Prostate cancer is the most common cancer detected in men and the second leading cause of all cancer deaths in men. It remains curable if diagnosed and treated at an early stage. Though screening tests are available, there remains substantial disagreement among various expert organizations as to the recommended prostate cancer screening guidelines for men. Such controversy exists because it is difficult to determine whether early cancer detection translates into a decreased mortality rate. While intervention with radical prostatectomy of early-stage prostate cancer may reduce disease-specific mortality, it may not reduce overall mortality. In this cohort of patients, comorbid illnesses play a key role, and death due to causes other than prostate cancer occurs in a significant percentage of patients with early-stage prostate cancer. As a result, life expectancy and comorbidities of each individual should be taken into consideration when deciding whether or not to screen and/or treat localized prostate cancer. This article reviews the issues in prostate cancer screening and the latest treatment options available for the various stages of prostate cancer.

Fortunately, prostate cancer possesses several ideal characteristics for screening. First, it is a substantial burden to public health as the number 2 cause of cancer death among men. Second, it has a long preclinical phase. And finally, prostate cancer is curable if found and treated in an early stage. Unfortunately, it remains unclear whether early detection of prostate cancer translates into decreased mortality in an aging population. Issues to discuss with the patient who is considering being screened for prostate cancer are listed in Table 1.

**Staging and Grading**

The tumor, nodes, and metastases (TNM) classification system of the American Joint Cancer Committee (AJCC) for prostate cancer is used to describe the extent of disease, evaluate the prognosis, and guide therapy. A simplified version of the 1997 TNM staging system for prostate cancer is presented in Table 2. The Gleason score is used to describe the histologic grade of the tumor, with grade 1 representing well-differentiated, slow-growing tumors; grade 2 representing moderately differentiated, intermediate-growing tumors; and grade 3 representing poorly differentiated, rapidly growing tumors. The Gleason score reflects the microscopic appearance of cancerous glands. The appearance is graded from 1 to 5, based on the degree of differentiation. One grade is applied to the cancerous glands of the largest area of the specimen, and a second grade is applied to the next largest area of cancerous glands. The 2 grades are added together to give a Gleason sum, or score. Gleason sums of 2 to 4 represent well-differentiated (grade 1) cancers; sums of 5 to 7 represent moderately differentiated (grade 2) cancers; and sums of 8 to 10 represent poorly differentiated (grade 3) cancers.

**Table 1. Key Facts on PSA Screening From Nationally Known Cancer Screening Experts**

<table>
<thead>
<tr>
<th>Fact</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Some medical experts and organizations endorse the use of the PSA test as a screening test for prostate cancer and some do not.</td>
</tr>
<tr>
<td>2.</td>
<td>It is unknown whether regular PSA screening will reduce the risk of death from prostate cancer. Ongoing studies are trying to find an answer.</td>
</tr>
<tr>
<td>3.</td>
<td>The individual who is considering undergoing testing, in consultation with a health professional, should make the decision about whether to undergo prostate cancer screening with the PSA test. The patient personally weighs the possible risks and benefits and makes a personal choice.</td>
</tr>
<tr>
<td>4.</td>
<td>An elevated PSA test result does not always mean that prostate cancer is present. It can also be caused by prostatitis or benign prostate enlargement.</td>
</tr>
<tr>
<td>5.</td>
<td>Prostate cancers detected by the PSA test are more likely to be confined to the prostate and consequently may be more curable than those detected by digital rectal examination (DRE) alone.</td>
</tr>
<tr>
<td>6.</td>
<td>Because of the long natural history of prostate cancer and the tendency of the disease to affect men over age 70, it has been difficult to determine which patients benefit from treatment.</td>
</tr>
<tr>
<td>7.</td>
<td>In general prostate cancer screening with the PSA and DRE is not recommended for men with less than 10 years to live because even if they have prostate cancer, they are likely to die from other diseases instead.</td>
</tr>
<tr>
<td>8.</td>
<td>Cancers detected by the PSA screening have a variable prognosis. Some are asymptomatic and are not destined to cause any significant morbidity or mortality. This is especially true for older men.</td>
</tr>
<tr>
<td>9.</td>
<td>A person with early prostate cancer can choose from among several options, including watchful waiting, radical prostatectomy, and radiation therapy. Although a cure is not possible for men with advanced prostate cancer, palliative options such as hormonal treatment are available.</td>
</tr>
<tr>
<td>10.</td>
<td>Neither a normal PSA test result nor a prostate biopsy that fails to show cancer can guarantee that prostate cancer is not present.</td>
</tr>
</tbody>
</table>

SCREENING TESTS

The screening tests available for prostate cancer include the digital rectal exam (DRE) and the prostate-specific antigen (PSA) test. When a patient has either an abnormal DRE or an elevated PSA, a transrectal ultrasound with needle biopsy of the prostate is typically the only means by which a diagnosis of prostate cancer can be made with any certainty. Unfortunately, prior to the development of PSA screening, most cancers detected by DRE alone were already at an advanced stage (T3 or greater). Not only does the PSA test detect more prostate cancers than the DRE, but it can also be used as a post-therapy cancer marker.

Typically, a total PSA value greater than 4.0 ng/mL has been considered the optimal cut-off point for most men between the ages of 50 and 70 years. However, there are many studies that suggest that 2.5 ng/mL is an appropriate PSA cut-off point for younger men in whom early prostate cancer detection and aggressive treatment would be most beneficial. However, the total serum PSA test, when used alone, is not specific for only prostate cancer, as indicated by the low positive predictive value from 2 separate studies. In fact, in the absence of prostate cancer, serum PSA levels vary with age, race, and prostate volume. The sensitivity, specificity, and positive predictive value of PSA and DRE are shown in Table 3. The sensitivity is the percentage of persons with the disease who have positive test results, the specificity is the percentage of persons without disease who have negative test results, and the positive predictive value is the percentage of persons with positive test results who actually have the disease. A recent meta-analysis of PSA and DRE as screening tests for prostate carcinoma found that the sensitivity, specificity, and positive predictive value for PSA were 72%, 93%, and 25%, respectively; and for DRE were 53%, 83%, and 18%, respectively. In this meta-analysis, 83% of cancers detected were localized.

Routine PSA screening can have considerable drawbacks because of its low positive predictive value. False-positive results can be costly both financially and in terms of the emotional suffering of patients who experience anxiety or undergo unnecessary prostate needle biopsy. Schroder and Kranse in a recent article noted that “lowering the PSA threshold for performing a biopsy will increase the rate of over-diagnosis and, potentially, overtreatment” of early stage prostate cancer. As they note, the important question that remains to be answered is whether the detection of missed cancers as a result of lowering PSA thresholds will reduce mortality and improve the quality of life among treated patients.

Several methods have been introduced to enhance the positive predictive value of the PSA. Measuring the change in total serum PSA level over time, known as PSA velocity, is one such method. (A PSA velocity greater than 0.75 ng/mL per year is considered high and may suggest the possibility of prostate cancer.) PSA velocity is gaining acceptance as a means for assessing prostate cancer risk. It appears to be more useful for assessing risk in men with lower PSA levels rather than as the deciding factor when considering further workup of patients with elevated PSA values.

Elevated PSA values need to be reconfirmed. According to an article by Eastham et al, it would be inadvisable for patients to be referred for biopsy based on an isolated elevation in PSA level.

<table>
<thead>
<tr>
<th>T: Primary Tumor</th>
<th>N: Regional Lymph Nodes</th>
<th>M: Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a Incidentally found tumor (ab) or diagnosed from biopsy (c)</td>
<td>N0 No regional lymph node involvement</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>T1b Tumor confined to 1 (a) or both lobes (b)</td>
<td>N1 Metastasis in 1 or more regional lymph nodes</td>
<td>M1 Distant metastasis present</td>
</tr>
<tr>
<td>T2 Tumor with extracapsular extension (a) or involving seminal vesicle (b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 Tumor involving adjacent organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Simplified TNM Staging System for Prostate Cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1a with N0M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1a with N0M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T1b or T1c or T2 with N0M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3 with N0M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4 or N1 or M1</td>
</tr>
</tbody>
</table>

* T1a indicates incidental histological finding in ≤5% of resected tissue; T1b, incidental histological finding in >5% of resected tissue. T1 is frequently encountered during transurethral resection of the prostate for benign prostatic hypertrophy. Adapted from Fleming et al. AJCC Cancer Staging Manual. 5th ed. Philadelphia, Pa: Lippincott-Raven, 1997.

| Table 3. Test Characteristics of the PSA and the DRE |
|-----------------|----------------|----------------|
| Abnormal PSA* | 67% | 97% | 43% |
| Abnormal DRE | 50% | 94% | 24% |
| Abnormal PSA and DRE | 34% | 99% | 49% |


* PSA >4.0 ng/mL.
They recommend that an isolated elevation in PSA level be confirmed several weeks later before proceeding with further testing.11

Another method for improving positive predictive value includes measuring the PSA density by dividing the total serum PSA level by the total volume of the prostate, as determined by transrectal ultrasound. This method, of course, requires referral to a urologist.

Some relatively recent developments in prostate cancer detection have been the use of measuring free to total PSA ratios and human kallikrein 2 (hK-2).12 Because PSA exists in protein-bound and protein-unbound forms, determination of the percentage free PSA is of greatest utility in patients with a normal DRE but an elevated PSA value. In a multi-institutional study by Catalona et al, it was determined that in men with total PSA levels between 4.0 and 10.0 ng/mL and nonsuspicious DRE, percentage free PSA can be used to optimize prostate cancer detection while reducing unnecessary prostate biopsies.13

Finally, the age-adjusted PSA level has been suggested as a means of enhancing the positive predictive value of the PSA test (Figure 2).14 In patients with benign prostatic hypertrophy (BPH) the age-adjusted PSA level will account for the high prevalence of BPH and will increase the positive predictive value of the PSA test for detecting prostate cancer. BPH is a prevalent condition in elderly men that may cause an elevation in the PSA level and whose incidence increases with age.

**Recommendations on Screening**

The American Cancer Society recommends that physicians offer yearly DREs and PSA screening to men who are 50 years of age and older and who do not have serious medical problems and have at least a 10-year life expectancy.15 The American Urological Association recommends that men considered to be at high risk because they have a first-degree relative with prostate cancer at an early age or because they are African American should begin testing at age 40 years.

The United States Preventive Services Task Force (USPSTF) does not recommend for or against routine screening for prostate cancer using DRE or PSA testing.16 The USPSTF concludes that PSA screening can detect early-stage prostate cancer, but notes that evidence demonstrating that early detection improves health outcomes and reduces mortality in all patients is lacking. The Task Force does suggest that a man who is interested in prostate cancer screening discuss the pros and cons of routine screening with his physician.

**Treatment**

**Intervention vs Observation**

Two randomized trials have been designed to answer the question of whether early intervention with radical prostatectomy is beneficial in terms of mortality. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) is a randomized controlled trial currently in progress that will compare conservatively managed patients (observation/watchful waiting) who have localized prostate cancer with patients treated with radical prostatectomy.17 The PIVOT study is the largest trial of its kind, and results are pending. A second randomized trial whose results were recently published compared radical prostatectomy with watchful waiting in patients with early prostate cancer, and found that radical prostatectomy significantly reduced disease-specific mortality but had no effect on overall survival.18 The authors of the study noted that the study follow-up period was long enough (median follow-up, 6.2 years) to determine whether the benefit of surgery would increase further after 10 years of follow-up. Death due to other causes occurred in 9% of men in the watchful waiting group vs 10% of men in the radical prostatectomy group.18

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**Figure 2. Increase in PSA Levels with Age**

Data from Oesterling et al.14

**American Cancer Society Recommendations on Screening for Prostate Cancer**

Annual digital rectal examination and prostate-specific antigen test for:
- All men 50 years of age and older who have at least a 10-year life expectancy
- Men 45 years of age who are thought to be at high risk because:
  - They have a first-degree relative diagnosed with prostate cancer at an early age and/or
  - They are African American
- Men 40 years of age who are thought to be at highest risk because:
  - They have 2 or more affected first-degree relatives diagnosed with prostate cancer at an early age
At least 3 retrospective studies have assessed survival outcomes in conservatively managed patients with prostate cancer. One retrospective study of men aged 65 to 75 years with conservatively managed, clinically localized prostate cancer found that histologic grade was a strong independent predictor of survival (Figure 3). Men with low-grade tumors experienced no loss of life expectancy. Cumulative 10-year mortality rates based on histologic grade were 46% for men with high-grade, poorly differentiated tumors; 24% for men with moderate-grade disease; and 9% for men with low-grade, well differentiated disease. Comorbidities were also a strong predictor of survival.

Two other studies provide evidence on survival for patients with early prostate cancer who either were managed conservatively or underwent radical prostatectomy. A retrospective study by Gerber et al focusing on men who had a radical prostatectomy performed for localized disease found that tumor grade was the most important factor in determining survival. The 10-year disease-specific survival rate following surgery was 94% for men with grade 1 tumors, 80% for men with grade 2 tumors, and 77% for men with grade 3 tumors. Another study by Chodak et al focusing on men who were conservatively managed for localized prostate cancer found that tumor grade once again was the single most important predictor for survival. The 10-year disease-specific survival rate was 87% for men with grade 1 or grade 2 tumors and 34% for men with grade 3 tumors. By comparing the results of these 2 studies, it may be possible to conclude that patients with high-grade, poorly differentiated, localized tumors would benefit from radical prostatectomy. On the other hand, men with clinically localized, well differentiated prostate cancer may experience no loss of life due to their prostate cancer should they opt for conservative management.

**TREATMENT OPTIONS**

Treatment options include watchful waiting, radical prostatectomy, radiation therapy, and hormonal therapy. In addition, a relatively new treatment modality is cryoablation of the prostate for localized prostate cancer. The treatment approach for men older than 70 years may not be the same as that for men younger than 70 years. Treatment with intent to cure can be offered to patients with an absence of serious comorbid conditions and a life expectancy of more than 10 years.

**RADICAL PROSTATECTOMY**

Any surgical intervention requires very careful patient selection and preoperative counseling. Preoperative risk assessment should focus on comorbid conditions that may predispose a patient to a multitude of perioperative complications.

Radical prostatectomy generally involves the complete removal of the entire prostate gland, seminal vesicles, and the ampulla of the vas deferens with or without a limited pelvic lymph node dissection. It is considered curative for patients with organ-confined prostate cancer, stages T1 and T2. A variety of surgical approaches currently exist. The 2 most common approaches are the retropubic and perineal approach. The advantage of perineal prostatectomy is decreased postoperative discomfort resulting from the avoidance of an abdominal incision. Disadvantages are the inability to perform a pelvic lymph node dissection and difficulty in preserving erectile function and urinary continence. Some authors have reported an increased incidence of fecal incontinence following this procedure.

Most centers nationwide currently perform a retropubic prostatectomy, as vast improvements in surgical technique have lessened overall blood loss and shortened inpatient hospital stays. An indwelling catheter remains in place for approximately 2 weeks postoperatively, and most men return to regular physical activities after 4 to 6 weeks. In addition to the recognized surgical complications, procedure-specific complications of radical prostatectomy include urinary incontinence, erectile dysfunction, and bladder neck contracture. The most recent surgical techniques for prostate cancer to gain popularity are minimally invasive surgeries, specifically laparoscopic and robotically assisted radical prostatectomy. Compared with open surgery,
these techniques have the potential to decrease hospital stays and facilitate a much earlier return to work and physical activities. The major drawback to these newer procedures is that they require a long learning curve, thereby limiting the number of centers currently offering such procedures.

**Radiation Therapy**

Conventional external-beam radiation is the most commonly used form of radiation therapy. Radiation therapy can be considered for patients with T1 or T2 tumors, low Gleason scores, and comorbid conditions, who would otherwise not be able to tolerate surgery.25

Men most likely to benefit from routine screening for prostate cancer are those who are 50 to 70 years of age.

As with surgical advancements, there have also been numerous advances in the management of prostate cancer patients using radiotherapy. These include much improved imaging techniques along with a generation of linear accelerators and conformal techniques capable of delivering high-dose radiation to target areas with relative sparing of the surrounding normal tissues.26 Conventional external-beam radiation may have another role following radical prostatectomy in patients who either have positive surgical margins or experience a rise in PSA after an initial nadir. Side effects of external-beam radiation include proctitis and cystitis complicated by incontinence, erectile dysfunction, and urethral strictures. Quality of life is a major concern of patients when they are choosing treatment options for prostate cancer. Men undergoing external-beam radiation therapy have worse bowel function and more dysuria than men undergoing radical prostatectomy.

Brachytherapy is an alternative form of radiation therapy involving ultrasound-guided or computed tomography-guided implantation of radioactive seeds. A noted advantage of brachytherapy over conformal radiation is that it is delivered in a single outpatient setting without the need for daily treatments over a period of several weeks. Men undergoing interstitial brachytherapy have less urinary incontinence than men undergoing radical prostatectomy.27 Ideal candidates for interstitial brachytherapy are patients with organ-confined disease, especially those patients at low risk for subsequent rise in PSA. Early studies would suggest that this form of prostate cancer therapy may be clinically efficacious only in a select subgroup of patients and may possibly be inadequate in others.28

**Hormonal Therapy**

Hormonal therapy is a form of treatment usually recommended for patients with locally advanced or metastatic prostate cancer. It is considered by most to be palliative therapy, but it can be used in conjunction with other therapeutic modalities. Most de novo prostate cancers are hormone dependent. Thus, most men who present with metastatic prostate cancer will respond to androgen deprivation. Orchiectomy has been considered the surgical "gold standard" treatment of advanced prostate cancer because of its immediate androgen-deprivation effects. However, it is an unpopular treatment option in younger men because of its inherent side effects — erectile dysfunction, loss of libido, hot flashes, and fatigue.

Diethylstilbestrol, an estrogen compound, was one of the first medical hormonal therapy options available for the treatment of prostate cancer. Its use today has severely diminished because of cardiovascular and thromboembolic side effects, and availability in the United States is limited. Fortunately, several alternative methods of medical hormonal therapy are available for the treatment of prostate cancer (Table 4).

Luteinizing hormone-releasing hormone (LHRH) analogs are considered first-line agents for men with metastatic prostate cancer. They are commonly used as monotherapy and can be given as intramuscular or subcutaneous injections at monthly, 3-month, or 4-month intervals. These agents, upon initiation, cause a surge in serum testosterone levels during the first week of therapy, possibly leading to a phenomenon known as tumor flare. Tumor flare can present a significant problem in patients with spinal cord compression, bone pain, or acute bilateral ureteral obstruction due to metastatic prostate cancer. However, tumor flare can be eliminated with combined androgen blockade using an LHRH agonist together with an oral antiandrogen medication. Castrate levels of testosterone are usually obtained in 2 to 3 weeks.

Nonsteroidal antiandrogens act on androgen receptors and inhibit binding of the active testosterone metabolite, dihydrotestosterone. The 3 most common nonsteroidal antiandrogens include flutamide, bicalutamide, and nilutamide. They are commonly given with an LHRH analog for a combined effect on androgen ablation and, more importantly, to prevent a tumor flare. Cyproterone acetate is a steroidal antiandrogen that also blocks androgen-receptor binding, but it is associated with cardiovascular complications and therefore is unavailable in the United States.29

Third-line medical agents include ketocona-
zole, an adrenal steroidogenesis inhibitor, and glucocorticoids in replacement doses. The 2 agents may be used together since ketoconazole causes diffuse adrenal insufficiency, while replacement doses of glucocorticoids prevent adrenal crisis by allowing for production of mineralocorticoids.

**Cryotherapy**

First introduced in the mid 1960s, cryotherapy of the prostate was plagued with numerous complications that curtailed its use in the treatment of prostate cancer. Currently, there is renewed interest in cryotherapy for the treatment of patients with low-grade and early-stage tumors because it can be performed on an outpatient basis.

Modern cryotherapy of the prostate involves placement of a urethral warming device, followed by the placement of 4 to 5 transperineal cryoprobes into the prostate. It has been a consistent finding that 2 freeze/thaw cycles (target temperature -40°C to 50°C) are more likely than a single cycle to result in prostate cancer ablation. Local control rates have varied. The positive biopsy rate after cryotherapy ranges from 8% to 25%, depending on the clinical stage. Complications from cryotherapy have included obstructive voiding symptoms, urethral sloughing, and urethral fistula formation. Although the Health Care Financing Administration has approved cryotherapy for the treatment of early stage organ-confined prostate cancer, further studies are needed to evaluate long-term survival outcomes.

**Watchful Waiting**

For patients with well-differentiated to moderately differentiated localized prostate cancer and a life expectancy of less than 10 years, watchful waiting is an acceptable option. Watchful waiting includes routine follow-up with serum PSA testing, DREs, and monitoring for the development of symptoms such as obstructive voiding symptoms, hematuria, weight loss, or new-onset bone pain. The decision to intervene depends on the biological behavior of the cancer. Patients with slow-growing cancers can continue to be observed, while those with more rapidly growing cancers could benefit from curative or palliative therapy. The PSA doubling time has been recommended as the cut-off point for the decision to intervene. A PSA doubling time of less than 2 years identifies patients at high risk for progression.

### Table 4. Hormonal Therapy for Prostate Cancer

<table>
<thead>
<tr>
<th>Level of Action</th>
<th>Therapy</th>
<th>Mechanism of Action</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testis</td>
<td>Orchiectomy</td>
<td>Surgical castration</td>
<td>Considered the “gold standard” of androgen deprivation</td>
</tr>
<tr>
<td>Prostate</td>
<td>Flutamide</td>
<td>Nonsteroidal antiandrogens (androgen receptor antagonists) that interfere with androgen receptor binding of testosterone and dihydrotestosterone by competitive inhibition</td>
<td>Considered as second-line antiandrogen treatment. Typically used in combination with LHRH agonist for combined androgen blockade</td>
</tr>
<tr>
<td></td>
<td>Bicalutamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nilutamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyproterone acetate</td>
<td>Steroidal antiandrogen (androgen receptor antagonists)</td>
<td>It is not available in the United States.</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Ketoconazole</td>
<td></td>
<td>Considered a third-line therapy. It is used for patients at risk for the flare phenomenon.</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoids</td>
<td>Inhibits adrenal steroidogenesis</td>
<td></td>
</tr>
<tr>
<td>Pituitary</td>
<td>Diethylstilbestrol</td>
<td>A semisynthetic estrogen compound</td>
<td>Second-line hormonal therapy because of significant cardiovascular side effects. It is not widely available in the United States.</td>
</tr>
<tr>
<td></td>
<td>Leuprolide injection (Lupron®) intramuscular (Viadur®) subcutaneous (Eliarg®) subcutaneous Goserelin® injection (Zoladex®) intramuscular</td>
<td>LHRH agonists provide medical means of castration by way of negative feedback to the pituitary gland</td>
<td>Considered as first-line antiandrogen treatment. Typically used as androgen deprivation monotherapy. Tumor flare can occur in the first few weeks of treatment in the absence of combined androgen blockade.</td>
</tr>
</tbody>
</table>

Data from Bishoff et al.23

LHRH = luteinizing hormone-releasing hormone.
TREATMENT SCENARIOS

LOCALIZED PROSTATE CANCER

Treatment decisions on localized organ-confined prostate cancer are based on life expectancy, comorbid illnesses, and tumor grade. Radical prostatectomy and radiation therapy can be considered for patients with stage T1 or T2 prostate cancers with low Gleason scores. Typically, radiation therapy has been offered to patients with comorbid conditions who are otherwise unfit for surgery and to patients with high-stage clinical disease (T3). An advantage of radical prostatectomy over radiation therapy is that radical prostatectomy facilitates determination of a patient's true pathologic stage compared to clinical stage. Studies have revealed that 7% to 26% of clinical stage T3 prostate cancer patients are actually overstaged. Nevertheless, men with low-grade, well-differentiated, localized cancers have the best prognosis in terms of median survival time regardless of the definitive treatment selected.

LOCALLY INVASIVE PROSTATE CANCER

Radiation therapy has traditionally been offered as therapy for prostate cancer that has extracapsular extension or involves the seminal vesicles. In some cases, brachytherapy can be combined with external-beam radiation to aggressively treat locally invasive disease. Additionally, treatment with combined radiotherapy and hormonal therapy seems to confer the best survival results. The Canadian Urologic Oncology Group reported a randomized trial comparing external radiotherapy alone with combined radiotherapy and hormonal therapy for locally advanced prostate cancer. The study concluded that there was better clinical, biochemical, and pathological control of locally advanced cancer, up to 36 months post-treatment, in the combined therapy group.

Some urologists may still consider radical prostatectomy for patients with locally invasive prostate cancer under special circumstances. Preoperative androgen deprivation offers a theoretical advantage by causing a down-staging effect. Although it may decrease the incidence of pathologically determined extracapsular extension, evidence has not shown a significant effect on survival or disease progression.

METASTATIC PROSTATE CANCER

Hormonal therapy, by surgical or medical means, is indicated for stage T4 prostate cancer. Antiandrogen therapy, administered as monotherapy or as combined androgen blockade, is the recommended medical means of castration, while bilateral orchiectomy remains the “gold standard” for surgical castration levels of testosterone. LH-RH analogs are used primarily as first-line monotherapy agents for men with metastatic prostate cancer. As reported by investigators of large prospective trials, palliative hormonal monotherapy by medical or surgical castration has proven effective in stabilizing median overall survival for up to 36 months. These agents, however, are known to cause a flare phenomenon if given alone. Thus, nonsteroidal antiandrogens are used in combination to prevent temporary worsening of symptomatic metastatic disease. Ketoconazole with replacement doses of hydrocortisone is a standard treatment option for patients with advanced prostate cancer that progresses despite androgen deprivation. Replacement doses of glucocorticoids will prevent adrenal crisis by allowing the production of mineralocorticoids.

Although some of the published data show a statistically significant benefit with combined androgen blockade, the data also show that combined androgen blockade is associated with higher toxicity rates and a worsened quality of life.

TREATMENT DILEMMAS

The average life expectancy for American men is 73 years. White males have a life expectancy of 74 years, and black males have a life expectancy of 67 years. However, the average number of years of life remaining decreases with age (Figure 4). Life expectancy should be taken into consideration when deciding on radical prostatectomy vs conservative management. Well-differentiated tumors have an overall good prognosis in terms of survival. On the other hand, poorly differentiated tumors have a poor prognosis in terms of survival. Thus, a patient in his late 70s diagnosed with well-differentiated adenocarcinoma of the prostate may opt for conservative management, while a patient in his 60s diagnosed with poorly differentiated adenocarcinoma of the prostate may opt for radical prostatectomy.

The risks of radical prostatectomy should also be taken into consideration. Prevalence of urinary incontinence after radical prostatectomy can be as high as 50% at 3 months of follow-up, and that of sexual dysfunction can be as high as 65% at 3 months of follow-up. Walsh et al reported the rates of urinary incontinence and sexual dysfunction after radical prostatectomy in 64 men. Quality-of-life surveys regarding urinary and sexual function were administered at 3, 6, 12, and 18 months (Figure 5). At 18 months, 93% of patients reported normal urinary control, and 86% reported normal sexual function.

A much larger study, the Prostate Cancer Outcomes Study (PCOS) trial, found more dismal long-term results in terms of erectile dysfunc-
tion but similar results in terms of urinary incontinence. In this trial, a total of 1291 men were diagnosed with clinically localized prostate cancer and underwent radical prostatectomy. After 2 years of follow-up, 44% of the men reported a complete inability to obtain an erection, and 9% of patients reported problematic incontinence.40

Health-related quality-of-life issues ultimately affect a patient’s decision-making process when choosing treatment for prostate cancer. Helgason et al have shown that patients highly value quality of life following treatment for prostate cancer and that they are often willing to choose a therapy that offers a shorter life expectancy but better quality of life following treatment.41

**CONCLUSION**

Do early detection and intervention positively affect survival rates for all patients? Retrospective studies have shown that men with clinically localized, low-grade tumors do, in fact, have an excellent 10- to 15-year survival rate. While intervention with radical prostatectomy in patients with early-stage prostate cancer may reduce disease-specific mortality, it may not decrease overall mortality. Analysis of trends in prostate cancer incidence shows that there has been an increased incidence of early-stage disease and a decreased incidence of advanced disease, reflecting the widespread use of PSA screening. As a result, disease-specific survival has improved as well.42,43 Death due to causes other than prostate cancer occurs frequently in a significant percentage of patients with early-stage prostate cancer.

It is evident that the most common cancer in men presents many challenges to both clinician and patient. Perhaps, above all, life expectancy should be taken into careful consideration when deciding whether or not to screen and/or treat men with localized prostate cancer.

**REFERENCES**