

CME ARTICLE

Treatment Options for Prostate Cancer: Part 2— Early and Late Stage and Hormone Refractory Disease

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This activity is designed for primary care physicians, medical oncologists, and urologists.

GOAL

To help primary care physicians, medical oncologists, and urologists care for the patient with prostate cancer and understand the current treatment options for prostate cancer.

OBJECTIVES

1. Review the prevalence of prostate cancer in the United States and understand the diagnostic and demographic factors contributing to its epidemiology.
2. Understand how to grade and stage prostate cancer.
3. Gain a historical perspective of prostate cancer therapies.
4. Recognize the current state of the art management techniques for all types of prostate cancer, including clinically localized disease and advanced prostate cancer.

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In Part 1 of this CME article, we reviewed the prevalence of prostate cancer in the United States and the current staging and grading systems. In this second part, we review treatment options for clinically localized disease and advanced prostate cancer. Clinically localized cancer (stages T1 and T2) may be treated by radical prostatectomy surgery (RP), either external beam radiation therapy (XRT) or seed radiation (brachytherapy), cryotherapy, or watchful waiting. Locally advanced prostate cancer (stages T3, T4) has been primarily treated with XRT, with or without the addition of hormonal therapy (HT), and metastatic disease (stages Tany N1 or M1) is treated primarily with HT. HT may include orchiectomy (surgical removal of the testicles) or the administration of medications for lowering production or blocking the effect of testosterone, which is considered the "fertilizer" for prostate cancer growth.

... MANAGEMENT OF CLINICALLY LOCALIZED DISEASE ...

Watchful Waiting

In general, watchful waiting should be limited to men with low-grade and early-stage cancers who have a limited life expectancy. Specifically, watchful waiting is appropriate for patients with well-differentiated tumors who have a life expectancy of less than 10 years.¹ It may also be suitable for patients with moderately-differentiated, low-volume prostate cancer who also have a life expectancy of less than 10 years, although the appropriateness of watchful waiting for these patients is less clear.

In one large, pooled data series,² 20% of patients with well-differentiated, 42% with moderately-differentiated, and 75% with poorly-differentiated prostate cancer developed metastatic disease within 10 years of diagnosis. Mortality rates at 10 years were 13%, 13%, and 66%, respectively. In a smaller, population-based series,³ researchers found similar metastatic rates but an increased mortality rate of 35% for moderately-differentiated cancers. The authors concluded that 4 to 8 years of potential loss

of life occurred when moderately- and poorly-differentiated tumors went untreated.

A recent study of the Surveillance, Epidemiology, and End Results (SEER) data confirmed that watchful waiting is not appropriate for men with poorly differentiated prostate cancer.⁴ Even at 5 years post-diagnosis, watchful waiting provided inferior disease-free and overall survival rates compared with RP and XRT for men with high-grade prostate cancer.⁴ It is important to note that the conclusions derived from watchful waiting studies of older men cannot be applied to younger, healthier men or to those with more advanced or aggressive disease.¹

As previously noted in Part 1 of this article (Figure 7), 10% to 15% of patients treated at Walter Reed Army Medical Center receive watchful waiting as primary management. The average age of these men is 74.5 years, 79% have Gleason sum 2 to 4 disease, and 74% have clinical stage T1 tumors (J.W.M., unpublished data, 1997).

Radiation Therapy

Clinicians have used radiation therapy for many years as a potential cure for localized prostate cancer and as a palliative treatment for painful skeletal metastases and local urinary obstruction.⁵ XRT has been the preferred route of delivery for the vast majority of patients, and technological advances are improving XRT delivery. Conventional XRT, delivered by a linear accelerator in a typical 6500-7000 cGy dose 5 days a week for 6 to 7 weeks,⁶ directs radioactive energy to the approximate location of the prostate gland. Recently, computerized tomography (CT) scan-based computer control and planning (three-dimensional conformal radiation therapy) have allowed delivery of a higher dose of energy with less radiation to the surrounding tissues, including the rectum and bladder.⁷ While some hospitals still provide conventional XRT, many larger hospitals and academic centers have switched to conformal radiation with hopes of reducing side effects and improving long-term efficacy.

Over the past 5 years, radioactive seed implantation (called interstitial brachytherapy) has become increasingly popular as an alternative, curative approach for localized disease.⁸ This is due to the development of transrectal ultrasound of the prostate (TRUS), which allows clinicians to accurately place radioactive seeds throughout the prostate gland via a transperineal approach under ultrasound guidance.

Efficacy. The ability of XRT or brachytherapy to cure localized prostate cancer depends on many factors—including stage, grade, prostate specific antigen (PSA) level, and other prognostic factors—and there is

some debate about the merits of radical prostatectomy versus XRT and/or brachytherapy for the average man with localized disease. The results of one study, in particular, raised a serious concern that XRT may have activated cancers into a faster growing phenotype in 80% of patients.⁹ In this study, only 20% of XRT patients had PSA levels <1.0 ng/ml, which indicate complete remission, at an average follow-up of 9 years after therapy. The remaining 80% of patients had steeply rising PSA levels, which suggested that the radiation-recurrent disease had an aggressive tumor doubling-time. Another separate, randomized trial, albeit small (approximately 120 patients) and performed in one hospital, showed that radical prostatectomy improved survival in patients with localized disease when compared with radiation therapy.¹⁰

Radiation oncologists claim that these studies suffer from selection bias, and they cite large case series that show XRT is as effective as surgery for the carefully selected man with clinically, organ-confined disease.¹¹⁻¹³ A large SEER database review of radical prostatectomy, XRT, and conservative treatment⁴ showed that 10-year overall survival was 83% (95% confidence interval [CI], 81% to 84%) and 76% (CI, 74% to 76%), for surgery and radiotherapy, respectively. While this finding was statistically significant, it was not adjusted for stage, grade, or PSA levels. The cause-specific 10-year survival for surgery versus radiotherapy was 94% versus 90%, 87% versus 76%, and 67% versus 53% for grades 1, 2, and 3, respectively. In this review, more than 24,000 men (average age, 65.8 years) received radical prostatectomy; 15,720 men (average age, 70.4 years) received radiotherapy. Since this review was based on an intent-to-treat analysis of more than 59,000 patients stratified by grade and clinical stage of cancer, any bias that would have been introduced by patients who did not have radical prostatectomy due to positive nodal metastases at the time of surgery was eliminated. In prior comparison studies without this type of analysis, surgery had an advantage because many radiotherapy patients were treated without lymph node staging and had occult nodal disease.

Unfortunately, such data stratified by pretreatment PSA level and/or Gleason grade are not yet available. Clinical research centers are starting to report nonrandomized series of surgery and radiation patients stratified by grade, stage, and, perhaps most importantly, pretreatment PSA. In one study,¹⁴ there was no significant difference in the disease-free survival rates between surgery and radiation patients after 5 years of follow-up when these 3 stratification prognostic factors were considered. In another study

of more than 1600 patients stratified by pretreatment PSA value, biopsy Gleason grade, and clinical T-stage,¹⁵ there was no difference in the 2-year disease-free survival rate when surgery and radiation patients were compared. We still do not know if there will be any meaningful differences in outcome between surgery and XRT when this stratification is used with longer follow-up periods.

Further, since TRUS-guided seed placement is a relatively recent advance, the cure rate beyond 5 to 7 years is unknown. The only available brachytherapy outcome data come from the centers that developed the technology, and we do not yet know how efficacious the treatment is in general practice.

Recurrence After Treatment. A rising post-treatment PSA level is generally the first indicator of recurrence.¹⁶ The American Society for Therapeutic Radiology and Oncology (ASTRO) has defined recurrence as 3 consecutive rises in the PSA level after the post-treatment nadir (the lowest PSA value the patient achieves after completion of radiation) was achieved.¹⁷ Although the date of recurrence is defined as the date halfway between the nadir date and the date of the first PSA rise, the PSA nadir itself is now recognized as an important prognostic factor.¹⁸ A recent study of combination XRT and brachytherapy suggests that a good long-term outcome of radiation therapy can be predicted when the nadir PSA decreases to ≤ 0.5 ng/mL.¹⁹

Combination Radiation and Hormone Therapy

Temporary, reversible hormone therapy given for a number of months before the start of radiation is a recent advance known as neoadjuvant hormonal therapy (NHT).²⁰ Hormone treatment may also start simultaneously with radiation and continue after radiation; this therapy is called adjuvant hormonal therapy (adjuvant HT).^{21,22}

A number of studies published in the mid-1990s support NHT and adjuvant HT for treating locally advanced prostate cancer. The Radiation Therapy Oncology Group (RTOG) compared radiation alone with radiation plus 4 months of NHT with a luteinizing hormone releasing hormone (LH-RH) agonist and the antiandrogen flutamide in more than 400 men with locally advanced (T3, T4) prostate cancer.²⁰ Progression-free survival was 36% in the radiation plus NHT arm and 15% in radiation-only patients ($P < 0.001$). Another RTOG study²¹ evaluated 945 men with locally advanced prostate cancer (T3/4 and/or N1-3) and compared radiation plus adjuvant HT using an LH-RH agonist with radiation and hormone therapy given only at relapse. The patients who received

radiation plus adjuvant HT had a significantly reduced rate of local and distance recurrence at 5 years. The local and distant failure rates were 16% and 17%, respectively, in the patients who received adjuvant hormonal therapy compared to 29% and 30% in the patients who received only radiation. Further, even at the relatively short follow-up of 5 years, men with high-grade disease (Gleason 8 to 10) had improved survival. Specifically, 35% of the adjuvant hormonally treated patients died compared to 44% of the radiation-only patients ($P = 0.03$). Finally, a randomized European study of over 400 men with locally advanced prostate cancer that compared radiation alone with radiation plus adjuvant LH-RH agonist therapy for 3 years²² showed that patients who received adjuvant HT had a significantly greater disease-free and overall survival rate after 5 years. The 5-year disease-free and overall survival was 85% and 79%, respectively, for the patients who received adjuvant hormones versus 48% and 62% in the patients who received only radiation ($P = 0.001$).

Unanswered questions about the specific role of NHT and adjuvant HT remain. These include the optimal duration of hormone therapy, whether LH-RH agonists are most beneficial alone or in combination with antiandrogens, and whether NHT and/or adjuvant HT is beneficial in earlier stage (T1, T2) patients who choose XRT or brachytherapy.

Radical Prostatectomy

Radical prostatectomy is the complete removal of the prostate gland and seminal vesicles through an anterior retropubic or perineal approach. If the cancer is confined within the prostatic capsule, this operation theoretically cures the patient. As with radiation treatment, the pretreatment clinical T-stage category, cancer grade, PSA value, and other prognostic factors such as race determine the likelihood of organ confined/curable disease. To determine if a patient is a candidate for surgery, urologists use nomograms that combine clinical stage, Gleason grade, and PSA level to predict the probability of organ confined cancer and other parameters such as seminal vesicle or pelvic lymph node spread.²³ These nomograms provide general guidelines for predicting the success of surgical treatment but are not always accurate. From 40% to 50% of men who undergo radical prostatectomy do not have organ-confined prostate cancer and have substantial risk of recurrence, and those with pathologic extension beyond the capsule who undergo the procedure have an approximate 30% to 40% disease recurrence and progression rate.²⁴ Residual tumor is

indicated by a rise in PSA level; after successful radical prostatectomy, PSA should fall to undetectable levels.

When the cancer is confined, however, radical prostatectomy success rates approach 90% at 15 years.²⁵ Two recent studies document excellent 10-year outcomes for contemporary-era radical prostatectomy patients. The SEER review¹⁴ discussed in the prior section on radiation therapy found 10-year disease-specific survival that ranges from 67% to 94%, depending on cancer grade. Another multicenter survey²⁶ involving more than 2600 men who had radical prostatectomy demonstrated 94%, 80%, and 77% 10-year survival rates for men with well-differentiated, moderate, and poor grade cancers, respectively.

Although long-term, disease-specific survival rates for radical prostatectomy patients stratified by multiple prognostic factors are not available, equations to predict disease recurrence have been used. Partin and associates²⁷ initially developed a mathematical model using the pathological stage Gleason grade, and pretreatment PSA level to predict post-surgery recurrence. This model was based only on patients with clinical stage B2 (T2) disease from one referral hospital who were treated by one surgeon. Our Department of Defense Center for Prostate Disease Research (CPDR) group created and validated a model that appears useful, even in the immediate postoperative period, for predicting the risk of recurrence after radical prostatectomy for all stages of disease.²⁸ This equation uses 4 prognostic factors—PSA, Gleason sum, pathologic stage, and race—to derive the relative risk of recurrence. In our study of 378 patients from one hospital and 91 patients from another hospital used for validation, the high-risk group defined by the equation and representing 119 out of the 378 patients had a 55.5% chance of recurrence at 3 years postoperatively and an 84.8% chance at 5 years.²⁸ These risk equations are likely to become useful in everyday practice as communication technology advances. The CPDR equation is available on the local-area computer network for the Urology Service at Walter Reed Army Medical Center and is used in daily practice to counsel patients.

Potential Disadvantages. Potential disadvantages of radical prostatectomy include a relatively high incidence of impotence despite nerve-sparing (anatomic) techniques and possible urinary incontinence. With the anatomic technique, preservation of potency depends on tumor stage and patient age; patients with lower-stage cancers and younger patients have less risk of impotence.²⁹ In one large series of men undergoing anatomic radical prostatectomy,²⁹ 40% to 65%

who were sexually potent before surgery retained potency adequate enough for vaginal penetration. In this study, only 6% of men required use of pads for urinary incontinence, but an additional, unknown proportion of men had occasional urinary dribbling.

Dramatically different results were obtained in a national survey of Medicare patients, in which more than 60% of men reported having no erections after surgery and an additional 30% had erections insufficient for intercourse.³⁰ In this study, more than 30% of men reported the need for pads or clamps and 63% of all patients reported some degree of incontinence.

Another recent, controversial article reporting the results of 94 radical prostatectomies performed by multiple surgeons³¹ reported that sexual function was preserved in just 22% of men, a lower proportion than previously reported. Men who underwent a unilateral nerve-sparing procedure (ie, a procedure in which the surgeon performing the radical prostatectomy preserves one of the two periprostatic nerve bundles that control erection) did not have a significantly higher potency rate than those who did not undergo the nerve-sparing procedure. Critics contend, however, that results of this procedure are much better with experienced surgeons.

Technical advances appear to be reducing the incidence of urinary incontinence. Urologic surgeons have made improvements in the operation, particularly at the apex of the prostate, that appear to increase the chance for full urinary control.

Therapeutic modalities are available to help counter these potential complications, which can significantly affect quality of life. For impotence, medical therapy, penile injections, intraurethral suppositories, vacuum tumescence devices, and penile prosthesis can be offered. For urinary incontinence, periurethral injection of collagen, artificial urinary sphincter, and nonsurgical therapy can be offered.³³

Cryotherapy

More than 20 years ago, the technique of freezing the prostate gland was developed. This technique fell out of favor due to complications, but then regained popularity due to TRUS and improved freezing equipment.³⁴ Since 1991, practitioners have offered cryotherapy using a computer-controlled device to deliver liquid nitrogen at -190°C via specialized cryoprobes and TRUS to monitor prostate freezing at more than 150 US sites.

The use of cryotherapy is diminishing once again,³⁵ however, due to a significant concern that the procedure produces a high incidence of impotence.³⁶

Clinical trials are still underway to assess long-term efficacy, and the Health Care Financing Administration (HCFA) has specifically recommended a multicenter clinical trial to examine the efficacy of prostate cryotherapy. Cryotherapy is more widely accepted for older patients and those having a local recurrence after primary radiation therapy, although even in these patients, the procedure is associated with an incontinence rate of approximately 40%.

... MANAGEMENT OF ADVANCED PROSTATE CANCER ...

The term "advanced prostate cancer" is synonymous with "incurable" for most patients and clinicians.³⁷ Traditionally, the definition of advanced disease referred only to disease stage and included only symptomatic stage D2 disease with bony or soft tissue metastases. However, patients with any extraprostatic disease have an increased risk of dying from prostatic cancer compared with patients with localized disease.³⁸ Since the majority of these patients are otherwise healthy with no competing morbidity, stages D1 (regional lymph node involvement), T4 (tumor is fixed or invades adjacent structures other than the seminal vesicles), and T3 (tumor has extended through the prostatic capsule) have been included in the revised definition of advanced prostate cancer since the late 1990s for most men. Patients with a persistent PSA elevation after prostatectomy, radiation therapy, or cryotherapy, as well as those with high PSA levels without evidence of metastases, should also be included in the definition of advanced disease in most cases.

Androgen ablation therapy has been the mainstay of treatment for stage D2 metastatic prostate cancer for more than 50 years.³⁹ Specific treatment options include orchiectomy, LH-RH agents, and combination hormonal therapy (CHT), which adds an oral nonsteroidal antiandrogen to the testicular ablation. Currently, estrogens are rarely used because they may cause cardiovascular toxicity.⁴⁰

The median survival of patients with metastatic prostate cancer treated with androgen ablation is approximately 3 years, although there is wide variation depending on disease severity.⁴¹ Many more patients have very early metastatic disease with fewer metastases than ever before, and survival of 5 years to 15 years is common.

LH-RH Agonists

Although current hormone therapies for advanced prostate cancer do not offer the prospect of a cure, all symptomatic patients with stage D disease should

receive hormone therapy to improve quality of life and relieve symptoms.⁴² LH-RH agonists are preferred for androgen ablation. In their depot formulations, LH-RH analogues are easily administered, produce castrate serum levels of testosterone in a short time, and are not associated with increased cardiovascular risk.⁴³ Open multicenter studies in patients with stage D2 prostate cancer have demonstrated that treatment with depot formulations of the LH-RH agonists is associated with an objective tumor response (no progression); normalization of, or at least a 50% decrease in, PSA; and improvement or stabilization of both local disease status and overall performance in nearly all patients.^{44,45} There are currently two Food and Drug Administration (FDA)-approved LH-RH agonists: Leuprolide acetate (Lupron) and goserelin acetate (Zoladex). They are available in 1-, 3-, or 4-month depot formulations.

Orchiectomy

Orchiectomy is the surgical removal of the testicles, the main source of testosterone, through a scrotal incision. It is a one-time minor operation that is well tolerated under local or regional anesthesia. The outcome of orchiectomy is equivalent to that of LH-RH agents, but most patients prefer depot LH-RH over orchiectomy⁴⁶ because of the psychological implications of the loss of the testicles.

An additional factor that limits the use of orchiectomy is that unlike medical hormonal therapy, the procedure is not reversible. While effective intermittent hormonal therapy (see later) is yet unproven, patients have expressed the desire for this approach, should it be proven efficacious, or should hormonal therapy side effects become troublesome.

Combined Hormone Therapy

The testicles produce 90% to 95% of circulating androgens, and the adrenal glands produce 5% to 10%. The concept behind CHT or total androgen blockade (TAB) is blockage of the potential effect of adrenal androgens on prostate cancer growth.⁴⁷ Because low levels of dihydroxytestosterone produced by the adrenals may continue to stimulate androgen-sensitive cells, it is hypothesized that the use of an antiandrogen in addition to an LH-RH agonist or after bilateral orchiectomy may offer an advantage over monotherapy.

Since initial reports of CHT appeared in the early 1980s, the clinical value of adding an antiandrogen to testicular androgen deprivation has been debated. There is some evidence that CHT results in improved response and survival rates, especially in men with sig-

nificantly advanced metastatic disease.⁴⁷⁻⁵⁰ The NCI-0036, EORTC-30853, Canadian Anandron, and Multinational Nilutamide Studies all showed a survival benefit of 7 months to 15 months with CHT.⁵¹ Further, this recent meta-analysis of randomized CHT studies⁵¹ showed a clear benefit of CHT (7.3- to 7.6-month survival benefit). However, the recently reported intergroup 0105-NCI trial of orchiectomy with flutamide versus orchiectomy with placebo showed no survival benefit from the addition of an antiandrogen to orchiectomy.⁵² A second meta-analysis (published 2 years before the previously mentioned meta-analysis)⁵³ found minimal benefit from CHT (ie, 2- to 3-month survival advantage). Most of the patients in all of these studies were men with significantly advanced metastatic disease.

The benefit of CHT in earlier advanced disease (minimal disease) may be less controversial. In men with minimal metastatic disease, both the NCI-0036 and EORTC-30853 studies showed that CHT is associated with a more pronounced survival advantage,^{48, 49} although the minimal disease subgroup in the NCI-0105 study did not show a survival benefit for CHT with orchiectomy.⁵²

Currently, there are three FDA-approved antiandrogen oral medications for use as CHT therapy: flutamide (Eulexin), bicalutamide (Casodex), and nilutamide (Nilandron).

Early Versus Delayed Hormone Therapy

Although most clinicians have traditionally used hormone therapy at the time of advanced prostate cancer diagnosis for palliation of such symptoms as bone pain, most believed that this therapy did not affect survival. However, in 1997, the Medical Research Council (MRC) in Great Britain published a landmark paper⁵⁴ suggesting that early hormone therapy prolongs survival when compared with delayed treatment for advanced, nonmetastatic (M0) and traditional D2 (M1) cancers. This study included 938 patients with M0, MX, or M1 prostate cancer; 469 received hormone therapy immediately and 465 received hormones only when they became symptomatic. Of these deferred patients, 181 (39%) were treated for bone pain progression and a full 159 (34%) were treated for local progression. Approximately 55% of men in both treatment arms had nonmetastatic (M0) disease, about 20% were staged as MX because they did not have a bone scan but had other evidence of metastatic disease, and approximately 25% had traditional metastatic disease. Patients who received delayed HT had higher rates of pathologic fracture, cord compression, ureteral obstruction, extraskelatal metastases, and

need for transurethral resection of the prostate—all very clinically relevant events. Sixty-seven percent of patients who died had prostate cancer as the primary cause of death. (Interestingly, this compares with only 41% of men who died of prostate cancer in the decades-old Veterans Administration Cooperative Urological Research Group (VACURG) studies,⁵⁵ clearly illustrating the increasing impact of prostate cancer on the modern man, who is living longer. Cancer-specific survival was superior ($P = 0.02$) in the immediate HT arm for all patients, and there was a more pronounced benefit for immediate HT in the subset of patients with M0 disease ($P < 0.001$). This may be analogous to current patients with PSA recurrence after prior local therapy. Otherwise, this study provides fairly compelling evidence in favor of early hormone therapy for patients with true metastatic disease.

A separate reanalysis of the VACURG data also suggests a survival advantage for younger patients with stage D disease and high-grade (Gleason score 7 to 10) tumors who undergo androgen ablation therapy at the time of diagnosis.⁵⁶ Despite this encouraging news, clinicians are concerned about possible long-term effects of hormone use—including osteoporosis, hot flashes, sexual dysfunction, and loss of muscle mass. One study has suggested that osteoporosis results from long-term androgen withdrawal.⁵⁷ Our group and others are studying this possibility in a prospective manner using age-matched controls, and early results suggest that hormone therapy may not significantly alter bone mineral density in these patients.⁵⁸ Hot flashes do occur in most patients on hormone therapy, and when they are troubling to the patient, low-dose megestrol acetate is an effective treatment.⁵⁹

Intermittent Hormone Therapy

A recent area of interest is the concept of intermittent hormone therapy (IHT).⁶⁰ IHT seems a reasonable progression in this current era of reversible androgen deprivation with LH-RH agents and antiandrogens, early use of hormonal therapy, and the manifestation of potential side effects with long-term hormone therapy. Animal and in vitro cell line studies suggest that IHT is beneficial, although human studies with sufficient safety and efficacy data are not yet available.⁶¹ To date, IHT studies have generally used CHT; therefore, we do not know if LH-RH alone will provide equal efficacy. In many cases, enthusiasm for IHT has been patient-driven, and it is incumbent upon physicians to inform patients that the long-term efficacy of IHT is unknown.

Hormone Refractory Disease

A decline in PSA level indicates a response to hormone therapy, and the vast majority of patients who had bone pain at the start of hormone therapy will have dramatic, rapid, and complete pain relief. Patients who do not respond to initial hormonal therapy should have the level of serum testosterone measured to ensure that it is indeed at castrate level.⁴¹ Those patients who experience a subsequent increase in PSA level or return of symptoms, including bone pain, are considered to have hormone refractory prostate cancer (HRPC), or what some clinicians also call stage D3 disease. This is an indicator of tumor progression and is the stage of prostate cancer most commonly associated with painful bone metastases.

Treatment of HRPC includes withdrawal of antiandrogens for those patients on combination hormone therapy⁶² and administration of a different antiandrogen or other second-line hormone therapy, cytotoxic chemotherapy, and/or radiopharmaceutical agents to treat symptomatic bone pain. Unfortunately, it is very difficult to measure the biological response to these treatment regimens in HRPC patients. The majority of patients have disease confined to bone, a site not readily amenable to objective response assessment. Bone scan response assessment is complicated by characteristically slow improvements in true responders and an inherent difficulty in distinguishing improvement from progression, as both may appear as an increase in signal intensity. Similarly, evaluation of soft-tissue disease, which may affect only a minority of HRPC patients, is difficult because it is not possible to determine if PSA declines reflect a true reduction in tumor bulk or a direct effect of treatment on the production of this serum marker. There have been attempts to quantify disease-related symptomatology using symptom score tools and quality-of-life scales, but these instruments are still being validated. Further, while overall survival and progression-free survival remain important endpoints in randomized, controlled studies, there is no accepted standard therapy for HRPC. To date, no drug has demonstrated a survival advantage over other acceptable therapies because objective responses occur infrequently and are difficult to define given the heterogeneity of diseased tissues.

For these reasons, disease palliation and pain control are now accepted efficacy endpoints and are recognized by the FDA for prostate cancer treatments. Mitoxantrone, a chemotherapeutic agent similar to adriamycin, was recently FDA-approved for HRPC in combination with prednisone or hydrocortisone and is effective in palliation of bone pain, although a

survival benefit has not been demonstrated.^{63,64} Current trials are also assessing the effect of other chemotherapies that may have some effect on bone pain in responsive patients. They include: ketoconazole, estramustine, vinblastine, and suramin.⁴¹ The combination of etoposide and estramustine is becoming more commonly used and is a somewhat effective but fairly toxic regimen.⁶⁵

To date, the FDA has approved two radioactive agents for treating painful bone metastases: strontium-89 and samarium-153-lexidronam.

Strontium-89. Strontium-89 is a beta-radiation-emitting medication that is injected intravenously and follows the same biologic pathway as calcium.⁶⁶ It is absorbed by the body's skeletal system, with greater absorption by the cancerous areas. While this absorption may kill some cancerous cells, it primarily works to reduce bone pain, with pain alleviation beginning 10 to 20 days after injection. Pain reduction lasts from 4 months to 15 months (average: approximately 6 months). If the pain returns, the patient can receive another injection as often as every 3 months. The agent's mechanism of action is unclear.

Multiple clinical trials involving more than 500 patients show that the majority of men experience relief after strontium-89 therapy. Ten percent to 50% had complete or dramatic response, with bone pain completely or virtually eliminated.⁶⁶ Depending on the study, a partial or complete response was reported by 20% to 97% of patients.⁶⁶ On average, 80% of the men reported a partial or complete response.

Samarium-153-lexidronam. Samarium-153-lexidronam has also undergone large-scale controlled testing in the United States and Europe.⁶⁷ Like strontium-89, this agent alleviated pain in the majority of patients, providing an onset of action of within 1 week in many patients.⁶⁷ The duration of pain control is variable, but a single samarium-153-lexidronam injection was typically effective for 3 to 4 months. Both strontium-89 and samarium-153-lexidronam may affect bone marrow function principally in the form of decreased platelet counts, but this side effect is relatively mild and reversible.

New Frontiers

The diagnostic, staging, treatment, and prognostic tools of prostate cancer will continue to evolve rapidly over the next decade for several reasons. First, the molecular genetic revolution will have a great impact on prostate cancer. Second, increased research funding is now being devoted to prostate cancer, and this will likely lead to bedside advances in the next few years. Third, with an aging and better informed popu-

lation, men and their families will demand better prostate cancer care.

Advances in Molecular Biology

A large number of genetic alterations have been observed in primary and metastatic tumors, and some are beginning to be used as prognostic biomarkers.⁶⁸ For example, our group has shown that overexpression of the p53 tumor suppressor protein and the bcl-2 oncogene protein are predictors of recurrence after radical prostatectomy⁶⁹ and can even be combined with traditional prognosis markers in risk equations.⁷⁰ Further, as computer-based medicine advances, this risk equation modelling will undoubtedly find its way into daily patient care.

Perhaps the biggest molecular discovery is the identification of an area on chromosome 1 that harbors a gene or genes that predispose men to familial prostate cancer.⁷¹ This gene, although not yet discovered, has been termed the HPC-1, or "hereditary prostate cancer one" gene. Continuing work in this area will lead to genetic testing for prostate cancer susceptibility and, hopefully, new treatment strategies. Although clinical trials are just starting, in vitro and animal model testing of gene therapy for prostate cancer with agents targeted to these biomarkers (such as p53) appear to hold promise.

... CONCLUSION ...

Prostate cancer is a very common disease that affects older American men. As our population ages and remains healthy longer, prostate cancer treatment will grow in importance. With the advent of PSA screening and increased public awareness, these cancers are being routinely discovered at an earlier clinical stage, and more men are candidates for curative local therapies. Radical prostatectomy, external beam radiotherapy, and seed radiation (brachytherapy) are the accepted treatments for clinically-localized disease. Neoadjuvant and/or adjuvant hormonal therapy is commonly used in conjunction with surgery or radiation. The intermediate-term efficacy, particularly with radiation, is very promising.

The specific treatment, however, depends on stage, tumor grade, pretreatment PSA level, and the desires of the patient and his family. Success of these treatments largely depends on stage, grade, PSA, and perhaps other prognostic factors. The "best" treatment for any individual is determined after careful counseling about the therapies and their side effects, including impotence and incontinence.

Patients with recurrent cancer after prior local treatment and men who present initially with metastatic disease are considered to have advanced prostate cancer. Hormone therapy is the primary treatment for these patients, and parenteral LH-RH agonist therapy, with antiandrogen oral agents, is the most common form of therapy. New studies suggest that early hormone therapy does prolong life for advanced prostate cancer patients.

Hormone-refractory prostate cancer remains a significant challenge, as no treatment has been proven to prolong survival. A new paradigm of improving quality of life and providing pain control with new chemotherapies and radiopharmaceutical agents has emerged.

More research funding is needed for prostate cancer, and it is hoped that molecular genetic advances will lead to better treatment for our patients.

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CME QUESTIONS: TEST #049808

Long Island Jewish Medical Center and Johns Hopkins University School of Medicine are accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. Long Island Jewish Medical Center, the Long Island Campus for the Albert Einstein College of Medicine, designates this continuing medical education activity for 1.0 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association. This CME activity was planned and produced in accordance with the ACCME Essentials and Standards for Commercial Support.

Instructions

After reading the article, "Treatment Options for Prostate Cancer: Part II," select the best answer to each of the following questions. In order to receive 1 CME credit, at least 7 of the 10 answers must be correct. Estimated time for this activity is 1 hour. CME credits are distributed on a yearly basis.

1. Which statement describes a candidate suitable for watchful waiting (no treatment) for prostate cancer?

- a) stage T3, Gleason 7, prostate specific antigen (PSA) value 20 ng/ml, age 50
- b) stage T1, Gleason 4, PSA value 4.5 ng/ml, age 78
- c) stage Tany N1M1 with painful bony metastases
- d) stage T2, Gleason 6, PSA value 8 ng/ml, age 57

2. What statement is true about radiation treatment for prostate cancer?

- a) conformal computer directed external-beam radiation is improving the delivery of higher radiation dose to the prostate gland
- b) radiation seeds or brachytherapy has increased in popularity over the last 5 years
- c) cancer recurrence after radiation is most commonly defined by a rising PSA value
- d) all of the above

3. Multiple studies in the mid-1990s have suggested that the combination of hormonal therapy and external beam radiation is more effective than radiation alone for men with locally advanced prostate cancer.

- a) true
- b) false

4. Which is the true statement regarding radical prostatectomy?

- a) involves open enucleation of a portion of the prostate involved with cancer
- b) is considered curative if all cancer is removed
- c) invariably results in impotence
- d) may be performed transurethrally

5. Success of radiation or surgery depends on which prognostic factors?

- a) the level of pretreatment PSA
- b) the grade of the cancer
- c) the clinical stage of the cancer
- d) all the above

6. Prostate cryotherapy is an accepted standard treatment in localized prostate cancer with equal efficacy to radical prostatectomy or radiation.

- a) true
- b) false

7. Which is the false statement regarding hormonal therapy in advanced prostate cancer?

- a) the efficacy of orchiectomy is equivalent to LH-RH agents
- b) orchiectomy is very popular because men like the permanent nature of this hormonal treatment
- c) LH-RH agents are available in 1-, 3-, and 4-month depot formulations
- d) intermittent hormonal therapy is being tested in clinical trials

(CME QUESTIONS CONTINUED ON FOLLOWING PAGE)

CME TEST FORM		<small>(PLEASE PRINT CLEARLY)</small>	
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(continued from previous page)

8. Which is the true statement regarding hormonal therapy in prostate cancer?

- a) flutamide, bicalutamide, and nilutamide are FDA-approved antiandrogen medications
- b) combined hormonal therapy with an antiandrogen may provide a survival benefit in advanced prostate cancer
- c) a recent large trial confirmed a survival benefit to early use of hormonal therapy at the time of diagnosis of advanced prostate cancer
- d) all the above are correct

9. Which is the true statement regarding hormone-refractory prostate cancer?

- a) mitoxantrone is an FDA-approved chemotherapy
- b) multiple agents have a confirmed ability to extend survival
- c) few options are available for bone pain
- d) strontium-89 is a hormonal medication to shrink bony tumors

10. Human Prostate Cancer-1 (HPC-1) is a genetic abnormality that appears to contribute to familial prostate cancer.

- a) true
- b) false