CLINICAL PRACTICE

Localized Prostate Cancer

Patrick C. Walsh, M.D., Theodore L. DeWeese, M.D., and Mario A. Eisenberger, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 68-year-old man presents with newly diagnosed prostate cancer. Over the past 3 years, his serum prostate-specific antigen (PSA) level has been slowly and steadily increasing (from 4.0 ng per milliliter to 4.3 ng per milliliter to 4.7 ng per milliliter). His digital rectal examination is normal; the prostate volume, estimated by means of ultrasonography, is 48 ml, and a needle-biopsy specimen reveals an adenocarcinoma with a Gleason score of 6 (the sum of the numbers associated with the most common and second most common histologic patterns — in this case, 3 plus 3). The adenocarcinoma involves 10% of 1 of the 12 cores. The patient otherwise is well, is taking no medication, and has normal sexual function. How should his case be managed?

THE CLINICAL PROBLEM

From the James Buchanan Brady Urological Institute, the Sidney Kimmel Comprehensive Cancer Center, the Department of Urology, Radiation Oncology and Molecular Radiation Sciences, and the Department of Oncology, Johns Hopkins Medical Institutions, Baltimore. Address reprint requests to Dr. Walsh at the James Buchanan Brady Urological Institute, 600 N. Wolfe St., Phipps 554, Baltimore, MD 21287-2101, or at pwalsh@jhmi.edu.

N Engl J Med 2007;357:2696-705.

In 2007, approximately 1 of 6 men in the United States received a diagnosis of prostate cancer, and 1 of 34 died from it.[1] The median age at diagnosis was 68 years; this is the highest age-specific incidence of any cancer. As compared with white men, black men have a 40% higher risk of the disease and twice the rate of death. The mortality due to prostate cancer has steadily declined for a decade, and it decreased by 4% per year between 1999 and 2003. This decrease may be attributable to several factors, including earlier detection of cancer and improved local and possibly systemic treatment.

The routine use of PSA testing has had a profound effect on the management of the disease. The lead time associated with PSA testing has been estimated to be as long as 10 years, which is reflected in the migration that has occurred in all stages of the disease over the past 25 years.[2] In 1982, one third of men presented with distant metastases, as compared with less than 5% of men today. However, because 30 to 50% of men who receive a diagnosis of prostate cancer may not have life-threatening disease, treatment decisions must take into account tumor staging and risk assessment, evaluation of coexisting conditions and life expectancy, and consideration of the efficacies and major side effects of multiple available treatment regimens. An informed patient must be a full partner in the decision-making process.[3]

STRATEGIES AND EVIDENCE

EVALUATION

The initial evaluation includes an assessment of the extent of the tumor and the patient's expected longevity. Three readily available clinical variables that correlate well with the pathological extent of the disease and the probability of cure are the Gleason score (Fig. 1), the PSA level, and the clinical stage (Table 1).

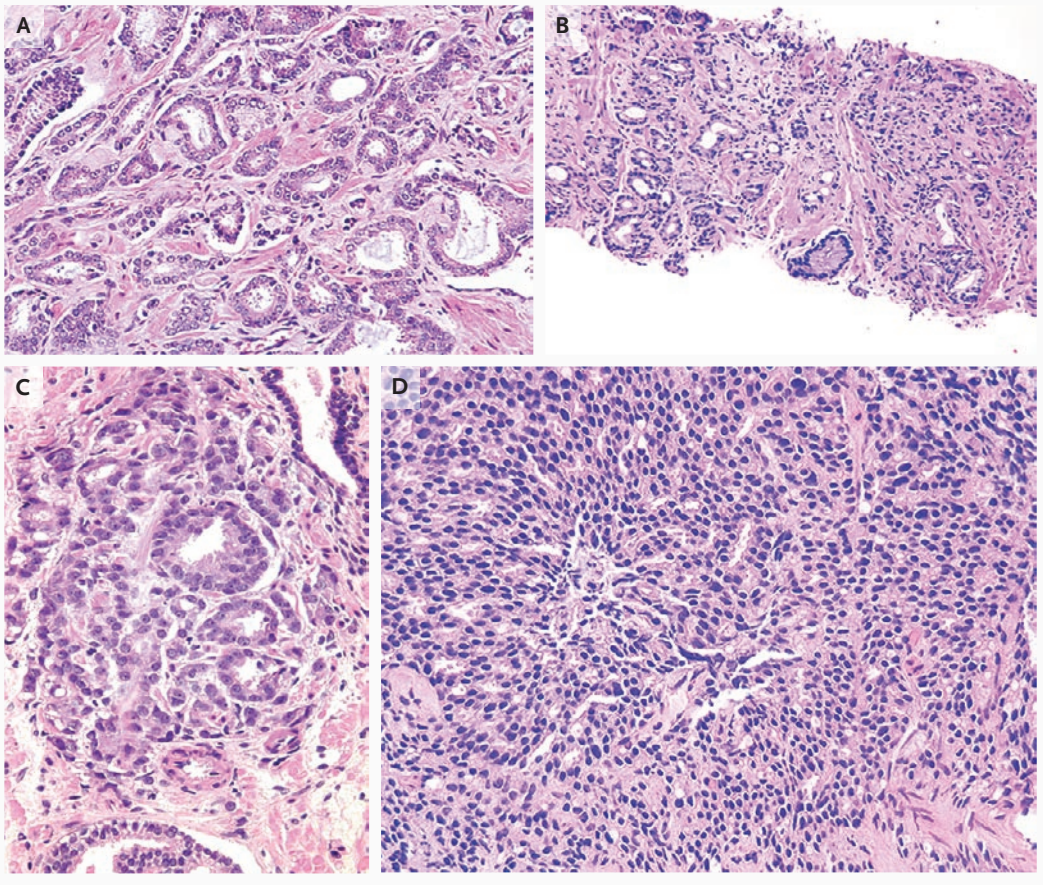

Figure 1. Histologic Specimens and Corresponding Gleason Scores.

Gleason scores represent the sum of the numbers associated with the most common histologic pattern plus the secondary pattern. Gleason grades correspond to a scale of 1 to 5, with 1 indicating low-grade carcinoma and 5 indicating high-grade carcinoma. Panel A shows individual, well-formed glands (Gleason score of 6, or 3 plus 3). Panel B shows primarily individual well-formed glands (left-hand side) with poorly formed, fused glands (right-hand side) (Gleason score of 7, or 3 plus 4). Panel C shows primarily poorly formed, fused glands with a few individual well-formed glands (center) (Gleason score of 7, or 4 plus 3). Panel D shows cribriform glands with only poorly formed glandular lumina (Gleason score of 8, or 4 plus 4). Photomicrographs are courtesy of Dr. Jonathan Epstein, Johns Hopkins Medical Institutions.

These three variables can be considered in combination with the use of a validated nomogram to estimate the probability of the progression of disease outside the prostate (an example of such a nomogram is available in the Supplementary Appendix, available with the full text of this article at www.nejm.org).[4,12] The pathological findings at radical prostatectomy can be categorized into one of four mutually exclusive groups: organ-confined disease, extracapsular extension, seminal-vesicle invasion, and lymph-node metastases. Because the pathological-stage groupings do not directly predict the outcome of any given form of treatment, validated Web-based nomograms have also been developed to predict biochemical failure 10 years after radical prostatectomy (see the Supplementary Appendix).[5-7,13]

Imaging

No forms of imaging accurately estimate the extent of tumor and its location within the prostate or in the area surrounding it. The National Comprehensive Cancer Network (NCCN) guidelines recommend imaging studies in only a selected group of patients (www.nccn.org/professionals/physician_gls/PDF/prostate.pdf)[14] (Table 1).

Table 1. Initial Evaluation of Prostate Cancer.*

Variable	Description
Gleason score	Estimation of tumor differentiation based on five histologic patterns (Epstein et al.[8]); composed of the sum of the numbers associated with the most common and second most common patterns (patterns 1 and 2 not seen in needle-biopsy specimens); tumor aggressiveness increases with the score (e.g., 3+4 is less aggressive than 4+4)
PSA	
PSA level†	Prostate-specific but not cancer-specific. To correct for elevations arising from benign disease, PSA density, free PSA, and PSA velocity can be measured (Freedland and Partin[9])
PSA density	PSA level divided by estimation of prostate volume by means of ultrasonography; adjusts PSA for prostate size; <0.1 in men without cancer
Free PSA	The molecular form of PSA not bound to alpha$_1$-antichymotrypsin; higher in men with benign disease; <15% suggests clinically significant or more aggressive disease
PSA velocity	Change in PSA in ng/ml/yr; >2 ng/ml/yr in the year before diagnosis indicates an increased risk of death from prostate cancer (D'Amico et al.[10])
Clinical stage‡	
T1	Tumor is not palpable
T1a	≤5% of resected tissue removed by means of transurethral resection
T1b	>5% of resected tissue removed by means of transurethral resection
T1c	Tumor identified by means of needle biopsy
T2	Tumor is palpable but confined to prostate
T2a	Tumor involves ≤50% of one lobe
T2b	Tumor involves >50% of one lobe
T2c	Tumor involves both lobes
T3	Tumor is palpable and extends beyond the prostate
T3a	Unilateral extracapsular extension
T3b	Bilateral extracapsular extension
T3c	Tumor involves the seminal vesicles
T4	Tumor is palpable and is fixed or invades adjacent structures
Imaging	
Bone scan	For patients with stage T1 or T2 disease (PSA >20 ng/ml or Gleason score >7), patients with stage T3 or T4 disease, and all men with bone pain
Pelvic CT scan or MRI	For patients with stage T1 or T2 disease if nomogram indicates >20% probability of lymph-node involvement and for patients with stage T3 or T4 disease
Assessment of life expectancy	Determined by means of standard nomograms (e.g., www.ssa.gov/OACT/STATS/table4c6.html)

* Information on the Gleason score, prostate-specific antigen (PSA) level, and clinical stage is used to assess the extent of disease (data are from Makarov et al.[4]) and prognosis after radical prostatectomy (data are from Han et al.,[5] Han et al.,[6] and Stephenson et al.[7]).

† Overall serum PSA levels correlate well with the extent of disease and prognosis, but there are exceptions. Because tumors that are more poorly differentiated produce less PSA per gram of tissue, some patients with advanced disease have low PSA levels. Conversely, some patients with very high PSA levels (sometimes >100 ng per milliliter) have organ-confined curable disease (usually confined to the anterior prostate).

‡ Most patients who receive a diagnosis of stage T1c disease have potentially curable disease. However, the prognosis is poorer in men with PSA levels greater than 10 ng per milliliter or Gleason scores of 7 or more. Data are from Gretzer et al.[11] The clinical stages in men with palpable tumors (stages T2 and T3) correlate well with prognoses because they reflect local tumor volume.

Assessment of Life Expectancy

The average age at diagnosis of prostate cancer is 68 years, and the average age at the time of death among men with metastatic disease is 80 years. Since PSA testing has advanced the diagnosis (i.e., the lead time) by 5 to 10 years and since a 65-year-old white man could be expected to live an average of 16.3 more years, and a black man 14.5 more years, the estimation of life expectancy is a key determinant in the selection of therapy. The NCCN

guidelines recommend the use of the Social Security Administration tables for estimating life expectancy (www.ssa.gov/OACT/STATS/table4c6.html). These guidelines also recommend the adjustment of predicted values by "adding 50% for patients in the best quartile of health and subtracting 50% for those in the worst quartile of health."[14] Similar tables that are specific to black men are also available (e.g., www.cdc.gov/nchs/data/nvsr/nvsr51/nvsr51_03.pdf).

TREATMENT

During the initial evaluation, if a patient is found to have localized prostate cancer with no extension to the seminal vesicles, regional lymph nodes, or a distant site, he is a candidate for one of three forms of therapy: expectant management, radiation therapy, or surgery. There are no data from randomized trials comparing all three approaches, and only one randomized trial has compared any two of these strategies: a Scandinavian trial compared radical prostatectomy with "watchful waiting."[15] The study population involved men with disease that was diagnosed on the basis of symptoms or signs (i.e., not by means of PSA screening) and thus was more advanced at diagnosis than is common today. Also, unlike expectant management today, the follow-up protocol for men in the watchful-waiting group was not structured to detect the earliest sign of progression in order to permit curative intervention. At 10 years of follow-up, as compared with watchful waiting, surgery had reduced the rate of progression to distant metastases (15.2% in the surgery group vs. 25.4% in the watchful-waiting group), decreased the rate of death from cancer (9.6% vs. 14.9%), and decreased death from all causes (27% vs. 32%).[15] However, the survival benefit was limited to men who were younger than 65 years of age at the time of treatment. This benefit was associated with an 11.0% absolute reduction in deaths from prostate cancer, as compared with only a 0.3% reduction among men 65 years of age or older.

The results of this trial suggest that more than 300 men 65 years of age or older would need to undergo surgery in order to prevent one death from prostate cancer at 10 years; thus, many older men who receive a diagnosis of screening-detected prostate cancer do not gain years of life with curative intervention. In selected older men who are considered to have low-risk disease, an alternative approach is careful monitoring, with treatment delayed until the disease progresses.

Expectant Management

Expectant management, which is also called active surveillance, is an appropriate strategy for patients who have a life expectancy of less than 10 years and for healthy men 65 years of age or older who are considered to have low-volume, low-grade prostate cancer (i.e., fewer than three cores involved with tumor, a Gleason score below 7, less than 50% involvement of any core, and a PSA density [the PSA level divided by the prostate volume] below 0.15 or a free PSA level above 15%).[16] There are a number of conservative ways to manage the disease in men with a short life expectancy, if progression occurs. These options include transurethral resection of the prostate, radiation therapy, and hormonal therapy. Healthy men 65 years of age or older who are likely to have low-volume disease are followed closely, with serum PSA testing and digital rectal examinations every 6 months and biopsies at frequent intervals. These tests are performed to detect progression when the disease is still curable. PSA testing alone is not sufficient for monitoring the disease, because 25% of patients with progressive disease have little or no increase in the PSA level.[17]

Although there are no data from randomized trials on the safety and efficacy of this approach, encouraging results have been reported from at least two centers. One case series involving 299 men included two groups of patients: men younger than 70 years of age with PSA levels below 10 ng per milliliter and Gleason scores of less than 7 and men 70 years of age or older with PSA levels below 15 and Gleason scores less than or equal to 7 (combined numbers 3+4). Follow-up for these men included assessment of PSA doubling times and periodic biopsies for a mean period of 64 months. A total of 34% of the men had evidence of disease progression, but overall, at 8 years only 0.8% had died from cancer.[18] In another study, involving 320 men enrolled in an expectant-management program during the period between 1995 and 2005, a total of 98 men underwent curative intervention because of signs of progression or personal preference after a median observation period of 26.5 months.[19] There was no evidence that a delay in surgery compromised curability in this group as compared with that of a cohort of matched contemporary patients who underwent immediate surgery. However, longer follow-up will be necessary to confirm these findings.

Conservative management is not ideal for pa-

tients younger than 65 years of age, because they have the most to lose if the tumor burden is underestimated at the time of diagnosis; this occurs in approximately 25% of patients with the use of current criteria.[16,20]

Radiation Therapy

Radiation therapy is another option for the treatment of localized prostate cancer. Previously, the use of nonconformal radiation therapy necessitated lower doses of radiation to avoid an unacceptably high risk of side effects; this resulted in a higher likelihood of cancer recurrence.[21] Currently, radiation therapy is most commonly delivered by means of conformal, externally applied techniques. Either three-dimensional imaging is used to localize the prostate and the beams are shaped to match the contour of the prostate, or radioactive iodine-125 or palladium-103 seeds are implanted directly into the prostate. Prospective studies have shown that higher doses of radiation can be delivered safely with the use of conformal techniques, with better cancer control than is achieved with the use of nonconformal techniques.[22,23]

The advantages of radiation therapy are that it is noninvasive or minimally invasive and it is less likely than radical prostatectomy to cause certain complications such as severe urinary incontinence.[24] In addition, radiation therapy can be used in the care of men with nonmetastatic prostate cancer of various degrees of severity, including men who are at higher risk for extraprostatic extension.

There are no data from well-controlled, randomized trials comparing the treatment outcomes of radiation therapy and surgery. Nonetheless, observational data suggest that the long-term disease control achieved with contemporary radiation therapy is similar to that achieved with radical prostatectomy.[25,26] Two prospective studies have shown that higher doses of radiation can be delivered safely with conformal techniques and that such doses are associated with increased survival rates without an increase in PSA levels.[22,26] Dose-escalated radiation with the use of conformal techniques causes intermittent rectal bleeding of grade 2 or higher (requiring transfusions, interventional radiology, or endoscopic or operative intervention) in 1.5 to 18% of patients[23,26] and causes impotence in 40 to 60% of patients.[26,27]

The most commonly used techniques are intensity-modulated radiation therapy and image-guided radiation therapy (Fig. 2). These techniques take advantage of sophisticated beam shaping and computed tomographic imaging systems that are incorporated into the linear accelerator and provide an enhanced ability to target the prostate, allowing for more accurate delivery of the highly sculpted beam to the prostate while minimizing doses of radiation to surrounding normal tissues such as the rectum. These techniques require sophisticated equipment and experienced staff, and patients should thus be referred to centers with considerable experience in their application.

Surgery

Radical prostatectomy involves removal of the entire prostate and seminal vesicles along with sufficient surrounding tissue to obtain a negative surgical margin; this procedure is often accompanied by a bilateral pelvic lymph-node dissection. The perceived advantage of radical prostatectomy is that there is no better way to cure a cancer that is completely confined to the prostate than total surgical removal.

Radical retropubic and perineal prostatectomies are performed through open incisions or laparoscopically, sometimes with robot-assisted methods. As compared with other approaches, laparoscopic approaches are associated with less blood loss during surgery, but this reduction in blood loss has not led to a reduction in the need for transfusion, nor has it led to a decrease in pain or the duration of hospitalization.[28] Furthermore, there is a concern among some surgeons that it is more difficult to obtain clear surgical margins laparoscopically, especially in patients who have organ-confined cancer. In one study of laparoscopic surgery, 7.7% of the patients with organ-confined disease had positive margins.[29] In contrast, in more than 7000 open operations performed by multiple surgeons, only 1.8% of the patients had positive margins.[30] An anatomical approach to radical prostatectomy (Fig. 3) has been used increasingly. In this approach, there is precise control of bleeding from the dorsal-vein complex and preservation of the cavernous nerves where appropriate.[31]

Observational data indicate that, as compared with earlier surgical approaches, the anatomical approach results in less blood loss, a 30-day mortality after surgery that is 10 times lower (0.2 to 0.4%), and, in the hands of an experienced surgeon using the nerve-sparing technique, reductions in the rates of the two most common surgi-

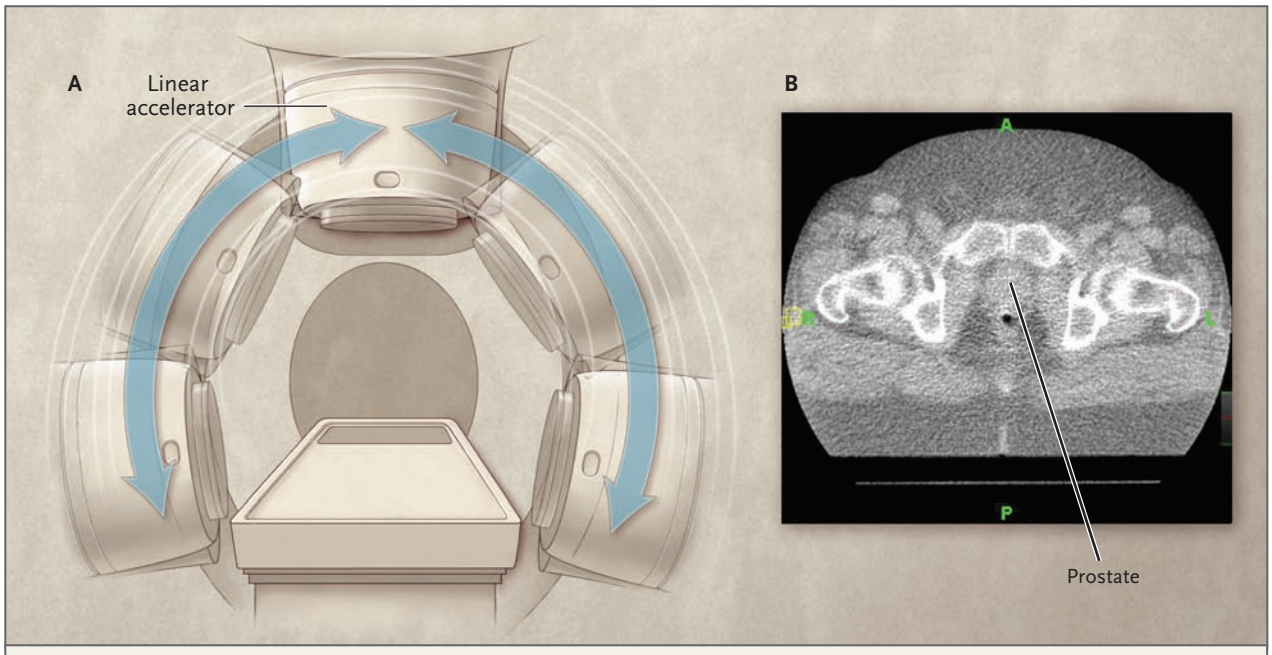

Figure 2. Image-Guided Radiation Therapy.

Panel A shows rotation of a linear accelerator gantry using radiography to obtain three-dimensional anatomical information. Panel B is a reconstructed cone-beam computed tomographic (CT) image of the prostate and surrounding tissues. The planning CT scan can be compared with this scan to ensure that the prostate position is correct.

cal complications: clinically significant incontinence (3%) and impotence (30%).[32,33] However, other estimates from studies in the United States have been less promising, with rates of incontinence as high as 74% and rates of impotence as high as 90%.[34,35] Thus, patients considering surgery should be referred to surgeons with considerable experience in order to optimize the likelihood of effective cancer control and to minimize the likelihood of complications.[36]

AREAS OF UNCERTAINTY

A comparison of cancer control after surgery with cancer control after radiation therapy is complicated by the rapid evolution of improved forms of radiation therapy and the long follow-up period necessary to show an effect on survival. Because long-term mortality data are not available, surrogate end points such as the PSA level are often used as biomarkers of freedom from disease recurrence. Although a PSA level that is higher than 0.2 ng per milliliter is a very sensitive indicator of disease recurrence after surgery, it is nonspecific; in a recent study, it was not associated with metastasis or death from cancer 25 years after surgery.[37] After radiation therapy, because the entire prostate is often not ablated, a different cutoff point is needed to indicate disease recurrence; the current cutoff point is a PSA level that is more than 2.0 ng per milliliter higher than the nadir after irradiation.[38] Although this definition is more specific for treatment failure, it lacks sensitivity. Thus, cancer control after surgery or radiation therapy as measured by these two different end points cannot be directly compared. Furthermore, selection bias in surgical series is impossible to quantify and can lead to a more favorable outcome. Finally, the safety of expectant management will be known only when data on long-term outcomes are available.

Without randomized trials involving patients who receive a diagnosis on the basis of PSA screening, it is impossible to make definitive treatment recommendations. Three large randomized trials are in progress to determine whether screening and treatment for prostate cancer will reduce deaths from cancer: the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO),[39] the European Randomized Study of Screening for Prostate Cancer (ERSPC),[40] and the Prostate Testing for Cancer and Treatment (ProtecT) trial in the United Kingdom.[41] Completion of the PLCO and ERSPC trials is expected within the next 5 years;

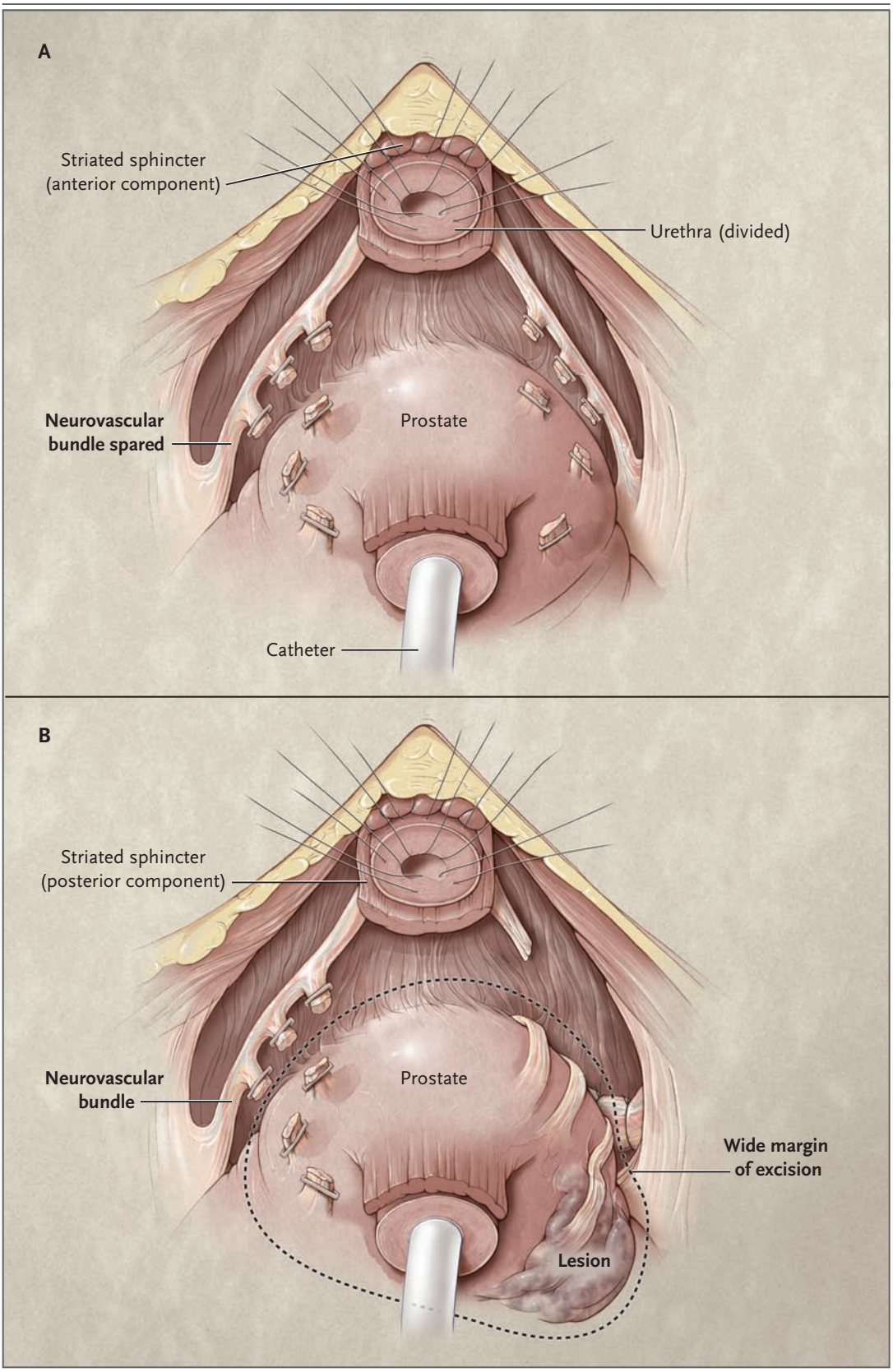

Figure 3 (facing page). Anatomical Approach to Radical Prostatectomy.

Panel A shows the surgical technique for nerve sparing during radical prostatectomy. Branches of the neurovascular bundle to the prostate have been ligated and divided. Panel B shows the surgical technique for unilateral wide excision of the neurovascular bundle on the right side.

however, because PSA screening of the control groups may occur outside these studies and definitive treatment with surgery or radiation therapy is not mandated, it is uncertain whether these trials will have sufficient power to address the primary end point of reductions in deaths from cancer. The ProtecT trial is a randomized treatment trial (comparing radical prostatectomy, conformal radiotherapy, and expectant management) nested within a screening trial; enrollment is not expected to be complete until May 2008. The Prostate Cancer Intervention versus Observation Trial (PIVOT) is a randomized trial of surgery versus observation in men who received a diagnosis by means of PSA screening; this trial has completed enrollment of 731 men, with a planned follow-up period of 15 years.[42] In contrast to the Scandinavian trial, patients in the observation group will be monitored closely, and at the time of progression, they will be offered surgery, irradiation, or hormonal therapy.

Two minimally invasive forms of therapy for the treatment of localized prostate cancer have been proposed: cryotherapy, which involves freezing the prostate by forcing pressurized argon gas through multiple 17-gauge needles that are placed through the perineum into the prostate, and high-intensity focused ultrasonography, in which the prostate is heated by a beam of focused ultrasound waves arising from and guided by an ultrasound probe that is placed in the rectum. However, there are insufficient data to provide support for their use as alternatives to surgery or radiation for localized prostate cancer.[43]

It remains unknown whether there is a role for adjuvant systemic therapy (chemotherapy or hormonal therapy) immediately after primary treatment in patients who are considered to be at high risk for recurrence on the basis of nomograms or adverse pathological findings in a radical-prostatectomy specimen.

GUIDELINES FROM PROFESSIONAL SOCIETIES

A multidisciplinary panel was convened by the American Urological Association to provide guide-

Table 2. Guidelines for the Management of Localized Prostate Cancer from the American Urological Association.*

Risk	Option	Recommendation
Low (PSA ≤10 ng/ml, Gleason score <7, and clinical stage T1c or T2a)	Active surveillance, brachytherapy, external-beam radiotherapy, radical prostatectomy	Consider patient's preference and health condition related to urinary, sexual, and bowel function; each treatment may improve, exacerbate, or have no effect on individual health, making no one treatment preferable for all; inform patient that two randomized trials showed that higher doses of radiation decreased the risk of prostate-cancer recurrence and one randomized trial showed that surgery may be associated with improved survival and a lower risk of cancer recurrence and cancer-related death than watchful waiting; determine the aim of second-line curative or palliative therapy during active surveillance and tailor follow-up accordingly
Intermediate (PSA 10–20 ng/ml, or Gleason score 7, or clinical stage T2b)	Active surveillance, brachytherapy, external-beam radiotherapy, radical prostatectomy	Consider patient's preference and urinary, sexual, and bowel function; inform patient that one randomized trial showed that the use of neoadjuvant and concurrent hormonal therapy for 6 mo may prolong survival among patients who have received conventional-dose radiotherapy, one randomized trial showed that radical prostatectomy may be associated with improved survival and a lower risk of cancer recurrence and cancer-related death than active surveillance, and two randomized trials showed that higher doses of radiation may decrease the risk of prostate-cancer recurrence; determine the aim of second-line curative or palliative therapy during active surveillance and tailor follow-up accordingly
High (PSA >20 ng/ml, or Gleason score 8–12, or clinical stage T2c)	Active surveillance, brachytherapy, external-beam radiotherapy, and radical prostatectomy are options; prostate-cancer recurrence rates are high with all of these options	Inform patient that one randomized trial showed that radical prostatectomy may be associated with improved survival and a lower risk of cancer recurrence and cancer-related death than active surveillance and one randomized, controlled trial showed that the use of adjuvant and concurrent hormonal therapy may prolong survival among patients who have received radiotherapy

* PSA denotes prostate-specific antigen.

lines for the management of clinically localized prostate cancer.[35] These recommendations, which are based primarily on observational data, given the lack of randomized, controlled trials, are summarized in Table 2.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has low-risk prostate cancer and meets the criteria suggesting the presence of low-volume disease (i.e., favorable pathological findings and a PSA density below 0.15). The patient should be informed that expectant management would be the approach with the fewest side effects and that limited available data suggest that he has approximately a 25 to 40% risk of progression, requiring definitive treatment, within 5 years. Although there are no randomized, controlled trials that show the absolute safety of this approach, available evidence suggests that with careful monitoring every 6 months and biopsies at regular intervals, deferring treatment until there are signs of progression is unlikely to affect the likelihood of cure. The options of surgery and radiation therapy should also be presented, with attention to the potential benefits and the side effects as well as patient preferences.[3]

No potential conflict of interest relevant to this article was reported.

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