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Prostate Cancer™ UPDATE

Conversations with Urologic Oncology Leaders

Bridging the Gap between Research and Patient Care

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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, and incorporate these data into management strategies in the local and advanced disease settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Inform prostate cancer 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.
- Counsel appropriately selected patients in the high-risk or advanced disease settings about the risks and benefits of chemotherapy, including emerging data on taxane-based regimens.

PURPOSE OF THIS ISSUE OF *PROSTATE CANCER UPDATE*

The purpose of Issue 1 of *Prostate Cancer Update* is to support these global objectives by offering the perspectives of Dr Dicker, Professor Peto, Dr Petrylak and Dr and Mrs Deeths on the integration of emerging clinical research data into the management of prostate cancer and to provide the perspective of a physician patient and his wife on dealing with prostate cancer and its treatment.

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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**.

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UPCOMING EDUCATIONAL EVENTS

Society of Surgical Oncology Annual Cancer Symposium
March 3-6, 2005
Atlanta, Georgia
Event website: www.surgonc.org/sso/meet2005/meeting/SSOPROG.html

10th National Comprehensive Cancer Network Annual Conference
March 16-20, 2005
Westin Diplomat
3555 South Ocean Drive
Hollywood, Florida
Event website: www.nccn.org/professionals/meetings/10thannual/default.asp

96th Annual Meeting of the American Association for Cancer Research
April 16-20, 2005
Anaheim, California
Event website: www.aacr.org/2005am/2005am.asp

41st American Society of Clinical Oncology Annual Meeting
May 13-17, 2005
Orange County Convention Center
Orlando, Florida
Event website: www.asco.org/ac/1,1003,_12-002092,00.asp

2005 American Urological Association Annual Meeting
May 21-26, 2005
San Antonio, Texas
Event website: www.aua2005.org/am05/?CFID=1463668&CFTOKEN=29660692

American Society of Clinical Oncology and American Association for Cancer Research Workshop: Methods in Clinical Cancer Research
July 30-August 5, 2005
Vail, Colorado
Event website: www.asco.org/ac/1,1003,12-002924-00_18-0036908,00.asp

2005 American Society for Therapeutic Radiology and Oncology Annual Meeting
October 16-20, 2005
Denver, Colorado
Event website: www.astro.org/annual_meeting/

Editor's Note

Turning points

A 57-year-old urologist is s/p radical prostatectomy for low-grade prostate cancer

It's been four months of emotional misery since your surgery. Although the tumor was low grade, you obsess about your own death and have become totally isolated from your wife of 34 years. From the beginning, she urged you to obtain a second opinion and possibly forego surgery, but you wouldn't listen. Now, rather than supporting you in the face of erectile dysfunction and stress incontinence, she is resentful.

Suddenly, you are facing a second onslaught — a myocardial infarction that transforms you once again into a patient in your own hospital. It is Valentine's Day, and the pitiful irony of your situation crashes down on your beleaguered soul. You are alone and without hope.

You hear a knock at your hospital room door. It is your wife, bringing the glowing smile that you have not seen in quite some time. From a bag tucked under her arm, she removes a "do not disturb" sign and attaches it to the door. She has candles, flowers, dinner, wine and endless affection. She climbs into bed with you and curls up by your side. You realize that perhaps things will be okay.

There are moments in all of our lives, in which divine inspiration or perhaps a programmed instinct for survival leads us to a new and hopeful path. For Jeff and Lenore Deeths, that moment occurred at a point of utter hopelessness, and now, seven years later, this devoted couple has largely recovered from the hurricane-like disintegration that started with Jeff's radical prostatectomy.

These very private people tell their stories in this issue of *Prostate Cancer Update* because they realize how important it is for physicians to understand what it's like to deal with prostate cancer and the impact of treatment.

Many other patients can identify similar moments when they too reached inside themselves to find the courage and optimism to move forward. Also in this issue, Adam Dicker discusses a patient with locally advanced disease, who was treated with radiation therapy and two years of androgen deprivation. This man has now regained his testosterone level, returned to normal function, and is without evidence of recurrence two years later.

It is challenging to imagine what it's like to regain libido and sexual function after living with chemical castration or to recover from fatigue, muscle weakness and vasomotor instability. So often we don't appreciate what we have until it is taken away, but sometimes we are offered a second chance.

Dan Petrylak discusses another patient with prostate cancer who experienced a life-altering turning point — a football coach who was bedridden due to the effects of widespread metastases. This patient made the courageous decision to enroll in the SWOG trial 9916, and was randomly assigned to the docetaxel-estramustine arm. Three weeks later, the man was asymptomatic and in his front yard mowing the lawn. It is impossible to imagine what he felt when he inhaled the fresh, sweet smell of the grass beneath his feet.

At our recent "Clinicians with Prostate Cancer" roundtable meeting and recording session, medical oncologist and prostate cancer survivor Gustav Magrinat commented on the importance of physicians conveying a sincere and heartfelt sense of optimism. So where do doctors find hope for these patients?

I believe that miracles happen every day to men with prostate cancer. This may be as simple as a couple sharing a romantic embrace or a man mowing the lawn. Some of these moments are more transient than others, but experienced clinicians use the memories of these triumphs to inspire patients who may be mired in hopelessness and despair.

Our job is to bring skills, knowledge and compassion to the bedside, but what they don't teach in medical school is that a force beyond all of us may intercede when all else fails. Every day we should remind our patients of this important possibility.

— Neil Love, MD
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Select publications

Deliveliotis C et al. **Prostate operations: Long-term effects on sexual and urinary function and quality of life. Comparison with an age-matched control population.** *Urol Res* 2004;32(4):283-9. **Abstract**

Hollenbeck BK et al. **Sexual health recovery after prostatectomy, external radiation, or brachytherapy for early stage prostate cancer.** *Curr Urol Rep* 2004;5(3):212-9. **Abstract**

Lintz K et al. **Prostate cancer patients' support and psychological care needs: Survey from a non-surgical oncology clinic.** *Psychooncology* 2003;12(8):769-83. **Abstract**

Steginga SK et al. **Prospective study of men's psychological and decision-related adjustment after treatment for localized prostate cancer.** *Urology* 2004;63(4):751-6. **Abstract**

Trask PC. **Quality of life and emotional distress in advanced prostate cancer survivors undergoing chemotherapy.** *Health Qual Life Outcomes* 2004;2(1):37. **Abstract**

Adam P Dicker, MD, PhD

EDITED COMMENTS

Optimal duration of hormonal therapy for prostate cancer

A couple of interesting recent research developments relate to the management of locally advanced prostate cancer. First, D'Amico et al reported results of a clinical trial that randomly assigned patients to receive radiation therapy with or without six months of total androgen suppression (D'Amico 2004; [1.1]).

The group that received hormonal therapy demonstrated a survival advantage, which was surprising because the trial did not accrue a large number of patients. These data raise the question of whether six months of hormone therapy is adequate, or whether we need longer-duration therapy.

Another related article that touches on the duration of hormonal therapy is by a group in Finland who evaluated cognitive function in men — with an average age of 65 — before and after six and twelve months of hormonal therapy (Salminen 2004).

They found a significant decline in memory, time to process information, recall and visuomotor function associated with the decrease in testosterone. Their data do not directly connect hormonal therapy with the decline in psychomotor function, but it is clear to those who treat prostate cancer that long duration therapy — more than one year — impacts patients' mental acuity.

Clinicians are interested in determining the maximally effective therapy that can be delivered with minimal side effects. When combined with radiation therapy, total androgen suppression may be equivalent to longer duration therapy with an LHRH agonist alone for the treatment of clinically localized prostate cancer.

Impact of endocrine therapy on local tumor control and distant metastases

In radiation oncology, it's almost a mantra that if we don't achieve local control, we won't achieve distant control. This is not only true in prostate cancer; it's also true in breast cancer. Zietman published an article that basically showed that the

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metastases rate in prostate cancer is increased when local control is not achieved (Coen 2002). Twenty years ago, everyone treated the whole pelvis with radiation to the nodes, because it was believed that is where prostate cancer spreads; however, that was not based on any evidence. Roach's Phase III trial, RTOG-9413, comparing whole pelvic to prostate-only radiation therapy and neoadjuvant to adjuvant combined androgen suppression, was the first to demonstrate that large-field radiation therapy with neoadjuvant and concurrent hormonal therapy had a benefit as measured by PSA (Roach 2003).

It appears radiation therapy will probably cure microscopic disease in the nodes, but only when combined with hormonal therapy. I don't anticipate that radiation therapy alone — at the dose we used, which was limited because of the small bowel — will cure micrometastatic disease. Some people believe hormonal therapy is synergistic with radiation. I've seen no evidence of that; rather, it probably has an additive effect.

I would not use the term "radiosensitizer" because hormonal therapy is active by itself, but it certainly augments radiation. I believe hormonal therapy plays a role, but how much of a role it plays locally is unclear. It's also not clear that the dose used in the Bolla study is sufficient to cure patients. A number of investigators are retrospectively examining their data from patients who received a Bolla-like therapy in various doses during different time periods to determine whether an increase in dose translates to decreased bony metastases and improved survival.

1.1 Three-Dimensional Conformal Radiation Therapy (3D-CRT) with or without Six-Month Androgen Suppression Therapy for Patients with Clinically Localized Prostate Cancer: Efficacy Data

	Number of events			
Outcome measure	3D-CRT (n=103)	3D-CRT + AST† (n=98)	Hazard ratio (95% CI)	*p*-value
PSA failure	46	21	2.86 (1.69-4.86)	<0.001
Survival free of salvage AST†	43	21	2.30 (1.36-3.89)	0.002
Prostate cancer-specific mortality	6	0	NA	0.02‡
Overall mortality	23	12	2.07 (1.02-4.20)	0.04

† Androgen suppression therapy; patients received either leuprolide acetate or goserelin plus flutamide.
‡ Log-rank *p*-value comparing cumulative incidence

SOURCE: D'Amico AV et al. **6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial.** *JAMA* 2004;292(7):821-7. **Abstract**

Counseling patients with low-risk disease about local therapy options

Counseling a 65-year-old man with low-grade, low-PSA disease about treatment options is difficult because reasonable data exist for all three major treatment modalities, and the outcome — cancer control and PSA levels — is similar. It becomes a discussion of quality of life and what side effects patients are willing to endure.

For patients 50 years of age or younger, I tell them we don't know the long-term cancer control rates and I usually steer them toward surgery. The brachytherapy data are now approaching 12 to 15 years of follow-up. I believe we perform brachytherapy well and the outcome data are good, but we have a better handle on outcomes with surgery. Older patients may have other competing risks to their health, whereas younger patients will generally be around for three or four decades, so long-term survival is what counts.

Postimplant CT to re-evaluate results

Based on retrospective data from Richard Stock, we know that to achieve good biochemical control, 90 percent of the prostate should receive approximately 145 Gray with an I-125 prostate implant (Stock 2002). That doesn't mean the patient won't be cured if only 85 percent of the prostate is treated, but if a postimplant CT dosimetry showed only 70 percent or less of the prostate was treated, I would have some concerns.

It doesn't matter whether the CT is performed on the day of the implant or one month later, but it's better to receive feedback as soon as possible after the implantation. It's difficult to remember problems you encountered in the operating room, especially if you performed multiple implants on the same day, and it's important to understand why one patient didn't receive a good dose.

When the prostate implant results in suboptimal coverage, I tell the patient we're not happy with what we achieved in the operating room and, assuming I understand why things didn't go well and the situation can be corrected, my preference is to reimplant the prostate. Others prefer supplemental external beam radiation therapy, but it is difficult to know what dose of radiation therapy to use. I've performed 500 to 600 implants in my career, and I've only had to reimplant twice. Assuming you didn't overdose the urethra or the rectum on the first implant, reimplantation shouldn't cause an increase in complications.

Incorporating chemotherapy into the treatment of prostate cancer

Two trials reported at ASCO 2004 demonstrated a survival advantage in patients with hormone-refractory disease receiving docetaxel-based therapy (Eisenberger 2004; Petrylak 2004). Docetaxel is being extensively evaluated in clinical trials in patients with metastatic disease that is not hormone refractory. Various randomized trials are evaluating hormones with or without chemotherapy in the nonrefractory population. We don't know if chemotherapy — particularly docetaxel-based chemotherapy — combined with hormones is beneficial

in patients with locally advanced disease. Chemotherapy regimens involving taxanes and estramustine have been evaluated, but estramustine has a number of side effects, including deep vein thrombosis. Those studies have been plagued with toxicities and haven't really moved forward.

Role of chemotherapy in PSA relapse and locally advanced disease

I usually refer patients with PSA relapse and no evidence of skeletal disease to medical oncologists who specialize in prostate diseases. I also encourage them to enroll in clinical trials that evaluate cytostatic therapy or some of the anti-androgen-type drugs. I believe most medical oncologists would be uncomfortable using cytotoxic therapy in a patient who does not have a positive scan. We don't have any evidence that simply reducing PSA in a patient with nonradiographic metastatic disease has an impact.

Chemotherapy has the potential to harm patients, and we don't know the optimal duration for chemotherapy. We have preclinical data evaluating the antiangiogenic effects of taxanes (both paclitaxel and docetaxel) in a variety of disease settings. I believe in the next year or two we'll see chemotherapy being combined more frequently with hormones and radiation therapy in the locally advanced disease setting.

We all agree that a Gleason eight, nine or 10 is locally advanced disease, but we see plenty of tumors with lower Gleason scores and 15 out of 15 positive biopsies. I put those patients in a locally advanced disease category because if they have surgery they will have positive margins, and some will have seminal vesicle and lymph node involvement. It's a gray area, but patients with a Gleason seven, PSA less than 10 and appropriate performance status may benefit from hormones and chemotherapy.

Select publications

Coen JJ et al. **Radical radiation for localized prostate cancer: Local persistence of disease results in a late wave of metastases.** *J Clin Oncol* 2002;20(15):3199-205. **Abstract**

D'Amico AV et al. **6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial.** *JAMA* 2004;292(7):821-7. **Abstract**

Eisenberger MA et al. **A multicenter phase III comparison of docetaxel (D) + prednisone (P) and mitoxantrone (MTZ) + P in patients with hormone-refractory prostate cancer (HRPC).** *Proc ASCO* 2004;**Abstract 4**.

Petrylak DP et al. **SWOG 99-16: Randomized phase III trial of docetaxel (D)/estramustine (E) versus mitoxantrone (M)/prednisone (p) in men with androgen-independent prostate cancer (AIPCA).** *Proc ASCO* 2004;**Abstract 3**.

Roach M 3rd 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(10):1904-11. **Abstract**

Salminen EK et al. **Associations between serum testosterone fall and cognitive function in prostate cancer patients.** *Clin Cancer Res* 2004;10(22):7575-82. **Abstract**

Stock RG et al. **What is the optimal dose for 125I prostate implants? A dose-response analysis of biochemical control, posttreatment prostate biopsies, and long-term urinary symptoms.** *Brachytherapy* 2002;1(2):83-9. **Abstract**

Similarities and differences between adjuvant hormonal therapy in breast and prostate cancer

Various reasons exist for the difference in the clinical research data between prostate cancer and breast cancer. First, breast cancer occurs in younger women while prostate cancer occurs in older men.

Obviously, a patient with a 40-year life expectancy is more interested in what happens long term than a patient with a 10-year life expectancy.

Second, the early hormonal treatments for prostate cancer were unpleasant. They consisted of castration and diethylstilbestrol (DES), which was discovered to be seriously cardiotoxic and would actually do more harm than good in terms of life expectancy. As soon as DES was no longer used and alternative means of turning off testicular function were discovered, trials began.

Hormonal therapy for prostate cancer substantially delays progression of the disease and moderately delays death from the disease. The effects of immediate hormonal treatment versus deferred hormonal treatment in a man with prostate cancer are comparable to the effects of five years of adjuvant tamoxifen in a woman with hormone-sensitive breast cancer. Additionally, hormonal therapy prevents a number of complications of metastatic disease, such as spinal metastases, ureteric obstruction and the need for further surgery.

The prostate cancer trials were not as large as the breast cancer trials, so the results were muddled by the deaths from other causes. The curves are similar, but the prostate trials have statistical noise from the large numbers of deaths that are unrelated to prostate cancer or its treatment. When patients are older, deaths from other causes confuse trial results.

Potential impact of early hormonal therapy for prostate cancer on survival

The problem with evaluating hormone therapy for prostate cancer is that only a few thousand men with prostate cancer were being randomly assigned to

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therapy, compared to tens of thousands of women with breast cancer. That is why the evidence of benefit in breast cancer is so much better.

In breast cancer, we have seen impressive decreases in death rates in middle-aged women as a result of early use of tamoxifen and chemotherapy. I believe the effects of earlier treatment with hormonal therapy in prostate cancer over the next five or 10 years will be comparable to that produced by tamoxifen in breast cancer.

Does bicalutamide have an adverse effect on mortality in patients with low-risk disease in the Early Prostate Cancer (EPC) program trials?

No good evidence indicates that bicalutamide treatment affects mortality from causes other than prostate cancer. Currently, the number of deaths from prostate cancer in the EPC trials is so limited that it is difficult to obtain any clear evidence of an effect on prostate cancer mortality.

The question as to the effect on overall mortality is well worth asking, but it needs to be answered by separate analyses of prostate cancer mortality and nonprostate cancer mortality. One should ask, "Is there any evidence of hazard?" No. "Is there any evidence of benefit?" At some point, the answer to that question may well turn out to be "yes."

No good evidence indicates that bicalutamide increases the overall death rate from causes other than prostate cancer. If you have no overall evidence and you begin looking for subgroups of this and subgroups of that, you're almost bound to find a subgroup in which the results seem favorable and a subgroup in which the results seem unfavorable, but that is just statistical noise.

Risk of false-negative results from subgroup analyses

Years ago, we published a paper in *The Lancet* that analyzed astrological birth signs as a subgroup in a trial evaluating aspirin as treatment for acute heart attack. The study proceeded with a controlled randomization of approximately 17,000 heart attack patients. There were 1,000 deaths in the placebo arm compared to 800 deaths in the aspirin-treated arm. That equates to a five standard error difference in mortality, which is an excellent result.

The Lancet agreed to publish the study; however, they insisted on knowing which subpopulation was going to derive benefit — older versus younger, male versus female, those with a previous infarct versus those without. The suggestion was completely ridiculous because if the treatment works that well, it's going to be of some value for everybody.

Dividing a five standard error difference into subgroups will result in false negatives. So, as an absolute matter of principle, we said "no." *The Lancet* refused to publish the data unless we complied with subgroup analyses. Finally, we relented. We classified patients according to astrological birth sign, performed a

subgroup analyses and sent the results to *The Lancet*. The paper was published August 13, 1988 (ISIS 1988). Aspirin didn't seem to work as treatment for heart attack if you're born under Libra or Gemini, but it produced halving of risk if you were born under Capricorn. It's just complete junk. And, actually, a lot of subgroup analyses are junk.

Select publications

Crawford ED. **Early versus late hormonal therapy: Debating the issues.** *Urology* 2003;61(2 Suppl 1):8-13. **Abstract**

Damber JE. **Decreasing mortality rates for prostate cancer: Possible role of hormonal therapy?** *BJU Int* 2004;93(6):695-701. **Abstract**

International Study of Infarct Survival Collaborative Group. **Randomised trials of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS -2.** *Lancet* 1988;2(8607):349-60. **Abstract**

Iversen P et al. **Bicalutamide (150 mg) versus placebo as immediate therapy alone or as adjuvant to therapy with curative intent for early nonmetastatic prostate cancer: 5.3-year median followup from the Scandinavian Prostate Cancer Group study number 6.** *J Urol* 2004;172(5 Pt 1):1871-6. **Abstract**

Iversen P et al; Casodex Early Prostate Cancer Trialists' Group. **Is the efficacy of hormonal therapy affected by lymph node status? Data from the bicalutamide (Casodex) Early Prostate Cancer program.** *Urology* 2004;63(5):928-33. **Abstract**

Labrie F et al. **Major impact of hormonal therapy in localized prostate cancer-death can already be an exception.** *J Steroid Biochem Mol Biol* 2004;92(5):327-344. **Abstract**

Miyamoto H, Messing EM. **Early versus late hormonal therapy for prostate cancer.** *Curr Urol Rep* 2004;5(3):188-96. **Abstract**

Moul JW et al. **Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy.** *J Urol* 2004;171(3):1141-7. **Abstract**

Peto R, Dalesio O. **Breast and prostate cancer: 10-year survival gains in the hormonal adjuvant treatment trials.** *Eur J Cancer Suppl* 2003;1(5):S101;**Abstract 328**.

Roach M 3rd et al. **Predicting long-term survival, and the need for hormonal therapy: A meta-analysis of RTOG prostate cancer trials.** *Int J Radiat Oncol Biol Phys* 2000;47(3):617-27. **Abstract**

Schellhammer PF, Davis JW. **An evaluation of bicalutamide in the treatment of prostate cancer.** *Clin Prostate Cancer* 2004;2(4):213-9. **Abstract**

Schroder FH et al. **Early versus delayed endocrine treatment of pN1-3 M0 prostate cancer without local treatment of the primary tumor: Results of European Organisation for the Research and Treatment of Cancer 30846--a phase III study.** *J Urol* 2004;172(3):923-7. **Abstract**

Sciarra A et al. **Antiandrogen monotherapy: Recommendations for the treatment of prostate cancer.** *Urol Int* 2004;72(2):91-8. **Abstract**

Walsh PC et al. **A structured debate: Immediate versus deferred androgen suppression in prostate cancer-evidence for deferred treatment.** *J Urol* 2001;166(2):508-15. **Abstract**

Wirth MP et al. **Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: Results from the second analysis of the early prostate cancer program at median followup of 5.4 years.** *J Urol* 2004;172(5 Pt 1):1865-70. **Abstract**

Recent Phase III trials evaluating docetaxel-based combinations in patients with hormone-insensitive metastatic disease

Our first studies evaluating docetaxel plus estramustine were performed in the laboratory in 1995. We were excited by what we saw in vitro and moved forward into a Phase I study that opened in February of 1996.

One of the old jokes about Phase I studies is that the first patient responds but then nobody else does. Well, the opposite happened in that study: The first patient didn't respond, but nearly every subsequent patient did. We saw promising responses in patients who were heavily pretreated. Median survival was close to 24 months, and that was the highest reported median survival of any study at that time.

This background provided the basis for SWOG-9916 (Petrylak 2004a, b), which is a randomized trial comparing docetaxel/estramustine to mitoxantrone/prednisone in men with progressive androgen-independent prostate cancer and soft-tissue or bony metastases. These were not the asymptomatic patients with rising PSA only. They had to progress by one of three criteria: bone scan, CT or PSA. The trial opened in October 1999 and closed in January 2003. We demonstrated a 20 percent reduction in the rate of death in favor of those patients who received docetaxel/estramustine; however, estramustine-related toxicity was problematic and included deep venous thromboses, cardiovascular events and nausea.

A related and important trial was TAX-327 (Eisenberger 2004), which compared docetaxel weekly or every three weeks plus prednisone to mitoxantrone/prednisone. Survival was improved with every three-week docetaxel. The data from both studies demonstrate for the first time that we have a chemotherapeutic agent — docetaxel — that results in prolonged survival for men with hormone-refractory prostate cancer (3.1).

Because the estramustine-related toxicity was problematic and the median survival and hazard ratios are similar for docetaxel/prednisone and docetaxel/estramustine, the FDA has recommended docetaxel/prednisone as the standard of care for hormone-refractory metastatic prostate cancer.

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3.1 Phase III Trials Demonstrating Survival Advantage from Docetaxel-Based Regimens in Patients with Hormone-Refractory Prostate Cancer

	Median survival	Hazard ratio	*p*-value
TAX-327 (n=1,006)[1]			
Docetaxel q3wk + prednisone	18.9 months	0.76	0.009
Docetaxel qwk + prednisone	17.3 months	0.91	0.3
Mitoxantrone	16.4 months	—	—
SWOG-9916 (n=674)[2]			
Docetaxel + estramustine	18.0 months	0.80	0.01
Mitoxantrone + prednisone	16.0 months	—	—

SOURCES: [1] Eisenberger MA. Presentation. *Proc ASCO* 2004;**Abstract 4**.
[2] Petrylak DP et al. Presentation. *Proc ASCO* 2004;**Abstract 3**.

Nonprotocol therapy for patients with hormone-refractory metastatic disease

The FDA approved docetaxel for patients with hormone-refractory metastatic prostate cancer, but they didn't specify when it should be utilized. Hormone-refractory prostate cancer is a continuum. In general, the first sign of disease breakthrough is a rising PSA, and the patient is often asymptomatic. Generally, after seven to 12 months, we start seeing changes in scans, and patients become symptomatic. A window exists during which markers are going up and the patient is asymptomatic, yet the patient may want treatment.

Often physicians will try a second hormonal manipulation, such as Nizoral®, high-dose bicalutamide or nilutamide. All of these seem to have a 20 percent to 40 percent rate of response and a median time to progression of about four months, but no proven survival benefit.

An interesting observation gleaned from a subanalysis of TAX-327 data is that the hazard ratios for survival are similar whether patients are asymptomatic or symptomatic, and the difference of two months in median survival is conserved for both symptomatic and asymptomatic patients.

It is difficult to decide whether to utilize docetaxel in patients who are asymptomatic but have rising PSAs. It is important to evaluate how rapidly the disease is progressing. Clearly, if the PSA is not rising rapidly, you have time to try other manipulations. In my experience, by the time those manipulations fail, patients need chemotherapy.

In asymptomatic patients with rapidly rising or rapidly doubling PSA levels, progression of soft-tissue disease or progression on bone scan, I consider initiating chemotherapy. During the initial PSA rise, unless the patient has visceral disease, I'm not in favor of using chemotherapy. I would utilize an investigational agent or a secondary hormonal manipulation.

To use a baseball analogy, docetaxel can be saved as the "relief pitcher" for late innings, or you can use it earlier as your starting pitcher. Either way, we know that docetaxel has a high response rate and a proven survival benefit.

Docetaxel-associated symptom improvement

In TAX-327, an improvement in quality of life occurred in patients receiving docetaxel compared to those receiving mitoxantrone/prednisone. Patients who are symptomatic from their disease often feel better, and we've seen dramatic improvements in symptoms such as bone pain.

We usually can control most of the side effects of chemotherapy, and patients are able to maintain a reasonable quality of life, continue to work and remain active in other areas of their lives. I tell patients that they have a 50/50 chance their symptoms will improve with docetaxel, but a flare may occur about a week after treatment is started.

Proposed CALGB trial evaluating docetaxel plus bevacizumab

The CALGB is planning to do a randomized trial of docetaxel with or without bevacizumab, which is a VEGF-inhibitor. An elevated serum level of vascular endothelial growth factor has been identified as an important prognostic factor in hormone-refractory prostate cancer, so it makes sense that using an antibody targeted against that particular target is effective.

We're in the process of designing a Phase I study using docetaxel plus bevacizumab plus an anti-EGFR agent. In renal cell cancer, that approach — combining bevacizumab plus erlotinib — has had promising results.

Earlier integration of medical oncologists in management of prostate cancer

In the community, urologists usually attempt a couple of hormonal manipulations and then send their patients to the oncologist. The optimal time to start chemotherapy is a bit of an art, and no FDA guidelines delineate the proper time to start chemotherapy.

Not all patients with hormone refractory disease should start chemotherapy. I believe patients should see an oncologist initially, but they should never lose contact with their urologist. The urologist is the primary caregiver who diagnoses the disease and may have removed the prostate. These patients will continue to depend on their urologists for problems and complications that develop from the prostate cancer, such as urinary tract obstruction, stinting and transurethral resections of the prostate.

Defining the optimal time to initiate hormonal therapy

Randomized trial data suggest that earlier hormone therapy is beneficial at the point of PSA progression, but no data absolutely indicate benefit in the asymptomatic patient with a rising PSA. We know from studies of combination therapy that patients at high risk will benefit from early hormonal therapy plus radiation therapy. Ed Messing's trial randomly assigned patients who had positive lymph nodes after prostatectomy to immediate hormonal therapy versus delayed hormonal therapy. The trial demonstrated that earlier hormonal therapy was beneficial (Messing 1999).

A number of important questions must be answered. Does a threshold value of PSA need to be defined for these patients? Does PSA doubling time depend on regional clinical characteristics? We need to investigate these questions.

Bone complications from hormonal therapy

Many patients receive androgen blockade at some point and face a whole new set of complications. Matt Smith presented interesting data at ASCO 2004, evaluating the Medicare database and analyzing patients with nonmetastatic disease who did or did not receive hormone therapy.

The single most important prognostic factor for the development of osteoporosis in these patients was whether they had androgen blockade. The rate of fractures was proportional to the duration of androgen blockade (Smith 2004). Other side effects include muscle wasting, loss of energy and diminished sexual function.

Use of maximal androgen blockade

The survival data from the SWOG studies — particularly SWOG-8494, in which Dave Crawford was the principal investigator — showed approximately a three-month improvement in survival in favor of combined blockade compared to an LHRH agonist alone (Crawford 1989, 1990).

I use maximal androgen blockade. Certainly, we've treated patients with more aggressive therapy for less of a survival benefit. I believe it can't hurt. And if it can't hurt and has a possibility to improve survival, I will use the combined blockade with bicalutamide, which is the easiest drug for me to administer and for the patient to receive.

Select publications

Crawford ED et al. **A controlled trial of leuprolide with and without flutamide in prostatic carcinoma.** *N Engl J Med* 1989;321(7):419-24. **Abstract**

Crawford ED et al. **Combined androgen blockade: Leuprolide and flutamide versus leuprolide and placebo.** *Semin Urol* 1990;8(3):154-8. **Abstract**

Eisenberger MA. Presentation. *Proc ASCO* 2004;**Abstract 4**.

Eisenberger MA et al. **A multicenter phase III comparison of docetaxel (D) + prednisone (P) and mitoxantrone (MTZ) + P in patients with hormone-refractory prostate cancer (HRPC).** *Proc ASCO* 2004;**Abstract 4**.

Messing EM et al. **Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer.** *N Engl J Med* 1999;341(24):1781-8. **Abstract**

Petrylak DP et al. **Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer.** *N Engl J Med* 2004;351(15):1513-20. **Abstract**

Petrylak DP et al. **SWOG 99-16: Randomized phase III trial of docetaxel (D)/estramustine (E) versus mitoxantrone(M)/prednisone(p) in men with androgen-independent prostate cancer (AIPCA).** *Proc ASCO* 2004;**Abstract 3**.

Smith MR et al. **Association between androgen deprivation therapy and fracture risk: A population-based cohort study in men with non-metastatic prostate cancer.** *Proc ASCO* 2004;**Abstract 4507**.

A urologist's initial reaction to a prostate cancer diagnosis

In 1997 I was diagnosed with prostate cancer, Gleason Grade 2+3. The news devastated me, even though the tumor was low grade. Upon diagnosis, most cancer patients feel they are going to die, and although I had treated and reassured many men with prostate cancer over the years, it was different being the patient. The cancer itself bothered me more than the treatment. I decided on radical prostatectomy, which my partner performed a month later.

I always told my own patients that the treatment decision was theirs because it was their life, but I strongly feel that I made a mistake in not discussing it with my wife so that she could understand why I made that decision. Subsequently, I insist that my patients have their spouse present during discussions so that both will know what is happening.

Transitioning from diagnosis through surgery to recovery

In retrospect, the first few months were difficult. I was unable to look ahead or anticipate anything in the future. I lived one day at a time, and went back to my routine of seeing patients. I was depressed after the surgery, though not clinically depressed. I didn't buy any new clothes for about six months; I felt it would be money wasted because I thought I was going to die. Four months after surgery I had a heart attack, a second life-threatening event that compounded these feelings. Although I am now back on my feet, sometimes I still feel depressed. I don't know if that is from realizing that I am not going to live forever or just normal aging.

Effect of prostate cancer on intimacy

The prostate cancer diagnosis and subsequent events made our marriage stronger in many ways. The intimacy and closeness with my wife has increased over time and we are more in tune with each other. What helped in this respect were the changes we made to our lifestyle. Six months ago I retired. Now, we have more time and we do a lot more together.

Dr Deeths is an Associate Clinical Professor of Urology at Creighton Medical School in Omaha, Nebraska.

Managing the side effects of prostate cancer surgery

After the surgery, I experienced incontinence and impotence, which were far more life altering than I imagined, even though I had previously treated many patients with these problems and advised them of various ways to control them. As an adult, I found it to be a significant event whenever I wet my pants or the bed. I used all the protection available and wore a very light day pad for a couple of years. The incontinence gradually improved and is no longer an issue.

Mrs Deeths' perspective

When I learned of his diagnosis, he had already decided on radical surgery. I felt left out because he didn't consult me about any part of it. I wanted to research the subject and consider other treatment methods. I wanted a second opinion about surgery because controversy still exists in this area. I was angry that he chose surgery for such a low-grade cancer when other, less drastic approaches were available. I thought if he hadn't undergone surgery, he would not have had the problems of incontinence and impotence.

I was less supportive than his nurse and I was having a hard time trying to keep my life together. My father died from prostate cancer, and that was on my mind. Jeff knew more than I did, and his being so stressed made me believe it was worse than I thought. That devastated me and left me with no reserve. After the surgery, he still projected the attitude that he was going to die, so I questioned the usefulness of the surgery.

When Jeff had his heart attack, he was talking about possibly dying. That was the turning point in this crisis for both of us. It takes something traumatic to make you understand that there's another side to life. I used yoga and humor to cope. It was ironic that it happened on Valentine's Day. Our dinner plans that day were cancelled, and on the following day I brought dinner, flowers and wine to the hospital room.

Despite protests from the nurse, we dined there together. That whole episode put some humor back into my life and brought us a new perspective — that life is transient and tomorrow may not exist, so we should live in the present, appreciating the moment. Subsequently, we decided to simplify our lives by proceeding with our plans to sell the house and move somewhere that required lower maintenance. We now enjoy a different lifestyle and do more together.

Those first six months were very difficult. Any spouse who is severely impacted needs confidence building, and their needs should be addressed. My advice to the spouse is to reach out to immediate and extended family for support and take a positive attitude. Look back on your life to another stressful event that you lived through, and believe that somehow this too will pass. There is more to life than sex. Look at the entire picture, value life and take it day by day.

Post-test:

Prostate Cancer Update — Issue 1, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. D'Amico et al reported randomized clinical trial results indicating that the addition of six months of androgen suppression therapy to 3-D conformal radiation therapy improved survival in patients with clinically localized prostate cancer.
   a. True
   b. False

2. Of the prostate cancer patients who experience erectile dysfunction following radiation therapy, approximately two thirds respond to treatment with medications such as sildenafil, tadalafil and vardenafil.
   a. True
   b. False

3. TAX-327 demonstrated a survival advantage for every three-week docetaxel plus prednisone in patients with hormone-refractory prostate cancer compared to:
   a. Weekly docetaxel plus prednisone
   b. Mitoxantrone
   c. Both a and b

4. In TAX-327, the hazard ratios for survival were similar for patients who were asymptomatic or symptomatic.
   a. True
   b. False

5. In SWOG trial 9916, reported by Petrylak at ASCO 2004, docetaxel/estramustine resulted in a survival benefit compared to mitoxantrone/prednisone in hormone-refractory prostate cancer.
   a. True
   b. False

6. Crawford and colleagues published data from SWOG-8494 demonstrating improved survival with combined androgen blockade.
   a. True
   b. False

9. Diethylstilbestrol (DES), an early hormonal therapy for prostate cancer, was found to be cardiotoxic.
   a. True
   b. False

7. At ASCO 2004, Matt Smith presented analyses of a Medicare database comparing patients with nonmetastatic prostate cancer who did or did not receive androgen blockade and demonstrated that fracture rate was related to the duration of androgen blockade.
   a. True
   b. False

8. Salminen and colleagues demonstrated that declines in mental acuity are related to long-term hormonal therapy for prostate cancer.
   a. True
   b. False

10. The Early Prostate Cancer (EPC) trials investigated _____ as a treatment for prostate cancer.
    a. Bevacizumab
    b. Estrogen
    c. High-dose bicalutamide
    d. LHRH analogues

11. In Roach's Phase III trial RTOG-9413, comparing whole pelvic to prostate-only radiation therapy and neoadjuvant to adjuvant combined androgen suppression, which of the following resulted in the best outcome?
    a. Whole pelvic radiation therapy with neoadjuvant and concurrent hormonal therapy
    b. Whole pelvic radiation therapy with adjuvant hormonal therapy
    c. Prostate-only radiation therapy with neoadjuvant and concurrent hormonal therapy
    d. Prostate-only radiation therapy with adjuvant hormonal therapy

Post-test Answer Key: 1a, 2a, 3c, 4a, 5a, 6a, 7a, 8a, 9a, 10c, 11a

Evaluation Form:

Prostate Cancer Update — Issue 1, 2005

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

Please answer the following questions by circling the appropriate rating:

5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	N/A = 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, and incorporate these data into management strategies in the local and advanced disease settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Inform prostate cancer patients about the specific risks and benefits of local and systemic therapies. . . . . 5 4 3 2 1 N/A
- Provide individualized counseling to patients regarding the choice and timing of endocrine therapy. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients in the high-risk or advanced disease settings about the risks and benefits of chemotherapy, including emerging data on taxane-based regimens. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Adam P Dicker, MD, PhD	5 4 3 2 1	5 4 3 2 1
Professor Sir Richard Peto	5 4 3 2 1	5 4 3 2 1
Daniel P Petrylak, MD	5 4 3 2 1	5 4 3 2 1
H Jeoffrey Deeths, MD and Mrs Lenore Deeths	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 N/A
Related to my practice needs. . . . . 5 4 3 2 1 N/A
Will influence how I practice. . . . . 5 4 3 2 1 N/A
Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
Overall quality of material. . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
Avoided commercial bias or influence. . . . . 5 4 3 2 1 N/A

Evaluation Form:

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.....

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.....

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As part of our ongoing, continuous, quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

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☐ No, I am not willing to participate in a follow-up survey.

Additional comments about this activity:

.....

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

Prostate Cancer™ UPDATE

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Prostate Cancer™

U P D A T E

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