Advancing age is a major risk factor for the development of prostate cancer. While only one in 10,000 men younger than age 40 will develop prostate cancer, the odds increase to one in 103 for those between the ages of 40 and 59 and one in eight for those between the ages of 60 and 79. Certain population groups are at higher risk, including African-Americans and those with a family history of the disease. Men with a first-degree relative (brother, father, uncle) with prostate cancer have a higher likelihood of developing the disease; however, mortality from the disease is not different from those with the sporadic form. The epidemiology of the disease was altered substantially in the early 1990s with the onset of PSA (prostate-specific antigen) blood screening, which led to a significant increase in the incidence of the disease.

Recently, two large randomized studies examined the rate of death from prostate cancer in patients who were screened versus a control population that was not screened. In the study conducted in the U.S., screening did not lead to a benefit in overall survival; while in a larger European study with longer follow-up, a lower rate of death from prostate cancer was noted. Of note, approximately 50% of the patients in the U.S. study who were placed in the no-screening group did undergo PSA testing, thus potentially contaminating the results.
The management of prostate cancer is accomplished through a multidisciplinary approach that utilizes the expertise of urologists and medical and radiation oncologists.

**PATHOLOGY**
The prostate gland is approximately the size of a walnut and is located at the base of the bladder (see Figure 1). The primary role of the prostate gland in male physiology is the secretion of the fluid components of semen. Thus, the most common type of cancer arising from the prostate comes from the glandular tissue—a type of cancer known as an adenocarcinoma. More than 95% of prostate cancers are adenocarcinomas. Unlike adenocarcinomas that develop in other parts of the body (e.g., lung and colon), adenocarcinomas that arise in the prostate grow through the stimulation of androgen (e.g., testosterone) and express in high concentrations the androgen receptor (AR), which is activated by testosterone. The remainder of prostate cancers are neuroendocrine (i.e., small cell) cancers and transitional cell carcinomas (arising from the special lining cells of the urinary tract—similar to bladder cancer). Sarcomas can also arise in the prostate gland but are exceedingly rare.

**CAUSES AND RISK FACTORS FOR PROSTATE CANCER**
It is likely that there is more than one underlying cause of prostate cancer, as there appear to be both genetic and environmental factors that contribute to its development. The role of genetics is an area of active investigation that will likely lead to significant advances in our ability to predict who will develop clinically significant prostate cancer. Such advances may lead to more accurate and detailed screening methods as well as molecular targeted therapies.

Further, blocking the interaction of testosterone and its derivatives with the AR form the basis for the most effec-
Disease. Many of the newer medical therapies that have been developed or are in development for prostate cancer are derivatives of this original approach.

**DIAGNOSTIC TESTING**

**Symptoms** – Most patients with early-stage prostate cancer do not have any symptoms of the disease and are diagnosed on the basis of screening. Urinary symptoms can occur that can be confused with the symptoms of benign prostatic hypertrophy (BPH). Bone pain, loss of appetite, weight loss, and fatigue are symptoms that can accompany metastatic disease. In rare but severe cases, nerve damage can occur, causing altered levels of sensation in the arms and legs, weakness in the legs, or a change in the level of bowel or bladder control.

**Biopsy** – A prostate biopsy is considered when there is reasonable clinical suspicion based on digital rectal exam (DRE) and PSA results that prostate cancer exists. The procedure involves the insertion of a transrectal ultrasound (TRUS) probe into the patient’s rectum, allowing visualization of the gland. Subsequently, 8 to 16 “cores” are obtained with a 15-mm-long core biopsy needle. It is recommended that, at a minimum, a 12-mm core biopsy be used. Biopsy results may show cancer or other conditions that are not cancer per se but will require surveillance: these include atypical small acinar proliferation (ASAP) and high-grade prostatic intraepithelial neoplasia (HG PIN). Either one of these conditions merits close follow-up and repeat biopsies, as they may suggest a high risk for the development of cancer.

**STAGING/GRADING**

The most common grading system is the Gleason grading system in which two scores are derived and then “summed.” The tumors are assigned a number 1 to 5, where 1 represents the least aggressive appearing pattern and 5 represents the most aggressive appearing pattern. The Gleason score (or sum) is the combination of the primary and secondary Gleason grade and is often quoted as such (e.g., “Gleason 3 + 3 = 6”) rather than the sum alone being stated. The reason for this is that the primary Gleason has a very strong prognostic value, and therefore, a Gleason 3 + 3 would be considered less aggressive than a Gleason 4 + 2. Gleason patterns 1 and 2 are very rarely found.

**TREATMENT STRATEGIES**

**Localized Prostate Cancer** – Many treatment options are available for patients with localized early-stage prostate cancer.

- Watchful waiting or active surveillance. The risk of disease progression is low in patients with Gleason scores 2 to 6 (with no pattern 4 or 5 present), T1 or T2a disease, and a serum PSA that is low and stable. Men with these features can be followed carefully and treated at the first sign of progression. Critical to the success of this approach is diligent surveillance and repeat biopsies (approximately yearly). Thus, active surveillance offers an opportunity to avoid or delay the side effects of radical treatment. The standards of care for surveillance (e.g., when to treat and how frequently to repeat biopsies) are in the process of development. A study conducted in Sweden in which patients were randomly selected to have surgery or active surveillance found that by 10 years there was a significant difference in the death rate from prostate cancer and an improvement overall in younger men (< 65 years old). Despite this, it is still possible that men with low-risk disease who are diligent in their follow-up can undergo active surveillance and deferred therapy.

- Radical prostatectomy. Radical prostatectomy involves the surgical removal of the prostate and seminal vesicles.
vesicles. Newer laparoscopic and robotic approaches offer the option of treatment with smaller incisions and shorter hospitalization. The surgeon may elect to remove the pelvic lymph nodes in higher risk cases or if there is an intra-operative finding suggesting more advanced disease. Following prostatectomy, a urinary catheter is held in place for several days and patients are back to full activity within 2.5 to three weeks.

- Radiation therapy – external beam therapy. Several approaches in the management of localized prostate cancer involve the delivery of radiation to the cancerous tissue. The range of radiation approaches includes standard external beam radiation therapy (the radiation comes from a machine and is aimed at the prostate while the patient lies on a table) to the more modern techniques of three-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT), which allow radiation treatment to be given at higher doses in the prostate and lower doses elsewhere. Brachytherapy is a form of radiation in which “seeds” containing the radiation are permanently placed in the prostate gland. Permanent implants in the form of iodine-125 or palladium-103 radioactive seeds may be used. Other radiation techniques, such as high-dose-rate (HDR) brachytherapy, a form of temporary radioactive seed implantation, are typically utilized in patients with higher risk disease in combination with external beam radiation and/or androgen deprivation. The outcome following radiation therapy can be enhanced for many with the addition of androgen-deprivation therapy (ADT) before and during radiation treatment. In particular, ADT has been shown to improve the overall survival following radiation in patients with intermediate- and high-risk disease.

**Other Approaches to Localized Prostate Cancer (Hormonal Therapy)** – Hormonal therapy in prostate cancer refers to any therapy that seeks to block the stimulation of the tumor(s) by testosterone. Hormonal therapy may be used at all stages of the disease and can induce prostate cancer cells into a prolonged state of hibernation and/or death.

Medications known as LHRH (luteinizing hormone releasing hormone) agonists are used to decrease testosterone production. This is frequently referred to as medical castration. LHRH agonists are given by injection and are available in preparations that exert their effect for periods ranging from one to 12 months. An equally effective alternative to taking hormonal medications altogether is to stop the production of testosterone by having an orchiectomy (surgical removal of the testes). When the testosterone level has been lowered, the PSA tends to drop quickly and the prostate shrinks. There are additional androgens produced in the adrenal glands. In some situations, the addition of oral medications called anti-androgens that prevent androgens from entering the prostate cells may be beneficial. The combination of these two types of hormonal medications is known as total androgen blockage or complete androgen deprivation.

These medications are occasionally used as primary treatment in many older patients with localized prostate cancer who do not undergo surgery or radiation. The duration of therapy with these medications varies. A commonly
used strategy known as intermittent androgen deprivation is used to minimize the side effects of ADT. Androgen deprivation poses a substantial risk of side effects. The absence of testosterone (caused by LHRH agonists or orchiectomy) can produce a loss in the desire for sex, weight gain, hot flashes, loss of muscle strength, fatigue, osteoporosis, and occasionally depressive symptoms. An important recent observation is that ADT may increase the risk for diabetes, stroke, and heart attack.

CLINICAL STATES OF PROSTATE CANCER
For most patients who develop recurrent prostate cancer after undergoing local therapy with radiation or surgery, prostate cancer is managed as a chronic medical condition with combinations of androgen-deprivation therapy, secondary hormonal therapy, and chemotherapy in addition to various supportive and palliative therapies. The contemporary classification of the disease reflects the fact that it typically involves the progression through a series of distinct clinical “states” (see Figure 2), defined by the presence or absence of metastatic disease as well as detailing whether or not the disease is progressing in the context of a normal or low testosterone level (referred to as the “castrate state”).

RISING PSA
Approximately 50,000 to 60,000 American men develop a rising PSA after having already received local therapy with “curative intent.” Not all men who experience a relapse of the disease in the form of a rising PSA will go on to develop metastatic prostate cancer and many postsurgery patients may be cured with radiation therapy (if they have previously undergone radical prostatectomy). The rate of change in PSA over time (usually expressed as the PSA doubling time, or PSADT) is the single most accurate predictor of both metastases and death in the rising PSA clinical state. One study demonstrated that one-half of the patients with a PSADT < 3 developed metastatic tumors in the bone within 2.25 years, whereas it took approximately four years in those with a PSADT of three to six months (P < 0.001). Many patients with a rising PSA will ultimately require hormonal therapy in one form or another and a substantial number will go on to hormonal therapy before they develop metastases.

TREATMENT OF METASTATIC DISEASE
The standard initial treatment for patients with metastatic prostate cancer is ADT. There is some evidence to suggest that patients with metastatic disease who are treated with total androgen blockade demonstrate increased survival compared with patients treated with medical castration (LHRH agonist only). In most treated patients, certain populations of tumor cells adapt to and grow despite low levels of testosterone. This is known as castration-resistant prostate cancer (CRPC) or hormone-refractory prostate cancer (HRPC).

A variety of secondary hormonal therapies are available and typically aim to further interrupt the ability of testosterone and its related hormones to stimulate the androgen receptor. A widely utilized drug is ketoconazole, which lowers the levels of testosterone-like hormones made by the adrenal glands. Other anti-androgens, such as nilutamide or flutamide, may be useful if a patient has received bicalutamide. Steroid drugs, like prednisone and dexamethasone, are also used, as are estrogens, such as diethylstilbestrol or estradiol. New drugs, such as abiraterone acetate, are showing promise in this area. Abiraterone is an inhibitor of CYP17, a critical enzyme in the production of adrenal androgens, and has shown response rates in the 50 to 85% range. MDV3100, a novel oral androgen receptor antagonist that was developed in a tumor model characterized by androgen receptor amplification, has been associated with significant responses in approximately 50 to 65% of patients, including many with prior chemotherapy exposure. This agent is currently being evaluated in a phase 3 study.

For many patients with advanced prostate cancer, pain and bone complications (e.g., fractures) become a substantial risk. For such patients, an approach that combines bone protection with chemotherapy is frequently utilized. One drug,
zoledronic acid, has been shown to reduce the rate of complications in the bone and is in widespread use in this setting. It is administered intravenously approximately once per month. A novel agent that targets RANK-ligand-induced bone loss, denosumab, is in late-stage development as a treatment for both bone loss and to prevent bone complications.

**CHEMOTHERAPY FOR CRPC**

Until recently, chemotherapy has been utilized with relatively little frequency in prostate cancer. This has had less to do with the effectiveness of chemotherapy against prostate cancer (many patients benefit significantly from chemotherapy) and more to do with the fact that definitive data from clinical trials of chemotherapy in this disease were lacking until the early part of this decade. It wasn’t until 2004 that an approach that utilized chemotherapy was shown to improve the survival of prostate cancer patients.

Two simultaneously conducted phase 3 studies were presented in 2004 that compared docetaxel chemotherapy to mitoxantrone, a drug that had been approved for use in prostate cancer for its potential to palliate pain and improve quality of life, but not to improve survival. The most important of the two studies was the multinational “Tax 327” study, which utilized three treatment arms: docetaxel (35 mg/m²) administered intravenously once per week, vs. docetaxel (75 mg/m²) given intravenously every three weeks, vs. mitoxantrone (12 mg/m²) administered every three weeks. In Tax 327, 90% of the patients had metastatic disease in the bone and approximately one-half had disease-related pain requiring opioid pain medications (e.g., morphine).

The results of the Tax 327 study demonstrated that the median survival of all docetaxel-treated patients was 18.2 months, compared with 16.4 months for those treated with mitoxantrone, a difference that was statistically significant. An analysis of the survival in the docetaxel every-three-weeks arm was 18.9 months, which was significant when compared with the 16.4-month survival in those treated with M/P, and translated into a hazard ratio of 0.76 and a P value of 0.009 – in layperson’s terms, this means that patients who received docetaxel first lived 24% longer. The docetaxel given every 21 days was also superior to mitoxantrone with respect to pain response rate (35% vs. 22%; P = 0.01) and PSA response rate (45% vs. 32%; P = 0.0005). Based on the improvement in survival observed in patients receiving the docetaxel/prednisone every 21 days in Tax 327, the U.S. Food and Drug Administration approved the use of docetaxel (75 mg/m² every 21 days) together with prednisone as frontline therapy for metastatic HRPC in May 2004.

Several new approaches to improving the efficacy of chemotherapy-based treatment are in development. Results are anticipated from an ongoing

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**Table 1. Prostate Cancer Staging (Adapted from the American Joint Committee Cancer Staging Manual, 6th Edition)**

| T1 tumors are those tumors that are not clinically palpable on DRE or visible on TRUS | T1a – incidental finding of cancer in ≤ 5% of the tissue resected during a transurethral resection of the prostate |
| T1b – incidental finding of cancer in ≥ 5% of the tissue resected during a transurethral resection of the prostate |
| T1c – tumor identified by needle biopsy (performed because of an elevated PSA) |
| T2 tumors are confined to the prostate, identified by DRE or TRUS | T2a – tumor involves one-half of one lobe or less |
| T2b – tumor involves more than one-half of one lobe but not both lobes |
| T2c – tumor involves both lobes |
| T3 tumors extend through the prostatic capsule | T3a – extracapsular extension (unilateral or bilateral) |
| T3b – tumor invades seminal vesicle(s) |
| T4 tumors are fixed or invade adjacent structures, such as bladder neck, external sphincter, rectum, levator muscles, or pelvic wall |
| N1 refers to regional lymph node metastasis |
| M1 refers to distant metastasis | M1a – nonregional lymph nodes |
| M1b – bone(s) |
| M1c – other site(s) |
phase 3 randomized double-blind study comparing standard docetaxel therapy to docetaxel/prednisone plus bevacizumab. The addition of bevacizumab to chemotherapy in other cancers has led to improvements in survival and responses to chemotherapy. The addition of calcitriol and vaccines has thus far not shown to be beneficial when added to docetaxel. In addition, early clinical studies suggest that ixabepilone has significant activity in men with HRPC both in chemotherapy-naive and previously treated patients. Lastly, cabazitaxel (XRP-6258) is a taxane antineoplastic agent that works through the disruption of the microtubule network that is essential for mitotic and interphase cellular functions. By disruption of this network, inhibition of cell division and subsequent cell death occur. Cabazitaxel has shown a promising safety profile and activity in patients progressing after docetaxel therapy. Therefore, cabazitaxel is currently being investigated in the management of prostate cancer that has been previously treated with docetaxel.

Therapies that seek to augment the body’s immune reaction against prostate cancer are also in late-stage clinical trials. In therapy based on the sipuleucel-T vaccine, dendritic cells (the cells that initiate an immune response) are removed from the body and incubated with a prostate cancer antigen (prostatic acid phosphatase) and reinfused into the body three times. Prior studies have suggested that patients who received this vaccine had a longer survival than patients who received a placebo, and the confirmatory studies are under way. Should this approach prove useful in late-stage disease, it is possible that these vaccines may be used to prevent or delay recurrence in patients who have been treated with radiation or surgery with curative intent.

CONCLUSION
Prostate cancer is a very common disease with an extremely varied natural history. The optimal management of patients with prostate cancer is highly individualized, based on the varied aggressiveness of the disease ranging from one that is capable of being observed without therapy to one that is lethal for many patients (see Table 1). The optimal treatment program for an individual patient is one in which a multidisciplinary team of clinicians is involved in clinical decision making and treatment planning. Further, the aging of the population raises the possibility that more men than ever will deal with advanced prostate cancer, highlighting the urgency for the development of new therapies. Investigation of new therapies in the form of clinical trial enrollment is a critical factor in proving their success or failure and should be encouraged whenever possible.

References