PCU | 2005 VOL 4 | ISSUE 2

Prostate Cancer™ UPDATE

Conversations with Urologic Oncology Leaders

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

FACULTY

Anthony V D'Amico, MD, PhD

Leonard G Gomella, MD

Robert Dreicer, MD

CME Certified

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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 2 of *Prostate Cancer Update* is to support these global objectives by offering the perspectives of Drs D'Amico, Gomella and Dreicer on the integration of emerging clinical research data into the management of prostate cancer.

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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.com** 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 **blue underlined text**.

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Dr D'Amico – No financial interests or affiliations to disclose. **Dr Gomella** – **Consultant:** AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, TAP Pharmaceuticals Inc. **Dr Dreicer** – **Grants/Research Support:** AstraZeneca Pharmaceuticals LP, Berlex Inc, Celgene Corporation, Eli Lilly and Company, Sanofi-Aventis; **Speakers Bureau:** Celgene Corporation, Sanofi-Aventis.

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Editor's Note

Where we're headed

DR LOVE: When you look into your crystal ball, what do you see for prostate cancer clinical research five years from now?

DR D'AMICO: I think in five years we'll have information on the impact of chemotherapy in earlier disease. There will be other chemotherapies at that point, which will have been proven in advanced disease, and we'll be getting ready to move those up and test those next in earlier-stage disease.

Concomitant with that, we'll have the answer as to whether PSA screening decreases mortality. My hope is that it will, particularly in high-risk subsets. Once that answer comes on board, the way we look at prostate biopsy will change — what level of PSA is the trigger point for biopsy, how PSA velocity plays into it, etc. As a result, prostate biopsies may only be directed at those people with the kind of cancers we need to diagnose and treat.

The other thing is genomics and proteomics. Investigators are trying to use these techniques to determine when to biopsy and when to treat and to determine who needs their prostate taken out versus other local or systemic therapies. These tools also may help us identify which patients in the metastatic setting are on the favorable and unfavorable ends of the curve. I think proteomics and genomics will become part of the patient selection process for future clinical trials.

And the final thing is, I'm very happy to see that in the last five years, patients have become more actively involved at different levels, from support groups to lobby groups. Patients have assisted with the design of trials and have encouraged participation. People like Michael Milken have also facilitated financial support for prostate cancer research. The patients' voice here — just like it was in breast cancer — is so important to keep research dollars coming and to obtain input on the important questions of men afflicted with the disease. All of this is a plus for where we're heading.

Interviewing Anthony D'Amico is a lot like being the batting practice pitcher for a big-league slugger — each question seems like a soft lob, which is followed by a titanic blast out of the park. The impromptu conversation snippet posted above is typical of the comprehensive and thoughtful answers Tony provides to almost

any question in the field. In this case, he crystalizes where we are and where we hope to be in a few years.

The other interviewees for this program provide additional perspective on this topic, particularly related to the need for interdisciplinary care to foster clinical research. One can make the argument that to a great extent, the future success of prostate cancer clinical research directly relates to the integration and collaboration of the physician specialties of the three speakers featured on this issue of *Prostate Cancer Update*.

Urologist Len Gomella sees his patients in an interdisciplinary clinic that includes medical oncologists and radiation oncologists like Dr D'Amico. On this program, Dr Gomella presents a patient with high-risk disease, who was managed using a multimodality approach with surgery, radiation therapy and endocrine treatment. On a previous issue of this series, he described the evolution of the multidisciplinary prostate cancer clinic at Thomas Jefferson University's Kimmel Cancer Center since 1996.

> We discuss patients in real time, face to face, and have the ability to really come up with a uniform plan and recommendation. Presenting the spectrum of options to patients and giving them the good things and bad things about different approaches is where we're at right now in prostate cancer today.
>
> We also wanted to create a setting that would serve as an educational conduit not only for the patient and their family but also for the trainees at our center — residents and fellows in radiation oncology, urology and medical oncology.
>
> After each clinic, we have a conference where pathology is reviewed and we discuss the patients' management, including suitability for protocols. We've written several papers and given a number of presentations about this clinic, and generally, patient satisfaction is extraordinarily high. It's a lot of effort, but when we go home at the end of the day, we feel we have not only done a service for the patient and their family, but also optimized our ability to learn more about the disease.
>
> ***— Leonard G Gomella, MD***

The interdisciplinary approach at Jefferson and other tertiary centers follows the path set by breast cancer where the early integration of medical oncologists into the treatment process was essential to moving research forward expeditiously. Also on this program, medical oncologist Robert Dreicer elaborates on the evolution of this concept in prostate cancer.

> Historically, prostate cancer patients were predominantly managed by my urologic colleagues, who for many years, were a group of surgeons somewhat unique, in that they managed all of urologic disease, including medical aspects.

That paradigm began to change in the late 80s and early 90s, with the recognition that medical oncology had an important role. Of course, there was also an evolving role of radiation therapy over the years. Traditionally, much of urologic research in cancer was surgical based and institution based; ie, "I have 2,000 cases and these are our outcomes. This is what we do."

As the NCI's National Prostate Cancer Project came on line — driven in part by urology — there was the introduction of the randomized clinical trial, as with the NSABP with breast and colon cancer in that same era; however, when you delay the trial process for several decades, it takes time to catch up.

Most patients who enter clinical trials come from the community setting, where interdisciplinary urologic oncology management is not the standard. There are certainly some communities in which it works very well, but there are others in which it doesn't work well at all.

We need to have young urologists entering clinical practice, who are well aware of the interdisciplinary nature of management and can help us evolve therapy of this group of diseases — prostate, bladder, renal and testes cancer — in an interdisciplinary way, and hopefully reproduce the model of our colleagues in breast and colon cancer, where interdisciplinary management results in clinical trials that get done relatively quickly.

Fortunately, we now have major academic urology thought leaders who are taking a leadership role in all of these areas. So, the problem from that end has clearly been fixed. But it takes time, and it's incumbent upon the urologist — the captain of the ship — to say, for example, to his or her patient, "You have high-risk disease, which will ultimately require the skill sets of a number of my colleagues. I'm going to refer you to a medical oncologist. He or she is not likely to need to do anything now, but I would like you to get to know each other, have a discussion about your disease from another perspective and obtain a sense of what's out there and what might be coming."

For example, in our interdisciplinary program at the Cleveland Clinic — patients with biochemical failure are seen by a GU medical oncologist from the start, and that works well. Having done that, the patient has a relationship with two doctors and moves forward. There's no reason for that paradigm not to work.

Every year, urology residents finish at our shop and other places, and they are well-trained individuals who understand the interdisciplinary nature of the disease. When they get into the community, they will work and act differently. So, it's a problem that will be fixed, but transitioning to the fix is taking time.

— Robert Dreicer, MD

The three researchers on this program share a similar view of the future of prostate cancer management. As with breast cancer, local and systemic therapy will be seamlessly provided by an integrated team that constantly seeks research avenues for improved outcomes. Effective tools for prostate cancer control already exist and new molecularly targeted approaches are on the horizon, and it will be essential that physicians and patients work together to see that these interventions are properly applied.

I plan on reinterviewing Dr D'Amico a number of times over the next few years to track our progress on the encouraging course he has outlined. My guess is that five years from now, a new series of research findings will have led to further research questions, but hopefully, our ability to expeditiously answer these will be improved as interdisciplinary research-based care becomes standard for all patients.

— Neil Love, MD
NLove@ResearchToPractice.net

Select publications

Carroll PR et al. **Fourth International Conference on Innovations and Challenges in Prostate Cancer: Prevention, Detection and Treatment.** *J Urol* 2004;172(5 Pt 2):3-5. No abstract available

Coleman J et al. **Highlights from the Society of Urologic Oncology 4th annual meeting.** *J Urol* 2005;173(3):938-41. **Abstract**

D'Amico AV et al. **Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy.** *N Engl J Med* 2004;351(2):125-35. **Abstract**

D'Amico AV et al. **Prostate specific antigen doubling time as a surrogate end point for prostate cancer specific mortality following radical prostatectomy or radiation therapy.** *J Urol* 2004;172(5 Pt 2):42-6. **Abstract**

Dotan ZA et al. **Pattern of prostate-specific antigen (PSA) failure dictates the probability of a positive bone scan in patients with an increasing PSA after radical prostatectomy.** *J Clin Oncol* 2005;23(9):1962-8. **Abstract**

Gelmann EP, Semmes OJ. **Expression of genes and proteins specific for prostate cancer.** *J Urol* 2004;172(5 Pt 2):23-6. **Abstract**

Kumar-Sinha C, Chinnaiyan AM. **Molecular markers to identify patients at risk for recurrence after primary treatment for prostate cancer.** *Urology* 2003;62(Suppl 1):19-35. **Abstract**

Lieberman R. **Evidence-based medical perspectives: The evolving role of PSA for early detection, monitoring of treatment response, and as a surrogate end point of efficacy for interventions in men with different clinical risk states for the prevention and progression of prostate cancer.** *Am J Ther* 2004;11(6):501-6. **Abstract**

O'Hara SM et al. **Multigene reverse transcription-PCR profiling of circulating tumor cells in hormone-refractory prostate cancer.** *Clin Chem* 2004;50(5):826-35. **Abstract**

Ornstein DK et al. **Serum proteomic profiling can discriminate prostate cancer from benign prostates in men with total prostate specific antigen levels between 2.5 and 15.0 ng/ml.** *J Urol* 2004;172(4 Pt 1):1302-5. **Abstract**

Papatsoris AG et al. **Novel biological agents for the treatment of hormone-refractory prostate cancer (HRPC).** *Curr Med Chem* 2005;12(3):277-96. **Abstract**

Petricoin EF et al. **Clinical proteomics: Applications for prostate cancer biomarker discovery and detection.** *Urol Oncol* 2004;22(4):322-8. **Abstract**

Anthony V D'Amico, MD, PhD

EDITED COMMENTS

Survival benefit associated with the combination of hormonal therapy and radiation therapy

The validation that the combination of hormonal therapy and external beam radiation therapy provides a survival benefit compared to radiation therapy alone is an important clinical message.

A number of randomized studies have evaluated this question, particularly in men with localized high-risk disease. "High risk" in this scenario is defined as a Gleason score of seven or higher or a PSA level greater than 10 ng/mL.

The most recent study, published in *JAMA* in August 2004, demonstrated a 10 percent survival benefit at five years for men who received six months of hormonal therapy in combination with radiation therapy compared to men who received radiation therapy alone (D'Amico 2004; [1.1]).

Hormonal therapy consisted of flutamide with either leuprolide or goserelin. Two questions remain in this scenario: (1) Is combined hormonal blockade necessary? and (2) Are six months of hormonal therapy adequate in patients with Gleason 8, 9 or 10 disease, even if it is T1c or T2?

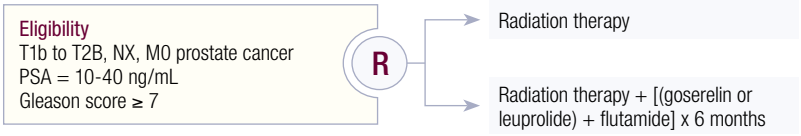
The studies preceding the trial published in *JAMA* were RTOG-9202 and the Bolla trial. The Bolla trial — an EORTC study — found that three years of hormonal therapy is better than no hormonal therapy (Bolla 2002). RTOG-9202 found that two years and four months was better than just four months of hormonal therapy. It was not an overall survival benefit but a cancer-specific survival benefit of 3.4 percent at five years (Hanks 2003).

The question still remains whether long-term hormonal therapy is necessary and safe. A European randomized study comparing three years to six months of hormonal therapy should answer the question more definitively. If long-term hormonal therapy truly is better, I suspect that older men (over 70 years of age), in whom occult cardiovascular disease can be prevalent, will benefit least, whereas younger men who don't have cardiovascular issues may benefit most.

Dr D'Amico is Professor and Chair of Genitourinary Radiation Oncology at Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, in Boston, Massachusetts.

1.1 Randomized Trial Comparing Six Months of Combined Hormonal Therapy Plus Radiation Therapy to Radiation Therapy Alone; in Patients with Clinically Localized Prostate Cancer

Accrual: 206 (Closed)



	RT + HT (n=102)	RT (n=104)	Log rank *p*-value
Five-year overall survival	88%	78%	0.04
Prostate cancer mortality	0%	6%	0.02
Progression-free survival*	82%	57%	0.002

RT = radiation therapy; HT = hormonal therapy

* Progression defined as date of initiation of salvage hormonal therapy

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**

D'Amico trial: Six months of combined hormonal blockade plus radiation therapy versus radiation therapy alone

The study we published in *JAMA* was a randomized trial in 206 men comparing 3D-conformal external beam radiation therapy (total dose of 70.35 Gray) with or without six months of combined hormonal blockade administered for two months before, two months during and two months after radiation therapy (1.1). In the study, 57 percent of the patients had a PSA that was greater than 10 ng/mL, and 73 percent of the patients had a Gleason score of 7 or higher. This was a study of patients with high-grade cancer. For the most part, patients had T1c disease. More than half the patients had PSA-detected disease, and about 50 percent had T2 or palpable tumors (D'Amico 2004).

The primary endpoint of the trial was progression-free survival. Because the effect of hormonal therapy on cancer-related death was higher than expected, we saw a difference in overall survival, just like the Bolla trial. At five years, progression-free survival was 82 percent for the patients treated with hormonal therapy plus radiation therapy versus 57 percent for those treated with radiation therapy alone. This means the patients treated with radiation therapy alone had a PSA elevation and were on hormonal therapy 25 percent more frequently (D'Amico 2004; [1.1]).

Cancer-specific mortality at five years was zero in the patients treated with hormonal therapy plus radiation therapy versus six percent in the patients treated with radiation therapy alone; overall survival demonstrated a 10 percent difference (88 percent versus 78 percent, respectively). The absolute number of

deaths due to prostate cancer was six in the radiation therapy-only arm and zero in the hormonal therapy plus radiation therapy arm (1.1). Out of 206 patients, a six-event difference in prostate cancer deaths was enough to account for a survival difference, mainly because we initially screened patients for cardiovascular disease. The hazard ratio for overall survival was two, which means a two-fold reduction in deaths in the men randomly assigned to combined hormonal therapy plus radiation therapy.

Role of combined hormonal blockade

Off protocol, in patients with high-risk T1c or T2 disease, I use six months of combined hormonal blockade because that is what I used in the study I conducted. In that study, about 27 percent of the patients did not complete the six months of flutamide, mainly because of elevations in their liver function tests (LFTs).

They weren't necessarily having toxicities from the flutamide, but we had a rule: if the LFTs exceeded two times the upper limit of normal, we discontinued the drug for that patient. Despite that, the survival benefit was still seen (D'Amico 2004).

It is an open question whether combined hormonal blockade is really necessary; however, without an answer from a randomized trial, I follow the results from the randomized trial we have. When we designed that trial in 1994, bicalutamide wasn't available, so flutamide was used. Today, bicalutamide is used because it's a once-a-day drug and it doesn't have the same LFT issues.

In patients who have T3 or T4 disease by palpation, I use exactly what the RTOG utilized in their randomized study: two months of neoadjuvant combined hormonal blockade, two months of combined hormonal blockade concurrent with radiation therapy and two years of an LHRH agonist alone (Hanks 2003).

Recent trials comparing two docetaxel-containing regimens to mitoxantrone plus prednisone in patients with hormone-refractory metastatic prostate cancer

In 2004, results from two trials comparing docetaxel-containing regimens to mitoxantrone plus prednisone in patients with hormone-refractory metastatic prostate cancer were published in the *New England Journal of Medicine* — one was SWOG-9916 by Dr Dan Petrylak, and the other was TAX-327 by Dr Ian Tannock (1.2). Both studies demonstrated a survival benefit of about two months for the docetaxel-containing regimen (Petrylak 2004; Tannock 2004).

One study combined estramustine with docetaxel (Petrylak 2004), and the other evaluated docetaxel alone (Tannock 2004). Both studies showed a similar prolongation in survival, but because estramustine increased toxicity, it is not considered a necessary part of the regimen. Two dosing regimens for docetaxel were evaluated: every three weeks and weekly. The every three-week regimen appeared to be better (1.2), although the FDA and others are going to validate that in the future. The currently accepted regimen for docetaxel is 75 mg/m^2 every three weeks.

1.2 Results from Two Randomized Trials Comparing a Docetaxel-Containing Regimen to Mitoxantrone Plus Prednisone in Patients with Hormone-Refractory Metastatic Prostate Cancer

	SWOG-9916[1]		TAX-327[2]*		
	D + E (n=338)	M + P (n=336)	D q3wk (n=332)	D weekly (n=330)	M (n=335)
Median survival	17.5 mo	15.6 mo	18.9 mo	17.4 mo	16.5 mo
Survival	36%	30%	50%	43%	40%
PSA response rate (≥50 percent decline)	50%	27%	45%	48%	32%
Partial response rate	17%	11%	12%	8%	7%

D = docetaxel; E = estramustine; M = mitoxantrone; P = prednisone

* All patients in TAX-327 received prednisone in addition to chemotherapy.
Median follow-up 32 months for SWOG-9916 and 20.7 months for TAX-327

SOURCES: [1] 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**

[2] Tannock IF et al; TAX 327 Investigators. **Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.** *N Engl J Med* 2004;351(15):1502-12. **Abstract**

Ongoing clinical trials evaluating docetaxel in patients with earlier-stage disease

We are conducting a trial in patients with high-risk disease. Patients are treated with radiation therapy and hormonal therapy with or without docetaxel. The chemotherapy will be administered for two cycles prior to the start of radiation therapy, concurrent with hormonal therapy, and weekly during radiation therapy, so it's approximately four months of chemotherapy.

Dr Howard Scher is conducting a trial of hormonal therapy with or without docetaxel in patients with rapidly rising PSAs (eg, doubling times less than three to six months) following surgery or radiation therapy. Dr Mario Eisenberger will be conducting a postoperative adjuvant study in men with high-risk features at prostatectomy (ie, seminal vesicle invasion, Gleason score of 8 to 10); patients will receive hormonal therapy and be randomly assigned to docetaxel or no further therapy.

It's important to select patients carefully for these studies. For example, the vast majority of patients with a PSA failure after local therapy don't die from prostate cancer. We know now that it's the rate of rise of the PSA — and not the PSA failure itself — that's important, so patients whose PSAs are rising quickly are the patients you want to enroll in these studies. The toxicity from chemotherapy occurs up front, and even younger men require some down time during the chemotherapy regimen. They have to be willing to accept an acute decrement in quality of life for a benefit that's not yet proven.

The study I'm conducting in men with high-risk disease is powered for a hazard ratio of 1.5, whereas the hazard ratio in our study with hormonal therapy was two. With the chemotherapy, we're hoping to see half the improvement that we saw with hormonal therapy. If we had a 10 percent benefit from hormonal therapy at five years, we'd be happy with a five percent benefit from chemotherapy.

I'm powering the study for survival, pending the validation of a surrogate (eg, progression-free survival). We evaluated progression-free survival in the study of hormonal therapy and radiation therapy because when that trial was designed in 1994, that endpoint was in vogue for hormonal therapy. The benefit from hormonal therapy was more than expected. We also saw a difference in survival; however, no data for chemotherapy in localized prostate cancer in a randomized setting indicate that progression-free survival can be used as an endpoint.

In our trial, prevention of bone metastases is a secondary endpoint that is clinically relevant. If you design a prostate cancer clinical trial powered for survival, you'll have plenty of power to go back and evaluate progression-free, disease-free and cancer-specific survival. But if you power the trial for an earlier endpoint, you may not have enough power to evaluate the ultimate endpoint. We expect this study will accrue in two years and be reported three to five years later.

Tolerability of docetaxel

Patients whose performance status is good — such as men under 65 years of age — will tolerate docetaxel well. They come in, receive the infusion, go home, have a couple of days with some symptoms and then go back to their routine. Toxic deaths are rare and few patients require hospitalization for complications. Growth factors can be used to bring up counts if need be, and these patients must have their blood counts monitored. This is a new arena, not for medical oncologists, but for the urologists and radiation oncologists who deal with patients with prostate cancer.

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(9327):103-6. **Abstract**

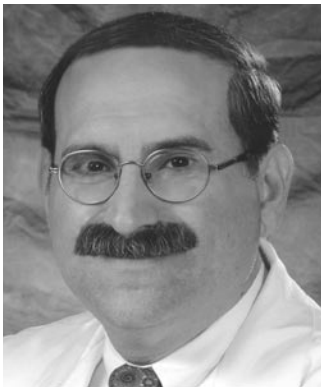
D'Amico AV et al. **6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial.** *JAMA* 2004;292(7):821-7. **Abstract**

Hanks GE et al; Radiation Therapy Oncology Group. **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. **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**

Tannock IF et al; TAX 327 Investigators. **Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.** *N Engl J Med* 2004;351(15):1502-12. **Abstract**

Duration and benefit of adjuvant hormone therapy



We generally recommend two to three years of adjuvant hormonal therapy when treating patients with locally advanced disease, which is based primarily on the data from recent trials. Bolla's EORTC trial showed superior outcomes in patients who received three years of hormonal therapy, and the RTOG-9202 showed two years of hormonal therapy resulted in a survival advantage (Bolla 2002; Hanks 2003).

Admittedly, the duration of hormone therapy is controversial. Some institutional studies have suggested as little as six months of hormonal therapy may be beneficial, and that's possible, but our recommendations rely on the larger multi-institutional trials with thousands of patients.

While the prospective randomized trials all show this approach is effective, particularly in patients with high-risk disease, it's not advantageous for all patients. Patients with low-risk disease do not appear to benefit from the combination of hormones and radiation, and the side effects may detract from the patient's quality of life and overall outcome. In the RTOG-9202 trial, an overall survival advantage was seen in patients with high Gleason's scores; however, in the patients with lower-risk disease, although the combination may enhance PSA control, we don't see much improvement in survival.

RTOG-9601: Radiation therapy with or without bicalutamide 150 mg

This Phase III randomized study is in patients with PSA relapse following radical prostatectomy. The study is closed to accrual and we are anxiously awaiting the data. This will be one of the most exciting trials to be reported because it will determine whether it's beneficial to combine hormonal manipulation with radiation therapy in the salvage setting.

RTOG-8531 showed that patients who received radiation and hormones together after radical prostatectomy for unfavorable prostate cancer had a survival advantage over patients who only received radiation therapy (Lawton 2005). I believe RTOG-9601 will also be a positive study because we know the effective-

Dr Gomella is the Bernard W Godwin Professor of Prostate Cancer and Chairman of the Department of Urology at Jefferson Medical College and Director of Urologic Oncology at Kimmel Cancer Center in Philadelphia, Pennsylvania.

ness of bicalutamide 150 mg in the adjuvant setting (Wirth 2004). Based on the Iverson and See data, it would be a stretch to think the combination would not be more effective than radiation therapy alone.

Bicalutamide 150 mg is approved in over 50 countries around the world; however, it has not received FDA approval in the United States. In Europe, bicalutamide is commonly used as step-up therapy in which patients receive oral agents, such as a 5-alpha reductase inhibitor, with a small dose of bicalutamide. The bicalutamide dose is then increased up to 150 mg before the patient is started on an LHRH analog as their definitive therapy.

Currently at our center, the medical oncologists' standard salvage regimen for patients whose disease is failing standard androgen ablation is bicalutamide 150 mg. We have seen responses to this regimen last for over a year and a half, so it appears to be reasonable salvage therapy and can be offered to patients.

It does appear that a small percentage of men may have an increased cardiac toxicity associated with the drug. The number of men who had adverse cardiac outcomes and the number of increased death rates in the low-risk arms of the EPC studies with bicalutamide 150 mg were low, but noticeable (Iversen 2004; Wirth 2004). These findings may have been statistical aberrations or statistical noise; nonetheless, they need to be further examined.

Although bicalutamide 150 mg is not currently approved for salvage therapy in the United States, I believe it's appropriate to discuss it with patients for whom it may be suitable, such as those who are sexually active and want to maintain their sexual functioning. Bicalutamide can preserve sexual function, whereas a high percentage of men on an LHRH analog therapy experience significant sexual dysfunction. Quality of life and determining what's important to the patient have become central issues when considering treatment alternatives in prostate cancer.

Intermittent hormonal therapy

Intermittent hormonal therapy is not considered the standard of care, but we do use it in select patients. The data on this therapy are conflicting — some preliminary European studies show that it doesn't adversely affect overall PSA recurrence or survival, whereas other studies report adverse outcomes in prostate cancer progression with intermittent therapy.

One of the challenges is that we are waiting for data on intermittent therapy from the large ECOG trial completed in the United States several years ago. The problem is that this trial evaluated intermittent therapy in patients with high PSA levels and metastatic disease. Most of us believe that for intermittent therapy to work, it will probably be most effective in patients with a low disease burden and minimal PSA elevation.

In fact, we know from the Messing trial that some patients with micrometastatic disease receive hormonal therapy and never have a recurrence (Messing 1999). Certainly some patients who choose to discontinue hormonal therapy will not

have disease relapse. This is anecdotal, but I have two young patients who had node-positive, micrometastatic disease with undetectable PSAs postoperatively.

After approximately three years of adjuvant hormonal therapy, they each asked me to take them off of hormonal therapy. They are now approaching almost 10 years since their diagnosis with no evidence of recurrence and they both have normal PSA levels.

What we really need are more studies on intermittent therapy for PSA-only recurrences with low levels (2.1). Because we don't have the data, we can't recommend intermittent therapy as a definitive treatment option; however, we can certainly discuss it with patients.

2.1 Ongoing Phase III Trials of Intermittent Androgen Deprivation

Protocol ID	Accrual	Eligibility	Protocol
SWOG-9346	1,745 in 12 years	Stage IV	Induction: CAD^1 x 8 Arm I: CAD^1 until disease progression Arm II: Observation until rising PSA or progressive disease, then CAD^1. If PSA normalizes after 8 courses, then observation; if not, then CAD^1.
CAN-NCIC-PR7	1,340 in 7 years	PSA progression without clinical evidence of metastases after radiotherapy	Arm I: IAS x 8 months If PSA falls to normal within 8 months, therapy stops until PSA rises to 10 ng/mL, then therapy resumes. At disease progression, CAD^2 initiated Arm II: CAD^2 until hormone resistance

CAD^1 = goserelin qmo + bicalutamide qd; CAD^2 = LHRH (buerelin or goserelin or leuprolide) + antiandrogen (nilutamide or flutamide or bicalutamide or cyproterone acetate) or bilateral orchiectomy
IAS = LHRH + antiandrogen as in CAD^2

SOURCE: NCI Physician Data Query, March 2005.

Survival advantage with chemotherapy in metastatic disease

The new data showing a survival advantage with docetaxel-based chemotherapy in patients with hormone-refractory prostate cancer are provocative (Eisenberger 2004; Petrylak 2004). The two large trials reported at ASCO in 2004 have made early chemotherapy a more viable option. The tolerability of docetaxel is also significantly better than the estramustine-based therapies that caused so much toxicity in the 1990s.

At this time, the average patient with a PSA recurrence who has not demonstrated metastatic disease is treated with hormonal therapy front line and, if that fails, another hormone intervention second line. My third line treatment is chemotherapy, because I believe our best opportunity to intercede and have a favorable outcome is in the earliest stages of progression.

For example, we learned that salvage radiation therapy after radical prostatectomy is more effective when used earlier rather than later. We used to initiate

salvage therapy when the patient's PSA reached 4 ng/mL, then 2 ng/mL, then 1.5 ng/mL. Now, for the best outcome, we initiate salvage radiation when the PSA reaches 1 ng/mL. I believe using chemotherapy earlier in the disease is reasonable to consider, although we don't have any good studies yet to say it should be utilized at the first evidence of PSA recurrence.

We are also seeing an emphasis on a multidisciplinary team approach and consulting with the medical oncologist earlier in the management of prostate cancer. Previously we didn't have effective chemotherapy regimens to offer patients — nothing demonstrated a statistically significant advantage in large prospective randomized trials until mid-2004, when the two positive docetaxel studies were reported. I believe we will see an intrinsic change in the management of these patients as a result of these data. In addition, other compounds will be available in the next couple of years that may further redefine how patients with PSA recurrence or progressive prostate cancer are managed.

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(9327):103-6. **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**.

Hanks GE 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. **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 follow-up from the Scandinavian Prostate Cancer Group Study Number 6.** *J Urol* 2004;172(5 Pt 1):1871-6. **Abstract**

Lane TM et al. **Long-term outcomes in patients with prostate cancer managed with intermittent androgen suppression.** *Urol Int* 2004;73(2):117-22. **Abstract**

Lawton CA et al. **Androgen suppression plus radiation versus radiation alone for patients with stage d1/pathologic node-positive adenocarcinoma of the prostate: Updated results based on national prospective randomized trial radiation therapy oncology group 85-31.** *J Clin Oncol* 2005;23(4):800-7. **Abstract**

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

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 follow-up of 5.4 years.** *J Urol* 2004;172(5 Pt 1):1865-70. **Abstract**

Docetaxel in patients with androgen-refractory disease

Microtubule complexes have been identified as particularly important targets in prostate cancer systemic therapy. A series of agents — the vincas, taxanes and estramustine — have activity at that level. The taxanes — docetaxel and paclitaxel — target those complexes as their primary mechanism of action and have been widely investigated.

Dr Petrylak at Columbia conducted a Phase I/II trial of docetaxel and estramustine. This study demonstrated an intriguing median survival of approximately 23 months, which caught people's attention.

We all recognize that prostate cancer is not breast or lung cancer, so objective response rates have to be considered carefully; prostate cancer is a disease that primarily involves bone only, with a smaller subset of patients with measurable disease. Survival data, even from a hypothesis-generating study like Dr Petrylak's, was important, so the Southwest Oncology Group launched SWOG trial 9916 to investigate whether an agent or combination exists that would provide a meaningful difference in survival (Petrylak 2004a and b).

A related trial was TAX-327, which compared weekly versus every three-week docetaxel versus the gold standard, mitoxantrone/prednisone (Eisenberger 2004; Tannock 2004). The survival data from both trials demonstrated a two to two-and-a-half month median improvement in survival, and the hazard ratios indicated a 20 to 24 percent reduction in prostate cancer death on the docetaxel arm.

That's a modest advance, but we need to put this in perspective. Ten years ago, chemotherapy was felt to be essentially of no utility in prostate cancer, and now we have objective response rates enough to provide a survival advantage. We all understand that it is not the "end all, be all," because it's still modest, but it is an important first step, and it changes how we think about the management of advanced disease.

Dr Dreicer is a Professor of Medicine at the Cleveland Clinic Lerner College of Medicine, Director of Genitourinary Medical Oncology and Associate Director of Experimental Therapeutics in the Departments of Hematology/Oncology and the Glickman Urological Institute at the Cleveland Clinic Foundation in Cleveland, Ohio.

Use of docetaxel in patients with metastatic disease

Although I was obviously delighted to see the results of SWOG-S9916 and TAX-327, in effect, it's created many more questions than were answered. The majority of the patients enrolled in the two trials had androgen-independent metastatic disease, and many, but not all, were symptomatic. Until that data were available, chemotherapy in a noninvestigational setting was used to palliate patients; therefore, most patients, at least theoretically, were treated when they had disease-related symptoms.

The question now is: Does the patient who has asymptomatic metastatic disease need to be treated at that time, or later? That's a critical question to which we don't know the answer. In my practice, for asymptomatic patients with low-volume disease, I have a discussion about what we know about the trials. As an academician, I have clinical research opportunities for some of these patients and certainly would steer them in that direction. When a patient is not interested in participating in a clinical trial, I review the data with them and try to arrive at a reasonable decision based on their individual perspectives.

Early versus deferred treatment of androgen deprivation therapy

Earlier versus deferred hormonal therapy is a major breaking point in the GU community — particularly among the zealous believers in early androgen deprivation and the more nihilistic among us. In my own practice, because we see a large number of patients with biochemical failure, I have alternative, immunomodulatory investigational options. Putting that aside, PSA doubling time is increasingly useful to predict which patients are more likely to develop systemic progression in the hormone-naïve setting.

I discuss the controversies of early androgen deprivation with patients and discuss why my colleagues are advocates of earlier therapy. When the patient asks me, ultimately, where I stand on the matter, I tell them that I respect the toxicity profile of androgen deprivation therapy. For a long time we have undersold the impact of androgen deprivation on quality of life.

I tend to advocate early androgen deprivation therapy for the motivated patient with a shortening PSA doubling time, which sometimes occurs after a relative period of stability. Now, is that correct? I don't know the answer to that question, but in my practice, that's the situation in which I talk to patients in a more proactive way about earlier hormonal therapy.

Use of PSA as an endpoint in clinical trials

With each passing year, the number of patients with locally advanced prostate cancer — who are perhaps destined to do poorly relatively early — continues to decline as we detect disease earlier. This impacts our ability to perform adjuvant studies of chemotherapy. Currently, the FDA would not accept PSA failure as a clinical endpoint, so we have to wait for clinical progression or death. The FDA is actively considering these issues, and at least one forum was held last fall at the FDA and another one is planned. Changes may be occurring in the agency's attitude toward PSA as an endpoint, but as of today, it's a dilemma. If we can

only perform one study a decade, it will be a long time before we can answer the question about adjuvant chemotherapy in the treatment of prostate cancer.

As a clinical trial endpoint, PSA remains problematic in some settings. In patients with biochemical failure only, using PSA failure as a parameter of response remains unproven; however, in the adjuvant setting, I think most of us who take care of these patients would clearly accept time to PSA failure as an endpoint in patients undergoing radical prostatectomy — albeit not the only endpoint.

Of course, reasonable assurances must be made to ensure that the PSA failures are real and not simply low levels of detectable PSA in patients who are not destined to progress. That's the optimal use of PSA in how we manage patients today, and it would be problematic to not use PSA failure as at least an intermediate endpoint.

Clearly, in studies of hormonal therapy, PSA failure would not be a useful endpoint. Biologic or targeted therapies are also potentially problematic unless we understand what these drugs do to PSA expression at the cellular level. With chemotherapy, we increasingly have reason to believe it would have validity in the postprostatectomy setting.

Time to delay of PSA failure is probably a good surrogate to activity. That's not to say you should end the trial based on that endpoint and not collect other data, but I believe it's an endpoint that will have some value and allow us to begin testing agents in the adjuvant setting without having to expose patients to Phase III investigations. It would allow us to perform hypothesis-generation studies and select agents that make rational sense based on some of these early endpoints, and then move on to formal Phase III studies.

In the metastatic setting, Dr Crawford presented data at ASCO 2004 that were based on the preliminary analysis of the SWOG randomized trial S9916. These data suggested that a three-month change in PSA was, in fact, a surrogate for survival in the androgen-independent setting (Crawford 2004). Is it the same in the hormone-naïve environment? I don't know, and that's an important question.

Select publications

Crawford ED et al. **Three-month change in PSA as a surrogate endpoint for mortality in advanced hormone-refractory prostate cancer (HRPC): Data from Southwest Oncology Group Study S9916.** *Proc ASCO* 2004;**Abstract 4505**.

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. **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**.

Tannock IF et al; TAX 327 Investigators. **Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.** *N Engl J Med* 2004;351(15):1502-12. **Abstract**

Post-test:

Prostate Cancer Update — Issue 2, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In men with localized prostate cancer, treatment with six months of combined hormonal blockade plus radiation therapy has been shown to be better than _____ _____.
   a. Two years of combined hormonal blockade and radiation therapy
   b. Three years of combined hormonal blockade and radiation therapy
   c. Radiation therapy alone
   d. All of the above
   e. None of the above

2. Ongoing clinical trials will evaluate the role of docetaxel in men with earlier-stage disease in which of the following settings?
   a. Patients with high-risk disease who are treated with radiation therapy plus hormonal therapy
   b. Patients with a rapidly rising PSA following surgery or radiation therapy
   c. Patients with high-risk prostate cancer following prostatectomy
   d. All of the above
   e. None of the above

3. Bicalutamide 150 mg is not FDA approved for the treatment of prostate cancer in the United States.
   a. True
   b. False

4. Bolla's EORTC trial showed superior outcomes in patients who received _____ year(s) of adjuvant hormonal therapy for the treatment of locally advanced prostate cancer.
   a. One
   b. Two
   c. Three
   d. Four

5. The FDA has accepted PSA response as a primary endpoint in clinical trials evaluating chemotherapy.
   a. True
   b. False

6. The RTOG-9202 trial of long-term adjuvant androgen deprivation in patients with locally advanced prostate cancer showed that patients with _____ prostate cancer received greater benefit from the combination of hormones and radiation therapy.
   a. High-risk
   b. Low-risk

7. The TAX-327 trial comparing weekly versus every three-week docetaxel/prednisone versus mitoxantrone/prednisone in patients with androgen-independent metastatic disease demonstrated a survival advantage for:
   a. Weekly docetaxel
   b. Every three-week docetaxel
   c. Mitoxantrone/prednisone

8. The SWOG trial 9916 demonstrated a survival advantage for docetaxel/estramustine compared to mitoxantrone/prednisone in patients with androgen-independent prostate cancer.
   a. True
   b. False

9. Dr Crawford presented data at ASCO 2004, which suggested that a three-month change in PSA was a surrogate for survival in the androgen-independent setting.
   a. True
   b. False

10. In TAX-327 and SWOG-9916, the PSA response rate (>50 percent decline) associated with docetaxel was approximately:
    a. 25%
    b. 35%
    c. 50%

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

Evaluation Form:

Prostate Cancer Update — Issue 2, 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.

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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
Anthony V D'Amico, MD, PhD	5 4 3 2 1	5 4 3 2 1
Leonard G Gomella, MD	5 4 3 2 1	5 4 3 2 1
Robert Dreicer, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity. . . . . 5 4 3 2 1 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

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.....

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

.....

Degree:

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FOLLOW-UP

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:

☐ Yes, I am willing to participate in a follow-up survey.

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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.com.

Prostate Cancer™ UPDATE

Editor	Neil Love, MD
Associate Editors	Michelle Paley, MD Richard Kaderman, PhD
Writers	Lilliam Sklaver Poltorack, PharmD Sally Bogert, RNC, WHCNP Douglas Paley Kathryn Ault Ziel, PhD
CME Director	Michelle Paley, MD
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Editorial Assistants	Patricia McWhorter Raquel Segura Tere Sosa Ginelle Suarez Arlene Thorstensen
Production Manager	Patricia Kappes
Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@ResearchToPractice.net
For CME Information	Melissa Vives,CME Coordinator Email: MVives@ResearchToPractice.net

This program is supported by education grants from AstraZeneca Pharmaceuticals LP and Aventis Pharmaceuticals, a member of the sanofi-aventis Group.

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AstraZeneca Pharmaceuticals LP and Aventis Pharmaceuticals,
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Last review date: May 2005
Release date: May 2005
Expiration date: May 2006
Estimated time to complete: 3 hours