SECTION 4 Cancer of the Prostate

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INTRODUCTION

Prostate cancer is a significant health care problem in the United States due to its high incidence and mortality, the costs associated with its detection and treatment, and the fact that no consensus exists on what constitutes the best form of treatment for any stage of this disease. Excluding superficial skin cancers, prostate cancer is the most common malignancy afflicting American men.

Since the advent in the late 1980s of prostate-specific antigen (PSA) level as an effective screening test, the medical community has witnessed a dramatic increase in the incidence of prostate cancer cases. Between 1985 and 1992, the age-adjusted incidence in the United States more than doubled, reaching a peak of more than 190 cases per 100,000 in 1992.1 Perhaps reflecting stage migration or more effective treatment for localized disease, 5-year cancer survival rates have increased from approximately 70% in the early 1980s to more than 90% a decade later.1 Since 1992, the incidence rate has steadily declined.

To date, no conclusive data confirm that screening reduces disease morbidity and mortality. Observations that support screening and early detection include the following: PSA screening improves detection of clinically important tumors without significantly increasing the detection of unimportant tumors; the disease is more burdensome at later stages; most PSA-detected tumors are curable using current techniques; and there is no cure for metastatic disease. However, until properly conducted trials of screening are completed, the benefits and risks of prostate cancer's early detection and the associated treatment methods should be discussed carefully with patients.

NORMAL PROSTATE ANATOMY AND HISTOLOGY

The prostate is an ovoid structure located between the urinary bladder superiorly and the pelvic floor inferiorly (Fig. 34.4-1). The urethra traverses this gland, entering its base below the bladder neck and exiting at the narrowed apex at the level of the urogenital diaphragm. The anterior surface of the prostate is attached to the pubis, and the posterior surface is flattened with a midline depression that lies against the rectal ampulla. The lateral and inferior surfaces of the gland are in contact with the levator ani muscles. The levator ani muscles have an almost vertical orientation, funneling inferiorly to surround the rectum and bracket the striated urethral sphincter and middle and apical portions of the prostate.2 The ejaculatory ducts enter the posterior surface laterally and pass obliquely toward the midline, where they end at the verumontanum on the posterior surface of the prostatic urethra. Because of the gland's location deep within the pelvis behind the pubic bone,

surgical as well as radiation-based approaches to expose and target the prostate and protect surrounding structures may be challenging.

FIGURE 34.4-1. Prostate and regional anatomy.

The prostate's anterior surface and the adjacent lateral pelvic floor are covered by the periprostatic fascia, which is formed by the prostatic and levator fasciae. Lateral to the gland, this layer is called the *endopelvic fascia*, and it covers both the pelvic floor and important underlying neurovascular structures. The prostatic venous plexus (of Santorini), a rich network of tributary veins that serve as the primary penile drainage, is seen within this fascial covering. Erectile nerves to the corpora cavernosa travel outside the prostatic capsule in the lateral pelvic fascia between the prostate and the rectum

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(see Fig. 34.4-1). The cavernous nerves arise from the pelvic plexus, contain both sympathetic and parasympathetic fibers, and pass beneath the arch of the pubis to supply the corpora cavernosa and the corpus spongiosum. These end in a network of nerve fibers around the cavernous vessels at the penile hilum. Appreciating these anatomic relationships intraoperatively is essential to avoid unnecessary injury and bleeding.3 The prostatic capsule, composed of condensed smooth muscle and connective tissue, blends with the prostatic sheath on the anterior and anterolateral surfaces of the gland and with the anterior lamella of Denonvilliers' fascia on the posterior gland surface.4 The puboprostatic ligaments extend anterolaterally from the surface of the gland to fix the apex of the prostate to the pubis.5 At both the apex and base, no clear capsule separates the prostate from the striated urethral sphincter or bladder neck, respectively. Prostatic glands can be seen in the substance of the urethral sphincter, and smooth muscle fibers from the detrusor blend with the muscular coat of the prostate. Separating the prostate from the rectum is a layer of fascia, Denonvilliers' fascia, derived from two layers of pelvic peritoneum in the retrovesical space.

While voluntary control of voiding begins with relaxation of the striated sphincter in the membranous urethra, smooth muscle components of the bladder neck and prostate contribute to continence in men.6 The preprostatic sphincter is composed of muscle elements from the bladder. These muscles encircle the urethra and travel along and insert into the urethra more distally. The preprostatic sphincter provides resistance to urine leakage and retrograde seminal ejaculation. A passive prostatic sphincter is located distal to the verumontanum and is related closely to the striated muscle elements of the prostatomembranous sphincter.7

The prostatic striated sphincter forms a thick muscle layer over the anterior surface of the gland. Distally, these fibers almost completely surround the gland, except for a posterior gap at the apex, and merge with muscles of the membranous urethral sphincter. Fibers of the membranous striated sphincter encircle the urethra, originating at the anterior decussation of the prostatic sphincter and inserting at the perineal body at the level of the perineal membrane. These sphincteric fibers insert broadly over the surface of the prostatic fascia near the apex and play an important role in regaining continence after radical

prostatectomy.8,9 and 10

The primary arterial supply to the prostate comes from the prostatovesical artery that descends inferiorly along the bladder base. The origin of this artery is variable, but it usually comes from the anterior division of the internal iliac artery. The prostatic artery divides at the base of the prostate into the large posterolateral branch and the smaller anterior branch. The superolateral gland may receive arterial supply from the middle and superior rectal arteries. Urethral branches from the prostatic artery enter the capsule posterolaterally below the bladder neck to supply the transitional zone and periurethral glands. Capsular branches, traveling in the neurovascular bundle posterolaterally to the gland, enter the capsule more distally and laterally, to supply the central and peripheral zones. Prostate parenchymal veins, as well as veins draining all deep pelvic structures, intercommunicate with the prostatic venous plexus lying within the periprostatic fascia on the anterior surface of the gland.11 The deep dorsal vein of the penis emerges beneath the symphysis pubis between the puboprostatic ligaments to join this plexus. The majority of venous blood drains directly into the prostatic and inferior vesical veins to the internal iliac veins.

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Seminal emission is a neural process mediated within the prostate. With sexual activity, parasympathetic nerves stimulate the prostatic acini to produce secretions. Sympathetic nerve activity closes the preprostatic sphincter, preventing retrograde ejaculation, and increases smooth muscle tone in both the prostatic parenchyma and capsule to deposit secretions in the urethra (emission).12,13 Ejaculation occurs with contraction of the striated bulbospongiosus muscle.

Preganglionic sympathetic nerves to the preprostatic sphincter and smooth musculature of the prostate gland originate at spinal level L2-3 and pass through the sympathetic chain ganglia to the superior hypogastric plexus. Here they synapse with postganglionic noradrenergic nerves, the cell bodies of which lie in the pelvic plexus lateral to the bladder and prostate. Parasympathetic innervation to the prostatic epithelium originates in the pelvic splanchnic nerves from spinal levels S2-4. These preganglionic neurons synapse in the prostatic plexus, located between the seminal vesicles and the prostate, and send short postganglionic fibers into the prostate stroma. Somatic motor output from the pudendal nerve arises from S1-3 and innervates the pubococcygeus muscle of the external striated sphincter. Some contribution to external sphincter tone may also come from the pelvic nerve.14,15,16 and 17 The prostatic nerve, which includes sympathetic, parasympathetic, and somatic fibers, travels with the neurovascular bundle and sends off main branches at the level of the prostate base. This nerve continues posterolaterally along the prostate and divides into apical branches and a branch to the ejaculatory duct. The main branches pierce the prostatic capsule, then travel along the fibromuscular trabeculae as acinar branches before reaching their terminals at muscular and glandular cells. Afferent nerves from the prostate travel through the pelvic plexus to reach sensory tracts in the spinal cord.

Lymph capillaries emerge from the fibrous stroma and anastomose to form a lobular network of channels. The major route of lymphatic drainage occurs along the prostatic artery to the obturator and internal iliac nodes. Secondary lymphatic drainage originates at the base of the prostate, where lymphatic trunks travel along the medial border of the

seminal vesicles to drain into the external iliac nodes. Two more minor routes are along capsular lymphatics on the posterior surface of the gland to the sacral and internal iliac lymph nodes.

The internal structure of the prostate has been organized into *lobes* or *zones*. Early descriptions of five lobes were based on the embryologic concept of the prostate beginning as five groups of epithelial buds that branch off of the urogenital sinus between gestational weeks 11 and 16. By successively branching and rebranching, a complex system of ducts is formed circumferentially around the urethra, forming anterior, posterior, median, and two lateral lobes. However, the zonal description of prostate structure is more commonly used in clinical practice today.18 According to this scheme, the prostate consists of two primary areas: the peripheral zone and the central zone. In the normal gland of young adults, these two zones make up 95% of the prostate mass. The remaining 5% of the gland is made up of the transitional zone, an anterior fibromuscular segment, and a preprostatic sphincter zone. It is well recognized that prostate cancer occurs primarily in the peripheral zone, while the adenomatous growth of benign prostatic hypertrophy occurs primarily in the transitional zone.

The prostatic parenchyma is composed primarily of glandular epithelium, yet 30% of its mass is composed of muscular elements. The secretory epithelium of the prostate is contained within tubuloalveolar glands with a simple branching architecture. These glands are lined with simple cuboidal or columnar epithelium under which lie flattened basal cells. Stromal smooth muscle and connective tissue surround most of the acini. Ducts draining each gland enter the urethra in several locations. Periurethral glands, not connected to the deep network of acini, drain into the urethra.

PATHOLOGY AND PATTERNS OF PROGRESSION OF PROSTATE CANCER

Approximately 75% of prostate cancers will arise in the peripheral zone of the gland. Another 15% may occur in the central zone, and 10% to 15% will be located in the transitional zone. Carcinoma within the peripheral zone of the gland may be palpable, on digital rectal examination (DRE), as firm nodules or induration. However, it is not uncommon for cancers to be nonpalpable. Gross examination of cancerous tissue in prostatectomy specimens often reveals a similarly firm and gritty texture on palpation; however, lesions can be extremely difficult to differentiate visually from the surrounding normal prostatic parenchyma.19 Histologically, 95% of prostate cancers or more are adenocarcinomas derived from prostatic acinar cells. Carcinomas tend to be multifocal and show heterogeneous glandular patterns of malignant growth.20 The glands are typically small or medium-sized, lined with a single layer of cuboidal or low columnar epithelium. The outer basal layer, found in normal and hyperplastic glands, usually is absent in carcinoma. In suspicious lesions, immunohistochemical staining for basal cells can assist in diagnosis.21 Cancerous acini are irregularly shaped and packed closely together with varying amounts of stroma. In some poorly differentiated tumors, cells in cords or sheets may replace the glandular pattern. Perineurial, lymphatic, and vascular invasions are common and are reliable signs of malignancy. The mechanism of transformation from benign to malignant adenocarcinomas is unclear; however, androgen stimulation appears to

play an important role in pathogenesis.22

Similar to other cancers, prostate adenocarcinomas are graded histologically. Pathologic interpretation of needle biopsy and prostatectomy specimens focuses on the degree of glandular differentiation, cytologic atypia, and nuclear abnormalities. Several grading systems have been proposed, of which the Gleason system is the most commonly used.23,24 This grading system recognizes the fact that prostate cancer is a multifocal disease with heterogeneous glandular patterns. Thus, two individual scores, each ranging from 1 to 5, are given to the two most predominant histologic patterns of prostate cancer. The two scores are added together to give the Gleason sum. Sums of 2 to 4 represent well-differentiated disease; 5 to 7, moderately differentiated disease; and 8 to 10, poorly differentiated disease (Fig. 34.4-2). In well-differentiated cancers, groups of small acini are spaced closely "back to back," with little intervening stroma and a loss of the normal myoepithelium that surrounds the glandular elements. Histologically, glands may show luminal distention with mucin (so-called colloid carcinoma) or may take on a cribriform or papillary organization.25,26 Moderately differentiated cancers are characterized by more haphazardly organized acini,

more pronounced nuclear anaplasia, and infiltration of surrounding normal glands. In poorly differentiated adenocarcinoma, cells appear to be in sheets or cords, and glandular components may not be discernible. There is pronounced nuclear anaplasia, and invasion of surrounding tissue may be seen. When comparing patients with similar Gleason sums, it is important to note that the major Gleason pattern score may have additional prognostic value. For instance, patients with 3+4 disease tend to do better than those with 4+3 disease. In our experience, 3-year actuarial PSA failure–free survival rates in patients treated with prostatectomy are approximately 82% for the former group and 77% for the latter.

FIGURE 34.4-2. Prostate cancer histology. **A:** Gleason grade 2 (200×). Glands are medium-sized and well developed, with only mild variation in gland size and shape, luminal blue mucin, and no basal cell layer. The glands are tightly packed with minimal intervening stroma and grow in circumscribed nodules, with a minimal peripheral infiltrative pattern. Nuclear features of malignancy include mild nuclear enlargement, granular chromatin, and nucleoli. **B:** Gleason grade 3 (200×). Glands are well developed, with more profound variation in contour and morphology. The glands grow in an infiltrative pattern as seen here, with extension into extraprostatic tissues. **C:** Gleason grade 4 (200×). Malignant cells have trabecular and glandular growth pattern, forming small solid nests and abortive, fused glandular lumens. This tumor has a highly infiltrative pattern with scattered small angulated nests. Malignant nuclear features include marked nuclear enlargement and macronucleoli. **D:** Gleason grade 5 (200×). Highly infiltrative growth pattern with single cells and small nests of malignant epithelial cells. Cytologic features include marked nuclear pleomorphism and anisonucleosis with irregular contours, coarse irregular chromatin distribution, and macronucleoli.

The histology of the remaining 5% of prostate cancers is heterogeneous, arising from stromal, epithelial, or ectopic cells. Nonadenocarcinoma variants can be categorized into two groups—epithelial and nonepithelial—based on the cellular

origin. Epithelial variants consist of endometrioid, mucinous, signet-ring, adenoid cystic, adenosquamous, squamous cell, transitional cell, and neuroendocrine carcinoma and

comedocarcinoma. Among the nonepithelial variants are rhabdomyosarcoma, leiomyosarcoma, osteosarcoma, angiosarcoma, carcinosarcoma, malignant lymphoma, and metastatic neoplasms (Table 34.4-1). An appreciation of histologic variants is important, because treatment and prognosis may be different.

TABLE 34.4-1. Examples of Nonadenocarcinoma Prostate Cancer Cell Types

Endometrioid carcinoma involves the prostatic urethra and periurethral prostatic ducts in the region of the verumontanum. Histologically, it resembles endometrial adenocarcinoma of the uterus with complex glands lined by stratified columnar epithelium.27,28 Clinically, this variant is more aggressive than simple adenocarcinoma and often is associated with metastases and a poorer prognosis. Another epithelial variant is mucinous adenocarcinoma. It is characterized by large accumulations of extracellular mucin and luminal distention.26,29 Overall prognosis is similar to that of adenocarcinoma. Signet-ring cell carcinoma is characterized by large cytoplasmic vacuoles that displace the nucleus and frequently is associated with poorly differentiated and aggressive adenocarcinoma.30 Associations with mucinous adenocarcinoma are not uncommon, and vacuoles may or may not be filled with mucin. The prognosis for patients with primary signet-ring cell carcinoma is poor, with a 3-year survival rate of 27%.31 Comedocarcinoma is characterized by nests of cells with central necrosis. Comedocarcinoma resembles poorly differentiated adenocarcinoma (Gleason grade 5) and usually carries a poor prognosis.32 A rare variant with a better prognosis is adenoid cystic carcinoma. Histologically, lesions resemble basal cell hyperplasia, and disease usually is organ-confined.33,34

Squamous cell carcinoma of the prostate accounts for 0.5% to 1% of all prostate cancers and sometimes is difficult to differentiate from disease originating from the bladder and urethra.35 Such histologic features as keratinization and intercellular bridging are seen, as is the lack of glandular differentiation. Clinically, patients present in fashions similar to those with adenocarcinoma; however, serum tumor markers such as acid phosphatase and PSA will remain normal.35,36,37 and 38 This epithelial variant is more aggressive than adenocarcinoma, with an average survival after diagnosis of approximately 14 months.39 Primary transitional cell carcinoma (TCC) of the prostate has also been reported, although secondary spread from the bladder is much more common.40 Primary prostatic TCC does not respond to hormonal therapy but has been shown to respond to combination therapy.41 Prognosis is variable, and TCC is best treated with primary surgery or combinations of chemotherapy, radiation therapy, and surgery. Neuroendocrine tumors of the prostate are rare and can present with paraneoplastic syndromes.42,43 Most patients tend to present with advanced disease at the time of diagnosis.44

Nonepithelial nonadenocarcinomas of the prostate are rare. Sarcomas represent fewer than 0.1% of prostate cancers and tend to occur in younger patients.45 The two most common types are rhabdomyosarcoma and leiomyosarcoma. The former is the most common prostatic tumor in the pediatric age group, whereas the latter tends to occur in adults.46 Both are extremely aggressive and tend to invade locally and hematogenously. Pathologically, rhabdomyosarcomas are solid neoplasms, with a histologic appearance that

ranges from primitive mesenchyma to well-differentiated, myofiber-type cells.47 Leiomyosarcomas tend to be bulky, with diffuse infiltration into the periprostatic soft tissues. Histologically, lesions show interlacing spindle cells, eosinophilic cytoplasm, and nuclear atypia accompanied by necrosis and hemorrhage.48 A multidisciplinary approach to treatment, including surgery, chemotherapy, and radiation therapy, is usually recommended.44 A third nonepithelial cancer of the prostate is malignant lymphoma. It usually affects young men and frequently is associated with non-Hodgkin's and Hodgkin's lymphoma.49 On histologic examination, lesions resemble lymph nodes consisting of small-cleaved lymphocytic cells or large diffuse lymphomas. Prognosis is usually poor, and prostatectomy may not prolong survival. Other metastases to the prostate include leukemia and local extension from rectal or bladder primary cancers. Metastases from other organs are rare.45

Prostate cancer may spread locally or distantly. Cancers can invade the seminal vesicles and bladder base proximally and the urethra distally. Extension through the prostatic capsule and into the periprostatic tissues is not uncommon; however, rectal invasion posteriorly is rare, owing to separation of the two organs by Denonvilliers' fascia. Lymphatic spread most often occurs in a stepwise manner and follows the normal pattern of lymphatic drainage. The obturator nodes are the primary sites of lymphatic metastases, followed by the perivesical, hypogastric, iliac, presacral, and paraaortic nodes. Hematogenous metastases primarily affect the bones and occur in up to 85% of patients who die of prostate cancer.50 The axial skeleton is particularly vulnerable, as the preprostatic and periprostatic venous complex communicates with Batson's plexus of the presacral veins. Osseous sites of involvement, in decreasing order of frequency, include the lumbar spine, proximal femur, pelvis, thoracic spine, ribs, sternum, and skull. Bone metastases are typically osteoblastic (80%). Osteolytic (5%) and mixed osteoblastic-osteolytic (15%) lesions are less common. Hematogenous spread to viscera can occur, but widespread visceral dissemination is rare. Lung and liver metastases are seen in approximately 25% and 20% of patients, respectively, with end-stage prostate cancer. The current tumor, node, and metastasis (TNM) staging system for prostate cancer is presented in Table 34.4-2.

TABLE 34.4-2. Prostate Cancer Staging

PREMALIGNANT LESIONS (PROSTATIC INTRAEPITHELIAL NEOPLASIA)

Prostate carcinoma often is accompanied by atypical lesions such as intraductal dysplasia or prostatic intraepithelial neoplasia (PIN). It has been estimated that approximately 70% of prostate tissue ultimately removed for carcinoma will also harbor

PIN.19,51,52 A presumptive precursor lesion to prostate cancer, PIN is characterized by large glands separated by modest amounts of stroma with an overall normal-appearing architecture.53,54 Glandular cells appear basophilic with enlarged nuclei, hyperchromatism, and anaplasia. Categorized into low- and high-grade PIN, the latter is

associated with significant epithelial hyperplasia. Unlike carcinoma, however, the basal cell layer surrounding the dysplastic cells remains intact. Moreover, an intact basement membrane has been demonstrated in PIN, in contrast to moderately and poorly differentiated adenocarcinoma.55 High-grade PIN has a zonal distribution similar to that of adenocarcinoma and appears to be directly associated with cancer grade and stage.52 In our experience, roughly 50% of patients with an initial diagnosis of high-grade PIN alone will later demonstrate carcinoma on repeat biopsy.56 Moreover, high-grade PIN may be associated with aggressive disease and a poorer prognosis.57 However, its true prognostic value requires further research, as cancers in the transitional zone seldom are accompanied by PIN and as many as 70% of early carcinomas may lack any high-grade PIN.51

The DNA content (ploidy) of cancerous lesions may correlate with patient outcomes. Patients with diploid cancers generally have better survival outcomes than do those with aneuploid cancers.58,59 In a study of nearly 900 patients with pathologically non–organ-confined disease (pT3), Hawkins et al.60 showed that DNA ploidy was a significant prognostic factor for both clinical and biochemical failure–free survival. Others have reported that immunohistochemical staining for p27, a nuclear protein inhibitor of the cell cycle, may be of value. Decreased p27 expression is seen with more aggressive disease. Cheville et al.61 showed that patients with low p27 expression had higher-grade tumors, increased tumor aneuploidy, and higher incidences of seminal vesicle and nodal invasion than did men with normal p27 expression.

STAGING

In addition to histologic examination, staging is also important in patient risk assessment and prognosis. The two most commonly used staging systems are the tumor, node, and metastasis TNM system and the Jewett staging system (see Table 34.4-2).19,62 In the Jewett staging system are four stages of prostate cancer, A to D, with subclassifications within each stage. Stage A disease is clinically nonpalpable disease found incidentally during surgery for benign prostatic hyperplasia (BPH). Stage A1 disease is well differentiated and involves less than 5% of a pathologic specimen. Stage A2 involves more than 5% of a specimen or is moderate to poorly differentiated. Stage B (T2) cancers are clinically palpable but confined to the prostate. Stage B1 cancers are 1.5 cm in diameter or smaller and involve only one lobe of the prostate. Stage B2 involves either several nodules in both lobes or a lesion larger than 1.5 cm. Stage C (T3 and T4) tumors are non–organ-confined with invasion of soft tissue outside the prostate. Stage C1 tumors invade through the prostatic capsule but have a negative surgical margin. Margins are positive for stage C2 tumors, and C3 tumors

invade the seminal vesicles. Stage D cancer is metastatic, with *D1* referring to microscopical pelvic lymph node involvement and *D2* to disease involving bones or distant organs (or both). Most clinicians use the TNM system.

Given that autopsy studies show a high prevalence of histologic evidence of prostate cancer in men (>30%) who die of other diseases, there is some concern that many cancers currently detected may be “insignificant” or of such low biologic potential that treatment is

not necessary and possibly harmful.63 Cancer grade, cancer stage, serum PSA level, and the age and health of the patient most often define the risk associated with a prostate cancer. Tumor volume also correlates with risk, although it cannot be determined *in vivo* with precise accuracy as yet. Generally, those cancers that exceed 0.5 mL are more likely to be associated with extraprostatic disease as compared to smaller cancers.64 Approximately 20% of autopsy or incidental cancers exceed this size. Similarly, higher-grade cancers (Gleason score 4 or 5) are also more likely to be associated with extracapsular disease and cancer progression as compared to lower-grade cancers. According to criteria of cancer size, grade, and stage, the vast majority of cancers currently identified by early detection efforts appear to be clinically significant. Indeed, at least one-third have adverse features, including extracapsular extension (ECE), seminal vesicle invasion, lymph node metastases, or very high-grade histology, all of which are associated with a significant risk of cancer progression, certainly without treatment and often with treatment.

EPIDEMIOLOGY

Excluding superficial skin cancers, prostate cancer is the most common malignancy afflicting American men. In 1999, some 179,300 new cases were diagnosed, and an estimated 37,000 prostate cancer deaths occurred, making it the second most common cause of cancer death, after lung cancer, in American men.1

Beginning in the late 1980s, PSA screening became a common practice, and the incidence of prostate cancer cases increased dramatically as a direct result. Between 1985 and 1992, the age-adjusted incidence in the United States more than doubled, reaching a peak of more than 190 cases per 100,000 in 1992.1 This increase was not unanticipated, as the introduction of any effective screening test should lead to detection of earlier-stage disease in more patients (i.e., stage migration).65,66 Stage migration has, in fact, occurred in the United States, and approximately three-fourths of prostate cancer cases diagnosed now are recognized while the disease is still clinically organ-confined, as compared to only one-fourth prior to the introduction of PSA screening.67,68 Perhaps reflecting patients' earlier disease stage at presentation and more effective treatment for localized disease, 5-year cancer survival rates have increased from approximately 70% in the early 1980s to more than 90% a decade later.1 Since 1992, the incidence rate has declined steadily as the pool of men with no previous diagnosis of lower-staged disease became slowly exhausted. Incidence rates today are approaching those before PSA screening.

Worldwide, prostate cancer ranks third in cancer incidence and sixth in cancer mortality among men. There is, however, a notable variability in incidence and mortality among world regions. The incidence per 100,000 is low in Japan and China at 8.51 and 1.08, respectively, and is intermediate in regions of Central America (24.77) and Western Africa (23.85). In North American countries, where PSA screening is widely adopted (e.g., in the United States), the incidence may be as high as 95.1 per 100,000.69 Although less variable than incidence, there remains a 30-fold difference in the age-standardized mortality rate between global regions, ranging from 0.7 per 100,000 in China, to 18.5 per 100,000 in North America, to 22.2 per 100,000 in the Caribbean.69 The basis for this difference is multifactorial and has been attributed to more aggressive screening and diagnosis in aging

populations, genetic predisposition, and environmental causes.

Predominantly a disease of elderly men, the clinical diagnosis of prostate cancer is rare before age 40 but increases steadily thereafter. Autopsy studies worldwide have shown that histologic disease increases with age and that roughly three-fourths of men older than 80 years will have some evidence of latent disease.70,71,72,73,74 and 75 In parallel, more than 80% of clinically apparent disease occurs in men older than 65 years.1 In the United States, it is estimated that 1 in 55 men between the ages of 40 and 59 will develop clinically apparent disease. This incidence climbs almost exponentially to 1 in 7 for men between 60 and 79. This association is also reflected in mortality rates, as prostate cancer accounts for 10.8% of cancer-related deaths in men between 60 and 79 years of age and 24.6% in those older than 80. As the proportion of older men increases in our population, the impact of prostate cancer will continue to grow. In fact, the doubling of age-adjusted mortality rates in Taiwan over the past three decades has been attributed mainly to aging of the population.76

Ethnic and racial differences are also seen in disease incidence and mortality. African Americans are in the highest-risk group, with an incidence of 224.3 cases per 100,000 for the period between 1990 and 1995. The incidence in white and Asian counterparts during that same period was considerably lower at 150.3 and 82.2 (per 100,000), respectively.1 In addition, African Americans tend to present with more advanced disease and may have poorer overall prognosis than their white counterparts. It has been reported that African Americans are 1.3 to 1.8 times more likely to present with distant disease and, stage for stage, African Americans have lower survival rates.77,78 The underlying cause for this difference has been attributed to social, economic, educational, hereditary, and dietary differences.78,79,80,81 and 82 Conlisk et al.83 reported that among African Americans, disease stage at presentation was inversely correlated with income and health insurance status. When one controls for access to medical care, the difference in disease stage at presentation and survival persists.77,84,85 Recent reports from nations with a large concentration of black patients demonstrate a high incidence of the disease nationally, suggesting a genetic association.86,87 Several investigators have shown that differences in testosterone levels or androgen receptor gene activity may contribute to the racial differences observed in prostate cancer.88,89,90, and 91

Migrant studies, particularly of Asian men, also suggest an environmental, social, or dietary etiology in prostate cancer. When migrants from a low-risk country such as Japan move to the United States, a high-risk nation, their prostate cancer incidence and mortality become severalfold higher than native Japanese counterparts.92,93 Other investigators have found a positive correlation between the number of years since migration to the United States and cancer risk.80 Although diagnostic biases exist between countries, the upward shift in risk nevertheless seems real. This rise in clinically detectable disease may be related to differences in diet. High fat intake has

been positively associated with increased risk in these studies and may, in part, explain the rising incidence of prostate cancer in Japan, as dietary habits become more Westernized.94

Family history of prostate cancer also contributes to risk. It has been reported that men

with prostate cancer are two to three times more likely than controls to have at least one first- or second-degree relative with prostate cancer.95,96 and 97 Keetch et al.95 reported that a patient with prostate cancer is 3.1 and 4.3 times more likely than a control to give a history of prostate cancer in his father and brother, respectively. Together with the observation that clustering of prostate cancer cases exists in some high-risk families, a hereditary component clearly exists.98,99 However, the role of specific gene activity and molecular mechanisms of disease remains largely unsolved and continues to be an area of active research. A word of caution is warranted in interpreting family history studies, however, as they are subject to recall, self-selection, and socioeconomic biases.100,101 and 102

The role of vasectomy and prostate cancer risk remains controversial. Retrospective and prospective cohort epidemiologic studies have demonstrated a relative risk of approximately 1.6 in men who underwent vasectomy.103,104,105 and 106 However, others could not confirm these findings and suggest that earlier studies were flawed by detection, control selection, and publication biases.95,107,108,109 and 110 In a recent metaanalysis that included five cohort and nine case-control studies, no causal association was found.108

In summary, prostate cancer is a disease of older men worldwide. It is more common in Westernized countries, in those with a family history of the disease, and in African Americans. The cause is likely multifaceted, with genetic, dietary, and social modifiers. Further investigation is necessary to elucidate the role and significance of each factor in prostate cancer induction and progression.

CHEMOPREVENTION AND DIET

Chemoprevention is the administration of medicines or other agents to prevent, slow, or reverse cancer progression. The concept of primary chemoprevention for prostate cancer has gained much interest in the 1990s because of the disease's high prevalence, slowly progressive nature, and long latency period.111,112 and 113 The ideal therapeutic intervention would arrest disease progression during this latency period and decrease the incidence of clinical disease. The success of chemoprevention, however, depends on consideration of several important factors. First, because “healthy” men are treated, the therapeutic agent must offer low to no toxicity and no side effects and must require a simple dosing regimen. Second, epidemiologic and laboratory evidence should support the agent's efficacy. Finally, the ideal patient is one at high risk for developing clinical disease and motivated to adhere to chronic dosing of chemopreventive agents.114

To date, several promising chemopreventive agents have been identified and are under laboratory and clinical investigation.115,116,117,118,119 and 120 Finasteride is among the agents now being tested in a large, phase III, randomized clinical trial, the Prostate Cancer Prevention Trial (PCPT).115,121,122 A joint effort of the Southwest Oncology Group (SWOG), the Eastern Cooperative Oncology Group (ECOG), and the Cancer and Leukemia Group B (CALGB), the PCPT is a 10-year study of 18,882 men, aged 55 or older, with normal DRE and a PSA level of less than 3.0 ng/mL, who have been randomized to either placebo or the 5α-reductase inhibitor finasteride (5 mg/d).123 Given prostate cancer's slowly progressive nature, the end point of prostate cancer mortality will not be pursued

because of long study duration and large sample size requirements. Instead, the primary end point of prostate cancer period prevalence, as determined by sextant prostate biopsy, is used. The PCPT is designed to have greater than 90% power in detecting a 25% reduction in period prevalence of biopsy-proven disease when it reaches its end point in mid-2004.

The use of finasteride to prevent disease seems rational, given that prostate cancer is androgen-responsive.124,125,126 and 127 An inhibitor of 5α-reductase, finasteride blocks the conversion of testosterone to its active metabolite dihydrotestosterone (DHT) and lowers the prostatic androgen levels.128 Bologna et al.124,129 have shown that finasteride can attenuate *in vitro* prostate cancer cell growth in a dose-dependent manner, and others suggest that the lower incidence of prostate cancer among Japanese men may be associated with lower 5α-reductase activity. In addition, as a chemopreventive agent taken chronically, finasteride is well absorbed orally and does not appear to have any clinically relevant drug interactions or toxicity.130 The frequency of side effects is low and includes decreased libido, impotence, and decreased ejaculate volume.123,128

Dietary manipulations have also gained much interest.131,132 and 133 Epidemiologic studies have shown that the incidence of clinically significant prostate cancer is much lower in parts of the world where people eat a predominantly low-fat, plant-based diet.69,134 In addition, migrant studies demonstrate that when men from a low-risk country move to the United States and begin eating a Westernized diet, their rates of prostate cancer increase severalfold and approach that of the host country.92 However, which component of a certain diet increases prostate cancer risk remains unclear. Researchers have suggested fat, soy, green tea, lycopene, selenium, and vitamins, among others, as modifiers of prostate cancer risk.

Dietary fat intake is positively associated with prostate cancer risk and may be a rational target for chemoprevention. In a case-control study from the Physicians' Health Study, those who had higher plasma α-linolenic acid levels (a fatty acid found in animal fat) had a two- to threefold increase in prostate cancer risk as compared to those with lower α-linolenic acid levels.135 Similarly, in a prospective cohort study of more than 47,000 men, Giovannucci et al.136 found that fat intake was directly correlated with risk of advanced disease and, specifically, animal fat, red meat, and α-linolenic acid were associated with the greatest risk [relative risk (RR) = 1.63, 2.64, and 3.43, respectively].136 Others have studied saturated fat and reported an attributable risk of 13% for saturated fat intake in excess of 26 g/d as compared to diets with less than 13 g/d. This suggests that 13% of prostate cancer cases may be preventable by reducing saturated fat intake to less than 13 g/d.137 In a recent prospective case-control study of men in whom prostate cancer was diagnosed, Fradet et al.138 found that survival was inversely associated with saturated fat intake. As compared to men ingesting less than 10.8% of dietary calories from saturated fat, those ingesting more than 13.2% had three times the risk of dying from prostate cancer (RR = 3.13) and were more likely to develop bone metastasis (RR = 3.4) at a median follow-up of 5.2 years.138

Evidence supporting a relationship between prostate cancer and dietary fat also comes from animal studies. Wang et al.139 injected prostate cancer cells (LNCaP) into mice and placed

them on a “typical American” diet containing 40% fat. In 3 weeks, prostate tumor growth was noted. The researchers then divided the animals into subgroups receiving diets containing approximately 40%, 30%, 20%, 10%, and 2% of calories as fat. Progression of prostate cancer ceased or was reversed in some animals placed on 10% to 20% fat diets. This was in contrast to continued tumor growth in groups ingesting higher amounts of fat. PSA levels were also lower in mice on the 2% fat diet as compared to those on the 40% fat diet.139

On a molecular level, much remains unknown. Myers and Ghosh140 recently postulated that the risk seen with high fat intake may be linked to 5-lipoxygenase products of arachidonic acid (a ubiquitous fatty acid found in animal fat) and that inhibition of 5-lipoxygenase could lead to prostate cancer cell death and apoptosis. However, the significance of genetic polymorphisms for 5-lipoxygenase and the role of other fatty acid metabolic pathways in prostate cancer risk remain elusive.

The worldwide difference in prostate cancer incidence may also be associated with dietary intake of soy proteins. In Asian countries such as Japan and the Republic of Korea, where prostate cancer incidence and mortality are just a fraction of that in North America, consumption of soy in the form of tofu, soy milk, tempeh, and miso is noted to be up to 90-fold higher than soy consumption in the United States.134 In a cross-national study of more than 40 nations, Hebert et al.134 found soy, on a per-calorie basis, to be the most protective dietary factor. This protective role may be associated with soy's phytoestrogenic components genistein and daidzein. Genistein and daidzein are isoflavonoids with weak estrogenic effect that may have the ability to delay growth of precancerous prostate lesions and prostate tumors.116,141 Davis et al.141 showed that genistein inhibits prostate cancer cell growth in culture and induces apoptosis through cell-cycle gene regulation in a dose-dependent manner. Others have demonstrated that genistein is an inhibitor of tyrosine kinase and suggest that genistein may act through inhibition of up-regulated tyrosine kinases in proliferative cancerous states.131,142,143 Although the association between soy and cancer risk seems convincing, a causal role remains obscure and awaits the rigors of prospective randomized studies. However, given that soy products are generally well tolerated and provide a cost-effective source of isoflavonoids, the scientific community's interest in soy as a chemopreventive agent will likely continue.120

To explain the difference in cancer incidence and mortality between nations, researchers have also suggested a chemopreventive role for green tea, a beverage consumed in high quantities in Asia.117,144*In vitro* studies by Yang et al.145 showed that polyphenol extracts from tea inhibited growth of cancerous cell lines and induced cellular apoptosis in a dose-dependent manner. Furthermore, *in vivo* studies by Mohan and Gupta et al.146,147 found that tea polyphenols inhibited ornithine decarboxylase, a testosterone-induced enzyme that is up-regulated in prostate cancer. Tea polyphenols' inhibition of ornithine decarboxylase in effect attenuates testosterone in the prostatic milieu and may be an important target for chemoprevention.

Tomatoes are rich sources of the carotenoid lycopene. With its potent antioxidant activity, lycopene may protect cellular components from reactive oxygen radical species and lower prostate cancer risk. Epidemiologic data show that lycopene consumption is associated

with decreased risk as well as a possible reduction in prostate tumor growth.148 In a cohort study of approximately 14,000 Adventist men over a 6-year period, consumption of tomato products was associated with lower prostate cancer risk.149 This finding was substantiated in a prospective cohort study from the Health Professionals Study, where lycopene intake from tomato-based foods was found to be inversely associated with risk.150 The investigators reported that men ingesting two or more servings of tomato sauce per week had a 36% reduction in cancer risk as compared to counterparts who did not consume tomato sauce. Little is known, however, regarding lycopene's exact mechanism of action or the specific role of different isomers in prostate tissue metabolism.

The role of another antioxidant, vitamin E, as a chemopreventive remains controversial. Epidemiologic and *in vivo* data are often conflicting, despite promising *in vitro* studies.118,151,152,153 and 154 Part of the difficulty in elucidating vitamin E's effect in chemoprevention is that oral supplements frequently contain different forms of vitamin E than that found naturally in foods. Given the fact that vitamin E exists as potentially eight different compounds, and that isoforms such as γ-tocopherol have been shown to have greater inhibitory effects on prostate cancer cell growth than α-tocopherol, further evaluation of vitamin E is warranted.154

Selenium has also been reported to lower prostate cancer risk. In a double-blinded clinical trial designed to determine whether selenium could lower skin cancer recurrences, Clark et al.155 found that men randomized to receiving selenium had a 63% reduction in prostate cancer incidence as compared to those randomized to receiving placebo. Similar findings were demonstrated in a nested case-control trial of the Health Professionals Follow-Up Study. The investigators found that higher selenium intake, as reflected in nail selenium levels, was significantly protective (odds ratio = 0.35 when comparing the highest and lowest quintile).156*In vivo* studies in the human prostate cancer cell lines have also shown that selenium inhibits cancer cell growth at physiologic doses and that its protective effect may be mediated through an androgen-sensitive gene that encodes for a selenium-binding protein.157,158

Attention has also focused on vitamin D's antiproliferative and prodifferentiation effect on the prostate.159,160 Investigators have demonstrated that 1,25-dihydroxyvitamin D_3 [1,25 $(OH)_2D_3$], the active metabolite of vitamin D, inhibits cellular proliferation in primary prostate cancer tissue cultures and in prostate cancer cell lines such as PC3, DU145, and LNCaP.119,161,162 Moreover, epidemiologic evidence shows an inverse relationship between prostate cancer risk and ultraviolet radiation, the primary source of endogenous vitamin D synthesis.163,164 This observation has led some to suggest that higher rates of prostate cancer in the elderly may be due in part to decreased sun exposure or a decline in the body's ability to synthesize $1,25(OH)_2D_3$ with aging.160 Similarly, others have proposed that the higher risk in men of African descent may be related to higher skin melanin content, which would decrease endogenous vitamin D production.114 Taken together, vitamin D and its synthetic analogues may prove to be useful chemopreventive agents for prostate cancer.

Although a relationship between diet and prostate cancer is apparent, whether manipulating the diet will lead to changes in cancer risk is the subject of ongoing clinical trials. In considering the future development of rational chemoprevention trials and test compounds,

one must appreciate the interdependence between the practical aspects of clinical trial design and the mechanisms in disease progression.165,166 A better understanding

of the latter may lead to clinical trials that are less restrained by the need for large sample populations and prolonged follow-up. For example, it has been shown that urokinase-mediated cell surface proteolysis and angiogenesis in human prostate cancer cells are important in metastasis and that specific inhibition could decrease the metastatic potential of cancerous cells.167,168 From this work, one could postulate the design of a chemopreventive agent aimed at preventing metastasis in patients who present with localized disease. As compared to primary chemoprevention, this may be easier to implement clinically as patients are more likely to be motivated and compliant with chronic therapy. Thus, a multidisciplinary approach that reflects our understanding of prostate carcinogenesis and tumor invasion is critical to study design of future chemoprevention trials.

PROSTATE CANCER EARLY DETECTION

Prostate cancer screening or early detection has been accomplished using DRE, measurement of serum PSA (and its various forms), transrectal ultrasonography (TRUS), and combinations of these tests. Although DRE can detect prostate cancer, it detects fewer cancers than does PSA testing and, unfortunately, many cancers detected using DRE are either locally or regionally advanced.169 Although serum PSA is a better screening test than DRE, DRE should not be abandoned, as it may detect some cancers associated with a normal serum PSA level. Therefore, DRE should be combined with serum PSA testing. TRUS should not be used a first-line screening study as it lacks high specificity, is relatively expensive, and adds little information to that already gained by the use of serum PSA testing and DRE.170 TRUS is used to guide prostate biopsy in those patients who have an elevated serum PSA level, an abnormal DRE, or both (Fig. 34-4.3).

FIGURE 34.4-3. Transrectal ultrasound image showing a characteristic hypoechoic abnormality *(arrow)* consistent with prostate cancer.

PSA is a serine protease produced by benign and malignant prostate tissues. Although it is produced in small amounts elsewhere, including breast tissue, endometrium, and in a few malignancies other than prostatic cancer, it should be considered to be organ-specific clinically.171,172,173,174 and 175 PSA circulates in the serum as uncomplexed (free or unbound) or complexed (bound) forms.176,177 and 178 Serum PSA is largely complexed by endogenous protease inhibitors, the most common being α_1-antichymotrypsin. Other proteins bind a smaller fraction.

Serum PSA may be elevated transiently in cases of prostatitis and after endoscopic urethral manipulation, prostatic biopsy and, to a more limited extent, ejaculation.179,180 Routine DRE actually has little effect on serum PSA, but most physicians defer PSA testing after such an examination.181 The half-life of serum PSA is 2.2 to 3.2 days.182,183 Therefore, one should wait approximately 4 to 8 weeks after significant prostate

manipulation, such as that which occurs with prostatitis or prostate biopsy, before obtaining serum PSA. It should be emphasized that the most common cause for an elevated serum PSA level is BPH, the incidence of which increases with age, as does the incidence of prostate cancer.

Serum PSA concentrations can be decreased by treatment with agents that lower serum testosterone, such as luteinizing hormone–releasing hormone (LHRH) agonists and antagonists, antiandrogens such as flutamide, and the 5α-reductase inhibitor finasteride, which is used for the management of presumed BPH and male-pattern baldness. Finasteride also lowers PSA levels by an average of 50%.184 Therefore, one can correct for the effect of finasteride on PSA by doubling the PSA level.185 Use of α-adrenergic antagonists such as terazosin (also used to manage obstructive voiding symptoms) has no appreciable effect on serum PSA levels.186

USE OF TOTAL SERUM PROSTATE-SPECIFIC ANTIGEN LEVEL AND DIGITAL RECTAL EXAMINATION FOR PROSTATE CANCER EARLY DETECTION

The risk of prostate cancer correlates with serum PSA concentrations and DRE findings. The positive predictive value of a serum PSA level between 4.0 ng/mL and 10 ng/mL is approximately 20% to 30%.187,188,189,190 and 191 For levels in excess of 10 ng/mL, the positive predictive value increases to 42% to 71.4%. The use of DRE complements serum PSA testing (Table 34.4-3).

TABLE 34.4-3. Probability of Prostate Cancer Based on Serum Prostate-Specific Antigen and Digital Rectal Examination

The majority of cancers (>80%) detected by serum PSA are clinically significant as defined by cancer grade and volume.192 In contrast to the use of DRE alone for early detection of prostate cancer, the majority of PSA-detected cancers are confined *clinically*. However, as many as 40% of cancers detected by the

use of serum PSA and DRE may have evidence of ECE, usually capsular penetration, if the prostate is removed surgically and examined pathologically.192

The frequency of PSA testing remains a matter of some debate. In men with a normal DRE and a PSA level in excess of 2.5 ng/mL, PSA testing should be performed annually, as approximately 50% of these patients may convert to having a PSA level exceeding 4.0 ng/mL.193,194 The test can be performed biannually in those with a normal DRE and serum PSA level lower than 2.5 ng/mL, as conversion in this group is much less likely. The likelihood of curable prostate cancer, either organ-confined or with ECE associated with low to intermediate cancer grade, is similar in men who have prostate cancer associated with serum PSA levels lower than 4.0 ng/mL and in those with levels of 4.0 to 5.0 ng/mL. Therefore, cure is not likely to be compromised in those with very low serum PSA levels initially who experience a limited rise in the PSA level over time.

Enhancing Prostate-Specific Antigen Test Performance

A number of different strategies have been developed to enhance PSA test performance, by increasing sensitivity in certain populations or specificity in others. These strategies include use of age-specific reference ranges, PSA velocity, PSA density, and the molecular forms of PSA (free or complexed PSA).

PSA density is a measurement that attempts to correct for elevated PSA levels due to BPH. *PSA density* is defined as the total serum PSA level divided by the prostate gland volume (in milliliters) measured by TRUS.195 As prostate gland volume increases with increasing amounts of BPH, PSA should rise as well. Prostate cancer releases more PSA into the serum than does BPH.196 The use of PSA density is limited by the need to perform TRUS, variations in the accuracy of TRUS to measure volume, and the fact that PSA levels due to BPH are a product of the ratios of both the stromal and epithelial components of BPH, which vary from patient to patient. Some have suggested that a PSA density cutoff of 0.15 may better discriminate between patients with elevated serum PSA levels due to BPH and those with elevated levels due to cancer.197 Catalona et al.198 showed that as many as 50% of prostate cancers may be missed if one uses this PSA density cutoff to determine the need for prostate biopsy. Still others have failed to show any utility for the use of PSA density in men with a normal DRE and PSA levels between 4.0 and 10.0 ng/mL.199 As BPH tends to occur in the transitional zone of the prostate and not in the central or peripheral zones, attempts to improve prostate cancer detection using transitional zone PSA density have been developed.200,201 However, like PSA density, these calculations are subject to error, require TRUS, and do not seem to be superior to the use of PSA testing alone in most patients. In addition, the failure to identify prostate cancer in those with larger prostate glands may simply be a product of biopsy sampling errors rather than true absence of the disease.

Age-specific PSA reference ranges are an attempt to compensate for the fact that the standard reference range of 0.0 to 4.0 ng/mL does not reflect age-related volume changes in the prostate due to BPH. A single cutoff may, therefore, be inappropriate for all ages. Many investigators have proposed age-related reference ranges to improve test sensitivity in younger men (who have less BPH and, therefore, would be expected to have lower levels of PSA) and to improve test specificity in older men (who are more likely to have BPH and higher PSA values that accompany it).202 Race may also have an impact on PSA levels, an issue that has been addressed by several authors (Table 34.4-4). Using age-specific reference ranges, cancer detection rates will increase 8% to 18% in men younger than 60 years and will decrease 4% to 22% in older men. Use of age-specific reference ranges decreases the overall biopsy rate in men undergoing screening. The biopsy rate has been shown to decrease approximately 21% in older men undergoing screening if age-specific reference ranges are used. However, the overall cancer detection rate will also decrease, as fewer elderly men, the group most likely to have prostate cancer, will undergo prostate biopsy. In one series, the overall cancer detection rate fell from 5.7% using the standard PSA cutoff point of 4.0 ng/mL to 3.8% using age-specific reference ranges. Of the T1c or nonpalpable cancers missed in the older patient population, the vast majority have favorable pathologic features suggesting that they may be of low biologic potential in this age group and that failure to detect them may have little impact on patient mortality or

morbidity. Use of age-specific reference ranges remains controversial: Some investigators have shown no benefit to their use as compared to use of the standard cutoff point of 4.0 ng/mL. Others have also argued cogently the likelihood that organ-confined cancers are similar in men with serum PSA values between 2.5 and 6.0 ng/mL, suggesting that any lead time gained by use of age-specific reference ranges will not likely translate into improved outcomes and that the increased costs—monetary, physical, and psychological—associated with the increased biopsy rates in men younger than 60 years may not be justified.

TABLE 34.4-4. Age-Adjusted Prostate-Specific Antigen Reference Ranges

PSA velocity refers to the rate of changes in serum PSA over time. PSA velocity is calculated using the following equation: 1/2 (PSA2 – PSA1/time 1) + (PSA3 – PSA2/time 2), where *PSA1* is the first, *PSA2* the second, and *PSA3* the third PSA measurement. Time represents the interval (in years) between PSA

measurements. At least three PSA measurements obtained over 24 months or at least 12 to 18 months apart are required for maximal accuracy. In the initial study, significant differences in PSA velocity were noted in patients found to have cancer and BPH many years before cancer diagnosis. Carter et al.203,204 found that a PSA velocity exceeding 0.75 ng/mL was highly predictive of prostate cancer using one assay (sensitivity 72% and specificity 95%). The use of PSA velocity is limited by the fact that multiple measurements using the same assay over a relatively long period are necessary for accuracy. In addition, there is substantial biologic and laboratory variability in serum PSA testing, and some suggest that only increases in serum PSA greater than 25% are likely to represent changes due to prostatic disease (BPH or cancer).

Perhaps the greatest enhancement of PSA testing has been based on the knowledge that PSA exists in the serum in both free (or unbound) and complexed forms (bound to serum proteins). Stenman et al.176 made the observation that the free form of serum PSA exists in a higher fraction in men without prostate cancer than in those with the disease. Others observed that the specificity of PSA testing for the detection of prostate cancer could be enhanced by calculating the free-to-total PSA ratio as compared to using total PSA alone.205 Partin et al.206 conducted a multiinstitutional trial evaluating the performance of both total and free-to-total PSA for the detection of prostate cancer in men with serum PSA levels between 4.0 and 10.0 ng/mL using the Hybritech assay (Hybritech, Inc., San Diego, CA). All men had a normal DRE and underwent systematic TRUS-guided prostate biopsy. Of 773 men, 379 (49%) were ultimately found to have prostate cancer. As expected, the total PSA was higher and free fraction was lower in those with prostate cancer as compared to those without the disease. Using a free PSA cutoff of 20% to provide 95% sensitivity, these researchers could achieve a specificity of 20%, eliminating 20% of unnecessary biopsies. For patients who had a normal DRE and total PSA concentration between 4.0 and 10.0 ng/mL, the probability of prostate cancer was 56%, 20%, and 8% for those with free PSA fractions of 0% to 10%, 15% to 20%, and more than 25%, respectively. Catalona et al.206 also demonstrated that the use of the percentage of free PSA in men with total serum PSA concentrations between 4.0 and 10 ng/mL could eliminate 29% of

unnecessary biopsies, if a cutoff of 20% free PSA was used as an indicator for prostate biopsy. Others have performed similar studies using the same or different assays and patient populations (i.e., ranges of total PSA).205,207,208,209,210,211,212 and 213 In these studies, the sensitivity and specificity for cancer detection varied from 71% to 100% and 24% to 95%, respectively, using cutoff points ranging from 14% to 28%.

As 13% to 20% of men with serum PSA concentrations between 2.6 and 4.0 ng/mL (upper limit of normal) will be found to have prostate cancer within 5 years, some have examined the usefulness of percentage of free PSA for the early detection of prostate cancer in these men.171,176,214 Catalona et al.208 used percentage of free PSA to screen 914 men aged 50 years or older who had normal DREs and total PSA concentrations between 2.6 and 4.0 ng/mL. Using a cutoff point of 27% free PSA, 90% of cancers were detected and 18% of unnecessary biopsies were eliminated. The positive predictive value of percentage of free PSA at this cutoff point was 24%, and 81% of 52 men who underwent radical prostatectomy were found to have organ-confined cancers. Of these cancers, 83% were considered to be clinically significant based on cancer volume, stage, and grade. Others have shown similar findings using a different PSA cutoff point.215

The percentage of free PSA may also be of value in predicting cancer aggressiveness. Carter et al.216 measured both total and percentage of free PSA serially in men from whom serum had been stored before the diagnosis of prostate cancer. Stored sera from men with aggressive cancers as defined by stage (T3, nodal or bone metastases), grade (≥7), or positive margins at the time of radical prostatectomy were compared to sera from men with less aggressive cancers (none of the previously mentioned features). Although total PSA levels were not different between both groups measured serially before the diagnosis, a statistically significant difference between the two groups with respect to percentage of free PSA was noted. All eight patients with aggressive cancers from whom serum was available for testing 10 years before diagnosis had free PSA fractions of 14% or less.

Clinicians should be aware of several issues when determining whether to use percentage of free PSA and in interpreting results of the assay. Age, prostate volume, and method of serum storage before processing may influence PSA ratios. Samples should be processed within 3 hours or stored at –70°C if processing is delayed; otherwise, the free PSA fraction may be degraded.217 Lower free PSA cutoff points may be possible in smaller gland volumes (i.e., <40 cm^3) while still maintaining an acceptable detection sensitivity of 90%.207 Several analytical issues must be understood. Assays performed by different methods may yield different results.191,218,219 The percentage of free PSA cutoff point advised by manufacturers of these assays varies. Therefore, clinicians must be well acquainted with the methods used for free PSA testing before interpreting the results. Finally, it must be emphasized that use of percentage free PSA improves specificity of detection; some cancers will be missed. Both physicians and patients must be aware of this, as some will find any decrement in sensitivity unacceptable. Percentage of free PSA testing may be used best when determining the need for a second prostate biopsy in patients with a normal DRE, a total serum PSA between 4.0 and 10 ng/mL, and a previously negative biopsy.

Future Refinements

Similar to use of percentage of free PSA, several investigators have assessed the measurement of complexed PSA (PSA bound to α_1-antichymotrypsin) for the detection of prostate cancer. Brawer et al.220 measured total, complexed, and free PSA in 75 men with prostate cancer and in 225 who had benign findings on prostate biopsy. At 95% sensitivity, the specificities of total, free, and complexed PSA were 21.8%, 15.4%, and 26.5%, respectively. Sokoll et al.221 reported similar findings and improved specificity for complexed PSA as compared to total PSA in men with total serum PSA concentrations between 4.0 and 10.0 ng/mL.

The ProstAsure Index (Horus Global HealthNet, Hilton Head Island, SC) examines the relationships between several variables, such as PSA, age, and prostatic acid phosphatase, using an artificial neural network to predict the risk of prostate cancer. Babaian et al.222 compared the ProstAsure Index with percentage of free PSA for prostate cancer detection in 54 men with prostate cancer, 77 with BPH, and 94 with no evidence of

either. A comparison of the receiver operating characteristics curves for both tests demonstrated that the area under the curve for the ProstAsure Index was higher than that for percentage of free PSA (0.95 vs. 0.86, respectively), suggesting a small but significant advantage for the index.

Other serum proteins have been identified that may, in the future, play a role in prostate cancer detection and evaluation. Prostate-specific membrane antigen (PSMA) is a 750–amino acid type 2 transmembrane glycoprotein distinct from PSA. Serum levels of PSMA are increased in patients with prostate cancer. Human kallikrein-2 is a serum protease that bears considerable homology to PSA. Neither PSMA nor human kallikrein-2 currently is being used routinely for prostate cancer early detection, but refinements in development of serum assays, as well as novel imaging and treatment techniques targeting these and yet-to-be discovered proteins, may have a significant impact on prostate cancer early detection, staging, and treatment.

PROSTATE BIOPSY AND ITS IMPACT ON RISK ASSESSMENT

Prostate biopsy is indicated in men with an elevated serum PSA level, an abnormal DRE, or a combination of the two. Prostate biopsy is best performed under TRUS guidance using a spring-loaded biopsy device coupled to the transrectal probe.223,224 Although prostate biopsy can be done using a transperineal approach, the transrectal approach facilitates more accurate needle placement and tissue sampling. Rather than just sampling an area abnormal on the basis of DRE or TRUS imaging, systematic biopsy strategies have been developed that improve cancer detection and risk assessment. DRE and TRUS each lack the sensitivity and specificity to guide performance of lesion-directed biopsy only. Traditionally, six (sextant) biopsies have been taken in most patients along a parasagittal line between the lateral edge and the midline of the prostate at the apex, midgland, and base bilaterally (Fig. 34.4-4).225 Recently, several investigators have assessed the impact of increasing the number of biopsies as well as sampling specific portions or zones of the prostate.225,226 and 227 Investigators have shown that more laterally directed biopsies of the peripheral zone will increase detection rates by 14% to 20% over the more traditional sextant technique. Chang et al.225 analyzed a biopsy scheme that involved tissue from a

minimum of eight sites, including bilateral apex, midlobar midgland, parasagittal midgland, and lateral base (see Fig. 34.4-4). They found that the parasagittal biopsies at the base added very little unique information to this scheme.

FIGURE 34.4-4. Prostate biopsy schemes. **A:** Traditional sextant (six-biopsy) technique. **B:** More contemporary technique, which samples the peripheral zone more laterally and improves cancer detection rates. (From ref. 225, with permission.)

As up to 30% of lesions may originate in the transitional zone, many investigators have examined the utility of specific transitional zone biopsies.228,229,230 and 231 Most have found that routine transitional zone biopsies add little unique information to that gained from routine peripheral zone biopsy schemes. Therefore, transitional zone biopsy should be considered in those with a high suspicion of prostate cancer based on serum PSA level and who have undergone previous peripheral zone biopsy without cancer detection. Patients should be advised that a negative prostate biopsy does not completely exclude cancer, as 13% to 31% of patients with an initially negative biopsy will be found to have cancer on subsequent biopsy.232,233

Although the primary goal of prostate biopsy is cancer detection, the information gained from the results, if positive, can be of considerable value in initial risk assessment. The number of cores with cancer as well as the cancer grade determined by biopsy correlate with the risk of ECE and cancer progression. As biopsy samples only a portion of the prostate, accurate grading may be hampered by sampling errors. Grade as measured by biopsy will correlate exactly with that determined by analysis of the entire prostate after radical prostatectomy 31% to 59% of the time.234,235 Most often, needle biopsy underestimates cancer grade. Grading errors appear to be more limited with the use of contemporary biopsy schemes, which have increased (>6) the number of cores taken.236

Prostate cancer volume correlates with both the risk of extracapsular disease and outcome after treatment. Although cancer volume currently is not well assessed by imaging, analysis of the number of biopsy cores involved with cancer as well as the extent of cancer within each core appears to be of value in this regard. Patients with multiple positive biopsies are at an increased risk of both ECE and recurrence after initial therapy. One series reported on 257 consecutive radical prostatectomy patients and demonstrated that the number of positive sextant biopsies and the Gleason score correlated with ECE ($P<.0001$ and $P = .0004$, respectively) in a comparison of patients with and without ECE.237 With respect to serologic recurrence, patients with fewer than three positive biopsies and a Gleason score of less than 7 were at a low risk for recurrence irrespective of preoperative PSA levels (14% risk with a mean follow-up of 2 years).237 Other investigators have substantiated these findings, noting that patients in whom more than 50% of biopsy cores are involved with cancer are at an increased risk of both ECE and disease recurrence after radical prostatectomy.238,239 and 240 Knowledge of the number of cores involved may give important information not provided by analysis of the PSA level, Gleason grade, and local T stage alone.241

Although TRUS-guided prostate biopsy usually is very well tolerated by patients,

approximately 24% of those undergoing the procedure will find it very painful. Hematospermia and hematuria are common, occurring in approximately 40% to 50% of patients.242,243 and 244 High fever is rare, occurring in 2.9% to 4.2% of patients. Antibiotic prophylaxis is commonly given, although the necessity for it has been questioned by some.242 Recent use of aspirin or nonsteroidal antiinflammatory agents is not a contraindication for this procedure.244

TO SCREEN OR NOT TO SCREEN?

The case for prostate cancer screening is supported by the following facts: The disease is burdensome; PSA testing improves

detection of clinically important tumors without significantly increasing the detection of unimportant tumors; most PSA-detected tumors are curable using current techniques; and there is no cure for metastatic disease. In addition, several investigators have shown a reduction in cause-specific mortality with screening.245,246 and 247 In a community-based, prospective, randomized trial of men between the ages of 45 and 80 years, Labrie et al.245 showed that patients randomized to PSA screening had a cause-specific mortality equal to one-third that of unscreened men. However, this study must be interpreted with caution, as fewer than 20% of men in this study were randomized to screening. In an independent, population-based, case-control study that looked at screening with DRE, Jacobsen et al.246 showed an association between decreased mortality and screening. However, the causal relationship between screening and decreased mortality remains to be proven. In the Prostate, Lung, Colon, Ovarian Trial supported by the National Cancer Institute, men are randomized to screening (with DRE and PSA testing) and to no screening, with cancer-specific mortality as the end point. However, the fact that therapy is not standardized and that screening will occur over only a limited period may make interpretation of results difficult. The efficacy of treatment also is currently being examined in Scandinavia, where two randomized trials compare watchful waiting with radiation or radical prostatectomy. A similar trial, Prostatectomy Versus Observation for Clinically Localized Carcinoma of the Prostate (PIVOT), is accruing patients in the United States. Patients must be informed of the risks and benefits of screening before it is carried out. It appears that many men who undergo screening in certain health care settings have no knowledge of having the test performed, suggesting that more discussion of this test with patients must occur.248 If screening and eventual treatment are to be offered to asymptomatic patients, they should be offered to those whose age and health status are such that they may benefit from early detection of a disease that may have a protracted natural history (Table 34.4-5). An algorithm for early detection is outlined inFigure 34.4-5.

TABLE 34.4-5. Average Life Expectancy and Life Expectancy Correlated with Patient's Perception of Health Status

FIGURE 34.4-5. Algorithm for the early detection of prostate cancer. *Whether one uses total prostate-specific antigen (PSA) or its variations (i.e., percentage free or age-referenced prostate-

specific antigen testing) for the initial screening for the disease is a matter of debate (see text). DRE, digital rectal examination; PIN, prostatic intraepithelial neoplasia; TRUS, transrectal ultrasonography.

INITIAL CANCER STAGING AND RISK ASSESSMENT

Historically, initial risk assessment was based on clinical staging—that is, the assessment of anatomic extent of the disease on the basis of physical examination and imaging. Although clinical stage (TNM) correlates with outcome, in a large percentage of patients who are believed to have organ-confined disease, evidence of disease beyond the prostate is identified at the time of radical prostatectomy. Alternatively, some patients with high-risk pathologic features may not experience disease recurrence. Therefore, many clinicians have focused their efforts on better risk assessment schemes that predict the likelihood of disease recurrence if patients are treated and the likelihood of clinical progression if patients undergo initial surveillance. This more modern concept of risk assessment is a product of the knowledge that disease may be better characterized by analyzing many criteria (e.g., serum PSA level, Gleason grade, cancer volume) in combination with clinical stage, as compared to the use of staging alone.

An accurate assessment of risk before definitive treatment is attempted would allow for a more realistic assessment of the likelihood of cure with various treatment options and, therefore, better treatment selection. In addition, such assessment would allow for more accurate prediction of who may be candidates for neoadjuvant or adjuvant treatment or novel clinical trials owing to the presence of high-risk cancer features.

IMAGING

Imaging plays an important role in staging. Both cross-sectional imaging of the pelvis and imaging of the bones (with radionuclide bone scanning) often are performed. However, imaging can be costly, and patients at low risk of advanced disease can be spared the cost and morbidity of cross-sectional imaging and radionuclide bone scanning. With the advent of widespread screening for prostate cancer, considerable stage migration has occurred, and the incidence of metastatic and regionally advanced prostate cancer has decreased. Several investigators have proposed guidelines for prostate cancer imaging that limit costs without compromising significantly the accuracy of staging. However, a recent analysis of the use of cross-sectional imaging [computed tomography (CT) or magnetic resonance imaging (MRI)] and bone scanning in a large cohort of patients cared for by urologists suggests that bone scans, CT, and MRI are overused, certainly in low-risk patients (i.e., PSA <10 ng/mL, stage <T2c, grade <7).249 In this latter group, 66% of patients were undergoing bone scans, and 24% either CT or MRI.

Radionuclide bone scanning has replaced the use of plain films for the detection of prostate cancer metastases. Although sensitive, bone scans have a low specificity. False-positive scans can occur due to trauma, degenerative disease, or Paget's disease. Lee and Oesterling et al.250,251 have conducted investigations to assess the ability of serum PSA level to predict bone scan findings (Fig. 34.4-6). In a cancer population representative of

newly diagnosed patients in the United States, serum PSA level was the best predictor of bone scan results. Of 852 patients with newly detected prostate cancer, 66% had a serum PSA concentration of less than 10 ng/mL. The likelihood of a positive bone scan due to metastases was 0.6% and 2.6% for those with serum PSA concentrations between 10.1 and 15 ng/mL and 15.1 and 20 ng/mL, respectively. Use of tumor grade, local tumor stage, or a combination of these variables did not enhance the predictive power of PSA testing. Many others have confirmed these results.252,253 On the basis of these results, one can omit the bone scan in patients with newly diagnosed, untreated prostate cancer who are asymptomatic and have serum PSA concentrations of less than 20 ng/mL and certainly in those with serum PSA concentrations of less than 15 ng/mL.

Given that there is some risk of bone metastases in this population, it is reasonable to perform a bone scan in those patients with either very high-grade or very high-stage disease.

FIGURE 34.4-6. Radionuclide bone scan showing increased uptake consistent with prostate cancer metastases.

Cross-sectional imaging of the pelvis with CT or MRI in patients with prostate cancer generally is performed to exclude lymph node metastases in patients who are believed to be candidates for definitive local therapy (Fig. 34.4-7). However, the incidence of lymph node metastases is currently low (<5%), and imaging is costly and its sensitivity limited. One review of the literature encompassing 15 series and 1354 patients with an incidence of lymph node metastases of 22% revealed a sensitivity of CT and MRI of approximately 36% and a specificity of 97%.254 The authors of this review suggested that only those patients with a very high risk of lymph node metastases (i.e., 45%) would benefit from cross-sectional imaging. Such patients would include those with a normal bone scan, Gleason score greater than 6, a palpable abnormality on DRE (i.e., T2 to T4 disease), and a serum PSA level of greater than 25 ng/mL.255

FIGURE 34.4-7. A computed tomography scan showing the presence of retroperitoneal adenopathy due to metastatic prostate cancer.

Radiolabeled monoclonal antibodies directed at PSMA have been used to stage newly diagnosed patients and identify sites of cancer recurrence after definitive therapy. Prostascint (Cytogen Corporation, Princeton, NJ) uses a murine monoclonal antibody labeled with indium 111 for the detection of lymph node and other soft tissue metastases.256,257 Imaging is performed 72 to 120 hours after administration of the agent. The sensitivity, specificity, and positive predictive value of the test in one patient population with a 37% incidence of nodal metastases was 75%, 86%, and 79%, respectively. In a more recent study of 160 patients imaged before pelvic lymph node dissection, the sensitivity, specificity, and positive and negative predictive values for

immunoscintigraphy were 62%, 72%, 62%, and 72%, respectively.258 The authors found the test, when considered in conjunction with certain combinations of PSA level and Gleason score, was effective in predicting the risk of lymph node metastases. The test has not gained wide popularity owing to difficulties with accurate interpretation, its cost, and the fact that similar information about risk may be gained by use of the serum PSA level, cancer grade, and cancer stage.

Whereas metastatic and regionally advanced disease are relatively uncommon at presentation, ECE and seminal vesicle invasion are not uncommon, occurring in approximately 20% to 40% and 8% of patients at presentation, respectively. Such patients are at an increased risk of recurrence with various forms of local therapy, and pretreatment knowledge of ECE

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would allow for more effective local therapy to be delivered (e.g., wide surgical excision, wider field, higher dose or combination radiation therapy). Whereas CT is a less reliable and efficient test for assessment of ECE or seminal vesicle invasion, as compared to other imaging modalities, both MRI using an endorectal probe and TRUS are used commonly to assess the integrity of the prostatic capsule and seminal vesicles. The performance of CT, MRI (body coil alone and endorectal coil), and TRUS in this regard is reviewed in Table 34.4-6 and Table 34.4-7. Given the wide range of test performance noted, other parameters of risk such as cancer grade, serum PSA level, and the number of positive biopsy samples must be taken into account when interpreting the results of either endorectal MRI or TRUS. Whereas TRUS is performed at the time of biopsy, endorectal MRI is, for the most part, used for staging only after a diagnosis has been made. Endorectal MRI may be of some value in staging intermediate-risk patients but provide little additional information in both low- and high-risk patients.

TABLE 34.4-6. Accuracy of Imaging for the Detection of Extracapsular Extension

TABLE 34.4-7. Accuracy of Imaging for the Detection of Seminal Vesicle Invasion

The routine use of endorectal imaging is limited due to problems with interobserver variability and variable diagnostic accuracy. The development of endorectal surface coils has allowed the application of three-dimensional magnetic resonance

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spectroscopy (MRS) to the evaluation of prostate cancer. Significantly higher choline and lower citrate levels are observed in areas of prostate cancer as compared with either normal prostate tissue or BPH (Fig. 34.4-8). Therefore, MRS may allow for estimation of prostate cancer volume and may improve sensitivity and specificity of cancer detection when combined with endorectal MRI. The addition of MRS to MRI recently was evaluated with respect to any improvements in cancer staging and localization. When more than 4.5 voxels per slice of prostate were involved with cancer, the risk of extracapsular invasion

was 43%. If more than 6 voxels were involved, this risk rose to 75%. The impact of MRS on the accuracy of staging (detection of ECE) was most apparent when inexperienced readers were evaluating the images, suggesting that the use of such technology may be most helpful in improving the accuracy of radiologists with less experience in magnetic resonance interpretation.259,260 With regard to cancer localization in patients with biopsy-proven prostate cancer, MRS in conjunction with MRI allows for improved ability to localize cancer to a sextant.261 When either MRI or MRS was positive for cancer, a sensitivity of 91% was achieved. When both were positive at the same site, a specificity of 92% was achieved. Nonetheless, more experience with this technique is necessary before it can be used routinely to guide and deliver treatment.

FIGURE 34.4-8. A: Representative reception-profile corrected T2-weighted fast spin-echo axial image taken from a volume data set demonstrating a large tumor in the right midgland: low T2-weighted signal intensity (*arrow*). **B:** T2-weighted fast spin-echo axial image with overlying point resolved spectroscopy (PRESS) selected volume (*bold white box*) and phase-encoded grid (*fine white line*) taken from a three-dimensional array of spectra. **C:** Corresponding 0.24-mL proton spectra with the major prostatic metabolites (choline-, creatine-, and citrate-labeled). Spectra in regions of cancer (left side of image) demonstrate elevated choline and reduced citrate relative to regions of healthy peripheral zone tissue. The prostate metabolite levels that are observed in different regions of zonal anatomy, benign prostatic hypertrophy, and cancer are described in detail in the text. **D:** Images can also be created from prostatic metabolite levels and overlaid on the corresponding anatomic images. The red area is where (choline + creatine) citrate ratios were greater than 3 standard deviations of healthy peripheral zone values.

PRETREATMENT SERUM PROSTATE-SPECIFIC ANTIGEN LEVEL, TUMOR STAGE, CANCER GRADE, AND VOLUME

Pretreatment serum PSA level is used extensively in both pretreatment risk stratification and in predicting the outcome after definitive local treatment.262,263 and 264 The serum concentration of PSA correlates well with cancer volume and stage. However, considerable overlap exists, making use of serum PSA alone inaccurate for clinical staging in most patients. Use of serum PSA level in conjunction with cancer grade and stage adds considerable sensitivity and specificity to the prediction of lymph node status as compared to the use of PSA level alone. Investigators have published nomograms and probability curves that aid in predicting pathologic cancer stage.265,266,267 and 268 Use of such nomograms allows a better assessment of preoperative risk and more appropriate selection of initial treatment (Table 34.4-8). It is important to note, however, that these aid in predicting the pathologic extent of disease and not necessarily the cure rates with treatment. In addition, they do not take into account other cancer features that may be predictive. As mentioned earlier in Prostate Biopsy and Its Impact on Risk Assessment, the number of positive prostate biopsies correlates with risk: Those patients in whom more than 50% of biopsy specimens prove positive or in whom two to three of three biopsy specimens on one side are positive are more likely to have ECE.

TABLE 34.4-8. Prediction of Pathologic Stage Using Digital Rectal Examination, Prostate-Specific Antigen, and Tumor Grade

By the use of Gleason grade, local tumor stage, percentage of biopsy specimens involved with cancer, and serum PSA level, pretreatment risk may be assigned. Table 34.4-9 is a summary of the findings from multiple analyses and can serve as a broad-based guide for pretreatment risk stratification. Future refinements in imaging and the use of molecular markers may further improve risk assessment.269,270 and 271

TABLE 34.4-9. Pretreatment Risk Assessment

THE IMPACT OF RISK ASSESSMENT ON TREATMENT SELECTION

The information presented suggests that risk assessment is possible and that it provides both patients and clinicians with important information. Low-risk patients are very good candidates for definitive local therapy using standard techniques. On the basis of age, comorbidity, and the long natural history of this disease in some cases, certain patients may be candidates for surveillance alone. High-risk patients are unlikely to be cured with standard therapy and are ideal candidates for clinical trials. Combined-modality therapy may be especially important in this group of patients.272 Intermediate-risk patients are candidates for modifications of standard therapy, given a significant risk of recurrence and the emerging knowledge that wide surgical excision and adjuvant radiation therapy may be useful after radical prostatectomy and that dose escalation, improved targeting, and

combined-modality radiation therapy may have value over standard radiation therapy techniques in this population.273,274,275,276 and 277

TREATMENT SELECTION FOR NONMETASTATIC (T1–T3N0M0) DISEASE

There is no consensus as to what constitutes the best form of treatment for any stage of prostatic disease. Treatment is indicated in those who are symptomatic and those who are at high risk of dying of prostate cancer or developing symptoms of the disease. Given that most patients in whom the disease is currently being detected fall into either the low- or intermediate-risk groups, immediate and aggressive treatment may not be necessary in some patients. Such patients must be informed of the potential risks and benefits of all forms of treatment as well as surveillance, which is an option for some patients. Treatment decisions should be based on cancer stage and grade as well as patient age and health. Both patient and physician bias may play a strong role in treatment selection, inasmuch as precise guidelines for treatment are not available for the majority of patients. Given the protracted and, in some cases, indolent nature of the disease, disease progression may be avoided using a variety of treatment methods. Indeed, the morbidity of different treatment

regimens may guide treatment selection in some patients.

Both patients and physicians must interpret the results (morbidity and cancer control rates) of various forms of treatment with caution. Often, the morbidity of treatment is reported using physicians' estimates. However, physicians generally underestimate the impact of the disease in almost all health-related quality-of-life domains.278 Given the protracted nature of prostate cancer, only a limited number of patients may die of their disease. Therefore, outcome often is assessed using end points other than cause-specific survival, the most common being PSA levels. After radical prostatectomy, the PSA level should fall to undetectable, usually within 6 weeks of surgery. A

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persistently detectable PSA level predicts clinical recurrence, although disease may not return for many years and may not lead to death.279 After cryotherapy and radiation therapy, PSA continues to be produced in most patients. What constitutes an acceptable PSA level after either form of treatment is a matter of some debate. Whereas some argue that low (i.e., <0.5 ng/mL) nadir levels should be reached, the American Society for Therapeutic Radiology and Oncology (ASTRO) defines biochemical recurrence after radiation therapy as three consecutive rises in serum PSA level above nadir.280,281 Failure cannot occur until nadir is reached. This method of defining outcome is very sensitive to the length of follow-up and the frequency of PSA testing.

NATURAL HISTORY AND SURVEILLANCE ALONE

Certain prostate cancers may grow slowly. In addition, many patients with this disease are elderly and may have concomitant illnesses. Therefore, watchful waiting or surveillance alone may be an appropriate form of management for selected patients with prostate cancer. Contemporary series documenting the true natural history of untreated prostate cancer are limited. Many series are composed of only carefully selected patients, many of whom may have received some form of treatment, often androgen deprivation, during follow-up.

Several investigators have reported the likelihood of local and distant tumor progression in patients who were untreated or who were treated with noncurative intent (i.e., androgen deprivation) (Table 34.4-10). The risk of local progression in these series ranges from 8% to 84%, while the risk of progression to metastatic disease ranges from 6% to 74%. The results should be interpreted with caution, as most patients were older (i.e., >70 years old) and had low-grade or low-stage disease (or both). Furthermore, follow-up in these studies ranged from 4 to 14 years after diagnosis, and such differences likely account for the wide

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range of local and distant progression reported. Therefore, the results may underestimate the risk of disease progression in the general populat