Diagnosis and Treatment of Localized Prostate Cancer

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Since widespread prostate cancer screening was introduced in the United States in the late 1980s and early 1990s, the incidence of prostate cancer has increased dramatically. Prostate cancer is now the most commonly diagnosed cancer in US men after skin cancer.[1] Due to screening efforts, the vast majority of newly diagnosed prostate cancers are found early, while still confined to the prostate gland. Although early diagnosis leads to the possibility of curative therapy for most patients, optimal treatment, indeed the need for treatment altogether, remains subject to debate. Using the case of a primary care clinic patient who has prostate cancer diagnosed via screening as a guide, this article reviews the controversies in screening for localized prostate cancer as well as in its diagnosis and treatment. Given the ubiquity of prostate cancer in the US population and the tens of thousands of patients diagnosed with localized disease each year, all physicians should familiarize themselves with these issues and the trends in the field.

TAKE HOME POINTS

- Although survival benefit has not yet been proven, screening for prostate cancer with the prostate-specific antigen (PSA) test in men older than 50 years is recommended by the American Cancer Society and American Urologic Association. Discussion of the potential harms and benefits of PSA screening is important in any conversation with all appropriate patients.
- Further work is needed to refine the PSA parameters and/or other biomarkers that identify high-risk tumors more accurately.
- Curative approaches for treating localized prostate cancer include radical prostatectomy and radiation therapy.
- The primary side effects of surgical and radiation-based treatments include erectile dysfunction and urinary incontinence.
- Active surveillance is a reasonable option for many men with low-grade localized prostate cancer.

PSA SCREENING

Case Presentation

A 65-year-old white man, LG, presents to his primary care physician for his yearly physical examination. Physically active and a nonsmoker, he has no medical problems and no significant family history of cancer. He reports experiencing nocturia twice per night, but has no increased urinary frequency, hesitancy, or dysuria. A routine screening test reveals a serum prostate-specific antigen (PSA) level of 2.8 ng/mL. In the prior year, his PSA level was 0.7 ng/mL. Because of this significant change, a repeat PSA test is performed 4 weeks later, which is reported as 2.7 ng/mL. Physical examination, including a digital rectal examination (DRE), is unremarkable.

Most prostate cancer diagnoses in the United States are made via PSA screening. Following the introduction of PSA screening, the incidence of prostate cancer has risen significantly. For example, prostate cancer incidence in the United States in 1985, before widespread screening, was 86,000 cases per year,[2] while in 2007, well into the PSA era, the incidence was 218,890 cases per year.[1] Prostate cancer is the second most common cancer among men in the United States after nonmelanoma skin cancer, and it is the third leading cause of cancer-related death.[1] While the incidence of prostate cancer has increased, there has been a decrease in prostate cancer–specific mortality since the establishment of widespread PSA screening.[3] Screening is presumed to be at least partly responsible for this decline, although this remains controversial. Observational studies in Europe and the United States that have compared the

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Table 1. Guidelines for Prostate Cancer Screening

American Cancer Society (www.cancer.org)
PSA screening at age 50 yr and continuing yearly until age 70 yr, or as long as life expectancy is > 10 yr; screening at age 45 yr for African Americans and those with a first-degree relative diagnosed with PCa before age 65 yr
American Urologic Association (www.urologyhealth.org)
PSA screening at age 50 yr and continuing yearly until age 70 yr, or as long as life expectancy is > 10 yr; screening at age 40 yr for African Americans and those with a family member diagnosed with PCa
US Preventive Services Task Force (www.annals.org/cgi/content/summary/137/11/917)
No recommendation for or against screening; patients and doctors should discuss potential harms and benefits
American College of Physicians (www.annals.org/cgi/content/full/126/6/480)
PSA screening should not be routinely performed for all men; physicians should be guided by patient preferences and interpretation of potential harms and benefits

PCa = prostate cancer; PSA = prostate-specific antigen.

pre– and post–PSA testing eras estimated that screening has accounted for a threefold decline in prostate cancer–associated mortality.[4,5] Large series have demonstrated that the incidence of high-grade, more aggressive prostate cancer is less common in screened populations and that the proportion of patients diagnosed with metastatic disease has also declined.[6,7] A recent study showed that screened populations have better PSA outcomes (lower PSA failure rates and longer postoperative time to doubling of the PSA level) after surgical treatment, suggesting that cure rates may be improved as well.[8]

Despite such indirect evidence of benefit, issues around prostate cancer screening continue to be debated. Unlike other screening tests such as mammography and colonoscopy, there have been no adequately designed prospective, randomized controlled trials proving the benefit of PSA screening, although there are 2 such trials currently being conducted in the United States and Europe. Results from these studies will not be available for several years.[9,10] Moreover, it is well accepted that the PSA test is imperfect. At the traditional cutoff for "normal" of 4.0 ng/mL, the test's positive predictive value (ie, the proportion of men with a PSA level > 4.0 ng/mL who have prostate cancer) is approximately 30%. It is only 25% with a PSA level between 4 and 10 ng/mL, the range that includes the majority of men who are tested.[11] In one series, PSA levels between 2 and 9 ng/mL had little association with volume or grade of prostate cancer.[12] The authors concluded that PSA levels in this range are more commonly the result of benign prostatic hypertrophy (BPH) than cancer.

Due to the low positive predictive value of the PSA test, it is difficult to determine which patients are most at risk for prostate cancer–related mortality. The lifetime risk of death from prostate cancer is approximately 3% for US men, despite autopsy series that show that the prevalence of prostate cancer among men older than 50 years is greater than 50%.[13,14] This suggests that a high proportion of men with prostate cancer will die with the disease but not from it. PSA screening therefore uncovers many clinically insignificant cancers and may ultimately expose some patients unnecessarily to the anxiety and morbidity associated with prostate cancer diagnosis and treatment. On the other hand, an estimated 27,000 men died of prostate cancer in 2006,[1] and many more suffered disease-related morbidity. Established PSA screening programs may prevent or delay these outcomes. However, our ability to predict an "insignificant" cancer prospectively is inadequate. The challenge is distinguishing prostate cancer that will one day become clinically significant from prostate cancer that will never threaten a patient's well being.

Guideline Recommendations

Based on favorable data and the successes of screening programs in other cancers, PSA screening has become the standard of care in most US primary care practices. This has occurred despite the absence of universally accepted screening guidelines (**Table 1**). The American Urologic Association and the American Cancer Society recommend initiating screening at age 50 years and continuing until age 70 years, or as long as life expectancy is greater than 10 years. The recommended age is lowered in higher-risk groups, such as African American men or men with a family history of prostate cancer. The US Preventive Services Task Force argues that there is a lack of evidence justifying screening and as such recommends discussing with patients whether or not to perform PSA testing. The American College of Physicians (ACP) encourages physicians to heed patient preferences prior to routine screening of all men over age 50 years and recommends discussing this option for men with life expectancy over 10 years. The ACP argues against earlier screening in African American men or in men with a family history of prostate cancer due to a paucity of data showing benefit.

PSA Threshold for Prostate Biopsy

Evaluating the case patient's PSA test results, one could argue that his level remains low, comfortably below the traditional cutoff of 4.0 ng/mL. Yet determination

of the appropriate PSA cutoff, like screening itself, is fraught with controversy as illustrated recently by analysis of the Prostate Cancer Prevention Trial (PCPT).[15] In this trial, nearly 19,000 healthy men older than 55 years with a PSA level below 3.0 ng/mL were randomly assigned to receive finasteride or placebo, and all patients underwent prostate biopsy by 7 years. At the end of 7 years, among 2950 men in the placebo arm who had never had a PSA level above 4.0 ng/mL, 449 (15.2%) had prostate cancer. Prevalence was 26.9% among those with a PSA level between 3.1 and 4.0 ng/mL and 6.6% in those with a PSA level less than 0.5 ng/mL. Even more alarming, 67 of the 449 (14.9%) cancers diagnosed were intermediate- or high-grade cancers.[15]

Should these findings lead to a lowering of the PSA threshold? Proponents argue that the PCPT proves that many aggressive cancers which are undiagnosed at a PSA cutoff of 4.0 ng/mL would be found using a lower threshold, which may lead to a survival benefit. Opponents, however, argue that lowering the PSA threshold would further increase the number of unnecessary biopsies. Presently, 44 men undergo biopsy to discover 1 case of high-grade cancer, and the number of those who undergo biopsy could increase significantly with a lower threshold. Moreover, an estimated 1.2 million men in the United States would be diagnosed with prostate cancer each year if the PSA cutoff were lowered to 2.5 ng/mL. While a minority of those with a PSA level between 2.5 and 4.0 ng/mL will have potentially aggressive disease and will benefit from an earlier diagnosis, many more will have low-risk disease and, as a result, may be subjected to overly aggressive or premature treatment.[16]

Techniques for Improving PSA Precision

Since PSA was first used as a screening tool, much effort has been focused on improving its precision. It is well established, for example, that the DRE, when positive, adds significantly to the positive predictive value of PSA and should be part of routine patient screening.[11] An early attempt at improving PSA screening utilized PSA density, based on the premise that cancer cells produce more PSA per unit of prostate tissue than do normal cells. When the PSA level is assessed in association with the prostate gland size, the specificity of the assay may improve. However, subsequent studies have not been able to reproduce the utility of this technique.[17,18]

Another technique for improving PSA precision is the measurement of free PSA, the proportion of PSA not bound to other proteins. A lower free-to-total PSA ratio is more commonly associated with a finding of cancer on biopsy.[19] Benign PSA (BPSA) is a form of free PSA more densely concentrated in the transition zone of the gland, the area giving rise to BPH more commonly than prostate cancer. Some studies suggest that measuring BPSA better predicts BPH and can therefore improve screening specificity.[20] Assays have also been developed for the direct measurement of PSA bound to alpha-1-antichymotrypsin (ACT), which is called complexed PSA.[21] In prostate cancer, as compared with benign prostate tissue, a higher proportion of PSA is ACT-bound. This test has outperformed total PSA and free PSA in many,[22–24] but not all,[25] studies.

Finally, high PSA velocity (ie, the increase in PSA level per year) and PSA doubling time may also be associated with a higher likelihood of cancer. PSA velocity has proven the most useful in determining prognosis once a prostate cancer diagnosis has been established. D'Amico et al[26,27] showed that a rise in PSA level exceeding 2.0 ng/mL in the year prior to diagnosis is associated with an increased risk of death due to prostate cancer. PSA velocity was an important consideration when assessing the case patient's laboratory test results. His increased PSA level from 0.7 to 2.8 ng/mL raised concern that if cancer were present, it could very well be an aggressive subtype demanding therapeutic intervention.

PROSTATE BIOPSY

Case Presentation Continued

Together, the patient and his physician weigh the risk of unnecessary biopsy and the risk of diagnosing a clinically insignificant cancer (one that might remain silent over the course of his lifetime) against the reasonable likelihood, based on PSA velocity, that any cancer present could be aggressive. The decision is made to refer him to a urologist for biopsy, the gold standard for prostate cancer diagnosis.

Transrectal ultrasonography is used to guide a typical transrectal 18-gauge core needle biopsy. Biopsy is usually performed with local anesthesia, and the procedure is generally well tolerated. Fewer than 1% of biopsies lead to hospitalization due to complications,[28] although a substantial proportion of patients report pain and discomfort associated with the procedure. In addition, in a series that evaluated complication rates in 5802 biopsy specimens, 50.4% of patients developed hematospermia and 22.6% developed hematuria.[29] Until the 2000s, a sextant needle biopsy was considered standard, but several studies have shown that cancer detection rates are improved significantly with more biopsy specimens.[30] Twelve- to 14-core needle biopsies are becoming the standard and are associated with no apparent increase in serious complications. Transient, clinically insignificant rectal bleeding or hematospermia may rarely occur due to the additional biopsy specimens.[31]

When invasive cancer is identified in 1 or more core biopsies, the pathologist assigns a Gleason score, which is a measure of the glandular architecture. Tumor cells with a lower score are more capable of forming glandular-appearing tissue than cells with a higher score. The pathologist grades the most prevalent cells in a tumor on a scale of 1 to 5, with 1 generally being the most differentiated and 5 being the least differentiated. The second most prevalent type of cell is similarly graded, and the 2 scores are added together to give an overall Gleason score. A score of 6 (Gleason 3 + 3) or below is considered low-grade, 7 (Gleason 3 + 4 or 4 + 3) is considered intermediate-grade, and 8 (Gleason 4 + 4) or above is considered high-grade disease.[32] Based on multiple retrospective series, these scores are strong prognostic factors. Low-grade cancers are associated with significantly more favorable outcomes.[33,34] Other aspects of the biopsy that provide prognostic information include the number of positive core biopsies and the amount of tumor present within each core.[35,36] Pathologists also report the presence or absence of perineural invasion of prostate cells. While the clinical significance of perineural invasion is unclear, it is correlated in most studies with extension of tumor cells beyond the confines of the prostate capsule.[37]

Physicians must keep in mind that prostate biopsy results are often inconclusive. Needle biopsies survey only a small percentage of the gland and therefore may inaccurately detect the extent or even presence of tumor. Moreover, biopsy Gleason score is often upgraded when pathologists analyze the entire gland after radical prostatectomy (RP). Several reports suggest that a significant percentage of low-grade cancers are upgraded to intermediate- or high-grade cancers after RP—over 50% in 1 series.[38–40] Since Gleason score at RP is a better predictor of prostate cancer–related outcomes than is biopsy Gleason score,[41] the possibility of underestimating the grade of tumor should be taken into consideration. Models have been devised to predict the probability of a significant Gleason score upgrade using PSA, clinical stage, and biopsy Gleason grade.[42]

Case Presentation Continued

LG undergoes biopsy, and pathologic evaluation of the specimens reveals a Gleason 3 + 3 adenocarcinoma in 2 out of 7 cores taken from the left lobe of the prostate. Cancer is present in approximately 5% of each positive core. No cancer is found in 7 cores taken from the right lobe. Perineural invasion is not present. Prostate volume, as estimated by ultrasound, is 32 mL.

Further Testing After Biopsy

Based on these biopsy results, LG has a low-grade prostate cancer likely involving a small volume of glandular tissue. In fact, it is distinctly possible that his increased PSA level was not a reflection of prostate cancer. His low-grade, low-volume disease may not be capable of producing the fourfold PSA increase to 2.8 ng/mL, and other factors such as BPH or local inflammation may be to blame. One group of researchers estimated that 25% of prostate cancers were not responsible for the PSA test results that prompted biopsy.[43]

Further staging via bone scan and/or computed tomography (CT) scan is not necessary for this patient. Although bone is the most common site of distant prostate metastases, only 1% of patients with a Gleason score of 7 or less, a PSA level of 50 ng/mL or less, and tumor confined to 1 lobe of the prostate will have an abnormal bone scan.[44] CT scans are capable of detecting locally advanced and soft tissue disease, but in an analysis of 244 patients, no patients with a Gleason score below 7 and a PSA level below 15 ng/mL had an abnormal CT scan.[45] For patients with higher grade and/or higher stage disease, these tests and others, such as pelvic or endorectal coil magnetic resonance imaging (MRI), may be indicated and may provide guidance for further management. If an imaging study shows distant metastasis, local therapy to the prostate is generally not indicated, and systemic treatment is used. If imaging shows locally advanced disease beyond the capsule of the prostate (stage cT3), optimal treatment is an area of controversy and may involve surgery, radiation therapy, systemic therapy, or a combination of treatments. For the case patient, given his clinical and pathologic profile, advanced disease was highly unlikely and further imaging was not recommended.

TREATMENT OPTIONS

Optimal treatment for low-risk patients such as LG is widely debated. Fortunately, his prognosis is excellent no matter which option he chooses—open RP, laparoscopic RP, robotic RP, external beam radiation therapy (XRT), brachytherapy, or no immediate treatment at all (**Table 2**). The first decision a patient in this situation faces is whether to seek treatment (*see* Active Surveillance). Once the decision is made to treat, both RP and XRT offer an excellent chance for cure. Men who are candidates for both types of local treatment often ask their doctors which is "better," surgery or XRT. Despite years of experience with each modality, this has been a difficult question to answer.

Surgery Versus Radiation Therapy

Several attempts to launch trials randomizing patients to surgery or XRT have been made, but none has adequately accrued patients. Thus, the 2 modalities

Table 2. Primary Approaches to Localized Prostate Cancer

Therapy	Advantages	Disadvantages/Side Effects
Open RP	Excellent cure rates when disease is limited to the prostate gland Widely used, well-established procedure Nerve-sparing approach minimizes side effects	Risk of ED Risk of urinary incontinence Exposure to risks of surgery and general anesthesia 10–14 days with Foley catheter postoperatively
Laparoscopic and robot-assisted RP	Cure rates similar to open RP in retrospective series Fewer surgery-related complications (eg, perioperative bleeding and DVT) Shorter hospital stay and time with Foley catheter	Surgeons have less experience than with open RP Early reports suggested higher positive surgical margin rate (rate likely diminishes as surgeons gain experience)
External beam XRT	Noninvasive Cure rates comparable with open RP for localized disease Periprostatic tissue and at-risk areas of pelvis may receive treatment Emerging technologies improve outcomes and may help minimize side effects	7–8 wk of daily treatment Likelihood of urinary urgency/dysuria during treatment Risk of ED and/or urinary incontinence Risk of radiation proctopathy Remote but appreciable risk of secondary malignancy
XRT with androgen ablation therapy	Cancer-related outcomes improved for intermediate- and high-risk disease, as hormonal therapy may potentiate XRT effects and treat micrometastases	May potentiate XRT-related side effects Decreased erectile function and libido Hot flashes Fatigue and weight gain
Brachytherapy	Convenient, single outpatient treatment Excellent outcomes for low-risk, low-volume disease Significant radiation dose drop-off at margins of the gland, possibly decreasing toxicity compared with external beam XRT	Risk for undertreating margins of the gland; therefore may not be optimal for higher-risk, high-volume disease Side-effect profile similar to external beam XRT Unknown if supplemental XRT adds benefit
Androgen ablation therapy	Avoids side effects of local therapy May forestall the onset of metastases; therefore it is a reasonable option for patients with shorter life expectancy May be administered safely to patients who are not eligible for surgery or XRT	Will not lead to cure; in time, the cancer will become refractory to treatment Decreased erectile function and libido Hot flashes Fatigue and weight gain Risk of osteopenia/osteoporosis
Active surveillance	Forestalls or avoids altogether the adverse effects of any treatment	Indicated only for low-risk, low-volume disease Requires close follow-up, including yearly biopsy Anxiety associated with living with untreated cancer

DVT = deep vein thrombosis; ED = erectile dysfunction; RP = radical prostatectomy; XRT = radiation therapy.

must be compared using retrospective studies, which are imperfect for several reasons. Surgical candidates tend to be younger and healthier with better prognoses than those who receive XRT, which may bias outcomes in favor of RP. Also, the natural history of low- and intermediate-grade disease is quite long, and studies with follow-up of at least 10 to 15 years are needed in order to draw definitive conclusions. Yet, XRT has seen great technical improvement, and higher doses are routinely delivered to the prostate more accurately today compared with 15 years ago. Kupelian et al[46] focused on PSA relapse-free survival in a more modern series of almost 3000 patients and showed that outcomes were similar among comparably staged patients undergoing XRT and RP when XRT is delivered at modern doses. Patients who received lower doses of XRT had significantly worse outcomes.[46] Another more recent variation in XRT, the addition of hormone therapy, also improves outcomes for patients with intermediate- and high-grade disease, but such therapy was rarely used in the most mature retrospective data sets. Thus, historical comparisons are difficult.

The chance for cure is high with surgery or radiation for patients with low-risk disease. Models using multiple clinical factors have been created to assess the chances of a favorable outcome after treatment. The Partin model uses clinical stage, Gleason score, and pretreatment PSA level to predict the probability of organ-confined disease, and therefore the likelihood of cure with surgical removal of the prostate.[47] In LG's case, the model estimates an 81% chance of having tumor confined to the prostate at the time of surgery. Nomograms developed by Kattan et al (available at www.nomograms.org.) based on similar factors predict the chances of 5-year recurrence-free survival after treatment.[48,49] More detailed models that take

into account endorectal coil MRI results and number of positive biopsy cores may be used to define risk more precisely for those with intermediate- and high-grade disease.[50] Using a nomogram, LG has an approximately 90% chance of remaining disease-free 5 years after surgery or XRT. Longer-term outcomes are needed to provide the most accurate information to patients, given the long natural history of this disease. Nonetheless, this patient has a high likelihood of a favorable outcome with any surgical or radiation-based approach, and thus particular attention must be paid to the potential side effects and tolerability of each therapeutic option.

Radical Prostatectomy

As with most surgeries, the best candidates for RP are generally healthy men with few comorbidities. Since the goal of the procedure is complete eradication of prostate cancer, ideal candidates are also those with a high likelihood of having organ-confined disease as predicted by the Partin model. The most common surgical technique is open RP with a retropubic approach where a midline incision is made from the umbilicus to the top of the pubis. A perineal approach may also be used, particularly for patients with low-grade disease. The advantage appears to be decreased blood loss and a shorter hospital stay. The retropubic approach allows sampling of pelvic lymph nodes during the operation. There is, however, little evidence that surveying lymph nodes provides meaningful benefit in patients with low-grade disease, since the chances of having lymph node involvement are low. It is not clearly established which patients should undergo lymphadenectomy.

Nerve-sparing technique. The actual dissection and removal of the prostate is technically challenging. Careful dissection may spare nerves responsible for urinary control and erectile function. Attempts to spare nerves need to be weighed carefully against the need for extensive resection based on tumor volume and aggressiveness. Criteria for the selection of patients for nerve-sparing surgery have been established. Patients considered to be at risk for extraprostatic extension, and therefore poor candidates for the procedure, include those with high-grade disease and a PSA level exceeding 20 ng/mL. One series showed that the incidence of positive surgical margins was 2.5% when patients were treated according to the criteria versus 11.8% when they were not.[51]

Nerve-sparing approaches have become favored when possible in an effort to avoid the major complications of RP, such as urinary incontinence and erectile dysfunction (ED). Retrospective series, single institutional experiences, and patient surveys have reported variable rates of urinary incontinence after RP. Most men have some degree of stress incontinence immediately after the procedure, but this generally resolves after a few months. In a study of over 1200 men who underwent RP, approximately 40% reported occasional urinary leakage at 24 months, but only 8.7% described incontinence as a moderate to severe problem.[52] Use of modern surgical techniques such as the nerve-sparing approach has led to an apparent fall in rates of urinary incontinence. Contractures of the bladder neck are extremely rare.

A more common complication after RP is ED. As with urinary continence, ED rates have improved over the past 15 years, particularly in the hands of experienced surgeons using the nerve-sparing approach. Many retrospective series have reported widely variable rates of ED after RP, depending on the age of the patient, the experience of the surgeon, and the era in which the RP was performed (pre– and post–nerve sparing). Results also vary based on whether patients or urologists are reporting the data, with ED rates consistently higher in patient-based surveys. For example, retrospective analysis of several thousand patients in the early 1990s showed that less than one third of patients maintained erectile function adequate for intercourse after RP.[53] In a more recent retrospective analysis of almost 3500 patients operated on by a single surgeon at a major research institution, up to 78% of men under age 70 years maintained erectile function sufficient for intercourse after bilateral nerve-sparing surgery.[54] While reliable data in this area are lacking, patients can be informed that age, pretreatment erectile function, and surgical technique are predictors of outcome.

Minimally invasive approaches. In the late 1990s, a laparoscopic approach to RP was developed. This minimally invasive, video-assisted procedure promised lower perioperative complications, such as bleeding, as well as shorter hospital stays. Also, proponents of the technique hypothesized that having the surgical field magnified by the laparoscopic cameras would allow for more successful nerve-sparing dissections. Because laparoscopic surgery requires a specialized skill set, laparoscopic RP gained traction across Europe and the United States slowly as urologists at specialized centers trained in the approach. The technique was opened to a larger number of urologists with the recent introduction of robot-assisted laparoscopic RP.

Laparoscopic and robot-assisted RP have never been compared head-to-head with the traditional open RP, and thus one must examine retrospective series to compare the 2 approaches. Some series focus on outcome

data from individual surgeons who have utilized both strategies, while other studies report data from single institutions in which different surgeons use different approaches. A recent review of this literature discussed these comparative studies.[55] Laparoscopic surgery was consistently associated with longer operative times but less blood loss during surgery, fewer postoperative complications (eg, thromboembolic disease or pain), and less time requiring a Foley catheter. Early reports from laparoscopic series appeared to indicate that rates of positive surgical margins were higher with laparoscopic RP. However, in later series in which the laparoscopic surgeons are more experienced, this difference diminishes. This raises an important problem for any study comparing the 2 approaches—laparoscopic surgeons are necessarily less experienced as a group than those performing the open procedure. In terms of urinary and sexual side effects, direct comparisons have been difficult due to different population sizes, population comorbidities, and experience levels of surgeons. Nonetheless, no study has suggested a significant difference between the procedures. The laparoscopic and robot-assisted techniques are too young for adequate comparison regarding PSA recurrence rates. Since laparoscopic and robot-assisted RP has clearly not proven superior to open RP, some experienced urologists in the United States feel that minimally invasive approaches should be considered less established until operators gain more experience and more definitive clinical studies are performed.

External Beam Radiation Therapy

Various forms of XRT have been used for the treatment of localized prostate cancer, including external beam XRT and brachytherapy. Patients receiving external beam XRT are generally treated 5 days per week for 7 to 8 weeks. Many patients experience mild urinary urgency or dysuria during the 8 weeks of treatment. Long-term urinary incontinence is unusual, but exact rates vary depending on the trial. In a cohort of approximately 1200 patients treated for localized disease in the mid 1990s, incontinence rates were 4% at 5 years among the 286 patients receiving XRT, as compared with 14% to 16% among the 901 who underwent RP. ED was also less common in the XRT group (63.5% versus 79.3%).[56] A more modern series shows comparable rates of incontinence and ED between RP and XRT patients.[57] The pattern of urinary symptoms and erectile function differ according to treatment. Men undergoing RP generally experience an improvement in symptoms in the months following surgery. The symptoms of XRT patients, on the other hand, tend to worsen over the course of several years before reaching a plateau.[57] Unlike surgery, external beam XRT is associated with more significant gastrointestinal (GI) toxicity. Many experience bowel irritation during treatment, including burning, diarrhea, and hematochezia. A small percentage will develop more serious radiation proctopathy. These symptoms usually dissipate shortly after treatment but can persist in approximately 5% of patients.

A rare but concerning side effect from XRT delivered anywhere in the body is secondary malignancy. In a large retrospective analysis from the Surveillance Epidemiology and End Results (SEER) database, over 50,000 men who received XRT for localized prostate cancer between 1973 and 1993 were compared with over 70,000 men who underwent RP. Among long-term survivors, XRT was associated with a small but statistically significant increase in secondary tumors, especially bladder cancer, rectal cancer, and sarcoma within the treatment field. The risk of developing a secondary malignancy was 1 in 70 for those surviving at least 10 years after XRT.[58] The 20-year and 30-year risk may be more profound. For this and other reasons, some physicians recommend RP for their young, otherwise healthy patients choosing between RP and external beam XRT for localized disease.

Newer technologies. Newer technologies, such as 3-dimensional conformal radiotherapy (3D-CRT), are currently used at most major centers in an attempt to improve outcome and decrease side effects. 3D-CRT allows radiation oncologists to define more precisely areas that should and should not receive doses of radiation. The American Society for Therapeutic Radiation and Oncology (ASTRO) convened a task force to review the data concerning 3D-CRT in prostate cancer. The panel concluded, based on numerous prospective and retrospective trials, that acute toxicity, particularly acute GI toxicity, was improved with 3D-CRT compared with conventional XRT.[59] 3D-CRT also improved long-term GI toxicity but was not associated with an improvement or worsening of long-term bladder or sexual side effects. Data suggest that 3D-CRT permits delivery of higher doses to the prostate, which may improve cancer-related outcomes, especially for those with less favorable clinical characteristics (Gleason score > 6, PSA level > 10 ng/mL). The limited period of follow-up prevents assessment of survival advantage for 3D-CRT.[59] A more recently developed technique, intensity-modulated radiation therapy (IMRT), delivers varying intensities of radiation along irregularly shaped contours. This allows physicians to define radiation fields further and permits higher dose escalations to the target. Reports suggest an improvement in some toxicity, particularly GI toxicity, as compared with 3D-CRT.[60]

Hormonal therapy. For patients with localized prostate cancer who are at increased risk for distant and local recurrence, emerging data suggest that adjuvant treatments improve outcomes. Adding hormonal therapy to standard XRT was a logical approach, since androgen-deprivation therapy (ADT), usually consisting of a luteinizing hormone–releasing hormone agonist, consistently induces responses in more advanced disease. Treatment with ADT in the setting of XRT may confer benefit by both enhancing XRT effect locally and controlling subclinical distant metastases.[61] Side effects associated with ADT include hot flashes, ED, loss of libido, fatigue, and decreased bone density. The addition of an antiandrogen, such as flutamide or bicalutamide, to ADT can exacerbate symptoms and increases the risk of gynecomastia. These effects largely resolve upon discontinuation of treatment, but quality of life is diminished during therapy, and there is some risk among older patients of permanent testosterone suppression.

In the 1990s, Bolla et al[62] established that 3 years of ADT after XRT for patients with high-risk localized prostate cancer improved survival compared with XRT alone. Consideration was then given to administering hormonal therapy prior to and during XRT (a neoadjuvant approach). When hormonal therapy was given 2 months before and during XRT, cancer-specific survival was improved compared with XRT alone.[63] Following this finding, it was shown that giving hormonal therapy before, during, and 2 years after XRT improved cancer-related outcomes further. However, those receiving longer durations of hormonal therapy reported worse side effects without clearly superior outcomes.[64] D'Amico et al[65] conducted a trial in which half of patients with intermediate- or high-grade disease or a PSA level greater than 10 ng/mL were given hormonal therapy 2 months prior to, 2 months during, and 2 months after XRT. The other half received XRT alone. After a median follow-up of 4.5 years, the XRT plus hormonal therapy arm showed an improvement in overall survival (88% versus 78%).[65]

These randomized controlled trials demonstrate the benefit of adding hormonal therapy to radiation, particularly in the high-risk subset of patients. Hormonal treatment before, during, and after XRT appears optimal. Yet several questions remain. What exactly should the duration of adjuvant therapy be? Hormonal durations can range from 6 months to 3 years. The optimal dose of radiation also remains unclear. In the studies above, 70 Gy was the maximum dose administered. Present technology allows the safe delivery of 78 Gy to the prostate. Would 78 Gy be just as effective as 70 Gy with hormonal treatment? These studies focused on intermediate- and high-risk patients. Would a short duration of hormonal therapy (neoadjuvant, adjuvant, or both) improve outcomes for low-risk patients such as LG? Presently, for low-risk patients choosing external beam XRT as local therapy, the standard of care is IMRT, if available, at doses of at least 72 Gy.

Brachytherapy

Brachytherapy consists of transperineal implantation of small radioactive pellets, or "seeds," into the prostate gland with ultrasound or MRI guidance. Unlike external beam XRT, only 1 outpatient visit is required. Proponents of the procedure argue that brachytherapy offers the best opportunity for dose escalation because the radiation source is in the prostate gland itself rather than a beam that must travel through other tissue. On the other hand, because the type of radiation delivered via seed implantation does not easily penetrate tissue, there is risk for undertreating the margins of the gland. Biochemical outcomes of brachytherapy in multiple trials for patients with low-grade, low-stage disease and low PSA level are excellent, with 5- to 10-year biochemical control rates between 87% and 96%.[66] Outcomes for those with intermediate- or high-grade disease are not as clear. While some have reported a 6-year biochemical-free survival of 90% for patients with Gleason 7 disease, others reported 5-year biochemical-free survival of 28%.[67,68]

The majority of patients report urinary symptoms, usually mild urinary frequency, urgency, or dysuria in the months immediately following treatment. Prostate swelling and urinary retention occur in 1% to 14% of patients,[69] results that appear to occur at higher frequency in those with larger gland volume.[70] As a result, the procedure is discouraged in any patient with a recent history of prostatitis, a history of transurethral resection of the prostate, or a gland size exceeding 60 g. The long-term side effect profile is similar to XRT, although the incidence of specific complications may differ. One analysis of brachytherapy and 3D-CRT from the 1990s showed that urinary toxicity persisted in 31% of patients 1 year after brachytherapy, higher than toxicity seen with 3D-CRT. Urinary stricture in particular was more prevalent in the brachytherapy group.[71] A more recent series showed that the rate of incontinence after brachytherapy is similar to that after 3D-CRT and RP. However, as seen with external beam XRT patients, the pattern of dysfunction differs from postsurgical complications, deteriorating over time.[57] Rectal complications from brachytherapy appear comparable with external beam treatment and seem to improve with time.[57] Rates of ED again depend on whether physicians or patients are reporting. In 1 patient survey, ED was reported in 73% of patients

receiving brachytherapy.[72] Physician-reported series suggest that potency is preserved more often for brachytherapy patients than for RP or external beam XRT patients. Physician-reported series, on the other hand, are often dramatically different. One series, for example, reported impotence in only 4% to 14% of men who were potent prior to treatment.[73]

Supplemental external beam XRT may enhance response to brachytherapy. The addition of external beam XRT allows further dose escalation and enables treatment to periglandular tissue, and, if indicated, seminal vesicles and lymph nodes. For patients with low- and intermediate-risk disease, however, external beam XRT does not appear to add benefit in terms of PSA-free survival. Results among high-risk cohorts are mixed. Results from a randomized clinical trial addressing this issue are pending.[74] Hormonal therapy would be a logical adjunct to brachytherapy, given its established utility in external beam treatment. However, there are no randomized trials addressing the issue, and retrospective analyses have provided conflicting results.[66]

Active Surveillance

Though LG's chance for cure is excellent with either surgery or XRT, one must ask, is cure necessary? As mentioned above, most men with prostate cancer do not die of the disease. Indeed, several recent studies confirm that expectant management, often called watchful waiting or active surveillance, is a reasonable choice for a large proportion of men with low-risk prostate cancers. The Connecticut Tumor Registry has followed 767 men with known prostate cancer who did not receive treatment. A 2005 update of the data showed that after a median follow-up of 24 years, 23% of men with Gleason 6 disease died of prostate cancer.[75] The pathology from these cases was recently reanalyzed, and most of the Gleason 6 cancers were upgraded to Gleason 7.[76] This suggests that outcomes would be improved for patients diagnosed with Gleason 6 prostate cancer using today's standards. It is also noteworthy that this study was initiated prior to the widespread use of the PSA screening test. Most of the patients in this registry were diagnosed via transurethral biopsy of the prostate. A PSA-screened population would likely be diagnosed sooner. PSA screening is estimated to provide a diagnostic lead-time of at least 5 to 10 years,[77] which could push cancer-specific survival to more than 30 years for the large majority of patients with low-grade disease. Of note, this study and other similar retrospective series do not record all morbidity associated with progression of disease. While these studies demonstrate that survival without treatment is quite long for those with low-risk disease, treatment may remain preferable if quality of life is significantly improved.

Perhaps the most important study examining the relative benefits of watchful waiting is the Scandinavian Prostate Cancer Group Study 4. This trial randomized 695 men diagnosed with prostate cancer to watchful waiting or RP. Approximately two thirds of the cancers were Gleason 6 or lower. The absolute risk reduction for death from prostate cancer was 5.4% in favor of the RP arm. Those receiving RP also had a 10% absolute risk reduction in incidence of metastases and an improvement in 10-year survival (73% versus 68%). RP appeared to benefit primarily those younger than 65 years, with no advantage detected for patients older than 65 years.[78] The results suggest that radical treatment should be considered for men diagnosed by age 65 years. While a small but significant absolute reduction in mortality was detected at 10 years, a reported 10% absolute risk reduction in incidence of metastases is perhaps more compelling. Those developing progressive or metastatic disease will likely suffer greater morbidity and are more likely to die of the disease with longer follow-up. Indeed, in a 2002 update of this cohort, rates of urinary obstruction were significantly higher in the watchful waiting group. Also, despite the morbidities associated with RP, subjective quality of life was no higher in the observed group compared with the RP group.[79]

When considering these results, several factors must be considered. First, the side effects from RP are considerable. In the 2002 update, rates of ED and urinary leakage were 35% and 28% higher in the RP group, respectively. Moreover, the absolute risk reduction of disease progression of 10% means that the majority of RPs were performed without benefit, at least at the current endpoint. Almost 20 RPs would need to be performed to prevent 1 death in 10 years. A patient at low risk for progression in the short term may look at these factors and reasonably choose to avoid the complications from RP.

It is also important to note that the population in this study was not PSA-screened. Most were diagnosed via a positive DRE, and 19% of patients had a PSA level greater than 20 ng/mL at diagnosis. Taking into consideration the lead time associated with PSA screening, most of the patients in the study would have been diagnosed years earlier had they been screened. Therefore, a screened population, like that in the United States, would have to wait much longer than 10 years to derive the 5% survival benefit seen in the trial. In the meantime, this screened population would have to endure the side effects of treatment for a longer period.

A sensible approach could entail close monitoring

of patients diagnosed with low-risk disease, withholding radical local therapy until certain criteria are met, and initiating radical local therapy well before disease-related symptoms occur. This approach, called active surveillance, could reduce the risk in mortality and progression of disease observed in the watchful waiting arm of the Scandinavian trial while forestalling or avoiding altogether the side effects associated with treatment. The challenges in devising an active surveillance approach include defining patient eligibility and outlining a monitoring strategy. Klotz[80] recently reviewed these and described an algorithm for active surveillance. Eligible patients should have a Gleason score of 6 or less, PSA level of less than 10 ng/mL, and stage T1c-T2a disease. These men should have fewer than 3 cores involved on biopsy, and disease should consist of less than 50% of any 1 core. PSA level is monitored every 3 months and prostate biopsy is performed yearly. Criteria for intervention with radical local therapy—surgery or radiation—include a PSA doubling time of less than 3 years or more aggressive disease on biopsy, such as an increase to Gleason 7.[80] Klotz's group is using this strategy in an ongoing phase 2 study initiated in 1995 that is following 423 patients. At 10 years, overall survival was 85% and disease-specific survival was 99.5%, with 65% remaining on surveillance.[81] Although a protocol for active surveillance is not yet fully established or validated, this strategy appears to be a reasonable approach for such a subgroup of prostate cancer patients.

CONCLUSION

Case Resolution

LG is currently weighing his options. He is wary of the side effects associated with treatment, but at the same time is reasonably anxious about the recent increase in his PSA level. He is also understandably anxious about harboring untreated cancer. His physician refers him to a multidisciplinary clinic, where he will discuss RP with a urologist, external beam XRT and brachytherapy with a radiation oncologist, and overall choices with a medical oncologist.

This case illustrates the controversies surrounding PSA screening and the appropriate threshold for biopsy. In addition, his low-grade disease, very common among PSA-screened patients, is amenable to multiple therapies, which illustrates the difficult choices patients must face. Much effort is being made among medical oncologists, radiation oncologists, and urologists to identify patients for whom treatment is required and those whose disease will never become clinically relevant. Until that time, patients need guidance by their physicians as they navigate their various options. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 8.

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