CLINICAL THERAPEUTICS

External-Beam Radiotherapy for Localized Prostate Cancer

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

A 69-year-old man undergoes a follow-up evaluation after testing showed an elevated serum prostate-specific antigen (PSA) level. One year previously, he had requested serum PSA testing after receiving counseling regarding its advantages and disadvantages. His serum PSA level at that time was 8.0 ng per milliliter, and prostatic intraepithelial neoplasia was detected on biopsy. His serum PSA level is now 11.0 ng per milliliter, and the apical prostate is indurated (clinical tumor stage, T2a). Transrectal prostatic ultrasonography shows a prostate gland 70 ml in size (twice normal size), needle biopsy reveals adenocarcinoma with a Gleason score of 7, and cancer staging shows no sign of spread beyond the prostate. A specialist recommends high-dose, image-guided external-beam radiotherapy.

THE CLINICAL PROBLEM

One in six American men receives a diagnosis of prostate cancer during his lifetime, usually after 60 years of age.[1] With approximately 234,000 new cases expected in 2006, prostate cancer is the most common noncutaneous malignant disease and is the third leading cause of cancer-related death in men.[1] The established risk factors for the disease include race, age, and family history.[2]

The prognosis for patients with prostate cancer is variable and depends on the tumor-related characteristics at diagnosis. In practice, the clinical tumor stage at presentation (according to the classification of the American Joint Committee on Cancer),[3] the histologic appearance (according to the Gleason score; scores range from 2 to 10, with higher scores indicating a poorer prognosis), and serum PSA values are used to assess the risk of spread of microscopic tumor beyond the prostate,[4-6] determine the risk of recurrence (Table 1),[4] and estimate the likelihood of therapeutic success.[5] The interaction among these factors can be assessed with the use of a predictive instrument, such as a nomogram,[7] that quantifies the risk for the individual patient.[6-8] Patients with higher Gleason scores, higher PSA levels, and rapidly rising PSA values (i.e., a PSA velocity of >2 ng per milliliter per year) have an increased risk of disease progression and cancer-related death.[5,8,9]

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Etiologic studies have identified several genes that are associated with susceptibility to prostate cancer and that may serve as a substrate for carcinogenesis.[10,11] Environmental factors such as dietary carcinogens and environmental agents may

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Table 1. Risk of Recurrence and Options for Initial Management of Clinically Localized Prostate Cancer, According to the National Comprehensive Cancer Network (NCCN).*

Risk of Recurrence	Management Options†
Low (stage T1–T2a, Gleason score of 2–6, and PSA <10 ng/ml)	
<10 yr	Expectant management, three-dimensional conformal radiotherapy, or brachytherapy
≥10 yr	Expectant management, three-dimensional conformal radiotherapy, brachytherapy, or radical prostatectomy with or without dissection of pelvic lymph nodes‡
Intermediate (stage T2b–T2c or Gleason score of 7 or PSA of 10–20 ng/ml)§	
<10 yr	Expectant management, three-dimensional conformal radiotherapy with or without brachytherapy, or radical prostatectomy with or without dissection of pelvic lymph nodes‡
≥10 yr	Three-dimensional conformal radiotherapy with or without brachytherapy or radical prostatectomy with or without dissection of pelvic lymph nodes‡
High (stage T3a or Gleason score of 8–10 or PSA >20 ng/ml)§	Three-dimensional conformal radiotherapy with androgen-suppression therapy¶ or radical prostatectomy‖ with dissection of pelvic lymph nodes
Very high (stage T3b–T4)	Three-dimensional conformal radiotherapy with androgen-suppression therapy¶ or androgen-suppression therapy¶

* Adapted with permission from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, version 2.2005.[4] Localized prostatic cancer is defined by the absence of nodal or distant metastases. Gleason scores range from 2 to 10, with higher scores indicating a poorer prognosis. According to the NCCN,[4] "These guidelines are a work in progress that will be refined as often as new significant data become available. . . . The NCCN guidelines are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN guideline is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment."

† The options within each category of risk are considered similar with respect to survival and disease recurrence on the basis of available data. The selection of an option is based on a variety of factors, including the quality of life and the risk of adverse effects, and should be discussed with the patient.

‡ Dissection of the pelvic lymph nodes is indicated unless the predicted probability of lymph-node metastasis is less than 3%.[6,7]

§ Patients with multiple adverse factors may be shifted into the next higher risk group.

¶ Long-term (2 to 3 years) androgen suppression is indicated; short-term (6 months) androgen-suppression therapy may be considered for selected patients with a single adverse high-risk factor.

‖ Radical prostatectomy is indicated only in patients with low tumor volume and no fixation to adjacent structures.

also promote somatic mutations that accumulate over a period of several decades (Fig. 1).[2,12] Progression from multifocal neoplasia originating in the prostate to metastatic dissemination occurs in several steps over time. The main pathways of spread to the lymph nodes and bone are lymphatic and hematogenous.

Radiotherapy can take the form of externally generated electromagnetic (x-ray) and particle (most commonly, proton) beams directed into the patient or radionuclides placed in or near cancerous tissue (brachytherapy). The biologic effects of radiotherapy result from ionization within the DNA helix, the interaction between radiation-induced chemical radicals and DNA, and the modification of other intracellular targets that are responsible for apoptosis and DNA repair (Fig. 1).[13] The entire prostate is the target of radiotherapy, because prostate cancer is often multifocal and is not always fully identified even with the use of extensive sampling on biopsy. In addition, the seminal vesicles, the pelvic lymph nodes, or both, may be included in the therapy for a portion of the total dose when the estimated risk of the spread of microscopic cancer to these structures exceeds approximately 15%.[6,7]

Doses of radiation are measured in Gray (Gy) units. One Gray is equivalent to 1 joule of radiation energy absorbed per kilogram of body weight. The probability of the eradication of the cancer improves with higher doses,[14-27] but so too may the risk and severity of adverse effects. The risk

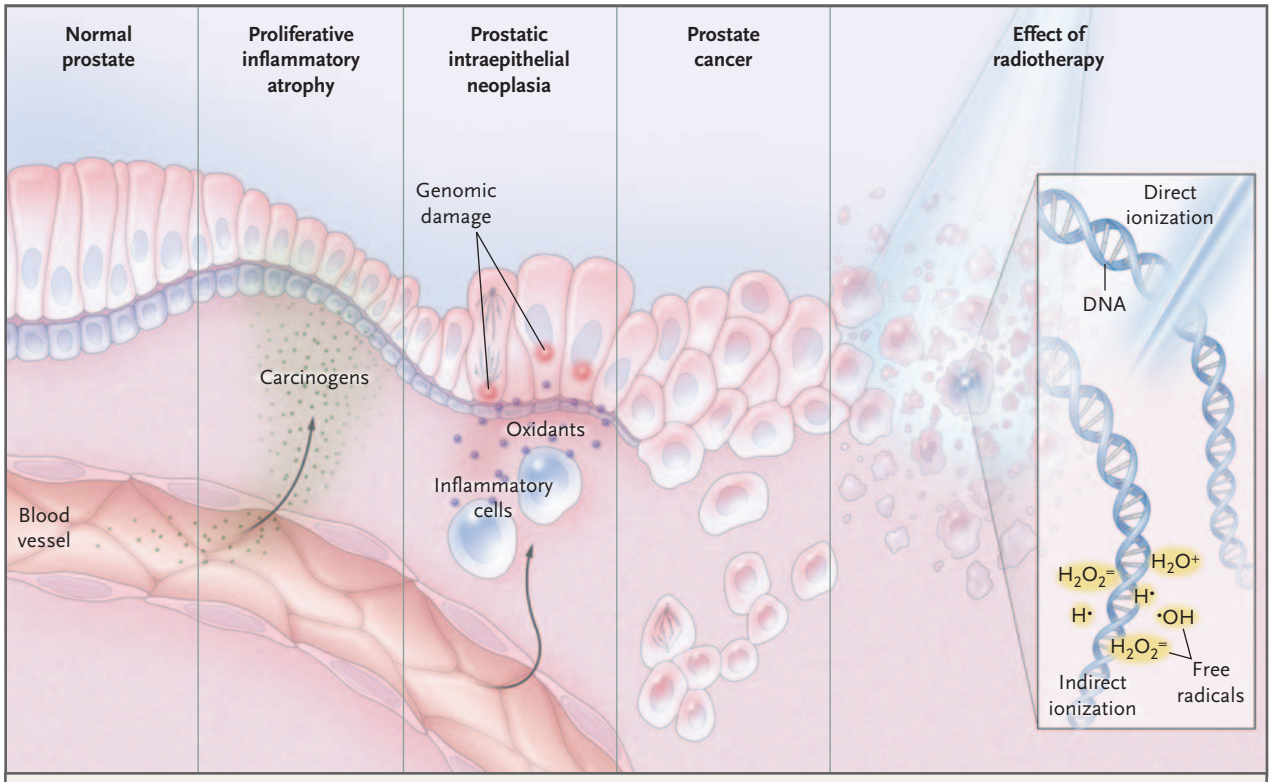

Figure 1. Genomic Damage Resulting in Prostate Cancer.

Genomic damage is induced by dietary carcinogens and inflammatory oxidants that give rise to proliferative epithelial cells that fail to mature into normal columnar epithelium. Proliferative inflammatory atrophy is thought to progress to prostatic intraepithelial neoplasia and prostate cancer through a multistep process. Radiotherapy interacts with the DNA helix of cancer cells and other intracellular targets, resulting in cell death.

of adverse effects is related to the proximity of the prostate to adjacent organs (especially the bladder and rectum) as well as variations in the patient's position during radiotherapy and random movement of the prostate between treatment sessions. The use of standard radiotherapeutic techniques reduces the effect of radiation on adjacent organs by directing multiple radiation beams at the prostate from several angles. The intersection of the beams, thus the region of the highest intensity of the radiation, is centered on the prostate (Fig. 2).

Two developments have improved the precision with which external-beam radiotherapy can be directed specifically to the prostate, limiting the potential for injury to other organs and permitting the use of higher doses of radiation. In the first development, known as three-dimensional conformal radiotherapy, image-guided techniques are used to ensure that the alignment of the beams conforms tightly to the target.[28] In the second development, known as intensity-modulated radiotherapy,[16-18] further enhancements allow modulation of the intensity of the dose in each of many minute pixels, or "beamlets," within each beam, resulting in steep gradients of intensity within the prostate and between the prostate and adjacent organs.

CLINICAL EVIDENCE

The two standard approaches to the management of early prostate cancer with a curative intent are radiotherapy (external-beam radiation, brachytherapy, or both) and radical prostatectomy. However, data from randomized trials that directly compare these two methods are lacking. Performing such trials is complicated by the rapid evolution of treatment techniques and the long clinical follow-up necessary to show an effect on survival.[29] Therefore, comparison studies of these approaches have relied primarily on retrospective analy-

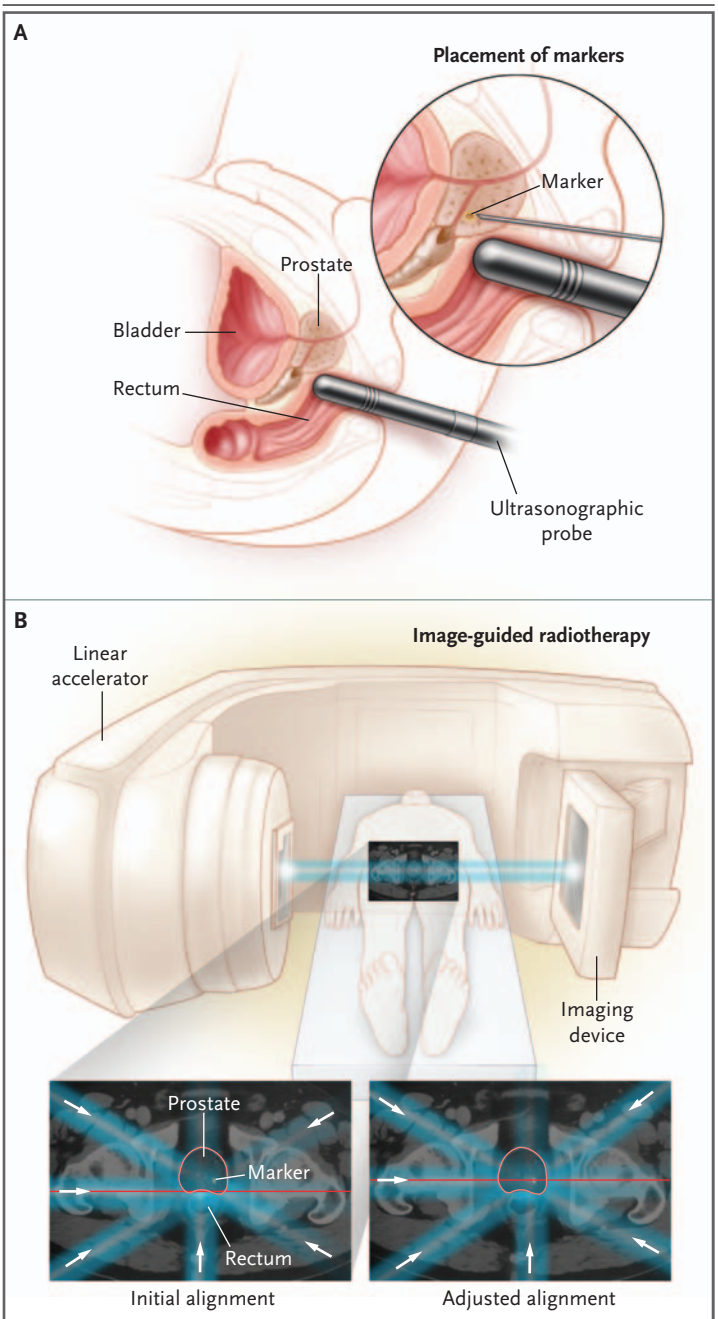

Figure 2. Image-Guided Radiotherapy.

Image-guided radiotherapy begins with the placement of intraprostatic markers (Panel A) and a planning session at which computed tomography is used to identify the markers, the prostate, and adjacent organs. The imaging device, which is integrated into the linear accelerator, is used to locate the markers. The x-ray beams are adjusted to ensure that the prescribed dose encompasses the prostate and that the dose to the adjacent organs is limited (Panel B).

ses. Unfortunately, such studies tend to be biased, because younger and healthier patients are apt to undergo surgery whereas older and less vigorous patients are usually treated with radiotherapy.

A recent comparison involved 2991 patients who underwent prostatectomy or received low-dose (<72 Gy) or high-dose (≥72 Gy) external-beam radiotherapy, brachytherapy, or a combination of these techniques.[22] At 5 years, the rate of event-free survival in the five study groups was 81% for prostatectomy, 51% for low-dose radiotherapy, 81% for high-dose radiotherapy, 83% for brachytherapy, and 77% for combination therapy, suggesting similar outcomes with these forms of therapy, except for low-dose external radiotherapy.

Results of randomized clinical trials of standard-dose radiotherapy, as compared with high-dose radiotherapy, are now emerging,[19,23,25,26] and other trials are in progress.[30,31] In the first of these clinical trials, there was a 45% reduction in disease recurrence among patients assigned to high-dose (78 Gy) radiotherapy, as compared with those assigned to the then-standard dose (70 Gy).[19] However, the incidence of moderate-to-severe rectal adverse effects was higher among those treated with high-dose therapy than among those receiving the standard dose. Other studies have noted a similar efficacy but with less severe adverse effects with the use of conformal radiotherapy with image guidance.[25]

CLINICAL USE

External-beam radiotherapy, prostatectomy, and brachytherapy are potentially curative therapies for prostate cancer. Expectant management (surveillance with intervention for disease progression or the onset of symptoms) and androgen-suppression therapy are alternatives for patients who are not candidates for curative therapy. The Clinical Practice Guidelines of the National Comprehensive Cancer Network (Table 1)[4] can be used to select one of these options on the basis of the risk of disease recurrence and the patient's life expectancy.[32]

External-beam radiotherapy has several advantages.[29] Because it is noninvasive treatment and has no surgical risks, it may be offered to patients who for reasons of age, general health, or specific coexisting conditions might tolerate prostatecto-

my poorly. In addition, urinary incontinence is less common after radiotherapy than after surgery. The most important disadvantage is the risk of adverse effects caused by the irradiation of normal organs, particularly the rectum. In addition, treatment with radiotherapy does not include pathological confirmation of disease stage; if spread beyond the prostate has occurred, it cannot be detected directly.

The few contraindications to external-beam radiotherapy tend to be relative, rather than absolute. However, radiotherapy may not be beneficial in some patients at an advanced age or with coexisting conditions that limit their life expectancy. Patients with active collagen vascular disease or inflammatory bowel disease or those with microvascular damage from hypertension or diabetes mellitus may be less able to tolerate radiotherapy than patients without those conditions.[33]

When external-beam radiotherapy is chosen, the specifics of treatment planning depend on the risks of extraprostatic tumor spread and disease recurrence (Tables 1 and 2).[4] Categories based on the level of risk form the basis of clinical practice guidelines that facilitate decision making, including the choice of a particular radiotherapeutic technique,[4] the extent of extraprostatic tissue treated,[5] the dose of radiation prescribed,[34] and the use of complementary treatments, such as androgen-suppression therapy (Tables 1 and 2).

Androgen suppression may be used with radiotherapy and is typically achieved with a gonadotropin-releasing–hormone agonist with or without oral antiandrogen therapy. A short course of androgen suppression (6 months) may be beneficial in patients with intermediate-risk disease who receive no more than 70 Gy of radiation,[35,36] but its role in high-dose radiotherapy is unclear.[16,22] Androgen-suppression therapy may also be given in an extended course that includes administration before radiotherapy (neoadjuvant), during radiotherapy, and for 2 to 3 years after radiotherapy (adjuvant) in patients with high-risk disease.[4,35]

Brachytherapy is an alternative to external-beam radiotherapy that is appropriate for some patients with low-risk disease (Table 1). It may also be added to moderate-dose (45 Gy) external-beam radiotherapy for patients with intermediate-risk disease.[4,37] In the most common form of brachytherapy, radioisotope iodine-125 or palladium-103 "seeds" are permanently implanted into the prostate, but in an alternative method, catheters are placed temporarily to serve as a conduit for a high-dose iridium-192 source.[38] Whether brachytherapy alone or combined with external radiotherapy is preferable to high doses of external radiotherapy alone is not known.

Image guidance for three-dimensional conformal radiotherapy is accomplished by several methods, but a typical approach uses gold markers that are implanted in the prostate under ultrasonographic guidance (Fig. 2A).[28] During a preparatory process known as "simulation," computed tomography is used to identify all markers, each of which is oriented spatially in relation to the prostate and the adjacent organs and to the trajectory of the multiple proposed beams. Information from this simulation is transferred to an integrated computerized planning system that formulates a patient-specific strategy based on the doses prescribed for radiotherapy to the prostate and the dose limitations imposed by the need to avoid adverse effects on the adjacent organs.

Before the radiotherapy is started, the patient should be asked about symptoms of urinary obstruction, because transient prostatic edema during therapy may worsen the severity of an obstruction. If such symptoms are present, a urologic evaluation is warranted, and therapies to improve urinary outflow should be considered. Patients may continue to take any medications, and restrictions on activity or diet are not routinely required. Instructions to maintain a full bladder during treatment may be given in order to displace adjacent tissues out of the radiation beam.

The total prescribed dose of radiotherapy is typically administered in daily fractions of 1.8 to 2.0 Gy at each outpatient session during a treatment period of several weeks. Before each treatment, an electronic imaging device in the linear accelerator identifies each marker, and the coordinates of the marker are determined. The radiotherapy beam is then realigned, the position of the prostate is "locked in," and the dose of radiation is delivered to within 2 mm of the intended location (Fig. 2B).[28] The duration of exposure to radiation is brief (a few minutes).

The patient's tolerance of radiotherapy is assessed at each visit. It is unusual for radiotherapy

Table 2. Principles of Radiotherapy, According to the National Comprehensive Cancer Network.

Three-dimensional conformal or intensity-modulated radiotherapy techniques should be used.
Doses of 70 to 75 Gy in 35 to 41 fractions to the prostate (with or without inclusion of the seminal vesicles for part of the therapy) appear to be appropriate for patients with low-risk cancers, whereas for patients with intermediate- or high-risk disease, doses of 75 to 80 Gy appear to provide improved disease control as assessed on serum PSA testing.
Patients with high- or very-high-risk cancers are candidates for radiotherapy to the pelvic lymph nodes with neoadjuvant or adjuvant androgen-suppression therapy, or both.
If target margins are reduced, such as for the administration of doses greater than 75 Gy, extra attention to daily image guidance, with the use of techniques such as implanted markers, transabdominal ultrasonography, or endorectal balloon, is indicated.

treatments to be postponed or discontinued because of adverse effects. The cost of image-guided intensity-modulated conformal radiotherapy varies, but it is approximately $38,000 for the treatment of a typical patient in the United States.

After the course of radiotherapy has been completed, measurements of serum PSA are obtained every 6 months for 5 years and annually thereafter, and an annual history-taking and digital prostatic examination are recommended.[4] If serial measurements showing rising PSA values are the sole sign of recurrence, a persistent level exceeding the nadir by 2 ng per milliliter is considered to indicate recurrence.[39] Initial monitoring of the rate of PSA increase (the PSA doubling time[7]) may be prudent. Patients with a doubling time of less than approximately 6 months are more likely to have metastatic disease and a higher risk of death in the near term than those with a doubling time of approximately 6 months or more.[40,41]

ADVERSE EFFECTS

Adverse effects are classified as acute or late, according to the time of occurrence in relation to radiotherapy.[42] The most common adverse effects are gastrointestinal, genitourinary, and sexual.

As an acute adverse effect, moderate-to-severe proctitis or (when pelvic nodal treatment is given) enteritis develops in 40% of patients treated with high-dose (>74 Gy) radiotherapy.[23,25,26,30,43] The symptoms include abdominal cramping, tenesmus, and urgency and frequency of defecation and are usually controlled with antidiarrheal agents or topical antiinflammatory preparations. Late gastrointestinal effects include urgency, frequency, and hematochezia. Strictures, ulceration, and perforation are rare. Moderate-to-severe late gastrointestinal effects occur in approximately 20% of patients treated with high doses of radiotherapy, as compared with approximately 10% of those treated with standard doses (approximately 70 Gy).[16,19,23,25,26,43,44] However, when highly conformal beams are used and the dose to the rectum is limited,[16,19,23,26,30] the rate of moderate-to-severe late gastrointestinal effects approaches that seen among patients who receive standard doses.

Moderate-to-severe acute genitourinary effects occur in approximately a third of patients[23,25,26,30,43] and are caused by irritability of the bladder detrusor or urothelial inflammation (cystitis, urethritis, or both) resulting in urgency, frequency, or dysuria. Prostatic inflammation may result in prolonged or incomplete voiding, especially in the setting of coincident benign hypertrophy. These adverse effects are often lessened with the short-term use of α_1-adrenergic–receptor antagonist medications. Late genitourinary effects are relatively uncommon, but bladder-neck or urethral stricture may cause retention, and a reduced bladder capacity may result in urgency and frequency. Acute and late genitourinary effects do not increase significantly with the use of high-dose radiotherapy.[16,19,23,25,26,30,43,44] Urinary incontinence is uncommon; approximately 1% of patients use protective pads intermittently or daily.[45]

Erectile dysfunction occurs in perhaps a third of patients after radiotherapy, as a result of the disruption of penile vasculature[46]; however, this disorder may also result from causes other than radiotherapy.[47] Because high doses of radiation to the corpus spongiosum double the risk of erectile dysfunction,[46] measures to reduce the corporal dose are now incorporated into the planning of radiotherapy.

Patients undergoing radiotherapy for prostate

cancer may have a small increase in the risk of second malignant diseases, as compared with those who undergo prostatectomy[48] but not as compared with the population at large, since patients receiving radiotherapy are typically older than surgical patients and often have other medical problems. With the exception of sarcoma within the irradiated volume (absolute risk, 0.03%), a causal relationship between radiotherapy and second cancers is uncertain.

AREAS OF UNCERTAINTY

Data comparing external-beam radiotherapy and expectant management, brachytherapy, or prostatectomy are limited, so it is uncertain which approach provides the ideal balance between cancer control and the quality of life. The comparison between external-beam radiotherapy and prostatectomy has not been the subject of a major randomized clinical trial involving current therapeutic methods.

Despite evidence that high doses of radiation reduce the recurrence of prostate cancer more successfully than do "standard" doses,[14-27] there is no conclusive evidence from clinical trials that cancer-related deaths are reduced and that the patient's quality of life is enhanced as a result of high-dose radiotherapy. The maximal tolerated dose that can be achieved with image guidance has not been determined. It is also not clear whether combining brachytherapy or androgen suppression with radiotherapy is preferable to radiotherapy alone when high doses of radiation are used.

Increasing the dose of radiation given at each treatment session may improve the efficacy of the therapy, even when the total dose is held constant or even reduced. One approach involves increasing the dose administered at each session by approximately one third (from 1.8 Gy to 2.5 Gy) while decreasing the number of sessions (from 44 to 28) and the total dose (from 79.2 Gy to 70 Gy).[49] However, this approach has not yet been adequately tested against the currently recommended approach (Table 1).

GUIDELINES

The Clinical Practice Guidelines of the National Comprehensive Cancer Network[4] are often cited (Table 1) and have been adopted by other organizations (including the American Cancer Society) that advise medical professionals and the public. The initial guidelines were published in 2000 and are updated annually, and they are available at www.nccn.org/professionals/physician_gls/default.asp. Because the guidelines do not imply a preferred choice among the standard options, and because they recognize the potential limitations of current clinical evidence, the principal recommendation is care in the context of a clinical trial.

The category of risk recurrence and life expectancy form the basis for the guidelines. External-beam radiotherapy is considered appropriate for patients in most categories of risk. Three-dimensional conformal radiotherapy or intensity-modulated radiotherapy should be used, and doses of 70 to 75 Gy are acceptable for the treatment of patients at low risk for recurrence, whereas doses of 75 to 80 Gy are suggested for those at intermediate or high risk. Image guidance is recommended for highly conformal radiotherapy. The addition of androgen-suppression therapy for 2 to 3 years is recommended for patients at high or very high risk. A shorter duration (6 months) of androgen suppression is optional for patients at intermediate risk who have more than one risk factor or for patients at high risk who have a single risk factor.

RECOMMENDATIONS

The patient described in the vignette has intermediate-risk prostate cancer,[4] a fast-paced PSA velocity (>2 ng per milliliter per year),[9] and a life expectancy exceeding 10 years.[32] He is a suitable candidate for either radical prostatectomy or external-beam radiotherapy with or without brachytherapy. He should be evaluated for urinary obstruction, and consultations with specialists in radiation oncology, medical oncology, and urology should be sought to provide a comprehensive and balanced discussion of the options. It should be emphasized that his chances of a recurrence of cancer and his long-term survival appear to be nearly equal with either surgery or radiotherapy; he should therefore consider the available information about adverse effects and the quality of life. Enrollment in a clinical trial should also be considered.

I recommend external-beam radiotherapy as the sole treatment for this patient, without irradiation of the seminal vesicles or pelvic lymph nodes. Image-guided intensity-modulated confor-

mal beams should be used to deliver a dose of 75 to 80 Gy to the prostate, with the final determination of the dose to be based on the proportion of adjacent organs that can be spared. The combination of brachytherapy and external-beam radiotherapy may not be superior to high-dose external-beam radiotherapy alone,[22] so I do not recommend this approach for this patient. I also do not recommend the addition of androgen suppression, since its role with high-dose image-guided delivery is not firmly established[16,22] and its use will increase the possibility of adverse effects.

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CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most clinical trials for publication only if they have been registered (see N Engl J Med 2004;351:1250-1). Current information on requirements and appropriate registries is available at www.icmje.org/faq.pdf.