



Shedding light on prostate cancer

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Prostate cancer is the most commonly diagnosed cancer in men in the United States, with 64% of all prostate cancers diagnosed in men over age 65.¹ With the widespread adoption of prostate-specific antigen (PSA) screening, 58% of men over age 50 were screened for prostate cancer in 2003, an increase of 17% from 2000.² The CDC reports that the number of deaths from prostate cancer in 2006 was 28,372 or 19.2 per 100,000 males.³ A high proportion of prostate cancer diagnoses are now made when tumors are nonpalpable and localized to the prostate gland.⁴ Many of these early-stage cancers are indolent or slow growing, do not progress, are not a threat to mortality, and do not lead to early death.

The United States has the highest worldwide incidence of prostate cancer, with rates rising with increasing age.⁵ As the aging population grows, so will the number of prostate cancer cases. Risk factors for the disease may be found in family history, a high-fat American diet, smoking, and other known cancer risks. There are many treatment forms for prostate cancer and a great deal of ambiguity regarding which treatment options are best for all patients. Treatment in the form of radical prostatectomy, external beam radiation, and brachytherapy are highly available and well utilized. Cryosurgery is a less common procedure with potential for increased use and effectiveness in the future. However, it is well known that these treatments result in high rates of both

incontinence and erectile dysfunction (ED), and research is mounting that some men who receive these treatments may only receive minor increases in life span.⁶ Moreover, disease recurrence is possible in 20% to 40% of treated patients requiring salvage procedures at a later point in time. This article will discuss the risk factors, signs and symptoms, diagnosis of prostate cancer, and disease staging and grading, as well as necessary lab and diagnostic tests, treatment options and patient education.

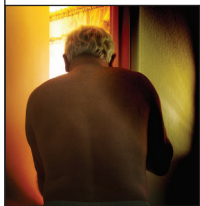
■ Risk factors

Well-documented risk factors for prostate cancer are advanced age, race and ethnicity, and family history, with advanced age the leading risk. Prostate cancer is almost never seen in men younger than age 40 and most commonly appears after age 50; as stated above, 64% of all cases occur in men over age 65.¹ While 90% of prostate-related cancer deaths occur in men over age 65, more men with prostate cancer die from a disease other than the prostate cancer, as evidenced by autopsy findings that suggest an age-specific prevalence rate as high as 80% by age 80.^{7,8}

The second most common risk factor associated with developing prostate cancer is race and ethnicity, with African-American men at greatest risk. From 2000 to 2004, the incidence of prostate cancer (per 100,000) in the United States was highest among African-American men (255.5), compared

with whites and Hispanic men (161.4 and 140.8). Incidence rates for Asian-American and American Indian/Alaskan Native men during the same period were much lower at 96.5 and 68.2, respectively.² The actual role of race and ethnicity in the development of prostate cancer may be more about environmental, socioeconomic, or dietary factors as incidence of prostate cancer in both Asian and African men are considerably lower than their American counterparts.⁹

A final common risk factor for prostate cancer is a family history of the disease. The risk of developing prostate cancer is more than doubled in men with a first-degree relative (father, brother, or son) also diagnosed with prostate cancer. The risk is further increased if a relative was diagnosed before age 60, if more than one first-degree relative has been diagnosed, or if a man's mother or sister was diagnosed with breast cancer.¹⁰



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Risk factors for prostate cancer are not amenable to change but can be used as indicators of the possible need for screening and secondary prevention measures. There are currently no definitive guidelines for the prevention of prostate cancer; however, there is growing evidence that diet, exercise, and maintaining a healthy weight may play a protective role. A growing body of research suggests that consuming a diet low in saturated fat (lean meat and fish) as well as eating lots of fruits and vegetables, is associated with a lower incidence of prostate cancer.^{7,11,12} Consuming a diet high in lycopene, especially from tomatoes has been shown to be beneficial.¹³

Obesity, while not a direct cause of prostate cancer, may interfere with the accuracy of screening, and may result in delayed diagnosis, and less favorable outcomes.^{14,15} In the Prostate Cancer Prevention Trial (PCPT), treatment with finasteride (Proscar, Propecia, a 5-alpha reductase inhibitor (5-ARI) was associated with reduction in overall risk of prostate cancer, as well as a reduction in the risk of clinically significant prostate cancer, including advanced tumors. Based on the evidence from these clinical trials, guidelines from the American Society of Clinical Oncology (ASCO) now suggest that healthy men who are regularly screened, and show no symptoms of prostate cancer, and men currently taking 5-ARIs for benign conditions should engage in a discussion with their healthcare provider about the pre-

ventive benefits and potential risks (including the possibility of high-grade prostate cancer) of 5-ARIs.^{1,16}

■ Signs and symptoms

In early stages of prostate cancer, the disease may be silent in that no signs and symptoms are readily evident.¹⁷ However, when symptoms do appear, they generally result from increased pressure of the enlarged prostate gland on surrounding urinary structures. Consequently, early symptoms of the disease tend to be those of lower urinary tract obstruction. The National Cancer Institute reports the following signs and symptoms of disease including: weak or interrupted urinary flow, frequent urination, and pain or burning during urination.¹⁷ It is important to remember that these symptoms of the increased pressure on the urinary structures may also stem from benign disease of the prostate such as benign prostatic hypertrophy. While hema-

turia may be present in men with prostate cancer, this is rare as a symptom of prostate cancer, but may be indicative of bladder or renal cell cancer.¹⁸ In men with metastatic prostate cancer, bone pain is the most common complaint.

In order to accurately assess for clinical signs and symptoms of prostate cancer, a thorough history and physical exam is essential. The patient should be asked about problems with urination common to prostate disease. The duration of the symptomatology should be determined as well as treatments used to reduce symptoms.

■ Diagnosis

The diagnosis of prostate cancer is confirmed following evaluation of clinical data that includes the patient report of symptoms, if present, digital rectal exam (DRE), PSA level, transrectal ultrasound, and positive findings for malignancy from prostate biopsy. For many patients, symptoms are absent or nonspecific as described above. The DRE is helpful in finding abnormalities in the prostate, but the exam covers only a small portion of the gland. Normal PSA values are between 0 and 4 ng/mL; values >4 ng/mL may warrant additional follow-up dependent on a number of patient characteristics including, but not limited to age, ethnicity, body mass index, height, and a family history of prostate cancer.

The American Urological Association (AUA) recently updated their guidelines for PSA testing, with baseline levels obtained at age 40. The AUA also recommends that biopsy following an elevated PSA should consider DRE results, as well as free and total PSA, patient age, PSA

velocity and density, family history, ethnicity, prior biopsy history, and comorbidities. Given the documented high rates and consequences of overtreatment for prostate cancer, the AUA recommends that practitioners inform all patients of both the benefits and risks of screening, and to discuss the active surveillance management option for men newly diagnosed with prostate cancer.¹⁹

Men with a family history of prostate cancer are more likely to seek regular PSA screening to monitor their levels than men without a family history of disease, leading to detection at an earlier, disease stage.²⁰ It is also important to note that, elevated PSA levels may also be the result of benign prostatic hypertrophy, older age, inflammation, or ejaculation within 2 days of testing.²¹ PSA testing has been shown to be of such questionable value among older adults that the U.S. Preventive Services Task Force no longer recommends it for men over age 75.³ Values lower than 4 ng/mL in African-American men and those who are obese call for additional follow-up by a healthcare provider as research has shown that these factors mitigate the usual threshold for biopsy.¹⁵ A recent study has shown that PSA testing is more effective in men on finasteride at detecting high-grade prostate cancer at an earlier stage.²² Thus, it is now recommended that practitioners discuss the role of this medication in men undergoing prostate screening.

Given the high incidence and prevalence of prostate cancer among African-American men, the role of screening in this population cannot be stated enough. It is essential that healthcare providers encourage participation in detection programs that target high-risk individuals, especially African-American men. This population should be tested at age 40. In addition, PSA values lower than 4 ng/mL in African-American men should be interpreted with caution and these patients should be referred for additional follow-up when appropriate.¹⁴

Controversy exists as to whether the PSA test should be used to screen the general population of men for the presence of disease as the goal of screening is to decrease mortality and improve quality of life. Diagnoses using PSA levels occurs when a man presents with symptoms or clinical signs indicative of possible disease. To date, the evidence does not support routine population screening with PSA,^{23,24} and testing has been associated with psychological harm.²⁵ The U.S. Preventive Services Task force has recently recommended that men over age 75 forgo PSA screening due to limited benefit and increased risk for physical and psychological harm.²⁶ Diagnosis of prostate cancer is confirmed following biopsy guided by transrectal ultrasound. The ultrasound is used to direct the placement of the needle to extract the specimens; the urologist may opt for a transperineal or transrectal approach to perform the biopsy.²¹

The biopsy results are categorized using a grading system, referred to as the Gleason staging system (see *Prostate carcinoma: Gleason grading system*). This system assigns a grade to each of the two largest areas of cancer in the biopsy samples. Grades range from 1 to 5, with 1 being the least aggressive and 5 the most aggressive. The two grades are then added together to produce a Gleason score. A score of 2 to 4 is considered low grade; 5 to 7, intermediate grade; and 8 to 10, high grade. A high Gleason score indicates that the cancer is more likely to grow quickly.²¹

■ Prostate cancer staging and grading

Disease stage is determined using data from the DRE, PSA test, and Gleason score. Men with negative DRE, low PSA values and low grade Gleason scores may not need to undergo further testing to stage their disease as these data suggest that the cancer remains localized to the gland. However, men with palpable abnormalities on DRE, elevated PSA values and Gleason scores greater than seven may benefit from additional testing to stage their disease.¹ These tests include bone scan, computed tomography scan, and magnetic resonance imaging (MRI) and ProstaScint scan to identify possible metastases. A pelvic, lymph node biopsy may be performed to identify cancer cells, and, if present, confirm the spread of disease beyond the gland.

Current staging relies on the TNM System developed by the American Joint Committee on Cancer.²⁷ This system categorizes and describes the extent of the primary tumor (T), whether the cancer has spread to the lymph node (N), and the absence or presence of disease metastases (M). There are four categories with subcategories for describing the extent of the tumor; they range from T1-to T4 (see *TNM staging of prostatic carcinoma*). Higher T values indicate greater involvement of surrounding tissues and structures beyond the prostate gland. The node (N) category is either X (no sample), 0 (no positive nodes), or 1 (lymph node involvement). Metastasis is categorized as 0 (no spread) or 1 with three subcategories indicating increased levels of disease spread to organs and bone.²¹ These data are then combined with the Gleason score to establish a man's disease stage between stage I and IV. Disease staging can then be used to guide the patient, significant other, and healthcare provider when discussing treatment options.²⁸

■ Treatment approaches

There are many treatment approaches for prostate cancer. The National Comprehensive Cancer Network has published evidence-based protocols to guide treatment of prostate cancer. These guidelines provide the standard of care for prostate cancer treatment. Research has been consistently focused on determining disease stage, inevitably guiding patients

Prostate carcinoma: Gleason grading system

GLANDS	
Differentiation	Distribution
1 'Round,' lined by single layer of cuboidal cells	Close packed in rounded masses; definite edge
2 More variable in size and shape	Separated up to one gland diameter; 'loose' edge
3a Irregular shape; medium to large size	Irregularly spaced apart; poorly defined 'edge'; surround normal structures
3b Small to minute glands, not fused or 'chained'	Very irregular spacing and distribution; no 'edge'; surround normal structures
3c Masses of cribriform or papillary epithelium with smooth outer surfaces	
4a Ragged masses of fused glandular epithelium; bare tumor cells in stroma	Ragged infiltrating masses that overrun normal structures; No smooth surfaces against stroma
4b Same as 4a; large clear cells	
5a Smooth, cribriform to solid masses; often central necrosis 'comedocarcinoma'	Ragged infiltrating masses that infiltrate stromal fibers
5b Anaplastic carcinoma with vacuoles and glands that suggest adenocarcinoma	

Source: Rubin R, Strayer D, eds. *Rubin's Pathology: Clinicopathologic Foundations of Medicine*. 5th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2008:776.

toward customized treatments.²⁹ However, once diagnosed with prostate cancer, patients face a number of treatment options as discussed below.

Radical prostatectomy

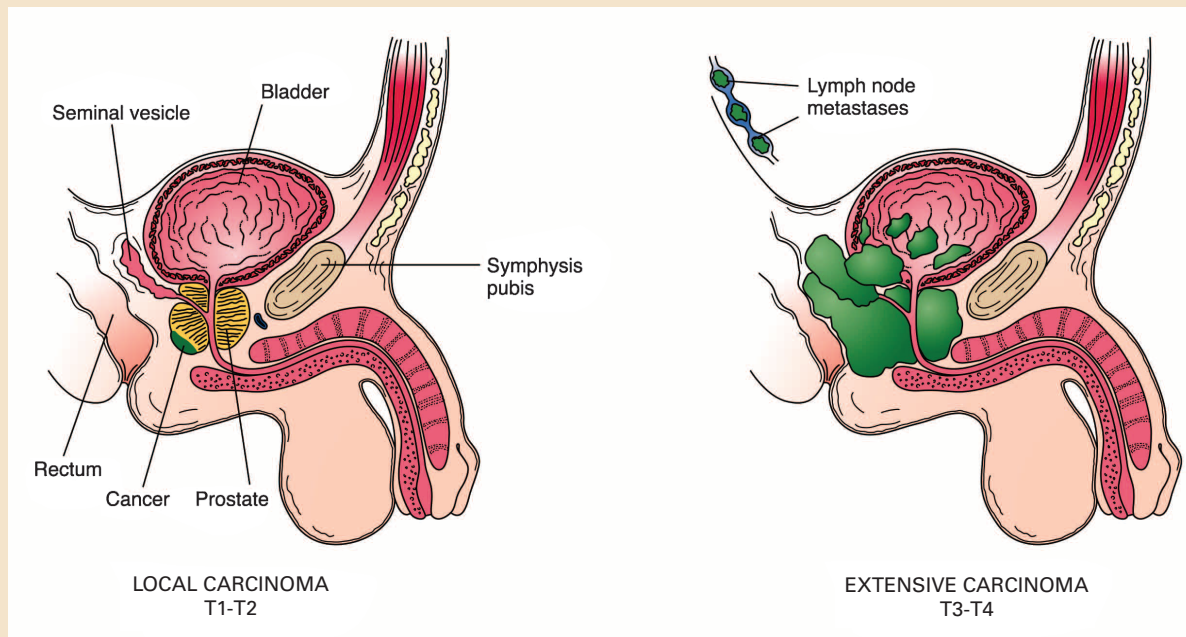
Radical prostatectomy is the excision of the prostate gland with possible pelvic lymph node dissection (PLND) and removal, with or without the removal of the nerve bundles responsible for penile erection. The two approaches to the procedure are open or laparoscopic with robotic systems; up to 40% of all radical prostatectomies are now robotic-assisted.³⁰ The open procedure is accomplished either through the retropericubic route or the perineal route. Surgical treatment carries the undesirable adverse reactions of ED and urinary incontinence (UI). Lymphedema is a rare, but possible consequence of PLND during radical prostatectomy procedures.

The rate of ED following radical prostatectomy has been reported to be greater than 80%, with older men in particular

reporting a greater incidence following prostate surgery.^{29,31} In fact, even in patients with radical prostatectomy where the nerve bundles are spared, 79% were unable to have erections adequate for intercourse.³² Evidence is beginning to accumulate in favor of oral phosphodiesterase type 5 inhibitors (for example, sildenafil) to manage ED following radical prostatectomy.³² While oral erectile agents are widely becoming more accepted to enhance erectile function after aggressive prostate cancer treatment, the effectiveness of these medications is dependent on intact nerve function.

UI is also a significant problem following radical prostatectomy. In one study, at least 50% of patients reported experiencing UI after radical prostatectomy.³³ Management of UI includes pelvic floor muscle training with or without biofeedback, electrical stimulation, compression devices (penile clamps), lifestyle changes, or a combination of strategies. However, clinical trials of these methods have failed to consistently support the benefits of medical in-

TNM staging of prostatic carcinoma



Source: Rubin R, Strayer D, eds). *Rubin's Pathology: Clinicopathologic Foundations of Medicine*. 5th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2008:778.

terventions.³⁴ UI usually improves over time, but some men will reach a plateau within 1 to 2 years following radical prostatectomy.³⁵

External beam radiation

External Beam Radiation Therapy (EBRT) was first introduced for the treatment of prostate cancer in the 1930s. Now greatly refined, the modern treatment beams carefully calculated doses of radiation, guided by transabdominal ultrasound or intraprostatic markers, into the prostate to destroy cancerous cells while avoiding surrounding, noncancerous tissue.³⁶ EBRT is typically used to treat the prostate and surrounding tissues or structures in cases of more advanced disease and is contraindicated in patients with a history of bowel disease, or prior pelvic radiation. Brachytherapy is indicated for use with low risk, localized disease. Because of the need for anesthesia, brachytherapy may not be an option for some patients with certain surgical risk factors.

The entire prostate is targeted in localized disease, but seminal pelvic lymph nodes may also be treated, when indicated in locally advanced or metastatic disease.³⁷ Standard treatment sessions, which last approximately 15 minutes, are performed 5 days a week over 4 to 6 consecutive weeks.³⁸ A major advantage of EBRT is that it is noninvasive and can be used as a treatment option on patients who present a sig-

nificant surgical risk. EBRT is, however contraindicated in patients with inflammatory bowel disease (for example, Crohn's disease, ulcerative colitis) or previous pelvic radiotherapy.³⁶ Early adverse reactions of treatment related to the untoward effect of radiation on local tissue are typically short-lived and include dysuria, urinary frequency and urgency, diarrhea, and proctitis. Long-term side reactions include ED for 10% to 30% of patients, bowel changes in fewer than 20% of men, and UI.³⁹

Brachytherapy

Brachytherapy, also referred to as interstitial radiation or seed implant therapy, consists of the permanent or temporary implantation of radioactive seeds directly into the cancerous prostate (see *Radioactive seeds used in brachytherapy*). The patient receives anesthesia prior to the procedure, which uses needles to implant the radiation source through the perineum with the help of transrectal ultrasound or MRI.³⁶ Brachytherapy may utilize low dose rate (LDR) or high dose rate (HDR) radiation either as monotherapy, in cases of low-to-moderate risk disease, or in combination with EBRT in more advanced disease. LDR therapy consists of the permanent implantation of lower-dose radiation sources while HDR consists of temporary insertion of high doses of radiation typically given in 10-to-30 minute

increments twice daily for 24 to 36 hours over short periods of time.^{39,40} As a minimally invasive procedure, the recovery from brachytherapy is minimal compared with the extended recovery time for surgical intervention and it does not require the daily commitment associated with EBRT (when used as monotherapy). Decline in physical and functional status can occur with brachytherapy, as with all treatment modalities, however, most men return to pretreatment levels within 1 year.⁴¹ Complications can result from irritation of local tissue and include irritative and obstructive urinary problems, which typically resolve without invasive intervention.⁴² ED has also been reported in 10% to 17% of men following brachytherapy.³⁸

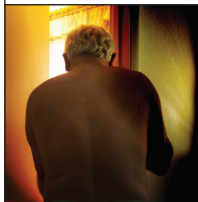
Cryotherapy

Primary cryotherapy has been an approved therapeutic treatment method for men with localized prostate cancer since 1996.⁴³ Cryotherapy, also referred to as cryosurgery or cryoablation, involves freezing the malignant cells in the

and stage disease and low, stable PSA values. Active surveillance is defined as initial surveillance of prostate cancer followed by active treatment if the tumor progresses to the extent that quality or quantity of life is affected.⁴⁵

The benefits of active surveillance lie in the avoidance of expensive treatments that have well-documented, adverse events. There have been a number of studies that have researched outcomes of men undergoing active surveillance and some that have compared patient outcomes to aggressive treatment modalities. In a pivotal study, Klotz⁶ analyzed the survival data of 299 men with low-risk, prostate cancer over age 70. Inclusion criteria for the study were prostate cancer stage less than or equal to T2a with PSA values less than or equal to 10 ng/mL. At 8 years, the study revealed a 99% disease-specific survival rate. This indicates the potential clinical applicability of active surveillance for patients with low grade and stage disease.

Men who undergo active surveillance live daily with the knowledge that they have cancer in their bodies and the associated uncertainty as to whether the cancer will grow, spread, and eventually cause their death. In a recent, qualitative report by Wallace and Storms on the needs of men with prostate cancer, one focus group participant stated, “The word *cancer* is followed closely in my mind with death.”⁴⁶ Moreover, research



For men with a 10-year life span, low-volume, nonpalpable, and early stage prostate tumors, active surveillance is an alternative to surgery.

prostate gland, causing cellular death. The cells are frozen through argon or nitrogen gases introduced through needles inserted via the perineum and guided by transrectal ultrasound. The procedure is generally performed under general or regional anesthesia as an outpatient. Salvage cryotherapy has become a popular alternative for treating prostate cancer following disease recurrence after radiation. ED continues to be a problematic outcome among men undergoing cryosurgery. The rate of ED following primary cryosurgery is between 80% and 90%, and can rise to 95% to 100% following salvage cryoablation.⁴³

UI related to cryotherapy is between 8% and 9%, which is lower than that seen among radical prostatectomy patients. Nerve sparing cryotherapy techniques currently being researched have significantly improved rates of ED, but are still considered experimental at this time.

Active surveillance

For men with a 10-year life span, low-volume, nonpalpable, and early stage prostate tumors, active surveillance is an alternative to surgery or radiation therapy. Men in active surveillance actively monitor their disease with the knowledge that treatment remains an option.^{44,45} Candidates for active surveillance are usually men age 65 and older with low grade

has found that even when men are asymptomatic or experience only occasional signs that the cancer is present, their uncertainty about the state of cancer is intense.⁴⁷ Psychosocial and educational nursing interventions can help patients transform prostate cancer from an aggressive cancer with the potential for early death into a chronic disease, similar to diabetes or hypertension, which requires periodic monitoring, management, and evaluation. Wallace and colleagues⁴⁸ are currently testing a Web-based program designed to help men manage the uncertainty associated with living with prostate cancer as a chronic illness. Patients undergoing active surveillance should be encouraged to schedule appointments with practitioners for PSA testing and evaluation of disease progression approximately every 6 months.

Hormone treatments

Androgen deprivation therapy (ADT) is a treatment option for men with all stages of prostate cancer whose goal is to reduce the level of male hormones. There are two common forms of ADT, orchiectomy and luteinizing hormone-releasing hormone (LHRH) agonists. However, use of LHRH agonists in men with localized, low-risk disease is controversial, and during the period between 1991 and 1999, there was a dramatic increase in LHRH agonists for all stages and grades

of disease.^{49,50} Hormone therapy may be used for men who are not candidates for surgery or radiation or can't be cured as their disease has spread beyond the prostate gland, or combined with radiation therapy for stage T3 cancers. In a recent review, neoadjuvant, hormonal therapy before surgery did not improve overall survival rates but did result in a significant reduction in positive surgical margins. Treatment with hormones after surgery did not improve overall survival but did result in significant 5- and 10-year disease-specific survival.⁵¹ Hormones used before and after radiotherapy also had significant survival benefits for treated patients. Although not supported by clinical guidelines, ADT is increasingly used as primary therapy in older men with localized prostate cancer.⁵² Controversy exists as to when treatment should be started and whether therapy should be intermittent or continuous.^{53,54} It is important to note that therapy is accompanied by a number of significant deleterious adverse reactions and includes far-reaching, quality of life consequences such as decreased bone density, which can increase the incidence of fractures, changes in body composition, and metabolism. These consequences can lead to the development of the metabolic syndrome, as well as an increased prevalence of cardiovascular disease, diabetes, anemia, cognitive dysfunction, sexual dysfunction, and hot flashes.^{55,56} Common LHRH analogs include leuprolide, goserelin, and triptorelin. LHRH antagonists such as abarelix (Plenaxis) are a newer type of drug that are believed to work like LHRH agonists, however, they appear to reduce testosterone levels quicker and do not cause the tumor flare commonly associated with LHRH agonists.

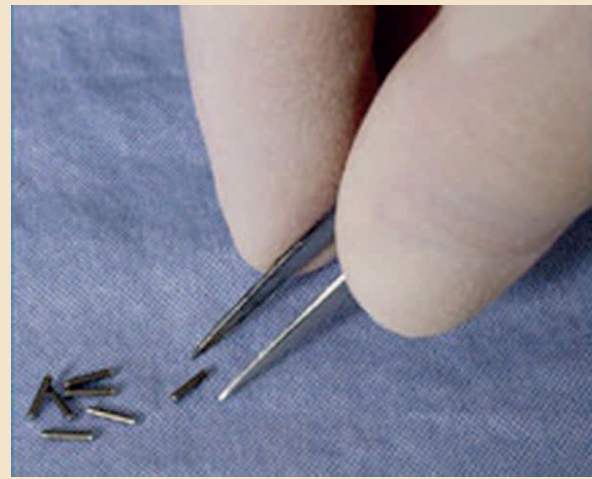
Chemotherapy

Docetaxel (Taxotere) chemotherapy treatment is now considered the standard of care for hormone refractory prostate cancer (HRPC).⁵⁷ A major issue for patients with HRPC is bone metastases and the resulting pain, fractures, and risk for spinal cord compression.⁵⁸ Lifestyle changes and calcium supplements may slow the rate of bone mineral loss.⁵⁹ Unfortunately, there are no second-line chemotherapeutic agents that are currently available for HRPC, although a number of clinical trials are underway testing the benefits of docetaxel with immediate versus delayed hormone ablation therapy as well as the development and testing novel targeted agents.⁵⁷

■ Patient education

While patient and family education are important components of traditional patient care, education and psychosocial support are increasingly important during all stages of prostate cancer. The increased emphasis on patient education is necessary because of the diverse prostate cancer treatment options and the current ambiguity associated

Radioactive seeds used in brachytherapy



with determining what treatments are appropriate for what patients.²⁷ Patients should be educated regarding all applicable treatment options, including aggressive modalities and active surveillance. The positive and negative aspects of each treatment option should be explained and patients should be informed of the adverse reactions associated with each treatment. In the case of aggressive treatments such as radical prostatectomy, radiation procedures, and cryosurgery, patients must be informed of the high risk for ED and incontinence, as well as diarrhea and rectal discomfort and incontinence associated primarily with radiation treatments. Patients should also be informed of the uncertainty associated with living with prostate cancer that has been found among patients undergoing active surveillance.⁶⁰

A number of studies have documented the need for supportive psychosocial interventions for men with prostate cancer and their preference for receiving education and support. There are a variety of local and national support services available to prostate cancer patients. US too.org (<http://www.ustoo.org>) and The American Cancer Society's Man to Man program (http://www.cancer.org/docroot/ESN/content/ESN_3_1X_Man_to_Man_36.asp) are two national organizations that provide both education and support to patients. Patients should also be encouraged to call local hospitals for prostate cancer support groups and organizations. The role of partners in prostate cancer decision-making, coping, and overall quality of life is instrumental and the subject of much research. In a qualitative study by Wallace and Storms, one participant stated that "my wife was my biggest helper."⁴⁶ The outcomes of prostate cancer, beginning with the selection of a treatment choice and extending toward quality of life outcomes, are greatly

impacted by the presence of a significant other, or partner in prostate cancer and thus they should be included in patient education whenever possible.

■ Future research

As the most commonly occurring cancer among U.S. men, NPs will likely see prostate cancer patients in many care settings, from the primary care practice, where vague urinary complaints lead to further assessment and diagnosis to emergency departments where patients present with prostate-cancer-related urinary obstructions. The treatments for prostate cancer are many and ambiguity continues regarding which treatments are best for which patients. It is important to note that aggressive treatments for prostate cancer can result in a number of adverse outcomes that may extend for years following treatment.

Prostate cancer is a highly researched area and investigation into ID of indolent disease characteristics as well as biomarkers for prostate cancer will help to better customize treatments for future prostate cancer patients. In addition, research into improved radiation and surgical techniques will continue to enhance patient outcomes. Uncertainty management interventions may help clinically appropriate, active surveillance patients to live with prostate cancer as a chronic illness. Scientific advances are seen in prostate cancer care frequently that must be implemented clinically to help patients to transcend all stages of the disease with the highest possible quality of life. **NP**

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The authors have disclosed that they have no financial relationship related to this article.

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