Update on the diagnosis and management of prostate cancer

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Early detection of prostate adenocarcinoma (prostate cancer) through screening tests such as a serum prostate-specific antigen (PSA) test and a digital rectal examination (DRE) enables primary care physicians and urologists to offer patients a broader choice of treatments that are also more likely to provide a cure. Whether men are being over treated or over diagnosed through the widespread use of screening tests remains controversial. This review aims to provide general practitioners with a better understanding of different prostate cancer tests that can be performed and to help them decide which patients should be referred to a urologist for an ultrasound-guided biopsy.

Key Words: prostate adenocarcinoma, early cancer detection, prostate-specific antigen, digital rectal exam

Introduction

The leading type of cancer in men in the United States and Canada is prostate adenocarcinoma. It is estimated that in 2008, there will be more than 230,000 cases of prostate cancer diagnosed in the United States and more than 24,700 cases diagnosed in Canada.[1] In Canada alone, it is estimated that over 4,000 men will die of prostate cancer this year and one in eight men will develop prostate cancer during his lifetime. Recent advances in screening in the last two decades have enabled physicians to detect prostate cancer earlier and to offer different treatment options tailored to patient health status and preference. Compared to 10 years ago, prostate cancer death rates have declined by 2.9% likely due to earlier detection and better treatment. Detecting prostate cancer as an occult condition enables physicians to find a cure while the disease is still confined to the gland. Once the malignancy is locally advanced (extends beyond the prostate capsule) or metastasizes to the pelvic lymph nodes, distant organs, or bones, a cure is not considered to be attainable. Physicians have thus been strongly motivated to detect prostate cancer early. Some physicians believe that prostate cancer mortality decreases with earlier detection, but this belief has been challenged by others.

Our objective in this review is to examine the importance of early detection of prostate cancer, particularly in the setting of the office of a primary care physician. While it remains controversial about whether early detection of prostate cancer decreases

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mortality, this review aims to inform the primary care physician about the usefulness of early prostate cancer detection, and also aims to provide information that can be used to guide treatment decisions for patients who may have this fatal disease. By acquiring knowledge of the basic diagnostic protocols, treatments, and side effects, the primary care physician will be better prepared to answer questions that an anxious patient might ask.

Background

In 1986 the US Food and Drug Administration (FDA) approved the use of a prostate-specific antigen (PSA) test to monitor disease progression in patients with prostate cancer. Shortly after, many asymptomatic men with no known disease underwent PSA testing, which led to early diagnosis of early-stage tumors.[2] In 1991, Dr. William Catalona, an expert in urological cancer, presented data that demonstrated the clinical usefulness of PSA screening for early detection of prostate cancer.[3] Despite the limitations of these findings, since they came from a non-randomized study, increasingly, PSA testing came to be widely used. Questions began to arise about the long term benefit of PSA screening, however, particularly when it identified clinically insignificant disease. The debate began about the merits of screening all men to detect early prostate cancer without the proven benefit of longer survival versus the merits of evaluating only symptomatic men in whom the suspicion of prostate cancer is higher. The American Cancer Society (ACS) has maintained its stand on early detection of prostate cancer: the ACS recommends that annual serum PSA tests and digital rectal exams (DREs) be performed in all men aged 50 and older. The ACS emphasizes the need for the physician to discuss the benefits, limitations, and goals of early prostate-cancer detection.[4] In contrast, the US Preventive Services Task Force (USPSTF) has concluded that "The evidence is insufficient to recommend for or against routine screening for prostate cancer using prostate-specific antigen testing or digital rectal examination."[5] Like the USPSTF, the American Academy of Family Physicians agrees that the choice should be left up to patients and their primary care providers.

In Canada, PSA testing has not yet been established as a formal recommendation for routine screening. Despite national guidelines that do not include routine PSA screening, a recent report found that nearly half of Canadian men over age 50 have had PSA tests done.[6] Our goal is not to convince the primary care physician to choose one side or the other of this controversial issue, but rather to review the literature on early cancer detection, prevention, and the benefit of early detection.

Epidemiology

Prostate cancer is one of the leading causes of death from cancer in men.[7,8] In 2007, the National Cancer Institute (NCI) reported that an estimated 218,890 new cases of prostate cancer were identified in the United States, and it was the most diagnosed malignancy in men. The report also noted that in the same year, approximately 27,000 deaths in the United States would result from prostate cancer. Worldwide, prostate cancer is the fourth most common malignancy in men.[9] The mortality rate for prostate cancer has steadily risen over the last few decades — sharply rising in the late 1980s and peaking in the early 1990s as a result of better detection. Since then, there has been a slow decline in prostate-cancer-related deaths, which are currently estimated to be 30 in 100,000 men worldwide.

According to the 2004 NCI survey, 17.6% of white men will develop prostate cancer during their lifetimes and 4.7% will die from prostate cancer. In African American men, the incidence of prostate cancer is 1.6 times higher than in white men. Similar results were found in the 2005 ACS survey: compared to white men, African American men had a 2.4-fold higher rate of mortality from prostate cancer, and they were diagnosed with prostate cancer at an earlier age. There are no clear reasons why this discrepancy exists. Some physicians suggest that this racial difference is a reflection of differences in socioeconomic factors, while others suggest that there may be a genetic basis to this difference and aggressive campaigns to increase both awareness of prostate cancer and screening for this disease should be implemented.[10] Autopsy studies examining early prostate cancer in young patients did not reveal any statistically significant difference in factors such as cancer stage or size between white and African American men.[11]

Risk factors

Age, of course, is a well-known, significant risk factor for prostate cancer. While Sakr et al noted that precancerous lesions can be found in men younger than 40 years old,[11] the incidence of prostate cancer rises rapidly after the fifth decade of life. In fact, the rate of prostate cancer diagnosis is 100 per 100,000 men in their 50s, and rises to 600 per 100,000 men in their 60s and 1000 per 100,000 men in their 70s.[12] Genetic and environmental components have been observed in prostate cancer. One study showed that a family history of prostate cancer increases a man's

risk of prostate cancer.[13] A meta-analysis of 22 reports found that men had a 2.5-fold increased relative risk of prostate cancer if they had a first-degree relative with this disease.[14] Men who have at least three immediate family members who were younger than 55 years old when they were diagnosed with prostate cancer are said to have a "hereditary" risk of prostate cancer. About 85% of cases of prostate cancer, however, are classed as sporadic (not hereditary).[15] Prostate cancer susceptibility genes have been isolated.

African Americans have the highest risk for developing prostate cancer. White men have the next highest risk of having prostate cancer, especially if they live in a cooler climate, possibly due to decreased vitamin D levels as a result of decreased sunshine. Low vitamin D levels have been associated with higher risk of developing prostate cancer.[16] Asian men and men who live in the Pacific Island have the lowest incidence of prostate cancer.

Environmental factors such as diet (especially a high intake of polyunsaturated fat), obesity, alcohol consumption, and tobacco use have also been implicated in prostate cancer. High animal fat intake and low vegetable consumption appear to increase the risk of prostate malignancy.[17,18] Furthermore, high fat intake has been found to induce chronic inflammation due to oxidation at the cellular level. Chronic prostatic inflammation exposes the prostate to carcinogens and subsequently renders prostate cells vulnerable to genome damage.[19,20]

Exposure to sexually transmitted diseases (STDs) has also been implicated in the development of prostate cancer. Human papillomavirus (HPV) is one such STD that is believed to cause prostate cancer. Some studies cast doubt on the existence of a link between HPV infection and prostate cancer.[21,22]

The benefits of a healthy diet and physical activity have been investigated to evaluate their potential in reducing the risk of prostate cancer. Vitamins and minerals are linked to the reduction of prostate cancer; Clark et al noted a decrease in prostate cancer in men taking selenium supplements.[23] Phytoestrogens, lycopene, and vitamin E have also been shown to play a role in preventing prostate cancer; large clinical trials to examine these factors are ongoing. Sexual activity has been found to offer a protective effect.[24] Vasectomy has been shown to be weakly correlated with increased incidence of prostate cancer,[25] but this may be due to patients having more frequent interactions with urologists, which increases detection.

In recent years, more consideration has been given to evaluating the potential effects of medications for preventing prostate cancer.

Hypercholesterolemia and a high-fat diet have been linked to an increased risk of prostate cancer.[26,27] Statin medications (such as simvastatin), which are used for lowering cholesterol, have been evaluated for a potential role in preventing prostate cancer. Recently published studies from the United States and Finland (where the rates of cancer are tightly monitored in a national registry), reported that statins reduced the rates of advanced prostate cancer, but they did not reduce the overall risk of prostate cancer.[28,29] In another recent study, non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin were linked to a reduction in rates of prostate cancer.[30]

Circulating testosterone is converted to more potent androgens by 5-alpha reductase in the prostate and can have a profound effect on prostate growth. The Prostate Cancer Prevention Trial (PCPT) deserves recognition for its elaborate work on 5-alpha reductase inhibitors. In a 10-year study, finasteride (Proscar, Merck, Inc.), a type 2, 5-alpha reductase inhibitor commonly given to men with benign prostatic hypertrophy (BPH), was used to reduce the risk of prostate cancer. This study reported a 24% reduction in the incidence of prostate cancer, but this was primarily in low-grade tumors.[31] A major concern was that this trial also found an increase in high-grade tumors in trial participants, and, as a result, the use of finasteride as a cancer prevention medication was diminished. Recent studies dispute that finasteride induces higher-grade cancer. These studies suggest that this observation occurred because finasteride facilitates the detection of high-grade cancers by improving the ability of PSA tests, DREs, and prostate biopsies to detect high-grade cancers.[32-34] Dutasteride (Avodart, GlaxoSmithKline), a newer generation 5-alpha reductase inhibitor, was shown to reduce prostate cancer in short-term studies.[35,36] The ongoing Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial will provide further insights into results with this medication.

Diagnostic tests

Prior to the 1980s and the introduction of PSA testing, early detection of prostate cancer was uncommon. Because prostate malignancy generally occurs in the periphery, away from the urethra, symptoms were seldom felt by the patient. When present, symptoms could consist of lower urinary tract symptoms, bone pain, and even renal failure. Prior to the introduction of the PSA testing, diagnosis was made upon finding an abnormal DRE result. Unfortunately, by then, the malignancy was likely to be locally advanced or metastatic.

Since the widespread use of PSA testing, there has been a tremendous reduction in the incidence of advanced prostate cancer.[37] Today, most cases of prostate cancer are detected from elevated PSA levels and/or from abnormal DREs. Early detection of prostate cancer has rapidly increased. New staging parameters have been developed to predict the true extent of disease, assess prognosis, and aid in determining the best treatment options. Stage T1 prostate cancer refers to a non-palpable tumor, and T1c cancer is a subset where malignancy is detected from an elevated PSA level. T2 disease indicates a palpable tumor, and T3 disease indicates that the cancer extends beyond the prostate capsule or to the seminal vesicles.

Digital rectal examination

A DRE allows the primary care physician to examine the contour, firmness, symmetry, and presence of nodules of the prostate. A DRE is a useful screening tool to detect prostate cancer, but it can miss cancer that is confined to the prostate, so this means it misses nearly half of the cases of prostate cancer.[38] When combined with a PSA test, an accurate DRE improves the detection of prostate cancer.[39] An abnormal DRE may detect prostate cancer that is higher grade and different from that detected by PSA tests. Anatomically, the prostate is divided into different zones; the peripheral zone is the most common site of malignancy and this may be palpable, unlike malignancies in the transitional zone, which may not be palpable but can manifest as obstructive urinary symptoms.

Prostate-specific antigen tests

PSA is produced by prostatic glands and secreted into the seminal fluid, which liquefies the ejaculate. The concentration of PSA in serum (which is expressed as ng/ml) is lower than the concentration in seminal fluid. Different prostate diseases, such as cancer, BPH, and prostatitis can affect serum PSA levels. Prostate disease can alter the normal microanatomy of the prostate gland, which then allows PSA to leak freely into the serum. An elevated PSA level is not specific for prostate cancer. There is no specific threshold or "normal" PSA level that would prevent over or under diagnosis of prostate cancer, or that would detect only life-threatening cancer. Prostate cancer is rarely found in a man with a serum PSA level of less than 2.0 ng/ml. In our office, needle biopsy of the prostate is recommended for men who are younger than 60 years old and who have a serum PSA of 3.5 ng/ml or higher or certain increases in PSA velocity (discussed later).

A large study addressed the clinical implications of using PSA determinations to detect prostate cancer.[40] The investigators evaluated and biopsied men who had a serum PSA level of at least 2.5 ng/ml or an abnormal DRE. They found that using this PSA cutoff, the diagnosis of prostate cancer was higher, but the specificity was lower than by using an abnormal DRE to make the diagnosis. This study did not, however, take into account age-related or race-related PSA, or PSA velocity.

In the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial that screened over 34,000 men for prostate cancer, a diagnosis rate of 18% was found in men who had a PSA > 4.0 ng/ml.[41] Thirty-four percent of the men who had a positive DRE were diagnosed with prostate cancer. Most men with prostate cancer had stage T1 to T2 disease. There did not appear to be any difference in cancer stage among men who had an abnormal DRE and those who had PSA levels less than 10 ng/ml. Men who had serum PSA levels greater than 10 ng/ml and had a positive DRE were found to have a higher stage of cancer.

In addition to having a higher rate of prostate cancer, men older than 50 have a higher rate of BPH. BPH may result in an elevated serum PSA level. Men with BPH may have a normal DRE (but enlarged prostate) and chronically fluctuating PSA levels. When clinical exam and serum PSA findings are inconclusive, other serum tests may be used to help determine whether a biopsy is warranted.

The PSA density test was developed to help detect prostate cancer when the prostate size is increased as a result of BPH. PSA density is calculated by dividing the serum PSA level by the volume of the prostate measured by transrectal ultrasound.[42] A PSA density value above 0.15 indicates an increased likelihood that the prostate harbors malignancy.[43] It is important to note that men with BPH who are treated with a 5-alpha reductase inhibitor, such as finasteride (Proscar) or dutasteride (Avodart), have a 50% reduction in their PSA levels after 6 months of treatment. To interpret the PSA value, it needs to be adjusted for use of a 5-alpha reductase inhibitor. For example, if a patient has a serum PSA of 4 ng/ml prior to starting treatment with a 5-alpha reductase inhibitor and 1 year later he has a serum PSA of 3.2 ng/ml, this should be interpreted as being equivalent to a PSA of 6.4 ng/ml had the patient not been taking a 5-alpha reductase inhibitor.

PSA velocity, the rate at which PSA rises, is another useful indicator to determine whether a patient should undergo a prostate biopsy. To determine PSA velocity, three consecutive PSA values are obtained. For PSA values between 4 ng/ml and 10 ng/ml, an increase in

PSA velocity that is greater than 0.75 ng/ml per year suggests the presence of prostate cancer. For PSA values below 4.0 ng/ml, an increase in PSA velocity of 0.35 ng/ml per year should trigger doing a prostate biopsy.[44]

Reduction in free PSA is another test that reflects the presence of prostate cancer. Most PSA is bound to protein, but 5% to 30% remains free. When prostate cancer is present, the total amount of PSA is not increased; rather, more PSA leaks into the serum as a result of architectural changes in the prostate. PSA produced in malignant prostate cells, however, tends to bind to serum proteins, thereby lowering the amount of free PSA. A ratio of free-to-total PSA can help determine whether the prostate harbors a malignancy. The lower the free-to-total PSA ratio is, the higher the likelihood that prostate cancer is present. There is no cut-off value, although several studies have used a free PSA of 0.18 ng/ml to 0.20 ng/ml as a cut-off value, and found a 90% sensitivity for detecting prostate cancer.[45]

Besides monitoring PSA levels and performing a DRE, it has been suggested that additional tests be done to help determine whether a patient should undergo a prostate biopsy. In one study, determining the value for free PSA, in addition to performing a DRE and determining the value for total PSA, helped reduce the number of false-positive prostate cancer screening tests.[46]

Often, a primary care physician will look for a cut-off value from a single serum PSA test. As previously stated, we use certain PSA levels to prompt us to recommend that a patient has a prostate biopsy. Many studies have attempted to provide serum PSA cut-off values. Morgan et al determined the age- and race-specific reference ranges for the PSA test that provide a high specificity and sensitivity for detecting prostate cancer.[47] According to their findings, the upper limit for a normal serum PSA value for white men is 2.5 ng/ml for age 40 to 49 years and 3.5 ng/ml for age 50 to 79 years; for African American men, the upper limit for a normal serum PSA value is 2.0 ng/ml for men aged 40 to 49 years, 4.0 ng/ml for men aged 50 to 59 years, 4.5 ng/ml for men aged 60 to 69 years, and 5.5 ng/ml for men aged 70 to 79 years.

Transrectal ultrasound-guided needle prostate biopsy

Needle biopsy of the prostate is recommended when the PSA level is abnormal or a DRE demonstrates significant asymmetry, induration, or nodularity of the prostate. A histologic diagnosis is required to make the diagnosis of prostate cancer. Once it is determined that the patient needs a prostate biopsy and the patient agrees, the patient should be instructed to stop taking anticoagulants (e.g., aspirin, Plavix, non-steroidal anti-inflammatory drugs [NSAIDs], and coumadin) for at least a week prior to the biopsy. The morning of the biopsy, the patient should expect to have a cleansing enema (usually a Fleet enema). He will receive one dose of oral fluoroquinolone 30 minutes prior to the biopsy. The procedure is usually and safely done in an office setting. The patient will be taken to the padded biopsy table and placed in a lateral decubitus fetal position (lying on his side in a fetal position). An ultrasound probe about the size of an adult's thumb is placed into the rectum. The seminal vesicles are identified and lidocaine is infiltrated to where the seminal vesicles meet the prostate, to perform a local block. No general anesthesia or light sedation is required unless the patient encounters significant pain or cannot tolerate an anal probe (for example, if he has a rectal stricture or fissure). The prostate is scanned under sonography and measured. Although hypoechoic lesions may appear in the prostate, these are not specific for prostate cancer. Under ultrasound guidance, an 18-gauge needle core biopsy device is used to perform a double-sextant 12-core, extended biopsy. Additional samples may be taken if there are suspicious lesions or nodules. After all 12 core samples are obtained and sent to the pathology laboratory, the patient can return home with instructions to continue taking antibiotics for 3 more days and to avoid anticoagulants for another week. The patient may expect to see hematuria, hematochezia, and hematospermia, which generally resolve on their own. Excessive bleeding warrants further evaluation. The risk of infection is 2%, and patients generally require hospitalization for intravenous antibiotics if they develop fever or infection. Vasovagal responses occur infrequently, and the procedure may be terminated and completed at a later date. The patient returns to see his urologist in 7 to 10 days to discuss the pathology results and is evaluated for any symptoms resulting from the prostate biopsy.

Previously, needle biopsy of the prostate involved taking only sextant cores. Recently, multiple studies have consistently demonstrated that many prostate cancers can be easily missed using this method. Review of radical prostatectomy specimens by a pathologist demonstrated that most sextant needle biopsies missed a harboring malignancy elsewhere within the prostate.[48]

A more extensive biopsy method (double sextant) improved the detection of early cancer. Generally, we take 12 needle-core biopsies in a double sextant

fashion. Biopsies are taken at the mid and lateral peripheral zones of the prostate. It is logical to assume that performing more biopsies would lead to increased cancer detection. In fact, several studies have examined the utility of taking additional biopsies. However, in one study, increasing the number prostate biopsies beyond double sextant did not lead to higher detection rates.[49] A recently published study of approximately 3500 patients found that extending the number of biopsies (that is, performing triple sextant biopsies) did not statistically improve the cancer detection rate, but did increase the number of clinically insignificant prostate cancers.[50]

Often, biopsy specimens that are reviewed by a pathologist are deemed to be benign lesions. These lesions include normal prostate tissue, hypertrophy of the prostate, and inflamed lesions of the prostate. Inflammation in the specimen may require further investigation to determine the etiology (which might be prostatitis or an STD, for example). The patient is informed that he should continue to have regular serum PSA tests and an annual DRE. A repeat serum PSA test should be performed 6 months after the prostate biopsy. If serum PSA levels continue to rise, or if other parameters such PSA density change, the patient should be referred for a repeat biopsy in case prostate malignancy was missed or was not present at the initial biopsy. Observations such as an enlarging nodule or new nodules related to an abnormal prostate should be recorded and monitored. In our office, if a patient continues to have a rising PSA level after a negative prostate biopsy, or if he has new findings on a DRE, we generally suggest a repeat biopsy to ensure that an occult malignancy was not missed.

Abnormal pathology specimens in prostate cancer can range from a precursor lesion to an aggressive malignancy. High-grade prostatic intraepithelial neoplasia (HGPIN) are precancerous lesions. If HGPIN are present, and if an adequate double sextant prostate biopsy was performed, then a repeat serum PSA test and careful monitoring with a DRE are warranted in 6 months. If less than a double sextant biopsy had been obtained, then the prostate biopsy should be repeated.[51] Occasionally, a diagnosis of "atypical small acinar proliferation" (ASAP) is made, which is not a definite diagnosis of prostate cancer, but instead suggests that the prostate cancer was marginally sampled. Recent evidence recommends that when ASAP is found, aggressive patient follow-up and serious consideration for a repeat biopsy are needed.[51]

The pathologist determines the location, volume, and grade of malignant lesions. A prostate tissue sample is assigned a Gleason grade from 1 to 5 depending on the differentiation and architecture of the glands. Grade 1 indicates the most differentiated glands and therefore is benign, and Grade 5 indicates the most undifferentiated glands. Two grades (from the most common and the second most common patterns) are added to obtain a Gleason score, which ranges from 1 to 10. Virtually no prostate specimens are assigned a Gleason score of 2 to 4. Gleason scores from 5 to 6 are considered to indicate low-grade lesions. A Gleason score of 7 (4+3 or 3+4) indicates an intermediate-grade lesion. A Gleason score of 8 or more indicates a high-grade tumor.

Most prostate tumors are located at the periphery of the prostate, and the rest are located in the transitional zone. Most tumors are multifocal and bilateral.

Many studies have examined the clinical significance of prostate cancer based on Gleason score, PSA level, and prostate volume. Some clinicians define prostate cancer to be clinically significant when the cancer has a Gleason score of 7,[53] while other authors consider tumors to be clinically significant when prostate volumes are greater than 0.5 ml, or when cancer extends to the seminal vesicle or beyond the prostate capsule and there is metastasis to the lymph nodes.[54] A recent investigation noted that increasing the number of biopsies in the prostate region increased the number of clinically significant prostate cancers.[55]

If the prostate cancer is of intermediate or high grade (Gleason score > 6, or PSA > 10 ng/ml), further imaging is warranted. A bone scan and computed tomography of the abdomen and pelvis are performed to look for the presence of bone lesions and lymphadenopathy, respectively. Metastasis to the bone is the most common extrapelvic site of advanced prostate cancer. If a bone scan is positive for uptake of a radioactive tracer, then the scan should be repeated without the tracer. This is important if there is uptake of a radioactive tracer in weight-bearing joints or if the patient has bone pain.

Standard double sextant biopsies have false negative rates ranging from 15% to 35% for detecting clinically significant prostate cancer.[56] The dilemma for both the healthcare provider and the patient is whether a repeat biopsy should be undertaken if clinical suspicion of cancer remains elevated. Patient monitoring should include PSA levels and DREs. A new finding in the DRE should prompt further investigation. Similarly, a PSA velocity greater than 0.75, a serum PSA level higher than 10 ng/ml, or a total-to-free PSA ratio of less than 0.2 raise clinical suspicions that the initial biopsy may have missed a malignancy. We recommend checking serum PSA levels every 6 months for the first year after a biopsy. The clinician should consider a patient's family

TABLE 1. **Indications to re-biopsy after initial needle biopsy of the prostate is negative for malignancy**

Inadequate specimen
High-grade prostatic intraepithelial neoplasia (HGPIN)*
Presence of atypical small acinar proliferation (ASAP)
Prostate-specific antigen (PSA) velocity (change in PSA level over time) > 0.75 ng/ml per year
Abnormal digital rectal examination (DRE) when compared to previous exam

*If double sextant biopsies not performed (at least 12 cores not obtained) or clinical suspicion remains elevated

history and concerns when recommending a needle-biopsy of the prostate. Whether or not a saturation biopsy (extending the number and areas of biopsy) provides better sensitivity than a double sextant biopsy is controversial.[57] Generally, we wait approximately 1 year before we re-biopsy. See Table 1 for indications to perform a repeat biopsy.

Treatment options

After the urologist has obtained the patient's test results — serum PSA value, Gleason score, and clinical cancer stage results from the biopsy — he or she will discuss with the patient not only the diagnosis but also the prognosis and treatment options. For organ-confined disease (stage T1 to T2c), radical prostatectomy is the standard treatment. It is imperative that the patient is informed about and understands his other options as well as the inherent risks and benefits of these options. Risks of surgical intervention include erectile dysfunction, urinary incontinence, or urinary retention due to urethral stricture disease.

Conservative therapy can be either watchful waiting or active surveillance. Watchful waiting has been used to manage patients who have a predicted life expectancy of less than 10 years. This decision is made on the premise that the patient will not gain any benefit from radical treatment. Rather, surgical intervention, hormone ablation, or radiation is reserved for palliative care for such things as bladder outlet obstruction or painful bony metastases.

Active surveillance, another form of conservative treatment, may be chosen by men who have prostate cancer but do not wish to undergo more drastic treatment. According to the 2007 American Urological Association (AUA) guidelines, the goals of active surveillance are "to provide definitive treatment for young men with localized cancers that are likely to progress and to reduce the risk of treatment-related complications for men with cancers that are not likely to progress." In our practice, we have seen younger patients who have elected to follow this treatment option for low-grade prostate cancer (typically Gleason score of 6 [3+3], serum PSA < 10 ng/ml). Ideal patients for active surveillance are those with good treatment compliance and low-grade, low-stage tumors. We monitor the patients' serum PSA values twice a year. If there is a significant rise (or consecutive rises) in serum PSA values, then a repeat biopsy is considered, to restage the prostate cancer. One criticism for this approach is that men with aggressive prostate cancer are undertreated. A commonly adopted way to monitor men on active surveillance is based PSA doubling time; serum PSA is checked every 6 months, and if the PSA has doubled in less than 3 years, radical treatment is recommended.[58]

Radiation therapy (external beam radiation, brachytherapy, and a combination of both) is an option for patients who do not wish to undergo surgery. Patients with significant comorbidities may benefit from this treatment modality. Risks include cystitis, proctitis, and gradual loss of erectile function.

Cryoablation (freezing) of the prostate is being used more frequently to treat prostate cancer. As with radiation, the prostate is not removed and no prolonged hospitalization or surgical procedure is required. However, long term data for cancer-specific survival is lacking. Erectile dysfunction is the most common side effect, as the neurovascular bundles for erections are ablated along with the prostate.

A newer modality has emerged to treat localized prostate cancer: high-intensity focused ultrasound (HIFU). This technique uses high, intense energy (non-ionizing radiation) that is emitted into prostate tissue in an accurate and precise manner. Thermal ablation of prostate tissue occurs as temperatures rise up to 100°C without injuring adjacent structures. This minimally invasive and precise technology offers advantages over external beam radiation and surgery by reducing side effects. As with cryoablation, long term data is unavailable. HIFU is approved for use in Europe, Japan, and Canada, and clinical trials of HIFU are currently underway in the United States.

Hormonal treatment with androgen deprivation therapy may be more appropriate for older men who are in poor health and_cannot tolerate a stressful procedure. Hormonal therapy is not curative but enables long term remission. Hormone deprivation may be achieved with intramuscular injections of luteinizing hormone-releasing hormone (LHRH) agonists (e.g., leuprolide or goserelin) combined with anti-androgens (bicalutamide, nilutamide) or via scrotal bilateral orchiectomy. Risks include decreased libido, gynecomastia, osteoporosis, and symptoms associated with low levels of testosterone. Men on hormonal ablation should have a dual-energy x-ray absorptiometry (DEXA) scan to be evaluated for osteoporosis and they should be given vitamin D and calcium supplements.

It is important to note that neo-adjuvant hormone treatment prior to radiation treatment has been found to decrease the incidence of prostate-related death.[59] After radiation treatment is completed, hormonal treatment is given for an additional 2 years.

If the patient ultimately decides to undergo radical prostatectomy, different approaches may be used. The open radical retropubic approach is still used, but is becoming less common. Minimally invasive laparoscopic radical prostatectomy with or without the daVinci robot is becoming increasingly more popular, due to the shorter hospital stay and decreased perioperative pain with this procedure, which cuts down on healthcare costs.

If a patient has locally advanced disease (such as cancer that involves the seminal vesicals or has extended to the prostatic capsule), surgical treatment may not be the best option and the patient may need to discuss other treatment options with his physician.

Table 2 summarizes the advantages and disadvantages of different treatments for adenocarcinoma of the prostate.

Post-treatment PSA monitoring

After a radical prostatectomy, a patient's serum PSA level should be undetectable (< 0.1 ng/ml). We usually monitor PSA levels every 6 months for the first 5 years after surgery and annually thereafter. Detectable PSA in prostate cancer patients after

TABLE 2. **Advantages and disadvantages of different treatment options for prostate cancer**

Treatment	Advantages	Disadvantages
Conservative treatment Watchful waiting Active surveillance	Lowers risk of treatment-related complications	Can delay aggressive treatment for potentially curable disease
Radiation External beam radiation Brachytherapy	Minimally invasive Reduces risk of surgical complications Option for poor surgical candidates	Cystitis Proctitis Gradual erectile dysfunction
Radical prostatectomy Retropubic Robotic/laparoscopic	Removes source of disease Standard of care	Invasive Highest risk of morbidity and mortality Urinary incontinence or retention Delayed recovery of erectile function
Hormonal treatment Androgen ablation Orchiectomy	Noninvasive Option for poor surgical candidates	Recurrence is common Osteoporosis Symptoms similar to that of low testosterone Gynecomastia
High-intensity focused ultrasound (HIFU)	Precise Minimally invasive option	Unknown long term data
Cryoablation	Minimally invasive Reduces risk of surgical complications Option for poor surgical candidates	More long term data needed Erectile dysfunction

treatment with surgery is defined as "PSA failure." Patients treated initially with radiation (external beam radiation or brachytherapy) reach a nadir (the lowest point) in PSA values. The American Society for Therapeutic Radiology and Oncology (ASTRO) defines "PSA failure" as three consecutive rises in PSA values following surgery or radiation for prostate cancer. No guidelines for defining PSA failure currently exist for cryotherapy, although many physicians have adopted the same ASTRO criteria used for surgery and radiation. If patients have PSA failure and their malignancy is considered to be localized to the prostate, salvage therapy may be an option. Similarly, patients with PSA failure months after undergoing radical prostatectomy may undergo radiation treatment of the surgical bed or they may undergo hormonal treatment. Regardless of the treatment used, PSA failure warrants a prompt visit to the urologist.

Summary

Early detection of prostate cancer through screening tests enables primary care physicians and urologists to offer patients a broader choice of treatments that are also more likely to provide a cure. Whether men are being over treated or over diagnosed through the widespread use of screening tests remains controversial. This review aimed to provide primary care physicians with a better understanding of different prostate cancer tests that can be performed and to help them decide which patients should be referred to a urologist for an ultrasound-guided biopsy.

Disclosure

None declared. □

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DISCUSSION

Question (Dr. Laroche):
What are factors that could falsely increase the PSA value with no underlying pathology?

Answer (Dr. Haas):
Manipulation of the prostate, such as catherization, biopsy, or even vigorous rectal examination can elevate the PSA. Urinary tract infection or prostatitis can raise PSA to very high levels. Vigorous sexual activity, bicycle or stationary bike riding, horse back riding within 4 to 5 days of testing may also result in false elevation. On the other hand, several classes of medications, such as 5-alpha reductase inhibitors, anti-inflammatory agents, and statins may decrease PSA levels.

Question (Dr. Greenberg):
What are the PSA levels to be expected after prostate cancer treatment, and what would be the role of the Primary Care physician in following these?

Answer (Dr. Haas):
Primary Care physicians should work closely with the urologist who treated the patient and communicate well regarding the appropriate follow-up. Patients after treatment for prostate cancer should be followed closely, examined regularly, and have their PSA evaluated according to regular schedule. I recommend follow-up every three to four months during the first year after treatment, four to six months after the first year, and every six months after the second year up to five years. Annual examinations should be carried out thereafter, presuming that the patient remains disease free.
The PSA should be zero or undetectable after radical prostatectomy, and any elevation or gradual rise in the PSA level heralds recurrent or residual disease. After therapies which do not remove the entire prostate, such as external radiation therapy, brachytherapy, cryosurgery or HIFU, PSA levels should nadir bellow 1 ng/ml, preferably bellow 0.5 ng/ml, and remain low. Occasional fluctuation of PSA levels may occur, but consistent rise on consecutive measurements may be evidence that the patient is failing. The Primary Care physician should then consult with the urologist regarding the timing of diagnostic studies and intervention.