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HOW TO USE THIS MONOGRAPH

This is a CME activity that contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. ProstateCancerUpdate.net includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in red underlined text.

Prostate Cancer Update: A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Prostate cancer is one of the most rapidly evolving fields in urology. Published results from clinical trials lead to the emergence of new surgical and radiation therapy techniques and therapeutic agents, along with changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing urologist and radiation oncologist must be well-informed of these advances. To bridge the gap between research and patient care, *Prostate Cancer Update* utilizes one-on-one discussions with leading urologic oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists urologists and radiation oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Critically evaluate the clinical implications of emerging clinical trial data in prostate cancer treatment.
- Inform patients about the specific risks and benefits of local and systemic therapies.
- Provide individualized counseling to patients regarding the choice and timing of endocrine therapy.
- Offer patients information regarding their prognosis with and without various therapeutic options.

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 5

Upon completion of this activity, participants should be able to:

- Discuss current trends in the use of radiation therapy for the management of prostate cancer.
- Review the role of brachytherapy and external beam radiation therapy combined with hormone therapy in the management of prostate cancer.
- Counsel patients who experience PSA recurrence after radical prostatectomy about potential treatment options, including radiation therapy and hormonal therapy.
- Counsel patients about the important outcome measures for radical prostatectomy, including the potential side effects.
- Discuss the role of intermittent androgen suppression with patients who are being counseled about hormonal therapy options.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 3 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only credits that he/she actually spent on the activity.

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As a provider accredited by the ACCME, it is the policy of Research To Practice to require the disclosure of any significant financial interest or any other relationship the sponsor or faculty members have with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

Michael J Zelefsky, MD	No financial interests or affiliations to disclose.
Joseph A Smith Jr, MD	No financial interests or affiliations to disclose.
Michael K Brawer, MD	No financial interests or affiliations to disclose.

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
bicalutamide	Casodex®	AstraZeneca Pharmaceuticals LP
flutamide	Drogenil®, Euflex®, Eulexin®	Schering-Plough Corporation
goserelin acetate implant	Zoladex®	AstraZeneca Pharmaceuticals LP
leuprolide	Lupron Depot®	TAP Pharmaceuticals
sildenafil citrate	Viagra®	Pfizer Inc [generics by many others]
triptorelin	Trelstar™ Depot	Debio Recherche

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Editor's Note

Acceptable Options

Our continuing medical education group focuses on the clinical implications of emerging research results. One of the comments we frequently receive from listeners to this audio series is that they find it very reassuring to learn that prostate cancer research leaders often struggle with the same controversial decisions as community-based physicians.

When credible research evidence fails to clearly define a single standard of care, judgment and perspective represent the next best options. As an organization committed to education, it is essential for us to uncover these areas of uncertainty and understand the various perspectives on these difficult issues. In performing needs assessments for our educational endeavors, we regularly turn not only to research leaders, but also to community-based physicians. This spring, we convened two working groups to learn more about the most common challenging decisions in the management of prostate cancer.

In April, we gathered 15 research leaders for a "think tank" during the American Urological Association meeting in Chicago. Several weeks later, we met in New York with 23 community-based urologists and radiation and medical oncologists. Drs Mitchell Benson, Adam Dicker, Leonard Gomella and Michael Zelefsky joined us for a daylong, case-based brainstorming session. This edition of *Prostate Cancer Update* includes several audio excerpts from the New York working group. These two events were interesting and thought-provoking, and what was most striking was the diversity of perspectives that exist on many key management questions, including the following:

1. What is appropriate counseling for men presenting with localized disease?

We showed the participants in these meetings video clips from interviews with more than a dozen men recounting their experience when first diagnosed with prostate cancer. The messages these patients received were clearly very different depending on the specialty of their treating physician. Many of the physicians at the two meetings commented on the depth of anxiety and fear that the initial diagnosis of prostate cancer carried. One urologist who has been in practice for more than 30 years said, "Seeing these videos is a real eye-opener for me." Others commented that patients often put on a "brave front" for their doctor and want to be "good patients." The education message is that when considering the "favorable" prognosis of men with T1c Gleason 3+3 tumors, experienced physicians also keep in mind that many or most patients at initial diagnosis are terrified that they will succumb to the disease.

2. Should adjuvant endocrine therapy be offered to men presenting with localized high-risk disease?

An interesting dichotomy exists for the treatment of patients with high-risk tumors. Those treated with radiation therapy routinely receive adjuvant androgen deprivation, but those treated with radical prostatectomy generally are not offered immediate endocrine therapy. In this program, Dr Zelefsky notes that this difference in the utilization of adjuvant endocrine therapy is a direct result of the available research evidence. The radiation oncology community has more thoroughly investigated the use of adjuvant endocrine therapy than the urology researchers.

On the audio excerpt of the New York meeting found in this issue, Dr Benson labels the conservatism towards postprostatectomy adjuvant androgen deprivation as intellectual inconsistency. "I'm aggressive with these patients. If we say to a man that we are going to do a radical prostatectomy because we want to give him the best statistical chance of being disease-free for as long as possible, and there is an adverse pathology report, I believe it's unconscionable not to give the patient information about additional therapy." Other physicians are just as convinced that careful PSA monitoring and early treatment for biochemical recurrence are preferable. Dr Joseph Smith defends that approach in this program.

3. At what point should therapy be recommended for postsurgical or postradiation PSA relapse, and which therapy is optimal?

Researchers agree that there is a lack of definitive research evidence to define a treatment standard in this very common clinical scenario. In this audio program, Dr Michael Brawer presents a man with a PSA relapse whom he chose to treat with intermittent androgen suppression; however, the risks and benefits for this type of treatment strategy compared to observation, continuous androgen suppression or antiandrogen monotherapy are unknown. In both the New York working group and the Chicago "think tank" meetings, there was remarkable heterogeneity in the approach to androgen deprivation and in the utilization of postprostatectomy radiation therapy or postradiation salvage radical prostatectomy for PSA relapse.

The other perspectives that must be considered in making these difficult decisions are those of the patients. We previously reported on a "town meeting" of more than 300 prostate cancer survivors and their partners. Electronic keypad polling was utilized to solicit input about clinical scenarios that were very similar to the ones discussed by our physicians' groups, and there was as much heterogeneity among the prostate cancer survivors as the physicians.

At the epicenter of this maelstrom of viewpoints is the contemporary provider of CME with the imprimatur to not only update physicians on new research data but also to serve as a conduit between the key constituents. This is a very different role from the "see one, do one, teach one" approach we had in training house staff to do procedures. And while working group meetings like the one in this audio program help us understand the varied perspectives of the key constituents, they also increase our awareness that the evidence base for the management of patients with prostate cancer is far from ideal.

—Neil Love, MD

Participants at the research leader "Think Tank"

Chicago, Illinois — April 24-25, 2003

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Participants at the Prostate Cancer Update Working Group Meeting

New York, New York — May 14, 2003

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Edited Comments by Dr Zelefsky

Trends in the use of radiation therapy for prostate cancer

Tremendous evolution has occurred in the use of radiation therapy in the treatment of prostate cancer, specifically with respect to the different types of radiation and adjuvant therapies. In the Patterns of Care Survey conducted by the American College of Radiology, we observed a dramatic shift over the last five to 10 years.

One trend is the increase in frequency of hormonal therapy in combination with radiation therapy. This is based on a number of randomized trials demonstrating a benefit for that combination, and these trials have also evaluated different ways of sequencing hormonal therapy (i.e., prior and concurrent, or after completion of radiation therapy). These trials demonstrated that hormonal therapy with standard radiation therapy seems to provide better outcomes (i.e., reduced PSA progression and reduced likelihood of distant metastases).

We also have new, more sophisticated, precise and targeted radiation therapy modalities; therefore, we're seeing fewer side effects. The emergence of 3-dimensional (3D) conformal radiotherapy and intensity-modulated radiation therapy (IMRT) has had a major impact on the treatment of prostate cancer. We can deliver unprecedented doses of radiation, and many studies have shown these higher doses translate into better results in terms of PSA control and other outcome parameters.

These new radiation therapy techniques are more exact, and we're seeing less morbidity and toxicity. This clearly has had an impact on the quality of life of these patients. In the last 10 years, interest and enthusiasm for brachytherapy has emerged, and we are seeing fewer side effects and better control rates with this technology.

SPIRIT trial: Brachytherapy versus radical prostatectomy in early-stage disease

We have no randomized trial data to help patients in the selection of optimal local therapy. The only way to know whether one therapy is better is to conduct a randomized trial comparing various treatments for patients with localized prostate cancer, although many believe it will be impossible to conduct such a trial in the United States.

I give a great deal of credit to the principal investigators of the SPIRIT trial. Great efforts have been made to optimize quality assurance within the trial so that optimal seed implant techniques and prostatectomy surgical techniques are used.

I support the trial, and we participate at our institution. While it is an important study, and I hope it accrues well, it will be difficult to accrue patients in certain parts of the country. For instance, it's not easy to enroll my patient population in such a trial. Many patients have preconceived notions about how they would like their prostate cancer treated, and they are reluctant to be randomized.

I've spoken with some of the principal investigators of the SPIRIT trial and have learned that accrual rates improve in settings in which patients are able to speak with a multidisciplinary team about the pros and cons of each of the therapies. When patients see that their own physicians have uncertainties about optimal therapy, they are more likely to consider participation.

SPIRIT Trial: Phase III Randomized Study of Radical Prostatectomy versus Brachytherapy in Patients with Stage II Prostate Cancer **Open Protocol**

Protocol ID: ACOSOG-Z0070
Projected accrual: 1,980 patients

Eligibility: T1c-T2a N0 M0, with no bilateral palpable disease, PSA ≤ 10 ng/mL, Gleason ≤ 6, prostate gland < 60 cc on TRUS or < 60 cc after neoadjuvant hormonal therapy

ARM 1: Radical prostatectomy
ARM 2: Brachytherapy with implanted iodine-125 or palladium Pd-103 seeds

Study Contacts:

American College of Surgeons Oncology Group
Paul Lange, MD, Protocol Chair
Tel: 206-543-3918

SOURCE: NCI Physician Data Query, October 2003.

Brachytherapy in combination with external beam radiation

The combination of external beam radiation therapy and brachytherapy is an excellent way to deliver a high dose of radiation to the prostate. Numerous studies demonstrate that higher doses of radiation translate into better results.

Not all patients, however, need this form of therapy. A patient with early-stage disease, a PSA less than 10 ng/mL, a Gleason score less than or equal to 6 and low volume disease could be effectively treated with external beam radiation therapy alone or brachytherapy alone. In patients with intermediate-risk disease and some aggressive features, or in patients with unfavorable-risk disease, higher doses are necessary.

Combining radiation therapy with hormonal therapy

At our institution, we have launched a Phase III trial randomizing patients with higher risk features to high-dose radiation therapy alone or lower doses of radiation therapy plus hormonal therapy. The question is: Will a high enough dose of radiation obviate the need for hormonal therapy in patients with more aggressive features?

All of the randomized trials demonstrating benefits from hormonal therapy in conjunction with external beam radiation therapy have used suboptimal radiation therapy doses. The questions are: In the setting of hormonal therapy, do we need these higher doses of radiation? If we use these higher doses of radiation, is hormonal therapy still necessary?

Among patients who have undergone biopsy years after treatment with radiation and hormonal therapy, we have seen an improved likelihood of disease eradication from the prostate. Hormonal therapy may have a radiosensitizing effect. In addition, randomized trials have shown a decrease in distant metastases among patients treated with hormonal therapy in combination with radiation. It may be argued that this simply represents a delay in the manifestation of distant metastases, or it could mean that some of these small tumor clones were prevented from disseminating. I believe that, especially in patients with high-risk disease, hormonal therapy may have both a local and a systemic effect.

Selection and timing of hormonal therapy

When prescribing hormonal therapy, we usually use an LHRH agonist and one month of an antiandrogen. Generally, we use the hormonal therapy prior to and in conjunction with the radiation therapy. For those patients with a Gleason score greater than or equal to 8 or those with T3 disease, we recommend at least six to 12 months, and more often two years, of adjuvant hormonal therapy based on the RTOG randomized trials.

Phase III clinical trials of adjuvant hormonal therapy in combination with radiation therapy for patients with prostate cancer

Protocol	Trial description	Schema
RTOG-9910, CTSU	Neoadjuvant MAB and XRT in patients with intermediate-risk prostate cancer	Arm 1: MAB x 8 w → (MAB + XRT) x 8 w Arm 2: MAB x 28 w → (MAB + XRT) x 8 w
EORTC-22991	XRT ± adjuvant bicalutamide and goserelin in patients with localized prostate cancer	Arm 1: XRT Arm 2: Bicalutamide days 1-30 + goserelin days 8 & 98 + XRT beginning day 8
EORTC-22961, EORTC-GU-22961	External XRT and six-month MAB ± long-term adjuvant LHRH analogue (triptorelin) for patients with locally advanced prostate cancer	Arm 1: XRT + 6 months MAB Arm 2: XRT+ 6 months MAB → (antiandrogen + LHRH analogue) x 2.5 y → LHRH analogue x 2.5 y
RTOG-P-0011, CTSU, RTOG-DEV-1037, CAN-NCIC-PR9	Adjuvant XRT with hormonal therapy versus XRT alone in patients with high-risk Stage II or III prostate cancer	Arm 1: XRT + goserelin or leuprolide q 1-4 months x 2 y + flutamide or bicalutamide daily x 1 month Arm 2: XRT Arm 3: goserelin or leuprolide q 1-4 months x 2 y + flutamide or bicalutamide daily x 1 month

MAB = maximum androgen blockade; XRT = radiation therapy

SOURCE: NCI Physician Data Query, October 2003.

PSA "bounce"

After radiation therapy, there is a "bounce" phenomenon. Over a period of two to three years, patients will have some natural fluctuations in their PSA level, which cause a great deal of anxiety. Patients need to be reassured about how their PSA will behave in the postradiation therapy period. If patients are prepared for the PSA fluctuations, they will certainly have less anxiety. Without hormonal therapy, it takes about 12 to 18 months for the PSA to gradually drop to its nadir. In some patients, the PSA continues to decrease for years after the completion of treatment. There may be occasional "bounces" here or there, which sometimes respond to antibiotic therapy or may gradually go down with time.

In a patient with a rise in PSA during the postradiation period, we recommend obtaining another PSA in about three to four months and follow it over a period of time to establish the PSA kinetics. If there are minor fluctuations in the PSA, we try to reassure the patient and do not initiate any particular therapy.

Personal research interests in radiation oncology

I have an interest in the role of intensity-modulated radiation therapy. We have been working for many years on dose escalations with these new conformal technologies and have demonstrated improved outcomes in terms of PSA relapse-free survival with these higher doses. These new technologies are now being used to reduce potential toxicities.

We are also looking at dose painting. This technique allows us to use imaging technologies such as MR spectroscopy and PET imaging to identify within the gland where tumor clones may be most abundant. We can then focus or intensify the radiation doses to those particular zones in the prostate. This may have a significant impact on further reducing toxicity. Dose painting allows us to target particular areas of the prostate with more intense doses while sparing the urethra and the rectum.

I also have a research interest in the utilization of new technologies in brachytherapy that further enhance the targeting of the seeds and reduce the toxicity. We've been working on intraoperative, computer-based technologies that provide feedback as to exactly where these seeds should be placed. This technique optimizes the placement of the seeds, helps reduce the dose to the urethra and ensures optimal coverage of the prescription dose to the prostate, resulting in a better quality implant.

We're also currently working on sophisticated modalities that give the operator feedback as to where the seeds are placed, so we can continuously modify the implant plan. Theoretically, before walking out of the operating room, you have the perfect implant. This is known as dynamic dosimetry. For the first time, the operator really has a handle on where the seeds are being dropped to ensure a very accurate implant.

Select publications

Brachytherapy in combination with external beam radiation

Chen CT et al. **Dosimetric analysis of urinary morbidity following prostate brachytherapy (125I vs. 103Pd) combined with external beam radiation therapy.** *Int J Cancer* 2001;96 (Suppl):83-8. **Abstract**

Ghaly M et al. **The effect of supplemental beam radiation on prostate brachytherapy-related morbidity: Morbidity outcomes from two prospective randomized multicenter trials.** *Int J Radiat Oncol Biol Phys* 2003;55(5):1288-93. **Abstract**

Kestin LL et al. **Pathologic evidence of dose-response and dose-volume relationships for prostate cancer treated with combined external beam radiotherapy and high-dose-rate brachytherapy.** *Int J Radiat Oncol Biol Phys* 2002;54(1):107-18. **Abstract**

Kovacs G, Galalae R. **Fractionated perineal high-dose-rate temporary brachytherapy combined with external beam radiation in the treatment of localized prostate cancer: Is lymph node sampling necessary?** *Cancer Radiother* 2003;7(2):100-6. **Abstract**

Lederman GS et al. **Retrospective stratification of a consecutive cohort of prostate cancer patients treated with a combined regimen of external-beam radiotherapy and brachytherapy.** *Int J Radiat Oncol Biol Phys* 2001;49(5):1297-303. **Abstract**

Merrick GS et al. **Does hormonal manipulation in conjunction with permanent interstitial brachytherapy, with or without supplemental external beam irradiation, improve the biochemical outcome for men with intermediate or high-risk prostate cancer?** *BJU Int* 2003;91(1):23-9. **Abstract**

Wang JZ, Li XA. **Evaluation of external beam radiotherapy and brachytherapy for localized prostate cancer using equivalent uniform dose.** *Med Phys* 2003;30(1):34-40. **Abstract**

Hormone therapy in combination with radiation therapy

Chen CT et al. **Does hormonal therapy influence sexual function in men receiving 3D conformal radiation therapy for prostate cancer?** *Int J Radiat Oncol Biol Phys* 2001;50(3):591-5. **Abstract**

Coblentz TR et al. **Multimodality radiotherapy and androgen ablation in the treatment of clinically localized prostate cancer: Early results in high risk patients.** *Prostate Cancer Prostatic Dis* 2002;5(3):219-25. **Abstract**

D'Amico AV. **Radiation and hormonal therapy for locally advanced and clinically localized prostate cancer.** *Urology* 2002;60(3 Suppl 1):32-7;discussion 37-8. **Abstract**

D'Amico AV et al. **Initial decline in hemoglobin during neoadjuvant hormonal therapy predicts for early prostate specific antigen failure following radiation and hormonal therapy for patients with intermediate and high-risk prostate cancer.** *Cancer* 2002;95(2):275-80. **Abstract**

Horwitz EM et al. **Subset analysis of RTOG 85-31 and 86-10 indicates an advantage for long-term vs. short-term adjuvant hormones for patients with locally advanced nonmetastatic prostate cancer treated with radiation therapy.** *Int J Radiat Oncol Biol Phys* 2001;49(4):947-56. **Abstract**

Karasawa K et al. **Rotational 3D-conformal radiation therapy (conformation therapy) combined with hormone therapy for the treatment of stage B2/C prostate cancer in Japanese men.** *Int J Radiat Oncol Biol Phys* 2003;56(1):208-12. **Abstract**

Lawton CA et al. **Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 85-31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavorable prognosis carcinoma of the prostate.** *Int J Radiat Oncol Biol Phys* 2001;49(4):937-46. **Abstract**

Lukka H. **Prostate cancer: Risk categories and role of hormones and radiotherapy.** *Can J Urol* 2002;9(Suppl 1):26-9. **Abstract**

Miller NL et al. **Impact of a novel neoadjuvant and adjuvant hormone-deprivation approach on quality of life, voiding function, and sexual function after prostate brachytherapy.** *Cancer* 2003;97(5):1203-10. **Abstract**

Parker CC et al. **Pre-treatment nomogram for biochemical control after neoadjuvant androgen deprivation and radical radiotherapy for clinically localised prostate cancer.** *Br J Cancer* 2002;86(5):686-91. **Abstract**

Pilepich MV et al. **Phase III Radiation Therapy Oncology Group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate.** *Int J Radiat Oncol Biol Phys* 2001;50(5):1243-52. **Abstract**

Roach M 3rd et al. **Race and survival of men treated for prostate cancer on Radiation Therapy Oncology Group phase III randomized trials.** *J Urol* 2003;169(1):245-50. **Abstract**

Roach M 3rd et al; Radiation Therapy Oncology Group 9413. **Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413.** *J Clin Oncol* 2003;21(10):1904-11. **Abstract**

Shipley WU et al. **Effect of a short course of neoadjuvant hormonal therapy on the response to subsequent androgen suppression in prostate cancer patients with relapse after radiotherapy: A secondary analysis of the randomized protocol RTOG 86-10.** *Int J Radiat Oncol Biol Phys* 2002;54(5):1302-10. **Abstract**

Zagars GK et al. **Addition of radiation therapy to androgen ablation improves outcome for subclinically node-positive prostate cancer.** *Urology* 2001;58(2):233-9. **Abstract**

Joseph A Smith Jr, MD

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Edited comments by Dr Smith

Assessing prognosis after radical prostatectomy

I review my patients' pathology reports, their preoperative PSA and other prognostic factors to come up with a rough estimate of their prognosis. I let them know whether their prognosis is good, poor or intermediate based upon their pathology. I may not be more specific than that, unless they request it. If they want to look at a nomogram together and come up with an exact figure, I'll do that with them as well.

Postprostatectomy adjuvant therapy with high-risk cancers

I believe in aggressive postoperative adjuvant therapy, but I don't believe very early treatment has been shown to be better than early treatment. In other words, regardless of the pathologic features and how poor the prognosis, I don't generally start treatment until there is evidence of PSA recurrence. If the patient's initial postprostatectomy PSA is undetectable, I may suggest a period of watchful waiting. I'll tell the patient that while their risk of PSA recurrence is very high, and that I may even be expecting it, that we may be able to withhold treatment until PSA recurrence is evident. I follow the same philosophy in the rare patient with positive nodes. I tell the patient that we can probably safely defer treatment until the PSA rise becomes evident.

Defining PSA recurrence

My definition of PSA recurrence varies. In the patient in whom I expect to see a PSA recurrence (i.e., the patient with positive nodes), I may consider any detectable PSA a sign of recurrence. Since I know it's going to happen, why wait until the PSA becomes 0.4 ng/mL? In a patient whose tumor had favorable histologic features, in whom I'm surprised to see a PSA recurrence, I may continue to follow a watchful waiting approach to see if he is one of the rare patients who will have a minimally detectable PSA without a subsequent rise.

PSA recurrence: Assessing the extent of the disease

To determine appropriate treatment for patients with PSA recurrence, it is important to assess whether the patient's disease is local, regional or systemic. If there's a significant possibility that the disease is only local, I'm more inclined to use postoperative radiation therapy. If I believe the disease is regional or systemic, I'm more inclined to use hormonal therapy from the start.

I consider a number of factors when attempting to determine the extent of the patient's disease recurrence. The recurrence is more likely to be systemic if the grade of the cancer was higher, the PSA recurrence occurred rapidly, the PSA never declined to an undetectable level or the PSA doubling time was rapid.

Selection of hormonal therapy for patients with PSA recurrence

The type of hormonal therapy selected varies from person to person, depending on their desires and ability to pay for the medication. If a man's sexual function has been preserved and it's important to him, then I'm more inclined to use antiandrogen monotherapy, such as bicalutamide, to try to preserve libido and sexual function. If a man's sexual function was not preserved or it's not an important parameter, then an LHRH analog could be used. Presumably, osteoporosis is also avoided with antiandrogen monotherapy; so there are some advantages. There are also some disadvantages, such as gynecomastia and breast tenderness, but I discuss the use of pretreatment breast irradiation because I believe it is effective. Ability to pay for these two hormonal therapies is also an important factor.

In some men with PSA recurrence, I use intermittent androgen suppression. I realize that its effectiveness is not proven, and ongoing studies are evaluating this approach. In terms of quality of life, intermittent androgen suppression has some advantages, especially when we're using an LHRH analog.

Use of intermittent androgen suppression for patients with PSA recurrence

In a patient with what appears to be a good-prognosis tumor who develops a very slow and late rise in his PSA, it would not be in his best interest to be on continuous androgen suppression for a decade or longer. I would likely treat that patient with hormonal therapy until his PSA was undetectable, which often is very quickly, perhaps within three months. If that were the case, I would continue hormonal therapy for at least another three months. Once I initiate hormonal therapy, I keep patients on it for six to nine months, then discontinue it and restart it when the PSA reaches some arbitrary value.

The point at which I restart therapy varies from person to person. Often, the patient is anxious to restart therapy. I tell them, "We'll restart therapy when we see a substantial change," and I don't necessarily define the substantial change. In other words, if their PSA is rising very slowly, I am more likely to keep them off therapy than if their PSA doubling time is rapid.

Most patients like the idea of intermittent therapy. When the PSA becomes detectable after radical prostatectomy, most men want treatment. Once they receive hormonal therapy and their PSA becomes undetectable, they feel very gratified and more reassured. Then, the idea of discontinuing hormonal therapy by going on intermittent therapy has some emotional appeal. They are more accepting of the fact that their PSA may rise and become detectable again. On the other hand, some patients who are feeling well and tolerating the hormonal therapy without difficulty don't want to rock the boat. In those men, I won't rock the boat either; I'll keep them on continuous therapy.

Phase III Randomized Study of Intermittent versus Continuous Androgen Suppression in Patients with Prostate-Specific Antigen Progression in the Clinical Absence of Distant Metastases after Prior Radiotherapy for Prostate Cancer

Open Protocol

Protocol IDs: CAN-NCIC-PR7, SWOG-JPR7, CAN-NCIC-JPR7
Projected accrual: 1,340 patients

Eligibility: Prior radiotherapy, either postradical prostatectomy or as primary management of prostate cancer, PSA rising and > 3 ng/mL, testosterone > 5 nmol/L, no evidence of metastatic disease

ARM 1: IAS (LHRH analog + antiandrogen) x 8 months. Monitor PSA q 2 months. If PSA falls to normal, discontinue IAS. Resume IAS x 8 months when PSA rises to 10 ng/mL.
ARM 2: Continuous (LHRH analog + antiandrogen) OR (bilateral orchiectomy + antiandrogen)

In Arm 1, IAS continues as long as PSA levels are controlled. At the time of disease progression, patients begin continuous hormonal treatment similar to Arm 2.

IAS = Intermittent androgen suppression

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SOURCE: NCI Physician Data Query, October 2003.

Clinical research on early hormonal therapy

Credit goes to the radiation oncologists who have been able to conduct a number of important trials in this area, such as the Bolla study and others, which have helped to define the role of hormonal therapy. The post-prostatectomy study published by Ed Messing evaluating early hormonal therapy in patients with node-positive disease and the Medical Research Council Study from Britain are also important trials. Those trials have put me into the early hormonal therapy camp. There are problems with all of these studies and none of them are definitive, but these and others are what lead me to utilize early hormonal therapy.

Mortality rates in landmark trials comparing immediate (diagnosis) versus deferred (progression) hormone treatment for advanced prostate cancer

Study (median follow-up)	Patient population	Protocol	Deaths from prostate cancer	
			With early hormonal therapy	Control
Medical Research Council Trial (Not reported)	Locally advanced or asymptomatic metastatic disease	Orchiectomy or LHRH analogue at progression vs at diagnosis	All patients: 203/469 (43%) M0 patients: 81/469 (17%)	All patients: 257/465 (55%) M0 patients: 119/465 (26%)
Bolla et al. (5.5 years)	T1-T2 Grade 3 T3-T4 all grades	Radiotherapy at diagnosis vs radiotherapy plus goserelin	12/207 (6%)	42/208 (20%)
Granfors et al. (9.3 years)	T1-4, pN0-3, M0	Radiotherapy at diagnosis vs radiotherapy plus orchiectomy	12/45 (27%)	20/46 (44%)
Messing et al. (7.1 years)	≤ T2, positive nodes, M0	Orchiectomy or goserelin at progression vs at diagnosis	3/47 (6%)	16/51 (31%)

DERIVED FROM:

Bolla M et al. **Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A Phase III randomised trial.** *Lancet* 2002;360:103-08. **Abstract**

Granfors T et al. **Combined orchiectomy and external radiotherapy versus radiotherapy alone for non-metastatic prostate cancer with or without pelvic lymph node involvement: A prospective randomized study.** *J Urol* 1998;159(6):2030–4. **Abstract**

Messing EM et al. **Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer.** *N Engl J Med* 1999;341:1781-8. **Abstract**

Prostate Cancer Working Party Investigators Group. **Immediate versus deferred treatment for advanced prostatic cancer: Initial results of the Medical Research Council Trial.** *Br J Urol* 1997;79(2):235-46. **Abstract**

Counseling men about radical prostatectomy

My role primarily is to advise patients about the pros and cons of surgery. I tell them whether or not they are surgical candidates, and I very clearly outline the side effects and what they can anticipate from surgery. We talk about the operation, specifically about the way we do it at Vanderbilt. In our hands, the procedure takes one and a half or two hours. Patients can expect to be in the hospital for two days and to wear a Foley catheter for a week to 10 days. Their risk of requiring a blood transfusion is one percent or less.

The exact words I use are, “Things can happen, and they can happen with any operation, but fortunately with this one we don’t usually have major perioperative complications.” Then, we focus on the most important outcome measures — tumor control, continence and potency. I outline the likelihood of being able to cure their cancer (i.e., maintaining an undetectable PSA forever). I’m not hesitant to use the word cure. We do cure patients with radical prostatectomy.

We specifically discuss the risk of incontinence and the pros and cons of a nerve-sparing procedure in their particular case. I tell them that there's a 90 percent chance that they'll be pad-free and that two percent of men have enough problems with incontinence that they will seek additional treatment, such as a sphincter or collagen injection.

Postoperative sexual function depends on the patient's age and preoperative sexual function and whether or not the nerves are spared. Eighty to 90 percent of men in their fifties without any preoperative sexual dysfunction are able to engage in intercourse postoperatively, perhaps with the use of sildenafil. I tell men in their late sixties that the chances of maintaining sexual function are less than 50 percent. I tell men in their seventies that more likely than not, they will have erectile dysfunction.

Postoperative sexual rehabilitation

There's no question that sildenafil helps, and most surgeons no longer have data about sexual function in men who don't use it. Even men who can achieve penetration without sildenafil often use it because it improves erectile function. Unfortunately, it doesn't help everybody. If a man has very poor postoperative erectile function, sildenafil is not very effective.

Early on in the postoperative period, I often recommend that my patients try the vacuum pump devices. Although they're completely noninvasive, younger men don't find them to be an acceptable long-term method. However, they are a good way to bridge the gap between the surgery and the time when erectile function returns. There can be improvements in sexual function for a full two years after surgery.

After waiting a sufficient period of time, a prosthesis may be considered for men who have failed to regain erectile function, especially if they have not had satisfactory results with the less invasive methods.

Select publications

Publications discussed by Dr Smith

The Medical Research Council Prostate Cancer Working Party Investigators Group. **Immediate versus deferred treatment for advanced prostatic cancer: Initial results of the Medical Research Council Trial.** *Br J Urol* 1997;79(2):235-46. **Abstract**

Bolla M et al. **Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin.** *N Engl J Med* 1997;337:295-300. **Abstract**

Bolla M et al. **Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial.** *Lancet* 2002;360(9327):103-6. **Abstract**

Messing EM et al. **Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer.** *N Engl J Med* 1999;341:1781-8. **Abstract**

Biochemical (PSA) recurrence

Carroll P. **Rising PSA after a radical treatment.** *Eur Urol* 2001;40 (Suppl 2):9-16. **Abstract**

Djavan B et al. **PSA progression following radical prostatectomy and radiation therapy: New standards in the new Millennium.** *Eur Urol* 2003;43(1):12-27. **Abstract**

Dreicer R. **Controversies in the systemic management of patients with evidence of biochemical failure following radical prostatectomy.** *Cancer Treat Rev* 2002;28(4):189-94. **Abstract**

Grossfeld GD et al. **Androgen deprivation therapy for patients with clinically localized (stages T1 to T3) prostate cancer and for patients with biochemical recurrence after radical prostatectomy.** *Urology* 2001;58(2 Suppl 1):56-64. **Abstract**

Grossfeld GD et al. **Patterns of failure after primary local therapy for prostate cancer and rationale for secondary therapy.** *Urology* 2002;60(3 Suppl 1):57-62; discussion 62-3. **Abstract**

Moul JW. **Hormonal therapy options for biochemical recurrence of prostate cancer after local therapy.** *Mol Urol* 2000;4(3):267-71;discussion 273. **Abstract**

Swindle PW et al. **Markers and meaning of primary treatment failure.** *Urol Clin North Am* 2003;30(2):377-401. **Abstract**

Sylvester J et al. **The role of androgen ablation in patients with biochemical or local failure after definitive radiation therapy: A survey of practice patterns of urologists and radiation oncologists in the United States.** *Urology* 2001;58(2 Suppl 1):65-70. **Abstract**

Intermittent versus continuous androgen suppression

De La Taille A et al. **Intermittent androgen suppression in patients with prostate cancer.** *BJU Int* 2003;91(1):18-22. **Abstract**

Gaston KE, Ornstein DK. **Pharmacotherapy for biochemical recurrences after therapy for localised prostate cancer.** *Expert Opin Pharmacother* 2002;3(6):657-69. **Abstract**

Goldenberg SL et al. **Clinical experience with intermittent androgen suppression in prostate cancer: Minimum of 3 years' follow-up.** *Mol Urol* 1999;3(3):287-292. **Abstract**

Grossfeld GD et al. **Intermittent androgen deprivation: Update of cycling characteristics in patients without clinically apparent metastatic prostate cancer.** *Urology* 2001;58(2):240-5. **Abstract**

Hurtado-Coll A et al. **Intermittent androgen suppression in prostate cancer: The Canadian experience.** *Urology* 2002;60(3 Suppl 1):52-6;discussion 56. **Abstract**

Irani J. **Intermittent androgen suppression in the management of prostate cancer: A phase II comparative study.** *Prostate Cancer Prostatic Dis* 2000;3(S1):S20. **Abstract**

Klotz L. **Hormone therapy for patients with prostate carcinoma.** *Cancer* 2000;88(12 Suppl):3009-14. **Abstract**

Leibowitz RL, Tucker SJ. **Treatment of localized prostate cancer with intermittent triple androgen blockade: Preliminary results in 110 consecutive patients.** *Oncologist* 2001;6(2):177-82. **Abstract**

Malone S et al. **Mature phase II study of intermittent androgen suppression therapy (IAS) in prostate cancer (PC): Efficacy and long-term side effect profile.** *Int J Radiat Oncol Biol Phys* 2003;57(2 Suppl):S174-5. **Abstract**

Pether M et al. **Intermittent androgen suppression in prostate cancer: An update of the Vancouver experience.** *Can J Urol* 2003;10(2):1809-14. **Abstract**

Prapotnich D et al. **A 10-year clinical experience with intermittent hormonal therapy for prostate cancer.** *Eur Urol* 2003;43(3):233-40. **Abstract**

Michael K Brawer, MD

Director, Northwest Prostate Institute,
Northwest Hospital

Edited comments by Dr Brawer

Intermittent androgen suppression in a man with postprostatectomy biochemical recurrence

History

At the end of 1998, this healthy 59-year-old man had a screening total PSA of 17.3 ng/mL and a complexed PSA of 14.7 ng/mL. On examination, he had a 30 cc benign gland. We performed an ultrasound-guided prostate biopsy with eight cores, including two transition zone cores. He had cancer in all but one of the cores; the majority of the cancer was Gleason 3+3, and one core from the left base was Gleason 3+4. His bone scan was negative and there was moderate heterogeneous activity in the prostate and a mildly suspicious right iliac lymph node on the ProstaScint® scan.

After a discussion of treatment options, he elected to undergo radical prostatectomy. Based on the number of positive cores with a high grade, I did not do a nerve-sparing procedure. Because of the results of the ProstaScint® scan, I did an extensive lymphadenectomy, which was negative. His final pathology revealed a 9.9 cc, Gleason 3+4 prostate cancer with bilateral seminal vesicle invasion.

Follow-up

We discussed the options of adjuvant radiation or hormonal therapy or an experimental chemotherapy protocol. He elected to watch his PSA prior to making any decisions about adjuvant treatment. Four months after the prostatectomy, his postoperative PSA reached its nadir at 0.2 ng/mL, and then it began to very slowly rise to 0.5 ng/mL 10 months after the prostatectomy. At that point, we again discussed possible interventions, and we started intermittent hormonal therapy with the LHRH agonist. Over the 42 months that he has been followed since his initial rise in PSA after surgery, he has received 18 months of active therapy and has been off of therapy more than half of the time.

Despite the non-nerve-sparing procedure, he maintains his potency. Even more amazing and unique in my personal series, he maintains his potency on the LHRH agonist. He must have an accessory location of some of the nerves. When he's on the LHRH agonist, he has some emotional issues, such as feeling less competitive in sports. Otherwise, he's done quite well.

Discussion

When we initially discussed hormonal therapy options, we also talked about continuous hormonal therapy. I presented the data from the Vancouver Group and went over the potential option of the intermittent approach. My current interpretation of the data suggests there is no detrimental effect, some improvement in quality of life and an economic benefit associated with intermittent androgen suppression.

We were interested in his amazing libido and potency through all of the treatments, and we checked his testosterone levels. When he's on the LHRH agonist, he becomes castrate almost immediately, and he has a rapid restoration of his testosterone level following the LHRH agonist. If he receives a three-month LHRH injection, by five months his testosterone is back to his normal level. Particularly in older patients, I see that most of the LHRH agonists have a more prolonged duration of castration than the prescribed three- or four-month interval.

After the impressive results from the Early Prostate Cancer bicalutamide trial, if this patient presented today, he would be an excellent candidate for high-dose bicalutamide. I've discussed switching him to bicalutamide, but he declined because he says he has done so well. If the LHRH agonist eventually affects his libido, switching to bicalutamide may be a reasonable option.

Given the data from the bicalutamide trial, I would now recommend this agent as first-line therapy immediately after having found the aggressive nature of his cancer on the pathology specimen.

Early Prostate Cancer (EPC) Program: Randomized, Placebo-Controlled Trial Evaluating Bicalutamide 150 Mg as Immediate Therapy Either Alone or As Adjuvant to Standard Care in Patients with Localized or Locally Advanced Prostate Cancer
Closed Protocol

Accrual: 8,113 patients

Eligibility: Localized or locally advanced (T1-T4, Nx/N0, M0) prostate cancer, treated with radical prostatectomy, radiation therapy or watchful waiting

ARM 1: Bicalutamide 150 mg daily
ARM 2: Placebo

SOURCE: See WA et al. **Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: First analysis of the Early Prostate Cancer program.** *J Urol* 2002; 168(2):429-35. **Abstract**

The Early Prostate Cancer (EPC) Trials: A comparison of the individual studies

Trial	N	Location	Tumor stage	Standard care	Duration of adjuvant bicalutamide
North American	3,292	U.S., Canada	T1b, T1c, T2, T3, pT4, N0-X, M0	RP and RT	2 years or until treatment failure
Capri	3,603	Europe, South Africa, Israel, Mexico, Australia	T1b, T1c, T2, T3, T4, any N, M0	RP, RT, and WW	≥5 years or until treatment failure
SPCG	1,218	Scandinavia	T1b, T1c, T2, T3, T4, any N, M0	RP, RT, and WW	≥5 years or until treatment failure

RP = radical prostatectomy, RT = radiation therapy, WW = watchful waiting

SOURCE: See WA et al. **Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: First analysis of the Early Prostate Cancer program.** *J Urol* 2002; 168(2):429-35. **Abstract**

Objective clinical progression in the Early Prostate Cancer Trial

	Bicalutamide (N=4,052)	Placebo (N=4,061)	Hazards ratio	*p*-value
Overall	363 (9%)	559 (13.8%)	0.58	<<0.0001
By trial				
Trial 23	83 (2%)	87 (2.1%)	0.93	0.65
Trial 24	181 (4.5%)	293 (7.2%)	0.57	<<0.0001
Trial 25	99 (2.4%)	179 (4.4%)	0.43	<<0.0001
By primary therapy				
RP or RT	NR	NR	0.63	<0.001
WW	NR	NR	0.53	<0.001
By disease stage				
Localized	NR	NR	0.72	<0.001
Locally advanced	NR	NR	0.46	<0.001

RP = radical prostatectomy, RT = radiation therapy, WW = watchful waiting, NR = not reported

SOURCE: See WA et al. **Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: First analysis of the Early Prostate Cancer program.** *J Urol* 2002; 168(2):429-35. **Abstract**

Local therapy in high-risk situations

This man presented in 1998. Today, in patients such as this, I've abandoned radical prostatectomy as first-line therapy and recommend neoadjuvant and adjuvant hormonal therapy in conjunction with external beam radiation and brachytherapy. The patients are treated with three months of an LHRH

agonist, followed by brachytherapy and then by external beam radiation. Thirty percent of the patients will receive an antiandrogen, such as bicalutamide, one week before the LHRH agonist. Patients will continue on the hormonal therapy for a year. That is a departure from some of the studies, but it's the way we've approached these patients.

PSA as a surrogate endpoint

With the development and refinement of PSA, we have an extraordinarily powerful tool for the detection and monitoring of prostate cancer. Hopefully, the regulatory agencies will begin to look at PSA and other intermediate endpoints as useful data for the approval of therapies.

PSA nadir and the length of time to the PSA nadir are not sufficient endpoints for the FDA or other agencies to support the approval of a novel therapy. However, the preponderance of evidence suggests that PSA is an extraordinarily useful tumor marker to predict an individual patient's outcome, as long as the therapy does not affect PSA independently of the tumor. This is, of course, a potential problem for PSA and hormonal therapy, because the androgen receptor regulates PSA gene transcription.

With respect to hormonal therapy, PSA outcome may be somewhat problematic. As we move to other therapies that don't affect the upstream transcription of PSA, we ought to use PSA and potentially other markers as useful surrogate endpoints. It would dramatically decrease the time and expense of clinical trials and allow us to develop novel therapies more rapidly.

Complexed PSA

While PSA has relatively good sensitivity, its specificity is problematic. The majority of men with an elevated PSA will not have prostate cancer, at least not on their initial biopsy. On that basis, we have spent a great deal of time trying to make PSA more specific. We've gone through a whole host of machinations, starting with the PSA derivatives (PSA velocity, age-specific PSA and PSA density) and then moving on to the molecular forms of PSA (free PSA and complexed PSA). A number of papers presented at this year's American Urological Association meeting support the benefit of complexed PSA relative to total PSA, both for initial testing and monitoring of patients.

PSA in ejaculate is completely in the free form, and the vast majority of PSA in the systemic circulation is complexed with protease inhibitors, including alfa-2-macroglobulin and, most importantly, alfa-1-antichymotrypsin. It is not known why this occurs, but we do know that the free form occurs in a greater percentage of men without prostate cancer and the complexed form occurs in a greater number of men with prostate cancer.

For a number of years, the free-to-total PSA ratio was calculated. This provided some enhancement in the test's specificity, but it had a number of problems. First, there was disagreement between the different manufacturers in what their assays read for a given patient's specimen. Also, the free form

of PSA was not very stable and required meticulous specimen handling. Most importantly, the free-to-total PSA ratio required the measurement of both the free and the total PSA. With the complexed PSA, we obviate the problem of stability, and we only need to measure the complexed PSA. Therefore, we don't need to measure two analytes, and the cost of PSA testing is cut in half.

Reduction in prostate cancer mortality

PSA has now been widely used for 17 or 18 years, and it may be that some of the reduction in prostate cancer mortality is related to early detection and definitive therapy for local disease. A question that will be answered through the Prostate, Lung, Colorectal and Ovary (PLCO) cancer trial is: Does conventional local therapy truly change the course of disease? In the Scandinavian trial, while prostate cancer mortality was reduced in men undergoing radical prostatectomy, the all-cause mortality was the same for men treated with "watchful waiting" or definitive therapy.

Randomized Trial Comparing Radical Prostatectomy with Watchful Waiting in Early Prostate Cancer **Closed Protocol**

Accrual: 695 patients

Eligibility: Clinical stage T1b, T1c or T2 prostate cancer

ARM 1: Radical prostatectomy
ARM 2: Watchful waiting

8-Year Cumulative Hazard Rates, Difference between Cumulative Hazard Rates and Relative Hazards

8-Year cumulative hazard rate	Watchful waiting (N=348)	Radical prostatectomy (N=347)	Difference	Relative hazard (95% CI)	*p*-value*
Disease-specific mortality (95% CI)	13.6% (7.9%-19.7%)	7.1% (3.3%-11%)	6.6% (2.1%-11.1%)	0.50 (0.27-0.91)	0.02
Rate of distant metastases (95% CI)	27.3% (19.4%-36%)	13.4% (8.6%-18.5%)	13.9% (8%-19.8%)	0.63 (0.41-0.96)	0.03
Rate of local progression (95% CI)	61.1% (47.8%-76.4%)	19.3% (12.7%-26.4%)	41.8% (35.2%-48.4%)	0.31 (0.22-0.44)	<0.001
Overall mortality (95% CI)	28.3% (20.2%-37.1%)	22% (15.3%-29.1%)	6.3% (-0.2%-12.7 %)	0.83 (0.57-1.2)	0.31

*log-rank test, CI=confidence interval

SOURCE: Holmberg L et al. **A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer.** *New Eng J Med* 2002;347;781-9.

The Prostate Cancer Intervention Versus Observation Trial (PIVOT) is a U.S.-based trial that randomizes men to radical prostatectomy or observation. Unlike the Scandinavian trial, PIVOT reflects the contemporary U.S. experience where PSA is the basis for the diagnosis in the majority of patients. Unfortunately, we will not know the results for many years. With PIVOT and the PLCO trial, we'll know whether early detection contributes to the reduction in prostate cancer mortality.

PIVOT Trial: Phase III Randomized Study of Prostatectomy versus Expectant Management with Palliative Therapy in Patients with Clinically Localized Prostate Cancer **Open Protocol**

Protocol IDs: VA-CSP-407, CLB-9492, E-VA407, SWOG-9450, PIVOT-1, NCI-T94-01310
Projected accrual: 1,050 patients

Eligibility: Clinically localized (T1a-c or T2a-c, NX, M0) prostate cancer, PSA ≤ 50 ng/mL

ARM 1: Radical prostatectomy
ARM 2: Expectant management with interventions reserved for symptomatic or metastatic disease

Study Lead Organizations:

Veterans Affairs Cooperative Studies
Program Coordinating Center - Perry Point
Timothy James Wilt, MD, MPH, Protocol Chair
Tel: 612-725-2158

Cancer and Leukemia Group B
Timothy James Wilt, MD, MPH, Protocol Chair
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Southwest Oncology Group
Daniel J Culkin, MD, FACS, Protocol Chair
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Eastern Cooperative Oncology Group
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Tel: 608-262-0475, 800-622-8922

SOURCE: NCI Physician Data Query, October 2003.

Other possibilities exist as to why prostate cancer mortality has declined. One explanation is that there's been more widespread use of early hormonal therapy, primarily because of the advent of the LHRH agonist. Data from a number of studies suggest, unlike the data from the VA cooperative trials, that early hormonal therapy may indeed offer a survival advantage. That may be one factor — perhaps the major factor — leading to this very encouraging reduction in prostate cancer mortality.

Select publications

Publications discussed by Dr Brawer

The Medical Research Council Prostate Cancer Working Party Investigators Group. **Immediate versus deferred treatment for advanced prostatic cancer: Initial results of the Medical Research Council Trial.** *Br J Urol* 1997;79(2):235-46. **Abstract**

Bolla M et al. **Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin.** *N Engl J Med* 1997;337:295-300. **Abstract**

Bolla M et al. **Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial.** *Lancet* 2002;360(9327):103-6. **Abstract**

Byar DP, Corle DK. **Hormone therapy for prostate cancer: Results of the Veterans Administration Cooperative Urological Research Group studies.** *NCI Monogr* 1988;(7):165-70. **Abstract**

de Koning HJ et al; European Randomized Screening for Prostate Cancer (ERSPC) Trial; International Prostate Cancer Screening Trials Evaluation Group. **Large-scale randomized prostate cancer screening trials: Program performances in the European Randomized Screening for Prostate Cancer trial and the Prostate, Lung, Colorectal and Ovary cancer trial.** *Int J Cancer* 2002;97(2):237-44. **Abstract**

Holmberg L et al; Scandinavian Prostatic Cancer Group Study Number 4. **A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer.** *N Engl J Med* 2002;347(11):781-9. **Abstract**

Messing EM et al. **Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer.** *N Engl J Med* 1999;341:1781-8. **Abstract**

See WA et al; Casodex Early Prostate Cancer Trialist Group. **Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: First analysis of the early prostate cancer program.** *J Urol* 2002;168(2):429-35. Erratum in: *J Urol* 2002;168(6):2558. *J Urol* 2002;168;4(Pt 1):1510. **Abstract**

Wilt TJ, Brawer MK. **The Prostate Cancer Intervention Versus Observation Trial (PIVOT).** *Oncology* (Huntingt) 1997;11(8):1133-9; discussion 1139-40, 1143. **Abstract**

Vancouver experience with intermittent androgen suppression

Bruchovsky N et al. **Intermittent androgen suppression for prostate cancer: Canadian Prospective Trial and related observations.** *Mol Urol* 2000;4(3):191-9; discussion 201. **Abstract**

Gleave M et al. **Intermittent androgen suppression for prostate cancer: Rationale and clinical experience.** *Prostate Cancer Prostatic Dis* 1998;1(6):289-296. **Abstract**

Gleave M et al. **Intermittent androgen suppression for prostate cancer: Rationale and clinical experience.** *Eur Urol* 1998;34(Suppl 3):37-41. **Abstract**

Goldenberg SL et al. **Clinical experience with intermittent androgen suppression in prostate cancer: Minimum of 3 years' follow-up.** *Mol Urol* 1999;3(3):287-292. **Abstract**

Hurtado-Coll A et al. **Intermittent androgen suppression in prostate cancer: The Canadian experience.** *Urology* 2002;60(3 Suppl 1):52-6; discussion 56. **Abstract**

Pether M et al. **Intermittent androgen suppression in prostate cancer: An update of the Vancouver experience.** *Can J Urol* 2003;10(2):1809-14. **Abstract**

Post-test: Prostate Cancer Update, Issue 5, 2003

Conversations with Urologic Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. Randomized trials have demonstrated that in men with locally advanced prostate cancer, hormonal therapy in combination with radiation therapy decreases rates of PSA progression and of distant metastases compared to radiation therapy alone.
   a. True
   b. False

2. Intensity-modulated radiation therapy (IMRT)
   a. Delivers unprecedented doses of radiation
   b. Provides better PSA control
   c. Produces less toxicity
   d. All of the above

3. Randomized clinical trials have demonstrated that the combination of brachytherapy and external beam radiation results in improved outcome compared to either modality alone in low-risk disease.
   a. True
   b. False

4. Intermittent androgen suppression has been proven in Phase III trials to be as effective as continuous androgen suppression in the treatment of patients with a PSA recurrence.
   a. True
   b. False

5. PSA recurrence is more likely to be systemic if the grade of the cancer was higher, the PSA recurrence occurred rapidly, the PSA never declined to undetectable or the PSA doubling time was rapid.
   a. True
   b. False

6. A randomized trial demonstrated an overall mortality advantage for patients treated with radical prostatectomy compared to watchful waiting.
   a. True
   b. False

7. The dose painting technique entails using imaging technologies such as MR spectroscopy and PET to identify exact tumor location within the gland.
   a. True
   b. False

8. The Messing trial compared orchiectomy or goserelin after local therapy versus no endocrine therapy in men with node-positive disease.
   a. True
   b. False

9. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) is a U.S.-based trial that randomizes men to:
   a. Radical prostatectomy or observation
   b. External beam radiation therapy or observation
   c. Brachytherapy or observation
   d. None of the above

10. The SPIRIT trial randomizes patients with early-stage prostate cancer to brachytherapy or radical prostatectomy.
    a. True
    b. False

Post-test Answer Key: 1a, 2d, 3b, 4b, 5a, 6b, 7a, 8a, 9a, 10a

Evaluation Form: Prostate Cancer Update, Issue 5, 2003

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = *Outstanding* 4 = *Good* 3 = *Satisfactory* 2 = *Fair* 1 = *Poor*

GLOBAL LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Critically evaluate the clinical implications of emerging clinical trial data in prostate cancer treatment. 5 4 3 2 1
- Inform patients about the specific risks and benefits of local and systemic therapies. 5 4 3 2 1
- Provide individualized counseling to patients regarding the choice and timing of endocrine therapy. 5 4 3 2 1
- Offer patients information regarding their prognosis with and without various therapeutic options. 5 4 3 2 1

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 5

Upon completion of this activity, participants should be able to:

- Discuss current trends in the use of radiation therapy for the management of prostate cancer. 5 4 3 2 1
- Review the role of brachytherapy and external beam radiation therapy combined with hormone therapy in the management of prostate cancer. 5 4 3 2 1
- Counsel patients who experience PSA recurrence after radical prostatectomy about potential treatment options, including radiation therapy and hormonal therapy. 5 4 3 2 1
- Counsel patients about the important outcome measures for radical prostatectomy, including the potential side effects. 5 4 3 2 1
- Discuss the role of intermittent androgen suppression with patients who are being counseled about hormonal therapy options. 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Michael J Zelefsky, MD	5 4 3 2 1	5 4 3 2 1
Joseph A Smith Jr, MD	5 4 3 2 1	5 4 3 2 1
Michael K Brawer, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

Evaluation Form: Prostate Cancer Update, Issue 5, 2003

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Will the information presented cause you to make any changes in your practice?

___Yes ___No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity.

_____

_____

What other topics would you like to see addressed in future educational programs?

_____

_____

What other faculty would you like to hear interviewed in future educational programs?

_____

_____

Degree:

☐ MD ☐ DO ☐ PharmD ☐ RN ☐ NP ☐ PA ☐ BS ☐ Other _____

To obtain a certificate of completion and receive credit for this activity, please complete the post-test, fill out the evaluation form and mail or fax both to: Research To Practice, Inc, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at www.ProstateCancerUpdate.net.