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Prostate Cancer™ UPDATE

Conversations with Urologic Oncology Leaders
Bridging the Gap between Research and Patient Care

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HOW TO USE THIS MONOGRAPH

This CME activity 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 urologic oncology. 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 practice, *Prostate Cancer Update* utilizes one-on-one discussions with leading urologic oncology and radiation 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 screening, prevention and treatment.
- Inform prostate cancer patients about the specific risks and benefits of local and systemic therapies.
- Offer patients information regarding their prognosis with and without various therapeutic options.
- Provide individualized counseling to patients regarding the choice and timing of endocrine therapy.
- Discuss chemotherapy and biologic therapy options in the treatment of prostate cancer.

PURPOSE OF THIS ISSUE OF *PROSTATE CANCER UPDATE:*

The purpose of Issue 2 of *Prostate Cancer Update* is to support these global objectives by offering the perspectives of Drs Klotz, Zietman and Dreicer on the integration of emerging clinical research data into the management of prostate cancer.

ACCREDITATION STATEMENT:

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

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Laurence Klotz, MD	Grants/Research Support: Abbott Laboratories Consultant: AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals Inc, Novartis Pharmaceuticals
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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
bicalutamide	Casodex®	AstraZeneca Pharmaceuticals LP
calcitriol	Rocaltrol®	Roche Laboratories Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxazosin mesylate	Various	Various
estramustine phosphate	Emcyt®	Pfizer Inc
finasteride	Proscar®	Merck and Company Inc
flutamide	Eulexin®	Schering-Plough Corporation
goserelin acetate	Zoladex®	AstraZeneca Pharmaceuticals LP
hydrocortisone	Various	Various
ketoconazole	Nizoral®	Janssen Pharmaceutica Products LP
letrozole	Femara®	Novartis Pharmaceuticals
leuprolide acetate implant	Viadur™	ALZA Corporation
	Lupron Depot®	TAP Pharmaceuticals Inc
mitoxantrone hydrochloride	Novantrone®	Serono Inc
nilutamide	Nilandron®	Aventis Pharmaceuticals Inc
prednisone	Various	Various
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP

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Editor's Note:

Is prostate cancer essentially breast cancer in men?

> The effects of hormonal treatment on prostate cancer mortality are about as extreme as the effects of hormonal treatment on breast cancer mortality. The breast trials involve larger patient numbers and there weren't some of the side effects involved with the early hormonal treatments of prostate cancer, which are no longer seen with the current hormonal treatments, and so prostate cancer really got undeservedly bad press. The fact is that hormonal treatment works about as well for prostate cancer as for breast cancer. … I think the negativism about the treatment of prostate cancer — the mistaken belief that you can't affect mortality — is wrong.
>
> *— Sir Richard Peto, Oxford University*
> *"Best of Oncology" 2003 ECCO meeting presentation*

On September 9, 1985, Richard Peto — a previously obscure Oxford statistician — changed cancer research forever. I have a grainy videotape of Peto's historic presentation at the NIH Consensus Conference on Early Breast Cancer, and you can see the glee in his eyes as he systematically destroys the widespread previously held belief that adjuvant tamoxifen had no effect on breast cancer mortality.

That day in Bethesda was the beginning of the mega-randomized adjuvant trial. Prior to this presentation, many individual breast cancer trials had failed to detect a mortality benefit from tamoxifen. Peto clarified this issue by explaining that to detect a significant impact of a therapy on an endpoint, it is critical for a study to have enough observed events, as opposed to enough enrolled patients or follow-up time.

Specifically, to detect an impact on mortality, enough deaths must be observed. Peto then went on to demonstrate that not enough deaths had occurred in the individual breast cancer trials to reliably evaluate whether a modest but humanly important survival benefit was present. However, when he combined these studies into a meta-analysis of virtually every randomized trial of adjuvant tamoxifen ever conducted, enough deaths were observed to detect a very substantial mortality reduction.

Over the years, I have recorded several interviews with Peto for our breast cancer audio series. In 1990 I was honored to attend a closed meeting of his breast cancer trialists' group in an ancient lecture hall in Oxford. Peto, a bit of a maverick, sent out premeeting questionnaires to the attendees to ascertain what they believed the second meta-analysis would demonstrate. For two days, he presented overhead transparencies (he still doesn't use slides or PowerPoint™ presentations) of the trialists' predictions and the actual results, which, of course, were vastly different.

Shortly after I started this series several years ago, I ran into Sir Richard (by this time he had been knighted for his work) at a meeting and asked why he wasn't doing a similar meta-analysis of adjuvant hormonal trials in prostate cancer. He confided in me that just such a study was ongoing, and he graciously invited me back to Oxford for his first presentation of these data in September 2002. Only two other US-based physicians were part of this small group, and I sat in the back of the room with one of them, Rowan Chleblowski, a medical oncologist who has published extensively on breast cancer but also participates in prostate cancer research.

Rowan and I were gaggle-mouthed as we watched the data unfold. The disease-free and overall survival curves for the relatively scant trials of adjuvant endocrine intervention of prostate cancer looked eerily similar to the old breast cancer graphs.

An unfortunate similarity between the breast and prostate cancer overviews is that public presentation of the actual data is embargoed until formal publication of the definitive paper. This often takes years. To this date, the only public discussion of this fascinating analysis was Peto's "Best of Oncology" lecture in Copenhagen at the 2003 ECCO meeting, during which he presented both the breast and prostate cancer overview. As a result, his presentation with slides is posted on the ECCO website (**http://www.fecs.be/conferences/ecco12/virtualmeetings.shtml**).

During the upcoming AUA annual meeting, our group will host a "think tank" of 12 prostate cancer research leaders. As part of the agenda for this event, we intend to show the web presentation of Peto's breast-prostate talk. This will be one of many topics discussed at the "think tank," and the proceedings will be recorded and edited into a special issue of this series. It will be extremely interesting to hear the responses of this diverse group of practitioners, which includes Edward Messing, the other American and only US-based urologist to attend the 2002 Oxford meeting.

Likely comments include the fact that Peto combined trials in which the primary local modality was surgery or radiation therapy. This methodology is based on the long-held belief in breast cancer that adjuvant therapy targets micrometastases irrespective of the type of local treatment. In contrast, urologic oncologists generally do not accept that premise regarding prostate cancer.

Another controversy will involve the fact that most of these adjuvant prostate trials treated patients at the onset of clinical rather than PSA progression.

Therefore, these data are not relevant to the current standard of care whereby most men are treated for biochemical failure rather than for clinically apparent disease.

The counterclaim to that argument is that no randomized trial has demonstrated that treating at PSA progression results in the same outcome as adjuvant treatment. Again, this is a long-held belief in urology that will challenge the Peto data.

To "muddy the waters" further, it is also interesting to consider that two small clinical trials in breast cancer have suggested that treating on tumor marker progression results in greater survival than waiting for clinical relapse. No breast cancer trial has ever compared adjuvant therapy to treating at biochemical relapse.

In this issue of *Prostate Cancer Update*, Laurence Klotz comments on the profound differences in the research cultures that exist in breast cancer and prostate cancer. He notes that his colleague at the University of Toronto, oncologist Dr Paul Goss, recently published a lead article in the *New England Journal of Medicine* on the use of an aromatase inhibitor in women who have completed adjuvant therapy with tamoxifen.

Dr Klotz notes that the Goss study garnered considerable attention and led to an immediate change in clinical practice of oncologists. He also points out that the benefits of therapy seen in that study were the same or perhaps less than those observed with the use of maximum androgen blockade (MAB) in prostate cancer. However, MAB has received a lukewarm reception by urologists.

Dr Klotz will also be at our "think tank," and it will be interesting to observe how this dialogue unfolds, particularly since he is presenting a paper at the AUA suggesting that the benefits of MAB using bicalutamide may be considerably greater than MAB with other antiandrogens.

In addition to the analogous research issues on endocrine therapy, many other fascinating similarities exist between breast and prostate cancer. Chemoprevention has been demonstrated to alter the natural history of both diseases, but the clinical implications are uncertain. For both types of cancer, current therapies have sexual implications, and the treatment options for local disease control have very different long-term implications.

Perhaps most encouraging is that the mortality rates for both breast and prostate cancer are significantly decreasing. Peto noted in his ECCO lecture that this reduction in mortality is likely the result of earlier diagnosis and earlier use of endocrine intervention for both tumors. Regrettably, the specialization of cancer care means that investigators in both fields rarely meet. This is unfortunate because each group might teach the other a great deal.

— Neil Love, MD

Edited comments by Laurence Klotz, MD

Prostate Cancer Prevention Trial

Three observations from the Prostate Cancer Prevention Trial (PCPT) are important with respect to prostate cancer management. The first is the 25 percent reduction in the rate of prostate cancer diagnosis in the finasteride-treated group. The second is that at the end of seven years, 25 percent of the patients in the placebo group had a positive biopsy. The third is the loss of libido and erectile function in the placebo group during the seven years of the trial.

Overdetection of early, low-risk prostate cancer

The high rate of prostate cancer detection in the PCPT is the latest piece of evidence indicating that screening may lead to increased rates of prostate cancer diagnosis. Another piece of evidence comes from the European Randomized Screening for Prostate Cancer (ERSPC) trial in which the rate of diagnosis in the screened arm was seven times higher than in the control arm, but mortality was the same. The inescapable conclusion is that we are diagnosing more patients with prostate cancer than the number of patients who are at risk of death from prostate cancer.

I don't believe we should stop screening just because we've had a phenomenal stage migration. However, we need to change the way we approach patients with favorable-risk, localized prostate cancer — patients with a mild PSA elevation or a normal PSA whose biopsies reveal small-volume, well-differentiated prostate cancer. Those patients are not likely to die from prostate cancer and should probably be followed rather than treated aggressively.

Regardless of age, the patient with a small microfoci of well-differentiated prostate cancer very possibly has minimal disease and may not need to be treated. Before the PCPT trial, it was believed that when the PSA went up, it reflected a larger volume of disease, which led to a biopsy. We've learned from the PCPT that we're diagnosing the 25 or 30 percent of patients with microfoci, and most of them should not be treated.

Effect of finasteride on the rate of prostate cancer and on tumor grade

The PCPT trial was unequivocally positive. In fact, it was stopped early because the results were so positive. Although 18,000 patients were enrolled, the results

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are based on the first 9,000 patients who underwent a biopsy. Compared to the patients receiving placebo, those treated with finasteride had a 25 percent reduction in the incidence of prostate cancer.

The rate of high-grade cancer was greater in the patients treated with finasteride. Two reasons may account for this difference in cancer grade. First, finasteride may artificially change the cancer grade. It's widely accepted that androgen deprivation therapy causes an upgrading of the Gleason score. Pathologists agree that a Gleason score can't be assigned after androgen deprivation therapy. It's also possible that finasteride interferes with androgen receptor function and predisposes patients to a higher-grade cancer.

Deciding whether patients should receive finasteride for prostate cancer prevention

To determine the value of finasteride in prostate cancer prevention, the results from the Medical Therapy of Prostatic Symptoms (MTOPS) trial must be considered. MTOPS was a large, four-arm, placebo-controlled trial in patients with benign prostatic hyperplasia (BPH) that evaluated an alpha-blocker (doxazosin) and finasteride. It demonstrated a definite benefit from treatment with the combination of an alpha-blocker and finasteride compared to either drug alone, and in terms of a reduced need for surgery, reduced urinary retention and improvement in symptoms.

Two positive trials evaluating the role of finasteride — one in patients with BPH and one in patients with prostate cancer — are relevant to the middle-aged man who's worried about prostate cancer. In a patient who has some enlargement of the prostate and is symptomatic, finasteride may reduce the symptoms and the likelihood of needing surgical intervention.

Use of finasteride is associated with a 25 percent reduction in the rate of prostate cancer, and it facilitates regrowth of hair. The potential downsides to finasteride include its impact on erectile function, which is uncommon and reversible, and a possible increased risk of high-grade prostate cancer. However, only two to four patients out of 1,000 actually develop higher-grade cancer.

Adjuvant hormonal therapy for patients with high-risk prostate cancer

Controversy exists about the management of patients with high-risk prostate cancer. The closest thing to a standard of care is external beam radiation plus two to three years of adjuvant hormonal therapy. However, data from several sources indicate that surgery may have a role for patients with high-risk disease. A randomized trial by Akakura et al from Japan demonstrated a survival benefit for patients with locally advanced prostate cancer who were treated with hormonal therapy and surgery compared to patients treated with hormonal therapy and radiation therapy.

Data from the Early Prostate Cancer (EPC) trial of adjuvant bicalutamide from Scandinavia demonstrated a survival benefit with bicalutamide compared to

placebo in patients with locally advanced disease. These data support the idea that patients with high-risk disease may derive benefit from adjuvant androgen deprivation — even those who have undergone radical prostatectomy. Data from Quebec indicate that patients treated with neoadjuvant hormonal therapy and surgery have a superior outcome compared to patients treated with hormonal therapy and radiation.

This whole concept of adjuvant hormonal therapy needs to be clarified. Based on a number of trials, early hormonal therapy offers a survival benefit. It has a role in patients with high-risk disease treated with radiation therapy. However, its role in patients who are treated with surgery is unknown. Conventional thinking indicates that in a small population of prostate cancer cells, a single androgen-independent cancer cell will eventually predominate despite androgen deprivation therapy.

However, the model of the "bystander effect" would suggest that an isolated androgen-independent cancer cell requires androgen-dependent cancer cells to survive. Hence, a role for more aggressive early therapy may exist, although it has yet to be proven. Over the next few years I foresee a shift toward earlier use of androgen deprivation therapy after radical prostatectomy in the adjuvant setting.

Meta-analysis of trials evaluating maximum androgen blockade

We've sold ourselves short in urology by discounting minor survival benefits. Paul Goss, at our center in Toronto, recently published a trial of letrozole in approximately 6,000 patients with breast cancer who were treated with five years of adjuvant tamoxifen. His trial demonstrated a very small disease-free survival benefit for letrozole that has been widely touted as being important.

In urology, we have comparable differences with maximum androgen blockade (MAB). There are at least six meta-analyses of nilutamide or flutamide plus medical or surgical castration versus castration alone. They all demonstrated approximately a 10 percent reduction in the hazard ratio for death at five years, which relates to about a three percent absolute survival benefit.

One study with 800 patients with a two-by-two factorial design — bicalutamide or flutamide combined with goserelin or leuprolide acetate — demonstrated that bicalutamide was approximately 12 percent better than flutamide in terms of risk of death. So the question is, "What conclusions can be drawn from the meta-analyses and this large randomized study?"

The statisticians contend trial results cannot be mixed, but that's not entirely true if certain conditions are fulfilled. In a situation where Drug A has been shown to be better than Drug B, and Drug B is superior to Drug C, you can then say Drug A is better than Drug C if the inclusion criteria for the trials are similar. The mathematics are quite complex, but it turns out that bicalutamide is 10 percent better than flutamide when both are combined with an LHRH agonist. Flutamide is 10 percent better than placebo when used in MAB. Scientifically, there is a reasonably sound basis for asserting bicalutamide plus castration is 20 percent

better than castration alone. This analysis will be presented at the 2004 AUA meeting for the first time.

Role of MAB in patients with high-risk disease

I primarily use MAB with bicalutamide in patients I consider to be at higher risk of death from prostate cancer, for whom I really want to provide every opportunity for long-term survival. The typical patient currently being treated with androgen deprivation is one who was initially treated with radiation therapy or a prostatectomy and three or four years later has a rise in his PSA. Since those patients have very long-term survival, they may be on androgen deprivation for eight, 10 or 15 years. Hence, I'm a little reluctant to add more to their therapy. However, in the patients with higher-risk disease, such as those with metastatic disease or a rapidly rising PSA, I'm much more aggressive with MAB than I was a year or two ago.

Select Publications

Akakura K et al. **Long-term results of a randomized trial for the treatment of Stages B2 and C prostate cancer: Radical prostatectomy versus external beam radiation therapy with a common endocrine therapy in both modalities.** *Urology* 1999;54(2):313-8. **Abstract**

Draisma G et al. **Lead-times and overdetection in PSA screening: an estimate based on results from the ERSPC Trial, Section Rotterdam.** Presented at the American Urological Association Annual Meeting 2003;**Abstract DP14.**

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802. **Abstract**

McConnell JD et al; Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. **The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia.** *N Engl J Med* 2003;349(25):2387-98. **Abstract**

Prostate Cancer Trialists' Collaborative Group. **Maximum androgen blockade in advanced prostate cancer: An overview of the randomised trials.** *Lancet* 2000;355(9214):1491-8. **Abstract**

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van der Cruijsen-Koeter IW et al. **Comparison of screen detected and clinically diagnosed prostate cancer in the 'European Randomized Study of Screening for Prostate Cancer.'** Presented at the American Urological Association Annual Meeting 2003;**Abstract 407.**

Edited comments by Anthony L Zietman, MD, MRCP, FRCR

Androgen deprivation combined with brachytherapy and external beam radiation therapy

Androgen deprivation is commonly utilized prior to brachytherapy to reduce the size of a large prostate. The Seattle group has retrospectively evaluated all of their patients treated with or without androgen deprivation and found no advantage to androgen deprivation prior to brachytherapy in patients with a favorable prognosis. In addition, for patients with an intermediate prognosis, the data suggests it may be disadvantageous, which is worrisome.

I have two concerns with Richard Stock's nonrandomized series looking at brachytherapy, external beam and androgen deprivation. First, the follow-up is relatively short, and since the effects of hormone therapy can last for months or years beyond treatment, one would expect the early data to look good. Longer-term data is necessary. Second, we know that androgen deprivation given prior to external beam therapy appears to work synergistically with radiation to enhance tumor control. However, the cell kill from low-dose rate brachytherapy is different and hasn't been well-characterized. If that cell kill is more cell-cycle dependent, which is possible, then taking cells out of cycle with androgen deprivation may actually increase resistance.

High-dose external beam radiation therapy

It is increasingly clear that eradication of cancer from the prostate requires high doses of radiation. In retrospect, the doses we routinely used well into the 1990s were inadequate and substantially inferior to radical prostatectomy. Cleveland Clinic's database evaluating patients treated with doses less than or greater than 72 Gray shows a significant divergence in outcome at eight years. MD Anderson's data suggest control for patients with intermediate prognosis is improved by high-dose radiation — 78 Gray. Four other randomized trials are underway and I suspect they, too, will be positive for high-dose therapy.

My concern with ultra-high doses of radiation is the morbidity. We need a prospective study to examine doses of 80 Gray or higher. Although our delivery is more conformal and we treat less of the rectum and bladder than before, we can't avoid radiating the prostatic urethra, and I'm concerned about late urethral

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morbidity. At Massachusetts General Hospital we have 42 long-term survivors who were treated with doses of 77 Gray proton beam radiation in the 1980s. With a median follow-up of 13 years, approximately 50 percent have experienced an episode of hematuria. On cytoscopy, we usually find telangiectasia at the bladder neck and, in some cases, prostatic urethral restrictures requiring transurethral resection, which increases the patient's risk for incontinence.

Radiation therapy plus androgen deprivation

The Radiation Therapy Oncology Group's two-by-two study design (RTOG-9413) evaluating radiation to the prostate alone versus radiation to the prostate and regional lymph nodes, with adjuvant therapy given for two months before and two months during radiation versus four months after radiation in patients with locally advanced prostate cancer. It demonstrated an advantage to whole pelvis radiation and neoadjuvant therapy, but only when the two were combined (Figure 2.1).

In RTOG-8531, patients with relatively poor prognosis locally advanced prostate cancer were randomly assigned to radiation therapy alone or radiation therapy plus total androgen blockade until relapse. A survival advantage was seen with hormonal therapy in patients with higher-grade tumors. In RTOG-9202, comparing radiation plus short-term versus long-term androgen deprivation, long-term therapy was advantageous in survival and disease-free survival, but only for those with centrally reviewed Gleason grades 8 through 10.

Patients with a favorable prognosis are generally treated with high-dose external beam radiation alone. For patients with an intermediate prognosis, we combine radiation with short-term neoadjuvant androgen deprivation. In patients with a

Figure 2.1

RTOG-9413: Four-Year Efficacy Outcomes

Treatment arm	n	Progression-free survival % (95% CI)	Biochemical failure % (95% CI)
WP RT + NHT	319	59.6 (53-66)	30.3 (24-36)
PO RT + NHT	316	44.3 (38-51)	42.8 (36-49)
WP RT + AHT	322*	48.9 (42-55)	36.7 (30-43)
PO RT + AHT	322	49.8 (43-56)	36.5 (30-43)
p-values**	-	0.008	0.048

CI = Confidence interval; WP RT = whole-pelvic radiotherapy; NHT = neoadjuvant hormone therapy; PO RT = prostate-only radiotherapy; AHT = adjuvant hormone therapy

*One patient is excluded from the progression-free survival analysis because disease status is unknown (n=321).

***p*-value is from either the log-rank test (progression-free) or Gray's test (biochemical failure) for comparing the four survival curves.

SOURCE: Roach M et al. *J Clin Oncol* 2003;21:1904-11. **Abstract**

poor prognosis, particularly those with Gleason grades 8 through 10, we continue androgen deprivation for two or three years based on the European study.

RTOG clinical trials of androgen deprivation

Data from Canada suggest it takes up to eight months to achieve maximal tumor response from androgen deprivation. RTOG has a trial in patients with an intermediate prognosis comparing four versus eight months of adjuvant androgen deprivation. In both arms, the last two months of therapy are concurrent with radiation, and the remainder is administered before radiation. The trial has accrued over a thousand patients, but it will be several years before we have results.

RTOG also conducted a trial for patients with rising PSAs after prostatectomy. The majority of patients also had positive surgical margins. Patients were randomly assigned to salvage radiation with or without high-dose bicalutamide — 150 milligrams — for two years. The trial is complete, and the first analysis is expected in a couple of years.

We know that in the short term, high-dose bicalutamide will favorably impact time-to-first-progression, but we don't know what its impact will be on survival and metastases. This trial will determine the efficacy of salvage radiation monotherapy, which I expect will only cure one-third of these patients.

LHRH agonist versus high-dose bicalutamide in patients who relapse

Matthew Smith has completed a study of bone and other effects in a trial that randomly assigned patients who relapsed after radiation or surgery to an LHRH agonist versus high-dose bicalutamide. The study included bone mineral density, body mass index, muscle mass and quality-of-life evaluations.

The data show approximately a five to seven percent bone loss with the LHRH agonist versus a one or two percent bone gain with high-dose bicalutamide during the first year of treatment. While all the patients gained fat and lost muscle, the patients on bicalutamide fared a little better. In addition, high-dose bicalutamide appeared preferable with regard to libido, general well-being and fatigue.

I use high-dose bicalutamide in patients who have failed a neoadjuvant LHRH agonist and external beam radiation, and who make it clear they do not want to experience the LHRH agonist again. Patients are happier with high-dose bicalutamide, and I precede it with prophylactic breast irradiation. In Smith's trial, all of the patients receiving bicalutamide developed gynecomastia.

In a Scandinavian study in which one of the randomizations was flutamide, investigators were able to reduce gynecomastia from approximately 75 percent to 25 percent by prophylactic breast irradiation. I find it reduces breast swelling, but not necessarily breast discomfort. Also, men on either LHRH agonists or high-dose bicalutamide often accumulate fat in the breast area that looks like gynecomastia, but it's fat, not breast tissue. Only weight loss will ameliorate that problem.

New techniques in the delivery of radiation

High-dose rate brachytherapy is expanding rapidly in community practices, even though we have more evidence supporting low-dose rate brachytherapy. With this newer form of brachytherapy, a temporary device is placed in the prostate, radiation is delivered and then the device is withdrawn. The process is repeated two or three times and is usually combined with external beam radiation.

It's expensive and inconvenient, but it has the potential advantage that the radioactive source is not left in the patient — although I don't believe there's much risk in that. It also allows one to adjust the strength of radiation at any point and provide a relatively smooth and tight distribution of radiation to the prostate. This has aesthetic appeal, but whether it is of clinical value still needs to be determined.

Hypofractionation, which involves decreasing the number of radiation treatments while simultaneously increasing the size of the daily dose, is another potential option. Biologic evidence indicates that prostate cancer is a unique cancer and it may be advantageous to deliver larger doses over a shorter period of time. It would certainly be more convenient for patients. RTOG and the Royal Marsden Hospital are each conducting a randomized trial comparing conventional fractionation in external beam radiation with these abbreviated courses.

Select Publications

Critz F et al. **Simultaneous radiotherapy for prostate cancer: 125I prostate implant followed by external-beam radiation.** *Cancer J Sci Am* 1998;4(4):359-63. **Abstract**

Hanks G et al. **Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: The Radiation Therapy Oncology Group protocol 92-02.** *J Clin Oncol* 2003;21(21):3972-8. **Erratum in:** *J Clin Oncol* 2004;22(2):386. **Abstract**

Holm H. **The history of interstitial brachytherapy of prostatic cancer.** *Semin Surg Oncol* 1997;13(6):431-7. **Abstract**

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Pilepich M et al. **Phase III trial of androgen suppression adjuvant to definitive radiotherapy. Long term results of RTOG study 85-31.** *Proc ASCO* 2003;**Abstract 1530.**

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Roach M et al. **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;21:1904-11. **Abstract**

Rossi C. **Conformal proton beam therapy of prostate cancer — Update on the Loma Linda University Medical Center experience.** *Strahlenther Onkol* 1999;175(Suppl 2):82-4. **Abstract**

Sogani P et al. **Experience with interstitial implantation of Iodine-125 in the treatment of prostatic carcinoma.** *Scand J Urol Nephrol Suppl* 1980;55:205-11. **Abstract**

Edited comments by Robert Dreicer, MD, FACP

Trials of chemotherapy for patients with advanced prostate cancer

At ASCO 2004, results from two large randomized trials in patients with advanced prostate cancer will be presented. One is a trial comparing mitoxantrone and prednisone to single-agent docetaxel administered in two different schedules (weekly or every three weeks). The other is the SWOG trial comparing docetaxel and estramustine to mitoxantrone and prednisone. Both of these studies have the potential to alter practice because they ask survival questions about the role of chemotherapy in patients with androgen-independent metastatic disease.

In a nonprotocol setting, chemotherapy is used for the management of disease-related symptoms. If a survival advantage were reported for a drug combination being compared to the gold standard — mitoxantrone and prednisone — which doesn't affect survival, a more widespread use of chemotherapy in advanced disease could occur. A survival advantage could also foster and stimulate ongoing clinical trials evaluating the use of chemotherapy in earlier stages of the disease where survival may also be impacted.

Report from the PSA Working Group

The PSA Working Group consisted of prominent urologists, medical oncologists and other researchers who presented an initial report a number of years ago and have now issued new guidelines. In the February 1, 2004 edition of the *Journal of Clinical Oncology*, the group published a report that defined the problem of a rising PSA after primary treatment (surgery or radiation) and the dilemma in interpreting how to evaluate drugs in that setting. It's a very important publication that provides a basis for conducting trials using similar endpoints so we can begin to interpret outcomes.

The PSA Working Group came up with a definition for biochemical failure, based on the best data published. In patients treated with prostatectomy, it was more straightforward: Biochemical failure was defined by the presence of a PSA of 0.4 ng/mL or greater. In patients failing after radiation therapy, it was more complex. The ASTRO definition was useful, but because it is not directly comparable to the prostatectomy failure definition, ASTRO is trying to revise

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their guidelines. The PSA Working Group suggested a very minor modification to the ASTRO definition.

Patients with a rising PSA may represent a million or a million and a half men in the United States. It's a very large group in which it is uniquely difficult to conduct trials. These patients don't have symptoms or measurable disease, yet many are obviously worried and anxious. Even worried and motivated patients do not want interventions that have a negative impact on their quality of life.

They prefer rational therapies with some evidence of activity, but we don't know how activity should be measured (e.g. a PSA decline to a certain value maintained for a month, a change in the PSA doubling time). The PSA Working Group discussed different ways of quantifying the impact of a particular therapy and its significance. Prospective trial evidence does not exist to suggest that a 50 percent drop in PSA for two months or a change in the PSA doubling time will alter the natural history of the disease.

One of the recommendations made by the PSA Working Group was that novel drugs should not be tested initially in this subgroup of patients. At times, discordance exists between PSA expression and tumor kinetics. Since the effects of novel drugs on PSA expression are unknown, they should be tested in patients with advanced disease in whom the assessment is more straightforward. On the other hand, the PSA Working Group stated that novel immune-modulating therapies would be appropriate to test in this group of patients. Immune modulation probably won't be as effective in patients with androgen-independent advanced disease, so patients with biochemical relapse are quite amenable to immune-modulating approaches such as vaccine strategies.

Role of hormonal therapy concurrent with salvage radiation therapy in patients with biochemical failure after prostatectomy

Data do not exist to support the use of hormonal therapy concurrently with salvage radiation therapy in patients with biochemical failure. This is clearly an area that needs to be investigated, but it will be very difficult because of the broad variability in the patients who are treated with salvage radiation therapy. The data supporting radiation therapy concurrent with hormonal therapy in patients with locally advanced prostate cancer come from both the RTOG and the EORTC trials, which evaluated two and three years of hormonal therapy. However, six months of hormonal therapy is widely used, even though no data support it.

Hormonal therapy selection in patients with biochemical failure

Based on extrapolation from the ECOG trial in patients with node-positive disease — the Bolla and MRC trials — early hormonal therapy impacts outcome. I point out to my colleagues who offer antiandrogen monotherapy or other approaches that all of those trials used testicular androgen suppression as their primary modality, not even combined androgen blockade. When I talk to patients I tell them, "We must extrapolate from the trials that utilized testicular androgen suppression." That's what I offer patients, and I acknowledge that I am likely in

the minority of physicians.

Combined androgen blockade for at least 30 days is a rational therapeutic approach for a patient with metastatic disease. Beyond that, I try to explain the evidence — some favorable, some less favorable — about combined androgen blockade, which includes a discussion of the potential cost differential and some minor potential toxicity issues. Then, it's the patient's choice. In the men with biochemical failure, for whom I would at some point suggest therapy, I would use LHRH monotherapy.

SWOG-S9921 adjuvant trial

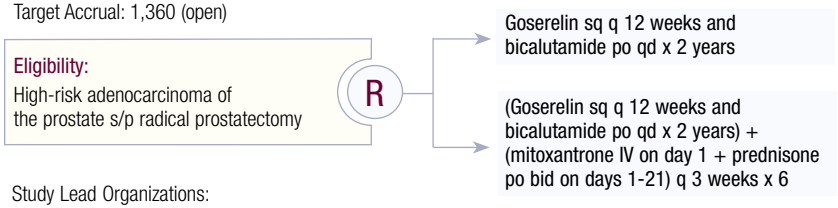
SWOG is currently conducting an adjuvant trial in patients with high-risk disease treated with prostatectomy that will compare two years of combined androgen blockade with or without six months of mitoxantrone and prednisone (Figure 3.1). The study was initiated in the late 1990s, and we hope it'll be completed so we have evidence about whether adjuvant therapy truly makes a difference in prostate cancer.

Figure 3.1

Phase III Study of Androgen Deprivation with or without Mitoxantrone Plus Prednisone

Protocol IDs: SWOG-S9921, CLB-99904, CTSU

Target Accrual: 1,360 (open)



Study Lead Organizations:

Southwest Oncology Group
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Cancer and Leukemia Group B
Nancy Ann Dawson, MD, Protocol Chair
Tel: 410-328-2565

SOURCE: NCI Physician Data Query, April 2004.

Select Publications

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;360:103-8. **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**

Scher HI et al. **Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: Recommendations from the Prostate-Specific Antigen Working Group.** *J Clin Oncol* 2004;22(3):537-56. **Abstract**

Post-test: *Prostate Cancer Update*, Issue 2, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the Prostate Cancer Prevention Trial (PCPT), finasteride was associated with a 25 percent reduction in the rate of prostate cancer diagnosis.**
   a. True
   b. False

2. **In the PCPT, patients receiving finasteride had a lower rate of high-grade prostate cancer than those receiving placebo.**
   a. True
   b. False

3. **The Medical Therapy of Prostatic Symptoms (MTOPS) trial was a large, four-arm, placebo-controlled trial in patients with benign prostatic hyperplasia (BPH) that evaluated:**
   a. The combination of an alpha-blocker (doxazosin) and finasteride
   b. Finasteride alone
   c. An alpha-blocker (doxazosin) alone
   d. All of the above
   e. None of the above

4. **In a meta-analysis of maximum androgen blockade (MAB) trials, patients treated with MAB had a three percent absolute survival benefit (10 percent relative reduction in mortality).**
   a. True
   b. False

5. **The efficacy of intermittent androgen suppression has been proven in multiple randomized clinical trials.**
   a. True
   b. False

6. **Cleveland Clinic's database evaluating patients treated with external beam radiation with doses less than or greater than 72 gray showed no difference in outcome at eight years.**
   a. True
   b. False

7. **The RTOG-9413 trial, a two-by-two study design comparing whole-pelvic versus prostate-only radiation and neoadjuvant to adjuvant combined androgen suppression, demonstrated:**
   a. An advantage to whole-pelvic (WP) radiation
   b. An advantage to neoadjuvant androgen suppression combined with WP radiation
   c. An advantage to A and B when combined
   d. None of the above

8. **Data from Canada suggest it takes up to eight months to achieve maximum tumor response from androgen deprivation.**
   a. True
   b. False

9. **DN-101 is a derivative of:**
   a. Vitamin A
   b. Vitamin B
   c. Vitamin C
   d. Vitamin D

10. **The SWOG-S9921 adjuvant trial has which of the following as the control arm:**
    a. No treatment
    b. Combined androgen blockade for two years
    c. Antiandrogen monotherapy for two years
    d. LHRH monotherapy for two years
    e. None of the above

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

Evaluation Form:
Prostate Cancer Update — Issue 2, 2004

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5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	NA = not applicable to this issue of *PCU*

GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *PCU* address the following global learning objectives?

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Laurence Klotz, MD	5 4 3 2 1	5 4 3 2 1
Anthony L Zietman, MD, MRCP, FRCR	5 4 3 2 1	5 4 3 2 1
Robert Dreicer, MD, FACP	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

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

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Prostate Cancer™ UPDATE

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