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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 CD or tape, review the monograph and complete the post-test and evaluation form on page 26-28 or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program and the website, **ProstateCancerUpdate.net**, where you will find 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.

Issue 3, 2003, of Prostate Cancer Update consists of discussions with three research leaders on a variety of important issues, including intermittent androgen deprivation, salvage radiation and hormonal therapy, early versus delayed hormonal therapy and watchful waiting.

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 3

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

- Develop an awareness of ongoing clinical trials of intermittent versus continuous androgen deprivation in order to counsel patients about their eligibility for participation.
- Evaluate research leader perspectives and clinical data related to salvage radiation and hormonal therapy in order to counsel patients about treatment options after failure of definitive local therapy.
- Review clinical trial data and research leader views on early versus deferred hormonal therapy in order to offer patients choices after local therapy.
- Evaluate the role of watchful waiting versus local therapy to determine for whom it would be an appropriate option.
- Review the advantages and disadvantages of different methods for delivering radiation therapy.

ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) by NL Communications, Inc. NL Communications, Inc is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

NL Communications, Inc 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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Laurence Klotz, MD, FRCSC	**Grants/Research Support:** Abbott Laboratories **Consultant:** Novartis Pharmaceuticals Corporation **Speakers' Bureau:** AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals, Inc
Paul F Schellhammer, MD	**Grants/Research Support:** AstraZeneca Pharmaceuticals LP **Consultant:** Schering-Plough Corporation **Stockholder:** Abbott Laboratories **Speakers' Bureau:** Dendreon Corporation
Anthony L Zeitman, MD, FRCR	No financial interests or affiliations to disclose.

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
bicalutamide	Casodex®	AstraZeneca Pharmaceuticals LP
finasteride	Proscar®	Merck and Company Inc
flutamide	Euflex®, Eulexin®	Schering-Plough Corporation
goserelin acetate implant	Zoladex® LA	AstraZeneca Pharmaceuticals LP
leuprolide acetate implant	Viadur™	ALZA Corporation
	Lupron Depot®	TAP Pharmaceuticals Inc
pamidronate	Aredia®	Novartis Pharmaceuticals Corporation
tamoxifen	Nolvadex®	AstraZeneca Pharmaceuticals LP
triptorelin	De-capeptyl® SR	Ipsen Ltd
	Trelstar™ LA	Debiopharm S.A.
zoledronate	Zometa®	Novartis Pharmaceuticals Corporation

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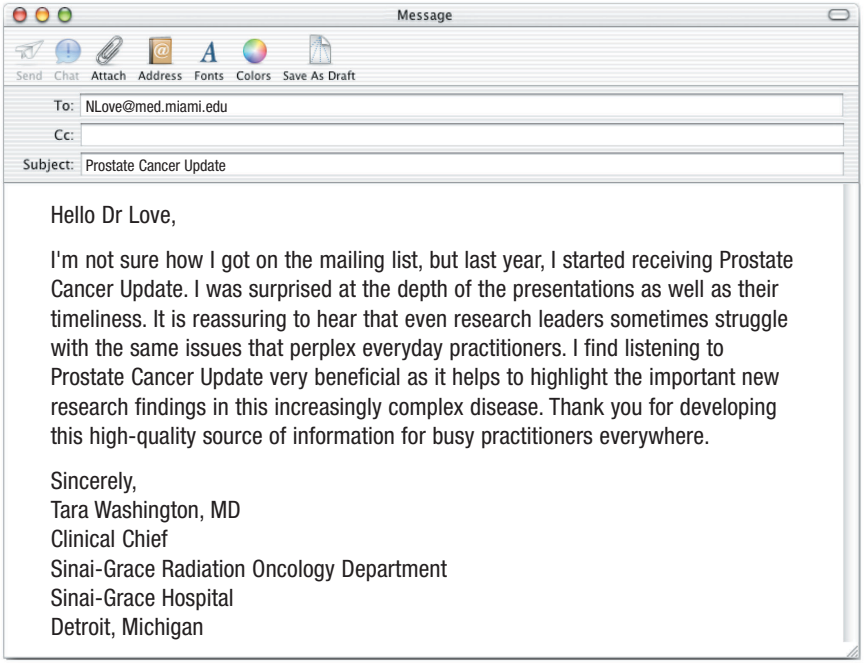
Editor's Note

Correspondence from the Front Line


Message

Send Chat Attach Address Fonts Colors Save As Draft

To: NLove@med.miami.edu

Cc:

Subject: Prostate Cancer Update

Hello Dr Love,

I'm not sure how I got on the mailing list, but last year, I started receiving Prostate Cancer Update. I was surprised at the depth of the presentations as well as their timeliness. It is reassuring to hear that even research leaders sometimes struggle with the same issues that perplex everyday practitioners. I find listening to Prostate Cancer Update very beneficial as it helps to highlight the important new research findings in this increasingly complex disease. Thank you for developing this high-quality source of information for busy practitioners everywhere.

Sincerely,
Tara Washington, MD
Clinical Chief
Sinai-Grace Radiation Oncology Department
Sinai-Grace Hospital
Detroit, Michigan

Dear Dr Washington:

Nothing brightens my day more than a supportive e-mail from a listener of our audio series, and I was particularly touched by your words. Having spent the last 15 years "grilling" cancer research leaders about how they manage patients in their clinical practice, I have become accustomed to the discomfort they often express when recounting therapeutic dilemmas that do not always have a correct answer. I'm glad these perspectives are reassuring to you, and I hope the insights of research leaders about what to expect from future research leaves you and the rest of our listeners optimistic for the future.

In terms of "issues that perplex everyday practitioners," you may wish to review the enclosed interview with Dr Paul Schellhammer — our first interviewee when we launched this series last year. Dr Schellhammer, a nationally recognized prostate cancer research leader, recounted his own

personal challenging experience with radical prostatectomy (including the rare complication of a psoas abscess). At that time, he was also struggling with the knowledge that his PSA was rising. In the enclosed follow-up interview, he recounts his decision to be treated with pelvic radiotherapy and eight months of combined androgen blockade.

Your note mentions that this is an "increasingly complex disease," and, as demonstrated by Dr Shellhammer's dilemma, the emergence of PSA testing as a means to follow men treated with radical prostatectomy and radiation therapy has left clinicians with an important subpopulation of patients for whom there is minimal clinical research data available to guide decisions.

Dr Shellhammer's personal experience with prolonged severe gastrointestinal toxicity from radiation therapy also highlights the limitations associated with clinical research data, which would have predicted relatively minimal side effects.

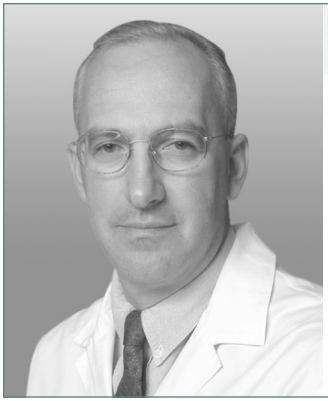
In his unique understated manner, Paul notes, "As a physician and scientist, it is interesting to experience the reality of what you read about." He also describes the mixed emotions experienced by many patients when completing therapy — relieved that it's over, but concerned about the permanence of the treatment's benefits.

As you stated, every physician who provides care for prostate cancer patients struggles with challenging issues like the management of biochemical recurrence in men. I hope that this audio series is helpful in thinking through these challenging situations.

Sincerely,

Neil Love, MD

P.S. In terms of being on the Prostate Cancer Update mailing list, our educational grant allows us to distribute the audio series without charge to all U.S.-based urologists and radiation oncologists. If you know of any of your colleagues who are not receiving the series but might be interested in it, please let me know and I will add their names to our subscription list.



Laurence Klotz, MD, FRCSC

Professor, Department of Surgery, University of Toronto

Chief, Division of Urology, Sunnybrook Health Science Centre

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Founder, Prostate Cancer Research Foundation of Canada

Founder and Chairman, Canadian Urology Research Consortium

Chair, Canadian Uro-Oncology Group

Chair, Global Genito-Urinary Oncology Group

Edited comments by Dr Klotz

Clinical benefit of maximum androgen blockade

I'm a moderate supporter of maximum androgen blockade, and I believe the pendulum has swung back too far against this approach. There are 27 prospective randomized trials, involving roughly 6,000 patients, all started in the 1980s. The mortality data show a minor survival benefit — about a 10 percent relative improvement and 3 percent absolute improvement at five years. In 2000, the group at Hopkins published an influential article entitled, "Complete androgen blockade for prostate cancer: What went wrong?" The article implies that we were mistaken, but to me, it's all about prolonging survival so I don't dismiss the minor survival benefit.

On the other hand, maximum androgen block (MAB) adversely impacts quality of life and it's costly, so one has to decide if it's worth it from a clinical perspective. When calculating the cost based on a three-month survival benefit, the cost per month of improved survival is actually quite reasonable compared to chemotherapy for lung cancer or hormone-refractory breast cancer. I believe patients in whom survival is the primary goal should be offered total androgen blockade with the understanding that there may be a modest effect on their quality of life.

Mechanisms of action of MAB and antiandrogens

It is believed that maximum androgen blockade blocks the adrenal androgens, but I think the mechanism of action is more likely inhibition of ligand-independent activation of the androgen receptor. There is evidence that EGF, IL6 and a whole slew of cytokines activate the androgen receptor in the absence of androgens and stimulate mitosis. Antiandrogens block this. There are significant levels of androgens from the adrenals — even in men on LHRH agonists — so it may be that both mechanisms are at work, but there's not a lot of evidence that adrenal androgens have much impact on cell growth.

In hormone-refractory prostate cancer, an antiandrogen works to some degree, and it can also work as an androgen receptor agonist — you obtain both effects. That explains the antiandrogen withdrawal effect where, if a patient is progressing on total androgen blockage and you stop the antiandrogen, there is a response. It acts as an agonist because you have androgen receptor mutations that reverse the effect of the antiandrogen, but in the nonhormone-resistant patient, it acts as an inhibitor.

High-dose bicalutamide therapy in the adjuvant setting

Bicalutamide 150 mg has just been approved in Canada for use in patients who've elected watchful waiting, which is not the indication for much hormone therapy, but at least it's now available. I think there's a role for bicalutamide in high-risk patients when it's used in the adjuvant setting after surgery, based on the Early Prostate Cancer (EPC) trials. The data showed a substantial difference in the time to a development of bone metastases in this subset of patients treated with two years of adjuvant bicalutamide. While the difference is not as impressive in the overall group, the EPC demonstrated an important benefit of adjuvant therapy to this subset of patients and no study had done that before.

Bicalutamide: An androgen receptor antagonist

Bicalutamide is a superior antiandrogen — not only because it has fewer side effects and it's administered only once a day — but it's also a more effective androgen receptor antagonist.

Antiandrogen implies the competitive blocking of the binding of dihydrotestosterone to the androgen receptor, but antiandrogens also act to a large degree as androgen receptor antagonists. In the absence of androgens, which is when they're mostly used, they block androgen receptor activation by nonligand-dependent mechanisms. Bicalutamide does that much more effectively than the other antiandrogens, but it wasn't around when all these randomized trials were conducted. It's possible that the survival benefit with bicalutamide is significantly greater than has been demonstrated with the other nonsteroidal antiandrogens.

Bicalutamide monotherapy versus LHRH agonists

Data from randomized trials in metastatic disease comparing bicalutamide to an LHRH agonist show a six-week difference in survival favoring the LHRH agonist. Efficacy includes long-term side effects and quality of life, and in the average 70-year-old being treated with hormonal therapy for a rising PSA, a minor difference in survival is not the issue.

When compared to LHRH agonists, monotherapy with bicalutamide has quality-of-life benefits that make it a very attractive therapy. In addition to patients having an increased likelihood of retaining sexual function, there is evidence that bicalutamide stabilizes bone mineral density. While it is not conclusive, the bone density data is very encouraging because we are treating patients early and many have a 15-year median life expectancy, so osteoporosis can become a major concern.

Cross-sectional study of bone turnover during bicalutamide 150 mg monotherapy for prostate cancer

Patient characteristics	Group 1 Hormone naïve (n = 15)	Group 2 GnRH agonist (n = 22)	Group 3 Bicalutamide monotherapy (n = 18)
Age (yr)	66 ± 2	66 ± 2	63 ± 2
Duration of hormonal treatment (mo)	0 ± 0	6 ± 0	6 ± 0
Gonadal steroids			
Testosterone (ng/dL)	397 ± 36	14 ± 2	678 ± 38
Estradiol (pg/mL)	27 ± 2	7 ± 1	50 ± 5
Biochemical markers of bone turnover*			
Urinary excretion of deoxypyridinoline (nmol BCE**/mmol creatine)	4.8 ± 0.3	7.3 ± 0.5	5.4 ± 0.4
Urinary excretion of N-telopeptides (nmol BCE**/mmol creatine)	24 ± 3	50 ± 4	22 ± 3
Osteocalcin (ng/mL)	22 ± 2	31 ± 2	18 ± 2

*Elevations correlate with increased rates of bone loss and predict fractures independent of bone mineral density.
**BCE = Bone Collagen Equivalents

DERIVED FROM: Smith MR et al. **Cross-sectional study of bone turnover during bicalutamide monotherapy for prostate cancer.** *Urology* 2003;61(1):127-131. Abstract

The downside of bicalutamide is gynecomastia — at least half of the patients complain of significant gynecomastia, nipple tenderness and pain — but there are a number of strategies likely to block that. The traditional one is local radiation to the breast and there's also an ongoing study with tamoxifen.

Phase II trial of intermittent androgen suppression

I was a principal investigator on a Phase II trial in Canada with 100 patients with PSAs greater than 6 ng/mL. The patients received eight months of androgen suppression, followed by discontinuation of therapy, and then resumption when their PSA was either greater than 10 ng/mL or greater than their pretreatment level, whichever was lower. This trial, as well as others, showed that intermittent therapy resulted in patients being off treatment about 50 percent of the time, which has significant quality of life benefits. And, based on historical controls, there doesn't seem to be any adverse effect on the median survival.

In this study, quality of life domains, including sexual function, generally returned to baseline three to four months after discontinuing therapy. The majority of patients had relatively prompt recovery of testosterone levels — 50 percent of patients had normal levels by four months and 35 percent recovered to just subnormal levels. In 15 percent of these men, levels remained castrate so one criticism of this approach is that, in spite of stopping therapy, not all patients are re-exposed to testosterone.

SWOG-JPR7: Phase III randomized study of intermittent versus continuous androgen suppression

This study is supported by the NCI Clinical Trials Support Unit, which means any member of any cooperative group trial in the United States or Canada can enter a

patient in the trial. The eligibility criteria require that patients have received radiation therapy, either as primary or salvage treatment, have a rising PSA of 3 ng/mL or greater and have no evidence of metastatic disease.

Patients are randomized between intermittent and continuous androgen suppression. The intermittent therapy consists of eight months of a LHRH analog and an antiandrogen for at least a month. Then, if their PSA drops to normal during treatment, they stop treatment and their PSA and testosterone levels are monitored every two months. When the PSA returns to their pretreatment level or 10 ng/mL — whichever is lower — they go back on therapy for another eight months. The continuous therapy consists of a LHRH analog with at least a month of antiandrogen therapy or a bilateral orchiectomy and an antiandrogen.

The primary endpoint is the time it takes for the patient to have a rising PSA in the face of castrate levels of testosterone. We're also looking at survival and quality of life endpoints.

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, CTSU
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

Study Contacts:

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NCIC-Clinical Trials Group

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Southwest Oncology Group

SOURCE: NCI Physician Data Query, April 2003

Intermittent androgen suppression in clinical practice

I support the current Phase III trial randomizing patients between intermittent and continuous androgen suppression, so I don't promote intermittent hormonal therapy off-protocol. I explain to patients that it's investigational and we don't know what impact the unstable hormonal milieu will have on survival. However, if a patient says, "Okay, I don't want to be randomized, I'll just go on the hormonal therapy," and then eight months later, he wants to go off treatment, I don't argue as long as they understand it's investigational.

When they understand the issues, approximately 95 percent of my patients opt for intermittent therapy. This approach has received a good deal of positive media attention in Canada, which may be one reason why it's widely accepted. Patients who've experienced the side effects of androgen ablation therapy love having a break from treatment. On the other hand, some patients who have a strong PSA response to hormonal therapy don't want to tamper with their treatment. With intermittent therapy, some patients become overly concerned when their PSA begins to rise, but they have to understand that this is expected.

Management of the patient at high risk for progression after surgery

If a patient is at high risk for progression after surgery — for example, a positive surgical margin — one has to decide whether adjuvant therapy is indicated. The difficulty is that positive surgical margins are compatible with cure in about 50 percent of patients, particularly if they're micro-focal. My approach is not to treat those patients with adjuvant therapy, but rather to wait for a rise in PSA and then treat, based on the interval between surgery and the rise.

If the PSA begins to rise, there are several protocols available, such as the RTOG protocol of radiation therapy plus hormones versus radiation alone versus hormones alone. Off-protocol, if it has taken more than a year for the PSA to rise, I treat with radiation. The data shows that almost all patients in whom the PSA never went to undetectable levels — or began to rise within the first year — have occult systemic disease, so I treat them with androgen ablation therapy.

Management of patients with a rising PSA after radiation therapy

For the patient with a rising PSA after radiation, there's a role for salvage therapy — either cryotherapy or surgery — in a very limited number of patients. Personally, I have zero enthusiasm for salvage prostatectomy, because I think it's impossible to perform that operation in a way that preserves quality of life and results in cure often enough to justify it. We use cryotherapy in selected patients, but for most, we offer the intermittent versus continuous androgen suppression trial. If they're not interested, they go on hormones and then we negotiate whether they go on the intermittent approach after eight months.

Androgen replacement therapy and the risk of prostate cancer

I'm very skeptical about the safety of testosterone replacement therapy (TRT) for men in their 40s. Prostate cancer occurs in 30 percent of men over 50, and by the age of 80, there are micro-foci in almost everyone. We need to understand what promotes or prevents the development of those micro-foci into clinical prostate cancer. Testosterone drives the growth of prostate cells, so my prediction is that if you take a large group of men and put them all on TRT, there will be a significant increase in their risk of clinically diagnosed prostate cancer.

I think most men on testosterone replacement are not severely hypogonadal, rather they're minimally hypogonadal, or they feel hypogonadal but their levels are in the normal range. Unless they are severely hypogonadal, I take

them off testosterone therapy. In a man with castrate levels, no one would question the use of hormone replacement, but if he develops prostate cancer, it requires some thought. If he's curable, I would treat him like any other patient — give him an appropriate local therapy for his prostate cancer and maintain his androgen replacement.

Prostate cancer prevention trials

In prostate cancer there's a 25-year window from inception to progression and I'm convinced the disease is preventable. The finasteride prostate cancer prevention trial has just about completed its seven-year endpoint, which is repeat biopsies. Clearly finasteride is an active agent — it's a hormone therapy and it shrinks the prostate. I am confident that it will result in a decreased rate of prostate cancer diagnoses on repeat biopsy, if only because the volume goes down. I don't know whether that will translate into a meaningful endpoint, like prostate cancer mortality. It's possible that the patients who develop prostate cancer on finasteride — who have been exposed to a long period of altered hormonal milieu — may have a biologically more aggressive form of prostate cancer.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) has a 10- to 15-year horizon for reporting, so it'll be awhile before we have results. I'm quite optimistic about these agents and I think this trial, as well as the finasteride trial, will have positive results. The other agent that looks promising is lycopene. I firmly believe that we're going to find a way to prevent prostate cancer in the next 10 to 15 years.

Select publications

Publications discussed by Dr Klotz

Laufer M et al. **Complete androgen blockade for prostate cancer: What went wrong?** *J Urol* 2000;164(1):3-9. **Abstract**

Intermittent versus continuous 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**

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

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**

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

Paul F Schellhammer, MD

Program Director, Virginia Prostate Center

Professor of Urology, Eastern Virginia Medical School and Sentara Cancer Institute

Trustee, American Board of Urology

Edited comments by Dr Schellhammer

Anxiety caused by discontinuing hormonal therapy

When my PSA became elevated after the radical prostatectomy, I was treated with radiation therapy and six months of combined androgen blockade — goserelin and bicalutamide. I am now in PSA remission, have discontinued those therapies and have been off hormonal therapy for three months.

I recognized that while taking therapy is a nuisance, it's also very comforting because you are doing something active. When I discontinued the therapy, I was relieved to be finished with the burden, but I realized that the antitumor effect of therapy was truly being tested for permanence and durability. Stopping therapy has resulted in some subclinical anxiety. While I've read about this in the past, I truly appreciate it now. Part of me says, "Gosh, why stop what's working? My 'crutch' is being taken away."

Tolerability and side effects of combined androgen blockade

I knew what the side effects were and I anticipated them. I had no breast effects whatsoever — no tenderness, no enlargement. I didn't have any mood swings or depression, and my wife didn't comment about any changes in my personality. The most dramatic change was fatigue — the feeling of not having the extra drive to accomplish things. I experienced a lack of vigor and vitality, which crept up on me very insidiously. I hardly knew it was happening. I was just more tired and looked forward to that mid-day nap and got to bed a little earlier. I play tennis and playing a set became much more of an effort.

Unfortunately, my thinking also became slower. As we age, we all lose some of our recall ability for places, names and facts, but this seemed to be an abrupt step down. I didn't anticipate it, but when it happened I said, "Well, I hope it is due to the therapy, which is reversible, rather than a lack of cerebral blood flow." I haven't been off therapy long enough to know. My testosterone is just barely starting to make its way up past the median castrate range, so I suppose I'm not physiologically recovered.

I had frequent hot flashes, which were bothersome. They weren't drenching sweats, but rather the kind of reaction one might have going into a tough exam or giving a talk — sweaty palms and feeling warm. Rarely did they wake me up at night. They were more annoying than incapacitating, like they are for some people. I experienced an amazing diminution of libido. It's a remarkable and dramatic transformation that I only really discussed with my wife and one or two other friends who are urologists. The feelings of tenderness and the hand-holding or kissing certainly weren't impacted in any way, but the arousal that often goes along with that — in the form of an erection or the feeling of a pelvic rush — wasn't there.

As a physician and scientist, it's interesting to experience what you've read about. You not only know what's happening, but you can feel it transpiring within your own body — like an internal experiment.

Duration of androgen deprivation

The information regarding androgen deprivation and salvage radiation therapy is very scant, and it's all a transferal from the clinical trials of primary therapy that showed a benefit from combining the two therapies. The optimal duration of therapy is unclear. We have information about two and three years of therapy but not about lesser duration. Several salvage protocols have used six months. Dr D'Amico was evaluating six months as primary therapy, and it seemed long enough but not too long, so I arbitrarily chose that as a convenient duration of therapy. I began external beam radiation therapy about one month after initiating androgen deprivation and continued the hormonal therapy for six months.

Personal experience with salvage radiation therapy

When recommending salvage radiation therapy for a rising PSA, I tell patients that I've approached the issue both scientifically and personally. The literature indicates that a minority of radiation oncologists currently recommend it. Combining androgen deprivation with radiation adds incremental benefit and is a reasonable choice, and that's the treatment I decided upon.

I experienced more radiation-induced proctitis than either the radiation oncologist or I anticipated. It was so intense during the last two weeks of treatment that we decided to reduce the dose to less than 65 Gy. The proctitis lasted for about three months. Now, when I counsel patients about radiation therapy, I have to put this experience aside, because it's not consistent with what others have reported to me. My tissues must have been particularly sensitive.

Impact of personal experience with prostate cancer on counseling patients

I believe there's a tendency for physicians — given the repetitive nature of their recommendations — to lose the sense of morbidity that may accompany

treatment and the potential variability between patients. Sometimes we are impressed that for certain patients hot flashes are overwhelming and for others they are not. Sometimes we may say, "Well, it might be an internal reaction to the same event," but that event certainly is different and it's not only perception, it's reality.

I live in a small community and news travels quickly, so patients will often ask me to relate to them my experiences with prostate cancer treatment. I do this only after discussing their treatment options in detail, because I don't want to immediately introduce biases into their decision-making.

Anxiety and follow-up PSA testing

I have a positive outlook on the future, but the PSA test is a constant reminder of my situation. I am apprehensive before the test and before opening the envelope with the test results. It's a tremendous relief when my PSA has not risen, even though it's only for another two, three or four months until the next PSA is done.

I presume that over time — with a good outcome and a low PSA — my anxiety will lessen. However, after a period of time with a normal or undetectable PSA, if a patient has a biochemical relapse, the whole scenario will be relived once again. I've thought that prostate cancer mimics life in its slow and steady attrition. You don't receive the cure label and you're constantly impressed by the fact that this underlying issue remains.

Early versus deferred hormonal therapy

I've been intrigued by the back and forth discussions about giving androgen deprivation early versus waiting until clinical failure occurs, which has been the defensive position of urologists. There are several trials that have looked at this issue and the one that rings strongest in most urologists' minds is the VA trial of 30 or 40 years ago, which didn't really demonstrate a benefit for earlier administration of DES. However, the patients in that study were much different than those we see today. They had a huge disease burden, with either a large primary or metastatic disease. It may not be appropriate to generalize the results of that study to our current group of patients who have minimal disease.

The Medical Research Council trial attempted to evaluate the issue of earlier versus later treatment, and they demonstrated a clear diminution in morbidity from the disease if androgen deprivation was administered at the time of diagnosis versus at some later time, either precipitated by symptoms or clinical progression. So, you could minimize urethral obstruction, vesicle outlet obstruction, skeletal events, paraplegia, spinal cord compression and so forth, all of which I think are worthwhile. They also showed a survival benefit in M0 disease. Now, as time goes on, that survival benefit becomes less obvious. If you're instituting a therapy in men who are in their late 60s or 70s and you follow them for 10 to 12 years, there are enough deaths from causes other than prostate cancer that will bring the curves together.

We have always treated prostate cancer relatively late with hormonal therapy. There is evidence that the best time to treat any cancer with any pharmacological agent is earlier rather than later. The entire rationale for adjuvant therapy is that mutations accumulate with time and if the volume of the disease is least and therefore the mutational capacity is least, then there is perhaps a window in which therapy could be curative. I know that sounds almost completely anathema to the thinking of urologists with regard to prostate cancer, but the test has never been applied early enough. In urology we say, "Well, it's good palliative therapy," which it is, but I think the mistake is that we say that's all it could be.

Update on the SPIRIT trial: Radical prostatectomy versus brachytherapy

Accrual to the SPIRIT trial has been discouragingly slow. Our center has randomized one patient out of 25 to whom the trial was presented. I'm not being overly pessimistic, but I'd be dramatically encouraged if I presented it to 25 people and 10 accepted. Other physicians have told me that they presented the trial to even more patients with a worse rate of acceptance, so the ratio might be a lot lower than one in 25. Patients recognize the importance of the trial and are very appreciative of what we're doing. I think that relinquishing control over their treatment decision-making is the overriding reason for choosing not to participate.

The Canadians have enrolled about five times as many patients to the trial as we have in the United States, which is a real tribute to their dedication to clinical trials. Another potential reason for the lower accrual rates in the United States is that our patients may not be simultaneously receiving an explanation of the risks and benefits of radiation therapy and prostatectomy. Once a patient has been directed toward one therapy, it's difficult to go back to "square one" and consider other options.

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, 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, April 2003

Select publications

Articles discussed by Dr Schellhammer

Bailar JC III, Byar DP. **Estrogen treatment for cancer of the prostate: Early results with 3 doses of diethylstilbestrol and placebo**. *Cancer* 1970;26:257–261. **Abstract**

Byar DP. **Proceedings of the Veterans Administration Cooperative Urological Research Group's studies of cancer of the prostate**. *Cancer* 1973;32:1126–1130. **Abstract**

Byar DP, Corle DK. **Hormone therapy for prostate cancer: Results of the Veterans Administration Cooperative Urological Research Group studies.** *NCI Monogr* 1988;7:165–170. **Abstract**

Medical Research Council Prostate Working Party Investigators Group. **Immediate versus deferred treatment for advanced prostatic cancer: Initial results of the Medical Research Council trial.** *Br J Urol* 1997;79:235–246. **Abstract**

Salvage therapy after failure of definitive local therapy

Chawla AK et al. **Salvage radiotherapy after radical prostatectomy for prostate adenocarcinoma: Analysis of efficacy and prognostic factors.** *Urology* 2002;59(5):726-31. **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**

Duchesne GM et al. **What to do for prostate cancer patients with a rising PSA? — A survey of Australian practice.** *Int J Radiat Oncol Biol Phys* 2003;55(4):986-91. **Abstract**

Katz MS et al. **Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer.** *J Clin Oncol* 2003;21(3):483-9. **Abstract**

Johnstone PA et al. **Initiation of salvage therapy for prostate cancer.** *Prostate Cancer Prostatic Dis* 2002;5(2):136-43. **Abstract**

Mosbacher MR et al. **Postprostatectomy salvage radiation therapy for prostate cancer: Impact of pathological and biochemical variables and prostate fossa biopsy.** *Cancer J* 2002;8(3):242-6. **Abstract**

Pollack A et al. **Prostate cancer DNA ploidy and response to salvage hormone therapy after radiotherapy with or without short-term total androgen blockade: An analysis of RTOG 8610.** *J Clin Oncol* 2003;21(7):1238-48. **Abstract**

Scherr D et al. **National Comprehensive Cancer Network guidelines for the management of prostate cancer.** *Urology* 2003;61(2 Suppl 1):14-24. **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**

Anthony L Zietman, MD, FRCR

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Director, Residency Training for Radiation Oncology, Department of Radiation Oncology, Genito-Urinary Oncology Unit, Massachusetts General Hospital

Edited comments by Dr Zietman

Impact of PSA screening on prostate cancer detection

With the advent of the PSA screening revolution, one would expect the median age at which we detect prostate cancer to be decreasing, but that is not the case. The median has remained the same, but the Gaussian peak is much more spread. We are detecting patients much younger with early disease, but we are also detecting an increasing number of older patients. These older men are the patients who perhaps don't need any treatment other than watchful waiting.

Watchful waiting in elderly patients

Over the past few years I've become very interested in the question, "Who really needs treatment?" Since about 1993 I've been recommending watchful waiting to elderly patients with small volume, low-grade disease. Paul Schellhammer and I recently reported on a couple of hundred patients with prostate cancer in their early 70s, each with a comorbid condition, who did not receive radical treatment.

It was striking to me that only one or two patients actually died of prostate cancer, but that so many patients found watchful waiting very difficult. Despite their doctors reassurance that prostate cancer was the least of their medical worries, approximately 50 percent of the patients elected treatment within five years, even though they had almost no signs of progression. So while watchful waiting is probably the right thing for an enormous number of elderly patients with early prostate cancer, it is a very difficult thing to do.

Watchful waiting in younger patients

Watchful waiting in younger men may be safe to do, but if a patient has a life expectancy of 20 or 30 years, you're probably only delaying treatment. It may be desirable to do so for one or two years while they deal with other big issues in their lives — maybe they plan to retire in a year and want to deal with treatment

then. You're only deferring the inevitable — it may be 5 or 10 years or more until they need to be treated, but I believe eventually they will need to be treated.

Efficacy of watchful waiting versus radical prostatectomy

There was an important trial reported in the *New England Journal of Medicine* in which one-half of the patients were managed expectantly and half received immediate radical prostatectomy. After eight years they found only a very small disease-specific survival advantage in patients who underwent radical prostatectomy rather than watchful waiting.

The trial involved Scandinavian patients — most of whom had palpable disease — who were not screen-detected and had a median PSA of around 10 ng/mL at the time of diagnosis. If we try to translate that to American patients, they are, on average, diagnosed by PSA approximately seven years before this point, so that eight-year data from the Scandinavian study could probably be translated to 15-year data for a US population. I think the difference between the two arms in the Scandinavian trial will diverge with time, but they haven't yet. As a result when I look at our patients, I think about that small survival advantage and their life expectancy and wonder how much we are actually gaining when we radically treat them.

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 disease (T1 – T2, NX, M0), PSA ≤ 50 ng/mL

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

Patients are followed every 3 months for 1 year and then every 6 months for 15 years.

Study Contacts:

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Veterans Affairs Cooperative Studies Program Coordinating Center
Perry Point & Cancer and Leukemia Group B

Daniel J. Culkin, MD, FACS
Protocol Chair
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Southwest Oncology Group

Timothy David Moon, MD
Protocol Chair
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1-800-622-8922
Eastern Cooperative Oncology Group

SOURCE: NCI Physician Data Query, April 2003.

Radical prostatectomy versus radiation therapy in younger patients

Currently in my practice, for patients in their 40s and early 50s, I recommend radical prostatectomy rather than radiation therapy. It's not that I can prove prostatectomy is superior, rather I just wonder what a younger man is doing with prostate cancer. Is his entire prostatic epithelium in some way genetically

dysfunctional such that if I treat him with radiation, he will go on to develop a new cancer in 10 or 20 years? I don't know the answer to that question. Also, I think younger men benefit from the prognostic information that's obtained at the prostatectomy.

Conformal radiation therapy

Phase III trials have shown an advantage to conformal over conventional radiation, so most of us use conformal therapy. There are new types of conformal radiation — proton beams — intensity-modulated radiation — that reflect technical advances that make treatment a bit more accurate. Whether that slightly increased accuracy translates into reduced morbidity or an increased cure rate, nobody knows yet. It has certainly increased cost of therapy. Whereas external beam radiation used to be comparable to radical prostatectomy in terms of cost, it is now much more expensive.

At this time, conformal therapy is almost entirely CT-scan-based. Some institutions are using MR-based planning and I believe functional MR will someday have a role with brachytherapy and perhaps external beam radiation. The idea of functional MR is to identify a dominant tumor focus and give that focus extra radiation. In the next decade I think we're going to see an enormous investigative push in this area. Whether it will be fruitful or not, I don't know.

Quality control in the delivery of radiation therapy

In terms of quality control, external beam therapy is delivered fairly well nationally. There is a national quality control body that compares academic centers with community centers and reports their findings every five years. The only substantial difference reported is that academic centers are bolder with external beam therapy. They use their conformal radiation to treat at higher radiation doses, which probably translates to an increased number of cures. That does not mean that radiation therapy in community practice is delivered badly, it's just delivered timidly.

As for brachytherapy, our patterns of care survey in 1994 revealed that 3 percent of early prostate patients were treated with brachytherapy, which increased to 27 percent by 1999 and I suspect it's 50 percent by now. We didn't have enough data from the 1994 and 1999 surveys to really draw conclusions, but I think quality control nationally is very loose. The American Brachytherapy Society is trying to develop quality control guidelines, but it's proving a difficult task.

Proficiency in brachytherapy

Radiation oncologists perform brachytherapy at many sites. We understand it well and we know its pitfalls. In the community, prostate brachytherapy is becoming a urologic procedure with radiation oncology backup rather than the other way around, and urologists are not as well-versed in the procedure. Legally, a radiation oncologist has to be involved in brachytherapy, but I think many radiation oncologists are abdicating their responsibility. They may be

present at the procedure or they may simply be involved in the planning or they may only write the prescription.

Brachytherapy is operator-driven and has a long, slow learning curve. Suboptimal results are usually due to inexperience and most urologists are only in their first one or two years of performing the procedure. The problem that usually occurs is that the seeds are misplaced, resulting in underimplantation of the target area. The seeds end up somewhere else, such as in the perineum or around the sphincter, with uncertain consequences. We haven't had time to document the patient outcomes, but we presume they will be worse.

External beam versus brachytherapy: Side-effect profiles

For men in their late 50s and older, selecting between brachytherapy and external beam therapy is not based on superiorit, but rather choosing between morbidities, and that's up to the patient.

Short-term, external beam therapy patients receive a mild, acute radiation prostatitis, a mild cystitis that manifests as urinary frequency and urgency, and they may experience proctitis, but it's generally minor. Brachytherapy patients experience an immediate, traumatic prostatitis with the insertion of the needles and then, about 10 to 14 days later, they experience edema of the prostate and urinary frequency and urgency. By three months, the side effects diminish and you can't really distinguish external beam patients from brachytherapy patients; however, there is no doubt that short-term, external beam patients have fewer problems.

Long-term effects of radiation therapy may include proctitis or persistent urinary symptoms, but the primary problem is erectile dysfunction. I think radiation oncologists and surgeons alike overstate the potency of our patients. When independent investigators have prospectively evaluated patients being treated with either brachytherapy or external beam radiation they find that in excess of 50 percent lose their erectile function. The risk of erectile dysfunction is even greater after surgery. Although there may be individual surgeons for whom it is less, if you look at national statistics, only about one-third of surgical patients retain useful erectile function without assistance.

Combination brachytherapy and external beam radiation

There's been a movement nationally to add external beam radiation to brachytherapy. The combination is very expensive with significant side effects, so we need to determine if there is a cancer advantage sufficient to warrant such heavy-duty treatment for low- and intermediate-risk disease.

The RTOG is about to open a trial looking at brachytherapy with or without external beam radiation. For the first part of the trial, we're looking for patients with intermediate-risk disease — PSAs greater than 10 ng/mL and Gleason scores of 7 — who might benefit from the addition of external beam therapy. The treatment will either be full-dose seed implant, palladium or iodine, or a reduced-dose implant together with 45 Gy external beam radiation. Androgen deprivation will not be allowed in the trial to avoid confounding issues.

Triple approach therapy including androgen deprivation

An enormous number of patients are receiving off-protocol, triple therapy consisting of external beam radiation, brachytherapy and androgen deprivation. I don't use triple therapy because I tend not to use hormone therapy with brachytherapy. We know from mouse experiments, *in vitro* experiments and clinical trials that hormone therapy, when added to external beam radiation, pulse high-dose radiation, is synergistic. But the method of cell killing by low-dose-rate brachytherapy is completely different. It is entirely possible that hormone therapy could actually reduce the cell killing by taking cells out of cycle. When the Seattle Group analyzed their large series of patients who had received prostate brachytherapy and stratified them by risk, they found that, in the intermediate-risk group, patients who had been given some hormone therapy first, did worse than those who'd had brachytherapy alone.

Neoadjuvant and adjuvant hormone therapy in combination with external beam radiation

Several randomized trials from the 1980s, published in the 1990s, showed that patients with intermediate-risk disease did better in terms of local control and disease-specific survival if they received neoadjuvant hormone therapy, which consisted of hormone therapy before and during radiation. That then became the standard of care. We're not sure whether hormone therapy and external beam radiation are additive or synergistic (they appear to be synergistic in the mouse model), and it might be that local control is substantially improved by the addition of hormone therapy.

The RTOG has conducted trials comparing external beam radiation with a short course versus a long course (two or three years) of adjuvant hormone therapy. For patients with high-risk features, Gleason 8, 9 and 10, there is a small but significant survival advantage eight years later for the longer course of hormone therapy.

Hormonal therapy based on risk

In our patterns of care survey we find most patients with high-risk and intermediate-risk prostate cancer are receiving hormone therapy, as well as 50 percent of early-stage patients. It has just become practice without evidence. In my practice, I don't use hormone therapy for patients at low risk. For patients at intermediate risk, I recommend neoadjuvant hormone therapy; for those at high risk, I use long-term adjuvant androgen deprivation.

No evidence supports the need for hormone therapy in patients at low risk (PSA less than 10 ng/mL, Gleason 6 or less). A randomized RTOG trial with 1,600 patients was completed several years ago. It doesn't plan to report for many years, but as far as we know now, radiation alone appears to be sufficient for men with low-risk disease.

For intermediate-risk disease (Gleason 7, a bulkier tumor, PSA of 10 to 20 ng/mL) we normally add neoadjuvant and concurrent hormone therapy. We're

conducting trials to determine what duration of neoadjuvant hormone therapy is the most efficacious. We found in animal models that you obtain the most benefit from the radiation treatment if you give it at the point when you have the maximal response to hormone therapy. That's why we're testing six months versus the current standard of two months of hormonal therapy, because we don't see much shrinkage after only two months. Off protocol, I give patients the single LHRH agonist injection at three months and plan for radiation three months later.

For patients with high-risk disease (Gleason 8, 9 and 10 or a lower Gleason grade with a PSA greater than 20 ng/mL) we generally use postradiation, adjuvant LHRH agonists for two or three years. European and American trials suggest two or three years is better than a short course, but whether two or three years is better, we don't know. In my practice, I generally review the situation after a year and if the patients are truly miserable on their LHRH agonist, as many of them are, I may stop then or I may just give a second year of therapy rather than a full three.

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 8wks → (MAB + XRT) x 8wks Arm 2: MAB x 28wks → (MAB + XRT) x 8wks
EORTC-22991	XRT ± adjuvant bicalutamide and goserelin in patients with localized prostate cancer	Arm 1: Bicalutamide days 1-30 + goserelin days 8 & 98 + XRT beginning day 8 Arm 2: XRT
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 + 6m MAB Arm 2: XRT+ 6m MAB → (antiandrogen + LHRH analogue) x 2.5 yrs → LHRH analogue x 2.5 yrs
RTOG-P-0011, CTSU, RTOG-DEV-1037, CAN-NCIC-PR9	Adjuvant XRT with hormonal therapy versus XRT alone versus hormonal therapy alone in patients with high-risk Stage II or III prostate cancer	Arm 1: XRT + goserelin or leuprolide q 1-4 months x 2 yrs + flutamide or bicalutamide daily x 1 m Arm 2: XRT Arm 3: goserelin or leuprolide q 1-4 months x 2 yrs + flutamide or bicalutamide daily x 1 m

MAB = Maximum androgen blockade; XRT = Radiation therapy

SOURCE: NCI Physician Data Query, April 2003

Hormonal therapy for systemic versus local disease

The primary intent of using postradiation, adjuvant hormonal therapy in patients with high-risk disease is to deal with micrometastatic disease. Interestingly, if those same patients underwent surgery rather than radiation for local therapy, they probably wouldn't receive adjuvant androgen deprivation therapy. In radiation, we have two randomized trials that have shown a survival advantage with the combination, so it's become the standard of care. It may be that if those same patients went into a randomized trial of hormonal

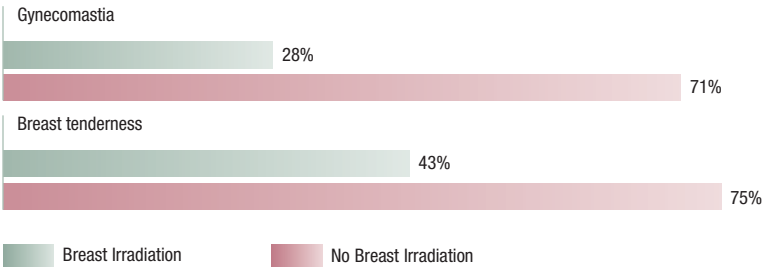
therapy following a radical prostatectomy, rather than radiation, that the results would also be positive and the practice patterns would change. In dealing with prostate cancer, we need to recognize that we are dealing with a systemic disease.

Toxicity profile: Bicalutamide 150 mg versus LHRH agonists

We've completed a randomized trial at Massachusetts General Hospital in which we compared the effects of high-dose bicalutamide to LHRH agonists with regard to body composition, bone mass and a number of psychological and quality of life endpoints. Until we analyze the data, it's too early to say, but it appears that bicalutamide has a less profound effect on body fat, less fatigue and bone mass goes up, not down. Also, my guess is that the quality of life will be better with high-dose bicalutamide than with an LHRH agonist.

There are some downsides to high-dose bicalutamide. Gynecomastia can affect 70 percent of men. However, we know from a Swedish trial that if you administer 1 to 3 doses of radiation to the breast prior to starting bicalutamide or flutamide, you can reduce the risk of gynecomastia from approximately 70 percent to about 25 percent. It also reduces breast tenderness, although to a lesser degree.

Effect of prophylactic breast irradiation therapy on antiandrogen-induced gynecomastia as reported by physicians after 12 months.



DERIVED FROM: Widmark A et al. **Does prophylactic breast irradiation prevent antiandrogen-induced gynecomastia? Evaluation of 253 patients in the randomized Scandinavian trial SPCG-7/SFUO-3.** *Urology* 2003;61(1):145-51. **Abstract**

Long-term androgen deprivation and bisphosphonates

We conducted a study of men on long-term androgen deprivation in which half were treated with pamidronate and half were not. Bone density was measured at six months and one year. After one year, for those who did not receive pamidronate, the median bone loss was about 5 to 7 percent. It was substantially less, or not at all, for those who did receive pamidronate. We didn't expect our trial to result in every patient receiving androgen deprivation therapy to be treated with pamidronate or, by extension, zoledronate, which is more convenient. And we don't know how clinically relevant the bone loss is and that still needs to be studied. We simply showed that there is bone loss and it can be prevented.

Salvage radiation

Despite the curative intent of radical prostatectomy, PSA goes up after the procedure in 30 to 50 percent of patients, depending on what series you review. So there's no question that failure is a problem after surgery, but where are the patients failing — locally or at distant sites? In a large series from the University of California at San Francisco, patients with a rising PSA after prostatectomy had their prostate beds re-biopsied and approximately 50 percent showed evidence of local failure. That would suggest that postoperative radiation, or salvage radiation given when the PSA rises, might cure some patients.

We, and many others, have looked extensively at the role of salvage radiation and it appears it cures about 30 percent of these patients. Why don't we cure more than 30 percent? I think because, even though the PSA comes down in 70 percent of those we treat, obviously 40 percent have distant disease as well, so the PSA subsequently rises.

We're selective in whom we treat with salvage radiation. If the PSA is going up rapidly, the original tumor was a Gleason 9 or 10 and there's extensive seminal vesicle involvement and positive lymph nodes, the chance of occult micrometastatic disease is so high that salvage radiation is a waste of time. For those patients, it's a question of hormonal therapy, either now or at some future time.

Combining hormone therapy and salvage radiation

The data is pretty thin with regard to combining hormone therapy with salvage radiation. We know that when we treat patients with even the standard dose of 64 Gy salvage radiation, subsequent local recurrences are rare. So, radiation is at least getting the job done in the tumor bed and hormone therapy would be added to eradicate micrometastatic disease, for which we'd consider three years of androgen deprivation.

While one might presume that the effect of high-dose bicalutamide on occult micrometastatic disease is the same as an LHRH agonist, we don't know for certain. The RTOG is conducting a trial in which all patients receive salvage radiation and half receive high-dose bicalutamide. About 900 of the projected 1,400 patients have been entered, so we should finish enrollment this year. I have patients enrolled in this study and, while it's double-blind, we can easily tell who is on the bicalutamide by the breast effects. About three or four weeks after starting bicalutamide, patients develop nipple tenderness. It takes a few months before they develop gynecomastia. Hot flashes are not a problem with the bicalutamide. Sexual dysfunction is not an immediate problem, as it is with an LHRH agonist, but it's still a problem. Even if a patient still has erectile function after surgery, the radiation and high-dose bicalutamide are a double assault and it's very unusual for patients to still have erectile function after two years.

PHASE III Randomized Study of Radiotherapy with or without Bicalutamide in Patients with PSA Elevation following Radical Prostatectomy for Carcinoma of the Prostate **Open Protocol**

Protocol IDs: RTOG-9601, SWOG-R9601, CTSU, RTOG-R9601

Projected accrual: 810 patients

Eligibility: Stage T3 N0 or pT2 pN0 with positive inked margin, postradical prostatectomy and pelvic lymphadenectomy for prostate cancer with PSA 0.2-4.0 ng/mL at study entry

Arm 1: Radiotherapy → bicalutamide x 2 yrs
Arm 2: Radiotherapy → placebo x 2 yrs

Recommended treatment for increasing PSA and bone metastases consists of maximal androgen blockage. Patients are followed every 3 months for 2 years, every 6 months for 3 years and annually thereafter.

Study Contacts:

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Protocol Chair
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Southwest Oncology Group

SOURCE: NCI Physician Data Query, April 2003

Select publications

Publications discussed by Dr Zietman

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

Widmark A et al. **Does prophylactic breast irradiation prevent antiandrogen-induced gynecomastia? Evaluation of 253 patients in the randomized Scandinavian trial SPCG-7/SFUO-3.** *Urology* 2003;61(1):145-51. **Abstract**

Zietman AL et al. **Conservative management of prostate cancer in the prostate specific antigen era: The incidence and time course of subsequent therapy.** *J Urol* 2001;166(5):1702-6. **Abstract**

Watchful waiting

Bacon CG et al. **The impact of cancer treatment on quality of life outcomes for patients with localized prostate cancer**. *J Urol* 2001;166(5):1804-10. **Abstract**

Chapple A et al. **Is 'watchful waiting' a real choice for men with prostate cancer? A qualitative study.** *BJU Int* 2002;90(3):257-64. **Abstract**

Choo R et al. **Feasibility study: Watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression.** *J Urol* 2002;167(4):1664-9. **Abstract**

Schmid HP et al. **Active monitoring (deferred treatment or watchful waiting) in the treatment of prostate cancer. A review.** *Eur Urol* 2001;40(5):488-94. **Abstract**

Schwartz E, Albertsen P. **Nomograms for clinically localized disease. Part III: Watchful waiting.** *Semin Urol Oncol* 2002;20(2):140-5. **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**

Post-test: Prostate Cancer Update, Issue 3, 2003

Conversations with Urologic Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In what percentage of patients did testosterone return to baseline levels four months after discontinuing therapy in a Phase II study of intermittent androgen deprivation?
   a. 20%
   b. 35%
   c. 50%
   d. 75%

2. Compared to androgen deprivation alone, maximum androgen blockade results in relative decrease in mortality over five years of approximately:
   a. 1%
   b. 3%
   c. 10%
   d. 12%

3. One of the most frequently occurring side effects of bicalutamide monotherapy is:
   a. Gynecomastia
   b. Fatigue
   c. Peripheral neuropathy
   d. Cognitive slowing

4. The Medical Research Council study demonstrated a survival advantage for early versus deferred androgen deprivation in patients with M0 disease.
   a. True
   b. False

5. A study reported in the *New England Journal of Medicine* in 2002, comparing radical prostatectomy (RP) to watchful waiting, demonstrated:
   a. Overall survival advantage for RP
   b. Disease-specific survival advantage for RP
   c. No difference in outcome between the groups

6. Phase III trials have failed to demonstrate an advantage of conformal over conventional radiation therapy.
   a. True
   b. False

7. According to Dr Zietman, what percentage of patients experience erectile dysfunction after external beam radiation or brachytherapy?
   a. <10%
   b. 25%
   c. 40%
   d. >50%

8. According to a Swedish trial, 1-3 doses of radiation to the breast will reduce the incidence of bicalutamide-induced gynecomastia from 70% to 25%.
   a. True
   b. False

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

Evaluation Form: Prostate Cancer Update, Issue 3, 2003

NL Communications 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 only upon receipt of our 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 3

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

- Develop an awareness of ongoing clinical trials of intermittent versus continuous androgen deprivation in order to counsel patients about their eligibility for participation 5 4 3 2 1
- Evaluate research leader perspectives and clinical data related to salvage radiation and hormonal therapy in order to counsel patients about treatment options after failure of definitive local therapy 5 4 3 2 1
- Review clinical trial data and research leader views on early versus deferred hormonal therapy in order to offer patients choices after local therapy 5 4 3 2 1
- Evaluate the role of watchful waiting versus local therapy to determine for whom it would be an appropriate option 5 4 3 2 1
- Review the advantages and disadvantages of different methods for delivering radiation therapy 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Laurence Klotz, MD, FRCSC	5 4 3 2 1	5 4 3 2 1
Paul F Schellhammer, MD	5 4 3 2 1	5 4 3 2 1
Anthony L Zietman, MD, FRCR	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 3, 2003

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Street Address: _____ Box/Suite: _____

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I certify my actual time spent to complete this educational activity to be ___ hour(s).

Signature: _____

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?

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

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Degree:

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

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