A Managed Care Perspective

on the Diagnosis, Evaluation and Treatment of

Prostate Cancer

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As the most frequently diagnosed cancer in men and the second-leading cause of male cancer deaths, prostate cancer remains a high priority in managed care oncology. Despite ranking as only the fifth-leading cancer in terms of direct treatment costs at $11.85 billion in 2010, increasing survivorship and the accompanying need for long-term management makes prostate cancer a growing concern among plan stakeholders and clinicians alike. In fact, prostate cancer leads all cancer types with a projected 36 percent increase in survivors between 2010 and 2020, with mortality steadily declining since the 1990s. While these data are promising and indicative of increased screening efforts and advances in treatment modalities, they also signal a pronounced need for ongoing care and intensive management in the disease state.

It is estimated that 241,740 men will be diagnosed with prostate cancer in 2012, and 28,170 will die of the disease. Incidence rates are significantly higher among African-American males than in whites, with mortality rates also being more than two times higher for the former demographic than the latter. In addition to race/ethnicity, age and family history of the disease are the other well-established risk factors for prostate cancer. Approximately 62 percent of cases are diagnosed in men ages 65 and older, and 97 percent of cases occur in men ages 50 and older. An increased risk for prostate cancer has also been linked to a diet high in processed meat and dairy foods, while obesity has only been correlated with an increased risk for aggressive disease.

Although some debate exists regarding the value of routine testing for early prostate cancer detection with the
prostate-specific antigen (PSA) test, the aforementioned risk factors play a role in considerations and current recommendations for screening. The American Cancer Society recommends that — beginning at age 50 — men who are at average risk for prostate cancer and have a life expectancy of at least 10 years receive information about the potential benefits and known limitations of testing for early prostate cancer detection. Those at high risk, including African-Americans and men with a close relative diagnosed with prostate cancer before age 65, should have this discussion with their health care provider beginning at age 45. If screening via the PSA test or digital rectal exam (DRE) results in suspicion of prostate cancer, clinicians have several different means of diagnosing and characterizing the disease before selecting the appropriate course of treatment.

DIAGNOSIS AND EVALUATION
Whether employed as screening methods or for further investigation of telltale symptoms, the PSA test and the DRE represent the initial measures in the diagnostic process for prostate cancer. In fact, since early-stage disease is often asymptomatic, a PSA test and a DRE may be the only means of detecting the disease outside of more invasive analyses. Patients with advanced disease may present with symptoms such as a slowed or weakened urinary stream, an urge to urinate more often and/or hematuria. In addition to initial detection, the DRE can likewise be used to further characterize the disease prior to biopsy and imaging studies, including whether the cancer is unilateral or bilateral or whether it has likely spread beyond the prostate gland to nearby tissue. Similarly, results from a PSA test may also be predictive of disease severity, with higher PSA levels indicating more advanced disease and a higher potential that the cancer has spread.

To confirm a diagnosis of prostate cancer, a biopsy must be performed to collect tissue for cytologic analysis. This is most often a core needle biopsy of the prostate guided by transrectal ultrasound, in which the clinician collects anywhere between eight and 18 core samples. Upon identification of cancerous cells, the pathologist who analyzed the prostate tissue samples typically assigns a Gleason grade (or pattern) to the most common tumor pattern and — since prostate cancers often have areas with different grades — a second grade to the next most common tumor pattern. These grades range from one to five, with five indicating the poorest prognosis (Table 1). The two grades are then added together to calculate the Gleason score (or sum) of the patient’s prostate cancer. This system is adjusted in special scenarios: If the highest grade comprises ≥ 95 percent of the biopsy, the grade for that area is counted twice in the Gleason score. Conversely, if three grades are present in a biopsy core, the highest grade is always included in the Gleason score, even if most of the core is taken up by areas of cancer with lower grades. The Gleason score ranges from two to 10, with 10 indicating the poorest prognosis and highest likelihood of metastasis. Cancers with a Gleason score of ≤ six are considered low grade or well differentiated, while those with Gleason scores of seven are considered moderately differentiated or intermediate grade. When a patient’s prostate cancer has a Gleason score of ≥ eight, it is considered poorly differentiated or high grade.

Unlike other cancers, prostate cancer patients frequently do not require imaging for staging purposes, because PSA-detected cancers are typically very early stage. However, for men with a high Gleason score or PSA (> 20 ng/mL is a typical cutoff), the risk for metastasis is high enough that imaging should be performed to be certain the disease is localized before curative therapy is applied. Since prostate cancer has a strong predilection for spread to the bones, a radionuclide bone scan may be among the first imaging studies ordered. Another common imaging study, computed tomography (CT), is useful in determining whether the prostate cancer has spread into nearby lymph nodes. A CT scan may clarify abnormalities seen on the bone scan, helping to differentiate uptake related to osteoarthritis from that associated with blastic or lytic abnormalities, which would be more suspicious for metastatic involvement. CT scans are also employed at the time of PSA recurrence to ascertain the involvement of other organs or structures in the pelvis.

<table>
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<tr>
<th>Grade/Pattern</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Tissue closely resembles normal prostate tissue; glands are small, well-formed and closely packed.</td>
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<tr>
<td>2</td>
<td>Tissue still has well-formed glands, but they are larger and have more tissue between them.</td>
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<tr>
<td>3</td>
<td>Tissue still has recognizable glands, but the cells are darker; at high magnification, some of these cells have left the glands and are beginning to invade the surrounding tissue.</td>
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<tr>
<td>4</td>
<td>Tissue has few recognizable glands; many cells are invading the surrounding tissue.</td>
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<tr>
<td>5</td>
<td>Tissue does not have recognizable glands; there are often just sheets of cells throughout the surrounding tissue.</td>
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and categorize men into either the biochemically recurrent (i.e., PSA-only but no imaging abnormalities) or metastatic stage. Although used less frequently, magnetic resonance imaging (MRI) scans can produce a more distinct image of the prostate than CT scans and reveal whether the cancer has spread outside of the prostate into surrounding structures such as the seminal vesicles or bladder.

TREATMENT CONSIDERATIONS

Given that most men diagnosed with prostate cancer are not destined to die from the disease, placing the cancer in the context of the patient’s comorbidities and general health status is critical to avoid overtreatment. For elderly patients or those with low-grade and early-stage disease, there is a paucity of evidence demonstrating that treating slow-growing prostate cancer with surgery or radiation will actually prolong survival. For such men, active surveillance is an important consideration. As opposed to so-called “watchful waiting,” active surveillance involves close monitoring to identify cancers that will behave aggressively enough to warrant treatment and then provide curative therapy for those men while continuing to monitor the indolent cancers, sparing those men from the potentially permanent adverse consequences of curative therapy.

However, in younger, healthier men or in those with aggressive forms of the disease, surgery or radiation serves as definitive therapy and provides a high potential for cure. Among surgical options, radical prostatectomy can be performed laparoscopically, with robotic assistance, or via a traditional open approach. As cure is the ultimate goal of this procedure, the entire prostate gland and some of the surrounding tissue, including the seminal vesicles, are removed. Similar to surgery, radiation therapy comes in several different forms, with the two main categories being external beam radiation therapy (EBRT) and brachytherapy. Advances in radiation therapy include intensity modulated radiation therapy (IMRT) and proton therapy, which are designed to deliver a higher dose of radiation to kill cancer cells but hopefully with fewer and generally minimal gastrointestinal and genitourinary side effects. Randomized data are not available to compare these treatments, and decision making is therefore complicated. Patients with intermediate- and high-grade cancers will typically receive androgen deprivation as part of their radiation treatment plan for up to three years. Despite being potentially curative, both radiation therapy and surgery can have significant side effects. Surgery is associated with a risk for incontinence and/or impotence, while radiation therapy is more often associated with gastrointestinal issues and impotence.

In situations where surgery and radiation therapy are not appropriate, androgen-deprivation therapy (ADT) is used. ADT agents exert their effect through the inhibition of androgens such as testosterone and dihydrotestosterone, which stimulate prostate cancer cell growth under normal conditions. The classes of agents include luteinizing hormone-releasing hormone (LHRH) analogs (e.g., leuprolide, goserelin, triptorelin and histrelin), LHRH antagonists (e.g., degarelix) and antiandrogens (e.g., flutamide, bicalutamide and nilutamide). Orchiectomy, or surgical castration, is also considered a form of ADT since > 90 percent of the androgens in males are produced in the testicles. While orchiectomy is likely the least expensive and simplest way to reduce androgen levels in the body, it is irreversible and often viewed as an undesirable procedure by patients.

Although ADT is extremely effective and the majority of men will respond to treatment, the cancer inevitably develops resistance, yielding the lethal castration-resistant form of the disease. Chemotherapy is primarily used in this setting. The standard first-line
A chemotherapy regimen is docetaxel and prednisone, which has been shown to palliate cancer symptoms and prolong survival for an average of approximately three months compared with mitoxantrone in patients with advanced prostate cancer that is no longer responding to ADT. For those patients whose hormone-refractory prostate cancer has progressed after treatment with docetaxel and other chemotherapy regimens, cabazitaxel was recently approved in combination with prednisone after a survival benefit was documented in comparison with prednisone alone. Similarly, abiraterone has demonstrated increased survival in this setting when administered in combination with prednisone and was approved by the U.S. Food and Drug Administration (FDA) in April 2011.

A truly innovative therapy, sipuleucel-T, was approved by the FDA in April 2010 for the treatment of advanced hormone-refractory prostate cancer. Described as a personalized therapeutic vaccine, sipuleucel-T is an autologous cellular immunotherapy designed to activate the patient’s own immune defenses against hormone-refractory prostate cancer. The vaccine is produced by taking antigen-presenting cells from the patient via leukapheresis and then processing the cells with fusion protein of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF) to sensitize them to prostate cancer cells. The cells are then reintroduced to the patient to provoke an immune response against the tumor. In clinical trials, sipuleucel-T improved median survival time by > four months compared with placebo (p < 0.01) in patients with asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer. In addition to bolstering the therapeutic armamentarium, this and similar immune-based therapies that eventually follow may have the potential to offer a more durable treatment response in contrast to the eventual development of resistance experienced with current therapies.

Supportive care is provided in prostate cancer centers upon relieving the pain associated with bone metastases in advanced disease. Beyond nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid painkillers, bisphosphonates (primarily zoledronic acid, but also pamidronate) and RANK-ligand inhibitors (denosumab) are often employed for this purpose. Denosumab, a fully human monoclonal antibody against RANK-ligand, was approved in November 2010 for the prevention of skeletal-related events in patients with bone metastases from solid tumors and may also be useful to prevent ADT-induced loss of bone mineral density. EBRT is frequently employed for relief of pain associated with bone metastases, and radiopharmaceuticals such as strontium-89 and samarium-153 are sometimes used when diffuse metastases or multiple sites of pain are present. Even in end-stage disease, these treatments may be used as part of a palliative care program.

A PROSPECTIVE VIEW IN MANAGED CARE

A relatively diverse array of therapies is available for the treatment of prostate cancer, and the list of FDA-approved agents continues to grow. In addition to the recent approvals of cabazitaxel and abiraterone, sipuleucel-T ushered in a new era of immune-based therapies, which offers significant promise for the future. Specific to the area of bone metastases in prostate
therapies. While this needs to change, especially given the increasing number of therapeutic choices, the long-term survival associated with prostate cancer will make genomic testing more costly and difficult to develop. Due to the differences in side-effect profiles and geographic differences in the availability of therapies, randomized trials of localized therapies are untenable. Effective treatments for the disease have always been developed in parallel, leaving clinicians with a menu of viable options. As all these treatments are costly, and long-term survival with side effects can be costly as well, the optimal means of controlling prostate cancer costs would be prevention. Unfortunately, positive data from phase 3 prevention trials have been greeted with limited enthusiasm.

While prostate cancer screening has been the virtual norm for several years, the United States Preventive Services Task Force (USPSTF) recently published draft recommendations against PSA-based screening for prostate cancer in asymptomatic men. After previously stating there was insufficient evidence to make a definitive judgment in the 2008 guidelines, the USPSTF gave the draft guidance a D recommendation in late 2011, indicating moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits; furthermore, the task force discourages use of the service. Meanwhile, the American Cancer Society stands by its recommendation for screening in men at average risk who are age 50 and older (45 and older for high-risk men), so payors will be faced with their own decision to make based on the available evidence. Certainly, men at high risk due to ethnicity or family history will continue to receive screening. Acknowledging the more positive data in support of PSA screening from the European study and applying screening sensibly, PSA testing remains our best current tool for detecting and characterizing prostate cancer. Mitigating our reaction to PSA results, applying more expensive imaging studies judiciously and optimizing treatment selection in the future will help ensure high value for cost in managing this disease. As health plans have become more accepting of even high-cost clinical tools as valuable for effectively staging and treating the disease, it is likely that insurers will stay the course with clinically sound means of management.

References