CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will advise patients of the benefits and risks associated with screening for, diagnosing, and treating prostate cancer

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A practical guide to prostate cancer diagnosis and management

ABSTRACT

Screening, diagnosis, and management of prostate cancer can be complicated, with no clear consensus about key issues. We present our approach, which reflects the guidelines of the American Urological Association (AUA).

KEY POINTS

The AUA recommends annual screening with both digital rectal examination (DRE) and prostate-specific antigen (PSA) testing starting at age 40 for all men whose life expectancy is more than 10 years. Guidelines from other organizations differ somewhat.

If the DRE is abnormal or if the PSA level is persistently higher than 2.5 µg/L, then biopsy should be considered.

In low-risk cases, active surveillance may be acceptable in lieu of immediate treatment. Patient education, accurate disease assessment, and compliance with monitoring are critical considerations.

The most common primary treatments are active surveillance, prostatectomy, interstitial brachytherapy, external beam radiotherapy, and cryotherapy. Newer ablative and focal therapies may offer an advantage in select patients. Which treatment to use is highly patient-dependent.

Single-institution, single-surgeon reports and advertisements tend to underestimate rates of impotence after prostatectomy, and as a result patients may have false expectations.

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Prostate cancer screening, diagnosis, and treatment present challenges to internists, urologists, and oncologists. For the internist, there is the ongoing debate about when and how often to screen with prostate-specific antigen (PSA) testing, as well as about how to interpret the results. For urologists and oncologists, there is no consensus on how to treat prostate cancer with the growing array of options, from surgery to cryoablation. Most therapies have not been compared in head-to-head trials, and anxious patients often approach their internist for help in navigating the maze of options.

This review summarizes current American Urological Association (AUA) guidelines,[1] as well as current practice patterns at the Glickman Urological and Kidney Institute of Cleveland Clinic regarding screening, diagnosis, risk assessment, treatment, and posttreatment management of prostate cancer. We try to explain the approved and the experimental treatments, outlining what we know about their advantages and disadvantages.

SCREENING: WHEN AND HOW

Screening for prostate cancer should involve both a digital rectal examination (DRE) and measurement of the serum PSA level. But when should screening start?

The AUA recommends annual screening with DRE and serum PSA test starting at age 40 for all men with a life expectancy of more than 10 years.[1]

The American Cancer Society[2] and the American College of Physicians,[3] in contrast, recommend that men who choose to undergo screening should begin at age 50, or at age 45 if

TABLE 1

Clinical staging and D'Amico risk criteria for prostate cancer

Clinical stage

T1c	Tumor identified on biopsy (prompted by elevated prostate-specific antigen [PSA])
T2a	Tumor palpable on ≤ ½ of one lobe
T2b	Tumor palpable on > ½ of one lobe
T2c	Tumor palpable in both lobes

D'Amico criteria

RISK	GLEASON SCORE	TUMOR STAGE	PSA (µG/L)
Low	≤ 6	T1c–T2a	≤ 10
Intermediate	7	T2b	10–20
High	≥ 8	T2c	> 20

BASED ON INFORMATION IN D'AMICO AV, WHITTINGTON R, MALKOWICZ SB, ET AL. BIOCHEMICAL OUTCOME AFTER RADICAL PROSTATECTOMY, EXTERNAL BEAM RADIATION THERAPY, OR INTERSTITIAL RADIATION THERAPY FOR CLINICALLY LOCALIZED PROSTATE CANCER. JAMA 1998; 280:969–974 AND GREENE FL. AMERICAN JOINT COMMITTEE ON CANCER. AMERICAN CANCER SOCIETY. AJCC CANCER STAGING MANUAL. 6TH ED. NEW YORK, NY: SPRINGER-VERLAG; 2002.

Before being screened, patients should understand the benefits and risks

they are black or have a family history of prostate cancer in a primary relative diagnosed before age 65. They also recommend that screening with PSA and DRE be stopped at age 75, given the low likelihood of death from de novo prostate cancer after this age. The AUA recommends that screening be stopped at age 75, but may be continued beyond age 75 if the patient has a life expectancy of 10 years or more.

Before being screened, patients should understand the benefits and the risks of testing. While a small subset of prostate cancers behave aggressively, the majority are slow-growing and pose minimal risk for the development of fatal disease.

A discussion of the rationale for these guidelines and their differences is beyond the scope of this review. Differences stem from the observation that most men treated for prostate cancer will likely not die from prostate cancer, but rather from another condition.

Digital rectal examination's role and limitations

The utility of DRE is limited to the detection of nodules, gross asymmetry, and gland fixation. DRE is not highly specific: only 40% to 50% of men who have abnormal findings on DRE have prostate cancer on biopsy.[5] Anyone who has an abnormal finding on DRE should undergo prostate biopsy. However, if a rectal mass is palpated or if the prostate is exquisitely sensitive, biopsy is not indicated.

Although DRE is not considered very sensitive, it remains an essential element of the clinical staging system for prostate cancer because it can detect cancers that produce little or no PSA (TABLE 1). Up to 23% of men with prostate cancer in one large cohort study had PSA levels of 4.0 µg/L or less (traditionally deemed normal) and were diagnosed on the basis of a positive DRE alone.[4,5]

DRE is highly inaccurate for estimating gland volume; it should not be used to gauge cancer risk.

Prostate-specific antigen: Caveats

PSA measurement was introduced as a clinical screening test for prostate cancer in the early 1990s, and it serves as the foundation for early detection.

PSA, a protein involved in seminal coagulation, is produced by the prostate epithelium and is mostly confined within the prostatic ducts. Cancer cells secrete PSA into the bloodstream at increased levels via a disrupted basement membrane in tumor-affected areas of the gland. Elevated PSA can also result from benign prostatic hypertrophy, prostatitis, and prostate biopsy.

PSA levels represent a continuum of prostate cancer risk, and no single PSA value is sensitive and specific enough to predict the presence of cancer.[6] Abnormal PSA cutoffs have been defined from 2.5 µg/L to 4 µg/L, and much debate surrounds this topic. Men who present with an elevated PSA (ie, > 2.5 µg/L) should be tested again. If the value remains high, then prostate biopsy should be considered. An elevated PSA level in older men with benign prostatic hypertrophy is not unexpected, and in these patients observation of the PSA value over time may prove valuable to assess the need for biopsy.

A useful adjunct in men with elevated PSA and benign prostatic hypertrophy is the percentage of serum PSA that is free rather than bound.[7] PSA produced by prostate can-

cer binds more avidly with serum proteins (alpha-1 chymotrypsin and alpha-2 macroglobulin), resulting in a lower percentage of free PSA. In men with an elevated PSA (ie, 4.1–10.0 µg/L), the percentage of free PSA provides an indication of whether the elevation is due to benign prostatic hypertrophy or to cancer: the lower the percent free PSA, the more likely an elevated total PSA represents cancer and not benign prostatic hypertrophy. The sensitivity of a free PSA less than 15% to detect prostate cancer is about 85%, and its use as a screening tool is under study.

Much attention has also been given to other PSA indices, namely, the PSA density (the PSA level divided by the prostate volume), the PSA velocity (the rate of increase in the PSA level over time), and the PSA doubling time. While these nuanced PSA measures are useful to predict disease severity and behavior, they are not routinely used in screening.

BIOPSY IS INDICATED IF EITHER TEST IS ABNORMAL

In the past, imaging of the prostate with transrectal ultrasonography was used as a screening tool to detect prostate cancer. Further research showed that only 15% to 20% of hypoechoic lesions detected on ultrasonography contained cancer.[8] Because of its low sensitivity and specificity, primary ultrasonographic screening (ie, transrectal ultrasonography alone) is not acceptable for screening or for diagnosis. Its main role is in guiding prostate biopsy.

Biopsy of the prostate with transrectal ultrasonographic guidance is indicated if either the DRE or the PSA level is abnormal. The standard of care is to use an 18-gauge biopsy needle-gun to obtain two to three tissue samples from each of six regions of the prostate, focusing on the outer peripheral zone, specifically the right and left bases, the mid-gland, and the apex.

Pathologic analysis of each tissue core takes into consideration the presence or absence of cancer, the Gleason score, and the percentage of the tissue sample volume that is occupied by cancer.

The Gleason grading system is based on the histologic appearance and reflects the degree of differentiation and aggressiveness of the cancer. The two most prominent tumor grades present are added to give a final Gleason score. For instance, a Gleason grade of 4+3=7 indicates a tumor with predominant Gleason grade 4 disease with a lesser amount of grade 3 disease. The number of positive core samples and the volume of cancer provide information on the severity of the cancer.

If the PSA is high but biopsy is negative

Prostate biopsy misses up to 30% of small cancers. Many of these are clinically insignificant, but about 20% of those missed cancers can be high-risk and thus merit identification. There should be a low threshold for repeating biopsy 1 year later in men who have a persistently high PSA or a rising PSA.

High-grade prostatic intraepithelial neoplasia is a common finding on biopsy. The incidence of de novo prostate cancer at 5 years in men with this finding is 22% to 26%.[9] Patients with multifocal high-grade prostatic intraepithelial neoplasia should be monitored with PSA testing and DRE every 6 to 12 months and should be considered for repeat "saturation" biopsy (ie, obtaining as many as 36 core samples).

IF CANCER IS FOUND, HOW RISKY IS IT?

Patients with a new diagnosis of prostate cancer must decide on a treatment plan. This decision is highly individualized, based on the patient's personal preferences, lifestyle, performance status (ie, his general well-being), disease severity, continence status, and sexual function.

When counseling patients about their disease and the treatment options, we consider three main factors:

- The severity of disease on biopsy
- The patient's current state of health and performance status
- The patient's understanding of and willingness to accept the adverse effects of the various treatments.

Pathologic features, the PSA level, and clinical stage determined by DRE are used to predict the severity of disease. Most data on the efficacy of treatments for prostate cancer are based on the incidence of biochemical re-

Percent free PSA is under study; a free PSA < 15% may mean that an elevated PSA is due to cancer, not benign prostatic hypertrophy

TABLE 2

Prostate cancer risk assessment tools

Risk before biopsy[a]
Prostate Cancer Prevention Trial nomogram[6]

Risk of recurrence after radical prostatectomy[b]
Stephenson nomogram[43]

Risk of recurrence after interstitial brachytherapy[b]
Potters nomogram[44]

Risk of recurrence after intensity-modulated radiotherapy[b]
Zelefsky nomogram[45]

Risk of death from cancer after radical prostatectomy
Stephenson nomogram[17]

Functional outcome prediction
Eastham nomogram[19]

[a] http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp
[b] http://www.mskcc.org/mskcc/html/10088.cfm

currence, ie, a rise in PSA level after primary therapy. The AUA and the D'Amico risk criteria use biopsy pathology, clinical stage, and the pretreatment PSA level to predict the likelihood of biochemical recurrence (TABLE 1).[10,11]

To rule out high-risk disease before starting a program of surveillance, repeat biopsy is advisable, but optional

DISCUSSING TREATMENT OPTIONS WITH THE PATIENT

Risk stratification helps guide discussions with patients about which treatment will likely afford the most benefit. When counseling patients about the severity of their disease, it is helpful to use a nomogram to show the likelihood of cure with the different treatment options (TABLE 2).[6,12–16]

Important to the consideration of treatment options are the patient's baseline performance status and life expectancy. Use of the Charlson Comorbidity Index and life expectancy nomograms can help make these assessments less subjective (TABLE 3).[17–20]

In our practice, we usually do not recommend treatment in men with low-risk or intermediate-risk prostate cancer who have a life expectancy of less than 10 years, as most of them will likely die of a cause other than prostate cancer. For patients with poor baseline performance status, surveillance or radiation therapy may be preferable to surgery. In younger patients, surgery may confer a more durable benefit.

Treatment options for prostate cancer (FIGURE 1) include active surveillance, radical prostatectomy, interstitial prostatic brachytherapy, external beam radiotherapy, cryotherapy, and, if the patient is enrolled in a research protocol, high-intensity focused ultrasound (HIFU). Level 1 data show that radical prostatectomy and external beam radiotherapy confer longer overall survival and cancer-specific survival compared with no treatment.[21,22] However, no such data exist to prove the superior efficacy of prostatectomy vs brachytherapy vs radiotherapy, for several reasons:

- No prospective, randomized clinical trials have directly compared these treatments
- Prostate cancer progresses slowly
- Definitions of treatment failure used in various studies have been inconsistent
- Clinical studies have been subject to selection bias.

ACTIVE SURVEILLANCE IS ACCEPTABLE FOR LOW-RISK PROSTATE CANCER

Active surveillance is an acceptable option for patients with low-risk prostate cancer (ie, if the Gleason score is ≤ 6, the tumor stage is T1c or T2a, and the PSA level is ≤ 10 µg/L). To rule out high-risk disease before starting a program of surveillance, repeat biopsy is advisable, although optional.

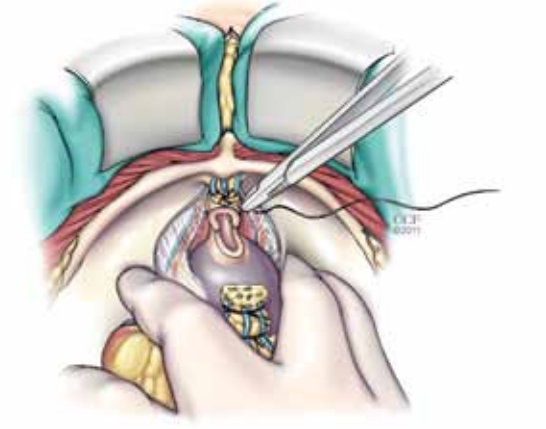
Active surveillance consists of PSA testing and DRE every 6 to 12 months, followed by repeat biopsy if significant changes are noted in either test. Some centers advocate biopsy with transrectal ultrasonographic guidance every year regardless of the PSA or DRE findings.

Whether a change in the PSA level is significant is subjective, but a recent phase 2 study in 453 patients[23] on a program of active surveillance used a PSA doubling time of less than 3 years as a criterion for repeat biopsy. Thirty-eight percent of the men had to undergo radiation therapy or surgery within 10 years, and 5 patients (1%) died of prostate cancer. The authors concluded that active surveillance did not put these patients at undue risk, and that this approach prevented

Treatment options for prostate cancer

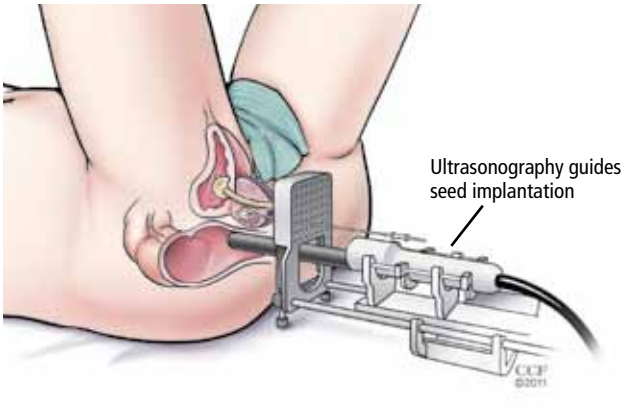
Options include active surveillance, radical prostatectomy, interstitial brachytherapy, external beam radiotherapy, cryotherapy, and, if part of a research protocol, high-intensity focused ultrasound and focal ablation (heat energy). All carry some risk of permanent incontinence and impotence. Level 1 data show that prostatectomy and radiation confer longer overall survival and cancer-specific survival vs no treatment, but no such data exist to prove the superiority of one treatment over another.

RADICAL PROSTATECTOMY



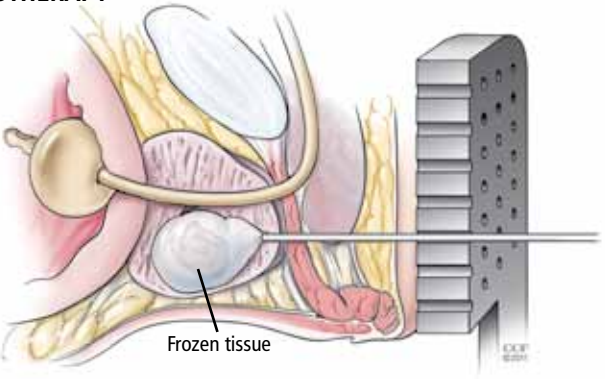
- For patients at any risk level
- Standard and minimally invasive laparoscopic options
- Requires hospital stay of 1–3 days, and Foley catheterization for 10–14 days
- Up to 70% of patients have incontinence in the first 3 months after surgery, but 82% to 94% regain continence at 12 months

INTERSTITIAL BRACHYTHERAPY



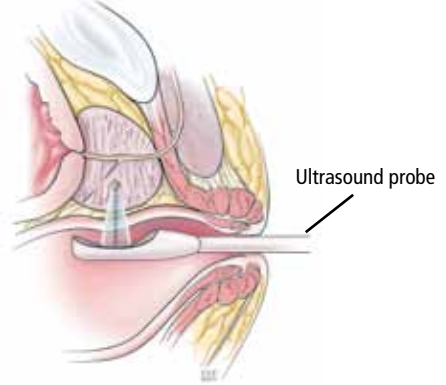
- For low-risk disease with low risk of extracapsular involvement
- High-dose radioactive "seeds" implanted under ultrasonographic guidance
- Single outpatient procedure
- Lower rate of incontinence, lower cost compared with surgery

CRYOTHERAPY



- Cryoprobe placed transperineally under ultrasonographic guidance; freeze-thaw cycles cause tissue damage and necrosis
- More study needed on long-term efficacy, acute complication rates, and late adverse effects

HIGH-INTENSITY FOCUSED ULTRASOUND



- Not yet approved in the United States, but available in Canada and Europe
- Transducer inserted rectally generates high-intensity beam that heats target prostatic tissue to a high temperature; no direct tissue penetration
- Low-cost, minimally invasive outpatient procedure
- No long-term efficacy data yet

CCF
Medical Illustrator: Joseph Pangrace ©2011

FIGURE 1

TABLE 3

Tools for evaluating performance status and life expectancy in prostate cancer

Performance status

Charlson Cormobidity Index[11,40]
http://www.biomedcentral.com/1471-2407/4/94/additional/

ECOG performance status[41]
http://ecog.dfci.harvard.edu/general/perf_stat.html

Life expectancy

Walz nomogram[10]

overtreatment of clinically insignificant prostate cancer.[23]

The risks of surveillance include the chance that cancer could progress to an incurable state during the surveillance period, greater anxiety for the patient, and, if prostatectomy becomes necessary, greater technical difficulty due to scarring from repeat biopsies. The benefit is postponement or complete avoidance of the adverse effects of treatment.

Debate continues over the potential dangers of deferred treatment of prostate cancer, but in certain patients it is an acceptable option. Patient education, accurate disease assessment, and compliance with monitoring are critical considerations.

We typically do not recommend treatment in men with low-risk or intermediate-risk prostate cancer whose life expectancy is < 10 years

RADICAL PROSTATECTOMY: SEVERAL OPTIONS, EQUIVALENT EFFICACY

Radical prostatectomy is widely used for treating prostate cancer of any risk level. The operation entails removing the prostate and seminal vesicles, as well as the pelvic lymph nodes in patients with intermediate or high-risk cancer.

This procedure was increasingly used in the 1990s with the introduction of PSA screening and nerve-sparing surgical techniques that preserve continence and erectile function.

Radical prostatectomy can be done via a standard open approach or a minimally invasive laparoscopic approach with or without robotic assistance. Open surgery, laparoscopic surgery, and robotic prostatectomy offer equivalent rates of oncologic efficacy, continence, and potency.[24] The more experienced the surgeon, the better the outcome is likely to be.

The average biochemical recurrence rate at 5 years after radical prostatectomy is approximately 6% for patients with low-risk cancer, 23% for those with intermediate-risk cancer, and 45% for those with high-risk cancer.[25] The rate of death from prostate cancer at 10 years is about 1% for patients with low-risk cancer, 4% for those with intermediate-risk cancer, and 8% for those with high-risk cancer.[12]

Secondary therapy

Pathologic staging of the surgical specimen after radical prostatectomy yields information that can be beneficial in terms of initiating early secondary therapy.

Patients with node-positive disease should immediately undergo androgen deprivation treatment.[26]

Evidence of positive surgical margins, seminal vesicle invasion, bladder neck invasion, and extracapsular extension also increase the risk of recurrence. This additional risk can be ascertained via the use of a postoperative nomogram. Patients at high risk of recurrence should be considered for early adjuvant external beam radiotherapy to the surgical field 3 to 6 months after surgery.

Advantages and disadvantages of radical prostatectomy

Advantages of radical prostatectomy include the ability to accurately stage the cancer with the surgical specimen and the ability to remove the pelvic lymph nodes in patients at intermediate and high risk. Another advantage is that postoperative surveillance is straightforward: PSA should become undetectable after surgery, and a measurable increase in PSA represents disease recurrence.

Disadvantages include:

- The risk of surgical complications (reported in 3% to 17% of cases)[24]
- An average hospital stay of 1 to 3 days (and a typical 3 to 6 weeks before returning to work)
- The need for a Foley catheter for 10 to 14 days
- The risk of incontinence and impotence, which are very distressing to patients.

Postoperative incontinence is typically defined as the need for any type of protective pad for leakage. Up to 70% of patients have incontinence in the first 3 months after surgery, but 82% to 94% of patients regain continence by 12 months.[24] A small percentage of patients (3% to 5%) have significant permanent incontinence.

Counseling about postoperative erectile dysfunction

All patients should be counseled about the risk of a postoperative decrease in erectile function, especially those with pre-existing erectile dysfunction. Potency is defined as the ability to have an erection suitable for intercourse (with or without phosphodiesterase type 5 inhibitors) more than 50% of the time. In men with bilateral nerve-sparing open prostatectomy, potency rates at 12 months have been reported between 63% and 81%.[13]

Data on potency rates vary widely because of differences in how potency was defined, selection bias, and the multifactorial nature of erectile dysfunction. Also, because single-institution, single-surgeon reports and advertisements tend to underestimate rates of impotence after radical prostatectomy by any approach, many patients have false expectations.

INTERSTITIAL BRACHYTHERAPY FOR LOW-RISK CANCERS

Interstitial brachytherapy delivers a localized, high dose (125 to 145 Gy) of radiation to the prostate, with minimal radiation dosing to the bladder, rectum, or other adjacent organs and tissues. "Seeds" or small pellets containing a radioisotope (iodine 125 or palladium 103) are stereotactically implanted through the perineum into the prostate under ultrasonographic guidance. Computerized mapping done before or during surgery helps determine the optimal placement of the seeds, the object being to cover at least 90% of the prostate with 100% of the radiation dose.

In permanent brachytherapy, the implants give off radiation at a low dose rate over weeks to months and are left in place permanently. In temporary brachytherapy, seeds are implanted to deliver a low or high dose rate for a specified period, and then they are removed.

"Implant quality," ie, delivery of more than 90% of the radiation dose, is a major predictor of success and can depend on both the available instrumentation and the skill of the operator.

Caveats about brachytherapy

The evidence in support of combining androgen deprivation therapy and interstitial brachytherapy is poor, and there is some evidence of increased rates of irritative voiding symptoms,[27] so this is generally not recommended.

Interstitial brachytherapy as monotherapy has usually been reserved for patients with low-risk cancer with a low likelihood of extracapsular disease extension or pelvic lymph node involvement. No randomized controlled clinical trial has compared brachytherapy with radical prostatectomy or external beam radiotherapy. One large long-term study reported an 8-year biochemical recurrence rate of 18% in patients with low-risk cancer and 30% in patients with intermediate-risk cancer.[28] The long-term efficacy of brachytherapy for intermediate- and high-risk prostate cancer is still under investigation.

After radical prostatectomy, PSA should decline to undetectable levels

Advantages and disadvantages of interstitial brachytherapy

Advantages. Interstitial brachytherapy is done as a single outpatient procedure. It can deliver a targeted high dose of radiation. And it is associated with a lower rate of posttreatment incontinence than radical prostatectomy, and a lower cost.

Disadvantages. There are limited data to support long-term cancer control in intermediate- and high-risk disease. Short-term adverse effects include dysuria, hematuria, urinary urgency, and urinary frequency in up to 80% of patients.[29] Voiding symptoms typically peak 1 to 3 months after the procedure and subside after 8 to 12 months. Erectile dysfunction has been reported in 30% to 35% of men at 5 years after the procedure. Other possible adverse effects include urethral stricture, incontinence, recurrent hematuria, rectal bleeding, proctitis, and the development of bladder cancer and other secondary cancers.

EXTERNAL BEAM RADIOTHERAPY

In external beam radiotherapy, radiation is delivered to the prostate and surrounding tissues via an external energy source. Electrons, protons, or neutrons are used, and although each has theoretical advantages over the others, all appear to have similar clinical efficacy.

As with brachytherapy, the object—and the challenge—is to deliver an effective dose of radiation to the tumor while sparing adjacent organs. Intensity-modulated delivery is a radiotherapy technique that delivers more of the radiation dose where we want it to go—and less where we don't want it to go. For prostate cancer, the target dose with intensity-modulated delivery is typically 75 to 85 Gy, in doses of 2 to 2.25 Gy for 30 to 36 days.

Androgen deprivation therapy before or after external beam radiotherapy augments the effects of the radiotherapy, particularly in patients with high-risk disease.[30]

The oncologic efficacy of intensity-modulated radiotherapy in patients at low and intermediate risk appears commensurate with that of radical prostatectomy. In one study,[31] in low-risk cases, biochemical disease-free survival rates were 85% for radiotherapy vs 93% for prostatectomy; in intermediate-risk cases, 82% for radiotherapy and 87% for prostatectomy; and in high-risk cases, 62% for combined androgen deprivation and radiotherapy vs 38% for prostatectomy.[31]

No randomized controlled trial has compared brachytherapy with radical prostatectomy or external beam radiotherapy

Advantages and disadvantages of external beam radiotherapy

Advantages. External beam radiotherapy is noninvasive. It can treat the prostate as well as areas outside the prostate in patients with intermediate- and high-risk disease, and it is proven effective for high-risk cancer when used in combination with androgen deprivation.

Disadvantages. On the other hand, radiotherapy requires a series of daily treatments, which can be inconvenient and burdensome to the patient. Its adverse effects are similar to those of brachytherapy, and it is expensive. Long-term adverse effects include irritative voiding symptoms (frequency, urgency, nocturia), hemorrhagic cystitis, bowel symptoms (pain with defecation, tenesmus, bleeding), and a significantly higher lifetime risk of a secondary malignancy, particularly of the bladder and rectum.[32]

External beam radiotherapy also induces tissue changes in the pelvis that make salvage surgery more difficult. Patients in whom radiotherapy is ineffective as monotherapy and who require salvage prostatectomy typically have poor outcomes in terms of disease control, continence, and potency.

COMBINED RADIATION THERAPY: BETTER, OR OVERTREATMENT?

Many patients are offered a combination of external beam radiotherapy and interstitial brachytherapy. The rationale is that the combination can boost the dose of radiation to the prostate and at the same time treat cancer that has extended beyond the prostate or to the pelvic lymph nodes.

The radiation dose in the combined approach is 45 to 50 Gy (vs 70 to 80 Gy in monotherapy), thereby minimizing toxicity.

This combination has not been shown to improve overall survival or cancer-specific survival compared with either therapy alone, and it likely constitutes overtreatment.[33] Adverse effects of combination therapy include erectile dysfunction, rectal and bladder toxicity, and secondary malignancy.

A serious complication associated more often with the combination of external beam radiotherapy and brachytherapy than other treatments is rectoprostatic fistula, a condition that requires complex reconstructive surgery and often requires permanent urinary and fecal diversion.[34]

CRYOTHERAPY: MORE STUDY NEEDED

Refinements in cryoablative therapy to destroy prostate tissue have improved the safety and efficacy of this procedure significantly over the past decade. The AUA consensus guidelines recognize cryotherapy as a viable primary cancer monotherapy, but it is most commonly used as a salvage therapy after failure of radiation therapy.

The procedure involves ultrasonographically guided stereotactic placement of cryoprobes into the prostate via a transperineal approach. Argon is pumped through the probes

under pressure to initiate ice formation, and repeated freeze-thaw cycles cause tissue damage and necrosis.

Rates of biochemical recurrence at 5 years in patients at low, intermediate, and high risk have been reported at 16%, 27%, and 25%, respectively.[35] The presence of viable cancer on biopsy specimens after primary cryoablation has been reported at 15%, compared with 25% after definitive radiation therapy.[35]

Advantages and disadvantages of cryotherapy

Cryotherapy can destroy cancer tissue in a minimally invasive way. It has no long-term delayed adverse effects, and it is a low-cost and convenient outpatient procedure.

On the other hand, we lack long-term data on its oncologic efficacy, acute complications, and late adverse effects. Acute complications occur in up to 16% of patients and include acute urinary retention requiring prolonged catheterization, hematuria, urethral sloughing, perineal pain, and incontinence.[36] Potential late effects include rectoprostatic fistula (< 1%), incontinence (< 5%), persistent hematuria, and chronic pelvic pain.[36]

Cryoablation therapy appears to have a more significant negative impact on sexual function than does brachytherapy.[37]

More study of the complications and efficacy of cryotherapy is needed before the procedure can be adopted as routine primary monotherapy.

HIGH-INTENSITY FOCUSED ULTRASOUND: NOT YET FDA-APPROVED

High-intensity focused ultrasound (HIFU) is not yet approved by the US Food and Drug Administration (other than in an approved research protocol) but is used in Canada and in certain countries of Europe and Asia. It involves the insertion of a transducer into the rectum that generates a high-intensity, focused beam that heats target tissue in the prostate to a high temperature. This temperature triggers a heat-shock response that leads to cellular apoptosis and tissue necrosis. The procedure can be done with or without magnetic resonance imaging (MRI) guidance.

Biochemical recurrence rates at 2 years after the procedure have been reported between 23% and 50%, but long-term efficacy data are lacking.[38,39]

Advantages and disadvantages of ultrasound

HIFU is a minimally invasive, low-cost, outpatient procedure that offers trackless delivery of energy to the prostate: ie, there is no direct mechanical penetration into the tissue.

Complications include rectal-wall injury, fistula, acute urinary retention, hematuria, and urethral stricture.

FOCAL ABLATION: GETTING ATTENTION, BUT STILL UNDER DEVELOPMENT

Focal ablation for prostate cancer has been receiving much attention. This treatment uses heat energy to destroy tumor cells, guided by high-resolution endorectal-coil MRI. The procedure is in the developmental stages and is available only in research protocols.

The procedure has several major hurdles to overcome before becoming acceptable for clinical practice. First, prostate cancer is multifocal, and microscopic tumor foci are likely present that are invisible even to MRI, so ablation of only part of the prostate leaves the rest of the gland at risk of continued or de novo tumor growth.

Second, a wide range of sensitivities and specificities have been reported for endorectal coil MRI for detecting prostate cancer: its sensitivity has ranged from 27% to 100%, and its specificity has ranged from 32% to 99%.[40]

More study of the newer treatments for prostate cancer is needed

ANDROGEN DEPRIVATION, AN ADJUVANT THERAPY

Androgen deprivation therapy (medical castration) is not effective as a monotherapy for prostate cancer. A large population-based study in men with localized prostate cancer showed no higher rate of overall survival at 10 years with primary androgen deprivation therapy than with conservative management.[41]

Androgen deprivation is achieved with a leutinizing hormone-releasing hormone agonist such as leuprolide (Lupron) or goserelin (Zoladex), or an antiandrogen drug such as flutamide or bicalutamide (Casodex), or a

combination of each.

Adverse effects include hot flashes, gynecomastia, decreased libido, erectile dysfunction, weight gain, and hyperlipidemia. Long-term effects include osteoporosis and a significantly higher risk of cardiac events, new-onset type 2 diabetes mellitus, and stroke.

Currently, the only recognized role for androgen deprivation therapy in prostate cancer is as an adjunct to external beam radiotherapy or as a treatment of metastatic prostate cancer.

Orchiectomy

The other way to eliminate testicular production of testosterone is surgical castration. Bilateral orchiectomy has advantages over medical androgen deprivation therapy in that it costs less, is highly reliable, and is done as a single treatment on an outpatient basis. Disadvantages include surgery-related morbidity and the irreversible nature of the procedure. The adverse effects are similar to those of androgen deprivation therapy.

POSTTREATMENT MONITORING

The management of patients with recurrent prostate cancer can be complex, and these patients should be referred to a medical or urologic oncologist.[42,43]

Often, a rise in PSA after primary therapy represents a regrowth of cancer; 30% to 60% of patients with a recurrence have metastasis, and nearly 20% will die from the disease. The average time from documentation of biochemical recurrence to metastatic progression is 8 years. The average time from metastatic progression to death is 5 years.[44,45]

After radical prostatectomy, the PSA level should be checked every 6 to 12 months for the first 2 years, then annually until the patient's life expectancy is only 10 years even without prostate cancer. PSA should reach undetectable levels within 4 to 6 weeks after surgery. Biochemical recurrence after surgery is defined as a PSA level of 0.2 µg/L or higher in two serial studies.

After radiation therapy or cryotherapy, monitoring is complicated by the presence of viable prostatic epithelium that continues to produce PSA. During the first 1 to 2 years after radiation therapy, a PSA "bounce" phenomenon is observed whereby PSA levels rise or fluctuate significantly. This bounce should not be mistaken for a recurrence of cancer. The most widely accepted definition of biochemical recurrence is based on the American Society for Therapeutic Radiology and Oncology "Phoenix" criteria, defined as the nadir PSA level plus 2.0 µg/L.[46]

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