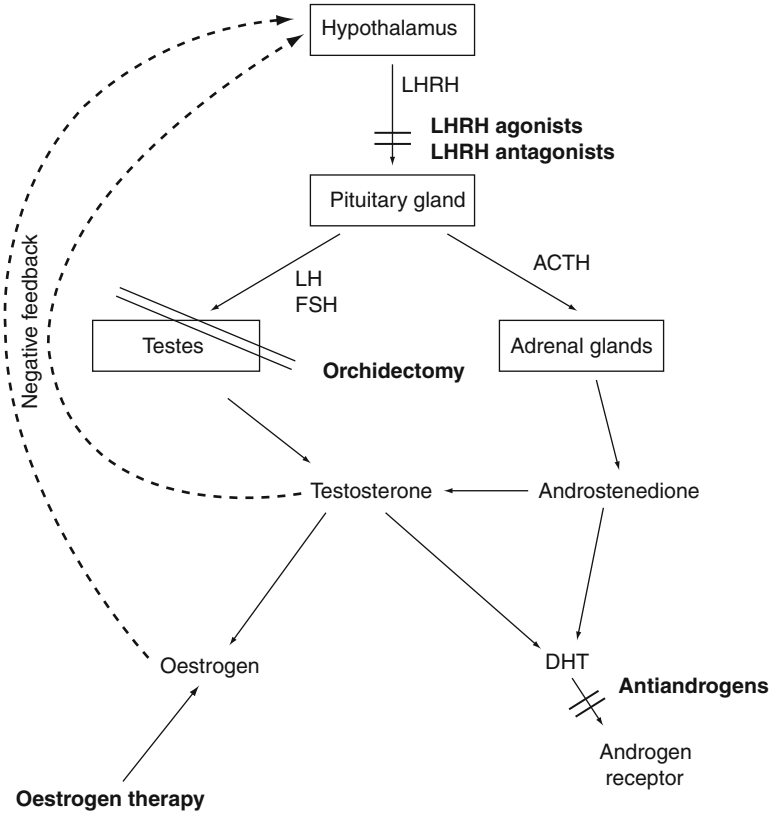

Fig. 18.1 The hypothalamic–pituitary–gonadal axis showing the site of action of the hormonal therapies for prostate cancer. *LHRH* luteinising hormone-releasing hormone, *LH* luteinising hormone, *FSH* follicle-stimulating hormone, *ACTH* adrenocorticotrophic hormone, *DHT* dihydrotestosterone

Table 18.1 Comparative studies of hormonal therapy in patients with metastatic prostate cancer (Anderson 2003)

Hormone therapy	Comparator	Patients	Duration of follow-up (months)	Overall survival outcome	Reference
Goserelin 3.6 mg per 28 days	Bilateral orchidectomy	358	Median 24	Median: 110 vs. 99 weeks	Kaisary et al. (1991)
Goserelin 3.6 mg per 28 days	Bilateral orchidectomy	283	Median 48	Median: 119 vs. 136 weeks	Vogelzang et al. (1995)
Bicalutamide 150 mg per day	Castration	852	Median 23	Median: 105 vs. 111 weeks	Tyrrell et al. (1998)
Flutamide 250 mg tds	Bilateral orchidectomy	104	Minimum 36 (median 69)	No difference	Boccon-Gibod et al. (1997)
Polyoestradiol phosphate	MAB	915	Median 18.5	Deaths: 58.1% vs. 58.9%	Hedlund and Henriksson (2000)

18.3 First-Line Hormone Manipulation of Prostate Cancer: The Therapeutic Options

18.3.1 Surgical Castration

Bilateral orchiectomy removes the testicular source of androgens and rapidly leads to castrate levels of testosterone. It is considered the gold standard therapy for hormone manipulation against which all other modalities of treatment are judged (Griffiths 1993) (Table 18.1). Surgical castration is the preferred therapeutic option in patients in whom the testosterone levels need to be rapidly lowered to avoid serious consequences from complications of advanced disease such as spinal cord compression or renal failure. This procedure rapidly lowers testosterone to very low levels (mean 15 ng/dL) (Oefelein et al. 2000) and not only reduces the painful symptoms of the disease but also slows overall cancer progression. Although orchidectomy may be reliable, economical, simple and safe to perform, it is not a popular option for men with prostate cancer due to the psychological effects associated with permanently losing one's manhood and the inevitable and irreversible adverse impact on libido and potency (Anderson 2003). Equivalent levels of testosterone suppression and oncological control by medically based castration therapies have resulted in limited use of orchidectomy in routine urological practice (Mcleod 2003).

18.3.2 Medical Castration

Medical castration is now the treatment of choice for men with advanced prostate cancer both by the patients themselves and by their doctors.

The following drugs are available to use in this context:

18.3.2.1 Diethyl Stilbesterol (DES)

The mechanism of action of oestrogens is complex. They act not only by reducing the secretion of LHRH, and thereby LH and testosterone (Fig. 18.1), but also by androgen inactivation and by direct suppression of Leydig cells. In addition, synthetic oestrogens have a suppressive effect on dihydroepiandrosterone sulphate (DHEA), which is the precursor for adrenal androgen production (Kitahara et al. 1997; Miyamoto et al. 1998) and may also be directly cytotoxic to the prostatic epithelium as noted in in vitro studies (Oh 2002). The Veterans' Administration Cooperative Urological Research Group studies in the 1960s showed that oestrogens achieved comparable cancer control to surgical castration but, at a dose of 5 mg/day, DES is likely to cause significantly more cardiovascular morbidity and even mortality (Byar 1973). With the advent of LHRH analogues and antiandrogens which do not carry the same risk of cardiovascular toxicity, the use of oestrogens has fallen out of favour.

Despite various attempts to overcome the cardiovascular toxicity of oestrogens, including parenteral administration of polyoestradiol phosphate

(PEP) and the use of antithrombotic medication such as low-dose aspirin or warfarin, ongoing concerns regarding cardiovascular complications have prevented the return of oestrogens into mainstream practice (Hedlund et al. 2008; Heidenreich et al. 2011; Seidenfeld et al. 2000).

18.3.2.2 LHRH Analogues

Buserelin was the first LHRH analogue to be used to treat prostate cancer. It is administered by subcutaneous injection for the first week followed by intra-nasal spray every 4 h but rapidly fell out of favour due to the frequency and less than optimal route and frequency of administration (Mcleod 2003). The newer LHRH analogues have the convenience of monthly or three monthly (goserelin, leuprorelin, triptorelin) or in some cases half-yearly (leuprorelin) and annual (histerelin) depot preparations. Their efficacy has been found to be to be equal to surgical castration or that of DES (Anderson 2003; Kaisary et al. 1991; Vogelzang et al. 1995).

Synthetic LHRH analogues work by acting as a competitive agonist at the LH receptors in the pituitary, and before they saturate the receptors, they initially stimulate the production of LH from the pituitary gland. Administration of LHRH analogues therefore causes an initial rise, or 'surge', in serum testosterone levels which can result in a 'flare' in clinical symptoms (Waxman et al. 1985). This effect can be minimised by the concurrent administration of antiandrogens started prior to the first injection of the LHRH analogue and continued for 1–2 weeks thereafter. Whilst the significance of this clinical flare in patients with extensive disease, or in those with significant back pain or early neurological sequelae, is undoubted (Thompson 2001; Waxman et al. 1985); we also need to consider whether this surge in the testosterone levels may also cause a subclinical stimulus to cancer growth.

18.3.2.3 GnRH Antagonists

Gonadotropin-releasing hormone (GnRH) antagonists are a more recent development, and their mechanism of action is quite different to that of the analogues. Rather than act as competitive agonists with the endogenous LHRH in the pituitary, they are genuine antagonists which immediately block the receptors, thereby blocking LH release and testosterone production and avoiding the initial testosterone surge seen with the LHRH agonists. Unlike the analogues, these agents also cause a reduction in FSH secretion from the pituitary, the significance of which is uncertain. GnRH blockers cause a rapid and profound fall in the testosterone levels, comparable with surgical castration, something which is not achieved by LHRH analogues for up to 28 days. The adverse event profile for these agents is small (Klotz et al. 2008) and whilst the use of the GnRH blocker abarelix has been restricted because of potential hypersensitivity reactions (Trachtenberg et al. 2002), degarelix has been licensed for use in the treatment of metastatic and symptomatic prostate cancer (Klotz et al. 2008) both in Europe and North America.

18.3.2.4 Antiandrogens

Steroidal antiandrogens such as cyproterone acetate and nonsteroidal agents such as flutamide, bicalutamide or nilutamide may be used either as monotherapy or else as part of a combined treatment regime together with an LHRH agonist. The nonsteroidal drugs are purely antiandrogenic and only block the androgen receptors in the prostate. When used on their own, nonsteriodal antiandrogens ensure preservation of normal circulating levels of testosterone and therefore have potential quality of life benefits in terms of maintaining potency and libido (Iverson et al. 2001). In addition to their antiandrogen properties, the steroidal antiandrogens also have central progestational effects, resulting in suppression of LH and thereby resulting in lower circulating testosterone levels leading to impotence and loss of libido (Anderson 2003). Their use has been limited by their liver (Parys et al. 1991) and possible cardiovascular toxicity (Seaman et al. 2007).

The use of flutamide is limited by excessive gastrointestinal side effects, but bicalutamide monotherapy has been extensively investigated and is known to have equivalent efficacy to LHRH agonists at a dose of 150 mg/day for patients with locally advanced prostate cancer (Iversen et al. 2000). Despite the better quality of life offered by bicalutamide, however, patients with metastatic prostate cancer have a reduced overall survival by

42 days compared to those treated with LHRH agonists, and for this reason, bicalutamide is not licensed for treating patients with metastatic disease.

18.3.3 Combined Androgen Blockade (CAB)

The persistence of low levels of circulating androgens from the adrenal glands was thought to be responsible for prostate cancer progression despite castration by surgical or medical means, and combining orchidectomy or LHRH analogues with an antiandrogen was considered to be the most effective means to combat the effects of these androgens at the level of androgen receptor in the prostate gland (Akaza 2011; Schmitt et al. 2001). Many randomised trials have sought to clarify the validity of this assumption and have compared either orchidectomy or LHRH analogues in combination with an antiandrogen or placebo (Eisenberger et al. 1998; Prostate Cancer Trialists' Collaborative Group 2000). A large meta-analysis of 8,275 patients from 27 studies concluded that CAB has a minimal overall 5-year survival benefit of between 2% and 5% (Prostate Cancer Trialists' Collaborative Group 2000). The side effects from combination therapy are increased due to the addition of antiandrogens and against this have to be balanced the benefit to be derived after 5 years of therapy. The number of men who have to be treated with combined androgen blockade for 5 years to prevent one additional death from prostate cancer is between 20 and 100, and this is at a cost of more than US$1 million per quality-adjusted life-year for CAB over orchidectomy alone (Loblaw et al. 2007), and it has been suggested that CAB is not used as standard therapy for first-line management of advanced prostate cancer but reserved for the failures of initial monotherapy (Miyamoto et al. 2004).

18.3.4 Intermittent Androgen Deprivation Therapy (IAD)

It has been hypothesised that if an androgen-dependent tumour which regressed following androgen withdrawal was re-exposed to androgens again, it would regain its potency for apoptosis, thereby retaining its androgen-dependent status for longer (Akakura et al. 1993; Klotz et al. 1986; Suzuki et al. 2010). Animal studies have certainly shown that androgen dependency was maintained for longer using intermittent androgen deprivation therapy (Akakura et al. 1993).

Quite apart from the theoretical advantage of prolonging androgen dependence, there can also be a very real advantage to intermittent therapy by reducing the adverse effects associated with that treatment. Whilst the long-term side effects of ADT such as osteoporosis, metabolic syndrome, cardiovascular toxicity, hot flashes and fatigue can be minimised, 'holidays' from treatment may also allow men to recover sexual function, during periods off treatment (Suzuki et al. 2010). In a recent review, 19 phase two studies and 8 phase three studies were analysed for quality of life issues and the potential benefits of intermittent androgen deprivation therapy. It was found that the oncological outcomes for intermittent ADT were at least as good as continuous ADT, but when it came to quality of life (QoL), especially recovery of sexual function, intermittent therapy was superior to continuous treatment (Abrahamsson 2010).

Although the superiority of IAD over continuous ADT, in terms of oncological control, may never be demonstrated, the results of two large randomised controlled trials (NCIC PR7 and SWOG 9346) are awaited to ascertain the quality of life benefits of intermittent therapy (Buchan and Goldenberg 2010).

18.4 When Is It Right to Commence Hormone Therapy?

18.4.1 Symptomatic Metastatic Disease

Symptomatic metastatic prostate cancer remains an absolute indication for immediate hormone manipulation, and successful outcomes for such patients treated with immediate ADT were confirmed from the VACURG studies nearly five decades ago (The Veterans Administration Cooperative Urological Research Group 1967).

The choice of ADT when treating patients with serious complications such as impending spinal cord compression or pathological fracture is determined by the requirement for a very rapid reduction in the levels of serum testosterone, and this can be achieved most effectively either by surgical castration (with castrate testosterone levels achieved at a mean 8.3 h) (Lin et al. 1994) or GnRH antagonists (Klotz et al. 2008). Whilst randomised controlled trials to confirm the benefits in this setting would be clearly inappropriate, we know that immediate hormonal therapy helps to achieve the best and quickest palliation of symptoms in patients with symptomatic metastases and reduces their risk from complications of the disease (Heidenreich et al. 2011).

18.4.2 Asymptomatic Metastatic Disease

The best time to commence ADT in men with metastatic disease who are asymptomatic is the night before they develop symptoms, but this is clearly impossible to predict (Kirk 2000). Although the outcomes in terms of overall survival have not been shown to be inferior to those in whom treatment was deferred until they become symptomatic (Nair et al. 2002; Walsh et al. 2001), patients commenced on ADT at the time of diagnosis went on to develop fewer complications such as pathological fractures, cord compression, ureteric obstruction or the need for TURP for bladder outflow obstruction (Kirk 2000). The choice of ADT in this group of patients, as well as the merits of continuous or intermittent treatment, has already been discussed in Sects. 18.3.3 and 18.3.4.

18.4.3 Lymph Node Only Metastatic Disease (M0 N1-3 Any T)

The pathological detection of lymph node metastases in men undergoing radical prostatectomy with curative intent has decreased over the years (Haese et al. 2002). Evidence to support the optimal management of this group is necessarily limited and was provided by the ECOG trial from 36 institutions in the United States where 100 patients with positive lymph nodes identified after radical prostatectomy for clinically localised prostate cancer were assigned to receive either immediate ADT (medical or surgical castration) or their treatment was deferred until they developed metastases confirmed on a bone scan. With a median follow-up of 11.9 years, this trial showed better outcomes for those treated at diagnosis in terms of overall, cancer-specific and progression-free survival (Messing et al. 2006). By contrast, another retrospective analysis showed no difference in overall survival between those who started immediate ADT after surgery, compared to those who received salvage ADT based on biochemical failure or disease progression (Gjertson et al. 2007), whilst in the EORTC 30846 study, patients confirmed to be node positive, and in whom no primary treatment was given to the prostate, no significant difference was identified between those receiving immediate versus delayed ADT with 13 years of follow-up (Schröder et al. 2009).

18.4.4 Locally Advanced Nonmetastatic Disease (M0 N0 T3/4)

The gold standard for treatment in patients with locally advanced disease but no evidence of nodal or skeletal spread is radical external beam radiotherapy in conjunction with 3 years of ADT (Bolla et al. 2010; Pilepich et al. 2005; Widmark et al. 2009).

In conjunction with radiotherapy, the use of ADT has unequivocally been shown to improve outcomes for patients on all counts in several trials (Bolla et al. 2010; Pilepich et al. 2005; Widmark et al. 2009). In the EORTC 22863 trial of external beam radiotherapy (ERBT) versus ERBT and ADT in patients with locally advanced prostate cancer, the 10-year clinical disease-free survival was 22.7% in the ERBT group and 47.7% in the combined treatment group, whilst prostate cancer mortality was 30.4% versus 10.3%, overall survival was 39.8% versus 58.1% with no evidence of increasing late cardiovascular toxicity

related to the ADT component of treatment (Bolla et al. 2010).

The Scandinavian prostate cancer group trial (SPCG7) specifically questioned the benefits of adding radiotherapy to immediate ADT. The prostate cancer-specific mortality at 10 years was 23.9% in the ADT alone group and 11.9% in the combined ADT and ERBT group with similar results for the overall mortality (39.4% versus 29.6%). Although urinary, rectal and sexual complications were slightly more common in the combined treatment group after 5 years, the addition of local radiotherapy to immediate ADT halved the 10-year prostate cancer-specific mortality and substantially decreased overall mortality with fully acceptable risk of side effects compared with immediate ADT alone (Widmark et al. 2009).

There is increasing interest in radical surgery as part of a multimodality approach to treatment in patients with locally advanced prostate cancer but a relatively low PSA and Gleason score. As with those patients treated with ERBT, these cases have also been shown to benefit from adjuvant ADT following surgery (Freedland et al. 2007; Schreiber et al. 2011).

ADT alone for men with locally advanced non-metastatic disease is best reserved for those who are not fit for radiotherapy, those who have bulky disease with a high PSA and a PSA doubling time of less than 1 year or in those who are symptomatic from the disease (Heidenreich et al. 2011).

18.4.5 Localised Disease (M0 N0 T1/2)

Despite the evidence to suggest that androgen deprivation is not the treatment of choice for men with localised prostate cancer, there has been a two- to threefold increase in the frequency of administration of ADT in this group of men over the last two decades (Cooperberg et al. 2003). There is no survival advantage for using primary ADT, with its unwanted systemic effects and side effects over local treatment such as radical prostatectomy or radical radiotherapy (Akaza 2006; Messing et al. 2006). Nevertheless, patients with localised disease who are deemed unsuitable for treatment with curative intent for whatever reason may eventually become a suitable candidate for ADT if symptoms develop or if their cancer progresses. The question which has to be addressed therefore is the ideal time when this treatment should be initiated. A population-based study of 19,271 men with localised prostate cancer comparing those who received ADT to those who were monitored until symptomatic progression showed that in men with poorly differentiated tumours, cancer-specific survival, but not overall survival, was improved with primary ADT (Lu-Yao et al. 2008). This benefit could not be demonstrated in patients with low-risk cancers (Messing et al. 2006). Considering the potential adverse effects associated with ADT, one should be mindful that any such treatment in this patient group should be individualised, and wherever possible, they should be offered a treatment with curative intent.

Again, the decision as to when to initiate ADT in men with a rising PSA after failed primary treatment can be a difficult one. The evidence to help us guide patients for the best depends on the grade and stage of the original tumour and the PSA kinetics following treatment (Anderson 2008; Studer et al. 2008), but the wishes of the patients can often confound this evidence-based approach to treatment.

Neo-adjuvant ADT in conjunction with radical prostatectomy has not shown any reduction in cancer recurrence rates after surgery although the positive surgical margin rates are reduced (Soloway et al. 2002). Adjuvant ADT for adverse histopathological findings following prostatectomy confers no survival advantage as noted in a recent Cochrane review (Kumar et al. 2006). By contrast, in conjunction with radiotherapy for localised prostate cancer, ADT is used both in the neo-adjuvant and adjuvant settings, and EORTC 22961 results have shown a definite overall survival advantage for both short- and medium-term ADT with the 3-year medium-term treatment providing superior outcomes (Bolla 2010; Poppel 2008).

Even after definitive curative treatment, pathologically confirmed stage T1 and T2 disease can

be associated with biochemical or clinical recurrence in up to 35% of patients (Freedland et al. 2005).

18.4.6 Summary

For patients with asymptomatic metastatic or locally advanced prostate cancer, the important question is: when should one initiate ADT? Information from the EORTC 30891 study of immediate versus deferred ADT in patients with advanced nonmetastatic prostate cancer provides helpful guidance for doctors and patients alike and can be extrapolated to guide the management of patients with a rising PSA after failed local treatment depending on the stage and grade of the primary tumour.

- Patients with a PSA at diagnosis of >50 ng/mL are likely to eventually die of prostate cancer and are therefore appropriate candidates for immediate ADT to prevent complications from progressive disease.
- Patients with a baseline of <8 ng/mL are at very low risk of dying from prostate cancer within 7 years of diagnosis and may never require ADT.
- For those with a PSA between 8 and 50 ng/mL, ADT should be initiated as soon as a PSA doubling time of <12 months is identified (Anderson 2008; Studer et al. 2008).

18.5 Side Effects and Quality of Life Issues

The first commandment for us as doctors is 'Primum non nocere' – 'First do no harm'. Despite the beneficial effects in terms of oncological control for ADT, one must be mindful of the potentially deleterious consequences and side effects of this form of treatment. The side effect profile of any form of hormonal manipulation in the short term is predictable and includes reduction in libido and sexual function. Of the various forms of therapy, nonsteroidal androgen monotherapy with bicalutamide would seem to provide the best chance at minimising these effects (Heidenreich et al. 2011; Iverson et al. 2001). Less predictable side effects such as hot flashes with LHRH analogues can be countered by the use of a progestational agent such as CPA or medroxyprogesterone (Irani et al. 2010). Patients on antiandrogens report breast swelling in up to 71% of cases (Higano 2003). This can be managed by tamoxifen or radiotherapy to the breast tissue prior to the initiation of treatment (McLeod and Iversen 2000).

In the longer term, side effects of ADT include osteoporosis, obesity, hyperlipidemia, insulin resistance, metabolic syndrome, diabetes and cardiovascular disease (Isbarn et al. 2009). The loss of bone mineral density is associated with an increased risk of osteoporotic fracture in up to 45% of patients (Smith et al. 2006), and this can have major significance as hip fractures in men are associated with a significant risk of death (Cree et al. 2000). The risk can be minimised by increasing physical activity, resistance-based exercise and the use of bisphosphonates or the monoclonal antibody denosumab (Heidenreich et al. 2011). Furthermore, metabolic syndrome (waist circumference >102 cm, serum triglyceride >1.7 mmol/L, blood pressure >130/80 mmHg, HDL cholesterol <1 mmol/L and glycaemia >6.1 mmol/L) has been identified in up to 50% of men on ADT, and this is thought to be one of the factors contributing to the possible increased cardiovascular comorbidity associated with ADT (Braga-Basaria et al. 2006). Whilst cardiovascular comorbidity with DES usage is well recognised, there is now increasing evidence to suggest that other forms of ADT may have similar consequences (Jones 2011; Saigal et al. 2007).

Any reduction in the overall QoL with ADT can be responsible for patients discontinuing ADT, and a lower QoL is reported in patients on therapy even after only 6 months of treatment (Saylor and Smith 2010). Although there are clear benefits in terms of better oncological outcomes with different types of ADT, more research is required to evaluate the full implications of the side effects of treatment so that we can recommend the right form of ADT for the right patient at the right time.

Indications for hormonal therapy: EAU guidelines (Hedlund and Henriksson 2000)

Hormonal therapy Indications for castration	Benefits
M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis) Even without a controlled randomised trial, this is the standard of care and must be applied and considered as level 1 evidence
M1 asymptomatic	Immediate castration to defer progression to symptomatic stage and prevent serious disease progression-related complication An active clinical surveillance protocol might be an acceptable option in clearly informed patient if survival is the main objective
N+	Immediate castration to prolong progression-free survival and even overall survival Might be questioned in single micrometastasis after extended lymph node dissection and radical prostatectomy
Locally advanced M0	Immediate castration to improve cancer-free survival
Locally advanced disease treated with radiotherapy	High risk d'Amico: combined and prolonged ADT Intermediate risk d'Amico If low dose (<75 Gy) RT: 6 months ADT If high dose (>75 Gy) RT: ADT questionable
Locally advanced asymptomatic unfit for local definitive treatment	Limited overall survival improvement not related to a cancer-specific survival benefit
Antiandrogens	
Short-term administration	To reduce the risk of 'flare' phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist
Nonsteroidal antiandrogen monotherapy	Primary monotherapy as an alternative to castration in patients with locally advanced prostate cancer (T3–4, any N or any T) No place in localised disease as a single treatment modality Combined with radiotherapy: no clear recommendation is possible at the present time Combined with radical prostatectomy: no place so far in an adjuvant setting

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Resistance to Chemical Castration: Second-Line Hormonal Treatment

19

Yohann Loriot, Christophe Massard, and Karim Fizazi

Contents

Y. Loriot, M.D. (✉) • C. Massard, M.D.
K. Fizazi, M.D., Ph.D.
Department of cancer medicine, Institut Gustave Roussy, 114 rue Edouard Vaillant, 94800 Villejuif, France and Paris-Sud University, Kremlin-Bicetre, France
e-mail: yohann.loriot@igr.fr; christophe.massard@igr.fr; karim.fizazi@igr.fr

19.1 Introduction

Prostate cancer is the most common cancer in Western countries and the second leading cause of cancer-related deaths in males (Jemal et al. 2010; La Vecchia et al. 2010; Guerin and Hill 2010). Although advanced disease is initially sensitive to androgen deprivation therapy (ADT), most deaths occur following progression toward castration-resistant prostate cancer (CRPC), which is currently incurable, and metastatic dissemination and resistance to ADT (Nelson et al. 2003). The tumor will eventually start to grow again in the absence of testicular androgens to form CRPC. CRPC is defined by the occurrence of progressive disease often characterized before the onset of symptoms by a rising titer of serum PSA under a low level of serum testicular androgen. Most patients will die from CRPC within 2–3 years of biochemical failure. Further, the development of novel therapies has been limited because of poor understanding of the molecular mechanisms of resistance to ADT (Attard et al. 2006). Until recently, only docetaxel-based chemotherapy had been shown to modestly improve survival, marking the first real advance after the identification of therapeutic castration by Charles Huggins in 1941 (Tannock et al. 2004; Petrylak et al. 2004). During the last decade, the androgen receptor (AR) axis has also been shown to remain active in both early and late metastatic prostate cancer (Chen et al. 2009), which provides a strong rational for the development of drugs that directly or indirectly target this receptor. In response, efforts for the development of secondary

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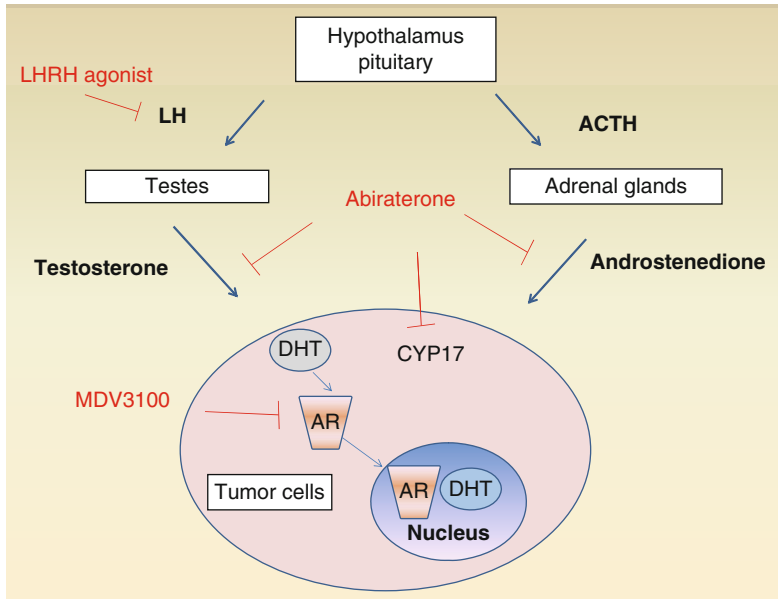

Fig. 19.1 Luteinizing hormone–releasing hormone (LHRH) released by the pituitary gland, under the regulation of GnRH produced by the hypothalamus gland, regulated androgen production from the testes. The androgens are also produced by the adrenal glands and, secondarily, in peripheral tissues including the prostate. In tumor cells, testosterone is converted to dihydrotestosterone (DHT) by the CYP17. DHT bind to the AR, a nuclear hormone receptor, which is able to bind to androgen response elements regulating the activation of genes involved in the growth, survival, and differentiation of prostate cells and prostate cancer cells

therapies targeting multiple mechanisms of retained AR signaling such as abiraterone (Attard et al. 2008) and MDV3100 (Scher et al. 2010) have been performed. In this chapter, we describe the current understanding of the biology of CRPC, highlight the implications for practice, and provide an overview of future potential endocrine therapies.

19.2 Androgen Receptor Signaling in Prostate Cancer

The AR belongs to the steroid hormone receptor family of ligand-activated nuclear transcription factors. It is divided into four distinct domains: an amino-terminal regulatory domain (AF-1 site), a DNA-binding domain, a hinge region containing a nuclear localization signal, and a carboxy-terminal ligand-binding domain (LBD) (AF-2 site). The LBD mediates high-affinity binding of the AR to ligand, with homology to other members of the steroid hormone receptor family. In the unbound state, the AR resides in the cytoplasm stabilized through binding to a complex of heat-shock proteins and cochaperone molecules including Hsp70, Hsp40, and Hsp90. Androgen binding leads to dissociation from HSPs, dimerization, phosphorylation, translocation to the nucleus, DNA binding, coactivator recruitment, and the activation of transcription of androgen-regulated genes. The highest affinity ligand for the AR is dihydrotestosterone (DHT), a product of testosterone metabolism by 5-[alpha] reductase, an enzyme expressed in both the normal prostate and prostate tumor cells. AR complex finally binds to DNA sequences called androgen response elements (AREs) in the promoter region of target genes (Fig. 19.1).

19.3 Mechanisms of Resistance to Androgen Deprivation Therapy

Because androgens and AR signaling pathways are regarded as the main oncogenic drivers in prostate carcinogenesis even in late stage disease,

they represent a relevant target for prostate cancer treatment. The clinical activity of ADT was first reported more than 70 years ago by Huggins and Hodges (1941) and remains the mainstay of systemic therapy, whether by orchiectomy or more prevalent pharmacologic strategies. Since Huggins, the treatment of patients with advanced or high-risk disease has been based on ADT, which improves survival in high-risk-localized disease and results in at least an 80% response rate when initiated in patients with newly diagnosed metastatic disease. Although survival data are limited, pharmacologic strategies that include the gonadotropin-releasing hormone (GnRH) agonists goserelin or leuprolide and, subsequently, the addition of the AR antagonists bicalutamide, flutamide, or nilutamide are well documented to improve the tumor marker prostate-specific antigen (PSA) and to reduce symptoms.

However, despite continuous ADT, the disease eventually progresses, usually after a delay of several years (Horwich et al. 2010). Although it is likely that multiple mechanisms lead to castration-resistance state, signaling through the AR remains the main oncogenic pathway driving CRPC. Several mechanisms of resistance to ADT have been described, including AR amplification, AR hyperactivation without any androgen binding, AR mutation in the AF-2 site, AR activation by steroids or other ligands, and AR activation by tyrosine kinases or other molecules.

Recently, CRPC has been shown to be driven by activation of the AR by alternative androgens, produced by adrenal glands such as dihydroepiandrostenedione (DHEA), DHEA-sulfate (DHEAS), and androstenedione activating both wild-type and mutant ARs (Tan et al. 1997). Some studies have reported that in castrated men, up to 10% of baseline-circulating testosterone is due to peripheral conversion of adrenal steroids (Hellerstedt 2003). Given these findings, agents that block adrenal conversion of steroid precursors into androgen such as aminoglutethimide, ketoconazole, or more recently abiraterone have been investigated for their therapeutic potential in CRPC. Several studies have also shown that intracrine androgen synthesis can activate the AR pathway and maintain cancer survival (Montgomery et al. 2008). Finally, some studies suggested that AR could be activated through its *N*-terminal domain (NTD) in the absence of androgen by stimulation of the cAMP-dependent protein kinase (PKA) pathway, interleukin-6 (IL-6), and by bone-derived factors which could represent a novel mechanism of antiandrogen resistance to castration (Nacusi and Tindall 2009)

19.4 Classical Strategies Targeting the Androgen Receptor

Even in patients with CRPC, maintaining testosterone levels within the castrate range through luteinizing hormone–releasing hormone (LHRH) analogues (or orchiectomy) is considered a standard of care in the context of progressing disease despite these therapies. This strategy is not supported by high level of evidence since they result from retrospective analysis that showed a relationship between medical castration discontinuation and reduced survival (Horwich et al. 2010).

Traditional and empiric use of second-line hormonal therapy in patients with CRPC has been supported by the demonstration of sustained AR expression and intact AR signaling, even as the disease evolves from androgen sensitive to castration resistant. Consequently, the use of hormonal therapy can remain effective.

One option following disease progression on antiandrogens is to test the "antiandrogen withdrawal syndrome," which is a standard practice in the setting of a rising PSA while on ADT. Antiandrogen withdrawal syndrome is based upon the observations made in the 1990s of clinical responses and PSA regressions after the discontinuation of oral antiandrogens like flutamide (Kelly and Scher 1993). Withdrawing antiandrogen may result in a biological response in 15–20% of cases because of these drugs behaving as agonists of the AR, likely as a consequence of AR mutations.

Estrogenic compounds represent another class of active agents in CRPC. For example, diethylstilbestrol reduces testosterone through reductions in LHRH secretions and directly targets the tumor. Some small studies assessing diethylstilbestrol showed a modest antitumor effect

(Oh et al. 2004; Serrate et al. 2009). However, thromboembolic toxicity is a significant concern with these agents.

Targeting the adrenal secretion of testosterone has previously been achieved by using glucocorticoids or ketoconazole (Small et al. 2004). Androgens produced by the adrenal glands may stimulate prostate cancer growth in the setting of low level of testicular androgen. Prednisone showed a similar biological response rate compared with an antiandrogen (flutamide), but increased benefits in terms of pain control and quality of life (Fossa et al. 2001). Ketoconazole, an antifungal agent, which acts through the inhibition of cytochrome P450, is also associated with a PSA response rate of approximately 20–40%, when combined with corticosteroids in phase I and II studies. A phase III trial-testing antiandrogen withdrawal, with or without ketoconazole (400 mg orally three times daily with hydrocortisone replacement therapy) demonstrated that 27% of patients receiving antiandrogen withdrawal with ketoconazole showed a greater than 50% decline in PSA, as opposed to only 11% of patients receiving antiandrogen withdrawal alone. Furthermore, patients who experienced a 50% decline in PSA while on ketoconazole had a median survival of 41 months, compared with 13 months in those who did not receive ketoconazole ($P<0.001$). Unfortunately, it was closed early, and therefore the contribution of this compound to overall survival when combined with corticosteroids remains unknown (Small et al. 2004). Ketoconazole therapy requires concomitant corticosteroid replacement treatment three times daily during treatment periods. There are also frequent drug–drug interactions.

Originally conceived as a hormonal therapy, but probably acting through microtubule perturbation, estramustine is a nitrogen mustard–estradiol conjugate that improved overall survival in combination with docetaxel when compared with mitoxantrone [hazard ratio (HR) = 0.77 (95% confidence interval, 0.63–0.93), $P=0.02$] (Petrylak et al. 2004). The routine use of estramustine, however, is limited by its toxicity, including a risk of thromboembolism.

19.5 Targeting the Androgen Receptor Axis with New Molecules in Castration-Resistant Prostate Cancer

19.5.1 Abiraterone Acetate

Abiraterone acetate is an irreversible inhibitor of cytochrome P450-17 (CYP17), with 17α-hydroxylase and C17,20-lyase inhibitory properties (Reid et al. 2008). Because CYP17 is a critical enzyme in the production of androgens and estrogens in the adrenal glands and tumor tissue (Barrie et al. 1994), abiraterone inhibits both adrenal androgen and intratumoral androgen synthesis. However, because of the upstream inhibition of 17α-hydroxylase, the levels of serum cortisol decrease, which can result in positive feedback on adrenocorticotropic hormone (ACTH) and a risk of hypokalemia and hypertension, which can be circumvented by the concomitant administration of dexamethasone or prednisone.

A phase I study assessed the safety of continuous daily administration of abiraterone (250–2,000 mg) without steroid adjunction in chemotherapy-naive men (Attard et al. 2008). No dose-limiting toxicity was observed; the most frequent side effects were related to mineralocorticoid syndrome, including hypertension, hypokalemia, and lower-limb edema. Antitumor activity was reported at all dose levels; in total, 66% of the patients exhibited a PSA decrease ≥30%, and 38% had a partial response by Response Evaluation Criteria In Solid Tumors (RECIST) criteria. A second phase I study (Ryan et al. 2010) evaluated the safety and tolerability of abiraterone acetate at doses ranging from 250 to 1,000 mg with steroids and confirmed the acceptable safety profile for further development.

Table 19.1 Abiraterone and MDV3100 pivotal trials

Trial	Disease setting	Treatment	Overall survival	Reduction in risk of death
COU-AA-301	CRPC postdocetaxel	Abi + P vs. placebo + P	14.8 vs. 10.9 months	HR = 0.65 RR = 35%
COU-AA-302	CRPC predocetaxel	Abi + P vs. placebo + P	Accrual closed in 2010	
AFFIRM	CRPC postdocetaxel	MDV3100 vs. placebo	18.4 vs. 13.6 months	HR = 0.63 RR = 37%
PREVAIL	CRPC predocetaxel	MDV3100 vs. placebo	Still ongoing in 2011	

ABi abiraterone acetate, *P* prednisone, *CRPC* castration-resistant prostate cancer, *HR* hazard ratio, *RR* reduction in risk of death

The 1,000-mg dose that offered consistent and well-tolerated pharmacologic target inhibition was selected for subsequent evaluation.

Several phase II studies were conducted (Attard et al. 2009a; Danila et al. 2010; Reid et al. 2010) in both chemotherapy-naïve and taxane-pretreated CRPC patients. In docetaxel-naive patients, the PSA response rate was 60–80% (Danila et al. 2010; Reid et al. 2010). Two phase II studies were conducted in postdocetaxel CRPC patients. In the first study, 47 patients were treated with abiraterone acetate 1,000 mg/day alone ($n = 10$), or combined with prednisone ($n = 37$). Declines in PSA, ≥30%, ≥50%, and ≥90%, were observed in 32 (69%), 24 (51%), and 7 (15%) patients, respectively. Among 35 patients evaluated by RECIST, 6 (17%) had a partial response (Attard et al. 2009a). The drug was well tolerated in the postdocetaxel setting with similar toxicities to predocetaxel patients.

As a result of these positive results, an international, multicenter, randomized, phase III, double-blind, placebo-controlled trial was done in 1,195 patients with metastatic CRPC, who had failed docetaxel-based chemotherapy, to compare the efficacy and safety of abiraterone acetate plus prednisone (AP) with those of placebo plus prednisone (PP) (de Bono et al. 2011) (Table 19.1). At the time of the preplanned interim analysis, treatment with abiraterone acetate plus prednisone resulted in a 35.4% reduction in the risk of death as compared with placebo plus prednisone (hazard ratio, 0.65; 95% confidence interval [CI], 0.54–0.77; $P < 0.001$). The median overall survival was 14.8 months in the abiraterone acetate group and 10.9 months in the placebo group. All the secondary end points analyzed provided support for the superiority of abiraterone acetate over placebo including the confirmed PSA response rate (29% vs. 6%, $P < 0.001$), the objective response rate on the basis of RECIST among patients with measurable disease at baseline (14% vs. 3%, $P < 0.001$), time to PSA progression (10.2 vs. 6.6 months), and median progression-free survival on the basis of radiographic evidence (5.6 vs. 3.6 months). On the basis of the PSA concentration, abiraterone acetate was associated with a 42% reduction in the risk of disease progression (hazard ratio, 0.58; 95% CI, 0.46–0.73; $P < 0.001$), and on the basis of radiographic imaging, it was associated with a 33% reduction in the risk of progression (hazard ratio, 0.67; 95% CI, 0.58–0.78; $P < 0.001$).

Adverse events associated with elevated mineralocorticoid levels due to CYP17 blockade (fluid retention and edema, hypokalemia, and hypertension), as well as cardiac disorders and liver-function test abnormalities were deemed of special interest and were more common in the abiraterone acetate group than in the placebo group (55% vs. 43%, $P < 0.001$). However, grade 3–4 hypokalemia (3.8% vs. 0.8%) and grade 3–4 hypertension (1.3% vs. 0.3%) were infrequent. The incidence of fluid retention and edema was higher in the abiraterone acetate group (31% vs. 22% in the placebo group; $P = 0.04$).

This trial showed, for the first time, that targeting the AR pathway can prolong overall survival in patients with metastatic CRPC, who have progressed after docetaxel-based chemotherapy, confirming the concept of targeting continued AR signaling. This study formed the basis of US Food and Drug Administration (FDA) approval of the abiraterone. Another placebo-controlled

randomized phase III study in the predocetaxel setting is now closed to accrual, after more than 1,000 patients have been randomized 1:1 for abiraterone acetate plus prednisolone versus prednisolone plus placebo. The results of this second trial are awaited.

19.5.2 Other Drugs Targeting Adrenal Androgens in Castration-Resistant Prostate Cancer

TAK-700 (orteronel) is a selective, but less potent, nonsteroidal inhibitor of 17,20-lyase. The selectivity for 17,20-lyase may improve the safety profile as compared with agents that inhibit both steps in the testosterone synthesis process and may, therefore, affect cortisol precursor synthesis. Preclinical studies indicate that TAK-700 has minimal effects on CYP drug-metabolizing enzymes. A recent open-label phase I and II trial was done in CRPC patients (Dreicer et al. 2010a, b). In the phase I trial, TAK-700 was given at five-dose levels (100, 200, 300, 400, and 600 mg twice daily) and was associated with a favorable safety profile, the most common side effects including gastrointestinal toxicities and grade 3 fatigue. Pharmacodynamic studies showed androgen synthesis suppression, with reductions in testosterone and DHEA-S (Dreicer et al. 2010a). In a phase II study, patients were treated at three-dose levels (300 mg BID, 400 mg BID, or 600 mg twice daily, with prednisone 5 mg twice daily also administered at the latter two-dose levels). Preliminary results on the first 57 patients enrolled confirmed a manageable toxicity profile, showing antitumor activity with a PSA decrease in 74% of patients receiving TAK-700 for more than three cycles (Dreicer et al. 2010a). The TAK-700 dose selected for the phase III studies in metastatic CRPC was 400 mg twice daily, with concomitant prednisone 5 mg twice daily. Two large phase III-randomized clinical trials are ongoing in both the post- and the predocetaxel settings. Moreover, a phase I and II trial is ongoing to evaluate the safety and efficacy of the combination with docetaxel.

HE3235 (17a-ethynyl-5a-androstane-3a, 17b-diol) is a synthetic androstenediol analogue with shown antitumor activity in preclinical CRPC models. HE3235 decreased AR expression in LNCaP cells in vitro, in CRPC LuCaP 35V xenografts, and blocked intratumoral androgen synthesis in the LuCaP 35V tumors. HE3235 did not inhibit CYP17, but inhibited the conversion of *d*-cholesterol to *d*-pregnenolone. A clinical phase I and II trial in CRPC men is ongoing, and preliminary results have been presented at the American Society of Clinical Oncology (ASCO) Genitourinary 2010 meeting with a promising antitumor activity (Montgomery et al. 2010).

19.5.3 New Androgen Receptor Inhibitors

19.5.3.1 MDV3100

MDV3100 is a novel AR antagonist that binds to the AR more avidly than bicalutamide. Unlike bicalutamide, MDV3100 also inhibits AR function by blocking nuclear translocation and DNA binding and has no agonist activity (Tran et al. 2009). In a large multicenter, open-label, dose-escalation phase I and II study performed in 140 CRPC patients, treated at doses ranging from 30 to 600 mg/day, the authors reported antitumor activity including PSA declines of >50% or more in 78 patients (56%), response in soft tissue in 13 out of 59 patients (22%), and bone disease stabilization in 61 out of 109 patients (56%) (Scher et al. 2010). At the 600-mg/day doses, two of three subjects had dose-limiting toxicities (seizure and rash, respectively). Fatigue was the most frequently reported adverse event, with grade 3 fatigue occurring in 9%, 15%, and 20% of patients treated at the 240, 360, and 480-mg/day dose groups, respectively. The dose of 240 mg/day was defined as the maximum-tolerated dose. A large, phase III, randomized, double-blind, placebo-controlled study was done to determine the benefit in overall survival of MDV3100 as compared with placebo in patients with progressive CRPC, previously treated with docetaxel-based chemotherapy. More than 1,100 patients were enrolled according to randomized 2:1 design (MDV3100 vs. placebo); the accrual was completed in 2010, and the results of the intermediate analysis were recently released (Table 19.1).

On November 3, 2011, the Independent Data Monitoring Committee has informed of positive results from a planned interim analysis in men with advanced prostate cancer previously treated with chemotherapy. MDV3100 successfully met the study's prespecified interim efficacy stopping criteria, demonstrating a clinically meaningful and statistically significant ($P<0.0001$) improvement in overall survival compared to placebo. As a result, the IDMC recommended that AFFIRM be stopped early and men who received placebo be offered MDV3100. As reported by the IDMC, MDV3100 produced a 4.8-month advantage in median overall survival compared to placebo. The estimated median survival for men treated with MDV3100 was 18.4 months compared with 13.6 months for men treated with placebo. MDV3100 provided a 37% reduction in risk of death compared to placebo (hazard ratio = 0.631). The IDMC further determined, considering the observed safety profile, that MDV3100 demonstrated a favorable risk-to-benefit ratio sufficient to stop the study. In addition to the AFFIRM trial in men with advanced prostate cancer previously treated with chemotherapy, MDV3100 is also being studied in the phase III PREVAIL trial in 1,700 men with advanced prostate cancer who have not received chemotherapy and the phase II TERRAIN trial in nearly 400 men whose disease has progressed while on luteinizing hormone–releasing hormone (LHRH) analogue or hormone therapy and a phase II study in hormone-naïve men.

19.5.4 Other Drugs Targeting Androgen Receptor

As part of MDV3100, other potent antagonists of human AR with affinity to AR superior to that of bicalutamide are in development in phase I and II trials in CRPC patients. ARN-509 is an AR antagonist that inhibits nuclear translocation and DNA binding of the receptor, thereby modulating expression of genes that drive prostate cancer growth. This drug is currently under investigation in a phase I and II study. BMS-641988, another AR antagonist, showed increased potency relative to bicalutamide in both in vitro and in vivo prostate cancer models, in particular, the resistant model to bicalutamide (Attar et al. 2009). However, its development was stopped after a first phase I study showed neurologic toxicity and poor efficacy (Rathkopf et al. 2011).

The transcriptional activity of most steroid hormone receptors is predominantly through the activation function (AF)-2 region in the LBD, the exception being the AR in which it is the AF-1 region in the NTD that contributes most of the transcriptional activity. AR LBD functions independently of the NTD and can still bind ligand even if the AF-1 region is deleted or mutated; however, no transcriptional activity can be achieved without the AF-1 region in the NTD. A new compound (EPI-001) targets the AF-1 region and inhibits transactivation of the amino-terminal domain of the AR, without interacting with the ligand-binding domain. This agent has the potential to be effective against the constitutively active AR splice variant lacking the ligand-binding domain, which has been reported as a putative cause of castration resistance (Andersen et al. 2010).

19.5.5 Concluding Remarks: Predicting Sensitivity to Secondary Hormonal Manipulations

Castration-resistant prostate cancer remains a clinical challenge in medical oncology with multiple treatment options available and in development. Secondary hormonal treatment targeting the AR and its ligands has become a cornerstone of therapy for patients with CRPC. Recent studies have demonstrated the efficacy of this strategy based on additional hormone blockade beyond castration especially with new drugs such as abiraterone and MDV3100. However, there is still a lack of clinical or biological markers predictive of sensitivity to secondary hormonal manipulations to help physicians in daily practice. Achieving this objective in clinical practice requires the identification of predictive biomarkers of sensitivity, the validation of assays to measure the biomarker, and separately, prospective

clinical trials designed to qualify the biomarker for the specific context of use. Time to castration resistance may be a useful clinical biomarker for predicting clinical benefit from further endocrine therapies. In relation to patient outcome following treatment with abiraterone in a small study, *TMPRSS2-ERG* rearrangements assessed using RT-PCR assay in circulating tumor cells were not predictive of PSA-decline rates or survival (Danila et al. 2011). By contrast, another study showed an association between the 90% PSA decline rate from baseline and the presence of *gene* rearrangements in CTCs assayed by FISH (Attard et al. 2009b). Studies are ongoing to identify potential predictors of response or resistance to AR-signaling targeting agents. In the future, tumor samples (initial prostate cancer, biopsy of a metastatic lesion, molecular characterization of CTCs) should allow the identification of various molecular alterations predictive for sensitivity to subsequent hormone manipulations (abiraterone or MDV3100).

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Targeted Therapies and Vaccination

20

Guru Sonpavde and Cora N. Sternberg

Contents

G. Sonpavde, M.D.
Texas Oncology and the Veterans Affairs Medical Center, Baylor College of Medicine,
501 Medical Center Blvd, Webster,
TX 77598, USA
e-mail: guru.sonpavde@usoncology.com

C.N. Sternberg, M.D., FACP (✉)
San Camillo and Forlanini Hospitals, Padiglione Flajani,
Circonvallazione Gianicolense 87, 00152 Rome, Italy
e-mail: cstern@mclink.it

20.1 Introduction

Until the first half of 2010, patients with metastatic prostate cancer progressing on androgen blockade had few therapeutic options. Antiandrogen withdrawal (AAWD) yields responses in 15–30% of cases that appear associated with a longer duration of prior antiandrogen therapy (Small and Srinivas 1995; Small et al. 2004; Scher et al. 2008). Addition of an antiandrogen or switching to a different antiandrogen may yield activity in a fraction of patients (Scher et al. 1997; Nakabayashi et al. 2005). Ketoconazole in combination with hydrocortisone yields activity in chemonaive as well as postchemotherapy contexts, although toxicities and potentially life-threatening drug interactions due to CYP3A4 inhibition present serious barriers to its usage (Galsky et al. 2009; Nakabayashi et al. 2010).

Docetaxel-based chemotherapy every 3 weeks is established as first-line chemotherapy for the

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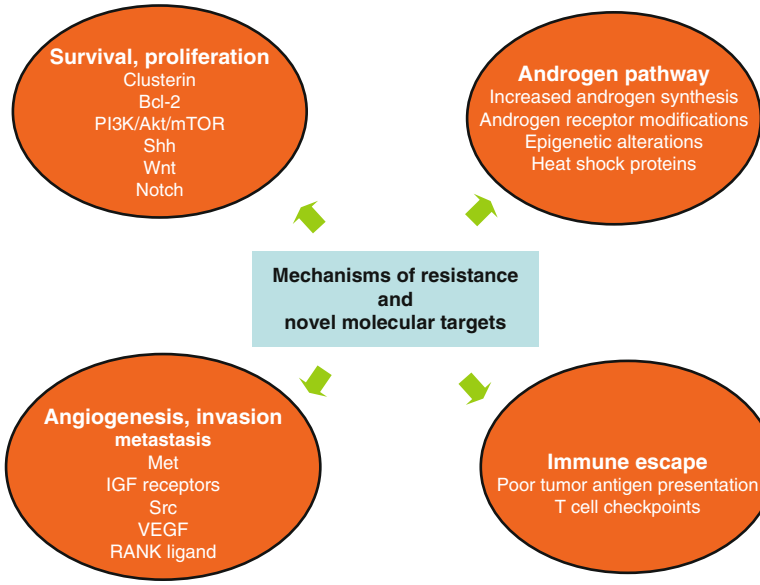

Fig. 20.1 Mechanisms of resistance and novel molecular targets

management of mCRPC based on the demonstration of a 21% increment in overall survival (OS) over mitoxantrone plus prednisone (MP) (Petrylak et al. 2004; Tannock et al. 2004). Docetaxel plus prednisone (DP) extended median OS to ~19 months, and 3-year survival to 18.6% (Berthold et al. 2008). Cabazitaxel, a novel taxoid, was approved by US regulatory authorities in 2010 based on an extension in median OS compared with mitoxantrone in patients with progressive disease following docetaxel therapy (15.1 months vs. 12.7 months, hazard ratio 0.70, $P<0.0001$) (de Bono et al. 2010). A phase III trial is comparing two doses of cabazitaxel with conventional docetaxel and prednisone first-line chemotherapy. Other novel taxanes similar to cabazitaxel that are not susceptible to the p-glycoprotein mediated efflux are undergoing early evaluation, e.g., tesetaxel and TPI-287. Platinums and epothilones have also exhibited modest activity (Ross et al. 2008; Rosenberg et al. 2007). Notably, satraplatin, an oral platinum, demonstrated a prolongation of PFS without an improvement in OS as second-line therapy for mCRPC (Sternberg et al. 2009b). However, given the toxicities of chemotherapeutic agents, a focus on tolerable biologic agents is desirable, especially in this elderly population. This chapter reviews the advances made since 2010 that have resulted in the addition of novel and paradigm shifting targeted agents to the therapeutic armamentarium. Additionally, promising emerging agents are discussed.

20.2 Insights into Molecular Biology of Prostate Cancer

A better understanding of key mechanisms driving the growth of prostate cancer has led to multiple recent therapeutic advances (Fig. 20.1). The role played by optimal tumor-associated antigen (TAA) presentation and inhibition of the T-cell negative regulatory checkpoints, cytotoxic T-lymphocyte antigen-4 (CTLA-4), and programmed death-1 (PD-1), in bolstering immune response, has been recognized (van Luijn et al. 2010; Smith-Garvin et al. 2009). It has also become evident that progressive disease after castration is associated with persistent androgen-dependent signaling (Attard et al. 2009d). Upregulated intratumoral enzymes synthesize testosterone from precursor adrenal steroids, which yields high intratumoral testosterone in castrate men compared to noncastrate men (Chen et al. 2009; Attard et al. 2009c; Stanbrough et al. 2006). Moreover, androgen receptor (AR) alterations including increased expression, increased sensitivity, constitutively active splice variants,

or mutations susceptible to promiscuous activation may all lead to upregulation of androgen-mediated signaling (Small and Srinivas 1995; Chen et al. 2009; Reid et al. 2008; Edwards et al. 2003; Gregory et al. 2001b, a; Dehm et al. 2008; Steinkamp et al. 2009; Taplin et al. 2003). In addition, upregulation in alternative pathways that mediate survival (clusterin, PI3K/Akt, bcl-2), invasion (Met, insulin-like growth factor, Src), angiogenesis (vascular endothelial growth factor), and stem-cell-like properties (sonic hedgehog) have been recognized to confer a poor prognosis and engender resistant tumors (Collins et al. 2005; Whang et al. 1998).

20.3 Sipuleucel-T for Minimally Symptomatic Metastatic CRPC

Sipuleucel-T is a cellular product consisting of autologous peripheral blood mononuclear cells obtained by leukapheresis and enriched for a CD54+ dendritic cell fraction pulsed with PA2024, a prostatic acid phosphatase (PAP)-GM-CSF construct. Encouraging initial results prompted the landmark IMPACT (IMmunotherapy for Prostate AdenoCarcinoma Treatment) trial (Small et al. 2006; Kantoff et al. 2010). A total of 512 men with relatively asymptomatic mCRPC and no visceral metastases were randomized to sipuleucel-T or placebo intravenous infusions every 2 weeks × 3 in a 2:1 ratio. Most patients (80–85%) were chemonaive and were required to be off steroids for 4 weeks. Patients who were pretreated with chemotherapy were required to be >3 months after chemotherapy. Each dose of sipuleucel-T or placebo contained ≥40 million cells expressing CD54, a marker for dendritic cell activation. Premedication with acetaminophen and an antihistamine was required prior to intravenous infusion over approximately 60 min.

The median survival was 25.8 months with sipuleucel-T compared with 21.7 months with placebo in conjunction with an extension of 3-year survival (31.7% vs. 23.0%, $P=0.032$). The treatment effect remained after adjustment for subsequent docetaxel. Of interest, there was no delay in the median time to progression. Only one patient in the sipuleucel-T group had an objective partial response. Confirmed PSA declines ≥50% were observed in 8 of 311 patients (2.6%) in the sipuleucel-T group, and 2 of 153 patients (1.3%) receiving placebo. Patients in the sipuleucel-T group with an antibody titer >400 against PA2024 or PAP lived longer. Toxicities were manageable, with chills reported in 54.1% of sipuleucel-T patients (vs. 12.5% with placebo), fever in 29.3% (vs. 13.7%), headache in 16.1% (vs. 5%), and flu-like symptoms in 9.8% (vs. 4.3%). These data led to the approval of sipuleucel-T by the US FDA in 2010, making it the first therapeutic vaccine to be approved for patients with any malignancy. An ongoing phase III trial is evaluating its impact in metastatic hormone-sensitive prostate cancer receiving androgen deprivation therapy (Table 20.1). Additionally, sequencing with abiraterone acetate is being evaluated in chemonaive patients in a phase II trial.

20.4 Emerging Vaccines

20.4.1 Novel Autologous Dendritic Cell-Based Targeted Vaccines

Dendritic cells (DCs) have been engineered to express CD40 receptors by adenovirus, which are engaged by $CD4^+$ T-helper cells within the lymph node paracortex to elicit potent cytotoxic lymphocyte activation (Hanks et al. 2005; Lapteva et al. 2007). A drug-inducible CD40 (iCD40) receptor was engineered that permits temporally controlled, lymphoid-localized, DC-specific activation (Iuliucci et al. 2001). iCD40-expressing DCs demonstrated a prolonged lifespan and significant preclinical activity and preliminarily, promising clinical activity (Table 20.1). In another approach designed to enhance DC survival, introduction of activated Akt into DCs appears promising in enhancing the efficacy of DC vaccines (Park et al. 2006).

20.4.2 Virus-Based Vaccines

Unlike the individualized customization for each patient inherent to autologous DC vaccines which

Table 20.1 Ongoing clinical development of immunotherapy for prostate cancer

Molecular target	Class of therapeutic agent	Line of therapy and setting	Phase of clinical trial	Design
CTLA-4	MAb	Second, metastatic CRPC	III	XRT → Placebo vs. ipilimumab
CTLA-4	MAb	First, metastatic CRPC	III	XRT → Placebo vs. ipilimumab
PSA	Virus-based antigen and costimulatory molecule	First, metastatic CRPC	III	Prostvac-Tricom + GM-CSF vs. placebo
PAP	Autologous DC vaccine expressing PAP-GM-CSF	First, metastatic hormone-sensitive prostate cancer	III	Androgen deprivation +/− sipuleucel-T
PAP	Autologous DC vaccine expressing PAP-GM-CSF	First, metastatic CRPC	II	Abiraterone + concurrent vs. initial sipuleucel-T
PSA	Virus-based antigen and costimulatory molecule	First, nonmetastatic CRPC	II	Flutamide +/− Prostvac-Tricom
PD-1	MAb	Salvage, metastatic CRPC	I	MDX-1,106
PSMA	Radioisotope Lu-177 tagged MAb	Nonmetastatic CRPC	II	KC + HC +/− Lu-MAb
PSMA	Radioisotope Lu-177 tagged MAb	First, metastatic CRPC	II	Lu-177-MAb
PSMA	Autologous DC vaccine expressing inducible CD40 activated in vivo	First or second, metastatic CRPC	I/II	BPX-101
PAP	DNA-based vaccine	Nonmetastatic hormone-naive	I/II	DNA vaccine
NY-ESO / Lage-1	Peptide vaccine in context of HLA type	First or salvage	I/II	Peptide vaccine
4 antigens	mRNA-based vaccine	First or salvage	I/II	CV9103 mRNA vaccine

increases the complexity and manufacturing costs, other approaches have the advantage of being off-the-shelf products. The inherent immunogenicity of poxviruses and the high level of gene expression render them promising vehicles to enhance the immune response against tumor antigens (Vergati et al. 2010; Drake 2010; Arlen et al. 2005). A limitation of poxvirus-based vectors is the rapid appearance of strong neutralizing antibodies against the vaccinia vector. The development of neutralizing antibodies to the initial priming vaccinia administration can be addressed by using avipox vectors as the booster vaccination (heterologous prime/boost vaccination) (Drake 2010; Harrington et al. 2002). Prostvac®-VF comprises two recombinant viral vectors (vaccinia and fowlpox) encoding transgenes for PSA and TRICOM, which includes costimulatory molecules, ICAM (intercellular addition molecules)-1 (CD54), B7.1 (CD80), and leukocyte function-associated antigen-3 (LFA-3) (CD58) (Sonpavde et al. 2010). In a double-blind placebo-controlled randomized phase II trial of patients with chemonaive, minimally symptomatic mCRPC, an extension of median survival was demonstrated (25.1 vs. 16.6 months, $P = 0.0061$), without an extension of progression-free survival. Further evaluation in phase III trials is planned (Table 20.1).

20.4.3 DNA-Based Vaccines

DNA-based vaccines comprise naked DNA plasmids encoding tumor antigens. Although the safety profile is excellent, DNA-based vaccines appear poorly immunogenic, partly owing to a low level of infection of antigen-presenting cell (APCs) (Drake 2010; Becker et al. 2010). This shortcoming has been addressed by multiple immunizations, improved delivery systems (gene gun, cationic liposomes), simultaneous cytokine administration (GM-CSF or IL-2), simultaneous presentation of non-self-antigens (e.g., hepatitis B surface antigen), and alterations of plasmid antigens (Vergati et al. 2010; Best et al. 2009; Pasquini et al. 1997; Binder and Srivastava 2005). Early clinical trials have evaluated DNA-based vaccines targeting PSA and PAP (Pavlenko et al.

2004; McNeel et al. 2009). Of eight patients with CRPC receiving GM-CSF and interleukin-2 in combination with a DNA vaccine carrying a PSA gene, a PSA-specific cellular and humoral response was detected in the highest dose cohort (Pavlenko et al. 2004). In another phase I/II trial, 22 patients with castration-sensitive prostate cancer with biochemical recurrence only were treated with plasmid DNA encoding PAP in combination with GM-CSF as an adjuvant (McNeel et al. 2009). Three patients (14%) developed PAP-specific IFN interferon-γ secreting CD8+ T-cells, and nine patients (41%) developed PAP-specific CD4+ and/or CD8+ T-cell proliferation. However, no antibody response was detected. PAP-specific interferon-γ secreting T-cell responses were detectable in six of eight men with a prolongation of PSA-doubling time ≥200% but in only 1 of 14 individuals without a change in PSA-doubling time ($P = 0.001$) (Becker et al. 2010). Moreover, HLA-A2-expressing individuals appeared to preferentially benefit.

20.4.4 Allogeneic Cell-Line-Based Vaccines

Allogeneic cell lines theoretically offer the advantage of induction of immune response to a range of resident tumor-associated antigens (Drake 2010). The GM-CSF-secreting vaccine GVAX (Cell GeneSys, South San Francisco, CA) consisted of a mixture of the hormone-sensitive (LnCaP) and hormone-resistant (PC-3) prostate cancer cell lines transduced with a replication-defective retrovirus containing cDNA for GM-CSF and then irradiated (Small et al. 2007; Higano et al. 2008). A phase III trial (VITAL-1) randomized 600 mCRPC patients without pain to GVAX or docetaxel/prednisone, and another phase III trial (VITAL-2) compared GVAX plus docetaxel to docetaxel/prednisone in metastatic CRPC patients with pain (Table 20.1). Unfortunately, preliminary analysis of the VITAL-2 trial after accruing 408 patients demonstrated shorter median survival (12.2 vs. 14.1 months, $P = 0.0076$) for GVAX/docetaxel (Small et al. 2009). Subsequently, an unplanned futility analysis of the VITAL-1 trial that had completed accrual (626 patients) indicated that there was a <30% chance of demonstrating an improvement in survival, which led to its termination. A combination approach of GVAX plus ipilimumab demonstrated activity correlating with immune events, although hypophysitis was observed at larger doses (Gerritsen et al. 2007). The future development of GVAX is unclear, given the disappointing results of the aforementioned phase III trials.

20.4.5 Peptide and mRNA Vaccines

Another vaccination strategy is to directly deliver peptides or mRNA, e.g., the NY-ESO-1 and LAGE-1 antigens, which are relatively specific for malignancies including prostate cancer (Nakada et al. 2003). Preclinical induction of immune responses and antitumor activity has been demonstrated (Zeng et al. 2001, 2002). Early trials are focusing upon HLA host subtypes. CV9103 is an mRNA-based vaccine that encodes for four prostate-specific antigens. This vaccine is characterized by no restriction to the patient's MHC genotype and cannot be integrated into the genome in the absence of reverse transcriptase. Preliminarily, over 70% of the patients in a phase I/II trial responded to at least one antigen.

20.5 T-Cell Checkpoint Inhibitors

CTLA-4, a negative regulator of T-cell response, inhibits recognition of self-antigens by T-cells and can downregulate the antitumor immune response. Ipilimumab, a CTLA-4 inhibiting monoclonal antibody, was recently reported to significantly prolong overall survival in patients with metastatic melanoma and was approved by the FDA for this indication (Hodi et al. 2010). Phases I and II clinical trials have demonstrated objective and PSA responses in patients with metastatic CRPC (Langer et al. 2007; O'Mahony et al. 2007). Based on these encouraging results, phase III clinical trials of ipilimumab vs. placebo have

Table 20.2 Ongoing phase III trials of biologic and antiandrogen agents for metastatic CRPC

Molecular target	Line of therapy	Control therapy	Experimental therapy
Endothelin receptor	First[a]	DP + placebo	DP + atrasentan
VEGF, PlGF	First	DP + placebo	DP + aflibercept
Src, Kit, PDGFR	First	DP + placebo	DP + dasatinib
Angiogenesis, immune mechanism	First	DP + placebo	DP + lenalidomide
Angiogenesis, immune mechanism	First	Placebo	Tasquinimod
Clusterin	First	DP + placebo	DP + custirsen
Clusterin	Second	DP + placebo	DP + custirsen
CYP17 (androgen synthesis)	First	Placebo-prednisone	Abiraterone acetate-prednisone
CYP17 (androgen synthesis)	First	Placebo-Prednisone	TAK700-prednisone
CYP17 (androgen synthesis)	Second or third	Placebo-Prednisone	TAK700-prednisone
Androgen receptor	First	Placebo	MDV3100
Androgen receptor	Second	Placebo	MDV3100
VEGFR2, Met	Third	Mitoxantrone-prednisone	Cabozantinib-prednisone
Endothelin receptor	First	DP + placebo	DP + zibotentan

Index: From www.clinicaltrials.gov accessed on 8 August, 2011
[a]Requires bone metastasis; D + P: docetaxel plus prednisone

been initiated in men with metastatic CRPC, with or without prior chemotherapy (Table 20.2) (Beer et al. 2011; Drake et al. 2011). These trials administer a brief course of radiation to a bone metastasis based on preclinical data demonstrating an augmentation of the immune response by altering tumor-cell phenotype and upregulating some TAAs, MHC class I, Fas, and TLR4 agonists (Garnett et al. 2004; Chakraborty et al. 2003; Apetoh et al. 2007; Chakraborty et al. 2004). Similarly, cyclophosphamide chemotherapy has also been shown to deplete inhibitory T_{REG} cells and enhance the activity of vaccination, and conversely an immune response to vaccination may augment the activity of subsequent chemotherapy (Audia et al. 2007; Antonia et al. 2006; Wada et al. 2009). However, ipilimumab carries the risk of nonspecific systemic upregulation of the immune system and immune-related adverse events including hepatitis, enterocolitis, and hypophysitis.

Programmed cell death-1 (PD-1) and its ligand PD-L1 (B7-H1) appear to be promising targets for immune checkpoint blockade (Drake 2010; Hirano et al. 2005; Iwai et al. 2005). Unlike early lethality in CTLA-4 knockout mice, PD-1-deficient animals demonstrate a mild form of late onset strain-specific autoimmunity (Nishimura et al. 2001). Early evidence indicates a favorable toxicity profile and tumors with higher baseline B7-H1 expression may derive a preferential benefit (Brahmer et al. 2010).

20.6 Immunotherapy-Related Response Criteria

Phase II trials in mCRPC and advanced prostate cancer are difficult to evaluate because prostate cancer is characterized by a poor ability to measure response since the most common site of metastases is bone, a nonmeasurable site by RECIST criteria (Eisenhauer et al. 2009). The validity of ≥30% or ≥50% PSA declines within 3 months as a surrogate for outcomes with biological agents is unproven (Scher et al. 2008). The Prostate Cancer Working Group (PCWG)-2 guidelines recommended time to progression endpoints also appear suboptimal, given the consistent absence of a signal of extension of clinical PFS in the setting of sipuleucel-T (Scher et al. 2008). Guidelines have been recommended to standardize methodology used for the calculation and employment of PSA-doubling time changes to provide a signal of activity (Arlen et al. 2008). Other intermediate surrogates for outcomes with

traditional chemotherapy, such as CTCs (circulating tumor cells) also require validation (de Bono et al. 2008). Therefore, overall survival is the only currently reliable endpoint for trials of immunotherapy. New immune-related (ir) response criteria were defined to more comprehensively capture all response patterns since four distinct response patterns have been observed. All patterns have been associated with favorable survival compared with patients with progressive disease by conventional criteria: immediate response, durable stable disease, response after tumor burden increase, and response in the presence of new lesions (Hoos et al. 2010; Wolchok et al. 2009). The recommendations permit the assessment of tumor burden as a continuous variable considering index and new lesions. The appearance of new lesions alone does not constitute ir-PD if they do not increase the tumor burden ≥25% and may qualify for partial response (≥50% decrease) or stable disease (<50% decrease to >25% increase) based on overall alterations in burden (Wolchok et al. 2009). Moreover, statistical models describing hazard ratios as a function of time and recognizing differences before and after separation of curves were suggested since survival curves with immunotherapy demonstrate delayed separation. These recommendations require prospective validation and may offer more useful criteria for clinical investigation.

20.7 Radiolabeled Monoclonal Antibody

Monoclonal antibodies (Mab) targeting specific protein expressed on the surface of tumor cells can be modified to deliver cytotoxic radionuclides, drugs, or toxins to the targeted cancer cell population (Tagawa et al. 2010). In prostate cancer, Mabs targeting PSMA are in the most advanced phase of development. PSMA is a type II membrane glycoprotein, which is markedly upregulated in prostate cancer (Tagawa et al. 2010). While single-agent activity of the naked antibody was marginal, deimmunized murine MoAb J591 (muJ591) has been chosen as a vehicle to deliver radioisotopes because of its high affinity for PSMA in animal models (Bander et al. 2003; Galsky et al. 2008). Intriguingly, this antibody may also have antiangiogenic activity owing to expression of PSMA in neovasculature (Milowsky et al. 2007). The 177 lutetium radioisotope can be administered in higher doses, with comparatively less radiation to the marrow and its gamma emission facilitates imaging (Tagawa et al. 2010). A randomized phase II trial is underway in nonmetastatic CRPC with a PSA-doubling time <10 months and/or absolute PSA ≥ 2 ng/ml, which evaluates the value of combining 177 lutetium-labeled J591 with ketoconazole plus hydrocortisone.

20.8 Abiraterone Acetate: CYP17 Inhibitor

Multiple studies have highlighted the relevance of androgen axis signaling despite suppressed serum androgens (Attard et al. 2009c, d; Chen et al. 2009). The key enzyme that mediates androgen synthesis in the testes, adrenal glands, and intratumorally is cytochrome P17 (CYP17). Abiraterone acetate (AA), a rationally designed potent, orally bioavailable, small molecule inhibitor of CYP17, catalyzes two key reactions (17-α hydroxylase and 17,20 lyase) involved in androgen biosynthesis. Phase I trials demonstrated substantial suppression of testosterone levels accompanied by antitumor activity, and a plateau of pharmacodynamic activity at 1,000 mg once daily (O'Donnell et al. 2004; Attard et al. 2008; Ryan et al. 2010). The primary adverse event was attributed to mineralocorticoid excess manifesting as hypokalemia, hypertension, and fluid overload that was alleviated by epleronone and occasionally required low-dose corticosteroids. Phase II trials demonstrated substantial activity in chemonaive or postdocetaxel patients with metastatic CRPC, which led to phase III trials (Attard et al. 2009b; Reid et al. 2010; Danila et al. 2010). A landmark phase III trial (COU-AA-301) compared AA (1,000 mg once daily) with placebo (both groups receiving prednisone 5 mg twice daily) for men with progressive mCRPC following docetaxel (but

ketoconazole naive) (de Bono et al. 2011). This trial demonstrated a significant extension in median survival (14.8 months vs. 10.9 months, HR = 0.646, $P < 0.0001$). A second international phase III trial is comparing AA (1,000 mg daily) plus prednisone (5 mg twice daily) with placebo plus prednisone (5 mg twice daily), in patients with asymptomatic or minimally symptomatic chemonaive mCRPC. Preliminary studies indicate that baseline androstenedione levels, AR gene amplification, and the *TMPRSS2-ERG* gene rearrangement may warrant exploration to predict responses to AA (Attard et al. 2009a, b; Ryan 2007; Palmberg et al. 2000).

20.9 Emerging Role of Novel Androgen-Axis-Targeting Agents

TAK-700 (Millennium Pharmaceuticals, Cambridge, MA) is a selective 17,20 lyase inhibitor that downregulates androgenic steroid production in vitro and in vivo. In a phase I/II trial of TAK-700 in metastatic CRPC, 96 chemonaive patients with mCRPC were treated in four cohorts: 300 mg twice daily ($n = 23$), 400 mg twice daily with prednisone ($n = 24$), 600 mg twice daily with prednisone ($n = 26$), or 600 mg daily without prednisone ($n = 24$). (Agus et al. 2011). The most common grade 3–4 side effects were fatigue (9%) and diarrhea (3%). At 12 weeks, PSA response rates (≥50% decrease) were 63%, 52%, 41%, and 62%, respectively. Declines in median dehydroepiandrosterone sulfate (DHEA-S), testosterone, and CTCs were observed. Of 43 patients with measurable disease, six exhibited a partial response. Currently, TAK-700 in combination with low-dose prednisone is being evaluated in separate phase III trials of chemotherapy-naive or postdocetaxel patients (Table 20.2).

MDV3100 is an AR antagonist that prevents nuclear translocation and coactivator recruitment of the ligand-receptor complex (Tran et al. 2009). A phase I/II trial of 140 men (of whom, 46% were chemonaive) demonstrated activity at all doses, including PSA declines ≥50% or more in 56%, soft tissue responses in 22%, and conversion from unfavorable to favorable CTCs in 49% (Scher et al. 2010). The median time to progression was 47 weeks, and the most common grade 3–4 adverse event was fatigue (11%). Based on these promising results, separate placebo-controlled phase III trials (without prednisone) are investigating MDV3100 in postdocetaxel (AFFIRM) and chemonaive (PREVAIL) men with mCRPC. Preliminarily, a 4.8-month extension in median survival was observed with MDV3100 (18.4 vs. 13.6 months, HR =0.631, p<0.001) in the post-docetaxel trial, and formal presentation and publication are awaited (Press release Medivation and Astellas. 3 November 2011). Multiple other novel agents with different mechanisms of activity targeting the androgen axis are in earlier stages of development, e.g., ARN-509, an AR antagonist, and TOK-001, an agent with a dual mechanism of action as both an anti-AR and androgen synthesis inhibitor (Vasaitis 2008).

20.10 Radium-223: Novel α-Emitting Radiopharmaceutical

Radium-223 is a novel potent α-emitting radiopharmaceutical, which has greater potency but a shorter range, rendering it potentially more active and less toxic than existing radiopharmaceuticals (samarium and strontium). Given the promising outcomes in a phase II trial, Ra-223 is being studied in a phase III trial that enrolled chemonaive as well as postchemotherapy patients with symptomatic bone metastases (Nilsson et al. 2007). On June 6, 2011, the preliminary results of this trial were announced in a press release (and updated at the ESMO [European Society of Medical Oncology] meeting in October 2011) and revealed a median overall survival of 14.0 months for radium-223 chloride and 11.2 months for placebo (two-sided P-value = 0.0022, HR = 0.699).

20.11 Emerging Targeted Biologic Agents

20.11.1 Single-Agent Therapy

Preliminary evidence of enhanced outcomes has been demonstrated with multiple classes of novel agents, which are being evaluated, either as monotherapy or in combination with docetaxel (Table 20.2). Single-agent therapy with cabozantinib (XL-184), an inhibitor of c-MET and VEGF

receptor tyrosine kinases, recently demonstrated promising results. In a phase II, multicenter study, patients with heavily pretreated mCRPC received cabozantinib 100 mg orally once daily (Hussain et al. 2011). After 171 patients were enrolled, randomization was suspended when 122 patients receiving cabozantinib showed clinical benefits (Hussain et al. 2011). During the 12-week lead-in period, all patients received cabozantinib. Responding patients were continued on open-label cabozantinib, and patients with progressive disease discontinued cabozantinib. Patients with stable disease were randomized to receive cabozantinib or placebo. At 12 weeks, disease-control rate, defined as partial response or stable disease, was seen in 68% of patients. Remarkable responses were seen at the 12-week bone scans which did not correlate with PSA. For the 31 patients who were randomly assigned to placebo (17 patients) or cabozantinib (14 patients), median PFS was significantly longer for cabozantinib (21 weeks vs. 6 weeks, $P=0.0007$). Of 108 patients with evaluable bone scans, 21 patients (19%) showed complete resolution, and 61 patients (56%) showed partial resolution (Hussain et al. 2011). Grade-3 fatigue, palmar-plantar erythrodysesthesia, and hypertension were seen in 16%, 6%, and 6% of patients, respectively.

Tasquinimod is a novel immune-stimulating and antiangiogenic agent that has preliminarily exhibited antitumor activity (Armstrong et al. 2011). In a randomized blinded phase II study, 206 men underwent 2:1 randomization and were assigned to therapy once-daily orally at an initial dose of 0.25 mg/day escalating to 1.0 mg/day over 4 weeks. The primary endpoint of PCWG2 criteria-defined progression confirmed an improved PFS of 7.6 vs. 3.3 months. Tasquinimod led to a transient increase in inflammatory lab markers such as CRP and fibrinogen and asymptomatic increases in amylase/lipase. Tasquinimod was associated with anemia, and the rate of composite cardiac events was acceptably low. Patients over 80 years required frequent dose reductions due to toxicities. A randomized phase III trial evaluating tasquinimod is ongoing in patients with metastatic chemonaive CRPC (Table 20.2).

Unfortunately, sunitinib malate did not extend survival compared with placebo (both arms received prednisone) following docetaxel in a randomized phase III trial. This large trial ($n=873$) compared the combination of prednisone with sunitinib ($n=584$) or placebo ($n=289$) for men with mCRPC progressing following docetaxel-based chemotherapy (Ou et al. 2011). The trial was reported as negative for its primary endpoint, improvement in survival by adding sunitinib to prednisone. In this multicenter, double-blind study, eligible men were stratified by ECOG performance status and progression type (PSA or radiographic) and randomized (2:1) to receive prednisone 5 mg BID and either sunitinib 37.5 mg or placebo on a continuous once-daily dosing schedule. The study was stopped for futility at the second interim analysis (September 2010) by the data monitoring committee. The most common treatment-related Grades 3/4 AEs were fatigue (18.8% vs. 7.3%) and anemia (6.2% vs. 5.5%). The median OS was similar for both arms at ~13 months. However, the median PFS improved with sunitinib (5.6 vs. 3.7 months, $P=0.0077$).

Similarly, zibotentan, an endothelin receptor antagonist, did not extend survival in metastatic or nonmetastatic patients with CRPC, which led to early cessation of the phase III trial. Novel classes of compounds targeting heat-shock proteins and histone deacetylases are being evaluated in early trials.

20.11.2 Combinations with Docetaxel

Unfortunately, the addition of bevacizumab to docetaxel and prednisone did not yield a statistical benefit in OS (Kelly et al. 2010). A total of 1,050 patients with chemonaive mCRPC were randomized to receive DP with either bevacizumab 15 mg/kg given intravenously q 3 weeks or placebo. Randomization was stratified by predicted 24-month survival probability by a previously published nomogram, age, and history of prior arterial thrombotic event (Halabi et al. 2003). Median OS was not statistically improved (22.6 vs. 21.5 months), although median PFS (9.9 vs. 7.5 months, $P<0.0001$) and PSA declines ≥50% (69.5% vs. 57.9%, $P=0.0002$), and objective response rates (53.2% vs. 42.1%, $P=0.0113$) were better with the combination.

The combination of docetaxel plus high-dose calcitriol (DN-101) was compared with docetaxel plus prednisone in an open-label phase III trial, Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT) (Scher et al. 2011a). Nine hundred fifty-three men with metastatic CRPC were randomly assigned to DN-101 plus weekly docetaxel or standard DP every 3 weeks. At an interim analysis, more deaths were noted in the experimental arm, and the trial was halted. The median OS was 17.8 months vs. 20.2 months in favor of standard DP ($P=0.002$). This outcome was considered possibly attributable to the weekly docetaxel schedule and/or lack of daily prednisone in the experimental arm.

Recently, randomized trials have not demonstrated improvements for combination of docetaxel with Bcl-2 antagonists (oblimersen, AT-101) or endothelin receptor antagonists (atrasentan) (Sternberg et al. 2009a; Sonpavde et al. 2011. A phase III trial is evaluating the combination of another endothelin receptor antagonist, zibotentan, with DP chemotherapy, although single-agent zibotentan did not yield improved outcomes. Other agents targeting angiogenesis (aflibercept, lenalidomide) as well as novel molecular targets (Src, insulin-like growth factor receptor, clusterin antisense oligonucleotide) are also being evaluated in combination with docetaxel (Table 20.2). However, at this time, trials have been unable to demonstrate an increment by combining docetaxel with a biologic compound. Recently, the phase III Mainsail trial evaluating the value of combining lenalidomide with docetaxel-prednisone was stopped due to absence of improved outcomes (press release November 22, 2011).

20.12 Prevention of Skeletal-Related Events

The utility of zoledronic acid for CRPC with bone metastasis to decrease skeletal-related events (SRE) has been established in a randomized trial when compared to placebo (Saad et al. 2004). Denosumab is a fully human monoclonal antibody that inhibits RANKL (receptor activator of NF-B ligand), which mediates osteoclast activity (Roodman 2004; Fizazi et al. 2003). A placebo-controlled phase III trial accrued 1,901 men and demonstrated improved skeletal outcomes for denosumab (administered subcutaneously very 4 weeks) compared with zoledronic acid in men with bone metastasis and CRPC, which led to its recent approval (Fizazi et al. 2011). Denosumab significantly delayed the time to first SRE (HR = 0.82; $P=0.008$) and subsequent SREs by 18%. The median time to first on-study SRE was 20.7 months for denosumab vs. 17.1 months for zoledronic acid. Greater suppression of the bone turnover markers uNTx and BSAP occurred with denosumab. Overall, adverse event rates (97% each) and serious AEs (approximately 60%) were similar. Hypocalcemia (13% and 6%), osteonecrosis of the jaw (2.3% and 1.3%), survival (HR 1.03; $P=0.65$), and time to cancer progression (HR 1.06; $P=0.30$) were similar for denosumab and zoledronic acid.

Denosumab was recently reported to delay the onset of bone metastasis in men with nonmetastatic CRPC with high-risk biochemical progression defined as PSA ≥ 8 ng/ml and/or PSADT ≤ 10 months (Sieber et al. 2011). Seven hundred sixteen patients were enrolled in this randomized, double-blind, placebo-controlled trial with 716 patients in each arm. Denosumab increased bone-metastasis-free survival (29.5 vs. 25.2 months, HR = 0.85, $P=0.028$), although overall survival (HR = 1.01, $P=0.91$) and PFS (HR = 0.89, $P=0.093$) did not statistically differ between groups. Adverse events included hypocalcemia (4.6%) and osteonecrosis of the jaw (1.7%).

20.13 Circulating Tumor Cells (CTCs)

The Prostate Cancer Working Group (PCWG)-2 guidelines recommend time to events as the preferable intermediate endpoints. However, these guidelines remain research tools and provide assistance in clinical management but have not been validated (Scher et al. 2008). Prospective studies have demonstrated that patients with unfavorable baseline CTCs (≥5 CTCs/7.5 ml) had shorter

median OS (11.5 vs. 21.7 months) (de Bono et al. 2008; Shaffer et al. 2007). Unfavorable posttreatment CTCs at 2–5, 6–8, 9–12, and 13–20 weeks also predicted shorter OS. CTCs predicted OS better than PSA decrements at all time points. The prognosis for patients with unfavorable baseline CTCs who converted to favorable CTCs (<5 CTCs/7.5 ml) improved (6.8–21.3 months), while the prognosis for those with favorable baseline CTCs who converted to unfavorable worsened (>26 to 9.3 months). These data led to US Food and Drug Administration approval of CTCs for the evaluation of CRPC. Prospective validation of the prognostic impact of CTCs was recently provided from the phase III trial that evaluated abiraterone acetate, where baseline LDH and CTCs, and CTC conversion to favorable within 12 weeks were key prognostic factors for OS (Scher et al. 2011b).

20.14 Conclusions

Since 2010, there have been four new agents approved by regulatory agencies for patients with mCRPC, including one chemotherapeutic agent, cabazitaxel, and three other agents including immunotherapeutic or biologic agents: sipuleucel-T, abiraterone acetate, and denosumab. The optimal sequencing of these agents requires elucidation. Current evidence supports initial sipuleucel-T for relatively asymptomatic patients without visceral disease, docetaxel-prednisone as frontline chemotherapy and cabazitaxel-prednisone or abiraterone acetate as second-line therapy. Multiple other androgen-axis-targeting and biologic agents are displaying early promise. A prominent role for the investigation of a tailored approach is warranted employing molecular biomarkers. A commitment to clinical trials is imperative in all settings.

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Suggested Reading

(2008) Cell genesys announces termination of VITAL-1 phase 3 trial of GVAX immunotherapy for prostate cancer [press release]. Cell Genesys, Inc, South San Francisco
Astrazeneca Press Release, 7 Feb 2011
CureVac presents convincing data from the first ever phase I/IIa clinical study with a mRNA based vaccine. Strong results in safety, tolerability and biological activity. Press release 4 Oct 2010
Southwest Oncology Group Newsletter A

How to Interpret Results?

21

Laurence Collette

Contents

L. Collette, PhD, M.Sc
Statistics Department, European Organisation for Research and Treatment of Cancer, Headquarters, Avenue Emmanuel Mounier 83/11, Brussels B-1200, Belgium
e-mail: laurence.collette@eortc.be

21.1 Introduction

The number of specialist medical journals and the number of scientific publications relating to the medical interventions against cancer increase constantly. A PubMed search for prostate cancer clinical trials published between January 1, 2001, and January 1, 2011, revealed over 5,000 citations, of which more than 2,000 were classified randomized controlled trials. During the same period, 267 citations of meta-analyses were found and as many as 1,470 reviews of trials and treatment of prostate cancer. Obviously, no one will ever find the time to appraise such an amount of information, and this does not include the more recent findings reported at oncology congresses! And importantly, even if one would have the ability to take in all that new information, this would still not be sufficient, because of the presence of intentional or unintentional bias in the way the data are reported and interpreted.

However, every clinician needs to make up his mind about the value of emerging treatments and therapeutic interventions. Most clinicians today are familiar with the hierarchy of clinical evidence (Table 21.1, Tannock 2003) and will rightly give more weight to reports from randomized studies than to those of nonrandomized or ill-controlled between cohort comparisons. The medical reader may however be less aware of the other various biases that may be introduced at every step of a clinical experiment, all of which have the potential to undermine the validity of the results. Bias may be inherent to the trial design

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Table 21.1 Levels of clinical evidence in the medical literature (Tannock 2003)

Level I	Adequately powered, high-quality randomized trial, or meta-analysis of randomized trials showing statistically consistent results
Level II	Randomized trials inadequately powered, possibly biased, or showing statistically inconsistent results
Level III	Nonrandomized studies with concurrent controls
Level IV	Nonrandomized studies with historical controls (i.e., typical single-arm phase II studies)
Level V	Expert committee review, case reports, or retrospective studies

itself, or may result from systematic differences in the way the endpoints are assessed, in the process of data collection, and/or data analysis that together or separately result in observed differences in outcome being erroneously attributed to an impact of the experimental treatment. Bias may also take the form of systematic favoritism in the way results are reported or in the way they are interpreted in the discussion and conclusion of the report. We will illustrate with examples, from the prostate cancer research field, a number of misuses of statistics and various types of bias that exist with the aim to help you identify them yourself when appraising a clinical trial report at congresses or in journal.

To ensure the clarity of these examples, we will however start by demystifying a few basic statistical concepts that are commonly found in clinical study reports.

21.2 Statistical Concepts Demystified

To illustrate the concepts, we will use the hypothetical example of a randomized phase III trial in advanced prostate cancer. Phase III randomized trials are designed to compare two or more forms of therapies by quantifying and comparing their respective effect on a specified evaluation criteria, the primary endpoint, which in our example will be overall survival. The study we consider is one of superiority: the trial is built to test if the overall survival with a new oral compound "WonderPill" is superior to that achieved with the current standard (intravenous) treatment "MarvelDrug" (Fig. 21.1).

21.2.1 Do the Trial Results Apply to My Practice?

Patients who participate in trials constitute a (random-like) sample from the population of patients susceptible to benefit from the new treatment. The clinician doing the study or reading its results is not so much interested in the treatment effect observed in the study sample than to extrapolate the results to the broader population of patients from whom the study sample is (hopefully) representative (Fig. 21.1).

The clinical trial is a controlled experiment that is carried out according to a protocol that defines all circumstances of the patient management (eligibility criteria to the study, examinations, frequency of visits, treatments, diagnostic of disease progression) but also the methodological circumstances of the trial (randomization method, data collection, data cleaning processes, endpoint adjudication, statistical analysis methods…) as well as legal or ethical aspects. From the methodological perspective, the WonderPill versus MarvelDrug study protocol should ensure that the two treated groups will differ only by the treatment they were given, and only this (which is achieved through randomization and compliance to a detailed protocol) will ensure that any observed differences between the two survival curves can legitimately be attributed to the treatment received.

However, one should keep in mind that protocol eligibility criteria (requesting in particular that patients be free of severe comorbidity, be in good performance status, etc.…) define the target population of interest in an often very restrictive way and that the protocol also specifies a very specific clinical practice (diagnostic methods, imaging and other examinations, frequency of follow-up).

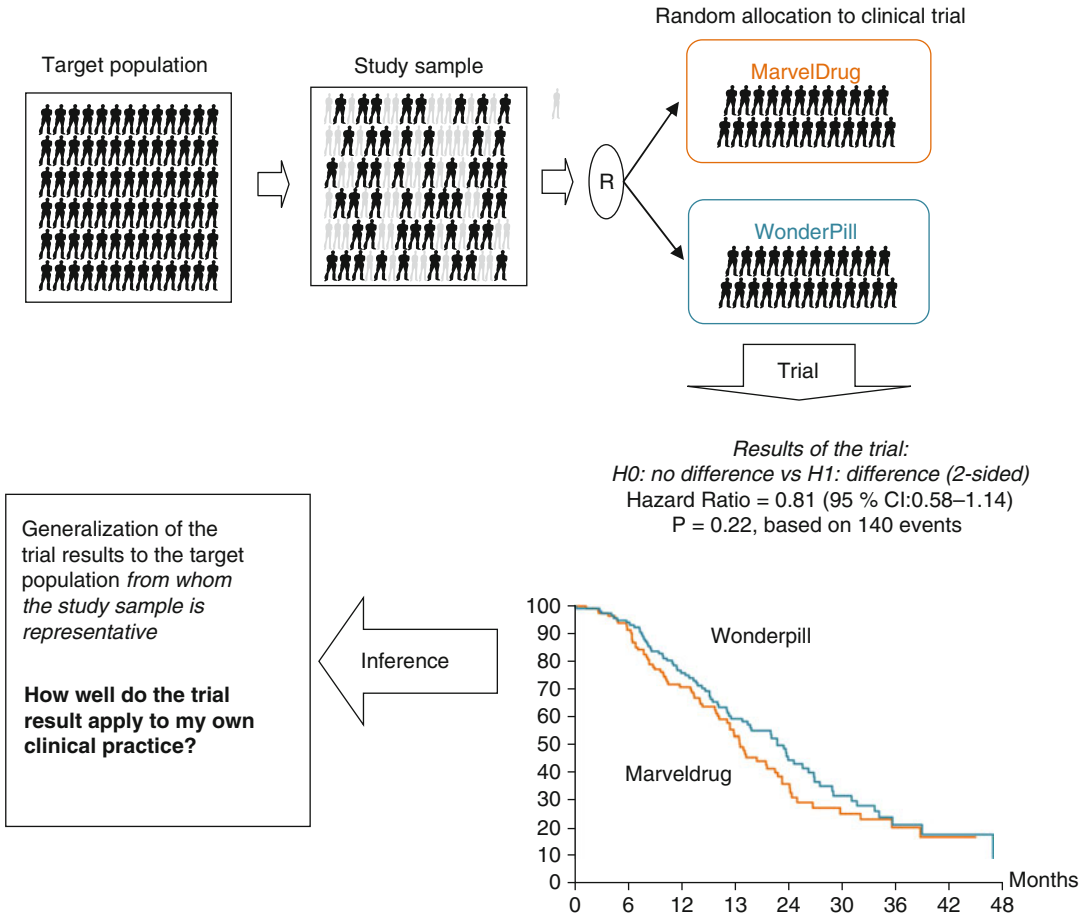


Fig. 21.1 A hypothetical phase III clinical trial testing the superiority of WonderPill over MarvelDrug for overall survival in advanced prostate cancer

In reading a study report, it is therefore essential to look at the "patient characteristics table" in the results to determine if the patient population actually entered in the study was representative for the entire population targeted by the study protocol. If a subset of the target population is overrepresented (e.g., only low-burden disease entered the trial), the results may not apply to the entire target population. In addition, in reading those data, you should address for yourself if the results are relevant to your own practice. They likely are not if, for instance, the diagnostic and follow-up work-up in your routine practice is not as intensive as it was in the trial, or if it uses, for example, different imaging or diagnostic devices, and obviously if the tested therapeutic strategy cannot easily be applied in your clinic.

For example, considering the report by Briganti et al. (2009) that shows that, among patients with node-positive disease, those with up to two positive nodes experienced excellent cancer-specific survival, which was significantly higher compared to that of patients with more than two positive nodes, and suggests this should be considered in the next revision of the TNM classification. The authors clearly specify that their results were obtained in a series of patients in whom pathological nodal staging was based on an extensive lymph node dissection. The mean number of nodes removed in their series

was 13.9, which is significantly higher than in limited nodal dissection series, where the mean number of nodes removed was as low as 5.8. As the number of positive nodes that can be found during pathological assessment is obviously related to the number of nodes available for examination, it would be incorrect to blindly apply the threshold of two positive lymph nodes when a less extended lymph node dissection is performed!

21.2.2 The Truth About *P* Values and Significance Level

The cornerstone of phase III clinical trials is the intention to conduct a statistical test assessing the effect of a certain treatment on outcome. In our example (Fig. 21.1), the statistical test will be assessing if there is a difference in the impact of WonderPill on overall survival compared to that of MarvelDrug. The value of the statistical test (a test statistic) is then converted into a *P* value.

The null hypothesis (denoted by H_0) generally states that overall survival in the two treatment groups is equivalent and that any observed difference in treatment is due to chance alone. The *P* value measures the likelihood that the difference observed in the study is due to chance fluctuations alone, when there is no systematic bias between the groups. The alternative hypothesis (denoted by H_1 or H_a) is the hypothesis that sample observations are influenced by some nonrandom cause, which, thanks to the control made through the study protocol and adherence to it, can legitimately be identified as the treatment the patient received.

When there are compelling reasons a priori to believe that the difference will only occur in one direction (generally favoring the experimental treatment), one-sided tests and *P* values are used. When it is expected that differences may occur in both directions, two-sided tests can be used.

In our example (Fig. 21.1), we were aiming for a two-sided test. Comparison of the survival curves yielded a *P* value of 0.22 for an observed hazard ratio of 0.81. This indicates that if the two treatments were truly equivalent, we would still have 22% chance of observing a difference of similar or larger magnitude due to random fluctuations only. *P* values can take any value between 0 and 1, as any probability measure.

Table 21.2 Hypothesis testing for a difference

	Reality (unknown)	
Our conclusion	H_0 is true (there is no difference)	H_0 is not true (there is a difference)
$P \geq \alpha$: accept H_0 (conclude there is no difference)	Correct decision	False negative (β)
$P < \alpha$: reject H_0 (conclude there is a difference)	False positive (α)	Correct decision (*power* $1-\beta$)

When this probability *P* is low enough, we decide that the evidence against H_0 is strong enough to conclude that a nonzero difference in the effects of WonderPill and MarvelDrug is truly present.

Because we need to make a dichotomous decision, either there is a difference or there is not, we will select a threshold (*a*, the statistical significance level, usually taken to be 0.05 for two-sided tests and 0.025 for one-sided tests) and we require $P < a$ to decide that *P* is "low enough" to declare that a nonnull treatment effect is present. Interestingly, the significance level $a = 0.05$ is a relatively arbitrary cut-off and it means that we are willing to accept a 5% chance of incorrectly concluding that a difference is present (Table 21.2) where none is. Thus, using the 5% significance level on average 5% of perfectly conducted trials with new treatments that have no added benefit over standard treatment will lead to false-positive findings. In practice, however, when $P < a$, one will never know if it is a true or a false-positive finding. Only repeated trials may tell. In our example, $P = 0.22$ is greater than 0.05; thus, we cannot reject H_0.

P values are often misinterpreted: be aware that *P* does not measure the probability that the observed difference is true (in our example, $P = 0.22$ does not mean that there is 22% chance that the true HR = 0.81)! The *P* value only quantifies the likelihood that such a difference arises by chance alone, in absence of systematic bias between the groups. Second, *P* values are influenced by the sample size

(the larger the sample size, the lower the *P* value associated with a given observed treatment effect). Thus, theoretically, any treatment effect can be turned into a statistically significant one by sufficiently increasing the sample size! Third, *P* values directly relate to the statistical test used. Two alternative rank tests (Logrank or Wilcoxon), applied to the same survival data, may not give the same conclusion! Finally, statistical significance is no guarantee for the clinical relevance of the treatment effect. Indeed, *P* values only indicate that a *nonzero* treatment effect is present. The medical relevance of the results must be assessed based on the treatment effect estimate and its associated 95% confidence interval. This interval, calculated from the observed data, gives a range of plausible values for the unknown true treatment effect. Its width gives an impression of the precision of the results (with narrower intervals obtained in studies having larger event numbers). If the trial was to be repeated independently under same conditions and a 95% confidence interval calculated each time, then on average 95% of these intervals would contain the true HR. We will see below that a significant *P* value may also be obtained when the true treatment effect is smaller than the minimum clinically relevant treatment effect specified in the trial protocol sample size calculation.

21.2.3 The Statistical Power Is Not a Number!

In Table 21.2 above, it is apparent that a second type of erroneous conclusion may be made during statistical inference, namely, the false-negative conclusion that H_0 is true when it is not (type II error β). This error is directly related to the statistical power of the test, or probability, to correctly conclude to a nonnull treatment effect when present. Nonstatisticians often believe that the statistical power is a *number* (80% or 90%). However, the statistical power is a *function* of the true (and unknown!) treatment effect. The size of a trial is indeed calculated to ensure a sufficiently high (≥80%) power of detecting a clinically meaningful minimum difference of interest, if it is truly present.

For example, for the study of WonderPill versus MarvelDrug to have 80% power to detect a treatment effect hazard ratio of 0.80 (e.g., an increase in median survival from 18.5 months with MarvelDrug to 23.1 months with WonderPill), one would need a study large enough to provide 640 deaths. (For time to event endpoints, the information contained in a study is measured in terms of the number of events, not the number of patients.)

Figure 21.2a shows how the statistical power decreases with decreasing magnitude of the true treatment effect. Thus, for a trial of given size (number of events), the risk of erroneously concluding to no treatment effect increases as the true treatment effect decreases. For the results given in Figure 21.1, Figure 21.2b shows that, with only 140 events, there is only 25% chance to detect by a statistically significant test a treatment effect of the size HR = 0.80, if it is present. Thus, the nonsignificant *P* value obtained in the results cannot be interpreted as a proof that the two treatments are equivalent. The trial was merely inconclusive due to inadequate statistical power, a common feature in the urological literature (Breau et al. 2006) as well as in the oncology literature (Bedard et al. 2007).

Figure 21.2a also shows that the likelihood of detecting a nonnull treatment effect (i.e., getting a significant *P* value $P<a$), with a study sized to detect a target HR of 0.80, is still 50% when the true treatment effect is 0.85 and 25% when the true treatment effect is 0.90! Thus, statistical significance may also be attained for *true* treatment effects that are smaller than the minimum clinically important difference specified in the study protocol.

21.2.4 A Difference Is a Difference Only if It Makes a Difference

Statistical significance may also be attained for *observed* treatment effects that are smaller than the minimum clinically important difference specified in the study protocol. This was recently discussed by Ocana and Tannock (2011) who argued that study results should be regarded as

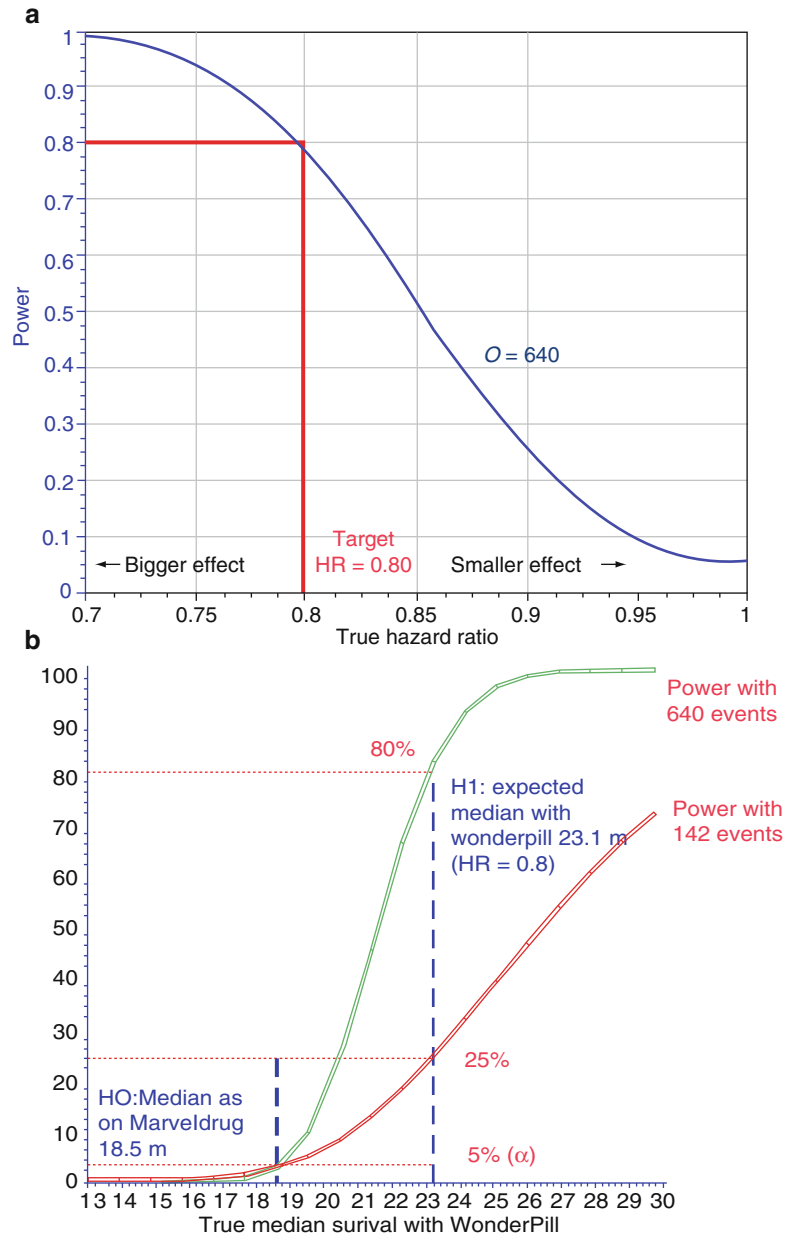


Fig. 21.2 Statistical power for a trial comparing overall survival with WonderPill versus MarvelDrug, with either 640 events. This number provides 80% power to detect a target hazard ratio (HR) of 0.80 if present. (**a**) The statistical power versus the true hazard ratio: the statistical power is 50% if the true HR is 0.85 and it equals *α* when there the two treatments are equal. (**b**) The power in relation to the median survival in the experimental arm

significant only if statistical significance is reached *and* if the observed treatment effect estimate exceeds the target effect specified in the protocol. We however disagree with this view as by definition of the statistical test; if the target treatment effect is set at HR = 0.80 and if the true treatment effect is indeed 0.80, the observed treatment effect, even in a perfectly sized study, has only 50% chance to be more extreme than 0.80. This is illustrated in Fig. 21.3. The same figure also show that the probability of observing a HR equal or more extreme than 0.80 is still over 20% if the true treatment difference amounts only HR = 0.85 and nearly 10% when it amounts HR = 0.89. Figure 21.4 shows the distribution of the observed HR in 1,000 simulations of a trial with $O = 640$ events and an underlying true HR = 0.80. It shows that the observed and true hazard ratios may be very different. Both figures illustrate the dangers of mistaking the observed hazard ratio for being the true underlying treatment effect.

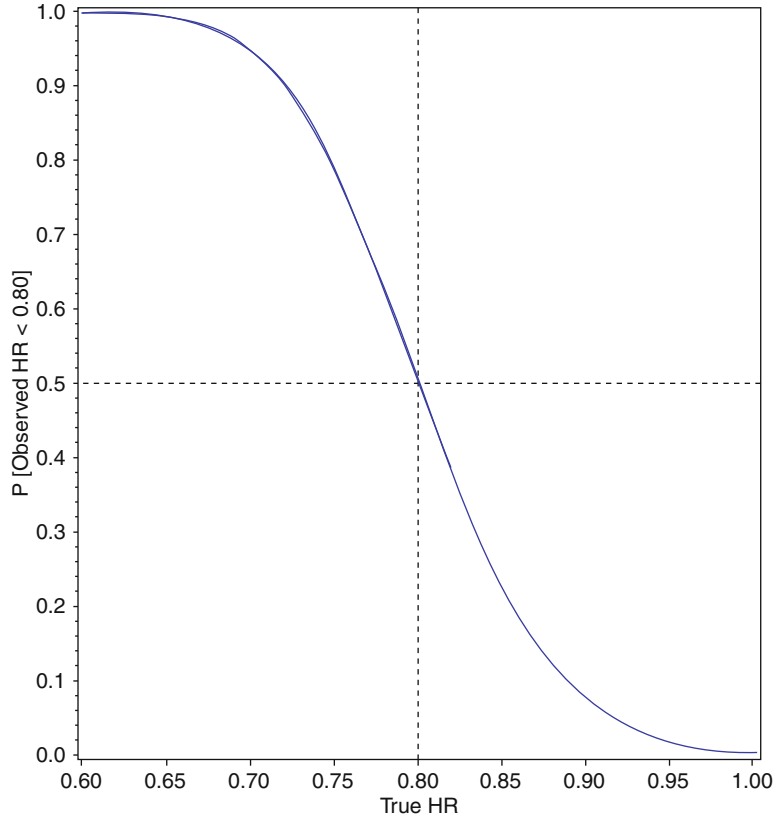


Fig. 21.3 Probability of observing a HR < 0.80 for scenarios of the true treatment difference ranging from HR = 0.6 to HR = 1.0

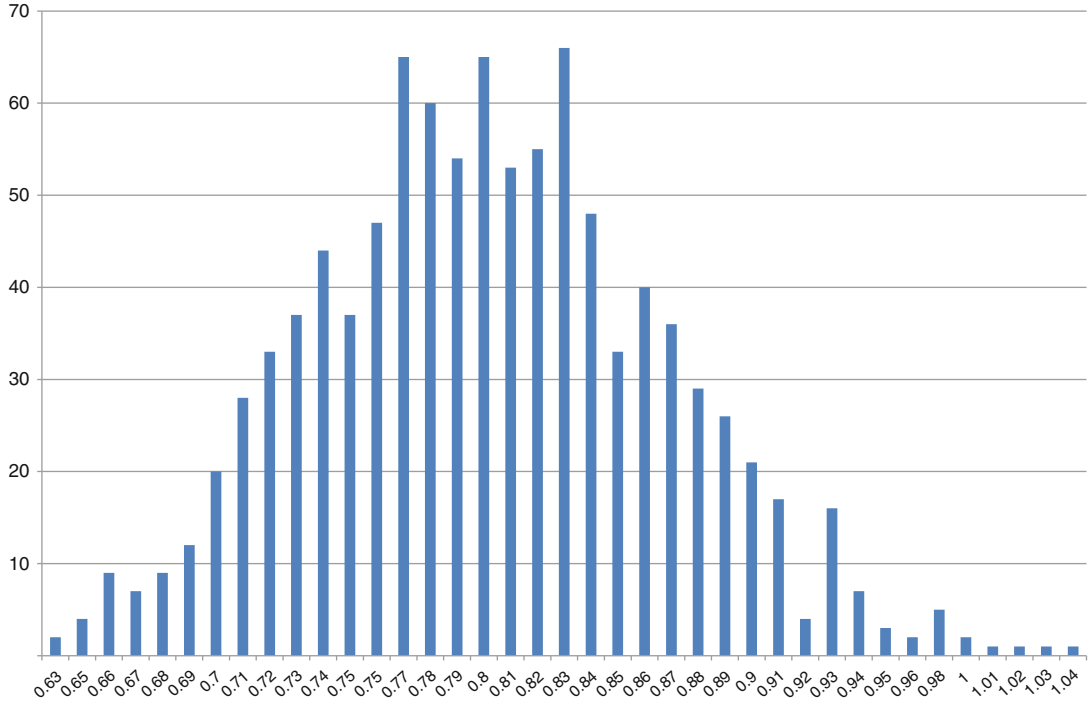


Fig. 21.4 Distribution of the observed hazard ratio in 1,000 simulations of a trial with $O = 640$ events and underlying true HR = 0.80. The horizontal axis shows the true HR, and the vertical axis shows the frequency in a set of 1,000 simulations

21.3 Reading the Literature with a Critical Eye

The reasoning involved in the process of reading a publication is, from the statistical point of view, very similar to the steps one takes when designing and conducting a clinical trial to its end. When reading a scientific paper, the reader should start by identifying the objectives of the research, then read the methods and the results, and then make his own judgment about their value. This should be done *before* reading/writing the discussion and conclusion! Indeed, biased reporting is not uncommon, and arguments in a discussion may seem very persuasive.

We will now illustrate some of the most commonly encountered biases.

21.3.1 Impressing with Numbers

When reading the report of a randomized trial seeking to demonstrate a difference between groups, the reader will naturally be more impressed by numerically larger numbers. There exists a variety of ways of numerically reporting the difference between the treatments, some of which may impress more than others. Table 21.3 below summarizes the survival results with 10-year median follow-up in the EORTC 22863 phase III trial of external irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk by Bolla et al. (2010).

If all of the following statements are correct, some certainly make a stronger impression of magnitude of the treatment difference than others:

(a) […] the median survival of the combined treatment group is 158% of the median with irradiation alone.
(b) […] a 58% improvement in median survival with androgen suppression.
(c) […] a 40% reduction in risk of death with androgen suppression.
(d) […] an 18.3% absolute improvement in 10-year overall survival rate.
(e) […] a 46% relative improvement in 10-year survival rate.

Table 21.3 Survival results in the EORTC phase III trial 22863

Irradiation alone		Irradiation plus long-term androgen suppression	
Median	95% CI	Median	95% CI
6.9 years	6.0–8.3 years	10.9 years	10.0–14.5 years
		Hazard ratio	95% CI
		0.60*	0.45–0.80
10-year survival	95% CI	10-year survival	95% CI
39.8%	31.9–47.5%	58.1%	49.2–66.0%

*$P = 0.0004$

(f) […] irradiation alone had a 67% higher risk of death.
(g) […] the number needed to treat for sparing one life at 10 years is 5.5 patients.

For those interested, this is how the figures were computed, based on Table 21.3:

(a) The ratio of the medians is 10.9/6.9 = 1.58.
(b) So 158% is the same as (a), but concentrating on the increase of 58%.
(c) The hazard ratio is 0.60, thus a 40% reduction of the risk of death.
(d) 58.1% − 39.8% at 10 years makes +18.3% *absolute* improvement.
(e) 58.1/39.8 = 1.46, thus a 46% *relative* improvement.
(f) The hazard ratio was 0.60, which is the ratio of the risk of death with irradiation and androgen suppression compared to irradiation alone; thus, the hazard ratio for irradiation versus the combined modality treatment is 1/0.60 = 1.67, or a 67% higher risk of death.
(g) As in (d), the absolute improvement at 10 years is 18.3% = 0.183, and the number of patients to treat to spare one death at 10 years is 1/0.183 = 5.46, rounded to 5.5.

21.3.2 The Temptation of Subgroup Analyses

> *The answer to a randomized controlled trial that does not confirm one's belief is not the conduct of several sub analyses until one can see what one believes. Rather, the answer is to re-examine one's beliefs carefully.*
>
> – Oei et al. (1999)

In today's dream for personalized medicine, subgroup analyses of clinical trial data seem a logical and very tempting step in data analysis, especially when the overall trial results are statistically or medically not significant. Indiscriminate subgroup analyses carry serious multiplicity concerns and the associated risk of overinterpretation. Indeed, the probability of at least one false-positive finding rapidly increases with the number of subgroups analyzed. If K tests are conducted at the 0.05 significance level, the overall risk of one or more of them turning out significant due to chance alone equals $(1-[1-a]^K)$; thus, for 10 tests with significance level $a=0.05$, that risk is 40.1%! So that $P<0.05$ has little meaning for a single test. If all attempted subgroup analyses were reported, the reader could in theory adjust for multiplicity by adopting for his interpretation a more stringent significance level for each test. The use of a/K would conservatively protect against type I errors. However, comparisons are often not reported (Mills 1993; Tannock 1996; Rui Wang et al. 2007) so that the number K is unknown to the reader, making such adjustment impossible.

By the law of averages, the whole being the sum of the parts, it is always possible to define a grouping of the patients such that the treatment effect in one group is more extreme than the overall effect in the trial and is less extreme in another. Furthermore, breaking down the study sample into numerous subgroups (for instance, age at baseline into four categories, or attempting several cut points dichotomizing a biomarker) induces multiplicity if tests are conducted in all subgroups. To protect against false-positive results, heterogeneity tests (interaction tests) should be conducted first and results in subgroups should only be considered valid after demonstration of significant heterogeneity. This test itself is however also associated with a type I risk.

To illustrate the multiplicity problem, we used the data of EORTC trial 30892 comparing cyproterone acetate (CPA) to flutamide in metastatic prostate cancer (Schroeder et al. 2004). This study of 310 patients of which 250 died showed no statistically significant differences with respect to overall mortality (HR for CPA/flutamide = 1.22, 95% CI: 0.95–1.57, $P=0.1252$). We created 20 completely random splits of the data into two subgroups of equal probability. Each time, we then tested for treatment effect in both subgroups. In two instances, the treatment effect turned out significant in one subgroup and not in the other. Figure 21.5 shows the survival curves in two subgroups for the eighteenth split, for which the test for heterogeneity of the treatment effect is even statistically significant ($P=0.032$)! In the first half of the patients, those on CPA fare significantly worse (HR = 1.59, 95% CI: 1.10–2.30, $P=0.013$) with 3-year survival rate of 45% compared to 55% for those on flutamide. In the second half of the patient, there is absolutely no difference between the two groups (HR = 0.92, 95% CI: 0.65–1.31, $P=0.657$) and the 3-year overall survival is 54% in both groups.

Another common problem with subgroup analyses is when these are defined on the basis of postbaseline assessments. Such problems will be illustrated in the next section. However, even when subgroups are defined by baseline characteristics, one should be mindful that, unless randomization was stratified for the factor, randomization may not have worked and imbalances between treatments may exist within the subgroup. False-negative results are also more likely because of lack of power in the subgroups.

Subgroup analyses are not wrong in themselves, as long as they are carefully conducted and interpreted. Data exploration is important to detect potential new signals that may form the basis for further research.

Guidelines for conducting or assessing reported subgroup analyses are proposed in Table 21.4. Further discussion of this topic can be found in Schultz and Grimes (2005) who also discuss multiplicity induced by interim analyses.

21.3.3 Comparing the Apples and Pears and Claiming All Are Oranges

The most common problem encountered in the literature comes from attempts to compare groups that are not defined at baseline, but are influenced

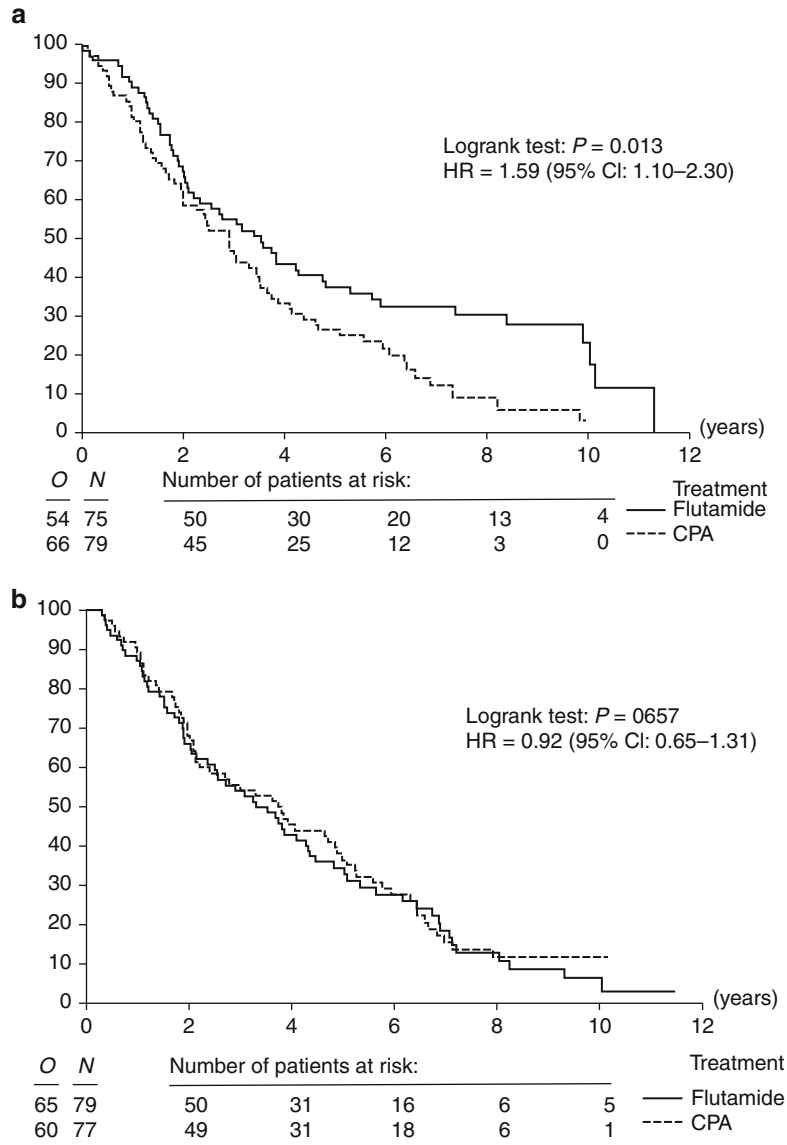


Fig. 21.5 Survival outcomes with flutamide and CPA in two randomly created subsets of patients from trial EORTC 30892 (**a**) Subset 1 and (**b**) complementary subset 2

by events occurring during the study itself. This leads to very biased comparisons that may however not be easy to identify by the reader. Such reports may get through the peer-review process of very-high-quality journals, with the risk of them receiving much more publicity than is legitimate. In the best instance, they will be criticized in letters to the editors, but these are less likely to be read than the original report.

Several examples taken below illustrate this problem.

21.3.4 Length Time Bias: Post-Hoc Analysis of Duration of Androgen Deprivation Therapy in RTOG 85-31 (JCO)

In 2009, Souhami et al. (2009a, and 2009b) reported in the Journal of Clinical Oncology a secondary analysis of the RTOG 85-31. In that paper, the authors analyzed the outcome of patients treated for locally advanced prostate cancer in the arm that combined radiation therapy

Table 21.4 Guidelines for subgroup analyses

In the protocol	Planned subgroup analyses must be specified in the protocol, with the methods intended for the analyses, and the multiplicity adjustment that will be applied to control type I errors
	Subgroup analyses should be conducted only if there is a sound rationale for conducting them!
In the abstract	Only preplanned subgroup analyses for the primary endpoint should be reported in the abstract. Post-hoc findings are only hypothesis generating and should not take prominence in the abstract
In the methods	The number of prespecified subgroup analyses performed and reported should be indicated. For each, the endpoint and the method used to assess heterogeneity should be indicated
	The number of post-hoc subgroup analyses performed and reported should be indicated. These should be clearly identified, as well as the rationale for conducting them. For each, the endpoint and the method used to assess heterogeneity should be indicated
	Indicate the potential effect on type I errors (false positives) due to multiplicity and how this effect is addressed. Describe the adjustments that were used
In the results	First assess heterogeneity of treatment effects across subgroups. Report effect estimates and confidence intervals in all subgroups. Interpret statistical tests of significance only if there is evidence of heterogeneity across subgroups. Clearly distinguish the subgroup analyses that were prespecified from those that were generated by the data themselves
In the discussion	Avoid overinterpretation of subgroup differences. Be properly cautious in appraising their credibility, acknowledge the limitations. Confront the findings with those from other studies

(Adapted from Rui Wang et al. 2007)

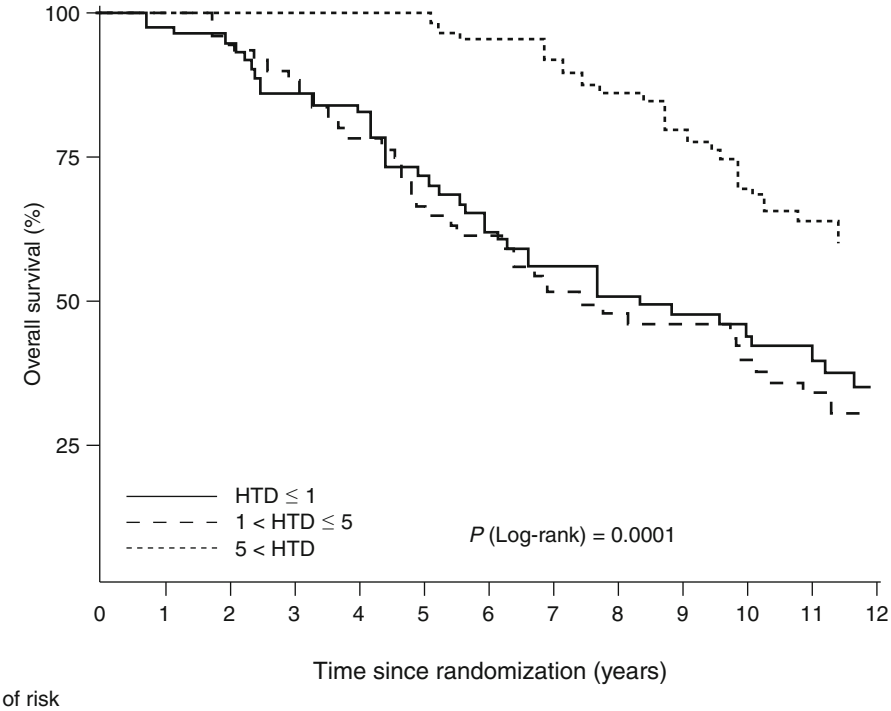
(65–70 Gy) with an intent for lifelong adjuvant monthly LHRH treatment. They then studied a subset of 189 patients who stopped adjuvant androgen suppression despite of absence of disease progression (i.e., did not comply with the protocol). Patients were then divided into three groups based on the tertiles of hormone therapy duration as follows: ≤1 year, more than 1 year, and ≤5 years, more than 5 years. They then compared those groups with Logrank test for the endpoints overall survival, disease-free survival, cause-specific mortality, local failure, and distant metastasis. They concluded that patients with androgen deprivation treatment for more than 5 years had an improved overall disease-specific and progression-free survival than patients with shorter duration of hormonal therapy. Based on these findings, the authors conclude that "decreasing hormonal therapy duration (HTD) to ≤5 years may have a detrimental effect on patients with locally advanced prostate cancer" because overall survival is significantly better in patients who received androgen deprivation therapy for >5 years (Fig. 21.6).

What is wrong with this analysis?

First, one should note that in order to receive x years of androgen suppression in a protocol that mandated androgen suppression until disease progression, a patient has to live at least x years and be disease-free for x years! Thus, all patients in group 3 (HTD >5 years, group 3), *by definition of the grouping*, enjoy a survival of 5 years or more, whereas if a patient died earlier than 5 years after radiation therapy, then, obviously, he had to be included in the group with HTD < 1 (group 1) or HTD of 1–5 (group 2) years.

The presence of such bias is evidenced in the paper by the fact that the overall survival curves in Fig. 21.6 show no event in group 2 (HTD of 1–5 years) for the first year on study and no event (no drop of the survival curves) in group 3 (HTD >5 years) until year 5. This is a very good example of *length time bias*, a specific form of selection bias. In general, this kind of bias may be removed by the use of a simple statistical method, known as the *landmark* method (Anderson et al. 1983), which consists in defining an observation time (e.g., 5 years) that is used to classify the patients into groups, whereas only the observations past that landmark are used to compare the groups. However, for this particular report, even that method would not be sufficient to provide support to the conclusion claimed by the authors.

Indeed, a second selection bias is present in the analysis, due to the exclusion of all patients who discontinued therapy because of death or disease progression. This is discussed in a letter



No. of patients of risk

HTD ≤1	67	55	40	27	13
1 < HTD ≤ 5	61	54	36	24	6
5 < HTD	61	61	58	49	19

Fig. 21.6 Overall survival by hormone therapy duration (HTD) in RTOG trial 85-31 (Reproduced with permission from Souhami et al. 2009a, b)

to the editor (Lin et al. 2010) who takes two examples. Example 1 is a patient whose cancer is simply not responsive to hormonal modulation. If the patient stops the hormonal therapy for any reason before the recurrence is detected, he counts as a failure and is classed in either the less than 1 year or 1–4 year HTD group. But the same patient who continued the hormonal therapy long term would be excluded from the analysis (and thus not be counted as a failure for the >5 year group) as long as he was still receiving hormonal therapy when the recurrence was detected. Example 2 is a patient who received therapy for 4 years, then develops myocardial infarction and dies 2 years later from cardiovascular complications. If upon myocardial infarction at year 4 hormonal therapy is stopped, the patient is counted as a death in the 1–4 year hormone therapy group, but if that same patient believes in the benefits of >5 year HTD and continues his hormonal therapy, he would *not* count as a death in the >5 year HTD group, because patients who die on hormone therapy are excluded from the analysis. This shows how this second selection of patients for the study that excludes 41% of patients allocated to the combined treatment group in the RTOG study induces further bias in favor of the longer duration group (group 3) by selecting out the nonhormone responsive patients. It also leads to underestimation the detrimental effects of hormones because patients who die while still being treated with hormonal modulation are excluded from the analysis, even if the longer duration of hormonal treatment contributed to that death (Lin et al. 2010).

This paper raised a number of reactions through letter to the editors. The authors diligently replied to these, but did not recognize fully

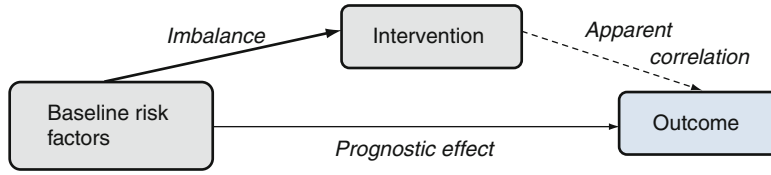


Fig. 21.7 Mechanisms of selection bias in a study assessing the effect of a nonrandomized intervention on an outcome: both *solid arrows* are necessary for an apparent correlation to be induced between the intervention and the outcome. In randomized trials, randomization ensures that the *top left solid arrow* is absent

the limitations of their analyses, which only report an artificial correlation built in the analysis methods used. They however recognized that their "secondary analysis was a hypothesis-generating exercise; only a properly designed phase III randomized trial can conclusively and unequivocally clarify this issue" (Souhami et al. 2009a, b). One may wonder however if such explorations are worth a publication.

21.3.5 Selection Bias in Assessing the Value of Radical Prostatectomy for Node-Positive Patients

Selection bias is present if the selection of patients for the studied intervention is confounded by patient factors that are also related to clinical endpoints. To illustrate the reasoning applied in identifying possible selection bias in a publication, we will use a report by Engel et al. (2010) discussing the value of continuing versus abandoning radical prostatectomy when positive lymph nodes are found during the surgery. The authors used a series of 938 lymph-node-positive patients from the Munich Cancer Registry: in 688, the radical prostatectomy (RP) was conducted, and in 250, the RP was abandoned. Data about age, grade, and PSA were available. The authors used multivariate Cox regression analysis to compare overall survival between the two groups. When reading such a report, the reader must pay a particular attention to the following question: are the two groups comparable in terms of risk factors? Was the decision to stop the surgery independent of baseline risk factors? Were appropriate and sufficiently effective statistical adjustments made to attempt to correct for selection bias?

If the answer to any of these questions is "no," then the reader must take great caution in reading the conclusions of the article because there is a risk to erroneously attribute the effect of patient selection to the intervention itself. When this mechanism is in place (Fig. 21.7), the correlation between the tested intervention (in this article radical prostatectomy) and the outcome (survival) is induced in whole or in part by a third factor (here baseline risk of both pathologically positive lymph node disease and shorter overall survival) that is correlated to both the intervention and the outcome. It is important to note that imbalances in strong prognostic factors between the intervention groups need not to be statistically significant for the above mechanism to be present!

The risk of selection bias in the article by Engel was discussed in an editorial by Studer et al. (2010). To address the first question above, a careful inspection of the tables showing the distribution of the available risk factors in the study is needed. Such an inspection shows that the two patient groups differ in many ways: PSA was >20 ng/ml in only 42% of the patients who underwent RP compared to 66% in the patients whose surgery was aborted; stage T4 was also five times less frequent in the operated group (4% vs. 20.9%), reflecting the fact that these parameters may have played a role in the decision to abort the surgery. Thus, in this study, the two groups are not balanced for risk factors and there is suggestion that these factors that are known risk factors for outcome may have been used in treatment decision.

The fact that a single positive node was found in 50.7% of the patients who underwent prostatectomy but only in 27.9% of the patients in whom RP was aborted speaks in the same direction, as

well as the figure showing that node-negative patients who underwent radical prostatectomy in the study have a better life expectancy – despite their prostate cancer – than the survival estimate for the general population (Engel et al. 2010; Studer et al. 2010).

Were appropriate statistical measure taken to adjust for these imbalances? The authors made due diligence in attempting to correct for these, by means of multivariate modeling. However, this is made very difficult by the fact that there is also a large amount of missing data for those key prognostic factors (that are also not balanced in the two groups): the clinical T stage was unknown in 16.1% of the analyzed node-positive patients who underwent prostatectomy and in 6.0% of those with aborted prostatectomy, and the number of positive lymph nodes retrieved was unknown in 40% and 62.8% of the patients, respectively.

Despite multivariate analysis, the selection bias in baseline factors cannot be properly accounted for due to the large amount of missing data. More efficient methods of statistical adjustment for confounding such as propensity score adjustment or matching exist (D'Agostino 1998) but could not have been used in this report, because of the missing data. However, one should keep in mind that any statistical method can only adjust for the impact of known and measured confounders; they do nothing about unknown confounders! Randomization is the only method that can, with sufficiently large sample size, also ensure comparability of groups for unknown or unmeasured risk factors! For further discussion about adjustment methods for confounding, we refer you to Wunsch et al. (2006). They reviewed the statistical techniques available to adjust for confounders (matching, stratification, multivariable adjustment, propensity scores, and instrumental variables) and the issues that need to be addressed when interpreting the results.

For another illustration of the diverging conclusions that may be obtained by a properly randomized study versus by an adjusted non randomized comparison of two treatments, we invite you to contrast results of two reports comparing short-term and long-term androgen suppression plus external beam radiation therapy and survival in patients with node-negative high-risk prostate cancer. In a pooled analysis, D'Amico et al. (2007) concluded that after adjusting for known prognostic factors, the treatment of node-negative high-risk prostate cancer using 3 years as compared with 6 months of androgen suppression with radiotherapy was not associated with prolonged survival in men of advanced age. In the randomized trial EORTC 22961, Bolla et al. (2009), the authors concluded that the combination of radiotherapy plus 6 months of androgen suppression provides inferior survival as compared with radiotherapy plus 3 years of androgen suppression in the treatment of locally advanced prostate cancer.

21.3.6 Biases in Nonrandomized Reports Comparing Immediate and Deferred Therapeutic Intervention

A number of clinical circumstances of prostate cancer require a decision to either initiate the treatment immediately or to defer its initiation until signs of disease progression (symptoms, or more commonly PSA increases) appear. This may be the decision to treat locally for small asymptomatic localized disease, the decision to initiate hormonal therapy in patients who cannot receive local treatment with curative intent, or the decision to give adjuvant irradiation after radical prostatectomy. If several randomized clinical trials were conducted to address each of those three questions, all those studies took a long time to complete due to the naturally long history of the disease. The clinical practice changed while these studies and the trial results, in particular those of the studies addressing the last two questions, are being criticized for not reflecting the current practice of initiation of deferred therapy (on the basis of PSA relapse, defined using very sensitive assays). Aside from the three major trials assessing immediate postoperative irradiation versus observation for patients with pathologically high-risk disease after radical prostatectomy (Thompson et al. 2006; Bolla et al. 2005; Wiegel et al. 2009) in particular, a number of secondary publication

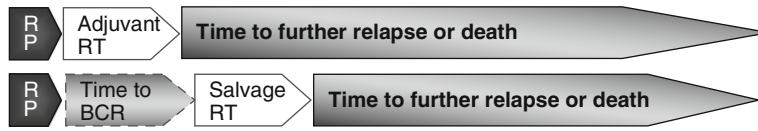


Fig. 21.8 Hypothetical timeline after radical prostatectomy (RP) for two patients receiving either adjuvant or salvage radiotherapy (RT) delivered upon biochemical relapse (BCR)

reported retrospective comparisons of patient series that were treated either immediately or upon (early) PSA relapse (Anscher et al. 1995; Valicenti et al. 1999; Catton et al. 2001; Taylor et al. 2003; Trabulsi et al. 2008; Budiharto et al. 2010). However, the validity of these nonrandomized results is questionable (Patel and Stephenson 2011). Indeed, several of the biases we illustrated in the preceding chapters are concomitantly present in these analyses:

(a) All retrospective analyses attempt to compare disease-free or survival rates in men who have received adjuvant radiotherapy with patients who had established biochemical relapse and therefore received salvage radiotherapy. As noted by Patel and Stephenson (2011), if the second group has *effective* biochemical relapse, patients in the comparator group who all had adjuvant radiotherapy only have a *theoretical* risk of biochemical relapse, and this group includes a proportion of patients who, had they not been given adjuvant radiotherapy, would never have experienced biochemical relapse. There is selection bias in the analysis since the patients with similar features who never recurred are de facto excluded from the salvage irradiation group. None of these retrospective studies could account for the true denominator in the salvage irradiation group (Patel and Stephenson 2011).

(b) By the same mechanism, there is also length time bias in the comparison since patients who would die for reasons unrelated to prostate cancer before experiencing biochemical failure are excluded from the salvage group but included in the adjuvant irradiation group. Length time bias is also evident in the studies that counted the survival time *from the date of* (*end of*) *irradiation*, such as the report by Budiharto et al. (2010). Indeed, as illustrated in Fig. 21.8, the time to event is *by definition* shorter in the group with salvage irradiation as compared to the group with immediate irradiation.

(c) Finally, confounding is likely to be present in such comparisons as the intention for treatment was not randomized but chosen for each patient individually. Therefore, risk factors for final outcome likely influenced the decision to treat immediately or later so that the mechanisms illustrated in Fig. 21.7 are all in place for bias to be present.

Given these limitations, we can safely conclude that randomized evidence is needed to provide the definitive proof that early salvage irradiation gives similar outcome to immediate adjuvant treatment for patients presenting with high-risk features, while reducing overtreatment by not irradiating the many patients who will not experience biochemical recurrence.

21.3.7 Issues with the Progression-Free Survival Endpoint in Randomized Phase III Trials

Due to the long-protracted natural history of prostate cancer and as new effective treatments emerge and are being used in clinical practice for the treatment of for the more advanced stages of the disease, the use of overall survival as the primary endpoint of phase III randomized trials comparing intervention in earlier stages of the disease becomes extremely difficult and costly. As a result, many trials nowadays use progression-free survival endpoints as their primary endpoint, despite that such endpoints so far cannot support regulatory approval of new agents (US FDA 2007; Pazdur 2008).

Depending on the setting, the progression-free survival endpoint may encompass different types of events such as skeletal-related events or symptomatic bone progression in studies assessing bisphosphonates or more commonly a combination of biochemical failure, clinical disease progression (locoregional and/or distant), and death.

Common to all such endpoints is the fact that their assessment requires repeated diagnostic tests (markers such as PSA or imaging such as CT-scans, MRI, bone scans) at scheduled intervals during follow-up.

In assessing the results of trials that use such endpoints, the reader must realize that unlike overall survival, a progression-free endpoint is subject to measurement errors and imprecision and to a risk of interpretation bias for those diagnostics such as bone imaging that involve a degree of subjective interpretation.

21.3.7.1 Inflation of the Median Time to Event Due to the Discreteness of the Assessments

Even for events that more objectively measured such as biochemical failure, a failure that is diagnosed at a given follow-up visit would in fact have occurred in the time interval from the preceding assessment to the present visit. This leads to over estimation of the time to failure (Carroll 2007; Panageas et al. 2007). Gignac et al. (2008) showed that, when the true median progression-free survival was 12 weeks, the information lag resulted in estimated median progression-free survival times increased to 15.6, 16.6, and 18.7 weeks for a 6-, 8-, or 12 weekly visit schedule respectively. Further simulation studies by Panageas et al. (2007) show that the bias in estimation does however not necessarily increase with an increase in the length of the assessment interval; instead, it depends on the timing of the interval relative to the true median. The bias will be smallest when the true median progression-free survival time is a multiple of the interval between visits (thus, if the true median is 12 weeks, the bias will be larger if visits are scheduled every 5 weeks, then if they are scheduled every 3 or 4 weeks).

It is important to note that because of the direct influence of the visit schedule on the reported median progression-free survival times, results from studies that used varying assessment schedules are not directly comparable!

21.3.7.2 Loss of Power and Biased Estimation of the Treatment Hazard Ratio in Relation to Infrequent Assessments

The frequency of assessments also directly impacts on the estimated treatment differences (Carroll 2007; Panageas et al. 2007; Gignac et al. 2008), even when the visits are scheduled symmetrically in the two randomized treatment groups.

Carroll (2007) shows that the hazard ratio is increasingly biased toward the null hypothesis of no difference as the interval between visits lengthens and the frequency of visits declines. As a consequence, statistical power falls and the number of events needed to maintain the specified statistical power increases. They suggest that to maintain statistical power to detect hazard ratios between 0.80 and 0.667, the interval between visits can afford to be no more than about one half of the median progression-free survival in the control arm.

21.3.7.3 Biased Treatment Effect Estimation Due to Imbalances in the Assessment Schedules Between Arms

From the remarks above, it becomes apparent that artificial differences between treatment groups may be caused by asymmetric schedule of visits between the two groups or by systematically prolonged delays in observation time in one arm compared to the other: if visits in arm A take place every 4 weeks and visits in arm B every 5 weeks, the median time to event for arm B will be inflated since the events will systematically be attributed to a later time in the arm where visits are less frequent! This type of bias is referred to as *evaluation-time bias* by Dancey who reviewed the possible sources of bias and variability in studies that use a progression-free survival endpoint (Dancey et al. 2009). Simulation studies

have demonstrated that differences in the timing of disease evaluations can significantly bias PFS analyses to the point of causing an apparent improvement in outcome when none existed (Freidlin et al. 2007; Panageas et al. 2007; Bhattacharya et al. 2009).

21.3.7.4 Evaluation Bias

In that same review, Dancey et al. (2009) recommend blinding in trials that use a progression-free survival endpoint. This is to prevent that knowledge of the treatment group influences the investigator for the assessments of the endpoint that involve a greater degree of subjectivity (e.g., review of images), or for the decisions to delay treatment and/or visits on the basis of toxicity or inconvenience for the patient. Physicians or patients may be biased toward earlier claim that progression has occurred in the arm that is considered to be the less intensive treatment option.

21.3.7.5 Bias Induced by the Statistical Methods

In the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, a whole section is devoted to the statistical methods of analyzing progression-free survival endpoints. The guidance is often interpreted as recommending that patients who stop taking randomized therapy prior to documented progression should be censored at the time when the treatment is stopped (Carroll 2007). However, this causes obvious problems in the analysis as censoring inevitably becomes informative in this setting. Indeed, patients who stop treatment in absence of progression generally do so because either of toxicity or general deterioration of the patient status that may be indicative of treatment failure. In such circumstances, if the prevalence of censoring differs between arms, naive censoring could lead to extremely biased results: taken to the extreme, a treatment that would be so toxic that all patients would stop treatment due to toxicity would have an estimated progression-free survival rate of 100% when using the method described above.

The impact of varying analysis methods and other sensitivity analyses are discussed in detail by Bhattacharya (2009) in a study of bevacizumab in late-stage breast cancer.

21.3.7.6 Further Challenges When Using a PSA or Other Biomarker-Based Endpoint

All the points discussed above apply equally to the clinical progression-free survival endpoint and to endpoints that incorporate biochemical relapse. PSA (or other biomarker measurements) measurements are more objective and more precise than the assessment of clinical progression of prostate cancer since both the primary disease and its major metastatic site (bone) are not measurable and thus disease progression cannot easily be quantified. However, the reader must pay special attention to the following aspects, when reading a report that uses a PSA-based endpoint:

- The definition of what constitutes biochemical failure differs according to disease setting and treatments. Consensus definitions are available only for castration-resistant prostate cancer (Scher et al. 2008) and for the assessment of relapse after primary local treatment with curative intent (AUA guidelines after radical prostatectomy (Cookson et al. 2007) and ASTRO-Phoenix definition after primary irradiation with or without neoadjuvant hormone therapy (Roach et al. 2006)). However, those guidelines are relatively recent so that between-trial comparisons with older studies even assessing similar treatments may be difficult. In 2007, Thomson et al. (2007) in a review of studies addressing localized prostate cancer had identified as many as 166 different definitions of biochemical failure!
- Because biochemical failure is defined differently depending on the treatment given, the use of this endpoint for randomized comparisons of different treatment modalities are generally biased. For example, the "Phoenix definition," was designed to make comparison between any radiation series possible but did not facilitate easy comparisons with surgical series (Nielsen et al. 2008). In castration-resistant prostate cancer, the Prostate Cancer Working Group emphasized the importance of understanding the effect of an agent on PSA

and that some drugs may modulate PSA expression independent of an effect on tumor cell growth or survival (Scher et al. 2008). They also advised against the reporting of PSA response rates as endpoint of trials in this disease and emphasize the importance of keeping patients on trial until radiological or symptomatic progression and not to discontinue therapy on the basis of a rise in PSA only (Scher et al. 2008).

- Differences between treatment groups in terms of PSA-based endpoints do not necessarily translate into differences in more clinically relevant endpoints (clinical progression-free survival or overall survival). For example, further analyses of RTOG trial 92-02 in which patients received differing durations of androgen suppression in combination with irradiation showed that observed differences in terms of time to biochemical progression or in terms of PSA doubling time did not translate into differences in overall survival (Sandler et al. 2003; Valicenti et al. 2006). There is in fact no definitive statistical proof that time to biochemical relapse or biochemical progression-free survival is surrogate for overall survival in prostate cancer (Collette 2008; Ray et al. 2009; Denham et al. 2008; Armstrong and Febbo 2009). The only setting in which biochemical failure is regarded as sufficient evidence of disease recurrence is after local treatment with curative intent, but as indicated above, comparisons between treatment modalities using this endpoint is difficult due to the lack of a unique definition of what constitutes treatment failure. Furthermore, each surrogate, when it exists, is dependent on the disease state and mechanism of action of the drug in question, so that a surrogate for one state or one therapy cannot necessarily be extrapolated to other disease states or drugs (Armstrong and Febbo 2009).
- More sophisticated PSA-based endpoints such as PSA doubling time are calculated on the basis of PSA measurements using a mathematical model. The methodology of calculating PSA doubling time is inconsistent in the literature and small variations in the method of calculation, and data acquisition can sometimes lead to wide variations in the calculated value (Daskivich et al. 2006). Prognostication based on PSA doubling time cut-offs (e.g., PSA doubling time after radical prostatectomy <9 months) is therefore also very dependent on the methods used in the original papers. The parameters of interest in this instance are method of analysis (the log-slope method is preferred), start and end values for the PSA measurements used in the PSA doubling time calculation (should be from the date of biochemical relapse for the disease indication until the start of the next PSA-altering treatment) and whether a minimum threshold value was used, if PSA measurements were measured at the same laboratory using the same assay, the spacing and number of PSA measurements (minimum three measurements taken over a period of minimum 3 months), and whether the nadir subtraction was done or not (Daskivich et al. 2006). There is also controversy about the value of PSA doubling time when measurements were obtained using an ultrasensitive assay (Chang et al. 2010).

21.3.8 Conclusions and Recommendations

The discussion in this chapter should hopefully provide hints to the reader of clinical reports for assessing the quality and medical relevance of published reports. A level of familiarity with statistics and methodology in the broader sense is indeed essential to reduce the vulnerability of the reader to misinterpretation, as well as is a good dose of critical thinking.

Readers of medical reports must always keep the presence of publication bias in mind. Publication bias is the decision to publish or not publish a study based on its results (Howland 2011). This bias is inherent to the process whereby editorial and journalistic criteria emphasize the newest and most striking research findings. These findings are often exaggerated in magnitude and may not be confirmed by later research that for the same reasons is less likely to get published.

The requirement for complete and transparent reporting of results through the adoption by most scientific journals of reporting guidelines such as CONSORT (http://www.consort-statement.org) and the further requirement to submit the study protocol with the manuscript should help the reader scrutinize the quality of the evidence presented in journals. Further requirements are the honest and full declaration of conflicts of interest and the correct assignment of authorship (Sharrock et al. 2011).

We suggest that readers of medical reports should get familiar with the reporting guidelines and their accompanying checklists. Such guidelines have been developed for a large number of types of studies. All existing guidelines are accessible through the website of the EQUATOR Network (http://www.equator-network.org). The EQUATOR Network is an international initiative that seeks to enhance reliability and value of medical research literature by promoting transparent and accurate reporting of research studies. The Center for Evidence-Based Medicine of the University of Oxford (http://www.cebm.net) offers further tools and downloads for the critical appraisal of medical evidence, including appraisal sheets for the assessment of randomized clinical trials.

Completing these checklists or appraisal sheets when reading reports of studies is certainly an efficient method for gradually gaining the methodological expertise needed for a correct interpretation of research reports.

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Management of Prostate Cancer: EAU Guidelines on Screening, Diagnosis and Treatment

22

Axel Heidenreich

Contents

22.1 Introduction

The most recent summary of the European Association of Urology (EAU) guidelines on prostate cancer (CaP) was published in 2011 (Heidenreich et al. 2011a; Mottet et al. 2011). The long version of these guidelines has been continuously updated, and it is available at the website of the European Association of Urology: http://www.uroweb.org.

A. Heidenreich, M.D., Ph.D.
Department of Urology, RWTH University Aachen, Pauwelsstr. 30, Aachen, 52074, Germany
e-mail: aheidenreich@ukaachen.de

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22.2 Epidemiology

In Europe, CaP is the most common solid neoplasm, with an incidence rate of 214 cases per 1,000 men, outnumbering lung and colorectal cancer (Jemal et al. 2008). CaP affects elderly men more often, and it is therefore a bigger health concern in developed countries. Thus, about 15% of male cancers are CaP in developed countries compared to 4% of male cancers in developing countries (Ferlay et al. 2010). There are large regional differences in incidence rates of CaP with a range from 68.8 in Malta to 182 in Belgium (Ferlay et al. 2010).

22.3 Risk Factors

The factors that determine the risk of developing clinical CaP are not well known, although three well-established risk factors have been identified: increasing age, ethnical origin and heredity.

If one first-line relative has the disease, the risk is at least doubled. If two or more first-line relatives are affected, the risk increases 5- to 11-fold (Bratt 2002). About 9% of individuals with CaP have true hereditary CaP, defined as three or more relatives affected or at least two who have developed early-onset disease, i.e., before the age of 55.

22.4 Classifications

The UICC 2010 Tumour Node Metastasis (TNM) classification is used throughout these guidelines (Sobin et al. 2009).

The Gleason score is the recommended for grading CaP. According to current international convention, the (modified) Gleason score of cancers detected in a prostate biopsy consists of the Gleason grade of the dominant (most extensive) carcinoma component *plus* the highest grade, irrespective of its extent (no 5% rule) (Gleason and Mellinger 1974).

In radical prostatectomy specimens, both the primary and the secondary Gleason grade are to be reported. The presence of the tertiary grade and its approximate proportion of the cancer volume should also be reported.

22.5 Prostate Cancer Screening

There is currently no evidence for introducing widespread, population-based, screening programmes for early CaP detection in all men (Ilic et al. 2007) (level of evidence: 2). To evaluate the efficacy of CaP screening, two large randomized trials have been published: the PLCO (Prostate, Lung, Colorectal And Ovary) trial in the USA and the ERSPC (European Randomized Screening for Prostate Cancer) in Europe (Andriole et al. 2009; Schröder et al. 2009a) (level of evidence: 1b).

The PLCO Cancer Screening Trial randomly assigned 76,693 men to receive either annual screening with PSA and DRE or standard care as the control (Andriole et al. 2009). After 7-year follow-up, the incidence of CaP per 10,000 person-years was 116 (2,820 cancers) in the screening group and 95 (2,322 cancers) in the control group (rate ratio, 1.22) (Andriole et al. 2009). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screened group and 1.7 (44 deaths) in the control group (rate ratio, 1.13). The PLCO project team concluded that CaP-related mortality was very low and not significantly different between the two study groups (level of evidence: 1b).

The ERSPC trial included a total of 162,243 men aged between 55 and 69 years (Schröder et al. 2009a). The men were randomly assigned to a group offered PSA screening at an average of once every 4 years or to an unscreened control group. During a median follow-up of 9 years, the cumulative incidence of CaP was 8.2% in the screened group and 4.8% in the control group (Schröder et al. 2009a). The absolute risk difference was 0.71 deaths per 1,000 men. This means that 1,410 men would need to be screened and 48 additional cases of CaP would need to be treated to prevent one death from CaP. The ERSPC investigators concluded that PSA-based screening reduced the rate of death from CaP by 27% but was associated with a high risk of overtreatment (level of evidence: 1b).

Both trials have received considerable attention and comments. In the PLCO trial, the rate of compliance in the screening arm was 85% for PSA testing and 86% for DRE. However, the rate of contamination in the control arm was as high

as 40% in the first year and increased to 52% in the sixth year for PSA testing and ranged from 41% to 46% for DRE. Furthermore, biopsy compliance was only 40–52% versus 86% in the ERSPC. Thus, the PLCO trial will probably never be able to answer whether or not screening can influence CaP mortality.

In a recent retrospective analysis CaP incidence, CaP metastasis and cause of death were evaluated between a group of 11,970 men who were included in the intervention arm of the ERSCP trial and a control population of 133,287 unscreened men during an 8-year observation period (van Leeuwen et al. 2010). The relative risk of CaP metastasis in the screened compared to the control population was 0.47 ($p<0.001$). The relative risk of CaP specific mortality was also significantly lower in the screening arm (RR 0.63, $p=0.008$). The absolute mortality reduction was 1.8 deaths per 1,000 men. Based on these data, the real benefit of the ESRPC trial will only be evident after 10–15 years of follow-up, especially because the 41% reduction of metastasis in the screening arm will have an impact.

Based on the results of these two large, randomized trials, most if not all of the major urological societies conclude that at present widespread mass screening for CaP is not appropriate. Rather, early detection (opportunistic screening) should be offered to the well-informed man (*see also* Sect. 22.6). Two key items remain open and empirical:

- At what age should early detection start.
- What is the interval for PSA and DRE.

The decision to undergo early PSA testing should be a shared decision between the patient and his physician based on information balancing its advantages and disadvantages. A baseline PSA determination at age 40 years has been suggested upon which the subsequent screening interval may then be based (Schröder et al. 2009a; van Leeuwen et al. 2010; Börgermann et al. 2010) (grade of recommendation: B). A screening interval of 8 years might be enough in men with initial PSA levels ≤1 ng/ml (Schröder et al. 2009a). Further PSA testing is not necessary in men older than 75 years and a baseline PSA ≤ 3 ng/ml because of their very low risk of dying from CaP (Carter et al. 2008).

22.6 Diagnosis and Staging of Prostate Cancer

The main diagnostic tools to detect CaP include DRE, serum concentration of PSA and transrectal ultrasound-guided biopsies.

In about 18% of all patients, PCa is detected by a suspect DRE alone, irrespective of the PSA level (Carvalhal et al. 1999) (level of evidence: 2a). A suspect DRE in patients with a PSA level of up to 2 ng/ml has a positive predictive value of 5–30% (Loeb and Catalona 2009) (level of evidence: 2a).

A threshold level of PSA that indicates the highest risk of CaP needs to be defined.

The level of PSA is a continuous parameter: the higher the value, the more likely is the existence of CaP. The finding that many men may harbour CaP, despite low levels of serum PSA, has been underscored by recent results from a US prevention study (Thompson et al. 2004) (Table 22.1, level of evidence: 2a). Table 22.1 gives the rate of CaP in relation to serum PSA for 2,950 men in the placebo arm and with normal PSA values.

Several modifications of serum PSA value have been described, which may improve the specificity of PSA in the early detection of CaP. They include PSA density, PSA density of the transition zone, age-specific reference ranges and PSA molecular forms.

In a prospective multicentre trial, CaP was found on biopsy in 56% of men with a f/t PSA < 0.10 but in only 8% of men with f/t PSA > 0.25 (Ilic et al. 2007) (level of evidence: 2a). These data have been confirmed in a recent screening test including 27.730 men with a serum PSA concentration between 2.1 and 10 ng/ml (Kobori et al. 2008). Using f/t PSA, the number of unnecessary biopsies decreased significantly, and the detection rate of CaP increased significantly. Nevertheless, the concept must be used with caution as several pre-analytical and clinical factors may influence the f/t PSA. For example, free PSA is unstable at both 4°C and at room temperature.

The two concepts of PSA velocity and PSA doubling time have limited use in the diagnosis of CaP because of several unresolved issues, including background noise (total volume of

Table 22.1 Risk of PCa in relation to low PSA values

PSA level (ng/ml)	risk of PCa
0–0.5	6.6%
0.6–1	10.1%
1.1–2	17.0%
2.1–3	23.9%
3.1–4	26.9%

PSA prostate-specific antigen

prostate, BPH), the interval between PSA determinations and acceleration/deceleration of PSAV and PSADT over time. Prospective studies have not shown these measurements can provide additional information compared to PSA alone (O'Brien et al. 2009; Vickers et al. 2009).

In contrast to the serum markers discussed above, the new biomarker PCA3 is measured in urine sediment obtained after prostatic massage (Deras et al. 2008). Determination of this CaP-specific RNA is experimental. At a population level, it appears to be helpful, but its impact at a single patient's level remains highly questionable. So far, none of the above biomarkers can be used to counsel an individual patient on the need to perform a prostate biopsy to rule out CaP. The molecular marker might help in the decision making process with regard to a repeat biopsy in men with a negative first biopsy but a persisting suspicion of CaP (Remzi et al. 2010; Ploussard et al. 2010). Men with a positive follow-up biopsy had significantly higher PCA3 scores as compared to men with a negative second biopsy (69.5 vs. 37.7, $p<0.001$). In men with a f/t PSA < 10%, PCA3 score was identified as a significant predictor of CaP. However, in men with a f/t PSA of 10–20% and >20%, the percentage of positive biopsies rose from 17.8% to 30.6% and from 23.9% to 37%, respectively, if a PCA3 score >30 was used.

Ultrasound-guided transrectal or transperineal laterally directed 18 G core biopsy has become the standard way to obtain material for histopathological examination (Hara et al. 2008; Takenaka et al. 2008). The need for prostate biopsies should be determined on the basis of the PSA level and/or a suspicious DRE. The patient's biological age, potential co-morbidities and the therapeutic consequences should also be considered. The first elevated PSA level should not prompt an immediate biopsy, but it should be verified after a few weeks by the same assay under standardised conditions.

At a glandular volume of 30–40 ml, at least eight cores should be sampled. More than 12 cores are not significantly more conclusive (Eichler et al. 2006) (level of evidence: 1a). Oral or intravenous quinolones are state-of-the-art preventive antibiotics with ciprofloxacin superior to ofloxacin (Aron et al. 2000) (level of evidence: 1b). Ultrasound-guided peri-prostatic block is state of the art (Adamakis et al. 2004) (level of evidence: 1b).On baseline biopsies, the sample sites should be as far posterior and lateral in the peripheral gland as possible. Additional cores should be obtained from suspect areas by DRE/TRUS. Indications for repeat biopsies are rising and/or persistent PSA, suspicious DRE and atypical small acinar proliferation (ASAP). The optimal timing is still uncertain. The later the repeat biopsy is done, the higher the detection rate (Merrimen et al. 2009). High-grade prostatic intraepithelial neoplasia (PIN) is only considered an indication for re-biopsy if it occurs multifocally (Merrimen et al. 2009) (level of evidence: 2a).

Diagnosis of CaP is based on histological examination (Van der Kwast et al. 2003). Ancillary staining techniques (e.g. basal cell staining) and additional (deeper) sections should be considered if a suspect glandular lesion is identified (Van der Kwast et al. 2003).

For each biopsy site, the proportion of biopsies positive for carcinoma and the Gleason score, using the system adopted in 2005 (Epstein et al. 2005), should be reported. A diagnosis of Gleason score 4 or lower should not be given on prostate biopsies (Epstein et al. 2005). The proportion (%) or length (mm) of tumour involvement per biopsy (Van der Kwast et al. 2003; Epstein et al. 2005) and – if present – extraprostatic extension should be recorded. The presence of high-grade PIN and perineural invasion is usually reported.

The extent of a single, small focus of adenocarcinoma, which is located in only one of the biopsies, should be clearly stated (e.g. <1 mm or <1%), as this might be an indication for further diagnostic workup before selecting therapy (Herkommer et al. 2004; Trpkov et al. 2006).

Table 22.2 Guidelines for the diagnosis of CaP

7.4	Guidelines for the diagnosis of CaP	GR
1.	An abnormal DRE result or elevated serum PSA measurement could indicate PCa. The exact cut-off level of what is considered to be a normal PSA value has not been determined, but values of approximately <2–3 ng/ml are often used for younger men	C
2.	The diagnosis of PCa depends on histopathological confirmation	B
	Biopsy and further staging investigations are only indicated if they affect the management of the patient	C
3.	TRUS-guided systemic biopsy is the recommended method in most cases of suspected PCa. A minimum of ten systemic, laterally directed, cores are recommended, with perhaps more cores in prostates with a volume >40 ml	B
	Transition zone biopsies are not recommended in the first set of biopsies due to low detection rates	C
	One set of repeat biopsies is warranted in cases with persistent indication (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at the initial biopsy) for prostate biopsy	B
	Overall recommendations for further (three or more) sets of biopsies cannot be made; the decision must be made based on an individual patient	C
4.	Transrectal peri-prostatic injection with a local anaesthetic can be offered to patients as effective analgesia when undergoing prostate biopsies	A

GR grade of recommendation

Table 22.3 Guidelines for staging of CaP

		GR
1.	Local staging (T-staging) of CaP is based on findings from DRE and possibly MRI. Further information is provided by the number and sites of positive prostate biopsies, the tumour grade and the level of serum PSA	C
	Despite its high specificity in the evaluation of ECE and SVI, TRUS is limited by poor contrast resolution, resulting in low sensitivity and tendency to understage CaP. Even with the advent of colour and power Doppler to assist in identifying tumour vascularity, the accuracy of TRUS in local staging remains inadequate. In comparison with DRE, TRUS and CT, MRI demonstrates higher accuracy for the assessment of uni- or bilobar disease (T2), ECE and SVI (T3), as well as the invasion of adjacent structures (T4). However, the literature shows a wide range in the accuracy of T-staging by MRI, from 50% to 92%. The addition of dynamic contrast-enhanced MRI (DCE-MRI) can be helpful in equivocal cases. The addition of MRSI to MRI also increases accuracy and decreases interobserver variability in the evaluation of ECE (Fuchsjager et al. 2008; Wang et al. 2007)	C
2.	Lymph node status (N-staging) is only important when potentially curative treatment is planned. Patients with stage T2 or less, PSA <10 ng/ml, a Gleason score ≤6 and <50% positive biopsy cores have a lower than 10% likelihood of having node metastases and can be spared nodal evaluation. Given the significant limitations of preoperative imaging in the detection of small metastases (<5 mm), pelvic lymph node dissection remains the only reliable staging method in clinically localized	B
	Currently, it seems that only methods of histological detection of lymph node metastases with high sensitivity, such as sentinel lymph node dissection or extended pelvic lymph node dissection, are suitable for lymph node staging in CaP	C
3.	Skeletal metastasis (M-staging) is best assessed by bone scan. This may not be indicated in asymptomatic patients if the serum PSA level is less than 20 ng/ml in the presence of well or moderately differentiated tumours	B
	In equivocal cases, ^{18}F-fluorodeoxyglucose-PET or PET/CT could be of value, especially to differentiate active metastases and healing bones	C

GR grade of recommendation

The decision to proceed with further diagnostic or staging workup is guided by which treatment options are available to the patient, taking patient's preference, age and comorbidity into consideration (Fuchsjager et al. 2008; Wang et al. 2007; Hoivels et al. 2008; Husarik et al. 2008; Schiavina et al. 2008; Heidenreich et al. 2002; Briganti et al. 2010; Beheshti et al. 2007). Procedures that will not affect the treatment decision can usually be avoided. A short summary of the guidelines on diagnosis and staging is presented in Tables 22.2 and 22.3.

22.7 Primary Local Treatment of Prostate Cancer

Therapeutic management of CaP even in clinically localized disease becomes more and more complex due to the various stage specific therapeutic options available. It is, therefore, advisable to (1) counsel patients with low- (PSA < 10 ng/ml and biopsy Gleason score 6 and cT1c-cT2a) or intermediate-risk (PSA 10.1–20 ng/ml or biopsy Gleason score 7 or cT2b-c) CaP in an interdisciplinary setting with an urologist and a radiation oncologist, (2) discuss neoadjuvant and adjuvant treatment options in patients with high-risk CaP (PSA < 20 ng/ml or biopsy Gleason score 8–10 or ≥cT3a) in a multidisciplinary tumour board and (3) thoroughly document which guidelines have been used for the decision making process if no multidisciplinary approach was possible.

It is usually impossible to state that one therapy is clearly superior over another as there is a lack of randomized controlled trials in this field. However, based on the available literature, some recommendations can be made. A summary, subdivided by stage at diagnosis, is found in the Table 22.2; below, a few suggestions are made with regard to the different treatment options available Table 22.3.

22.7.1 Active Surveillance

Active surveillance (AS) must be differentiated from watchful waiting (WW). While the later is based on a delayed symptomatic non-curative treatment in patients who are no candidates for an aggressive local therapy, the former must be seen as a curative approach. Patients with CaP are initially not treated (very-low-risk disease), followed and treated with a curative intent while on progression during follow-up.

AS was conceived with the aim of reducing the ratio of overtreatment in patients with clinically confined low-risk CaP based on early data (Chodak et al. 1994; Albertsen et al. 1998) demonstrating that men with well-differentiated prostate cancer have a 20-year prostate cancer-specific survival rate of 80–90%. Only data from non-mature randomized clinical trials of AS with follow-up <10 years are currently available.

According to recent data, men with low-risk CaP and a life expectancy >10 years are good candidates for active surveillance, and only about 30% of men will require delayed radical intervention (Klotz et al. 2010). Men with a life expectancy >15 years are at a higher risk of dying from CaP (Al Otaibi et al. 2008) (level of evidence: 3).

Different series have identified several eligibility criteria for enrollers (Klotz 2010):

- Clinically confined PCa (T1–T2)
- Gleason score ≤7
- ≤3 biopsies involved with cancer
- ≤50% of each biopsy involved with cancer
- PSA < 10 ng/ml

Moreover, different criteria were applied to define cancer progression (Klotz 2010), although all groups used:

- A PSA doubling time with a cut-off ranging between ≤2 and ≤4 years
- Gleason score progression to ≥7 at re-biopsy, at intervals ranging from 1 to 4 years

However, the role of PSA-DT to identify the need for intervention has recently been challenged (Krakowsky et al. 2010). In a cohort of 290 men who underwent AS for low-risk CaP, 35% developed biopsy progression (Gleason score ≥7, >2 positive cores or >50% core involvement). PSA-DT was not significantly associated with biopsy progression ($p = 0.83$) nor was PSAV ($p = 0.06$) (Ross et al. 2010). In another study, 36% of men under AS demonstrated disease progression on re-biopsy (Al Otaibi et al. 2008). The 5-year progression-free probability was 82% for patients with a negative first repeat biopsy compared with 50% for patients with a positive re-biopsy. Both trials underline the need for annual surveillance re-biopsies to adequately monitor men under AS.

22.7.2 Conservative Management in Locally Advanced CaP

The literature reporting on deferred treatment for locally advanced CaP is sparse. In a recent prospective randomized clinical phase-III trial (EORTC 30981), 985 patients with T0-4 N0-2 M0

CaP not eligible for local treatment with curative intent were randomly assigned to immediate androgen-deprivation therapy (ADT) or received ADT only on symptomatic disease progression or occurrence of serious complications (Studer et al. 2006a). After a median follow-up of 7.8 years, immediate ADT resulted in a modest but statistically significant increase in overall survival but no significant difference in CaP mortality or symptom-free survival. The time from randomization to progression of hormone-refractory disease did not differ significantly. The median time to the start of deferred treatment after study entry was 7 years. In this group, 126 patients (25.6%) died without ever needing treatment (44% of the deaths in this arm). Furthermore, the authors identified significant risk factors associated with a significantly worse outcome (Studer et al. 2008a): in both arms, patients with a baseline PSA > 50 ng/ml were at a >3.5-fold higher risk of dying of CaP than patients with a baseline PSA ≤ to 8 ng/ml. If the baseline PSA was between 8 and 50 ng/ml, the risk of CaP death was approximately 7.5-fold higher in patients with a PSA doubling time <12 months than in patients with a PSA doubling time >12 months. The time to PSA relapse following a response to immediate ADT correlated significantly with baseline PSA, suggesting that baseline PSA may also reflect disease aggressiveness.

22.7.3 Radical Prostatectomy (RPE)

RPE is the only treatment for localized CaP that has shown a cancer-specific survival benefit when compared to watchful waiting in a prospective, randomized trial (Bill-Axelson et al. 2005, 2008). Most of the patients recruited were of intermediate risk and did not harbour screen-detected CaP so that these data cannot be automatically transferred into daily routine practice. Nerve-sparing RPE represents the approach of choice in all men with a normal erectile function and organ-confined disease. The need and the extent of pelvic lymphadenectomy are discussed controversially. The risk of lymph node involvement is low in men with low-risk CaP and <50% positive biopsy cores (Heidenreich et al. 2011b). In men with intermediate- and high-risk CaP, an extended pelvic lymphadenectomy should always be performed (Briganti et al. 2006).

Management of cT3 CaP primarily has to be a multimodality approach due to the high likelihood of positive lymph nodes and/or positive resection margins (Yossepowitch et al. 2007; Ward et al. 2005; Pierorazio et al. 2010; Joniau et al. 2007; Van Poppel and Joniau 2008; Loeb et al. 2007). Overstaging of cT3 CaP is relatively frequent and occurs in 13–27% of cases (Yossepowitch et al. 2007; Ward et al. 2005). The problem remains the selection of patients before surgery that have neither lymph node involvement nor seminal vesicle invasion. Nomograms, including PSA level, stage and Gleason score, can be useful in predicting the pathological stage of disease (Joniau et al. 2007). RP for clinical T3 cancer requires sufficient surgical expertise to keep the level of morbidity acceptable and to improve oncological outcome with excellent 5-, 10- and 15-year cancer-specific survival rates of 95%, 90% and 79%, respectively (Van Poppel and Joniau 2008; Loeb et al. 2007).

Neoadjuvant androgen deprivation does not provide a significant advantage in overall survival and progression-free survival and therefore has no role in the treatment of prostate cancer (Shelley et al. 2009).

Adjuvant androgen deprivation therapy following RPE has always been controversial (Kumar et al. 2006). Although the only prospective randomized trial demonstrated a significant survival advantage for immediate androgen-deprivation therapy in N + disease (Messing et al. 2006a), it has to be acknowledged that most patients had gross nodal disease and that 70% also had positive margins and/or seminal vesicle invasion. It is not known if adjuvant androgen deprivation in patients with minimal nodal involvement will result in the same positive results. The most recent update on the early prostate cancer (EPC) trial has shown that there is no benefit to overall survival by adding bicalutamide 150 mg/day to standard care (McLeod et al. 2006). In patients with microscopic lymph node involvement only, no final recommendations can be made (Table 22.4).

Table 22.4 Guidelines and recommendations for radical prostatectomy

	LE
Indications	
In patients with low- and intermediate-risk localized CaP (cT1b–T2 and Gleason score 2–7 and PSA <20) and a life expectancy >10 years	1b
Optional	
Patients with stage T1a disease and a life expectancy >15 years or Gleason score 7	3
Selected patients with low-volume high-risk localized PCa (cT3a or Gleason score 8–10 or PSA >20)	3
Highly selected patients with very high-risk localized PCa (cT3b–T4 N0 or any T N1) in the context of multimodality treatment	3
Recommendations	
Short-term (3 months) neoadjuvant therapy with gonadotrophin releasing-hormone analogues is not recommended in the treatment of stage T1–T2 disease	1a
Nerve-sparing surgery may be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c, Gleason score <7 and PSA <10 ng/ml)	3
Unilateral nerve-sparing procedures are an option in stage T2a disease	4

LE level of evidence

22.7.4 Radiation Therapy

Three-dimensional conformal radiotherapy (3D-CRT) is the gold standard, and intensity-modulated radiotherapy (IMRT), an optimized form of 3D-CRT, is gradually gaining ground in centres of excellence.

For external radiotherapy, a dose of at least 74 Gy is recommended for the management of low-risk CaP as it has been shown that the biochemical disease-free survival is significantly higher when compared to a dose <72 Gy (69% vs. 63%, $p=0.046$) (Kupelian et al. 2005).

For intermediate-risk CaP, many series have shown a significant impact of dose escalation on 5-year progression-free survival in cT1c–T3 CaP, with a dose ranging from 76 to 81 Gy (Peeters et al. 2006).

In patients with high-risk disease, external irradiation with dose escalation improves 5-year biochemical disease-free survival (D'Amico et al. 2008) but seems insufficient to cover the risk of systemic relapse. For intermediate and high localized CaP, a combination of external irradiation with 6 months androgen deprivation has resulted in a 13% improvement in 8-year overall survival rate ($p<0.001$) (D'Amico et al. 2008; Bolla et al. 2009). For locally advanced CaP, the data of the EORTC-22961 trial demonstrate a 4.7% benefit in overall survival after a median follow-up of 5.2 years in favour of 3-year androgen-deprivation therapy when compared to short-term ADT (Bolla et al. 2009).

Therefore, concomitant (± neoadjuvant) and adjuvant androgen deprivation for 3 years is mandatory and represents the current standard in the radiotherapeutic management of high-risk CaP.

Various prospective randomized trials have evaluated the oncological efficacy of androgen-deprivation therapy (ADT) with or without external beam radiation therapy (EBRT) (Widmark et al. 2009; Warde et al. 2010; Mottet et al. 2010). The SPCG-7 trials included 875 men with locally advanced CaP who were randomly assigned to endocrine treatment or to ADT with EBRT at a dose of at least 70 Gy (Widmark et al. 2009). After a median follow-up of 7.6 years, the cancer-specific mortality was significantly higher in the ADT arm (23.9 vs. 11.9%) as was the overall mortality (39.4% vs. 29.6%) and the PSA failure rate (74.7% vs. 25.5%, $p<0.0001$). Recently, two prospective randomized clinical trials with regard to the same issue have been presented as abstracts (Warde et al. 2010; Mottet et al. 2010). The Canadian group randomized 1,205 men with locally advanced CaP to receive ADT or ADT with EBRT at a dose of 65–69 Gy (Warde et al. 2010). After a median follow-up of 6 years, the addition of EBRT significantly reduced the risk of death (HR: 0.77, $p=0.033$) with a 10-year cumulative disease-specific death rate of 15% versus 23%. The French group randomized 263 patients with locally advanced CaP to receive ADT of ADT and EBRT (Mottet et al. 2010). At a minimum follow-up of 5 years, the combined treatment achieved significantly superior results with regard to progression-free survival (60.9% vs. 8.5%, $p=0.001$), locoregional progression (9.7% vs. 29%, $p=0.0002$) and metastatic progression (3% vs. 10.8%, $p=0.018$) (Table 22.5).

Table 22.5 Guidelines and recommendation for definitive radiation therapy

	LE
In localized prostate cancer T1c–T2c N0 M0, 3D-CRT with or without IMRT is recommended even for young patients who refuse surgical intervention. There is fairly strong evidence that low-, intermediate- and high-risk patients benefit from dose escalation	2
For patients in the high-risk group, short-term ADT prior to and during radiotherapy results in increased overall survival	2a
Transperineal interstitial brachytherapy with permanent implants is an option for patients with cT1c–T2a, Gleason score <7, PSA ≤10 ng/ml, prostate volume ≤50 ml, without a previous TURP and with a good IPSS.	2b
Immediate post-operative external irradiation after radical prostatectomy for patients with pathological tumour stage T3 N0 M0 improves biochemical and clinical disease-free survival	1
An alternative option is to give radiation at the time of biochemical failure but before PSA rises above 0.5 ng/ml	3
In locally advanced prostate cancer T3–T4 N0 M0, overall survival is improved by concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external irradiation for patients with a WHO 0–2 performance status	1
For a subset of patients with T2c–T3 N0-x and a Gleason score 6, short-term ADT before and during radiotherapy may favourably influence overall survival	1b

LE level of evidence

22.7.5 Irradiation to the Pelvic Lymph Nodes

With regard to the potential benefit of irradiation of the pelvic lymph nodes in men with high-risk localized CaP, the GETUG-01 trial randomly assigned 444 patients to receive EBRT to the prostate (66–70 Gy) or to the prostatic bed and the pelvic lymph nodes (46 Gy) (Pommier et al. 2007). Five-year progression-free survival and overall survival were similar in both arms so that there is no general indication for irradiation to the pelvic lymph nodes.

22.7.6 Innovative Techniques

Intensity-modulated radiotherapy enables radiation oncologists to increase radiation doses homogeneously, up to as much as 86 Gy within the target volume, while respecting the tolerance doses in organs at risk.

The Memorial Sloan-Kettering Cancer Center has the largest experience with this technique, and its results have now been updated, reporting on disease control and toxicity in two cohorts of patients (Budäus et al. 2012; Pinkawa et al. 2011):

- In the first cohort, 561 patients with organ-confined disease were treated with a dose of 81 Gy.

The 8-year actuarial PSA relapse-free survival rates for patients in favourable-, intermediate- and unfavourable-risk groups were 85%, 76% and 72%, respectively, according to the then-current American Society for Radiation Oncology (ASTRO) definition.

- In the second cohort, 478 patients with organ-confined disease were treated with a dose of 86.4 Gy. The 5-year actuarial PSA relapse-free survival according to the nadir plus 2-ng/ml definition was 98%, 85% and 70% for the low-, intermediate- and high-risk groups, respectively.

22.7.6.1 Proton Beam and Carbon Ion Beam Therapy

In theory, proton beams are an attractive alternative to photon beam radiotherapy for CaP because they deposit almost all their radiation dose at the end of the particle's path in tissue (the Bragg peak), in contrast to photons, which deposit radiation along their path. Additionally, there is a very sharp fall-off for proton beams beyond their deposition depth, meaning that critical normal tissues beyond this depth could be effectively spared. In contrast, photon beams continue to deposit energy until they leave the body, including an exit dose.

Only one randomized trial which has incorporated proton therapy in one arm has recently reported long-term results (Cahlon et al. 2008). The proton radiation oncology group (PROG) 9509 trial randomly assigned 393 men with clinically localized CaP to receive EBRT with 70.2 versus 79.2 Gy of combined photon and proton radiation. At a median follow-up of 9.4 years, the estimated 10-year biochemical progression rate

for patients receiving standard dose was 32% compared with 17% for patients receiving high dose ($p<0.001$). Prostate cancer symptom indices did not differ significantly between both groups with regard to urinary obstruction/irritation (23.3 vs. 24.6, $p=.36$), urinary incontinence (10.6 vs. 9.7, $p=.99$), bowel problems (7.7 vs. 7.9, $p=.70$) and sexual dysfunction (68.2 vs. 65.9, $p=.65$). However, a prospectively randomized trial using equivalent doses of IMRT and photon radiation will be needed to evaluate the oncological efficacy of photons.

22.7.7 Transperineal Low-Dose Rate Brachytherapy

Transperineal brachytherapy is a safe and effective technique for low-risk CaP. There is consensus on the following eligibility criteria (Talcott et al. 2010):

- Stage cT1c–T2a N0, M0
- A Gleason score ≤6 assessed on a sufficient number of random biopsies
- An initial PSA level of ≤10 ng/ml
- ≤50% of biopsy cores involved with cancer
- A prostate volume of <50 cm^3
- A good international prostatic symptom score (IPSS)

Results of permanent implants have been reported from different institutions with a median follow-up ranging between 36 and 120 months (Ash et al. 2000). Recurrence-free survival after 5 and 10 years was reported to range from 71% to 93% and from 65% to 85%, respectively. There is no benefit in adding neoadjuvant or adjuvant androgen deprivation to LDR brachytherapy (Husarik et al. 2008).

22.8 Adjuvant EBRT for pT3 or pT × R1 PCA

Three prospective randomized trials have assessed the role of immediate post-operative radiotherapy. Although different in inclusion criteria, all trials concluded that immediate post-operative radiotherapy significantly improves 5-year clinical or biological survival by about 20% ($p<0.0001$) (Taira et al. 2011; Bolla et al. 2005; Wiegel et al. 2009). Immediate post-operative radiotherapy proved to be well tolerated with a risk of grade 3–4 urinary toxicity in ≤3.5%.

The updated results of the SWOG 8794 trial (Thompson et al. 2009; Swanson et al. 2008) with a median follow-up of 11.5 years show that adjuvant radiation significantly improved 15-year metastasis-free survival, (46% vs. 38%, $p=0.036$) and overall survival (47% vs. 37%, $p=0.053$) compared to a delayed radiotherapy.

Thus, for patients classified as T1–T2 N0 (or T3 N0 with selected prognostic factors), pT3 pN0 with a high risk of local failure after radical prostatectomy due to positive margins and/or invasion of the seminal vesicles and negative PSA, two options can be offered within the frame of an informed consent:

- *Either* an immediate radiotherapy with 60–64 Gy to the surgical bed (Taira et al. 2011; Bolla et al. 2005; Wiegel et al. 2009) upon recovery of urinary function
- *Or* clinical and biological monitoring followed by salvage radiotherapy with at least 66 Gy ideally when the PSA rises but does not exceed 0.5 ng/ ml (Bolla et al. 2009)

22.9 Follow-up of Prostate Cancer Patients

Patients diagnosed with CaP who underwent local treatment with curative intent are usually followed for at least 10 years or until high age makes follow-up superfluous (Table 22.6). Determination of serum PSA together with a disease-specific history can be supplemented by DRE if locally recurrent disease is suspected.

22.10 Alternative Local Treatment Options of Prostate Cancer

Besides RPE, EBRT and/or brachytherapy, cryosurgical ablation of the prostate (CSAP) and high-intensity focused ultrasound (HIFU) have emerged as alternative therapeutic options in

Table 22.6 Guidelines for follow-up after primary treatment with curative intent

	GR
In asymptomatic patients, a disease-specific history and a serum PSA measurement supplemented by DRE are the recommended tests for routine follow-up. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually	B
After radical prostatectomy, a serum PSA level of more than 0.2 ng/ml can be associated with residual or recurrent disease	B
After radiation therapy, a rising PSA level over 2 ng/ml above the nadir PSA, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease	B
Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence	B
Detection of local recurrence by TRUS and biopsy is only recommended if it will affect the treatment plan. In most cases, TRUS and biopsy are not necessary before second-line therapy	B
Metastasis may be detected by pelvic CT/MRI or bone scan. In asymptomatic patients, these examinations may be omitted if the serum PSA level is less than 30 ng/ml, but data on this topic are sparse	C
Routine bone scans and other imaging studies are not recommended in asymptomatic patients. If a patient has bone pain, a bone scan should be considered irrespective of the serum PSA level	B

GR grade of recommendation

patients with clinically localized CaP who are not suitable for RPE (Babaian et al. 2008). However, at time of writing, data from CSAP are not extensive enough to be considered in treatment recommendations.

Indications might be:

- Low- or intermediate-risk CaP
- Prostate size should be <40 ml at the time of therapy

Long-term results are lacking, and 5-year biochemical progression-free rates are inferior to those achieved by radical prostatectomy in low-risk patients. Patients must be informed accordingly. The results of a randomized trial of EBRT versus CSAP in patients with clinically localized CaP have been published recently (Donnelly et al. 2010). Two hundred forty-four men with low- and intermediate-risk CaP were assigned to both treatment arms, and all men received neoadjuvant ADT. After a median follow-up of 100 months, there were no differences with regard to disease progression at 36 months, overall and disease-specific survival. However, patient numbers are too small to draw significant clinical conclusions.

22.11 Hormonal Therapy

22.11.1 LHRH: Analogues and Antagonists

Luteinising hormone-releasing hormone (LHRH) agonists have become the 'standard of care' in hormonal therapy because these agents:

- Have the potential of reversibility and enable the use of intermittent androgen-deprivation therapy
- Avoid the physical and psychological discomfort associated with orchiectomy
- Have a lower risk of cardiotoxicity as it is observed with diethylstilbestrol (DES)
- Result in equivalent oncological efficacy (McLeod 2003; Seidenfeld et al. 2000)

In contrast to the agonists, LHRH antagonists result in a rapid decrease in luteinising hormone (LH), follicle-stimulating hormone (FSH) and testosterone levels without any flare. In a recent, prospective, randomized, phase-III trial, 610 men with PCa requiring ADT were randomized to receive degarelix or leuprolide for 12 months (Klotz et al. 2008). At the end of the observation period, degarelix was not inferior to leuprolide but achieved a more rapid suppression of testosterone within the first 3 days and avoided any flare phenomenon. In an additional analysis of secondary end points, a significantly lower risk of PSA progression and PCa-specific death in favour of degarelix was described for patients with advanced disease and high-baseline PSA levels (Tombal et al. 2009). However, only 11% of the patients treated with leuprolide have received flare protection with bicalutamide, and the number of patients who were included in the subgroup analysis is too small to draw any clinically relevant conclusions.

The rapid and effective castration of LHRH antagonists plays an important role in patients with symptomatic metastatic disease (bone metastases, neurological symptoms due to impending spinal cord compression, subvesical obstruction). Its benefit in other clinical situations remains to be proven.

22.11.2 Anti-androgens

The use of steroidal anti-androgens has resulted in significantly poorer survival data when compared to goserelin. Both non-steroidal anti-androgens, nilutamide and flutamide, have produced conflicting results so that these agents do not play a clinically important role in the hormonal treatment of PCa as monotherapy.

As primary anti-androgen monotherapy, bicalutamide, 150 mg/day, has been compared to medical or surgical castration in two, large, prospective, randomized trials with identical study design, including a total of 1,435 patients with locally advanced M0 or M1 PCa (Kaisary et al. 2001). A pooled analysis showed:

- In M1 patients, a significant improvement in overall survival (OS) with castration (Tyrrell et al. 1998a).
- In M0 patients ($N=480$), no significant difference was noted in OS based on the Kaplan-Meier test, but median survival was lower in the bicalutamide arm at 63.5 months compared with 69.9 months in the castration arm (Tyrrell et al. 1998b).

In conclusion, monotherapy with non-steroidal anti-androgens might be an option with high-dose bicalutamide in locally advanced or highly selected well-informed metastatic patients (low PSA). The clinical benefits however remains marginal if any and therefore monotherapy with bicalutamide does not represent the recommended standard of care.

22.11.3 Maximum Androgen Blockade (MAB)

From the most recent systematic reviews and meta-analyses, it appears that at a follow-up of 5 years, MAB with non-steroidal anti-androgens provides a small, but statistically significant, survival advantage (<5%) when compared to LHRH monotherapy (Schmitt et al. 2001; Moul 2009). It remains debatable whether this small advantage can be meaningful when applied to everyday clinical practice. Furthermore, it has to be recognised that patients under MAB experience a significant impairment of quality of life (QoL) in the field of sexuality, cognitive function and thermoregulation (Cruz Guerra 2009).

22.11.4 Intermittent Androgen Deprivation (IAD)

Intermittent androgen deprivation alternates androgen blockade with treatment cessation to allow hormonal recovery between treatment cycles, thus potentially improving tolerability and QoL (Abrahamsson 2010). Several phase-III trials have demonstrated non-inferiority of IAD compared to CAB in metastatic or biochemically recurrent disease. The largest trial, SWOG 9346, randomized 1,134 men with stage D2 CaP to intermittent and continuous ADT after 7 months of induction ADT with PSA reduction <4 ng/ml (Hussain et al. 2006). A PSA reduction to <0.2 ng/ml, <4 ng/ml and >4 ng/ml was identified as significant prognostic cut-off points with regard to median survival, achieving 75 months, 44 months and 13 months, respectively. These important results are the only available information from this large cohort. The formal survival comparison is awaited. In another small trial comprising 100 men with PSA progression following local treatment, the duration of the first off-treatment interval of <40 weeks was associated with a significantly shorter time to development of CRPCa (HR = 2.9, $p=0.03$) and an increased PCa-specific death rate (HR = 3.8, $p=0.04$) (Yu et al. 2010).

Data of oncological equivalence in efficacy have been reported from a prospective randomized trial including 478 patients with M1 (40%) or N + (N1–N3) disease (de Leval et al. 2002). After a median follow-up of 50.5 months, no significant difference was observed in the median PFS (16.6 months in IAD compared with 11.5 months in CAB [$p=0.17$], neither in the entire population nor in the N + or M1 populations). The SEUG

trial based on 766 patients and a mean follow-up of 55 months observed the same lack of survival difference or overall QoL benefit in the IAD group (da Silva FE et al. 2009).

It must be acknowledged that, so far, the threshold at which ADT must be stopped or resumed is empirical (Abrahamsson 2010; Boccon-Gibod et al. 2007). Nevertheless, several points are clear:

- Intermittent androgen deprivation is based on intermittent castration, and therefore, only drugs leading to castration should be considered.
- The initial (induction) cycle must last between 6 and 9 months.
- The treatment is stopped only if patients have a clear PSA response, empirically defined as a PSA level lower than 4 ng/ml in metastatic patients or 0.5 ng/ml in relapsing patients.
- The treatment is resumed when there is either clinical progression, or the PSA value rises above an empirically fixed threshold (usually 4 ng/ml in non-metastatic and 10–15 ng/ml in metastatic situations). Treatment is continued as in the induction cycle, for between 6 and 9 months, depending on the time required to reach a PSA nadir.
- A strict follow-up must be applied, with clinical examination every 3–6 months, with PSA measurements performed at the same time and always by the same laboratory.

In conclusion, IAD is currently widely offered to patients with PCa in various clinical settings, and its status should no longer be regarded as investigational.

22.11.5 Immediate Versus Deferred Androgen Deprivation

The most appropriate time to introduce hormonal therapy in patients with advanced PCa remains controversial. According to the EORTC 30891 trial, immediate ADT for locally advanced asymptomatic disease in men not amenable for local therapy only had a positive impact on PFS but did not favourably influence specific survival and QoL (Studer et al. 2006b). In a subanalysis of this trial, however, it was demonstrated that patients with an initial PSA > 50 ng/ml and/or a PSA doubling time (PSA DT) <12 months harbour a high risk to die of prostate cancer and might, therefore, be good candidates for immediate ADT to prevent or to delay complications from progressive disease.(Studer et al. 2008b). However, survival is significantly better when compared to the group of patients with delayed ADT until symptoms due to progressive disease occurred. In a similar approach, the EORTC 30846 trial randomized 235 men with lymph node-positive PCa, but no local treatment, to early versus delayed ADT by medical or surgical castration (Schröder et al. 2009b). After a median follow-up of 13.4 years, the 10-year cumulative incidence of PCa-specific death was similar between both groups (55.6% and 52.1% in the delayed and the immediate group, respectively). However, the trial was too underpowered (early closure) to be able to make reliable clinical conclusions.

With regard to PSA rise after RP, there are no prospective, randomized, clinical trials available. Only one retrospective analysis of 1,352 patients with rising PSA after RPE is available for analysis (Moul et al. 2004). Of these 1,352 men, 355 started ADT at different PSA serum levels, while 997 remained without hormonal manipulation until detection of metastatic disease. Early ADT improved the bone metastasis-free interval only for patients with a Gleason score >7 PCa or a PSA-DT < 12 months; there was no statistically significant difference in OS or cancer-specific survival (CSS).

The Cochrane Library review extracted four good quality randomized controlled trials (Byar 1973; Jordan et al. 1977; 1997; Messing et al. 1999), which were all conducted in the pre-PSA era and included patients with advanced PCa who received early versus deferred ADT as primary therapy. According to the analysis, early androgen suppression significantly reduces disease progression and complication rates due to the progression itself, but does not improve CSS, and provides a relatively small benefit in OS, with an absolute risk reduction of 5.5%, which does not become evident until after 10 years (Nair et al. 2002).

Since 2002, the level 1 evidence suggesting immediate ADT in every pN + patient following RP has been questioned (Messing et al. 2006b). Recently, the analysis of 719 patients from the

SEER (surveillance, epidemiology and end results, part of the US National Cancer Institute) database questioned the real impact of immediate ADT in pN + patients after RP (Wong et al. 2009).

Based on a systematic review of the literature, no final recommendation can be made on the timing of hormonal therapy in advanced asymptomatic PCa (Morgan and Dearnaley 2009).

22.11.6 Follow-up of Patients with PCa

During long-term therapy, ADT reduces bone mineral density (BMD) and increases the risk of fractures (Serpa Neto et al. 2010). In the absence of associated risk factors, it is recommended that the BMD is regularly measured, based on the initial T-score:

- Every 2 years, if the initial T-score <−1.0
- Every year, if the T-score is between −1.0 and −2.5

There is limited information about the optimal level of testosterone necessary to achieve in the treatment of PCa (Schulman et al. 2010). Recent studies have suggested lower testosterone levels may be associated with improved outcomes. In a study of 73 men with non-metastatic PCa treated with LHRH androgen suppression (Morote et al. 2006), patients experiencing testosterone breakthroughs had a reduced biochemical survival rate. The mean survival without androgen-independent progression in patients with testosterone breakthroughs (increase >32 ng/dl) was 88 months versus 137 months in those without breakthrough increases ($p<0.03$). In a retrospective series of 129 men with metastatic PCa treated with LHRH agonists, the risk of death was significantly correlated to the Gleason score ($p=0.01$), the PSA level at 6 months ($p=0.01$) and the serum testosterone level at 6 months (HR =1.32, $p<0.05$) (Perachino et al. 2010). Although this retrospective analysis demonstrated a significant correlation between serum testosterone at 6 months, it remains unclear why only about 70% decreased their testosterone levels below 50 ng/dl since, in many previous studies, about 97% of the patients lowered the testosterone below 50 ng/dl.

In view of these findings, the measurement of serum testosterone levels, as well as serum PSA levels, should be considered as part of clinical practice for men on LHRH therapy. The timing of testosterone measurements is not clearly defined. The first evaluation of testosterone level can be recommended at 3 months after initiating LHRH therapy to check the nadir testosterone level achieved before re-administration of the agonist drug. A 6-month assessment of the testosterone level might be performed to evaluate the efficacy of treatment and to ensure the castration level is being maintained.

If this is not the case, switching to another LHRH agent, surgical orchiectomy or addition of an anti-androgen can be attempted. In patients with rising PSA and/or clinical signs of progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state.

Routine imaging procedures in stable patients are not recommended and should only be used in specific situations. Table 22.7 summarises the guidelines for follow-up procedures after hormonal therapy.

Besides oncological follow-up, urologists have to screen patients for the development of metabolic sequelae associated with ADT. Medical or surgical castration causes changes in body composition, alterations in lipid profiles and decreased insulin sensitivity (Faris and Smith 2010). Although little is known about the optimal strategy to mitigate the adverse metabolic effects, the Prostate Cancer Working Group recommend an emphasis on existing treatment strategies to reduce the risk of diabetes and cardiovascular disease (Saylor and Smith 2009).

22.12 Diagnosis and Treatment of Relapse After Curative Therapies

22.12.1 Definition of Recurrence

Following RP, a confirmed PSA value >0.2 ng/ml (i.e., two consecutive increases) represents recurrent cancer (Stephenson et al. 2006). Following RT, a PSA value of 2 ng/ml above the nadir after

Table 22.7 Guidelines for follow-up after hormonal therapy

Recommendation	GR
Patients should first be evaluated at 3 and 6 months after the initiation of treatment. As a minimum, tests should include serum prostate-specific antigen (PSA) measurement, digital rectal examination (DRE), serum testosterone and careful evaluation of symptoms in order to assess treatment response and side effects	B
If patients undergo intermittent androgen deprivation (IAD), PSA and testosterone should be monitored in 3-month intervals during the treatment pause	C
Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given	C
In patients with stage M0 disease and a good treatment response, follow-up is scheduled every 6 months and should include (as a minimum) a disease-specific history, DRE and serum PSA determination	C
In patients with stage M1 disease and a good treatment response, follow-up is scheduled for every 3–6 months. As a minimum, this should include a disease-specific history, DRE and serum PSA determination and is frequently supplemented with measurements of haemoglobin, serum creatinine and alkaline phosphatase	C
Patients (especially with M1b status) should be advised about the clinical signs that could suggest spinal cord compression	
When disease progression occurs, or if the patient does not respond to the treatment given, follow-up needs to be individualized	C
Routine imaging of stable patients is not recommended	B

GR grade of recommendation

Table 22.8 Guidelines on treatment options for PSA relapse following local treatment

Recommendations	GR
Local recurrences are best treated by salvage RT with 64–66 Gy at a PSA serum level ≤0.5 ng/ml	B
Expectant management is an option for patients with presumed local recurrence who are too unfit or unwilling to undergo RT	B
PSA recurrence indicative of systemic relapse is best treated by early ADT, resulting in decreased frequency of clinical metastases if poor prognostic risk factors such as PSA-DT <12 months or Gleason score 8–10 are present	B
Luteinising hormone-releasing hormone analogues/orchiectomy or bicalutamide, 150 mg/day, when hormonal therapy is indicated. It has to be considered, however, that bicalutamide, 150 mg/day, is inferior to castration in patients with M0 and M1 disease	A

GR grade of recommendation

RT represents recurrent cancer (Roach et al. 2006).

Local failure following RP might be predicted with an 80% probability by a PSA increase >3 year after RP, a PSA-DT > 11 months, a Gleason score < 7 and stage ≤pT3a pN0, pTx R1. Systemic failure following RP might be predicted with >80% accuracy by a PSA increase <1 year after RP, a PSA-DT of 4–6 months, a Gleason score of 8–10 and stage pT3b, pTxpN1. In a cohort of 148 men with rising PSA and a PSA-DT < 12 months following local treatment, the PFS was associated with Gleason grade ($p = 0.006$), PSA at time of treatment ($p < 0.001$) and PSA-DT ($p < 0.001$) (Slovin et al. 2005). The median PFS was 19 months, with a 3- and 5-year metastasis PFS of 32% and 16%, respectively.

Prostatic biopsy after RT is necessary only if local procedures such as salvage RP are indicated in an individual patient.

Treatment can then be guided by the presumed site of failure, the patient's general condition and personal preferences (Table 22.8).

Imaging studies such as bone scintigraphy or CT to determine the site of recurrence are of no additional diagnostic value, unless the PSA serum levels are >20 ng/ml or unless the PSA velocity is >2 ng/ml/year (Cher et al. 1998; Kane et al. 2003; Gomez et al. 2004). Endorectal coil imaging might represent a useful technique to detect local recurrences after RP if PSA serum levels exceed 2 ng/ml (Gomez et al. 2004). Similar data were achieved in a cohort of 64 patients with PSA progression following external beam RT (Cirillo et al. 2009; Westphalen et al. 2010). The diagnostic accuracy to detect locally recurrent PCa was highest at a PSA level >2 ng/ml.

Positron emission tomography (PET) with ^{11}C-choline is not indicated as a routine imaging study in the clinical situation of PSA rise after local treatment with curative intent (Picchio et al. 2011; Castellucci et al. 2009; Giovacchini et al. 2010; Cimitan et al. 2006). The detection rate of

^{11}C-choline PET/CT appears to be strongly dependent on PSA levels at the time of diagnosis, pathological stage at time of initial diagnosis, previous biochemical failure and older age. Furthermore, the probability of false-positive results in up to 20% of patients has to be considered when interpreting PET results.

The timing and mode of treatment of PSA-only recurrence after RP or RT remain controversial. After RP, the usually accepted therapeutic options are:

- Radiation therapy to the prostatic bed and/or pelvic lymph nodes
- (Complete) androgen blockade (CAB)
- Intermittent androgen deprivation (IAD)

All other options which have been reported are still experimental, and these should be discussed individually with the patient. Ideally, these options should be further tested in prospective clinical trials before they can be recommended as a standard treatment option:

- Salvage pelvic lymphadenectomy or salvage metastasectomy
- Combination of anti-androgens with 5-α-reductase inhibitors
- Early chemohormonal approaches

These same therapeutic options besides external beam RT may be applied to PSA recurrences following RT. In addition, salvage RP, cryotherapy, HIFU or brachytherapy may be discussed in carefully selected patients.

22.12.2 Management of PSA Relapse Following RP

There have been many studies on the use of RT for PSA-only recurrence following RP. As confirmed by various studies, the pre-radiation PSA level is critically important for optimal treatment results. Stephenson et al. (2007) identified a significant relationship between PSA serum concentration at the time of RT and therapeutic outcome: the 6-year biochemical-free survival was 48% in men with PSA < 0.5 ng/ml, whereas it was only 40%, 28% and 18% in men with PSA levels of 0.51–1 ng/ml, 1.01–1.5 ng/ml and >1.5 ng/ml, respectively.

In a subanalysis of the SWOG 8,974 trial, Swanson et al. (2007) showed that men in all categories of post-RP PSA level (<0.2, 0.2–1.0, >1.0 ng/ml) showed an improvement with salvage RT in metastasis-free survival. However, the therapeutic benefit was most evident in the presence of minimal PSA serum levels. Even in men with PSA-DT ≤6 months, salvage RT has been reported to improve PCa-specific survival if it is given within 2 years following a rise in the PSA level (Trock et al. 2008).

Currently, local recurrences after RP are best treated by salvage RT with 64–66 Gy at a PSA serum level ≤0.5 ng/ml.

It is still controversial whether or not the boundaries of salvage RT should be extended to include the pelvic lymph nodes. Recently, a significantly increased risk of PSA failure rate following salvage RT depending on the Roach formula was reported in a cohort of 258 men (Goldner et al. 2010). Biochemical failure at 5 years was 0% in patients with <15% probability of lymph node metastases compared with 42% in patients with >15% probability. Adjuvant RT added to adjuvant ADT in men with positive lymph nodes following RP and extended pelvic lymphadenectomy significantly improved CSS compared with ADT alone (Da Pozzo et al. 2009). However, this retrospective analysis in 250 patients only underlines that optimal local cancer control is essential for good long-term results.

22.12.3 Management of PSA Failures After RT

In a recent review of the data of the Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) comprising 2,336 patients with PCa, Grossfeld et al. (2002) demonstrated that 92% of patients, who had initially been irradiated, received ADT for secondary treatment of PSA progression. In the absence of salvage procedures, the mean time interval from biochemical to clinical progression is approximately 3 years.

Alternative therapeutic options in these patients are salvage RP, cryotherapy, HIFU and interstitial RT (Heidenreich et al. 2006, 2008,

2010; Stephenson et al. 2004; Stephenson and Eastham 2005; Pisters et al. 1997, 2008, 2009; Cespedes et al. 1997; Eisenberg and Shinohara 2008; Warmuth et al. 2010; Murat et al. 2009; Uchida et al. 2011; Lukka et al. 2011). Salvage RP has not gained widespread acceptance because of its associated morbidity, namely, incontinence, local recurrences and rectal injuries. However, in well-selected patients, the procedure may result in long-term disease-free survival.

Recently, data have been reported on the oncological and functional outcome of patients who underwent radical salvage therapy for locally recurrent PCa after various types of modern state-of-the-art RT, performed in or after the year 2000 (Heidenreich et al. 2010). Forty (72.7%) and 15 (27.3%) patients demonstrated organ-confined and locally advanced PCa, respectively. On multivariate analysis, significant predictors of organ-confined PCa with negative surgical margins were:

- Biopsy Gleason score prior to salvage RP < 7 ($p=0.02$)
- <50% positive biopsy cores ($p=0.001$)
- PSA-DT >12 months ($p=0.001$)
- Low-dose brachytherapy ($p=0.001$)

In general, salvage RP should be considered only in patients with a low co-morbidity, a life expectancy of at least 10 years, an organ-confined PCa ≤ T2, Gleason score ≤7 and pre-surgical PSA <10 ng/ml. Salvage RP should be performed in experienced centres only.

22.12.4 Salvage Cryosurgical Ablation of the Prostate (CSAP) for Radiation Failures

High-intensity focused ultrasound (HIFU) or salvage cryosurgery have been proposed as an alternative to salvage RP, as both have the potential advantage of less morbidity but equal efficacy (Pisters et al. 1997; Cespedes et al. 1997). In a recent study, the 5-year biochemical-free survival was only 50% in a cohort of men who underwent partial CSAP for radio-recurrent PCa (Eisenberg and Shinohara 2008). In an online data registry, the outcomes of 279 patients who underwent CSAP were analysed after a median follow-up of 21.6±24.9 months (Pisters et al. 2008). The 5-year biochemical-free survival was 54.5%, according to the Phoenix classification. The rates of urinary incontinence and rectal fistula were 4.4% and 3.3%, respectively. Recently, Pisters et al. [145] performed a case–control study on salvage cryosurgery versus salvage radical prostatectomy for radio-recurrent prostate cancer. Compared to salvage cryotherapy, salvage radical prostatectomy resulted in superior biochemical disease-free survival (prostate-specific antigen greater than 0.4 ng/ml, salvage cryotherapy 21% vs. salvage radical prostatectomy 61% at 5 years, $p<0.001$) and in superior overall survival (at 5 years salvage cryotherapy 85% vs. salvage radical prostatectomy 95%, $p=0.001$). There was no significant difference in disease-specific survival (at 5 years salvage cryotherapy 96% vs. salvage radical prostatectomy 98%, $p=0.283$). After adjusting for post-radiation therapy biopsy Gleason sum and pre-salvage treatment serum prostate-specific antigen on multivariate analysis, salvage radical prostatectomy remained superior to salvage cryotherapy for the end points of any increase in prostate specific antigen greater than 0.4 ng/ml (HR 0.24, $p<0.0001$) and overall survival (HR 0.21, $p=0.01$).

Considering HIFU, available results remain questionable (Warmuth et al. 2010) even if some recent results are of interest. The largest cohort is based on 167 patients with a mean follow-up of 18 months. No rectal complication was observed (Murat et al. 2009). Based on the poor quality of the currently available data (Uchida et al. 2011; Lukka et al. 2011), HIFU still cannot be recommended as a standard care procedure in patients with relapsing PCA after radiation therapy.

22.12.5 Treatment of Relapse After Hormonal Therapy

Various different terms have been used to describe prostate cancers that relapse after initial hormonal ablation therapy, including hormone-resistant PCa (HRPCa), androgen-independent cancers and hormone-independent cancers (Bubley et al.

Table 22.9 Definition of castration-resistant PCa (CRPCa)

Castrate serum levels of testosterone (testosterone <50 ng/dl or <1.7 nmol/l)
Three consecutive rises of prostate-specific antigen (PSA), 1 week apart, resulting in two 50% increases over the nadir
Anti-androgen withdrawal for at least 4 weeks for flutamide and for at least 6 weeks for bicalutamide
PSA progression, despite consecutive hormonal manipulations
Progression of osseous lesions: progression or appearance of two or more lesions on bone scan or soft tissue lesions using RECIST (Response Evaluation Criteria in Solid Tumours) and with nodes >2 cm in diameter

Table 22.10 Summary of treatment after hormonal therapy

Recommendations	GR
It is recommended to stop anti-androgen therapy once prostate-specific antigen (PSA) progression is documented	B
Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect is apparent	B
No clear-cut recommendation can be made for the most effective drug for secondary hormonal manipulations because data from randomized trials are scarce	C

GR grade of recommendation

1999; Scher et al. 2008). The castrate-resistant, but still hormone-sensitive, PCa (CRPCa) has been clearly characterized, with new drugs targeting either the androgen receptor (AR), MDV3100 or androgen synthesis (abiraterone, orteronel) (Scher et al. 2010; de Bono et al. 2011; Massard and Fizazi 2011). It is important to differentiate CRPCa from true HRPCa. Although CRPCa responds to secondary hormonal manipulations, true HRPC is resistant to all hormonal measures. Table 22.9 lists the key defining factors of CRPCa. The recommendations for management of patients who fail hormonal therapy are summarised in Tables 22.10 and 22.11.

It is recommended to continue ADT with LHRH analogues, despite PSA progression, based on the data of Manni et al. (1988). This idea is further supported by data from a multivariate post-randomization Cox regression analysis of 102 men with localized, unfavourable PCa who

Table 22.11 Recommendations for cytotoxic therapy in castrate-resistant prostate cancer

Recommendations	GR
Ideally, patients with cancer-resistant prostate cancer (CRPCa) should be counselled, managed and treated in a multidisciplinary team	B
In non-metastatic CRPCa, cytotoxic therapy should only be considered in clinical trials	B
In patients with a rise in prostate-specific antigen (PSA) only, two consecutive increases of PSA serum levels above a previous reference level should be documented	B
Prior to treatment, PSA serum levels should be >2 ng/ml to assure correct interpretation of therapeutic efficacy	B
Potential benefits of cytotoxic therapy and expected side effects should be discussed with each individual patient	C
In patients with metastatic CRPCa, and who are candidates for cytotoxic therapy, docetaxel, 75 mg/m^2 every 3 weeks, has shown a significant survival benefit	A
In patients with symptomatic osseous metastases due to CRPCa, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options; if not contraindicated, docetaxel should be preferred based on the significant advantage in pain relief and QOL	A
Cabazitaxel or abiraterone should be considered as effective second-line treatment following docetaxel	A
Second-line docetaxel may be considered in previously responding patients to docetaxel. Otherwise, treatment is tailored to the individual patient	B

GR grade of recommendation

underwent RT plus 6 months of ADT (D'Amico et al. 2009). The time-to-testosterone recovery (TTR) had a significant impact on the risk of CSS ($p=0.03$). If TTR increased to >2 years, none of the patients died due to PCa.

22.12.6 Secondary Hormonal Therapy

There are many therapeutic options available for the patient with progressive disease following ADT. They include anti-androgen withdrawal, addition of anti-androgens, oestrogenic compounds, adrenolytic agents and novel approaches (Heidenreich et al. 2001; Di Lorenzo et al. 2010). Although many second-line treatment regimes have resulted in prolonged PFS, none of the

approaches have resulted in an improved OS or CSS. However, second-line endocrine manipulation might be used to prolong the time until chemotherapy has to be initiated in patients with no or minimal metastatic burden and a slow PSA doubling time >1 year. In patients with extensive metastatic disease, especially with predominant skeletal metastases or a rapid PSA doubling time <6 months, primary chemotherapy with docetaxel should be considered. Summarises the various treatment modalities and the responses to be expected.

New promising hormonal agents are under development. Both have led to the redefinition of CRPCa (cells resistant to castration but still androgen sensitive) and hormone refractory status (cells definitively resistant to any hormonal manipulation) highlighting the continuing major role of the AR in these patients. The first agent, MDV3100, is a novel anti-androgen which blocks AR transfer to the nucleus, in contrast to currently available drugs where the AR remains able to transfer to the nucleus (Scher et al. 2010). In a dose-finding study in 140 patients with progressive, metastatic CRPCa, a PSA decline >50% was seen in 56% patients. Responses in soft tissue metastases and stabilised bone disease were observed in 22% and 56%, respectively. The results of phase-III clinical trials are awaited.

The second agent is the CYP17 inhibitor, abiraterone acetate. In a recent prospective randomized phase-III trial, 1,195 patients who had previously received docetaxel were recruited to receive 5 mg of prednisone twice daily with either 1,000 mg of abiraterone acetate or placebo [153]. After a median follow-up of 12.8 months, overall survival was longer in the abiraterone acetate-prednisone group than in the placebo-prednisone group (14.8 vs. 10.9 months; $p<0.001$). All secondary end points, including time to PSA progression (10.2 vs. 6.6 months; $p<0.001$), progression-free survival (5.6 vs. 3.6 months; $p<0.001$) and PSA response rate (29% vs. 6%, $p<0.001$), favoured the treatment group. Abiraterone acetate has been FDA-approved for the treatment of patients with progressive CRPCA following chemotherapy with docetaxel.

Orteronel is another newly developed CYP17 inhibitor which only interferes with the 17,20-lyase and thereby maintains cortisol levels, prevents mineralocorticoid excess and may allow dosing without the use of prednisone [154].

22.13 Non-hormonal Therapy (Cytotoxic Agents)

Based on prospective, randomized, phase-III trials, docetaxel at 75 mg/m^2 at 3-week intervals in combination with prednisone represents the cytotoxic regime of choice in men with CRPCa resulting in a median survival benefit of 3 months and a significant improvement of pain and quality of life as compared to mitoxantrone (Petrylak et al. 2004; Tannock et al. 2004). The beneficial effect of docetaxel is independent of age, pain or performance status at initiation and the presence of symptomatic or asymptomatic metastatic disease (Armstrong et al. 2010). The most appropriate indication for chemotherapy is the clinical scenario of symptomatic metastases. In asymptomatic patients, timing of treatment is not so clear and must be discussed individually. In patients with high PSA serum levels or a rapid PSA-DT < 6 months, chemotherapy should be initiated early. Early start of chemotherapy in metastatic CRPCa patients results in significant survival improvement as compared to patients with delayed initiation of systemic cytotoxic treatment. Currently, the only role for chemotherapy in non-metastatic, CRPC patients is in clinical trials, and patients should be advised to participate.

Several poor prognostic factors have been described, such as visceral metastases, pain, anaemia (Hb < 13 g/dl), bone scan progression and prior estramustine before docetaxel. Patients were categorized into three risk groups: good risk (0–1 factor), intermediate risk (2 factors) and high risk (3–4 factors), leading to three different median OS: 25.7, 18.7 and 12.8 months, respectively (Armstrong et al. 2010).

Since all patients who receive docetaxel-based chemotherapy for CRPCa will progress within 6–8 months, there have been many clinical trials investigating the role of salvage chemotherapy. The results suggest that one of the potential approaches is docetaxel re-challenge in previously responding patients as has been shown in

retrospective trials (Loriot et al. 2010; Buonerba et al. 2010; Eymard et al. 2010). In all other situations, vinorelbine, mitoxantrone and molecular-targeted therapy might be considered (Ohlmann et al. 2011; Fizazi et al. 2010). Recently, second-line satraplatin (Sternberg et al. 2009) chemotherapy failed to show any significant survival improvement in a large randomized trial and was rejected by the FDA and the EMA.

Positive results have been recently presented from a prospective, randomized, phase-III trial comparing the therapeutic efficacy of the taxane derivate, cabazitaxel, combined with prednisone versus mitoxantrone combined with prednisone in 755 patients with CRPCa, who had progressed after or during docetaxel-based chemotherapy (de Bono et al. 2010). Patients in the cabazitaxel arm experienced a significantly increased OS (15.1 vs. 12.7 months, $p<0.0001$) and an improvement in PFS (2.8 vs. 1.4 months, $p<0.0001$). Treatment-associated, WHO grade 3–4, side effects developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, $p<0.0002$) and non-haematological toxicities (57.4% vs. 39.8%, $p<0.0002$), respectively.

Finally the Sipuleucel-T vaccine has been FDA-approved for CRPCa, based on a large phase-III trial on 512 patients, with 4.1 months overall survival benefit but no disease progression difference between the vaccine and the placebo arms, representing the first available positive result of vaccines in PCa (Kantoff et al. 2010). Its place in the current treatment algorithm still is being considered

22.14 Palliative Therapeutic Options

Many patients with CRPCa have painful bone metastases and are not amenable for chemotherapy making effective palliative treatment options necessary. A multidisciplinary approach is required with input from medical oncologists, radiation oncologists, urologists, nurses and social workers.

Critical issues of palliation must be addressed while considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression (i.e., palliative external beam RT, cortisone, analgesics and anti-emetics).

Common complications due to skeletal metastases include bone pain, vertebral collapse or deformity pathological fractures and spinal cord compression. The use of zoledronate has demonstrated a clinically significant effect in terms of prevention of skeletal complications and pain reduction, or even total relief of pain, in patients with CRPCa (Saad et al. 2002). Patients with CRPCa metastatic to the bone, who were given zoledronic acid, 4 mg every 4 weeks, experienced a significant reduction in the number of skeletal-related events and pathological fractures and a significant increase in time to the first skeletal-related event. In the most recent, prospective, randomized trial, the RANKL inhibitor, denosumab, was compared to zoledronic acid in a cohort of about 1,900 patients with CRCaPa and bone metastases (Fizazi et al. 2011). The times to first and subsequent on-study skeletal-related events were significantly reduced by 18% in the denosumab arm. There was no statistically significant difference with regard to overall disease progression and survival. The frequency of treatment-associated side effects, especially the frequency of osteonecrosis of the jaw, was similar between both arms.

Regarding bone metastases, spinal cord compression is the most devastating complication. It must be considered as an emergency, requiring immediate whole spine MRI and steroids. A surgical decompression must be systematically discussed and followed by external beam radiotherapy If, however, primary surgery is not appropriate for medical reasons, radiotherapy in combination with corticosteroids should be offered.

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Better Patients' Perspective

23

Louis J. Denis

Contents

L.J. Denis, M.D., FACS
Director Oncology Centre Antwerp,
Secretary Europa Uomo,
Chair US TOO Belgium
Oncology Centre Antwerp,
Lange Gasthuisstraat 33–37,
2000 Antwerpen, Belgium
e-mail: louis.denis@skynet.be

23.1 Introduction

The three million men living with the diagnosis of prostate cancer are the proof of burden of the disease on civil society. The fact that the incidence remains around 30% of all male cancers and the ever-decreasing mortality coupled to the ageing of our populations will increase the prevalence for the next decades (Ferlay et al. 2010; Siegel et al. 2011).

Worse increased detection by the best all time cancer marker, the famous prostate-specific antigen (PSA) test, and improved imaging by ultrasound and magnetic resonance methodology will further increase this prevalence. In popular terms, one man out of eight faces the risk of being diagnosed with prostate cancer in his lifetime in the year 2011.

Despite the obvious progress in diagnosis and treatment, mirrored in the table of contents of this book, almost no progress has been made in primary prevention of the disease.

Massive programs on all aspects of cancer have been launched in Europe and the USA, aptly named "Europe against Cancer" and the "War against Cancer" even including a US National Prostate Cancer Program, during the last decades of the previous century. These efforts led to a number of initiatives on lifestyle and nutrition that pretend that 20–50% of cancers in Europe are avoidable through lifestyle changes (Coebergh et al. 2010; World Cancer Research Fund 2007).

Unfortunately, the outcomes in prostate cancer are restricted to circumstantial evidence in most, if not all, of the nutritional research.

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Table 23.1 Better patients' perspective

The rise and fall of PSA
Indications for endocrine treatment
Population screening for prostate cancer
Choice of primary treatment/innovative drugs and technology
Europa Uomo's partnerships

Improved understanding of the natural history and biology of prostate cancer opened new perspectives for patients. Innovations promise extended survival with enhanced quality of life

Hereditary disease and obesity are of clinical interest and practice. Our Europa Uomo's policy tends to relate cardiac health to prostate health, and we foster control of obesity and an exercise program Feel+ for prostate cancer patients (Moyad 2010; Denis et al. 2011).

Despite this slow development in primary prevention, it is clear that the first decade of the new millennium brought the research results of previous decades to clinical practice as well as a number of innovations in diagnosis and treatment. Out of a long list as presented in Table 23.1, we believe that a better understanding of the natural history and biology of prostate cancer has been as important as the development of new drugs or new technology.

Insights in the rise and fall of the PSA test, the randomized trials on endocrine treatment and screening, the chronocity, and long-term survival as well as choosing the primary treatment have contributed to the decrease in mortality and improved patient outcomes. Most important is the basic fact that all advances in cancer management come in small steps and never in a quantum leap. This is also true for prostate cancer where cure is often elusive while long-term control of disease may be satisfactory to the patient in terms of survival and quality of life.

We are optimistic that the new European research program as European Partnership for Action Against Cancer (EPAAC) based on partnership in research especially translational research and health services will open basic research on the genome and improved health care to the patients.

We do feel that the development of patient support groups as Europa Uomo played a small role in this process (Denis 2007).

23.2 Better Patient Perspectives

23.2.1 The Rise and Fall of the PSA Test

The history of blood markers in relation to prostate cancer started in 1933 with the discovery of the acid and alkaline phosphatases. For about 50 years, acid phosphatase was the leading marker for defining progression or remission of an active cancer. This situation persisted up until the 1980s with few changes in incidence and mortality of the disease.

Around the mid-1980s, three events changed this situation. Transrectal ultrasound (TRUS) became popular and allowed visualization of the prostate measuring the volume and identification of hypoechoic lesions as diagnostic for cancer. Confirmation was easy with the development of a spring-loaded biopsy gun that permitted easier, painless, and directed biopsies of the gland. However, most important was the introduction of the prostate-specific antigen (PSA) blood test in routine clinical practice. Described in the ejaculate, it was recognized as a protease specific to the prostate gland which could be measured in the blood. As a control marker after radical prostatectomy, it was quickly accepted as a marker of progression of the disease once cancer was demonstrated. Subsequently, a wave of enthusiasm to use the PSA test as a diagnostic marker for cancer tripled the detection rate and the number of curative treatments for prostate cancer. Still concerned voices were heard on the possible detection of the latent cancers (found on autopsy reports), the benign course of early diagnosed, untreated prostate cancer, and the conviction that elderly men die with but not by prostate cancer.

The simplistic concept that an increased PSA test over 4 ng/ml indicated cancer in men over 55 years of age that could be cured by a radical prostatectomy became routine practice. The increased incidence of PSA testing led to an increased incidence in cancer with a considerable shift in stage and grade providing hope for better outcomes and increased survival. This led to an increase in overall survival in the USA and a corresponding decrease in mortality over the next decades. No wonder that this wave of enthusiasm

Table 23.2 PSA and prostate cancer (PCPT)

PSA	Number	Cancer (%)	HG cancer (%)
<0.5	486	6.6	0.83
0.6–1.0	791	10.1	1
1.1–2.0	998	17	2.1
2.1–3.0	482	23.9	4.6
3.1–4.0	193	26.9	6.7
Total	2.950	15.2	2.26

continued into the new millennium with support from professionals and patients.

However, this epidemic of prostate cancer diagnosis increased the lifetime risk of 9–16% relative to the overall use of the PSA test. Even compared to the expected ageing of the population, it became evident that a great number of the newly diagnosed cancers really belonged to the indolent cases only found at autopsy. The PSA test was obscured by the simultaneous presence of benign prostatic hyperplasia (BPH) as the positive predictive value over 4 ng/ml is only 30%. A further confidence in the test was lost in the Prostate Cancer Prevention Trial showing that 15% of patients with "normal" PSA levels had cancer and that 15% of these had high-grade cancer.

We believe in the educational value of showing these results repeatedly as in Table 23.2.

As the pendulum went in the other direction, we are now confronted with reports from health authorities and epidemiologist/public health professionals to diminish the excessive use of the PSA test in our populations. Though a legitimate concern in public health, we prefer to control the plethora of PSA tests by increased knowledge on the pros and cons especially in general practice. The PSA test should not be a routine request for each individual patient but its merits and deficiencies explained for each application. The PSA test in asymptomatic men with normal DRE is outside the routine recommendations for preventive testing. Still with the existing fear and anxiety for any cancer, including prostate cancer, we feel that this simple test should not be denied to the patient who asks for it. Caution and expertise with the practitioner may still result in the cancer diagnosis of an indolent tumor but does not need invasive treatment or overtreatment of any kind including endocrine treatment.

We realize that the PSA test is not the ideal biomarker reaching 100% sensitivity and specificity. It is as all biomarkers nudged between detecting all cancers present and avoiding more investigations to confirm absence of disease (specificity). There always will be a trade-off between reducing biopsies and missed cancers.

A solution resides in a battery of tests, new and better assays and avoiding the prevalence of BPH. The latter is difficult over the age of 60 where the cutoff for biopsy should be 3 ng/ml. On the other side of the spectrum, at age 45, PSA < 0.65 ng/ml allows retesting at the age of 55. This kind of evaluation is technically possible within continuing care of general practice or specialized prostate cancer centers with electronic data filing. Until then, we handle both patient and the PSA test with due respect. We only have so far the DRE and PSA as routine in making the diagnosis and the PSA test remains the best.

The vast experience with the PSA test established new patient orientation before PSA testing and afterwards. Lives have been saved but at the prices of overtreatment. More innovations are targeted to the cancer, but attention given to overdiagnosis remains a better perspective for the patient.

23.2.2 Indications for Endocrine Treatment

One of the many paradoxes in prostate cancer management is that two Nobel prizes were awarded in the last century for research in endocrine management of the disease, one to C. Huggins for the demonstration that castration was excellent treatment for symptomatic metastatic prostate cancer and the second one to A. Schally for analysis of the natural LHRH decapeptide. Subsequent

research developed agonists to the natural LHRH demonstrating that surgical castration could be safely replaced by medical castration.

Thousands of industry-directed publications discussed the action and advantages of a number of LHRH agonists followed by more on the relative merits of monotherapy with or without antiandrogens.

The final consensus after four international meetings resulted in a compromise. There was indeed as shown in a meta-analysis a small 6% difference in combination or maximal androgen blockade (CAB or MAB) which, however, did not compensate for the added toxicity of combining two drugs.

Antiandrogens were advised as monotherapy in order to preserve potency, and recently a new class of LHRH antagonists were introduced to avoid the so-called flare-up of disease after the first injection of an agonist.

The earlier diagnosis with the PSA test and subsequent biopsy by 5–10 years on the pure clinical diagnosis resulted in many years of endocrine treatment aiming for castrate levels of serum testosterone. The side effects of long-term androgen deprivation became a clinical issue questioning the benefit to the patient. The resulting balance of opinion is complex and can only be solved by tailoring the treatment to the individual patient.

What the patient has to remember:

1. Endocrine treatment in with androgen deprivation (ADT) does not cure prostate cancer.
2. However, ADT is able to extend life by controlling the disease. Endocrine sensitivity of the tumor is dependent on the host and on the biological composition of the cancer. About 20% of primary endocrine treatments show either incomplete deprivation and/or endocrine lack of response which in the later stages of the disease is called hormone resistant. Serum testosterone levels have to be checked to confirm this diagnosis.

   There is usually a PSA response which is not enough to believe that the given endocrine treatment is satisfactory and most effective. We expect the PSA response to fall below 4 ng/ml or better 2 ng/ml to meet our expectations.
3. In regard to the long list of side effects of ADT, it is now accepted that intermittent endocrine treatment may be a good option in endocrine sensitive cancers and/or low-risk disease.
4. The indications for endocrine treatment are obligatory in symptomatic and/or metastatic disease. Poorly differentiated cancers and PSA levels above 50 ng/ml seem a natural invitation to this treatment.
5. Out of the natural history of prostate cancer and the experience of our huge screening trials, it became clear that some small (less than 0.5 cc) well-differentiated cancers were frequently diagnosed in autopsy series (depending on the number of prostate cuts) but were clinically indolent. The question was: "Do these indolent cancers need immediate treatment which in this stage of disease is surgery or radiotherapy?" Urologists faced the same dilemma some 30 years ago in defining the indications for curative treatment for T1a disease diagnosed in the resected tissue of a TURP specimen.

   The logic in the face of an overdiagnosis and consequent overtreatment in the European randomized screening study (ERSPC) confirmed by longitudinal studies catched on. Even in the absence of a randomized trial (several are ongoing), active surveillance is accepted as a possible treatment choice in most guidelines.
6. Another conservative treatment remains watchful waiting. Here the patient's life expectancy is judged to be limited by extreme old age or comorbidity. Depending on the stage of the cancer, the clinician may decide to withhold endocrine treatment in line with the slow growth of prostate cancer. Here treatment is based on the appearance of symptoms. Of course following this logic, the physician should be cautious to make the diagnosis of prostate cancer before evaluating the health status of the patient. To

Table 23.3 Active surveillance vs. watchful waiting

Active surveillance	Watchful waiting
Fit patient	Comorbidity/age
Low-risk cancer	Any cancer
PSA evolution define treatment (+ biopsies)	Symptoms define treatment
Option: cure	Option: palliation

Active surveillance (AS) and watchful waiting (WW) are treatments based on the knowledge of the natural history of prostate cancer

our surprise, the difference between these two forms of delayed treatment is sometimes misunderstood by the clinician. The two forms of no treatment are compared in Table 23.3.

7. Endocrine treatment is given in combination treatment with external radiotherapy in stage T3 tumors. This treatment has been confirmed in several randomized trials, and debate is centered on the duration of endocrine treatment. This policy is in line with endocrine concomitant treatment in advanced disease as in N+ patients.

The evolution of endocrine treatment for prostate cancer is based on evidence and meets the criteria of better perspective for the patients in terms of survival, quality of life, and cost-efficacy.

23.2.3 Population Screening for Prostate Cancer

Despite the much heralded success of diagnosing prostate cancer in the preclinical phase by the use of the PSA test, a confirmation by randomized clinical trials was missing until 2009.

The fact that prostate cancer becomes incurable once it invades other tissues forms the basis for the assertive search and treatment in localized disease. The conclusion that PSA was and remains one of the most accurate cancer biomarkers as compared to mammography for breast cancer or blood positive stools for colon cancer led the way to case finding in individual practices as part of a routine preventive checkup or to opportunistic screening in patients with unrelated conditions. Unfortunately, it is not enough to find more cancers. We have to show that the mortality of the disease decreases leading to increased survival.

It takes a randomized prospective study to prove the point. In the early 1990s, we introduced joined by Erasmus Rotterdam a few pilot studies to prove that a randomized study based on the PSA test, a DRE, and TRUS followed by biopsy was feasible and acceptable by the population. The positive results led to the start of the European randomized study of screening for prostate cancer (ERSPC). Around the same time, a more ambitious randomized study on prostate, lung, colon, and ovarian cancer screening (PLCO) was launched in the USA.

Table 23.4 ERSPC vs. PLCO

Feature	ERSPC	PLCO
No. of men	162.387	76.693
Screen interval	4 years	1 year
Median FU	9 years	7 years
Prostate cancer	9.297	5.142
PC deaths	540	94

The first results from both studies were simultaneously published in 2009 in the same issue of the *New England Journal of Medicine*. The first worldwide response was confusion as it seemed that both studies were flawed and that PSA screening did not decrease the mortality by prostate cancer. A comparison between the main basic figures in both studies testifies to the required efforts and relatively low specific death by prostate cancer as shown in Table 23.4.

However, the report of the Swedish chapter experience of the ERSPC 1 year later (supported by the US NCI) with a longer follow-up showed a 44% decrease in PCa mortality eliminated any doubt that PSA screening reduces the specific mortality of the disease.

Unfortunately, screening can cause harm if followed by the logical sequence of curative treatment of localized PCa mainly by its known side effects as impotence and urinary and/or stool incontinence. They related directly to the quality of life in most long-term survivors of primary treatment.

Inherent to any screening activity is overdetection and worse overtreatment of indolent cancers. One conservative move to reduce this problem is active surveillance, delayed curative treatment in newly diagnosed PCa, becoming an acceptable primary treatment option in most guidelines.

Another obstacle to be solved is the low figure of benefit for the individual patient. The 2009 published figures needed to screen (NNS) 1,410 men and another 48 men needed to be treated (NNT) to prevent one PCa death are discouraging. However, as predicted, we see these numbers falling with longer follow-up in line with the 15-year needed follow-up to evaluate the natural (treated) history of PCa. We can only hope to

solve the balance benefit vs. harm by distinguishing the biological lethal cancers from the potentially "benign" small cancers at the time of diagnosis. Further collaboration in the ongoing clinical trials and basic research is needed to close this controversy.

In the meantime, there is consensus among the ERSPC trialists that population screening for PCa based on PSA only is not recommended as long as with further follow-up, quality of life (QOL), and cost-efficacy results net benefit for public health and patients alike are guaranteed.

Two caveats are in order. The individual, informed patient is entitled to a PSA test with adequate counseling concerning his chances of facing PCa in his lifetime. Out of all ongoing studies, one may conclude that only men expected to survive longer than 10 years and without lower urinary tract problems should be candidates for screening.

The low (>3%) death rate over the 11-year follow-up in the ERSPC study by prostate cancer supports the 10-year statement.

The leading screenings study (ERSPC) for PCa opened clearer options for patients and better perspective for population and individually screened men.

23.2.4 The Choice of Primary Treatment/Innovative Drugs and Technology

The long natural history of prostate cancer somewhat unevenly distributed between the ages of 50 and 75, and the classification from low to high risk leaves plenty of choice for a variety of primary treatments.

A dilemma for doctors and patients alike remains the vast choice of more or less invasive curative treatments available even after subtraction of all the indications to consider delaying treatment in active surveillance or watchful waitng.

Surgery and radiation have both been advocated for more than a century. Innovations have been introduced in both curative treatments, for surgery from perineal to retropubic to laparoscopic and recently robot-assisted surgery. For radiation, we witnessed technical innovations in external radiation techniques and the popularization of brachytherapy or combinations. Others forms of energy to destroy the prostatic tissue as cryosurgery or high focused ultrasound have made remarkable progress. The promising possibilities of cancer imaging in the prostatic tissue allow the possibility of focal therapy still in very early clinical stage. Even systemic endocrine therapy has been advocated with the sole intention to control, but not cure the cancer. When it comes to cancer, doctors like to combine treatments to obtain a major, total tissue destruction.

Randomized clinical trials confirmed the best outcomes in combining radiation with endocrine treatment in pre- or concurrent modes and varying duration for locally advanced disease.

All these forms of treatment have their own specific indications, making outcomes comparisons difficult to impossible.

Several randomized trials are ongoing involving active surveillance, radiation, and surgery in the hope to clarify some choices for the doctor and patient. At this moment in time, the outcomes for the patient not only in terms of specific cancer survival but especially in measuring health-related quality of life (HRQOL) as well as cost-efficacy are unknown as the many subclassifications on cancer stage, grade, and biological aggression leave room for debate.

We expect the treating physician to inform the patient on all treatments currently available and the expected side effects. Unfortunately, physicians quote the best outcomes published in the literature, while the patients have unrealistic expectations based on statistical counseling that do not predict for the individual. Consulting the internet without guidance is a prescription for misled confusion, but even professional journals print questionable P-results and omit relative risk and odds ratios on treatment results. Worse the perceptions of the patients especially on psychosocial and wellness problems are not fully evaluated in our culture of cancer-centered treatment rather than patient-centered care. It must be clear that a 50-year-old prostate cancer patient has

Table 23.5 Manifesto Europa Uomo

1.	To find ways and means to promote quality of life for prostate cancer patients and their families
2.	To promote the dissemination and exchange of evidence-based as well as factual and up-to-date information on prostate cancer
3.	To promote prostate awareness and appropriate diagnosis and prognosis
4.	To emphasize the need for appropriate early detection
5.	To campaign for provision of and access to optimum treatment
6.	To ensure quality, supportive care throughout and after treatment
7.	To promote multiprofessional quality care and appropriate medical infrastructure
8.	To acknowledge good clinical practice and promote its development
9.	To ensure that all men fully understand any proposed treatment options, including entry into clinical trials and their right to a second opinion
10.	To promote the advancement of prostate cancer research

different care needs as compared to the elderly cancer patients. As Harry Belafonte sings on the birds and the bees, "now that I am ninety three I don't care a damn you see."

The complexity of the treatment in high-risk PCa introduces the concept of prostate cancer units (PCU) of excellence as centers with a critical patient load and multifunctional collaboration and having the expertise of innovative health technology available to improve outcomes. We do agree on these advantages while we plead for keeping track of the emotional and social patient needs by interactive communication and continuous information between the intra- (hospital) and extramural (community medicine) to assist all patients in all needs.

We believe that this development will provide better outcomes for scientific evaluation, quality of care control, and general, holistic patient care.

We will not discuss the merits for better outcomes by evidence-based research as it is clear from the recent publications that chemo, endocrine, and immunological treatments showed life extending and QOL results in a number of trials. We only can hope that they will become available as soon as possible in our social health-care systems. Less direct but as important are the new treatments on bone health preservation by bisphosphonates and denosumab. We live in hope to see not only the mortality of PCa reduced but as important the life of the patients enhanced with quality and hope for long-term survival in acceptable, functional health.

23.3 Europa Uomo: The European Prostate Coalition

We have witnessed a continuation of improvement in all aspects of optimal medical management centering on the disease. Most of these improvements were steps in a chronic interaction between clinical research and best practice. It remains evident that the prime stakeholders of clinical progress remain the patients aspiring for cure, control of the disease, and enhanced quality of life.

There is little that patient groups can do in this progress except to plead for research support, access, and service of best quality practice, tailored treatment for the individual patient, and overcome the inequalities in treatment and care in Europe.

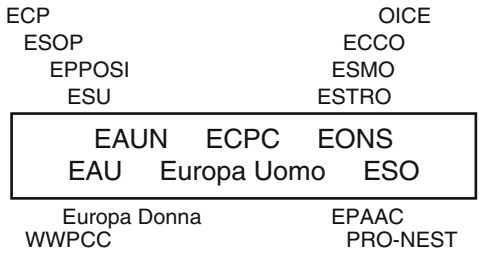
However, we feel strongly that our advocacy role is focused on holistic patient care involving a treatment policy on the patient first and then on his disease involving quality of life and wellness in psychosocial and financial domains. We enjoy a number of rights in some European nations which we would like to balance with patient obligations. The latter directed towards a fair distribution of scarce health funds, facilitation of translational research, and support of existing, functional partnerships with many professional societies.

Europa Uomo, the European Prostate Coalition, established in 2004, advocates patient-centered care that we expressed in a manifesto presented in Table 23.5. The ten points cover our

Table 23.6 Proactive prostate cancer call out

Governments to be aware of prostate diseases
Governments to support research biomarkers
Remember the risk factors of prostate cancer
Tailored treatment to the individual patient through appropriate use of PSA test
Partnership building to reduce burden of disease, identify common actions, and overcome inequalities in medical treatment and holistic care

Table 23.7 Partnerships Europa Uomo



EUomo Europa Uomo, *EAU* European Association of Urology, *ESO* European School of Oncology, *ESU* European School of Urology, *ECCO* European CanCer Organization, *ESMO* European Society for Medical Oncology, *ESSO* European Society of Surgical Oncology, *ESTRO* European Society for Therapeutic Radiology and Oncology, *EONS* European Oncology Nursing Society, *EORTC GU* European Organization for Research and Treatment of Cancer Genito-Urinary Group, *ESOP* European Society of Oncology Pharmacy, *EPPOSI* European Platform for Patients' Organizations, Science and Industry, *EAUN* European Association of Urology Nurses, *ECP* European Cancer Prevention Organization, *OECI* Organization of European Cancer Institutes, *ECPC* European Cancer Patient Coalition, Europa Donna, *WWPCC* World Wide Prostate Cancer Coalition, *EPAAC* European Partnership for Action Against Cancer, *PRO-NEST* Prostate Research Organizations-Network of Early Stage Training

policies ranging from quality of life for patients and families to promote the advancement of prostate cancer research.

The time and ideas were positive for a fast development supported by other patient groups and professional societies in particular the European Association of Urology (EAU). This development prompted a proactive prostate cancer call out resulting in five statements and about 20 partnerships with professional and patient groups as presented in Tables 23.6 and 23.7.

The decision of the European Commission to invite patient support groups to participate in the European Partnership for Action Against Cancer (EPAAC) is a confirmation of the integration of patients in cancer clinical research. In the mean time, we worked on our own identity as a patient group to define our role in social health care and express the needs of the patient community as well as for each individual patient. The holistic approach, privileged information channels, further education on understanding psychological and emotional distress, and shared decision policies as well as sharing experiences help enormously to face the challenge of a chronic, potentially lethal disease in an advanced age group. All this resulted in a well-informed, respectful patient as a collaborator in his own treatment. Reciprocal respect carries the day and facilitates the burden of chores for health professionals and patients alike.

We are far from reaching our vision and mission in health care, but these first steps have been rewarding and acknowledged. We are convinced that complete transparency of our health-care systems will solve unanswered questions as patient-related outcomes and professional satisfaction and well-being. A close collaboration will open frontiers in health care and better perspective for both.

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