Prostate, Seminal Vesicle, Penis, and Urethra

Brett W. Cox and Michael J. Zelefsky

Contents

B. W. Cox
Department of Radiation Oncology, Memorial Sloan-Kettering
Cancer Center, 1275 York Avenue, New York, NY 10065, USA

M. J. Zelefsky (✉)
Department of Radiation Oncology, Chief,
Brachytherapy Service, Memorial Sloan-Kettering Cancer
Center, 1275 York Avenue, New York, NY 10065, USA
e-mail: zelefskm@mskcc.org

Abstract

- Late histologic changes in irradiated benign prostate ducts include variable ductal atrophic change, cytologic and nuclear atypia, basal cell hyperplasia, increased foreign body giant cell reaction to corpora amylacea, nuclear pleomorphism, nuclear vacuolation, hyperchromatic DNA, and presence of prominent nucleoli.
- In the later phases of fibrosis, TGF-beta and PDGF, among others, simulate the proliferation of fibroblasts and the synthesis or extracellular matrix constituents and MMPs.
- Irradiated urothelial cells demonstrate changes including nuclear pleomorphism, swollen cytoplasm, and altered labeling indices as compared to non-irradiated urothelial cells.
- The most common acute urinary morbidities during external beam radiation therapy for pelvic malignancies are classified as irritative and are caused by acute

inflammation and epithelial denudation of the urethra and possibly the bladder neck.

- In patients treated for prostate cancer, brachytherapy is associated with more late GU toxicity, but less late GI toxicity, than external beam RT.
- The main sexual side effects of radiation therapy to the pelvis are impotence, decreased libido, decreased ejaculate, and painful ejaculation.
- Late genitourinary toxicities of radiation therapy to the pelvis include chronic cystitis, chronic urethritis, bladder neck contracture, urethral strictures, hematuria, and urinary incontinence.
- Rectal complications are the main late toxicities that limit dose escalation in prostate cancer.
- Modern highly conformal techniques can be used to minimize dose to the penile bulb and cavernosa whenever possible, and MRI identification of the apex of the prostate may be helpful in this regard.
- For erectile dysfunction in the post-treatment setting, first-line phosphodiesterase inhibitors such as sildenafil 25–100 mg po prn, tadalafil 10 mg po prn, vardenafil 5–20 mg po can be considered.

Abbreviations

BPH	Benign prostatic hyperplasia
CTGF	Connective tissue growth factor
PSA	Prostate-specific antigen
IGRT	Image-guided radiation therapy
IMRT	Intensity-modulated radiation therapy
NVB	Neurovascular bundle
3D-CRT	Three-dimensional conformal radiation therapy

1 Introduction

In men, malignancies of the bladder, rectum, and prostate account for approximately one-third of all new cancer diagnoses. Radiation therapy is often used in the treatment of these and other pelvic and lower extremity malignancies, exposing the distal male urogenital tract, including the prostate, seminal vesicles, penis, and urethra, to potential toxicity. Toxicities to these organs can negatively affect genitourinary, gastrointestinal, and sexual quality of life. It is essential that the treating oncologist has an understanding of the treatment-related toxicities of these tissues, their management, and the radiation dose-volume constraints that guide treatment planning. It is further essential that these radiation planning parameters are properly integrated with increasingly common clinical scenarios such as the use of

concurrent chemotherapy, biologic agents, and altered fractionation radiation regimes which can influence further the potential for normal tissue complications.

This chapter will first briefly highlight the landmark events in the history of radiotherapy for the distal male GU tract and assess the current state of the field. A detailed review of the gross anatomy, histology, and radiation histopathology of the organs of the distal male GU tract then follows. A description of each organ-related radiation toxicity is then reviewed along with the appropriate dose–volume constraints that should guide treatment planning. Finally, guidelines for the clinical management of common radiation-related toxicities are offered. Biocontinuum of adverse early and late effects are shown in Fig. 1.

2 Anatomy and Histology

2.1 Anatomy

The distal male urogenital tract extends from the lower pelvis to the ventral portion of the body and includes the prostate gland, seminal vesicles, urethra, and penis. The testicles, which are also a part of the distal male urogenital tract, are addressed in a separate chapter. The primary roles of the distal urogenital tract are to generate components of the seminal fluid, serve as a conduit for urine and semen, and facilitate sexual intercourse. Highly detailed anatomic descriptions and atlases are available in both textbook (Gray 1995; McAninch 2008) and publication (Meyers 2001; Walz et al. 2010) form. It is increasingly clear that there can be significant variations between individuals in terms of the form and structure of the prostate gland, neurovascular bundles, external urethral sphincter, prostatic ligaments, and vascular supply to these structures.

2.1.1 Prostate Gland

The prostate gland lies within the lower pelvis immediately superior to the musculofascial floor. It is the largest accessory gland of the male reproductive tract, weighing approximately 30 grams in men without prostatic pathology. A fibrous capsule surrounds the gland, which is continuous with the surrounding connective tissue stroma, but is not present at the apex of the prostate. The fascia surrounding the prostate gland is variably adherent to the capsule. Shaped like an inverted tapered cylinder, the prostate base is immediately caudad to the bladder and its tapered apex cephalad to the urogenital diaphragm. The apex contains muscle fibers continuous with the urogenital diaphragm. The prostate lies posterior to the symphysis pubis, connected via the puboprostatic ligaments, and anterior to the rectum, separated from it by the anterior portion of Denonvilliers fascia (rectovesical septum), a thin

Fig. 1 Clinical pathologic course: prostate gland, seminal vesicles, and penis (with permissions from Rubin and Casarett 1968)
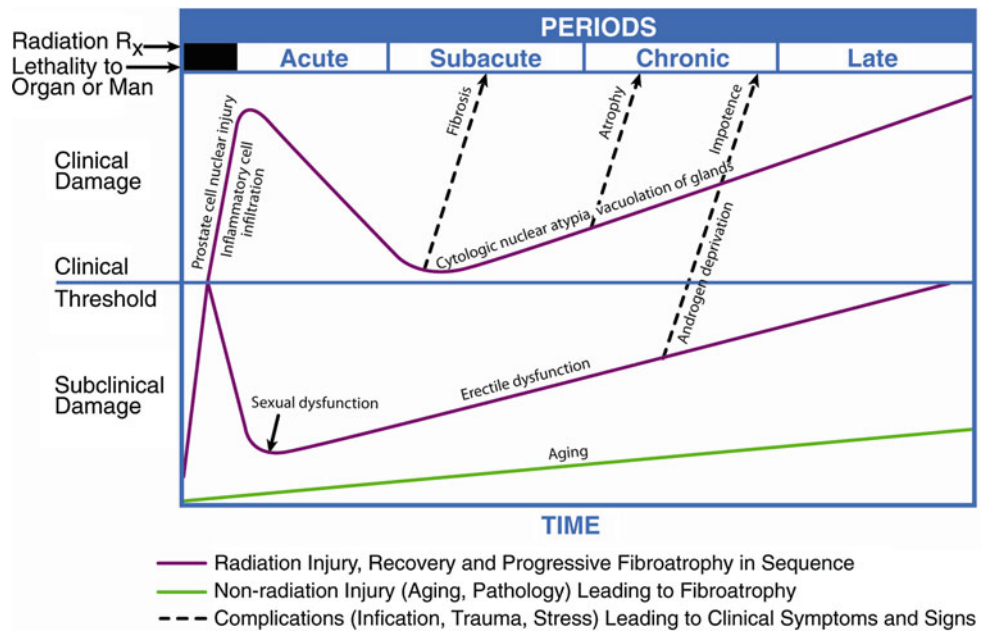
layer of connective tissue that separates the prostate and seminal vesicles from the anterior rectal wall. The prostatic urethra passes through the gland from the base of the bladder to the membranous urethra. The ejaculatory ducts course from the convergence of the ducti deferens and the seminal vesicles obliquely, anteriorly and caudally, through the posterior prostate to communicate to join with the prostatic utricle to open into the prostatic urethra.

The blood supply of the prostate gland is from the prostatic branches of the inferior vesicle, pudendal, and middle rectal arteries. Venous drainage is shared with the penis, urethra, and lateral pelvic organs via the dorsal venous plexus (Santorini's plexus) to the internal iliac vein. The predominant course of lymphatic drainage is to the internal iliac nodes, but alternative drainage routes to the obturator, external iliac, sacral, vesicle, and rarely the periaortic lymph nodes are common. The prostate gland has dual autonomic innervation from the prostatic nerve plexus. Parasympathetic innervation is provided by the pelvic splanchnic nerve (S2-4) and sympathetic innervation is provided by the inferior hypogastric plexus (T10-L2). The neurovascular bundle (NVB) courses between fascial layers on the posterior lateral surfaces of the prostate gland and is intimately related to the dorsal surfaces of the seminal vesicles.

The prostate has been anatomically described in terms of both lobes and zones (McNeal 1981). There are four lobes of the prostate: anterior, posterior, median, and lateral. The anterior lobe is located anterior to the urethra and contains no glandular tissue, just fibromuscular stroma. The median lobe lies in the center of the gland, with the urethra anteriorly and the ejaculatory ducts posteriorly. The paired right and left lateral lobes are the largest lobes and contain the bulk of glandular tissue, being separated into halves by the prostatic urethra. The posterior lobe lies at the dorsal portion of the gland and can be palpated via a digital rectal examination.

The zonal anatomy of the prostate (Fig. 2) was first described by McNeal in 1981 and is used more commonly. This system is based on embryonic development patterns and includes four prostatic zones described relative to the urethra: the peripheral zone, the central zone, the transition zone, and the anterior fibromuscular stroma. The peripheral zone is a horseshoe-shaped structure extending posteriorly and laterally around the inner regions of the prostate gland and contains approximately 70 % of the prostatic glandular tissue. It is embryologically derived from a double row of developing prostatic ducts that extend posterolaterally from the distal urethra. The central zone contains approximately 25 % of the glandular tissue and is formed from developing ducts that grow cephalad, posteriorly and laterally into the mesenchyme surrounding the ejaculatory ducts. It is a cone-shaped volume extending from the bladder base to the verumontanum, encompassing the ejaculatory ducts. The transition zone lays anteromedial to the central zone and surrounds the mid-prostatic urethra. Benign prostatic hypertrophy occurs most commonly in the transition zone. The fibromuscular stroma is the anterior part of the prostate and contains little to no glandular tissue but does account for one-third of the total bulk of tissue within the prostatic capsule.

2.1.2 Seminal Vesicles

The seminal vesicles consist of two lobulated glands posterior to the bladder and prostate gland that converge medially. They are inferior and lateral to the ampulla of the ductus deferens and lie against the fundus of the bladder.

Sacral Flexure of the Rectum

Rectal Fascia
(Posterior Lamella, Waldeyer's Fascia)

Perineal Flexure of the Rectum

Seminal Vesicle

Rectovesical Pouch

Right Ureter

Muscular Layer

Tunica Muscularis

Serosal Layer
(Visceral
Peritoneum)   **Urinary Vesical**

Subserosal Layer

Prostate and Seminal Vesicles
are examined Rectally through
Palpation and through Transrectal
Sonography (◫ Fig. 5.250).
The Rectal Fascia (Waldeyer's Fascia)
and the Rectoprostatic Fascia
(Denonvilliers' Fascia) are important
in Staging the Spread of Rectal
and Prostate Cancer. A Surgical
Approach to the Prostate can
be done by Suprapubic Access
Extraperitoneally, Retropubically
through Retzius' Space,
transversically (Through the
Bladder), or Transperoneally.

Retropubic Space
of Retzius

Pubovesical M.
(res.)

Urogenital Diaphragm

**Membranous Part of the
Urethra** and External
Urethral Sphincteric M.

Crus of Penis

Corpus Cavernosum
of Penis

Corpus Spongiosum
of Penis

Epididymis

Testis

Glans Penis

Prepuce of Penis

Scrotum with Dartos M.

Presacral Fascia

Anus

External Ani Sphincteris M.

Levator Ani M. (res.)

Rectoprostatic Fascia
(Dononvilllier's Fascia)

Prostate

Bulbourethral Gland
(Cowper's Gland)
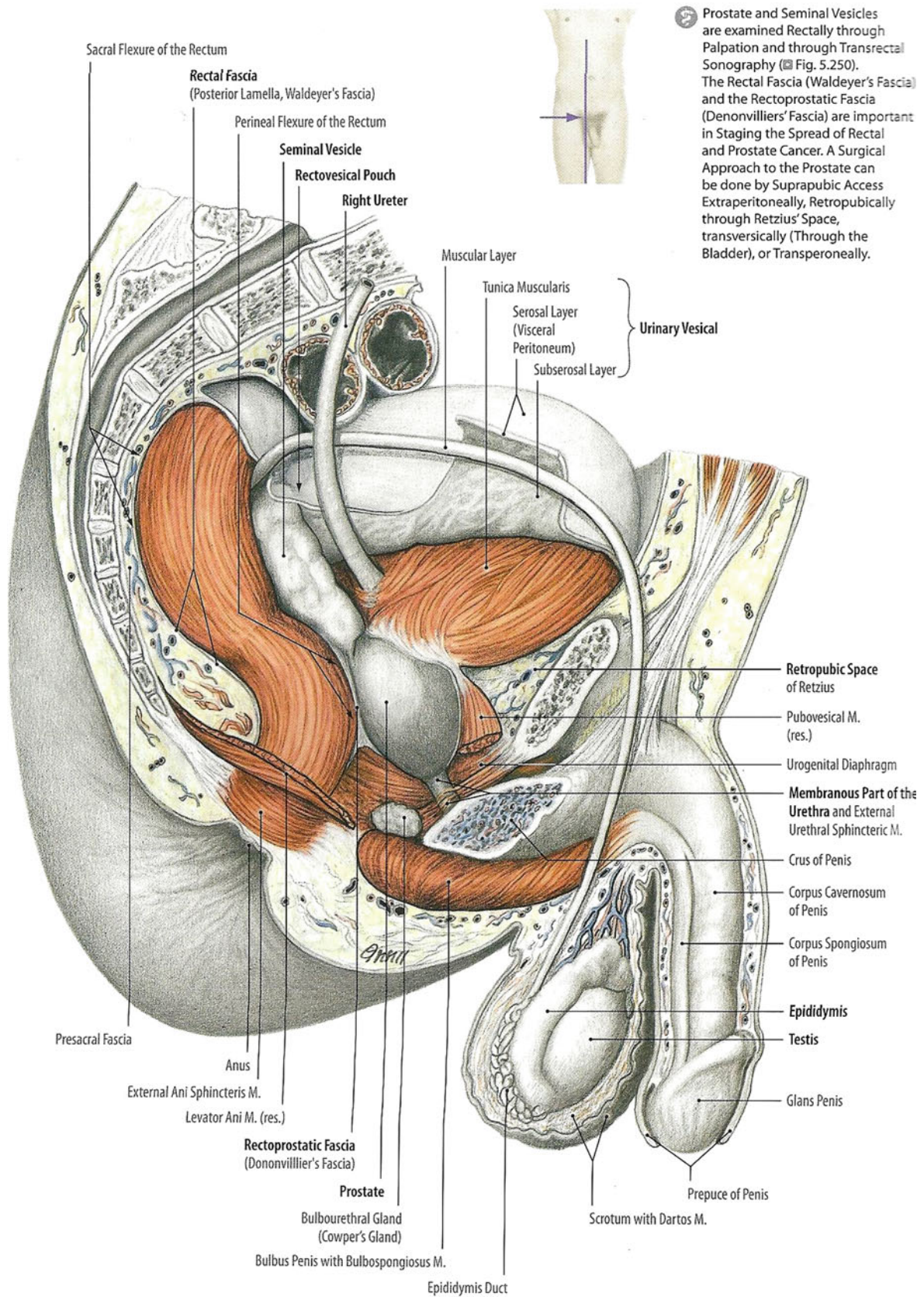
Bulbus Penis with Bulbospongiosus M.

Epididymis Duct

Fig. 2 Anatomy of the prostate (with permissions from Tillman 2007)

The majority of these glands lie in the retroperitoneum and are enclosed by dense fascia, except for the most cephalad portion, which is intraperitoneal. Their cephalad surface abuts the posterior bladder and their caudad surface interfaces with the anterior rectum at the rectovesical (Denonvilliers') fascia. The ureters lie medial to each seminal vesicle. The seminal vesicles converge with the vas deferens to form the ejaculatory ducts which enter the prostate gland. They produce alkaline secretions that are added to the semen. Their blood supply is from the inferior vesicle artery and vein and middle rectal artery and vein. Their main lymphatic drainage is to the internal iliac lymph nodes. Sympathetic innervation is via the superior lumbar and hypogastric nerve, which regulates rapid contraction of smooth muscle cells during ejaculation. Parasympathetic innervation is from the pelvic splanchnic nerve and from the inferior hypogastric plexus.

2.1.3 Male Urethra

The male urethra courses from the base of the bladder to the tip of the penis and is subdivided into prostatic, membranous, and spongy portions. It provides a conduit for urine and semen to be excreted from the body. The prostatic portion enters the anterior portion of the prostate gland and travels with slight anterior concavity so that it courses posteriorly toward the mid gland before resuming an anterior position at the prostatic apex. The change from the posterior to anterior course happens at a sharp, approximately 35-degree angle, at the level of the verumontanum, a midline protrusion along the posterior urethra where the ejaculatory ducts enter the prostatic urethra. The prostatic urethra is about 3-cm long and is the widest and most compliant portion of the urethra. The membranous urethra is approximately 1-cm long and extends through the urogenital diaphragm from the apex of the prostate gland to the bulb of the corpus spongiosum. The external urethral is a complex anatomic and physiologic structure closely related to the urogenital diaphragm. The innervation for the external sphincter travels near the apex of the prostate. The external sphincter is a circular muscle under partial voluntary control (innervated by the somatic nervous system) in the urogenital diaphragm and regulates the passage of urine through the urogenital diaphragm. Once the urethra enters the penile bulb, it becomes the spongy (penile) urethra which extends to the navicular fossa at the tip of the penis. The spongy urethra is about 6-cm long and is contained in the corpus spongiosum.

2.1.4 Penis

The penis is subdivided into three portions: the root, the body, and the glans. The root is anchored to the os pubis, symphysis pubis, and ischium by the crura and suspensory ligaments. The body of the penis extends between the root and the glans, a dome-shaped extension of the corpus spongiosum. The penis contains three erectile bodies, each encased in a fascial cover: two paired corpora cavernosa and the corpus spongiosum. All corpora are further encased together by the fibrous Buck's fascia. The spongy urethra courses within the corpus spongiosum after entering this structure at the penile bulb, the most proximal portion of the spongiosum. The penile skin rests upon Colles' fascia, which is continuous with Scarpa's fascia of the abdominal wall.

The arterial supply of the penis and urethra is from the internal pudendal arteries which branch into the deep penile artery, the bulbourethral artery, and the dorsal artery of the penis. The deep artery supplies the corpora cavernosa, while the others supply the remainder of these organs, including the urethra and corpus spongiosum. There are multiple routes of venous drainage of the penis. The superficial dorsal vein is external to Buck's fascia, while the deep dorsal vein lies deep into this thick fascial layer between the paired dorsal arteries. The dorsal veins join the pudendal plexus and eventually the internal pudendal vein. The penile skin and superficial fascia's main route of lymphatic drainage is to the superficial inguinal lymph nodes. The predominant lymphatic pathway for the glans penis is through the external iliac nodes. The urethra drains to the internal and common iliac lymph nodes.
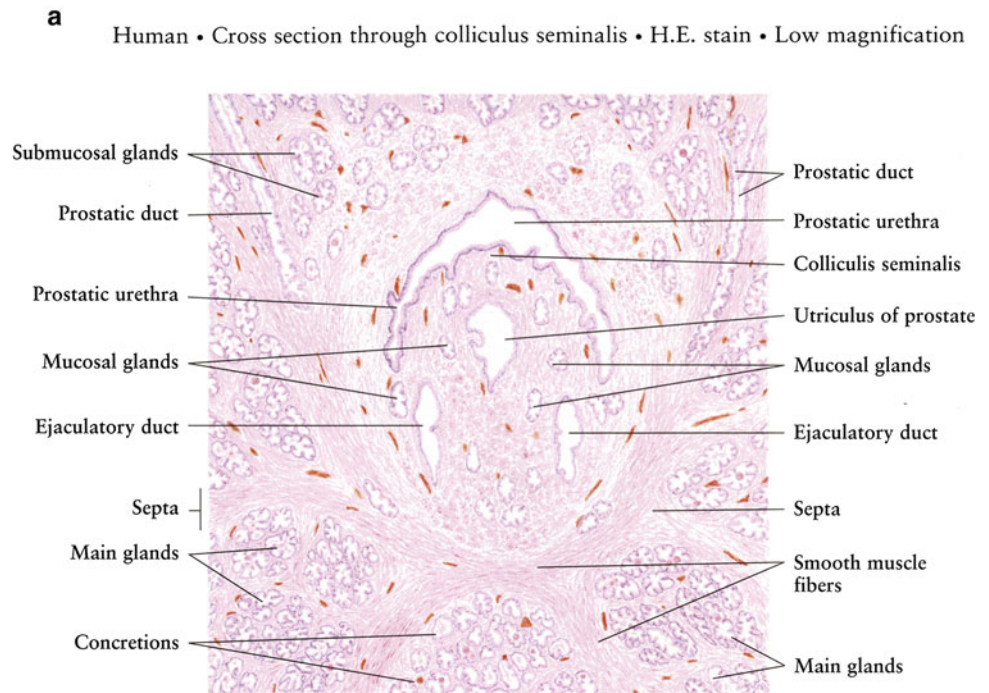
The anatomy of the pelvic floor is challenging to visualize on CT or MRI, and hence definition of the penile bulb varies. This may contribute to inconsistent reports (5–15). The penile bulb appears as an oval-shaped, hyperintense midline structure on T2-weighted MR images; on axial CT imaging it is bounded by the crura, corpora spongiosum, and the levator ani muscle. At University of California-San Francisco, the bulb is defined as the most proximal portion of the penis sitting immediately caudal to the prostate.

2.2 Histology

2.2.1 Prostate Gland

Many excellent textbook references are available with detailed descriptions of the histology of the organs of the distal male genitourinary tract (McAninch 2008; Bostwick 1998). Several cellular subtypes are evident upon histologic examination of the prostate, including basal, secretory, neuroendocrine, urothelial, and ejaculatory duct cells (Fig. 3a, b). Under the thin fibrous capsule of the prostate are smooth muscle layers and layers of collagen which also surround the prostatic urethra, forming the involuntary sphincter. Deeper to this layer is the prostatic stroma, which encases the glandular compound tubuloacinar secretory units, numbering 30–50. These units are arranged concentrically into three groups based on their relationship to the

Fig. 3 Histology **a** Prostate
gland. **b** Prostate gland: Acini
c Penis **d** Penis corpus
cavernosum (with permissions
from Zhang 1999)

a Human • Cross section through colliculus seminalis • H.E. stain • Low magnification

Submucosal glands
Prostatic duct
Prostatic urethra
Mucosal glands
Ejaculatory duct
Septa
Main glands
Concretions

Prostatic duct
Prostatic urethra
Colliculis seminalis
Utriculus of prostate
Mucosal glands
Ejaculatory duct
Septa
Smooth muscle fibers
Main glands

b Human • H.E. stain • High magnification

Concretion
Lumen
Smooth muscle fibers in connective tissue

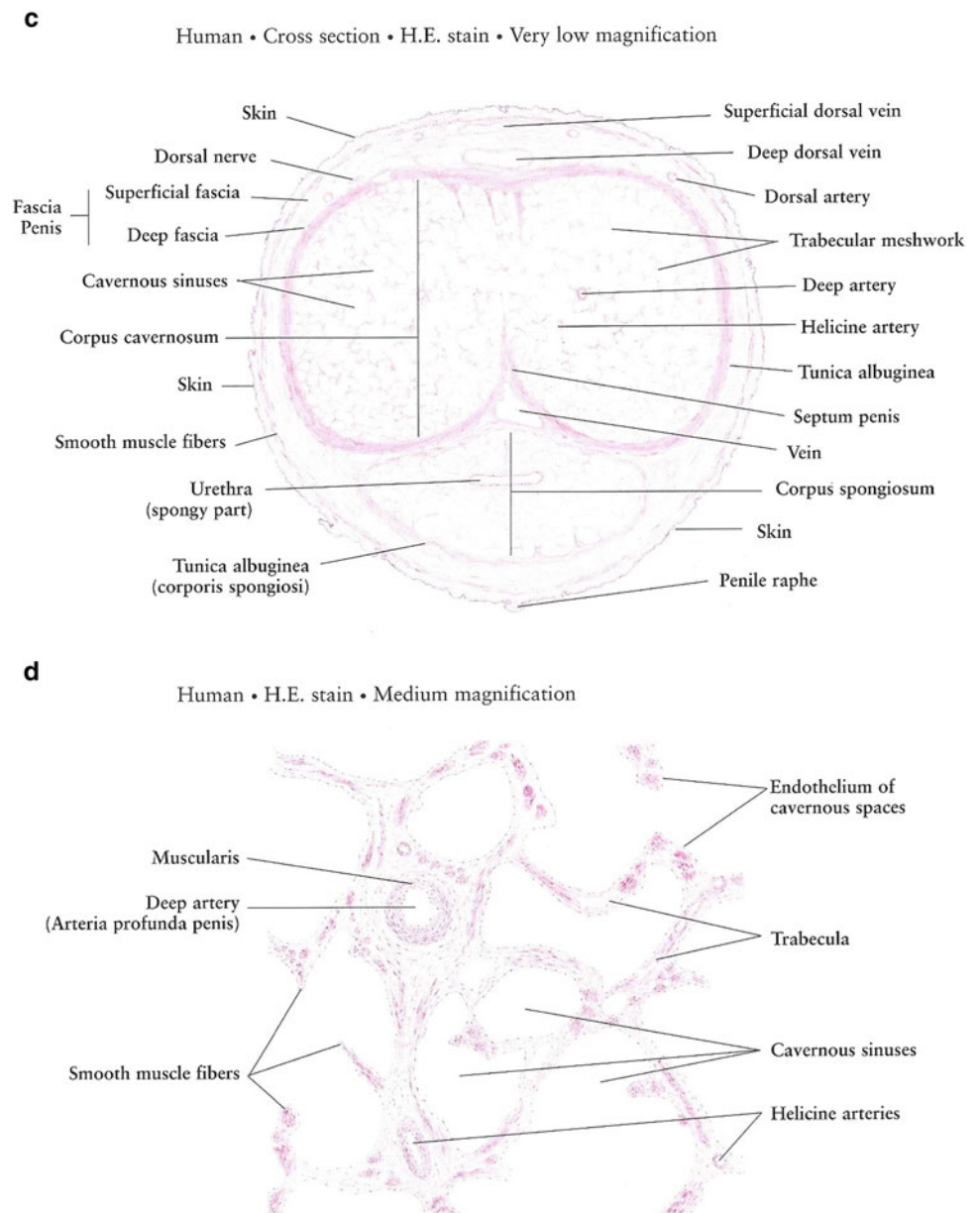Simple (glandular) epithelium
Capillaries
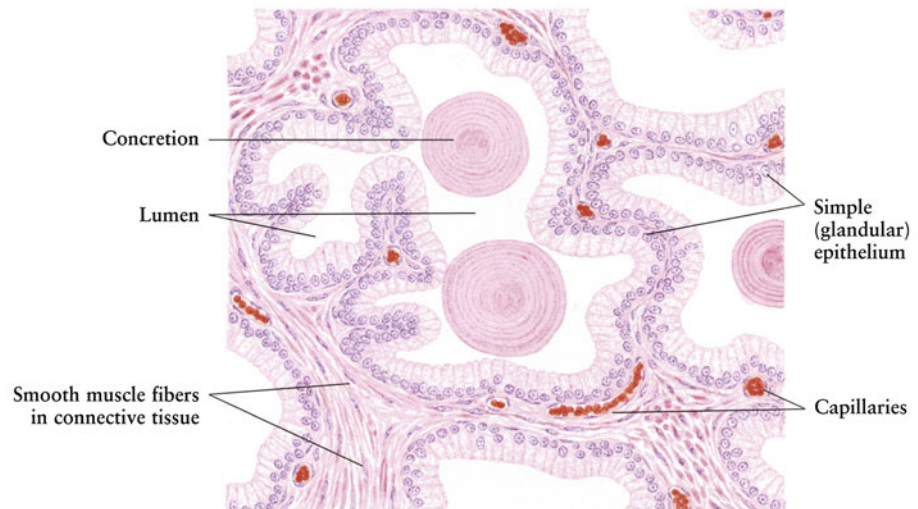
urethra. The majority of these ducts open on the floor of the prostatic urethra near the verumontanum. The main group is farthest from the urethra and constitutes the largest in number. The mucosal and submucosal glands, along with their adjacent stroma, undergo hyperplastic change with age, leading to compression of the urethra and symptoms consistent with benign prostatic hyperplasia (BPH).

The glandular acini are highly redundant and are lined by two layers of cells: a luminal layer of tall columnar cells and a layer of cuboidal cells adherent to the underlying basement membrane. Between prostatic glands is

fibromuscular stroma containing smooth muscle, collagen, and elastic fibers. In parenchymal portion, glands consist of a simple high cuboidal/low columnar epithelium.

2.2.2 Seminal Vesicles

Histologically, each seminal vesicle consists of a single coiled tubular structure that forms a large irregular lumen with many mucosal folds. The epithelium is composed of mixed columnar and pseudostratified columnar cells with mucosal crypts generated by infoldings of the mucosa. It is surrounded by two muscular layers that contract to create

Fig. 3 (continued)

c

Human • Cross section • H.E. stain • Very low magnification

Skin — Superficial dorsal vein
Dorsal nerve — Deep dorsal vein
Superficial fascia — Dorsal artery
Fascia Penis
Deep fascia — Trabecular meshwork
Cavernous sinuses — Deep artery
Corpus cavernosum — Helicine artery
Skin — Tunica albuginea
Smooth muscle fibers — Septum penis
Vein
Urethra (spongy part) — Corpus spongiosum
Skin
Tunica albuginea (corporis spongiosi) — Penile raphe

d

Human • H.E. stain • Medium magnification

Endothelium of cavernous spaces
Muscularis
Deep artery (Arteria profunda penis)
Trabecula
Cavernous sinuses
Smooth muscle fibers
Helicine arteries

positive pressure to move secretions through the lumen and into the ejaculatory duct. The duct of each seminal vesicle combines with the ductus deferens to form the ejaculatory duct.

2.2.3 Urethra

Deep into the superficial urethral mucosa is the submucosa which contains smooth muscle, elastic tissue, and other stromal elements. The superficial histology of the urethra is dependent on its anatomic subsection. In the prostatic portion, it is lined with transitional epithelium. In the spongy portion, it contains stratified columnar epithelium until the navicular fossa, where a transition to non-keratinizing stratified squamous epithelium is seen. The lamina propria of the spongy portion of the urethra merges with the surrounding corpus spongiosum.

2.2.4 Penis

In the penis, cavernous bodies are irregular and lined with simple squamous endothelium and contain venous blood. The cavernous spaces of the cavernosa are larger than those of the spongiosum and have thinner stromal trabeculae, allowing the cavernosa to become more turgid than the corpus spongiosa when the penis is tumescent. (Fig. 3c, d).

2.2.5   Penile Bulb

The penile bulb consists of corpus cavernosum and responds during sexual arousal becoming distended, and is the base of the penis when erect.

3   Physiology and Biology

3.1   Physiology

The actively secreting prostate ductal areas contain pseudostratified columnar epithelium, while ducts with less secretory activity demonstrate simple columnar or high cuboidal epithelial cells. Within some ductal lumens are prostatic concretions, also called corpora amylacea, which are of uncertain physiologic significance. These concretions become more numerous with age and often calcify.

3.1.1   Prostate

The prostate gland is arranged in three concentric groups: 1. Main, one-half glandular; 2. Submucosal, one-fourth fibrous tissue; 3. Mucosal, one-fourth involuntary muscle (Fig. 4).

The prostate gland is influenced by the male sex hormones, i.e., testosterone and adrenal androgens which are converted into dihydrotestosterone (DHT) which is $30 \times$ more potent that testosterone. The DHT stimulates growth of the normal prostate glandular epithelium. The prostate gland secretes prostate acid phosphatase and prostate-specific antigen (PSA) which are incorporated into seminal fluid of which only a small fraction enters circulating blood (i.e. 4 Ng/ml). As the prostate enlarges and undergoes malignant transformation, PSA increases to >4 Ng/ml and serves as a biomarker for cancer increasing to 4.0–10.0 Ng/ml. In addition the prostate gland secretes prostatic acid phosphatase (PAP), an enzyme that regulates prostate cell growth and metabolism of the glandular epithelium. The fibronolysin in the secretions liquefies semen.

3.1.2   Seminal Vesicles

Seminal vesicle secretions consist largely of prostaglandins (accounts for the name of prostate gland) which during ejaculation discharges its secretions and assists in flushing out the semen through the urethra.

3.1.3   Urethra and Penis

During its erectile stage due to filling of its vascular spaces, allows for penetration of the vagina and its ejaculate of semen via the urethra, initiates the fertilization of the ovum (Fig. 4).

3.1.4   Penile Crura: Sexual Performance

Male sexual performance consists of specific sequence of events (Fig. 4):

Sexual arousal → libidinous desire → erection → ejaculation → orgasm → detumescence

- Sexual arousal and libido are multifactorial and depend on the sex partner and level of testosterone. Arousal sensation via pudendal nerve S_2–S_4 somatic fibers).
- Erection occurs with pelvis splanchnic (S_2–S_4 parasympathetic) innervations, penile vasodilatation of corpora cavernosum, and spongiosum-dependent patent inferior vesicle arteries and arterioles and mediate veno-occlusion, entrapping blood in penis to allow for vaginal penetration.
- Ejaculation and orgasm via sympathetic via nerves.
- Detumescence results with vasoconstriction of arterioles, diverting blood from corpora cavernosum and spongiosum into the periprostatic venous plexus via dorsal vein of the penis, via alpha-adrenergic receptor activation.

3.2   Biology

3.2.1   Prostate

The ducts of the prostate functional units empty into the prostatic urethra. The secretory elements (ducts) are surrounded by smooth muscle and connective tissue that separate the secretory units. Prostatic secretions are expelled into the urethra and join other components of the seminal fluid when these smooth muscle units contract. Prostatic secretions are alkaline (pH 6.5) and serous, containing acid phosphatase, carbohydrates, lipids, lipofuscin, hormones, citric acid, amylase, and fibrolysin, which act to liquefy the seminal fluid.

Late histologic changes in irradiated benign prostate ducts include variable ductal atrophic change, cytologic and nuclear atypia, basal cell hyperplasia, increased foreign body giant cell reaction to corpora amylacea, nuclear pleomorphism, nuclear vacuolation, hyperchromatic DNA, and presence of prominent nucleoli. Several metaplastic changes have been noted, including mucinous metaplasia, squamous metaplasia, and Paneth-like cell change. There is no significant difference in the histologic appearance of irradiated benign glands when the patients are treated with androgen deprivation therapy (Gaudin et al. 1999; Magi-Galluzzi et al. 2003). The surrounding stromal cells also undergo chronic inflammatory processes. The molecular and cellular mechanisms underlying this chronic inflammatory change are well described. Briefly, after the initial insult of radiation therapy, a cascade of inflammatory mediators is initiated including TNF-alpha, interleukin-1, and interleukin-6 (Haase 2004; Bentzen 2006). In the later phases of fibrosis, TGF-beta and PDGF, among others, simulate the proliferation of fibroblasts and the synthesis or extracellular matrix constituents and MMPs. Connective
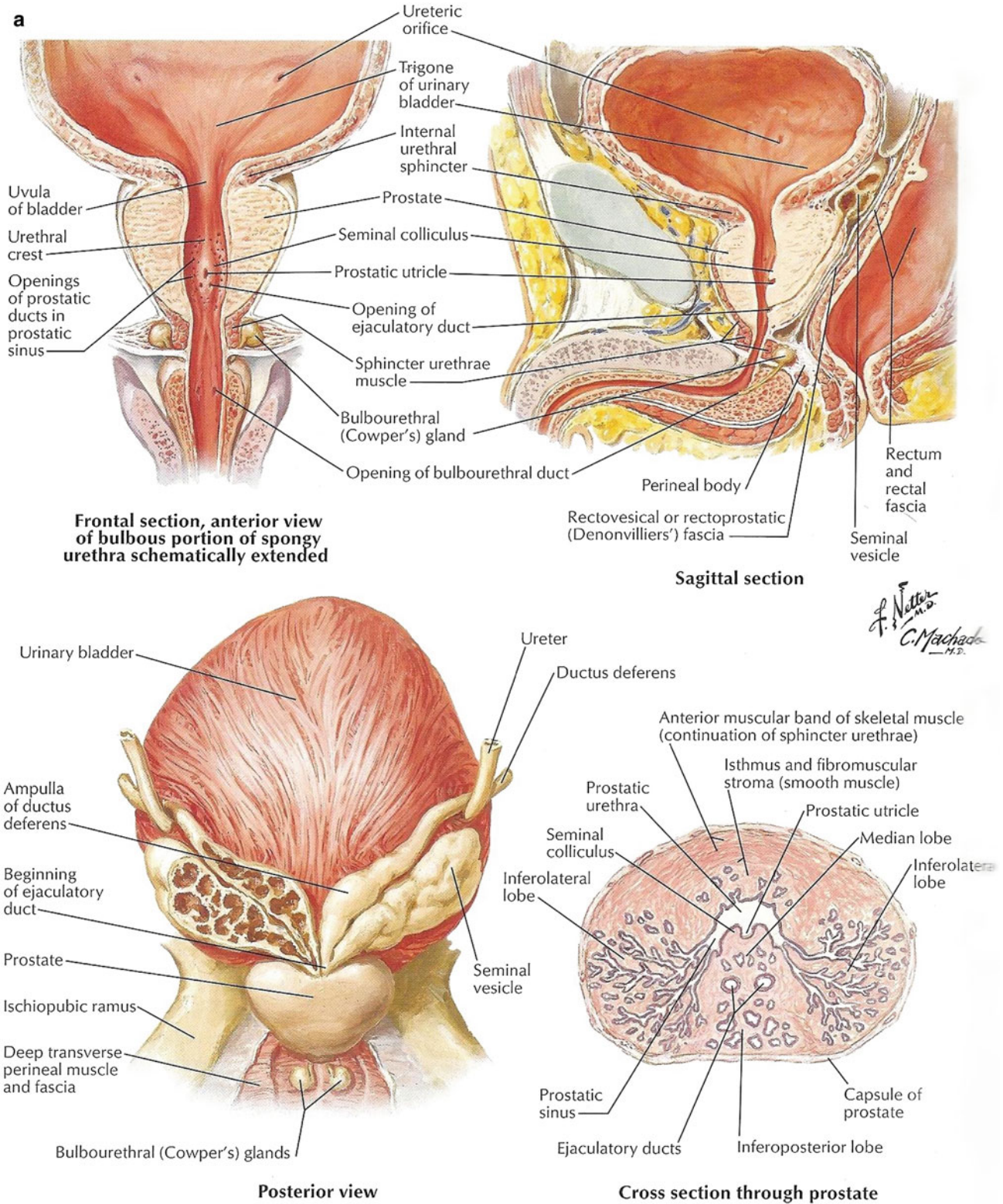
Fig. 4 Physiology of prostate (**a**) Urethra and penis (**b**) Penile Crura: sexual performance (**c**) (with permission from Netterimages.com)
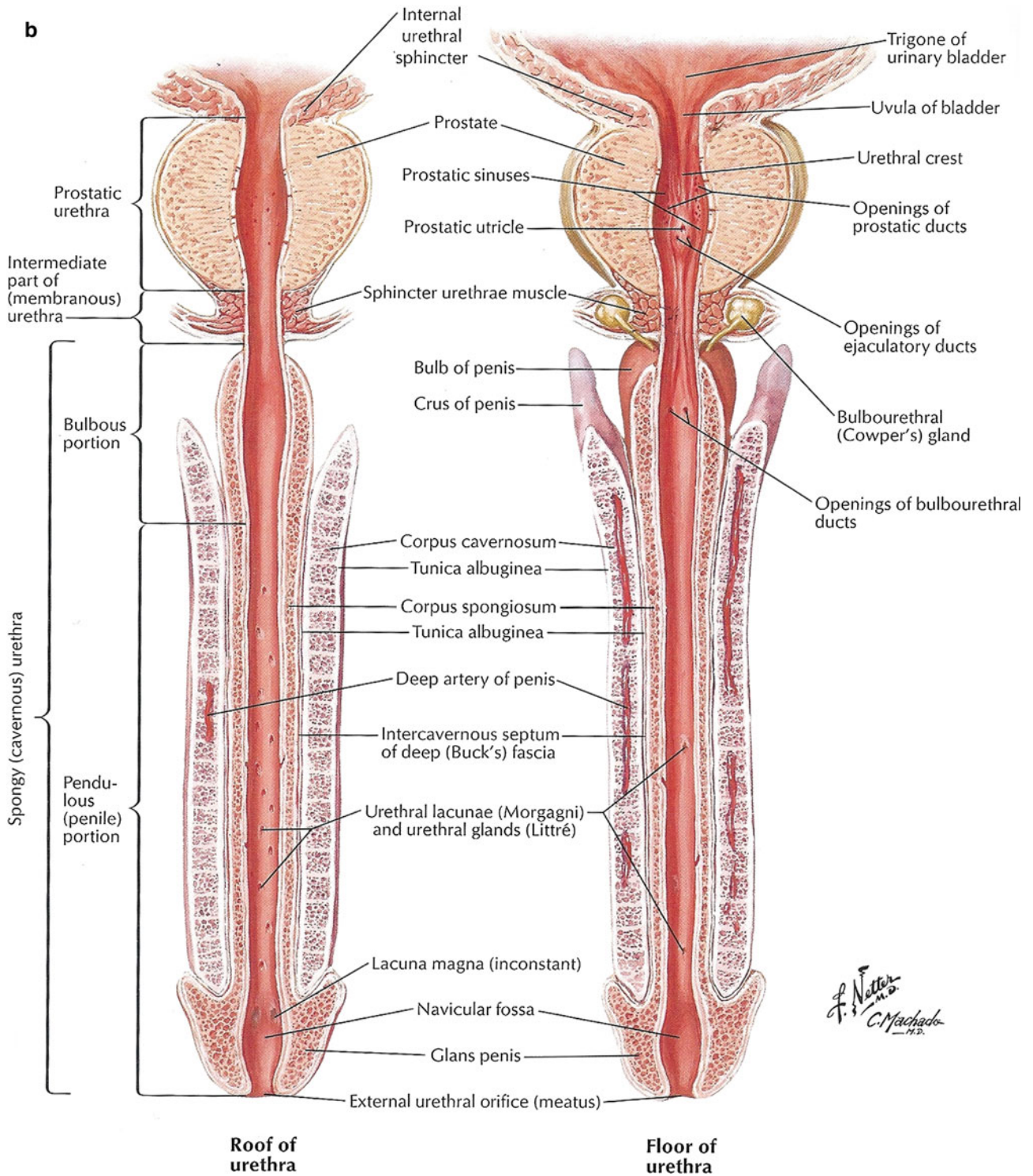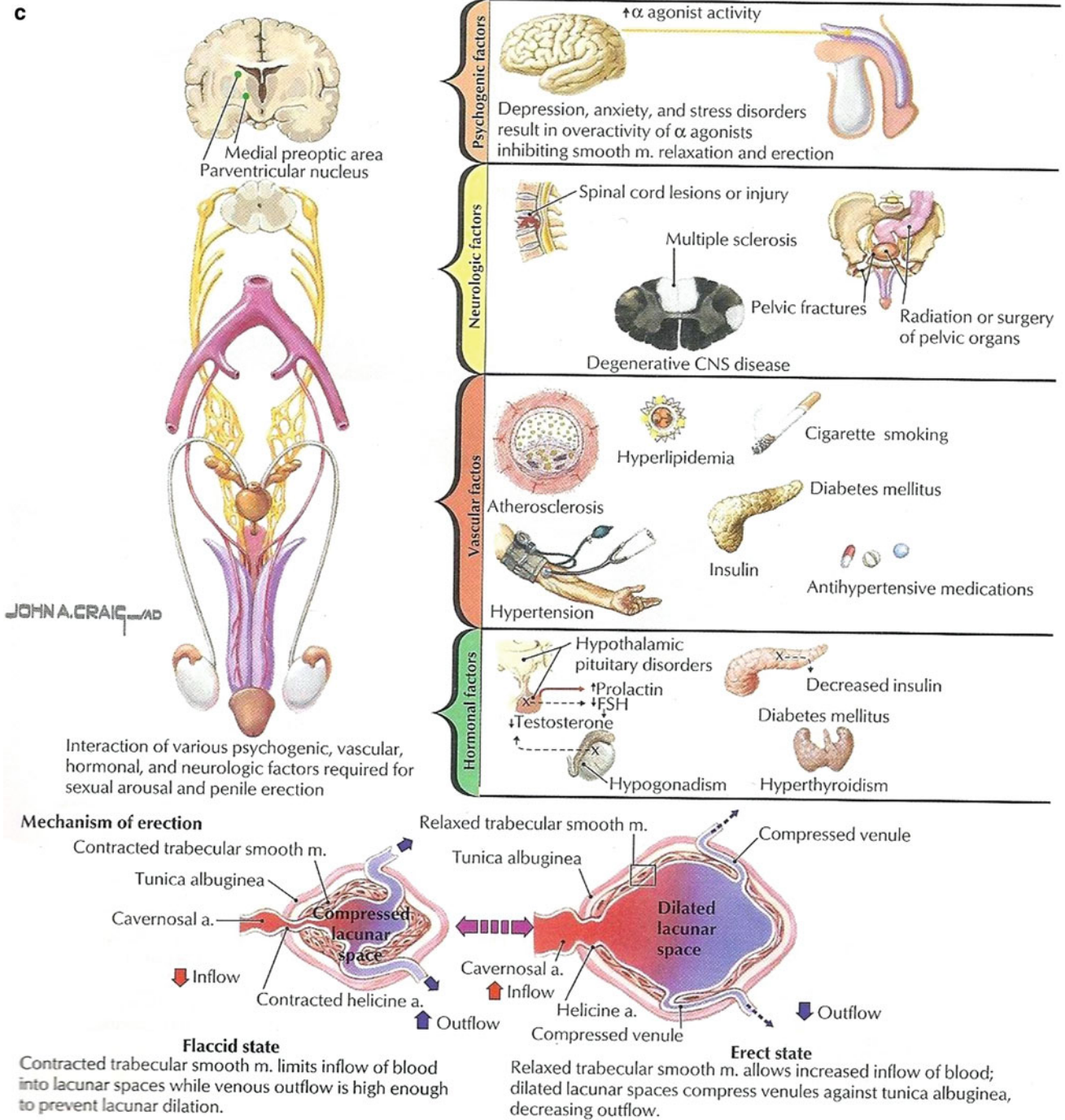
b

Internal urethral sphincter

Trigone of urinary bladder

Uvula of bladder

Prostate

Prostatic urethra

Prostatic sinuses

Urethral crest

Openings of prostatic ducts

Prostatic utricle

Intermediate part of (membranous) urethra

Sphincter urethrae muscle

Openings of ejaculatory ducts

Bulb of penis

Bulbous portion

Crus of penis

Bulbourethral (Cowper's) gland

Openings of bulbourethral ducts

Corpus cavernosum

Tunica albuginea

Corpus spongiosum

Tunica albuginea

Spongy (cavernous) urethra

Deep artery of penis

Intercavernous septum of deep (Buck's) fascia

Pendu-lous (penile) portion

Urethral lacunae (Morgagni) and urethral glands (Littré)

Lacuna magna (inconstant)

Navicular fossa

Glans penis

External urethral orifice (meatus)

Roof of urethra

Floor of urethra

Fig. 4 (continued)

c

Medial preoptic area
Parventricular nucleus

JOHN A.CRAIG—AD

Interaction of various psychogenic, vascular, hormonal, and neurologic factors required for sexual arousal and penile erection

Psychogenic factors

↑α agonist activity

Depression, anxiety, and stress disorders result in overactivity of α agonists inhibiting smooth m. relaxation and erection

Neurologic factors

Spinal cord lesions or injury

Multiple sclerosis

Pelvic fractures

Radiation or surgery of pelvic organs

Degenerative CNS disease

Vascular factors

Hyperlipidemia

Cigarette smoking

Diabetes mellitus

Atherosclerosis

Insulin

Antihypertensive medications

Hypertension

Hormonal factors

Hypothalamic pituitary disorders

↑Prolactin
↓FSH
↓Testosterone

Decreased insulin

Diabetes mellitus

Hypogonadism

Hyperthyroidism

Mechanism of erection

Contracted trabecular smooth m.

Tunica albuginea

Cavernosal a.

Compressed lacunar space

↓Inflow

Contracted helicine a.

↑Outflow

Flaccid state
Contracted trabecular smooth m. limits inflow of blood into lacunar spaces while venous outflow is high enough to prevent lacunar dilation.

Relaxed trabecular smooth m.

Compressed venule

Tunica albuginea

Dilated lacunar space

Cavernosal a.

↑Inflow

Helicine a.

Compressed venule

↓Outflow

Erect state
Relaxed trabecular smooth m. allows increased inflow of blood; dilated lacunar spaces compress venules against tunica albuginea, decreasing outflow.

Fig. 4 (continued)

tissue growth factor (CTGF) further promotes fibrotic change (Vozenin-Brotons et al. 2003).

3.2.2 Seminal Vesicles

The seminal vesicles produce a viscous fluid containing high amount of fructose that nourishes the sperm. Other components include simple sugars, amino acids, ascorbic acids, and prostaglandins.

4 Pathophysiology

4.1 Prostate Gland

Several publications have documented the effects of various modalities of radiation therapy on prostatic tissues (Bostwick et al. 1982; Gaudin et al. 1999; Sheaff and Baithun 1997). In general, radiation changes are similar in patients receiving external beam radiation and brachytherapy, although the brachytherapy-associated changes may be more marked (Magi-Galluzzi et al. 2003).

Early histologic changes in the irradiated prostate, seen after several weeks, include nuclear contraction, signs of cytoplasmic injury, and small areas of early necrosis. These areas of injury and necrosis initiate the well described processes of acute inflammation, where polymorphonuclear cells, macrophages, and lymphocytes are recruited in a characteristic chronological pattern. As treatment progresses, a mixed acute-late inflammatory histology appearance predominates that gradually gives way to fibrotic change once radiation treatment has been completed.

Recruitment of cells typically involved in the chronic inflammatory process is also evident. Specifically, macrophages are seen in the early phase of fibrosis, which chemically recruit fibroblasts, which in turn transform to fibrocytes. Additionally, vascular changes are noted, including endothelial cell damage, intimal hyperplasia, marked arterial luminal narrowing, arterial medial thickening, cytoplasmic swelling, hyaloid changes of the capillary wall, and thinning of the capillary network (Sheaff and Baithun 1997; Herrmann 2006).

Prostate cancer cells respond differently than benign prostate cells after radiation therapy has been administered. This response, although characteristic, is quite variable, ranging from significant treatment-related changes to no apparent change after radiation therapy (Gaudin et al. 1999). Prostate cancer cells with no evident effect had an appearance similar to pre-treatment specimens. Prostate cancers with profound radiation changes demonstrated several characteristic morphologic changes including a decrease in the number of neoplastic glands, with residual glands in a more irregular morphology and some individual scattered cells not associated with glands. The cells demonstrated abundant cytoplasm with vacuolated and reticulated changes but little nuclear pleomorphism. In contrast to radiation changes in benign prostate tissues, radiation changes in prostate cancer cells were not associated with nuclear pleomorphism or prominent nucleoli. Furthermore, benign glands with radiation changes were extremely reactive to immunohistochemical stains for cytokeratin 34[beta]E12 and had a variable staining pattern to antibodies specific for prostate-specific antigen (PSA), while cancerous glands with radiation changes were not reactive to cytokeratin 34[beta]E12 were intensely immunoreactive for PSA. Additionally, while benign glands tended to maintain a lobular architecture, cancerous areas are arranged in a random, infiltrative morphology.

Part of the issue in determining the effects of irradiation of the prostate gland is the presence of a prostate cancer, which is the most common reason to treat the gland. Initially, following 60–70 Gy doses, necrosis of the cancer cells occur. Months to years later, the glandular epithelium are reduced in size and becomes atrophic and are replaced by fibrosis. The residual glands appear as "pale ghosts," the columnar epithelium changes to cuboidal with pyrokinetic nuclear squamous metaplasia form irregular islands surrounded by dense fibrosis, foreign body giant cell reactions around corpora amylacea. Vascular changes are quite severe with obliteration of arterioles with internal forming cells.

Despite these characteristic changes, histopathologic interpretation of biopsies of a patient treated with radiation therapy is fraught with difficulty (Bostwick 1982). The risk of misinterpretation is that benign radiation changes will be mistaken for prostate cancer. In general, rebiopsy after radiation treatment (Fig. 5a–d) is reserved for the setting of a rising PSA after treatment when an isolated local recurrence is suspected and salvage brachytherapy or surgery is being considered. The presence of malignant cells in the biopsy specimen after radiation therapy should not be automatically interpreted as treatment failure. Prostate cancer cell death is a post mitotic event in a cancer with a long potential doubling time, meaning that regression of viable cancer is evident to at least 3 years after treatment (Crook et al. 2000). Furthermore, nearly 50 % of men with positive biopsies after brachytherapy and a short course of external beam treatment had viable cancer cells on planned repeat biopsy. Interestingly, only 27 % of these men experienced a biochemical failure (Goldstein 1998). Prestidge et al. reported serial post-treatment biopsies have demonstrated that a higher number of indeterminate biopsies after treatment eventually become negative after brachytherapy treatment (Prestidge et al. 1997). In general, if radiation biopsies show profound treatment effect in the adenocarcinoma, these patients are unlikely to fail therapy.

Fig. 5 Post-RT histologic changes in the prostate gland. **a** Postradiation (∼7000 cGy) squamous metaplasia in non-neoplasic prostatic glands with mild cytologic atypia. H&E, ×192. **b** Foreign body giant cell reaction around corpora amylacea 26 months after irradiation. No resudial epithelium can be recognized. H&E, ×192. **c** Well-differentiated adenocarcinoma in the lower field contrasting with normal glands in the upper field prior to radiation. Compare with (**d**), obtained 30 months after irradiation with ∼7000 cGy (same magnification): there is no residual carcinoma, and the field displays extensive stromal fibrosis. The remaining, nonneoplastic glands show atrophy and extensive squamous metaplasa. H&E, ×192 (with permission from Fajardo 2001)
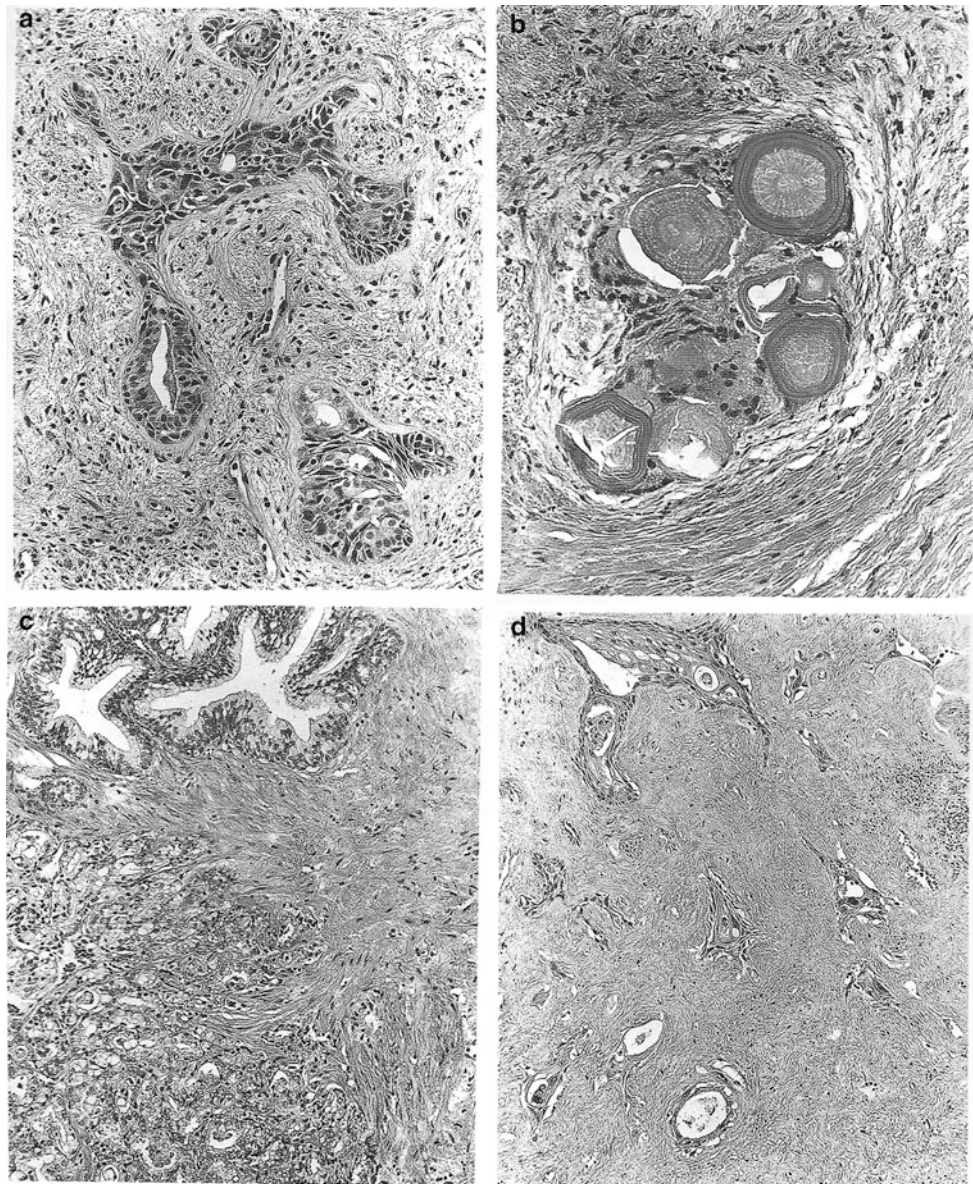
There are also histological changes from the use of androgen deprivation therapy alone. Androgen stimulation is an important component of normal prostate metabolism. 90–95 % of circulating testosterone is made by the testes, with the remainder produced by the adrenal glands. In the prostate gland, testosterone is converted into dihydrotestosterone by alpha-5-reductase. Dihydrotestosterone stimulates growth of both normal prostate tissue and prostate adenocarcinoma cells. When androgen deprivation is administered, consistent effects can be seen regardless if combined androgen blockade (LHRH agonist and peripheral androgen receptor blocker) or anti-androgen monotherapy (LHRH agonist alone) is used. Degenerative phenotypes are noted, including nuclear pyknosis, and vacuolization of the cytoplasm (Tetu 1991; Armas 1994).

Furthermore, androgen deprivation also suppresses the histological changes commonly used to diagnose adenocarcinoma, such as increased nuclear size, nuclear pleomorphism, and prominent nucleoli. Therefore, care must be taken in the histological evaluation of patients who have received androgen deprivation therapy prior to prostate biopsy because there is a risk of underestimating both tumor extent and Gleason score. Rigorous examination of the specimen for scant individual malignant cells and special immunohistochemical stains are essential in this clinical situation (Vernon 1983).

In addition to the above commonly used strategies of androgen blockade, other agents, such as estrogens and 5-alpha reductase inhibitors also cause histological changes in normal and malignant prostate cells. The effect of

estrogen administration on prostate histology is mainly of historical interest, as estrogens are not commonly used in contemporary treatment algorithms. However, estrogens induce the above changes seen with modern anti-androgen regimens and further cause a unique effect of squamous metaplasia in benign and malignant prostate cells (Schenken 1942; Franks 1960). Finasteride and dutasteride block the conversion of testosterone to dihydrotestosterone in the prostate gland by inhibiting 5-alpha reductase and are used in a variety of clinical situations including BPH and androgenetic alopecia. Their use has been found to have minimal influence on prostate cancer cells and does not typically interfere with pathologic diagnosis or the prognosis of Gleason grade (Yang et al. 1999; Carver et al. 2005; Iczkowski et al. 2005). These agents do reduce PSA values by approximately 50 % (Etzioniet al. 2005) and prostate size by about 25 % (Thompson et al. 2003). Furthermore, 5-alpha reductase inhibitors do appear to have the ability to affect the incidence and grade of prostate cancers in men who use them (Andrioleet al. 2005). The most compelling argument for this comes from the Prostate Cancer Prevention Trial, which demonstrated that healthy men treated with 5-alpha-reductase inhibitors had a 24.8 % reduction in the risk of developing prostate cancer. In this cohort, certain risk factors while on finasteride were predictive of Gleason score ≥ 7 disease, including higher absolute PSA values, increasing PSA values, an abnormal digital rectal examination, and older age (Thompson et al. 2003, 2007).

4.2 Seminal Vesicles

Radiation effects on the seminal vesicles are more obvious than in the prostate gland. The normal complex arborizing glands are reduced to narrow cavities with a few branches embedded in dense collagen scoring.

Radiation also causes changes in the urothelium (Antonakopoulos et al. 1982, 1984; Stewart 1986). Irradiated urothelial cells demonstrate changes including nuclear pleomorphism, swollen cytoplasm, and altered labeling indices as compared to non-irradiated urothelial cells. Loss of tight junctions is noted, allowing hypertonic urine access to the interstitial area, leading to chemical fibrotic injury and increasing the probability of bacterial infection and subsequent inflammatory damage. These morphological changes correlate clinically with the onset of irritative urinary symptoms encountered after a course of radiation therapy (Marks et al. 1995). When bulbomembranous urethral strictures are examined histologically, there is an initial ulceration of the urothelium that develops into proliferative changes of stratified squamous epithelium with interposed elongated myofibroblasts and multinucleated

giant cells that produce abundant collagen (Baskin et al. 1993). The myofibroblasts are thought to be a primary causative factor for stricture formation. The ubiquitous stromal changes of radiation therapy are also noted, including obliterative endarteritis, ischemia, and fibrosis.

4.3 Penis and Urethra

Penis and urethra are incidentally irradiated in treating prostate gland cancers. In laboratory rats after single fraction doses of 1,000 and 2,000 cGy, after 5 months, the animals had impaired responses to central and peripheral stimulation, at both doses, increased with the higher dose; the number of nerve fibers positive for nitric oxide synthase.

In each penile segment decreased significantly by approximately 25 % compared to control. The mechanism for radiation-induced erectile dysfunction was attributed to defective vascularity of penile tissues as well as peroneal nerves and smooth muscle.

5 Clinical Syndromes (Endpoints)

Patients undergoing radiation to the distal male GU tract are at risk for developing both acute and late genitourinary, gastrointestinal, and sexual toxicities. Acute toxicities are attributable to effects from acute inflammation, while late toxicities are usually attributable to radiation-induced fibrosis, vascular damage, and altered patterns of vasculature. Late effects of radiation are particularly multifactorial, being affected by comorbidities, genetic factors, and other cancer treatments in addition to radiation-related variables such as total dose, dose per fraction, fractionation schedule, and dose–volume parameters. With modern teletherapy techniques such as intensity modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), in addition to improvements in brachytherapy, the overall morbidity of external beam radiation therapy has been significantly reduced despite higher contemporary prescription doses. The addition of systemic agents, such as cytotoxic chemotherapy or androgen deprivation therapy, may alter the risk of these toxicities (Zelefsky et al. 2000; Valicenti et al. 2003; Liu et al. 2004; Feigenberg et al. 2005; Zapatero et al. 2005; Lawton et al. 2008).

5.1 Sexual Dysfunction after Radiation Therapy

The main sexual side effects of radiation therapy to the pelvis are impotence, decreased libido, decreased ejaculate, and painful ejaculation. Recent reports demonstrate the rate

of radiation-related erectile dysfunction is of the order of 35–55 % (Cahlon et al. 2008; Mantz et al. 1997; Potosky et al. 2000; Hamilton et al. 2001). The process of tumescence is a complex process, depending on afferent cavernous nerves supplying the penis with nitric oxide. Relaxation of the afferent internal pudendal and accessory pudendal arterioles and cavernosal smooth muscle occurs, which allows for filling of the trabecular space. Increased venous resistance prevents outflow, causing trapping of blood, and contraction of the bulbocavernosus and bulbospongiosus muscles further increase intratrabecular space pressure. In general, radiation-induced impotence is thought to manifest within the first 2 years after treatment (van der Wielen 2007). The decline in ability to obtain and maintain erections after therapy has historically been thought to be caused by radiation exposure of tissues involved in the process of tumescence, including the afferent neurovascular bundles, the penile bulb, and the corpora cavernosa (Fisch et al. 2001; Roach et al. 2004; Wernicke 2004). However, a recent publication has demonstrated that radiation-induced erectile dysfunction is mainly due to afferent arterial insufficiency, with only a small percentage of cases due to changes in veno-occlusive capacity (Zelefsky and Eid 1998). Additionally, several publications suggest that doses to structures such as the penile bulb are not predictive of post-therapy impotence (van der Wielen et al. 2007; Hoogeman et al. 2008; Solan 2009). Regardless, modern radiation techniques are able to minimize radiation dose to these tissues that are at risk, including the penile bulb and base of the penis, possibly decreasing the rates of radiation-related erectile dysfunction (Sethi et al. 2003; Buyyounouski et al. 2004). However, sparing the neurovascular bundle with external beam techniques is not yet achievable, given its close proximity to the prostate, need for the appropriate PTV margins to account for interfraction and intrafraction motion, and continuing trends of dose escalation.

5.2   Erectile Dysfunction

The evaluation of radiation-related erectile dysfunction is complex, depending on the method of assessment, toxicity scale used, time since radiation, and radiation technique used for treatment (Rosen et al. 1997; Litwin 1998; Talcott et al. 1998). Additionally, a multitude of other factors can exacerbate post-treatment erectile dysfunction, including existing peripheral vascular disease, diabetes mellitus, smoking history, hypertension, hypercholesterolemia, administration of androgen deprivation therapy, and other medications (Hollenbeck et al. 2004; Goldstein et al. 1984). Androgen deprivation contributes to erectile dysfunction because physiologic amounts of testosterone contribute to sexual desire (O'Carroll 1984), homeostasis of the erectile

apparatus and nerves (Saad et al. 2007), and cavernous vasodilation (Aversa et al. 2000).

The social situation of the patient also has a significant role on sexual function, including the presence or absence of a willing partner and the physiological and emotional impact of cancer diagnosis and treatment on the patient (Goldstein et al. 1984; Fiorino et al. 2009). Furthermore, independent of a diagnosis of cancer, loss of erectile function is common in men between 40- and 69-years old, with up to 26 out of every 1,000 men developing ED each year (Johannes et al. 2000). It is therefore difficult, if not impossible, to define the radiation parameters clearly causing sexual dysfunction and the time frame in which they manifest after treatment.

It is recommended by Quantec authors that patients undergo pre- and post-RT assessment of ED using the IIEF. Patients can be grouped into five groups according to their scores; for example, in none (D'Amico et al. 2004; Chen et al. 2001; van der Wielen et al. 2007; Goldstein et al. 1984), mild (Macdonald et al. 2005; Merrick et al. 2002; Zelefsky et al. 1999; Weber et al. 1999; Rosen et al. 1999), mild to moderate (Wallner et al. 2002; Zelefsky et al. 2006; Wernicke et al. 2004; van der Wielen et al. 2008; Skala et al. 2007), moderate (Selek et al. 2004; Roach et al. 2004; Pinkawa et al. 2009a, b; Mangar et al. 2006), and severe (Fisch et al. 2001; Cahlon et al. 2008; Brown et al. 2007). It is important that the evaluation of ED is performed with a detailed history including sexual, medical, and psychosocial status and other laboratory tests (Rosen et al. 1997, 1999; Kratzik et al. 2005; Rosenberg 2007). Further clinical studies may be needed to validate the IIEF for the assessment of ED after RT.

5.3   Acute and Late Effects from Penile Radiation

The main acute toxicity of irradiation of the penis is the skin reaction (see "Thyroid"). However, some relevant radiation-specific literature is available on this topic and merits discussion (Crook et al. 2009, 2010). After interstitial penile brachytherapy, moist desquamation appears to be the only significant acute toxicity, peaking 2–3 weeks after treatment and taking several months to heal. Patients are also at risk for acute post-treatment adhesions which usually present with a split or deviated urine flow from the meatus. Common late complications include penile soft tissue necrosis and urethral stenosis, which occurs in about 10 % of men treated with interstitial penile brachytherapy for squamous cell carcinoma (Crook et al. 2009). Soft tissue necrosis usually appears as an area of progressive ulceration that typically takes place 6–18 months after brachytherapy (Delannes et al. 1992). Ulcerations leading to necrosis can

be exacerbated by thermal injury or traumatic episodes to the penis, including biopsy. Radiation-induced penile urethral strictures occur between 1 and 3 years after treatment and can present with altered urodynamics, divergent stream, pain, or hematuria. The skin can also undergo chronic atrophic change after treatment, including thinning of the dermis and epidermis, formation of irregular pigmentation patterns with gain or loss of natural pigment, increased skin sensitivity or pain, and formation of teleangectatic vessels.

5.4   Radiation-Induced Urinary Incontinence

Following RT for prostate cancer, the rate of RT-induced urinary incontinence is of the order of 1–4 % in men who have no history of invasive prostatic procedures (Talcott et al. 1998; Potosky et al. 2000; Hamilton et al. 2001). This rate increases when the patient undergoes surgical procedures to the prostate gland before or after radiation treatment. Furthermore, a history of intercurrent illness, especially diabetes mellitus, increases the risk of late GU toxicity. Investigators at Fox Chase Cancer Center found that diabetics treated with three-dimensional conformal radiation therapy for prostate cancer had increased rates of late Grade 2 GU toxicity (Herold et al. 1999). Additionally, they reported that diabetics had an early onset of late toxicity (median 10 months versus 20 months for non-diabetics).

In limited circumstances, radiation therapy can cause chronic improvement in urinary function. Specifically, reports of improved urinary function and quality of life have been noted in patients with significant pre-treatment irritative or obstructive symptoms (Chen et al. 2009). The proposed mechanism for these improvements is a radiation-induced reduction in prostate volume (Coia et al. 1995).

5.5   Fecal Incontinence

Although rare, radiation-induced fecal incontinence profoundly effects quality of life. Two large, modern studies have demonstrated that the chance of using pads of fecal incontinence at any time after treatment is approximately 10 % and the probability of needing regular use of pads after 2 years of treatment is approximately 3 % (Peeters et al. 2006c; Fiorino et al. 2008). Profound incontinence is even rarer, with the chance of needing multiple pads per week years after treatment is less than 1 %. Fecal incontinence is thought to be multifactorial. Contributing factors probably include decreased absorptive capacity of irradiated rectal mucosa, chronic inflammatory changes leading to urge incontinence, neurovascular damage to the afferent nerves controlling the anal sphincter, and direct muscle damage to the sphincter itself. Prior abdominal or anorectal surgery or trauma increases the probability of fecal incontinence after treatment (Peeters et al. 2006c; Fiorino et al. 2008).

When the endpoint of fecal incontinence is considered, there is also a strong correlation of clinical endpoint with dose–volume parameters (Peeters et al. 2006c; Fiorino et al. 2008). Unlike late rectal bleeding, where the high dose regions are most predictive, it appears that a large volume of rectum receiving an intermediate dose is most predictive of late fecal incontinence. Fiorino prospectively studied a cohort of over 500 patients and found that there was less than 1.5 % probability of late fecal incontinence requiring pads when V40 < 65 %. Peeters essentially confirmed this finding. Furthermore, the location of radiation exposure also predicts for late fecal incontinence. Several authors have reported that inclusion of large portions of the distal rectum, including the anorectum, predisposes that patient to late rectal bleeding (Vordermark et al. 2003; al-Abany et al. 2004; Heemsbergen et al. 2005). Modern IMRT and 3D-CRT techniques have obviated the need to include large portions of the anorectum in the treatment field and should yield decreases in incontinence rates. See " Radiation Induced Rectal Toxicity" for further discussion of this issue.

5.6   Diagnosis

5.6.1   Atrophy

Irradiation of the prostate gland leads to interstitial fibrosis. Atrophy and calcifications can be seen on CT and MR images (Fig. 6a, b). Radiation changes are also seen in the seminal vesicles, which lose volume and demonstrate low T2-weighted signal intensity on MR images after radiation. The prostatic and membranous urethras are very sensitive to radiation. The irradiated urethral tissue often develops strictures.

5.6.2   Persistence of Cancer

As aforementioned in the pathophysiology section, a vexing issue is persistence of cancer cells, the same is true for follow-up assessment by serial MRIs in follow-up. Comparing pre- to post-RT MRIs might be helpful in this regard, as is MR spectroscopy. Figure 6c illustrates an example of the utility of MR spectroscopy in defining tumor in the prostate.

Fig. 6 Imaging changes in the prostate gland. **a**, **b** T2-weighted MR images of the prostate. The zonal anatomy is indistinct (compared to a normal untreated gland), and the peripheral zone shows low signal intensity. **c** Images from a patient with stage T2 adenocarcinoma of the prostate: fast spin-echo T2-weighted axial endorectal magnetic resonance (MR) spectroscopic image through the midgland. Prostate carcinoma appears as an area of abnormal low signal intensity (C) in the normally high signal intensity peripheral zone (N). MR spectra from the area of carcinoma (C) in the right peripheral zone demonstrates abnormal elevation of the choline peak and an abnormally low citrate peak. In comparison, MR spectra from an area of normal peripheral zone (N) demonstrates a normal high citrate peak and a normal low choline peak. Tumor in the right peripheral zone demonstrates contact with a smooth and apparently intact prostatic capsule. Postradiation changes in the prostate. This patient underwent radiation therapy for prostate cancer. The axial (**a**) and the coronal (**b**) T2-weighted fast spin echo magnetic resonance images show a small, feature gland with a dark peripheral zone indicative of radiation changes in the prostate (with permission from Bragg et al. 2002)
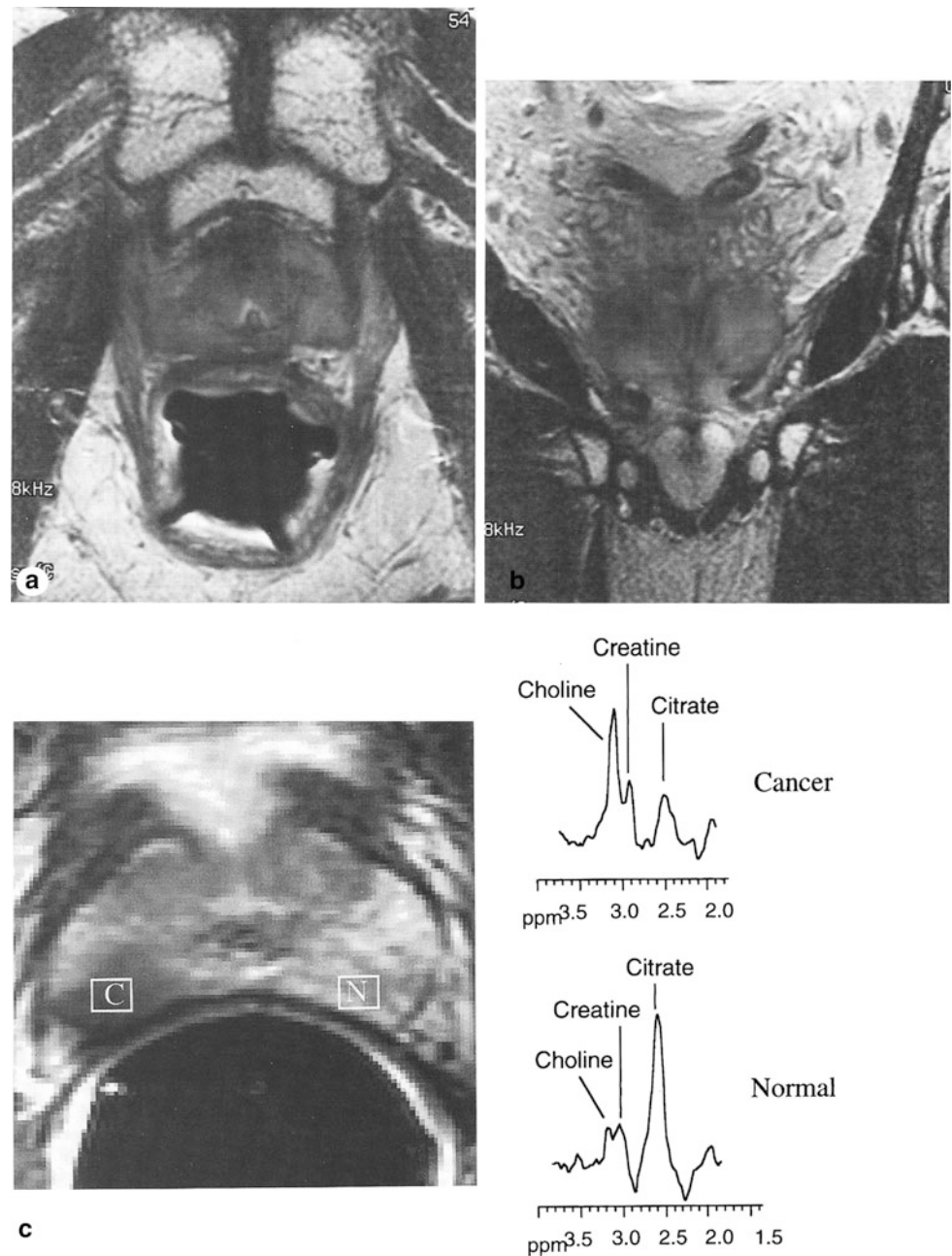
6   Dose, Time, Fractionation: Radiation Tolerance, Predicting RT-Induced Injury and Recommended Dose–Volume Constraints

Since Burman et al. (1991) reported on the modeling of dose–volume effects based on clinical outcomes from the 2D era, the advent of increasingly advanced radiation technologies has led to careful study of the effect of dose–volume relationships on normal tissues during radiation treatment. A great deal of literature is available examining toxicities from and recommended treatment parameters for radiotherapeutic treatment of pelvic malignancies, including those of the distal male GU tract.

6.1   Rectal Constraints

6.1.1   General Rectal Constraints

Although the rectum is covered in a separate chapter, a discussion of this organ is merited here, as the appropriate dose–volume rectal constraints for prostate cancer radiotherapy is the most published area of normal tissue

tolerance in this malignancy. The reason for this interest in rectal tolerance is clear. Unlike bladder toxicity, late rectal toxicity has been found to be directly and consistently correlated with physical treatment parameters such as dose and volume. Rectal complications are the main late toxicities that limit dose escalation in prostate cancer. General trends can be drawn from the available clinical literature regarding these constraints for conventionally fractionated radiation therapy despite institutional differences in prescribed dose, extent of contouring, radiation techniques, and outcomes measurement. Moderate to severe late rectal effects are dose dependent, occurring in around 25 % of men treated with 78 Gy and 13 % in men treated with 70 Gy (Pollack et al. 2002; Peeters et al. 2006a, b; Zietman et al. 2005). Despite this dose dependency, several reports indicate that careful planning techniques and intensity modulation can mitigate this toxicity and allow dose escalation without excess late GI toxicity (Zelefsky et al. 2002; Beckendorf et al. 2004; Peeters et al. 2006a, b).

Numerous studies have been published with late rectal bleeding as an isolated clinical endpoint with consistent contouring of the rectum. Jackson et al. from MSKCC reported on 171 patients treated with 3D conformal radiation therapy to a dose of 70.2 or 75.6 Gy. They found a significant dose–volume correlation with RTOG ≥ 2 late bleeding and recommended, for the techniques and doses used, V40 < 60 % and, for patients treated with 75.6 Gy, a V77 < 14 % (Jackson et al. 2001). An Italian intergroup published two papers using RTOG ≥ 2 late bleeding endpoints in patients treated in the range of 70–78 Gy and ultimately suggested the following dose–volume constraints: V50 < 60 %, V60 < 45 %, and V70 < 25 % (Fiorino et al. 2002, 2003). The recommendation of V70 < 25 %, using the same endpoint, was independently confirmed by the group at William Beaumont Hospital using adaptive image-guided radiation with prescription doses between 70.2 and 79.2 Gy (Vargas et al. 2005). Peeters et al. found that a V65 > 30 % was highly predictive for late bleeding requiring transfusions or interventional laser coagulation in patients treated between 68 and 78 Gy (Peeters et al. 2006c). When SOMA-LENT Grade ≥ 2 late bleeding criteria was used as the clinical endpoint, recommendations are similar: V50 < 55 %, V60 < 40 %, V70 < 25 %, and V75 < 5 % (Fiorino et al. 2008; Fellin et al. 2009). In addition to these straightforward dose–volume constraints, several groups have generated normal tissue complication probability models and nomograms for late rectal bleeding that are generally consistent with the above studies (Rancati et al. 2004; Söhn et al. 2007; Valdagni Rancati et al. 2008).

Dose–volume constraint recommendations are only slightly altered when all forms of late rectal toxicity are included in outcomes analysis. The MD Anderson group reported on rectal complications from their randomized dose escalation trial and found that the rates of rectal complications were similar in both arms (70 and 78 Gy) but found a significant increase in late rectal complications when V70 > 25 % (Storey et al. 2000a, b; Kuban et al. 2008). When a different subset of patients treated in the same general dose range was evaluated from the same institution, the investigators found that the percentage of the rectum exposed to a certain dose, rather than an absolute volume, was predictive of late rectal toxicities. In this paper, the following recommendations were made: V60 < 40 %, V70 < 25 %, V75.6 < 15 %, and V78 < 5 % (Huang et al. 2002). Analysis of the high dose arm (74 Gy) of RTOG 94-06 yielded a recommendation to keep the V65 < 50 % to keep late rectal toxicity Grade I or less (Michalski et al. 2004). A recent report from MSKCC analyzing 478 patients treated to 86.4 Gy found a 4 % rate of CTCAE 3.0 late rectal toxicity with V47 < 53 % and V75.6 < 30 % at a median follow-up of 53 months (Cahlon et al. 2008). Numerous studies have found results similar to the results seen in these trials (Fonteyne et al. 2007; Karlsdóttir et al. 2008).

Taking these individual publications into account, there is general agreement that multiple dose–volume constraints in the intermediate (30–50 Gy) and high range (>70 Gy) regions of a histogram are prudent to shape the dose–volume histogram appropriately and to minimize the probability of late rectal bleeding to rates <10 %. It is also clear that while the volume of the rectum receiving a high dose is more predictive of late rectal toxicity, the amount of rectum receiving lower doses also predicts rectal toxicity, particularly with non-IMRT techniques. The distribution of dose on the rectum is also important, as increasing doses to the posterior rectal wall and upper rectum are associated with increase rates of late rectal toxicity (Skwarchuk et al. 2000; Fiorino et al. 2002; Heemsbergen et al. 2005; Peeters et al. 2006d; Munbodh 2008). A summary of recommended dose/volume constraints for late rectal injury is provided in Table 1. See "Radiation Induced Rectal Toxicity" for additional discussion.

6.1.2 Stool Frequency

Stool frequency has also been correlated with treatment-related dose–volume parameters. Fonteyne et al. reported that the rate of mild diarrhea was correlated with the volume of the rectum receiving 40 Gy, and chronic rectal urgency was correlated with the volume of the rectum receiving 70 Gy (Fonteyne et al. 2007). Similarly, Peeters reported that both the V40 and the mean rectal dose were predictive of stool frequency (Peeters et al. 2006c). See "Biophysiopathology of the Microvasculature and Microcirculation" for additional discussion.

6.1.3 Brachytherapy

The prostate brachytherapy literature has consistently demonstrated that very small volumes of the rectum can tolerate very high doses of radiation, which is an important consideration in this era of highly conformal dose escalation. Snyder et al. found that when the rectum was contoured as a hollow structure from 9 mm below the prostate apex to 9 mm above the top of the seminal vesicles, the rate of grade 2 or greater proctitis was dependent on the volume of rectum receiving the prescription dose of 160 Gy. The rates of proctitis per absolute volume of rectal wall receiving prescription dose were: 0 % if < 0.8 cc, 7–8 % between 0.8 and 1.8 cc, and 25 %, and 24–25 % if > than 1.8 cc (Snyder et al. 2001). D'Amico's group also found that the absolute volume of rectum receiving 100 Gy was predictive of needing argon plasma coagulation for late proctitis after brachytherapy, with no patients needing intervention when the volume of rectum receiving 100 Gy was below 8 cc, whereas 20 % of men needed intervention with argon plasma coagulation when the volume of rectum receiving 100 Gy was greater that 8 cc (Albert et al. 2008). Han et al. found a similar outcome when endoscopically proven radiation proctitis was used as the endpoint and the rectum was contoured as a solid structure, with the volume of the rectum receiving at least 100 % of the prescription dose being 2.5 cc in patients with endoscopically-confirmed proctitis and 0.6 cc in those with no evidence of bleeding (Han and Wallner 2001). The maximum point dose to the rectum after brachytherapy is also predictive of RTOG ≥ 2 bleeding, with a 0.4 % toxicity rate for a maximum point dose of 150 Gy, a 1.2 % rate for a maximum point dose of 200 Gy, and a 4.7 % rate for a maximum point dose of 300 Gy (Waterman and Dicker 2003). Therefore, it is clear that small volumes of the rectum can receive very high doses, leading investigators to embrace more precise brachytherapy strategies, and by extrapolation, external beam treatments in combination with increasingly effective real-time image guidance solutions in an effort to dose escalate the prostate safely while sparing more of the rectum from the very high dose regions. It is evident that the smaller the amount of rectum irradiated, the less likely that late rectal bleeding will occur.

6.1.4 Acute GI Toxicities

Dose volume constraints and their effect on acute GI toxicities from pelvic radiation has been studied less. Nonetheless, these appear also to be highly dependent on dose–volume parameters, typically with mean rectal dose and the volume of rectum receiving greater than 60 Gy. Peeters examined GI effects in the first 6 weeks of treatment and found that the mean rectal dose as well absolute and the relative amount of rectum receiving 5, 15, and 30 Gy were predictive of acute GI toxicity (Peeters et al. 2005a).

Vavassori and Cheng also reported DVH correlations with rates of acute toxicity, including the mean dose, and the minimal dose to 10, 20, and 50 % of the rectum (Vavassori et al. 2007; Cheng et al. 2008). Other authors have offered more specific recommendations. Nuyttens' group found that a V75 < 11 cc and a mean dose < 38 Gy minimized acute rectal toxicity (Nuyttens et al. 2002). Another report looking at patients treated with 78 Gy found that a V65 Gy < 20 % was protective against any grade I or higher acute GI toxicity (Karlsdttir et al. 2004). Of note, most of the above studies looking at acute side effects contoured the rectum as a solid structure, including the luminal contents. A summary of recommended dose/volume constraints for acute rectal effects is provided in Table 2.

6.2 Bladder Constraints

The bladder limits the ability to escalate dose in prostate cancer treatment, particularly with adequate rectal constraints, and knowledge of appropriate dose–volume constraints for this organ is important for the treating physician. Compared to the rectum, there are less available data regarding dose–volume relationships, likely due to the difficulty of estimating the volume of the bladder receiving a certain dose unless stringency bladder filling protocols are used. Emami predicted whole bladder tolerance using data from the era of 2D treatment. He recommended a tolerance dose of 65 Gy to keep the probability of serious urinary toxicity less than 5 % and 80 Gy to keep the probability of serious toxicity less than 50 % (Lyman et al. 1991). An excellent review of the literature refined these recommendations and concluded that the whole bladder can be safely irradiated to 30–50 Gy, dysfunction injury is rare with maximum point doses < 65 Gy, and the risk of organ failure is likely at whole bladder doses in the range of 50–60 Gy (Marks et al. 1995). Several studies from the 3D conformal and IMRT era have confirmed that even a small volume of the bladder receiving more than 75 Gy is predictive of severe late toxicity (Cahlon et al. 2008) (Cheung et al. 2007; Zelefsky et al. 2008a, b, c) (Lips et al. 2008; Sanda et al. 2008), suggesting that the bladder behaves like a serial organ.

There also appears to be differential tolerance to radiation exposure in the various regions of the bladder. One study of over 500 patients looked at radiation dose distribution and on surface maps of the bladder found that the dose to the trigone >47 Gy was predictive of an increased probability of late urinary toxicity (Heemsbergen 2008). Most centers have synthesized the available dose–volume and anatomic information by attempting to minimize the hot spots in the bladder while using an intermediate dose constraint such as V47 < 53 % or V40 < 50–60 %. See "Urinary Bladder" for further discussion.

Table 1 Recommended dose–volume constraints from large studies intended to minimize the risks of LATE rectal toxicity for patients with treated with modern radiation techniques and doses for prostate cancer

References	Prescription Doses (Gy)	Suggested constraints	Comments
Jackson et al (2001)	70.2 or 75.6	V40 Gy < 60 % V77 Gy < 14 % (for patients treated at 75.6 Gy)	Bleeding endpoint RTOG Grade ≥ 2 Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure
Fiorino et al. (2002)	70–76	V50 Gy < 60 % V60 Gy < 50 %	Bleeding endpoint Modified RTOG Grade ≥2 Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure Included non-conformal patients; excluded pts with rectal volume >100 cc
Fiorino et al. (2003)	70–78	V50 Gy < 60 % V60 Gy < 45 % V70 Gy < 25 %	Bleeding endpoint Modified RTOG Grade ≥ 2 Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure V70 more predictive for Grade 3 bleeding
Vargas et al. (2005)	70.2–79.2	V70 Gy < 25 %	Bleeding endpoint CTC 2.0 Grade ≥ 2 Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure Chronic rectal toxicity, mostly bleeding V50 also correlated (no specific constraints suggested)
Peeters et al. (2006c)	68 or 78	V65 Gy < 30 %	Bleeding endpoint Bleeding requiring lasers/transfusions Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the Sigmoid flexure V55-V65 correlated with V65 most predictive; independent impact of abdominal/pelvic surgery
Fiorino et al. (2008)	70–78	V50 Gy < 55 % V60 Gy < 40 % V70 Gy < 25 % V75 Gy < 5 %	Bleeding endpoint SOMA/LENT Grade ≥ 2 Rectum solid structure contoured With the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure Prospectively scored patients; previous abdominal/pelvic surgery independently predictor of bleeding (suggested V70 < 15 %); V75 best predictor of Grade 3 bleeding
Fellin et al. (2009)	70–80	V75 Gy < 5 %	Bleeding endpoint SOMA/LENT Grade ≥ 2 Rectum solid structure contoured with the caudal limit = first CT slice above the anal verge, cranial limit = first CT slice below the sigmoid flexure Prospectively scored patients; previous abdominal/pelvic surgery independently predictor of bleeding (suggested V70 < 15 %) and best predictor of Grade 3 bleeding
Storey et al. (2000a, b)	70 or 78	V70 Gy < 25 %	General toxicity endpoint GI RTOG Grade ≥ 2 Rectum 11 cm long starting 2 cm below ischial tuberosities
Huang et al. (2002)	70 or 78	V60 Gy < 40 % V70 Gy < 25 % V75.6 Gy < 15 % V78 Gy < 5 %	General toxicity endpoint GI RTOG Grade ≥ 2 Rectum 11 cm long starting 2 cm below ischial tuberosities
Michalski et al. (2004)	74	V65 Gy < 50 %	General toxicity endpoint GI RTOG Grade ≥ 2
Fonteyne et al. (2007)	74–80	V40 Gy < 84 % V50 Gy < 68 % V60 Gy < 59 % V65 Gy < 48 %	General toxicity endpoint GI RTOG Grade ≥ 2 All patients were treated with IMRT technique

(continued)

Table 1 (continued)

References	Prescription Doses (Gy)	Suggested constraints	Comments
Karlsdóttir et al. (2008)	70	V40 Gy < 70 %	General toxicity endpoint GI RTOG Grade ≥ 2 A number of cut-offs predictive of toxicity; V40–V43 most predictive
Kuban et al. (2008)	70 or 78	V70 Gy < 25 %	General toxicity endpoint GI RTOG Grade ≥ 2 Rectum 11 cm long starting 2 cm below ischial tuberosities

Modified from Table 1 of Fiorino et al. (2009)

Table 2 Recommended Dose–Volume Constraints From Large Studies Intended to Minimize the Risks of ACUTE Rectal Toxicity for Patients with Treated with modern radiation techniques and doses for prostate cancer

References	Prescription Dose range	Suggested constraints	Comments
Nuyttens et al. (2002)	72–80 Gy 2 Gy/fr	V75 Gy < 11 cc Mean dose < 38 Gy	≥G2 modified RTOG toxicity; acute toxicity during treatment retrospectively assessed; solid rectum including filling
Karlsdóttir et al. (2008)	70 Gy 2 Gy/fr	V40 Gy, V70 Gy	≥G2 modified RTOG toxicity; acute toxicity during treatment; solid rectum including filling
Peeters et al. (2005b)	68–78 Gy 2 Gy/fr	Mean dose V30 Gy, V35 Gy, V60 Gy, V65 Gy absolute V50 Gy, V60 Gy, V65 Gy % rectum length > 5 Gy, > 30 Gy absolute rectum length > 5 Gy, > 15 Gy, > 30 Gy	≥G2 modified RTOG toxicity; acute toxicity during treatment prospectively assessed; rectal wall; DVH of the first 6 weeks of treatment
Michalski et al. (2004)	78 Gy 2 Gy/fr	V65 Gy < 20 %	≥G1 modified RTOG toxicity; acute toxicity within 120 days after onset of RT prospectively assessed; solid rectum including filling
Vavassori et al. (2007)	70–81.6 Gy 1.8–2 Gy/fr	Mean dose	≥G2 modified RTOG toxicity; acute toxicity within one month after RT completion prospectively assessed; solid rectum including filling
Cheng et al. (2008)	63–80 Gy 1.8–2 Gy/fr	Mean dose Minimal dose to 10 %, 20 %, 50 % of rectum	≥G2 RTOG toxicity; including patients who underwent prostatectomy; acute toxicity within 90 days after RT completion prospectively assessed; solid rectum including filling
Arcangeli et al. (2009)	56 Gy 3.5 Gy/fr	V53 Gy < 8 %	≥G2 RTOG toxicity; acute toxicity within two months after RT completion prospectively assessed; solid rectum including filling

Modified from Table 3 of Fiorino et al. (2009)

6.3 Erectile Apparatus Constraints

The appropriate anatomic structures upon which to place dose–volume constraints in an effort to preserve potency after radiation therapy remain undefined. Zelefsky and Eid have recommended limiting to dose to various structures, including the penile bulb, proximal penis, neurovascular bundles, crura, and corpora cavernosa out of concern for sexual morbidity (Zelefsky and Eid 1998). The preponderance of the literature in this realm relates to the dose received by the penile bulb (Fisch et al. 2001; Merrick et al. 2002; Wernicke et al. 2004; Mangar et al. 2006). These publications found that a median dose to the bulb less than 52 Gy (Roach et al. 2004) or a V50 < 20 % and a V40 < 40 % (Mangar et al. 2006) were associated with decreased rates of impotence. However, other studies were not able to demonstrate an effect of penile bulb dose on potency (Kiteley et al. 2002; Selek et al. 2004) (Incrocci et al. 2002). In general, the treating physician should utilize modern highly conformal techniques to minimize dose to the penile bulb and cavernosa whenever possible (Sethi et al. 2003), especially with modern imaging techniques like MRI which permit precise identification of the apex of the prostate (Algan et al. 1995; Perna et al. 2009).
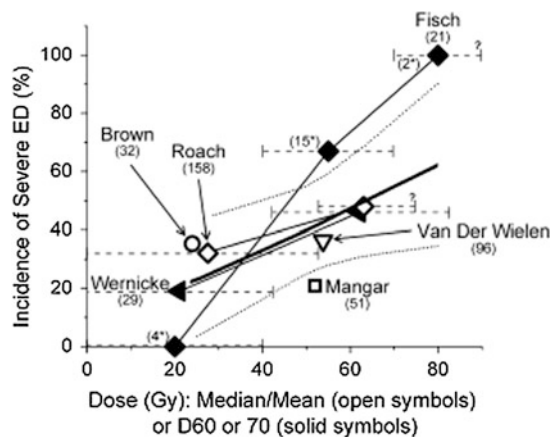
Fig. 7 Dose response for erectile dysfunction (ED) from Quantec (with permission from Roach et al. 2010). Incidence of erectile dysfunction according to the radiation close to the penile bulb. The x axis values are estimated according to the range of doses reported. The data for Fisch et al. (2001) at 20, 55, and 80 Gy, represent the reported rates of erectile dysfunction at <40, 40–70, and >70 Gy, respectively. Similarly, for Wernicke et al. (2004), each symbol represent the erectile dysfunction at ≤42 versus >42 and <52.5 versus ≥52.5 Gy respectively. The *dashed horizontal lines* reflect the dose ranges ascribed to each data point. The upper x-axis range of the highest data point for Fisch et al. (2001) and Roach et al. (2010) are unknown. The mean dose of van der Wielen et al. (2008) and Mangar et al. (2006) are estimated from the subgroup data. The x-axis values for Wernicke et al. (2004) are D60 and for Fisch et al. (2001) or D70 (i.e. minimum dose received by 60 or 70 % of the volume of the penile bulb). A *thick solid line* represents the fitted model with sample size correction. Dotted lines represent 90 % confidence intervals

The current consensus is the penile bulb/crura provides the basis for the tolerance doses for erectile dysfunction. Reviewing the literature, Roach et al. concluded as the mean/median dose increased from 20 to 80 Gy, the incidence of erectile dysfunction increased from 20–30 % to 90–100 % (Fig. 7; Roach et al. 2010 Quantec paper). On the basis of data available, Roach et al. recommend the mean dose to 95 % of the prostatic bulb volume to <50 Gy, and it is prudent to limit the D_{70} and D_{90} to 70 and 50 Gy, respectively. (Roach et al. 2010, Quantec paper ref). Further, they acknowledge, "...that the penile bulb may not be the critical component of the erectile apparatus, but it seems to be a surrogate for yet to be determined structure(s) critical for erectile function for at least some techniques." A summary of clinical and dose/volume parameters that have been correlated with erectile dysfunction is provided in Table 3.

6.4 Penile Dose–Volume Constraints

Some generalities can be made from the published literature regarding the dose–volume guidelines for the penis. In general, skin desquamation is the most common and severe acute toxicity for this organ, the pathophysiology, dose–volume considerations, and management of which is thoroughly addressed in a separate chapter. Desquamation during penile cancer treatment is common by necessity regardless if the patient is treated with external beam radiation or brachytherapy. It is known that treatment of a penile cancer requires significant doses of radiation, as an increased risk of treatment failure is seen in squamous cell carcinomas if the total dose is <60 Gy or the dose per fraction is <2 Gy (Sarin et al. 1997; Zouhair et al. 2001).

The most frequent and challenging late toxicities from radiation treatment of the penis are urethral stenosis and penile soft tissue necrosis. Some technique and dose–volume guidelines are available in the literature to assist the practitioner in minimizing the risk of these complications. For urethral stenosis, hypofractionated external beam treatment regimens beyond 2 Gy per day and implant geometries and/or loading techniques that do not attempt some degree of urethral sparing are associated with higher stenosis rates (Rozan et al. 1995; Crook et al. 2009). In the circumstance of penile radionecrosis, the modality of treatment makes a difference, with brachytherapy causing higher rates of necrosis than external beam radiation (Crook et al. 2009). The size of the penile tumor is also prognostic, with bulky tumors or >T3 tumors having higher rates of necrosis after radiation therapy (Mazeron et al. 1984; Rozan et al. 1995). Dose also clearly plays a role, as Rozan et al. also found that doses in excess of 60 Gy were associated with higher rates of necrosis (Rozan et al. 1995) while Chaudhary et al. found 0 % necrosis at doses of 50 Gy (Chaudhary et al. 1999). However, as previously mentioned, 50 Gy is considered a subtherapeutic dose for most squamous cell carcinomas of the penis because it is associated with an increased rate of local failure.

6.5 Seminal Vesicle Constraints

There is scant literature available regarding dose–volume limits of the seminal vesicles themselves as an isolated organ. Most of the available literature regarding seminal vesicle tolerance is from prostate cancer literature, specifically looking at the question of toxicity and outcomes varying with amount of the seminal vesicles included in the target volume. PSA level, clinical stage, volume of disease, and Gleason score are predictive of seminal vesicle invasion, with 99 % of men with biopsy proven Gleason score 6 or less disease unlikely to have invasion of the seminal vesicles in the PSA era (Han et al. 2004). In general, inclusion of increasing amounts of the seminal vesicles in addition to the prostate for localized disease causes increased doses to the bladder and rectum (Bayman and Wylie 2007). However, it is unclear if these increased doses lead to a detriment in quality of life. Pinkawa et al.

Table 3 Parameters associated with erectile dysfunction, from Quantec Roach et al. 2010

Reference	N	Assessment method[a]	Prescribed dose, treatment	OAR definition	Severe ED rate (%)	Correlated parameters	
						Dose–volume	Clinical
Fisch et al. 2001	21	Questionnaire[b]	65–72 Gy, 3D	Penile bulb	33[c]	D70 ≥ 70 Gy[d]	No other endpoints analyzed
Roach et al. 2004	158	Patient report (RTOG)[e]	68.4 Gy, 73.8 Gy, 3D	Penile bulb[f]	41	Median penile bulb dose ≥ 52.5 Gy[f]	No other endpoints analyzed
Wernicke et al. 2004	29	Questionnaire[b]	66–79.2 Gy, 3D	Penile bulb[g]	NS	D30 ≥ 67 Gy[f] D45 ≥ 63 Gy[f] D60 ≥ 42 Gy[f] D75 >20 Gy[f]	Alcohol and smoking not significant, dose and volume significant
Selek et al. 2004	28	Questionnaire[b]	78 Gy. 3D	Penile bulb[g]	35.7% at 2 y	Mean dose to penile structure 38.2 Gy, no dose–volume effect was found	Up to 68 % may have had ED post-treatment? ED correlated with hypertension
Mangar et al. 2006	51	Questionnaire[b]	64 Gy, 74 Gy. 3D	Penile bulb, crura and cavemosum[h]	24	Dl 5, D30, D50, D90 of penile bulb[f]	Adjusted for age, bulb volume, hypertension, and previous pelvic surgery
Zelefsky et al. 2006	561	Patient report (NCI)[i]	81 Gy. IMRT	j	49	Not evaluated	Hormone therapy
Brown et al. 2007	32	Questionnaire[b]	NS. EMRT	Penile bulb	34	No relationship noted	Hypertension, pre-RT erectile function
Cahlon et al. 2008	478	Patient report (NCI)[i]	86.4 Gy, IMRT	j	30	Not evaluated	Age >70 y, diabetes hormone therapy
van der Wielen et al. 2008	10	Questionnaire[b]	68 versus 78 Gy	Penile bulb	36	No correlations between ED and dose–volume of crura, or the penile bulb[j]	Adjusted for diabetes and history of cardiovascular disease
Pinkawa et al. 2009a, b	123	Questionnaire[b]	70.2–72 Gy, 3D	NS	73[k]	Not evaluated	Age, diabetes

OAR organs at risk; *ED* erectile dysfunction; *RTOG* radiation therapy oncology group; *NCI* National Cancer Institute;
[a] All assessments are patient-reported, based on questionnaires of morbidity scoring scales (e.g., RTOG, NCI), as noted
[b] All questionnaires are self-administered
[c] Potency scale declined ≥2
[d] DX is dose delivered to the x % penile bulb volume
[e] RTOG radiation morbidity scoring scale
[f] Penile bulb was defined as proximal portion of the penis
[g] The penile bulb is here specifically defined as proximal enlargement of the corpus spongiosum that is secured to the urogential diaphragm and covered by the bulbospongiosus muscle
[h] The penile bulb was here defined as a structure whereas the crura and cavernosum as a separate one
[i] NCI common toxicity criteria for adverse events
[j] Penile bulb not defined as a specific structure
[k] No erections firm enough for sexual intercourse

examined a cohort of 283 patients who were either treated to the prostate alone or to the prostate and seminal vesicles to a dose of 72 Gy. Although the prostate and seminal vesicle group had higher volumes included for any dose point on the bladder and rectal dose volume histogram, there was no appreciable difference in quality of life between the two groups (Pinkawa et al. 2009a, b).

Minimal conclusions can be made based on the radiographic and histologic observation of seminal vesicle tissue treated with radiation therapy. Based on MRI radiographic analysis, over one-third of patients with radiation to the seminal vesicles had decreased intraluminal fluid contents or disseminated low signal tubular intensity (Chan and Kressel 1991). These radiographic analyses are consistent with previous pathologic studies of irradiated patients and have shown that replacement of normal perivesical fibro-adipose tissue and luminal narrowing secondary to fibrotic change (Bostwick 1982).

Due to the lack of published literature on the subject, further dose–volume recommendations cannot be made for the seminal vesicles.

7 Chemotherapy Tolerance

7.1 Androgen Deprivation and Radiation Therapy

ADT in conjunction with radiotherapy is routinely recommended for patients with locally advanced prostate cancer. Randomized trials have demonstrated improved outcomes, including an overall survival benefit compared with radiotherapy alone. In addition, studies have demonstrated that ADT can improve local eradication of the locally advanced tumors by reducing the size of the mass or the concurrent elimination of tumor clonogens inherently resistant to radiotherapy, or both. ADT can effectively reduce the size of larger prostate volumes by 30–40 %, thereby improving the ability to deliver maximal radiation dose levels without exceeding the tolerance of the surrounding normal tissues. This section will outline the putative mechanisms of benefit for ADT with radiotherapy, summarize the results of published randomized trials, and highlight the indications for its use in clinical practice.

Randomized trials have demonstrated improved outcomes when ADT is combined with EBRT delivered at dose levels of 70 Gy.

8 Special Topics

8.1 Host Factors

Diabetes mellitus has been found to have a higher risk of late rectal bleeding (Herold et al. 1999; Skwarchuk et al. 2000). Investigators from Fox Chase Cancer Center reported that 13 % of patients treated with external radiation for prostate cancer from 1989 to 1996 treated with 3D-CRT had diabetes mellitus. When these patients were analyzed, patients with either type I or type II diabetes experienced significantly more late grade 3 toxicity (28 vs. 17 %) (Herold et al. 1999). The mechanism by which diabetes affects late toxicity is thought to be secondary to microvascular damage contributing to late radiation effects. Aggressive rectal blocking was promoted for diabetic patients in the 3D era, and prescription doses were often lowered for these patients before the advent of IMRT (Fiorino et al. 2008).

8.2 Acute Gastrointestinal Toxicities of Radiation Therapy

Patients treated with pelvic radiation therapy are at risk for acute GI toxicity secondary to acute inflammatory changes involving the rectal and small bowel mucosa. Clinical manifestations of acute GI toxicity are wide ranging and include abdominal cramping, abdominal pain, tenderness with defecation, mucous discharge, tenesmus, rectal urgency, and increased frequency of bowel movements. It can be difficult to differentiate between acute rectal and small bowel toxicity during treatment, especially when the pelvic lymph nodes are included in the treatment field. In general, symptoms of abdominal pain, increased flatus and abdominal cramping are usually from acute small bowel toxicity (acute enteritis) while tenderness with defecation, rectal urgency, and tenesmus are typically associated with rectal toxicity (acute proctitis). Similar to acute genitourinary effects, gastrointestinal signs and symptoms typically begin in the first two weeks of irradiation and resolve within 4 months after completion of therapy.

A range of acute GI toxicity rates have been published in the literature, with 8–45 % of prostate cancer patients treated with radiation having moderate to severe acute GI side effects, with rates depending on such heterogeneous variables as radiation technique, inclusion of pelvic lymph nodes in the irradiation portal, use of androgen deprivation therapy and toxicity instrument used (Cahlon et al. 2008; Fiorino et al. 2009). With contemporary external beam doses of the order of 78 Gy, 40 % of men have moderate to severe acute GI toxicity, with higher rates of toxicity seen in patients whose pelvic lymph nodes are included in the irradiation field (Peeters et al. 2006a, b; Zietman et al. 2005; Dearnaley et al. 2007).

Several coexisting medical conditions can alter the probability of acute GI toxicity during radiation therapy. Androgen deprivation therapy before treatment has been found to decrease acute toxicity by decreasing the volume of the prostate and therefore the amount of rectal wall receiving high dose radiation (Peeters et al. 2005b; Vavassori et al. 2007). Furthermore, patients with diabetes mellitus are more likely to experience acute severe diarrhea and patients with hemorrhoids have significantly higher rates of acute rectal bleeding, tenesmus, and overall GI toxicity during treatment (Peeters et al. 2005b). The administration of antihypertensives and anticoagulant medications during treatment may also lessen the likelihood and severity of acute GI symptoms (Peeters et al. 2005b). Based on these factors, Valdagni et al. have published

nomograms that are predictive of acute rectal toxicity, with use of anticoagulants being protective and history of diabetes mellitus, hemorrhoids, mean rectal dose, and pelvic nodal irradiation predisposing to increased toxicity (Valdagni et al. 2008).

Several publications have confirmed an association between the risk of developing acute and late GI reactions after pelvic radiotherapy (Peeters et al. 2005a; Vargas et al. 2005; Zelefsky et al. 2006), and some authors have proposed a causal relationship, so-called consequential late damage from acute toxicity. However, this mechanism for late toxicity has never been definitely proven. In general, when rectal dose volume parameters are considered, the impact of acute toxicity rates on late toxicity disappears. Likely explanations for the correlation between acute and late GI effects include the possibility that patients who experience severe acute effects are more likely to report late effects. However, some authors continue to explore the potential for at least a partial consequential role for acute reactions to contributing to late GI toxicity (Wang et al. 1998) (Heemsbergen et al. 2006).

8.3 Acute Genitourinary Toxicities of Radiation Therapy

The most common acute urinary morbidities during external beam radiation therapy for pelvic malignancies are classified as irritative and are caused by acute inflammation and epithelial denudation of the urethra and possibly the bladder neck. Symptoms from urethritis and cystitis tend to occur within 2–4 weeks of initiation of radiotherapy and can continue for several weeks after the completion of radiation, when re-epithelization is complete. During external radiation over 50 % of patients experience some degree frequency, urgency, and dysuria (Ryu Winter et al. 2002; Zietman et al. 2005; Peeters et al. 2006a, b; Dearnaley et al. 2007). In general, these irritative symptoms resolve within 4 weeks after the completion of external radiation therapy (Pinkawa et al. 2008). Although less common, acute obstructive symptoms including hesitancy, intermittency, dribbling, and incomplete emptying, are also noted in approximately one-third of patients undergoing radiation. The probability of obstructive symptoms is proportional to the size of the prostate gland, particularly in glands larger than 43 cm^3. (Pinkawa et al. 2008). Acute obstructive symptoms tend to linger longer than irritative symptoms, resolving 8 weeks or more after treatment.

The acute and late urinary toxicity profiles for external beam radiation therapy and brachytherapy are slightly different. Men treated with brachytherapy tend to have more severe irritative symptoms, longer lasting GU symptoms, higher rates of obstructive symptoms, and lower rates of GI toxicity as compared to men treated with external beam radiation therapy (Lawton et al. 1991; Gelblum et al. 1999; Pickles et al. 2010). In a contemporary matched pair analysis for men having EBRT or LDR brachytherapy, men receiving brachytherapy had a higher overall rate of acute Grade 3 GU toxicity (2.9 vs. 0.7 %) and catheterization rates for obstructive symptoms of (15 vs 0 %). Brachytherapy patients also had more late GU toxicity, but less late GI toxicity, than the external beam arm (Pickles et al. 2010). These results are consistent with other similar analyses. In men receiving brachytherapy, prostate size and pre-treatment urinary function are important considerations. One study from MSKCC found that pre-implant IPS scores >7 and prostate volumes >35 cc were predictive of increased rates of acute urinary morbidity (Gelblum et al. 1999).

8.4 Late Genitourinary Toxicities of Radiation Therapy

Late genitourinary toxicities of radiation therapy to the pelvis include chronic cystitis, chronic urethritis, bladder neck contracture, urethral strictures, hematuria, and urinary incontinence. The mechanism of late toxicity is thought to be from changes in the microvasculature of the affected tissue, including increased endothelial proliferation and an obliterative endarteritis, leading to hypoxia, fibrosis, epithelial atrophy, and other vascular changes including telangiectasia formation. The overall rate of late GU toxicity with modern radiation techniques is relatively rare. Analysis of RTOG randomized trials found an overall rate of approximately 10 % Grade 3 or higher toxicity (Lawton et al. 1991, 2008.

Approximately one-half of moderate to severe late GU toxicity is from urethral strictures (Lawton et al. 1991). In men treated with between 60 and 70 Gy for prostate cancer, the incidence of urethral strictures is 0–5 % for those without a prior TURP and 5–15 % for those with a prior TURP (Coia et al. 1995). The time to stricture is usually in the range of 2 years, but symptoms before diagnosis are retrospectively reported as slowly progressive. Cystoscopy is the diagnostic test of choice for a suspected stricture. Strictures have a pale "washed leather" appearance on cystoscopy and are accompanied by other stigmata of radiation, including induration and telangiectasia.

8.5 Late Gastrointestinal Toxicities of Radiation Therapy

Late gastrointestinal effects of radiation therapy include hematochezia, anorectal ulcerations and strictures, mucous discharge, pain, rectal urgency, incontinence, mucosal

changes including telangiectasia and congestion, and chronic loose stools. Fistulas are a very rare late complication usually associated with unnecessary biopsies or procedures involving the portion of the rectum that received radiation, especially in the setting of prior prostate brachytherapy. In general, late genitourinary side effects can take up to 2 years after radiation treatment to develop and are likely clinical manifestations of the chronic pathologic inflammatory processes seen in the rectal microvasculature including submucosal alterations with atypical fibroblasts, abundance of collagen, thickened arterioles, and telangiectatic veins (Coia et al. 1995). Crook et al. found that in a cohort of approximately 200 patients treated for prostate cancer with external beam radiation, 67 % of patient only had minor GI side effects, 9 % reported rectal bleeding, 20 % reported rectal urgency, and 4 % had a grade 3 GI toxicity (Crook et al. 1996). The most common late GI toxicity is late rectal bleeding. However, the evaluating oncologist must remember that a myriad of non-radiation etiologies for bleeding must be included in the differential diagnosis, including metachronous malignancy and less serious conditions such as hemorrhoids and benign anal lesions. Furthermore, the lifetime prevalence of rectal bleeding in the overall population is estimated to be around 18–25 %, with most of these patients having an episode in the previous 1 year (Crosland 1995; Talley and Jones 1998). Bleeding is more common in younger patients (Talley and Jones 1998) and those who regularly examine their stool or toilet paper after bowel movements (Kang 2003).

IMRT techniques are especially useful in minimizing GI toxicity when the pelvic lymph nodes are irradiated because GI toxicity is greater with this larger field (Sanguineti et al. 2006; Guerrero Urbano and Nutting 2004; Luxton et al. 2004; Mangar et al. 2005). The most significant published experience is from Memorial Sloan-Kettering Cancer Center (MSKCC), where patients treated with IMRT had significantly less GI toxicity a decade after treatment when compared to a similar cohort of men treated with conventional techniques to lower total doses (5 % for high dose IMRT arm vs. 13 % for low dose conventional arm) (Zelefsky et al. 2008a, b, c).

Other clinical parameters, most notably prior surgery, diabetes mellitus, and a history of androgen deprivation therapy, are associated an increased risk of rectal bleeding after radiation therapy to the pelvis. Prior surgery to the abdomen or pelvis is consistently associated with a significantly higher risk of rectal bleeding after surgery. Peeters examined a cohort of 641 patients and found that prior abdominal surgery significantly increased the risk of needing blood transfusion or laser coagulation after radiation with an HR of 2.7 (Peeters et al. 2006c). Fiorino found that prior abdominopelvic surgery increased the risk of post-

radiation bleeding with an even higher HR of 4.4 (Fiorino et al. 2008). Other publications have confirmed this finding (Fonteyne et al. 2007; Smit 1990). The mechanism by which prior surgery promotes post-radiation bleeding is undefined; possible explanations include spatial fixation of bowel in these patients preventing normal anatomic motion which "smears" hot spots in patients without history of surgery or decreased blood supply to the irradiated area causing poor healing of tissues after treatment (Fiorino et al. 2009).

Androgen deprivation therapy has been variably associated with the development of late rectal bleeding. In the neoadjuvant setting, it is generally accepted that it may decrease rates of late rectal toxicity by creating a more favorable anatomy and by reducing the amount of rectum in the irradiated field (Zelefsky and Harrison 1997; Forman et al. 1995; Sanguineti et al. 2003). However, it is critical to note that this advantage is only seen when the treatment planning process accounts for the downsizing of the prostate gland. If not accounted for, an increased rate of late rectal toxicity can be seen (Schultheiss et al. 1995).

Unlike the neoadjuvant setting, adjuvant androgen deprivation has been found to be associated with increased rates of late rectal bleeding after radiation therapy in numerous studies. Patients who receive adjuvant androgen deprivation therapy have approximately a 2–3 times greater risk of grade 2 or higher late rectal bleeding as compared to patients who did not. The mechanism by which androgen deprivation may increase rectal bleeding is not clearly defined. Considering neoadjuvant androgen deprivation is not consistently associated with late rectal bleeding, the most plausible mechanism is inhibition of the normal tissue repair processes that normal occur after the insult of radiation therapy.

8.6 Biopsy of the Distal Rectum After Prostate Brachytherapy

Physicians should be aware of the high risk of morbidity in biopsying the distal rectum after a prostate brachytherapy procedure. Numerous publications have shown a causative effect between biopsy procedures of the anterior rectal wall and progressive ulcerations/fistulas, especially when the procedure was performed for rectal bleeding after radiation therapy (Gelblum and Potters 2000; Theodorescu et al. 2000; Tran et al. 2005). These studies are also consistent in demonstrating that biopsies performed to evaluate rectal bleeding after prostate brachytherapy typically show only histologic stigmata of chronic radiation changes. It is strongly recommended that biopsies of the anterior rectal wall be avoided as a part of the workup for rectal bleeding after prostate brachytherapy unless a rectal malignancy is

suspected. When they do occur, these lesions are clinically difficult to manage. Repairs of vesicorectal or urethrorectal fistulas are complex surgical procedures involving excision of the fistula site and multilayer interposition of well-vascularized, non-irradiated tissue. Rarely, partial pelvic exenteration with urinary and/or fecal diversion is necessary when less morbid open repair is impossible.

9 Prevention and Management of Radiation Toxicity

Even with the more stringent attention to minimizing dose to normal tissues of the distal pelvis in the planning process, acute and late morbidities will occur. Proper management of these toxicities will contribute to improved quality of life of the patient during and after treatment and will increase the likelihood of successfully completing the prescribed course of radiotherapy. A variety of medications and conservative management techniques can bring relief of symptoms, the recommendations below are certainly not meant to be exhaustive (see Table 4). It is up to the managing physician and the patient to determine the most effective appropriate management strategy for each clinical situation. For the medications listed, review the latest manufacturer-provided instructions to ensure proper indications for use, dosing, route of administration, frequency of use, and side effect profile.

9.1 Erectile Dysfunction

For erectile dysfunction in the post-treatment setting, first-line phosphodiesterase inhibitors such as sildenafil 25–100 mg po prn, tadalafil 10 mg po prn, vardenafil 5–20 mg po can be considered. Treatment with these phosphodiesterase inhibitors can significantly improve function in approximately 2/3 of patients with radiation-induced impotence (Weber et al. 1999; Zelefsky et al. 1999; Incrocci et al. 2001, 2006). It also appears that early versus later use of these agents is associated with improved erectile function and a more favorable health-related QOL (Miller et al. 2006; Schiff et al. 2006). There are also ongoing multi-institutional studies examining these agents before and during radiation therapy to see if they have a protective effect against the development of erectile dysfunction after radiation therapy. Counseling and social support have also been found to improve post-radiation erective dysfunction, with one study showing that attending four counseling sessions improved levels of overall distress and global male sexual function at 3 months (Canada et al. 2005). If ED is refractory to counseling and oral agents, referral to a urologist and consideration of trimix injections, bimix

injections, and penile prostheses can be offered to the patient with varying degrees of success. For cases of drying of the ejaculate, which is quite distressing to some patients, there is no proven intervention. It is therefore important for the pre-treatment informed consent process to include this subject so that the patient is aware of the potential for this toxicity.

9.2 Skin Reactions

Skin reactions may be seen during definitive treatment of pelvic malignancies, particularly for penile cancers or during irradiation of the pelvic lymph nodes. For skin dryness or irritation, Aquaphor (OTC) original or healing ointment or Eucerin (OTC) lotion of cream applied to the affected area two or three times a day will bring relief. For moist desquamation, Domeboro soaks (OTC) for 20 min or Silvadene cream 1 % applied for three or four times a day is recommended. Strict attention to skin hygiene in the genital and perineal area is essential during periods of wet desquamation, with sitz baths for perineal desquamation and baking soda and water soaks for testicular or penile desquamation. Telfa (OTC) non-adhesive pads helps with symptoms from the affected area rubbing against clothing or other parts of the body. Hyrdogel wound dressings also bring symptomatic relief. Diphenhydramine 25–50 mg po every 6 h or the use of 0.5–1 % hydrocortisone cream will address pruritic symptoms. For patients recovering from penile desquamation, sexual activity should be held for several weeks, after which time a lubricant without desiccants, irritants, or alcohol should be used. For vigorous desquamations out of proportion to clinical situation or radiation dose, testing for connective tissue diseases or HIV must be considered.

During the management of the penile cancer patient, acute skin reactions remain the most common management challenge. However, these patients can also experience acute adhesions, late strictures, and areas of soft tissue necrosis, the management recommendations of which Crook et al. have published elegantly (Crook et al. 2009, 2010). Acute adhesions can often be managed by dilation with a thoroughly lubricated 18 French Foley catheter. For areas of penile radionecrosis or ulceration, expectant management with best supportive care is recommended with biopsy reserved for only scenarios where there is a high likelihood of tumor recurrence. Biopsy of areas of benign necrosis carries a great risk of leading to deeper and more extensive necrotic involvement. Best supportive care of radionecrotic penile lesions includes fastidious skin care and hygiene, oral analgesics, culture of any areas of suspected infection with appropriate topical or oral antibiotics if positive, and corticosteroids/Vitamin E topically as appropriate. Anecdotal reports exist of particularly deep or

Table 4 Commonly prescribed medications in the management of radiation toxicity of the distal male genitourinary tract

Medication	Indication	Dose	Notes
Skin			
Aquaphor (OTC)	Dry desquamation	Apply to affected area BID-TID	Emollient
Eucerin (OTC)	Dry desquamation	Apply to affected area BID-TID	Emollient
Domeboro soaks (OTC)	Moist desquamation	Moist soak 20 min BID-TID	Astringent
Silvadene cream 1 %	Moist desquamation	Apply to affected area TID	Antibacterial
Telfa (OTC)	Moist desquamation	Apply to affects area as needed	Tissue protectant
Hydrogel wound dressings	Moist desquamation	Apply to affects area as needed	Tissue protectant
Hydrocortisone cream 0.5–1 %	Pruritis	Apply to affected area TID	Topical corticosteroid
Urinary			
Naproxen 220 mg	Dysuria	220 mg PO BID	NSAID
Pyridium	Dysuria	200 mg PO TID-QID	Mucosal topical analgesic
Tamsulosin	Bladder outlet obstruction	0.4-0.8 mg po qd	Selective Alpha 1a blocker
Alfuzosin	Bladder outlet obstruction	10 mg po qd	Selective Alpha 1a blocker
Doxazocin	Bladder outlet obstruction	1–8 mg po qd (start at lowest dose)	Alpha 1 blocker
Terazosin	Bladder outlet obstruction	1–10 mg po qhs (start at lowest dose)	Alpha 1 blocker
Tolterodine	Bladder spasm	2 mg po bid	Anticholinergic
Flavoxate	Bladder spasm	100–200 mg po tid-qid	Anticholinergic
Oxybutynin	Bladder spasm	5 mg po bid-tid	Anticholinergic
Gastrointestinal			
Loperamide	Diarrhea	4 mg po once, then 2 mg po after each unformed stool, maximum 16 mg/day	Anti-diarrheal
Atropine/diphenoxylate	Diarrhea	1–2 tabs po tid-qid, maximum 8 tabs/day	Anti-diarrheal
Simethicone	Flatus	80–150 mg po bid	Anti-flatulent
Metamucil	Constipation	1–3 tablespoons qd with meals, mix with juice	Bulking agent
Colace	Constipation	100 mg po bid	Stool softener
Bisacodyl	Constipation	10 mg po or pr	Laxative
Senna	Constipation	2–4 tabs po qd-bid	Stool softener and laxative
Fleet enema	Constipation	1 pr as needed	Cathartic
Anusol HC	External anal dermatitis/proctitis	1–2.5 % ointment QID for external use/ 25 mg supp pr bid-tid	Topical steroid
ProctoFoam HC	Proctitis	2.5 % apply pr tid-qid	Topical steroid
Erectile dysfunction			
Sildenafil	Erectile dysfunction	25–100 mg po qd or prn	Do not use with nitrates, use great caution in patients with coronary artery disease or hypertension
Tadalafil	Erectile dysfunction	10–20 mg po qd or prn	Do not use with nitrates, use great caution in patients with coronary artery disease or hypertension
Vardenafil	Erectile dysfunction	5–20 mg po qd or prn	Do not use with nitrates, use great caution in patients with coronary artery disease or hypertension

Modified from Eric K Hansen and Mack Roach III (editors), Handbook of Evidence-based Radiation Oncology, 2007, Springer Science + Business Media, LLC, New York, New York

painful lesions responding to courses of hyperbaric oxygen (Crook et al. 2009). The management of late radiation-induced urethral strictures is discussed in detail below.

9.3   Acute Dysuria

For radiation-related acute dysuria related to prostate cancer treatment, NSAIDS such as naproxen 220 mg po bid are excellent front-line agents. Pyridium 200 mg po tid-qid is also effective but will turn the urine orange and is bothersome for some patients. If infection is suspected, a urine analysis and culture is recommended. Patients receiving radiation are susceptible to urinary tract infections from simulation procedures (catheterization, urethrograms, interstitial fiducial marker placement), urinary retention from obstructive symptoms, and from loss of epithelial integrity from inflammation. Front-line antibiotics for simple urinary tract obstructions include trimethoprim/sulfamethoxazole DS 1 tab po bid for 5–7 days and ciprofloxacin 250 mg po bid for 3–7 days. Consider the possibility of prostatitis, with a tender and boggy prostate on exam. If present, antibiotics may be necessary for several months.

For patients with symptoms of bladder spasm (classically frequency, urgency, and dysuria without hesitancy or intermittency), anti-cholinergic agents can be considered. For example tolterodine 2 mg po bid, flavoxate 100–200 mg po tid-qid, or oxybutynin 5 mg po bid-tid. In patients with chronic radiation cystitis or hematuria, pentoxifylline 400 mg po tid or vitamin E 1000 IU po qd have been reported to improve healing and fibrotic reactions by promoting submucosal blood flow. Pentoxifylline should be used with extreme caution in patients with a history of CNS or retinal hemorrhage.

9.4   Obstructive Symptoms

Obstructive symptoms should be screened for before and during treatment of the patient with prostate cancer. Formal urodynamic studies have been found to be of great use in predicting urinary obstruction or retention after radiation therapy. One study from University of California, San Francisco discovered that peak flow rate before prostate implant was highly predictive of acute urinary obstruction after the procedure (Ikeda and Shinohara 2009). Based on this study, the role of pre- and post-radiation urodynamic studies will likely expand in the future for both brachytherapy and external beam patients. While undergoing radiation treatment, patients reporting urgency or dysuria in combination with hesitancy and intermittency are likely experiencing obstructive symptoms, and the degree of urinary retention can be confirmed with a post-void residual bladder scan. Review the patient's medication list for agents that can increase obstructive symptoms, including anti-cholinergics, antihistamines, decongestants, and antispasmodics. Alpha-blockers are the agents of choice for obstructive symptoms, especially selective alpha-1a blockers such as tamsulosin 0.4–0.8 mg po qd or alfuzosin 10 mg po qd. These agents act by blockade of the α_{1a}-adrenoreceptor, which is the predominant subtype in the human prostate stroma. Blockade reduces prostate smooth muscle tone and inhibits the dynamic component urinary obstruction (Forray et al. 1994), inhibits growth of prostate cells, and leads to increased apoptosis in benign and prostate cancer cells (Tahmatzopoulos et al. 2004). Less specific alpha blockers are also effective but are more likely to cause hypotensive changes and take longer to decrease symptoms. These medications should be started at the lowest dose level and the patient should be carefully screened for symptoms. These agents include doxazocin 1–8 mg po qd and terazosin 1-10 mg po qhs. If complete, or near complete obstruction, Foley catherization may be indicated. If this is the case, some physicians discontinue radiation until the catheter is removed.

9.5   Urethral Strictures

Urethral strictures are typically managed with simple endoscopic urethrotomy or balloon dilation. Open repair is typically reserved for patients with multiply recurrent of complex strictures. The possibility of other causes than late radiation fibrosis causing the worsening symptoms must be considered, including recurrence of tumor. Furthermore, any intervention has the potential to worsen the fibrotic process, so the short-term benefits of any potential procedure should be carefully weighed against potential to worsen the long-term clinical situation. Merrick et al. reported that approximately one-third of recurrent strictures requiring repeat urethrotomy become refractory obliterative strictures requiring suprapubic urinary diversion (Merrick et al. 2006). Therefore, in some cases, conservative management may offer a superior therapeutic ratio. In a subset of patients, chronic self-catheterization can be used with success for strictures that are refractory to or not appropriate for surgical management (Marks et al. 1995). More complex interventional management options, especially for complex of refractory strictures include: excision and primary urethral anastomosis urethroplasty; prostatectomy with vesicourethral reanastomosis; onlay flap urethroplasty; suprapubic urinary diversion; or combined abdominal-perineal urethroplasty.

9.6   Urinary Incontinence

For the very rare occasion of radiation-related urinary incontinence or decreased urethral resistance, surgical interventions are again the mainstay of treatment. Treatment options include injection of substances such as collagen or implantation of artificial sphincters. For chronic urinary bleeding, endoscopic evaluation followed by coagulation or application of dilute formalin, alum, or silver nitrate has been shown to be effective. For refractory or brisk bleeding causing anemia, a bladder diversion procedure or substitution can be considered (Marks et al. 1995).

9.7   Altered Bowel Movements

9.7.1   Symptoms of Diarrhea

Symptoms of diarrhea during or after radiation therapy should be carefully evaluated. The practitioner should evaluate duration and severity of symptoms, including urgency, association with urination, consistency of stool, presence of abdominal cramping and gas, and weight changes. An infectious process should be ruled out, if clinically indicated. For radiation-induced diarrhea not responsive to a low residual, high pectin diet, try loperamide 4 mg × 1 and then 2 mg po after each unformed stool. If still refractory, atropine/diphenoxylate 1–2 tabs po three to four times a day may improve symptoms. Tincture of opium should be reserved for extremely refractory cases. For bothersome flatulence, simethicone 80–150 mg po at morning and night or over the counter Beano 1–3 servings before meals is effective.

9.7.2   Symptoms of Constipation

Patients occasionally develop constipation during or after treatment. If constipation does not respond to conservative measures like an increase in fiber and hydration, several agents can be considered: Metamucil 1–3 tablespoons in juice with meals will act as a bulking agent, Colace 100 mg po bid will soften stool, Bisacodyl 10 mg po or pr acts a laxative, and Senna 2–4 tabs po qd-bid acs a both a laxative and stool softener.

9.7.3   Acute Radiation Proctitis

For acute radiation proctitis or tenesmus, anti-inflammatory medications may be useful in the acute setting if symptoms are not accompanied by bleeding. Several topical steroidal agents also bring relief, including Anusol HC 25 mg suppositories two to three times a day or proctofoam HC 2.5 % applied pr 2–3 times per day. For perianal pain or irritation, rule out fungal infection or rectal fissure, then use hydrocortisone cream 1–2.5 % applied four times a day or a 1:1:1

ratio of Desitin cream, 2 % lidocaine jelly, and nystatin cream applied to the perianal area. Also consider sitz baths and temporarily switching from dry toilet paper to a moistened product without alcohol-based agents like baby wipes. For symptomatic inflamed hemorrhoids, OTC Preparation H suppositories are usually effective. If not, offer steroid suppositories for internal hemorrhoids or hydrocortisone 1–2.5 % for external hemorrhoids.

If chronic diarrhea persists or starts after pelvic radiation therapy, malabsorptive conditions should be considered and ruled out by a gastroenterologist, if necessary. Helpful dietary changes include increasing fiber intake and decreasing intake of dairy containing products or fatty foods. If no change, loperamide, diphenoxylate/atropine, or difenoxin/atropine can be considered. For symptoms of radiation proctitis, rectal bleeding or radiation-induced rectal ulceration, encourage a high fiber diet with plenty of hydration. Steroid suppositories as listed above should be first-line agents. If not effective, a hydrocortisone retention enema pr qhs (retaining for 1 hour) or mesalamine rectal suspension enema pr qhs can be attempted. Sulfasalazine or sucralfate po may also bring relief. If still no improvement, referral to a gastroenterologist is appropriate, where argon plasma coagulation or application of dilute formalin may be attempted. Other potentially effective treatment options include pentoxifylline, vitamin E, and hyperbaric oxygen.

9.8   Rectal Bleeding

The evaluation of a patient with rectal bleeding and a history of radiation therapy varies between physicians. Endoscopy is typically the diagnostic intervention of choice, but the extent of necessary evaluation (rectoscopy, sigmoidoscopy, or full colonoscopy) is unclear. When to perform a diagnostic intervention as opposed to observation and conservation management of rectal bleeding is also controversial. In general, if the bleeding is accompanied by other gastrointestinal symptoms, including change in bowel habits, painful defecation, abdominal pain, or new constitutional symptoms, diagnostic intervention is warranted. Furthermore, the timing of onset of rectal bleeding can offer diagnostic clues as to the etiology. Most radiotherapy-related late GI toxicities begin to manifest within 3 years of treatment (Fiorino et al. 2009). Although rectal dose–volume and spatial considerations have been found to be predictive of late rectal toxicity, endoscopic findings of apparent radiation change after treatment do not always correlate administered dose distributions (van Lin et al. 2007; Goldner et al. 2007). Regardless, endoscopic evaluation of a patient with rectal bleeding and other symptoms should occur until a source of bleeding is diagnosed (Moore

et al. 2000). Further management of symptomatic radiation proctitis is discussed below.

10 Future Direction and Research

Standard methods to define the penile bulb and associated critical structures should become more widely used. A standard method to score ED should be more widely adopted. Systematic prospective clinical trials that attempt to relate the three-dimensional dose–volume parameters from all of the potentially critical structures to clinical outcomes should be considered. Such studies may help to identify which pelvic structures are critical for ED. Dosimetric/imaging studies estimating uncertainties in the overall accumulated "true dose distribution" should be considered. This may be a key cause of inconsistencies between reported results. Anatomic studies to better define the critical anatomic sites for RT-associated ED may be helpful. Well-characterized data (including full dose distribution and imaging information) should be pooled from multiple studies where possible.

11 History and Literature Landmarks

Approximately 20 years after Roentgen reported the discovery of X-rays in 1895, Pasteau and Degrais first reported the use of radiation therapy to treat prostate cancer (Chassagne et al. 1985). By the 1950s, contemporary external beam radiation therapy was generally acknowledged as curative for localized prostate cancer (Bagshaw 1967; Del Regato 1967). Further technical refinements over the next several decades led to the development of three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy (IGRT) which allowed escalation of dose while sparing adjacent critical normal structures, leading to less short- and long-term toxicity rates and improved clinical outcomes (Leibel 2000; Leibel et al. 2002; Cahlon et al. 2008; Zelefsky et al. 2008a, b, c; Morris et al. 2005). Multiple randomized trials have confirmed that the dose escalation permitted with these modern techniques has led to improved clinical outcomes in patients with prostate cancer treated with external beam radiation therapy (Zietman et al. 2005; Peeters et al. 2006a, b; Dearnaley et al. 2007; Kubanzker et al. 2008; Zietman et al 2010). Furthermore, given the unique radiobiology of prostate cancer with a low α/β ratio of the order of 1.85 (Daşu 2007), an emerging body of data suggests that hypofractionated radiation schedules, where a higher dose per fraction is delivered in a smaller number of fractions, may be superior to conventional fractionation schemes in terms of both tumor control and toxicity profile for adenocarcinoma of the prostate. Many such treatment schedules have been reported with promising early results (Lloyd-Davies et al. 1990; Lukka et al. 2005; Tsuji et al. 2005; Soete et al. 2006; Yeoh et al. 2006; Junius et al. 2007; Martin et al. 2007; King et al. (in press); Livsey et al. 2003; Kupelian et al. 2007; Madsen et al. 2007; Fuller et al. 2008).

Refinements in permanent low-dose-rate interstitial and temporary high-dose-rate interstitial brachytherapy techniques have led to these modalities being curative as monotherapy in the low risk setting (Zelefsky et al. 2007; 2007) and beneficial as a boost added to external radiation in higher risk disease (Zelefsky et al. 2008a, b, c). Additionally, HDR brachytherapy is now being used to deliver hypofractionated re-irradiation as salvage treatment to those patients who have recurrence after external beam radiation therapy (Lee et al. 2007; Tharp et al. 2008). These definitive and salvage brachytherapy procedures have added to the fund of knowledge regarding the tolerance of normal tissues to radiation while introducing new considerations into dose–volume guidelines. Furthermore, ongoing national studies are examining the possible role for adding chemotherapy to definitive radiation and neoadjuvant, concurrent, and adjuvant androgen deprivation therapy for high risk group prostate cancer patients. The outcomes of these combined chemoradiation studies will likely further change and further refine our understanding of accepted normal tissue tolerances of radiotherapy.

References

al-Abany M, Helgason A et al (2004) Dose to the anal sphincter region and risk of fecal leakage. Acta Oncol 43(1):117–118

Albert M, Song J et al (2008) Defining the rectal dose constraint for permanent radioactive seed implantation of the prostate. Urol Oncol 26(2):147–152

Algan OGE, Hanks GE et al (1995) Localization of the prostatic apex for radiation treatment planning. Int J Radiat Oncol Biol Phys **33**(4):925–930

Andriole G, Bostwick D et al (2005) The effects of 5[alpha]-reductase inhibitors on the natural history, detection and grading of prostate cancer: current state of knowledge. J Urol 174(6):2098–2104

Antonakopoulos GN, Hicks RM et al (1982) Early and late morphological changes (including carcinoma of the urothelium) induced by irradiation of the rat urinary bladder. Br J Cancer 46(3):403–416

Antonakopoulos GN, Hicks RM et al (1984) The subcellular basis of damage to the human urinary bladder induced by irradiation. J Pathol 143(2):103–116

Arcangeli SL, Strigari et al (2009) Clinical and dosimetric predictors of acute toxicity after a 4-week hypofractionated external beam radiotherapy regimen for prostate cancer: results from a multicentric prospective trial. Int J Radiat Oncol Biol Phys 73(1):39–45

Armas O (1994) Clinical and pathobiological effects of neoadjuvant total androgen ablation therapy on clinically localized prostatic adenocarcinoma. Am J Surg Pathol 18(10):979–991

Aversa A, Isidori AM et al (2000) Androgens and penile erection: evidence for a direct relationship between free testosterone and cavernous vasodilation in men with erectile dysfunction. Clin Endocrinol 53(4):517–522

Bagshaw M (1967) Linear accelerator supervoltage therapy: VII. Carcinoma of the prostate. Radiology 85:121–129

Baskin LS, Constantinescu SC et al (1993) Biochemical characterization and quantitation of the collagenous components of urethral stricture tissue. Journal Urol 150(2):642–647

Bayman NA, Wylie JP (2007) When should the seminal vesicles be included in the target volume in prostate radiotherapy? J Clin Oncol 19(5):302–307

Beckendorf V, Gurif S et al (2004) The GETUG 70 Gy vs. 80 Gy randomized trial for localized prostate cancer: feasibility and acute toxicity. Int J Radiat Oncol Biol Phys 60(4):1056–1065

Bentzen SM (2006) Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat Rev Cancer 6(9):702–713

Bostwick DG (1982) Radiation injury of the normal and neoplastic prostate. Am J Surg Pathol 6(6):541–551

Bostwick D (1998) Pathology of the prostate. WB Saunders Company, New York

Brown MW, Brooks JP, Albert PS et al (2007) An analysis of erectile function after intensity modulated radiation therapy for localized prostate carcinoma. Prostate Cancer Prostatic Dis 10:189–193

Burman C, Kutcher GJ et al (1991) Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 21(1):123–135

Buyyounouski M, Horwitz E et al (2004) Intensity-modulated radiotherapy with MRI simulation to reduce doses received by erectile tissue during prostate cancer treatment. Int J Radiat Oncol Biol Phys 58(3):743–749

Cahlon O, Zelefsky MJ et al (2008) Ultra-high dose (86.4 Gy) IMRT for localized prostate cancer: toxicity and biochemical outcomes. Int J Radiat Oncol Biol Phys 71(2):330–337

Canada A, Neese L et al (2005) Pilot intervention to enhance sexual rehabilitation for couples after treatment for localized prostate carcinoma. Cancer 104(12):2689–2700

Carver BS, Kattan MW et al (2005) Gleason grade remains an important prognostic predictor in men diagnosed with prostate cancer while on finasteride therapy. BJU Int 95(4):509–512

Chan TW, Kressel HY (1991) Prostate and seminal vesicles after irradiation: MR appearance. J Magn Reson Imaging 1(5):503–511

Chassagne D, Court B et al (1985) Cancer of the prostate: technics of curietherapy. Review of the literature and experience at the Institut Gustave-Roussy. Bull Cancer 72(6):578–584

Chaudhary AJ, Ghosh S et al (1999) Interstitial brachytherapy in carcinoma of the penis. Strahlenther Onkol 175(1):17–20

Chen CT, Valicenti RK et al (2001) Does hormonal therapy influence sexual function in men receiving 3D conformal radiation therapy for prostate cancer? Int J Radiat Oncol Biol Phys 50:591–595

Chen R, Clark J et al (2009) Individualizing quality-of-life outcomes reporting: how localized prostate cancer treatments affect patients with different levels of baseline urinary, bowel, and sexual function. J Clin Oncol 27(24):3916–3922

Cheng J, Schultheiss T et al (2008) Acute toxicity in definitive versus postprostatectomy image-guided radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 71(2):351–357

Cheung MR, Tucker S et al (2007) Investigation of bladder dose and volume factors influencing late urinary toxicity after external beam radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 67(4):1059–1065

Coia LR, Myerson RJ et al (1995) Late effects of radiation therapy on the gastrointestinal tract. Int J Radiat Oncol Biol Phys 31(5):1213–1236

Crook J, Malone S et al (2000) Postradiotherapy prostate biopsies: what do they really mean? results for 498 patients. Int J Radiat Oncol Biol Phys 48(2):355-367

Crook J, Esche B et al (1996) Effect of pelvic radiotherapy for prostate cancer on bowel, bladder, and sexual function: the patient's perspective. Urology 47(3):387–394

Crook J, Ma C et al (2009) Radiation therapy in the management of the primary penile tumor: an update. World J Urol 27(2):189–196

Crook JJ, Jezioranski JV et al (2010) Penile brachytherapy: technical aspects and postimplant issues. Brachytherapy 9(2):151–158

Crosland A (1995) Rectal bleeding: prevalence and consultation behaviour. BMJ 311(7003):486–488

D'Amico AV, Manola J et al (2004) 6-month androgen suppression plus radiation therapy vs. radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 292:821–827

Daşu A (2007) Is the alpha/beta value for prostate tumours low enough to be safely used in clinical trials? Clin Oncol 19(5):289–301

Dearnaley D, Sydes M et al (2007) Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol 8(6):475–487

Del Regato JA (1967) Radiotherapy in the conservative treatment of operable and locally inoperable carcinoma of the prostate. Radiology 88(4):761–766

Delannes M, Malavaud B et al (1992) Iridium-192 interstitial therapy for squamous cell carcinoma of the penis. Int J Radiat Oncol Biol Phys 24(3):479–483

Emami B, Lyman J et al (1991) Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21(1):109–122

Etzioni R, Howlader N et al (2005) Long-term effects of finasteride on prostate specific antigen levels: results from the prostate cancer prevention trial. J Urol 174(3):877–881

Feigenberg SJ, Hanlon AL et al (2005) Long-term androgen deprivation increases Grade 2 and higher late morbidity in prostate cancer patients treated with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys 62(2):397–405

Fellin G, Fiorino C et al (2009) Clinical and dosimetric predictors of late rectal toxicity after conformal radiation for localized prostate cancer: results of a large multicenter observational study. Radiother Oncol 93(2):197–202

Fiorino C, Sanguineti G et al (2003) Rectal dose–volume constraints in high-dose radiotherapy of localized prostate cancer. Int J Radiat Oncol Biol Phys 57(4):953–962

Fiorino C, Fellin G et al (2008) Clinical and dosimetric predictors of late rectal syndrome after 3D-CRT for localized prostate cancer: preliminary results of a multicenter prospective study. Int J Radiat Oncol Biol Phys 70(4):1130–1137

Fiorino C, Cozzarini C et al (2002) Relationships between DVHs and late rectal bleeding after radiotherapy for prostate cancer: analysis of a large group of patients pooled from three institutions. Radiother Oncol 64(1):1–12

Fiorino C, Valdagni R et al (2009) Dose–volume effects for normal tissues in external radiotherapy: pelvis. Radiother Oncol 93(2):153–167

Fisch BM, Pickett B et al (2001) Dose of radiation received by the bulb of the penis correlates with risk of impotence after three-dimensional conformal radiotherapy for prostate cancer. Urology 57(5):955–959

Fonteyne V, De Neve W et al (2007) Late radiotherapy-induced lower intestinal toxicity (RILIT) of intensity-modulated radiotherapy for prostate cancer: The need for adapting toxicity scales and the appearance of the sigmoid colon as co-responsible organ for lower intestinal toxicity. Radiother Oncol 84(2):156–163

Forman JD, Kumar R et al (1995) Neoadjuvant hormonal downsizing of localized carcinoma of the prostate: effects on the volume of normal tissue irradiation. Cancer Invest 13(1):8–15

Forray C, Bard JA et al (1994) The alpha 1-adrenergic receptor that mediates smooth muscle contraction in human prostate has the pharmacological properties of the cloned human alpha 1c subtype. Mol Pharmacol 45(4):703–708

Franks L (1960) Estrogen-treated prostatic cancer: the variation in responsiveness of tumor cells. Cancer 13:490–501

Fuller DB, Naitoh J et al (2008) Virtual HDR CyberKnife treatment for localized prostatic carcinoma: dosimetry comparison with HDR brachytherapy and preliminary clinical observations. Int J Radiat Oncol Biol Phys 70(5):1588–1597

Gaudin PB, Zelefsky MJ et al (1999) Histopathologic effects of three-dimensional conformal external beam radiation therapy on benign and malignant prostate tissues. American J Surg Pathol 23(9):1021–1031

Gelblum DY, Potters L (2000) Rectal complications associated with transperineal interstitial brachytherapy for prostate cancer. Int J Radiat Oncol Biol Phys 48(1):119–124

Gelblum DY, Potters L et al (1999) Urinary morbidity following ultrasound-guided transperineal prostate seed implantation. Int J Radiat Oncol Biol Phys 45(1):59–67

Goldner GB, Tomicek et al (2007) Proctitis after external-beam radiotherapy for prostate cancer classified by Vienna Rectoscopy Score and correlated with EORTC/RTOG score for late rectal toxicity: Results of a prospective multicenter study of 166 patients. Int J Radiat Oncol Biol Phys 67(1):78–83

Goldstein N (1998) The histology of radiation therapy effect on prostate adenocarcinoma as assessed by needle biopsy after brachytherapy boost. Correlation with biochemical failure. Am J Clin Pathol 110(6):765–775

Goldstein I, Feldman MI et al (1984) Radiation-associated impotence. A clinical study of its mechanism. JAMA 251(7):903–910

Gray H (1995) Gray's Anatomy. New York, Barnes and Noble.uerrero Urbano, M. T. and C. M. Nutting (2004). Clinical use of intensity-modulated radiotherapy: part II. Br J Radiol 77(915):177–182

Guerrero Urbano MT, Nutting CM (2004) Clinical use of intensity-modulated radiotherapy: part II. Br J Radiol 77(915):177–182

Haase O (2004) Fibrosis and cytokine mechanisms: relevant in hadron therapy? Radiother Oncol 73(Suppl 2):S114

Hamilton AS, Stanford JL et al (2001) Health outcomes after external-beam radiation therapy for clinically localized prostate cancer: results from the prostate cancer outcomes study. J Clin Oncol 19(9):2517–2526

Han BH, Wallner KE (2001) Dosimetric and radiographic correlates to prostate brachytherapy-related rectal complications. Int J Cancer 96(6):372–378

Han M, Partin A et al (2004) An evaluation of the decreasing incidence of positive surgical margins in a large retropubic prostatectomy series. J Urol 171(1):23–26

Heemsbergen W (2008) GU toxicity after RT for prostate cancer: dose maps and dose surface data to identify dose–effect relationships. Radiother Oncol 88:83–84

Heemsbergen WD, Hoogeman MS et al (2005) Gastrointestinal toxicity and its relation to dose distributions in the anorectal region of prostate cancer patients treated with radiotherapy. Int J Radiat Oncol Biol Phys 61(4):1011–1018

Heemsbergen W, Peeters S et al (2006) Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage. Int J Radiat Oncol Biol Phys 66:3–10

Herold DM, Hanlon AL et al (1999) Diabetes mellitus: a predictor for late radiation morbidity. Int J Radiat Oncol Biol Phys 43(3):475–479

Herrmann T (ed) (2006) Clin Radiat Biol. Elsevier, Munich

Hollenbeck B, Wei J et al (2004) Neoadjuvant hormonal therapy impairs sexual outcome among younger men who undergo external beam radiotherapy for localized prostate cancer. Urology 63(5):946–950

Huang EH, Pollack A et al (2002) Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 54(5):1314–1321

Iczkowski KA, Qiu J et al (2005) The dual 5-alpha-reductase inhibitor dutasteride induces atrophic changes and decreases relative cancer volume in human prostate. Urology 65(1):76–82

Ikeda T, Shinohara K (2009) Peak flow rate is the best predictor of acute urinary retention following prostate brachytherapy: our experience and literature review. Int J Urol 16(6):558–560

Incrocci L, Koper PCM et al (2001) Sildenafil citrate (Viagra) and erectile dysfunction following external beam radiotherapy for prostate cancer: a randomized, double-blind, placebo-controlled, cross-over study. Int J Radiat Oncol Biol Phys 51(5):1190–1195

Incrocci L, Slob AK et al (2002) Sexual (dys)function after radiotherapy for prostate cancer: a review. Int J Radiat Oncol Biol Phys 52(3):681–693

Incrocci L, Slagter C et al (2006) A randomized, double-blind, placebo-controlled, cross-over study to assess the efficacy of tadalafil (Cialis®) in the treatment of erectile dysfunction following three-dimensional conformal external-beam radiotherapy for prostatic carcinoma. Int J Radiat Oncol Biol Phys 66(2):439–444

Jackson A, Skwarchuk MW et al. (2001) Late rectal bleeding after conformal radiotherapy of prostate cancer (II): volume effects and dose-volume histograms. Int J Radiat Oncol Biol Phys 49(3):685–698

Johannes CB, Araujo AB et al (2000) Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. J Urol 163(2):460–463

Junius S, Haustermans K et al (2007) Hypofractionated intensity modulated irradiation for localized prostate cancer, results from a phase I/II feasibility study. Radiat Oncol 2(1):29

Kang J (2003) Factors associated with the frequency of stool examination: effect on incidence of reported rectal bleeding. Eur J Gastroenterol Hepatol 15(5):531–533

Karlsdóttir Á, Muren LP et al (2008) Late gastrointestinal morbidity after three-dimensional conformal radiation therapy for prostate cancer fades with time in contrast to genitourinary morbidity. Int J Radiat Oncol Biol Phys 70(5):1478–1486

Karlsdttir A, Johannessen D et al (2004) Acute morbidity related to treatment volume during 3D-conformal radiation therapy for prostate cancer. Radiother Oncol 71(1):43–53

King CR, Brooks JD et al (2009) Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. Int J Radiat Oncol Biol Phys (in press)

Kiteley RA, Lee WR et al (2002) Radiation dose to the neurovascular bundles or penile bulb does not predict erectile dysfunction after prostate brachytherapy. Brachytherapy 1(2):90–94

Kratzik CW, Schatzl G, Lunglmayr G et al (2005) The impact of age, body mass index and testosterone on erectile dysfunction. J Urol 174:240–243

Kuban DA, Tucker et al SL (2008) Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 70(1):67–74

Kupelian PA, Willoughby TR et al (2007). Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. Int J Radiat Oncol Biol Phys 68(5):1424–1430

Lawton CA, Won M et al (1991) Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. Int J Radiat Oncol Biol Phys 21(4):935–939

Lawton CA, Bae K et al (2008) Long-term treatment sequelae after external beam irradiation with or without hormonal manipulation for adenocarcinoma of the prostate: analysis of Radiation Therapy Oncology Group studies 85–31, 86–10, and 92–02. Int J Radiat Oncol Biol Phys 70(2):437–441

Lee B, Shinohara K et al (2007) Feasibility of high-dose-rate brachytherapy salvage for local prostate cancer recurrence after radiotherapy: the University of California-San Francisco experience. Int J Radiat Oncol Biol Phys 67(4):1106–1112

Leibel S (2000) Prostate cancer: three-dimensional conformal and intensity modulated radiation therapy. PPO Updat 14:1–9

Leibel S, Fuks Z et al (2002) Intensity-modulated radiotherapy. Cancer J 8(2):164–176

Lips I, Dehnad H et al (2008) High-dose intensity-modulated radiotherapy for prostate cancer using daily fiducial marker-based position verification: acute and late toxicity in 331 patients. Radiat Oncol 3(1):15

Litwin MS, Lubeck DP et al (1998) Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: results of the CaPSURE database. J Urol 159(6):1988–1992

Liu M, Pickles T et al (2004) Impact of neoadjuvant androgen ablation and other factors on late toxicity after external beam prostate radiotherapy. Int J Radiat Oncol Biol Phys 58(1):59–67

Livsey JE, Cowan RA et al (2003) Hypofractionated conformal radiotherapy in carcinoma of the prostate: five-year outcome analysis. Int J Radiat Oncol Biol Phys 57(5):1254–1259

Lloyd-Davies RW, Collins CD et al (1990) Carcinoma of prostate treated by radical external beam radiotherapy using hypofractionation. Twenty-two years' experience (1962–1984). Urology 36(2):107–111

Lukka H, Hayter C et al (2005) Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. J Clin Oncol 23(25):6132–6138

Luxton G, Hancock SL et al (2004) Dosimetry and radiobiologic model comparison of IMRT and 3D conformal radiotherapy in treatment of carcinoma of the prostate. Int J Radiat Oncol Biol Phys 59(1):267–284

Macdonald AG, Keyes M et al (2005) Predictive factors for erectile dysfunction in men with prostate cancer after brachytherapy: is dose to the penile bulb important? Int J Radiat Oncol Biol Phys 63:155–163

Madsen BL, Hsi RA, et al (2007). Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. Int J Radiat Oncol Biol Phys 67(4):1099–1105

Magi-Galluzzi C, Sanderson H et al (2003) Atypia in nonneoplastic prostate glands after radiotherapy for prostate cancer: duration of atypia and relation to type of radiotherapy. Am J Surg Pathol 27(2):206–212

Mangar SA, Huddart RA et al (2005) Technological advances in radiotherapy for the treatment of localised prostate cancer. Eur J Cancer 41(6):908–921

Mangar SA, Sydes MR et al (2006) Evaluating the relationship between erectile dysfunction and dose received by the penile bulb: using data from a randomised controlled trial of conformal radiotherapy in prostate cancer (MRC RT01, ISRCTN47772397). Radiother Oncol 80(3):355–362

Mantz CA, Song P et al (1997) Potency probability following conformal megavoltage radiotherapy using conventional doses for localized prostate cancer. Int J Radiat Oncol Biol Phys 37(3):551–557

Marks LB, Carroll PR et al. (1995) The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. Int J Radiat Oncol Biol Phys 31(5):1257–1280

Martin JM, Rosewall T et al (2007) Phase II trial of hypofractionated image-guided intensity-modulated radiotherapy for localized prostate adenocarcinoma. Int J Radiat Oncol Biol Phys 69(4):1084–1089

Mazeron JJ, Langlois D et al (1984) Interstitial radiation therapy for carcinoma of the penis using iridium 192 wires: the Henri Mondor experience (1970–1979). Int J Radiat Oncol Biol Phys 10(10):1891–1895

McNeal J (1981) The zonal anatomy of the prostate. Prostate 2(1):35–49

Merrick GS, Butler WM et al (2002) The importance of radiation doses to the penile bulb vs. crura in the development of postbrachytherapy erectile dysfunction. Int J Radiat Oncol Biol Phys 54(4):1055–1062

Merrick G, Butler W et al (2006) Risk factors for the development of prostate brachytherapy related urethral strictures. J Urol 175(4):1376–1380

Meyers R (ed) (2001) Practical surgical anatomy for radical prostatectomy. Urol Clin North Am 28:473–490

Michalski JM, Winter K et al (2004) Toxicity after three-dimensional radiotherapy for prostate cancer with RTOG 9406 dose level IV. Int J Radiat Oncol Biol Phys 58(3):735–742

Michalski JM, Gay H et al (2010) Radiation dose–volume effects in radiation-induced rectal injury. Int J Radiat Oncol Biol Phys 76(Suppl 3):S123–S129

Miller D, Wei J et al (2006) Use of medications or devices for erectile dysfunction among long-term prostate cancer treatment survivors: potential influence of sexual motivation and/or indifference. Urology 68(1):166–171

Moore EM, Magrino TJ et al (2000) Rectal bleeding after radiation therapy for prostate cancer: endoscopic evaluation. Radiology 217(1):215–218

Morris DE, Emami B et al (2005) Evidence-based review of three-dimensional conformal radiotherapy for localized prostate cancer: an ASTRO outcomes initiative. Int J Radiat Oncol Biol Phys 62(1):3–19

Munbodh R, Jackson A et al (2008) Dosimetric and anatomic indicators of late rectal toxicity after high dose intensity modulated radiation therapy for prostate cancer. Med Phys 35(5):2137–2150

Nuyttens J, Milito S et al (2002) Dose–volume relationship for acute side effects during high dose conformal radiotherapy for prostate cancer. Radiother Oncol 64(2):209–214

O'Carroll R, Bancroft J (1984) Testosterone therapy for low sexual interest and erectile dysfunction in men: a controlled study. Br J Psychiatry 145:146–151

Peeters S, Heemsbergen W et al (2005a) Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy. Int J Radiat Oncol Biol Phys 61:1019–1034

Peeters S, Hoogeman M et al (2005b) Volume and hormonal effects for acute side effects of rectum and bladder during conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 63:1142–1152

Peeters S, Heemsbergen W et al (2006a) Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 24:1990–1996

Peeters STH, Heemsbergen W et al (2006b) Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 24(13):1990–1996

Peeters STH, Hoogeman MS et al (2006c) Rectal bleeding, fecal incontinence, and high stool frequency after conformal radiotherapy for prostate cancer: Normal tissue complication probability modeling. Int J Radiat Oncol Biol Phys 66(1):11–19

Peeters STH, Lebesque JV et al (2006d) Localized volume effects for late rectal and anal toxicity after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 64(4):1151–1161

Perna L, Fiorino C et al (2009) Sparing the penile bulb in the radical irradiation of clinically localised prostate carcinoma: a comparison between MRI and CT prostatic apex definition in 3DCRT, Linac-IMRT and Helical Tomotherapy. Radiother Oncol 93(1):57–63

Pickles T, Keyes M et al (2010) Brachytherapy or conformal external radiotherapy for prostate cancer: a single-institution matched-pair analysis. Int J Radiat Oncol Biol Phys 76(1):43–49

Pinkawa M, Fischedick K et al (2008) Toxicity profile with a large prostate volume after external beam radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 70(1):83–89

Pinkawa M, Gagel B et al (2009a) Erectile dysfunction after external beam radiotherapy for prostate cancer. Eur Urol 55:227–236

Pinkawa M, Piroth M et al (2009b) Impact of the target volume (prostate alone vs. prostate with seminal vesicles) and fraction dose (1.8 Gy vs. 2.0 Gy) on quality of life changes after external-beam radiotherapy for prostate cancer. Strahlenther Onkol 185(11):724–730

Pollack A, Zagars G et al (2002) Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 53(5):1097–1105

Potosky AL, Legler J et al (2000) Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the prostate cancer outcomes study. J Natl Cancer Inst 92(19):1582–1592

Prestidge BR, Hoak DC et al (1997) Posttreatment biopsy results following interstitial brachytherapy in early-stage prostate cancer. Int J Radiat Oncol Biol Phys 37(1):31–39

Rancati T, Fiorino C et al (2004) Fitting late rectal bleeding data using different NTCP models: results from an Italian multi-centric study (AIROPROS0101). Radiother Oncol 73(1):21–32

Roach M 3rd, Winter K et al (2004) Penile bulb dose and impotence after three-dimensional conformal radiotherapy for prostate cancer on RTOG 9406: findings from a prospective, multi-institutional, phase I/II dose-escalation study. Int J Radiat Oncol Biol Phys 60(5):1351–1356

Roach M 3rd, Nam J et al (2010) IJROBP, Radiation dose–volume effects and the penile bulb. Int J Radiat Oncol Biol Phys 76(Suppl 3):S130–S134

Rosen RC, Riley A et al (1997) The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 49(6):822–830

Rosen RC, Cappelleri JC et al (1999) Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 11:319–326

Rosenberg MT (2007) Diagnosis and management of erectile dysfunction in the primary care setting. Int J Clin Pract 61:1198–1208

Rozan R, Albuisson E et al (1995) Interstitial brachytherapy for penile carcinoma: a multicentric survey (259 patients). Radiother Oncol 36(2):83–93

Ryu J, Winter K et al (2002) Interim report of toxicity from 3D conformal radiation therapy (3D-CRT) for prostate cancer on 3DOG/RTOG 9406, level III (79.2 Gy). Int J Radiat Oncol Biol Phys 54(4):1036–1046

Saad F, Grahl A et al (2007) Effects of testosterone on erectile function: implications for the therapy of erectile dysfunction. BJU Int 99(5):988–992

Sanda M, Dunn R et al (2008) Quality of life and satisfaction with outcome among prostate-cancer survivors. New Engl J Med 358(12):1250–1261

Sanguineti G, Cavey ML et al (2006) Is IMRT needed to spare the rectum when pelvic lymph nodes are part of the initial treatment volume for prostate cancer? Int J Radiat Oncol Biol Phys 64(1):151–160

Sanguineti G, Marcenaro M et al (2003) Neoadjuvant androgen deprivation and prostate gland shrinkage during conformal radiotherapy. Radiother Oncol 66(2):151–157

Sarin R, Norman AR et al (1997) Treatment results and prognostic factors in 101 men treated for squamous carcinoma of the penis. Int J Radiat Oncol Biol Phys 38(4):713–722

Schenken J (1942) The effect of DES and DES dipropionate on carcinoma of the prostate gland. J Urol 48

Schiff J, Bar-Chama N et al (2006) Early use of a phosphodiesterase inhibitor after brachytherapy restores and preserves erectile function. BJU Int 98(6):1255–1258

Schultheiss TE, Hanks GE et al (1995) Incidence of and factors related to late complications in conformal and conventional radiation treatment of cancer of the prostate. Int J Radiat Oncol Biol Phys 32(3):643–649

Selek U, Cheung R et al (2004) Erectile dysfunction and radiation dose to penile base structures: a lack of correlation. Int J Radiat Oncol Biol Phys 59(4):1039–1046

Sethi A, Mohideen N et al (2003) Role of IMRT in reducing penile doses in dose escalation for prostate cancer. Int J Radiat Oncol Biol Phys 55(4):970–978

Sheaff MT, Baithun SI (1997) Effects of radiation on the normal prostate gland. Histopathology 30(4):341–348

Skala M, Rosewall T, Dawson L et al (2007) Patient-assessed late toxicity rates and principal component analysis after image-guided radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 68:690–698

Skwarchuk MW, Jackson A et al (2000) Late rectal toxicity after conformal radiotherapy of prostate cancer (I): multivariate analysis and dose-response. Int J Radiat Oncol Biol Phys 47(1):103–113

Smit W, Helle PA et al (1990) Late radiation damage in prostate cancer patients treated by high dose external radiotherapy in relation to rectal dose. Int J Radiat Oncol Biol Phys 18:23–29

Snyder KM, Stock RG et al (2001) Defining the risk of developing grade 2 proctitis following 125I prostate brachytherapy using a rectal dose–volume histogram analysis. Int J Radiat Oncol Biol Phys 50(2):335–341

Soete G, Arcangeli S et al (2006) Phase II study of a four-week hypofractionated external beam radiotherapy regimen for prostate cancer: report on acute toxicity. Radiother Oncol 80(1):78–81

Söhn M, Yan D et al (2007) Incidence of late rectal bleeding in high-dose conformal radiotherapy of prostate cancer using equivalent uniform dose-based and dose-volume-based normal tissue complication probability models. Int J Radiat Oncol Biol Phys 67(4):1066–1073

Solan A, Cesaretti J et al (2009) There is no correlation between erectile dysfunction and dose to penile bulb and neurovascular bundles following real-time low-dose-rate prostate brachytherapy. Int J Radiat Oncol Biol Phys 73(5):1468–1474

Stewart FA (1986) Mechanism of bladder damage and repair after treatment with radiation and cytostatic drugs. Br J Cancer Suppl 53:280–291

Storey MR, Pollack A et al (2000) Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. Int J Radiat Oncol Biol Phys 48(3):635–642

Storey M, Pollack A et al (2000) Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. Int J Radiat Oncol Biol Phys 48:635–642

Tahmatzopoulos A, Rowland R et al (2004) The role of alpha-blockers in the management of prostate cancer. Expert Opin Pharmacother 5(6):1279–1285

Talcott JA, Rieker P et al (1998) Patient-reported symptoms after primary therapy for early prostate cancer: results of a prospective cohort study. J Clin Oncol 16(1):275–283

Talley NJ, Jones M (1998) Self-reported rectal bleeding in a United States community: prevalence, risk factors, and health care seeking. Am J Gastroenterol 93(11):2179–2183

Tanagho EA, McAninch JW (eds) (2008) Smith's General Urology. New York, McGraw Hill

Tetu B (1991) Effect of combination endocrine therapy (LHRH agonist and flutamide) on normal prostate and prostatic adenocarcinoma. A histopathologic and immunohistochemical study. Am J Surg Pathol 15(2):111–120

Tharp M, Hardacre M et al (2008) Prostate high-dose-rate brachytherapy as salvage treatment of local failure after previous external or permanent seed irradiation for prostate cancer. Brachytherapy 7(3):231–236

Theodorescu D, Gillenwater JY et al (2000) Prostatourethral-rectal fistula after prostate brachytherapy. Cancer 89(10):2085–2091

Thompson IM, Goodman PJ et al (2003) The influence of Finasteride on the development of prostate cancer. N Engl J Med 349(3):215–224

Thompson IM, Pauler Ankerst D et al (2007) Prediction of prostate cancer for patients receiving finasteride: results from the prostate cancer prevention trial. J Clin Oncol 25(21):3076–3081

Tran A, Wallner K et al (2005) Rectal fistulas after prostate brachytherapy. Int J Radiat Oncol Biol Phys 63(1):150–154

Tsuji H, Yanagi T et al (2005) Hypofractionated radiotherapy with carbon ion beams for prostate cancer. Int J Radiat Oncol Biol Phys 63(4):1153–1160

Valdagni R, Rancati T et al (2008) Development of a set of nomograms to predict acute lower gastrointestinal toxicity for prostate cancer 3D-CRT. Int J Radiat Oncol Biol Phys 71(4):1065–1073

Valicenti RK, Winter K et al (2003) RTOG 94-06: is the addition of neoadjuvant hormonal therapy to dose-escalated 3D conformal radiation therapy for prostate cancer associated with treatment toxicity? Int J Radiat Oncol Biol Phys 57(3):614–620

van der Wielen G, Mulhall J et al (2007a) Erectile dysfunction after radiotherapy for prostate cancer and radiation dose to the penile structures: a critical review. Radiother Oncol 84(2):107–113

van der Wielen GJ, van Putten WLJ, Incrocci L (2007b) Sexual function after three-dimensional conformal radiotherapy for prostate cancer: results from a dose-escalation trial. Int J Radiat Oncol Biol Phys 68:479–484

van der Wielen G, Hoogeman M et al (2008) Dose-volume parameters of the corpora cavernosa do not correlate with erectile dysfunction after external beam radiotherapy for prostate cancer: results from a dose-escalation trial. Int J Radiat Oncol Biol Phys 71(3):795–800

van Lin ENJT, Kristinsson J et al (2007) Reduced late rectal mucosal changes after prostate three-dimensional conformal radiotherapy with endorectal balloon as observed in repeated endoscopy. Int J Radiat Oncol Biol Phys 67(3):799–811

Vargas C, Martinez A et al (2005) Dose–volume analysis of predictors for chronic rectal toxicity after treatment of prostate cancer with adaptive image-guided radiotherapy. Int J Radiat Oncol Biol Phys 62(5):1297–1308

Vavassori V, Fiorino C et al (2007) Predictors for rectal and intestinal acute toxicities during prostate cancer high-dose 3D-CRT: results of a prospective multicenter study. Int J Radiat Oncol Biol Phys 67(5):1401–1410

Vernon S (1983) Pre-treatment and post-treatment evaluation of prostatic adenocarcinoma for prostatic specific acid phosphatase and prostatic specific antigen by immunohistochemistry. J Urol 130(1):95–98

Vordermark D, Schwab M et al (2003) Association of anorectal dose–volume histograms and impaired fecal continence after 3D conformal radiotherapy for carcinoma of the prostate. Radiother Oncol 69(2):209–214

Vozenin-Brotons M-C, Milliat F et al (2003) Fibrogenic signals in patients with radiation enteritis are associated with increased connective tissue growth factor expression. Int J Radiat Oncol Biol Phys 56(2):561–572

Wallner KE, Merrick GS et al (2002) Penile bulb imaging. Int J Radiat Oncol Biol Phys 53:928–933

Walz J, Burnett AL et al (2010) A critical analysis of the current knowledge of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. Eur Urol 57(2):179–192

Wang CJ, Leung SW et al (1998) The correlation of acute toxicity and late rectal injury in radiotherapy for cervical carcinoma: evidence suggestive of consequential late effect (CQLE). Int J Radiat Oncol Biol Phys 40(1):85–91

Waterman FM, Dicker AP (2003) Probability of late rectal morbidity in 125I prostate brachytherapy. Int J Radiat Oncol Biol Phys 55(2):342–353

Weber DC, Bieri S et al (1999) Prospective pilot study of sildenafil for treatment of postradiotherapy erectile dysfunction in patients with prostate cancer. J Clin Oncol 17(11):3444–3449

Wernicke AG, Valicenti R et al (2004) Radiation dose delivered to the proximal penis as a predictor of the risk of erectile dysfunction after three-dimensional conformal radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 60(5):1357–1363

Yang XJ, Lecksell K et al (1999) Does long-term finasteride therapy affect the histologic features of benign prostatic tissue and prostate cancer on needle biopsy? Urology 53(4):696–700

Yeoh EE, Holloway RH et al (2006) Hypofractionated versus conventionally fractionated radiation therapy for prostate carcinoma: updated results of a phase III randomized trial. Int J Radiat Oncol Biol Phys 66(4):1072–1083

Zapatero A, Valcarcel F et al (2005) Risk-adapted androgen deprivation and escalated three-dimensional conformal radiotherapy for prostate cancer: does radiation dose influence outcome of patients treated with adjuvant androgen deprivation? A GICOR study. J Clin Oncol 23(27):6561–6568

Zelefsky MJ, Levin EJ et al (2008) Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 70(4):1124–1129

Zelefsky MJ, Yamada Y et al (2008) Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. Int J Radiat Oncol Biol Phys 71(4):1028–1033

Zelefsky MJ, Eid JF (1998) Elucidating the etiology of erectile dysfunction after definitive therapy for prostatic cancer. Int J Radiat Oncol Biol Phys 40(1):129–133

Zelefsky MJ, Harrison A (1997) Neoadjuvant androgen ablation prior to radiotherapy for prostate cancer: reducing the potential morbidity of therapy. Urology 49(3A Suppl):38–45

Zelefsky MJ, McKee AB et al (1999) Efficacy of oral sildenafil in patients with erectile dysfunction after radiotherapy for carcinoma of the prostate. Urology 53(4):775–778

Zelefsky MJ, Kelly WK et al (2000) Results of a phase II study using estramustine phosphate and vinblastine in combination with high-dose three-dimensional conformal radiotherapy for patients with locally advanced prostate cancer. J Clin Oncol 18(9):1936–1941

Zelefsky M, Fuks Z et al (2002) High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 53(5):1111–1116

Zelefsky M, Chan H et al (2006) Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. J Urol 176:1415–1419

Zelefsky M, Kuban D et al (2007a) Multi-institutional analysis of long-term outcome for stages T1–T2 prostate cancer treated with permanent seed implantation. Int J Radiat Oncol Biol Phys 67(2):327–333

Zelefsky M, Yamada Y et al (2007b) Five-year outcome of intraoperative conformal permanent I-125 interstitial implantation for patients with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 67(1):65–70

Zelefsky M, Nedelka M et al (2008) Combined brachytherapy with external beam radiotherapy for localized prostate cancer: reduced morbidity with an intraoperative brachytherapy planning technique and supplemental intensity-modulated radiation therapy. Brachytherapy 7(1):1–6

Zietman A, DeSilvio M et al (2005) Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 294(10):1233–1239

Zietman A, Bae K et al (2010) Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95–09. J Clin Oncol 28(7):1106–1111

Zouhair A, Coucke PA et al (2001) Radiation therapy alone or combined surgery and radiation therapy in squamous-cell carcinoma of the penis? Eur J Cancer 37(2):198–203