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HOW TO USE THIS MONOGRAPH

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

Prostate Cancer Update: A CME Audio Series

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 patient care, *Prostate Cancer Update* utilizes one-on-one discussions with leading urologic oncology and radiation oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists urologists and radiation oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

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

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

PURPOSE OF THIS ISSUE OF *PROSTATE CANCER UPDATE*

The purpose of Issue 1 of *Prostate Cancer Update* is to support these global objectives by offering the perspectives of Drs Carroll, Smith and Hussain on the integration of emerging clinical research data into the management of prostate cancer.

ACCREDITATION STATEMENT

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

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Peter R Carroll, MD	Grants/Research Support: TAP Pharmaceuticals Inc Consultant: iMetrikus Inc Honorarium: AstraZeneca Pharmaceuticals LP
Matthew R Smith, MD, PhD	Grants/Research Support and Consultant: AstraZeneca Pharmaceuticals LP, Novartis Oncology
Arif Hussain, MD	Grants/Research Support: AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals Inc, Berlex Inc, Bristol-Myers Squibb Company, Cytogen Corporation, Novartis Pharmaceuticals, Pfizer Inc Consultant: Cytogen Corp

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
goserelin acetate	Zoladex®	AstraZeneca Pharmaceuticals LP
bicalutamide	Casodex®	AstraZeneca Pharmaceuticals LP
pamidronate	Aredia®	Novartis Pharmaceuticals
zoledronic acid	Zometa®	Novartis Pharmaceuticals
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
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Editor's Note

Doctors with cancer

When our CME group prepared to launch this series almost three years ago, our first task was to read and listen. The clinicians who comprise our content team have considerable experience in cancer education, but in planning new programs we always seek to understand the most controversial and problematic questions that occur in translating emerging research data into practice for each unique tumor type.

Our initial perusal of the prostate cancer literature quickly provided a plethora of highly challenging management issues, many of which are being addressed in ongoing clinical trials. Two of the most provocative are discussed by the speakers on this program — watchful waiting in very early stage disease and management of PSA relapse.

When I asked Peter Carroll what he believed was the single most important area of future clinical research in prostate cancer, he immediately zeroed in on the patient with very early stage disease. By contrast both Matt Smith and Arif Hussain commented on the numerous questions about management of biochemical relapse. Dr Smith reviews his landmark research on the secondary effects of androgen deprivation and Dr Hussain presents new data on the potential role of chemotherapy in this situation.

While a great deal of optimism surrounded the launch of this series, our group's interest in these and other prostate cancer controversies was considerably increased by two extraordinary events in the first few months of the project. First, a 42-year-old member of our staff, who visited a physician for a routine check-up, arrived at work the next day pale and shaken.

Unbeknownst to him, and without a precipitating family history, a PSA had been drawn and was found to be minimally elevated. After a couple of weeks of indecision, he agreed to extended pattern prostate biopsies, one of which showed Gleason 6 disease in 2 percent of one core.

He was advised to have a radical prostatectomy but declined, and currently more than two years later, his PSA is 1.7 ng/mL, he feels well, and he has not been rebiopsied. Every man in our office now routinely clarifies the specific tests to be done on any blood sample because we have observed first hand — for better or worse — the implications of a PSA assay.

The other experience was even more eye opening. To better understand issues in prostate cancer, we invited about a dozen research leaders — over a period of several months — to spend a day with our CME team in Miami as "visiting

professors." One of the first visitors was a quiet, unassuming, tanned, very kind and pleasant urologist whose CV was filled with numerous important publications.

As I shared coffee with Dr Paul Schellhammer, he casually mentioned that after a career in prostate cancer clinical research, he had been diagnosed with the disease 18 months previously and was treated with radical prostatectomy. At the time of the interview Paul had just learned that his PSA level was increased and he was sifting through treatment options.

I hesitantly asked if he would be willing to share his experiences with our national audience of listening physicians by telling his story on a recorded interview. Paul agreed without hesitation, and what followed was one of the most edifying educational experiences of my career.

Because of the many emails and comments we received about Dr Schellhammer's interview, I met with him again more than a year later. At that point, he had completed regional radiation therapy and eight months of complete androgen blockage with bicalutamide and goserelin, a regimen he has studied extensively.

Paul's clinical experience with thousands of men with prostate cancer did little to prepare him to walk in the shoes of his patients. During the initial interview, he spoke about the intense concern he experienced about potential clinical progression and the appeal of unproven and potentially toxic treatment options like chemotherapy.

In the second interview, he verbalized his surprise at the extent of morbidity with radiation therapy, and how these symptoms affected his lifestyle. He also described subtleties of cognitive impairment with androgen ablation that had not been reported in clinical trials.

Two more related experiences over the next couple of years convinced our group that there was a very valuable yet untapped resource in continuing medical education. Another visiting professor, medical oncologist Dr Mary Ellen Taplin, confided in the middle of the interview that her husband was diagnosed with a brain tumor. Dr Taplin noted that while seeking opinions at four major referral centers, she and her husband received four very different treatment recommendations. Dr Taplin also related how differently she now perceives the experience of the family members of cancer patients.

Finally, after spending considerable time reviewing the evolution of her research on locally advanced prostate cancer, a more recent "visiting professor," radiation oncologist Dr Colleen Lawton mentioned that her father had been recently diagnosed with the disease.

Most remarkably, Dr Lawton's father had developed locally advanced prostate cancer and received (from another physician) the same therapy his daughter had a central role in developing. During the interview, Colleen eloquently elaborated on her experiences on the "other side of the stethoscope."

While driving home from my interview with Dr Lawton, I reflected on the profound challenge every doctor faces in attempting to understand the patient's perspective.

I was struck by the potential impact of gathering and disseminating information about the perspectives of physicians who have had a personal experience with specific illnesses. Below you will find details of a unique project we are launching to explore this fascinating area. Your assistance will be much appreciated.

—Neil Love, MD

Doctors with Cancer:

Research To Practice is launching a unique continuing medical education project and we seek your assistance. Our intention is to gather information via an anonymous survey of physicians with either a personal diagnosis of cancer or an immediate relative or spouse with a cancer diagnosis. The data will identify patient and family needs to be addressed in our CME programs. The survey may be completed by phone or email and a modest honorarium is available to a limited number of participants.

To launch this project, we are seeking physicians (or their spouses or immediate family members) in either of the following situations:

1. A prostate cancer diagnosis
2. A diagnosis of any cancer for which chemotherapy has been administered

For more information please go to CliniciansWithCancer.com or email me (NLove@ResearchToPractice.net).

Thank you for your assistance.

Patient and Physician Perspectives on Screening and Treatment of Prostate Cancer

Chan EC et al. **Physician perspectives on the importance of facts men ought to know about prostate-specific antigen testing.** *J Gen Intern Med* 2003;18(5):350-6. **Abstract**

Cohen H, Britten N. **Who decides about prostate cancer treatment? A qualitative study.** *Fam Pract* 2003;20(6):724-9. **Abstract**

Hilsman WJ. **Deciding on radiation therapy: A patient's perspective.** *Semin Urol Oncol* 2000;18(3):200-4. **Abstract**

Love N et al. **How do prostate cancer survivors perceive treatment trade-offs for hypothetical clinical situations?** *Poster*, 2003 American Urological Association Meeting.

Lubeck DP et al. **A review of measurement of patient preferences for treatment outcomes after prostate cancer.** *Urology* 2002;60(3 Suppl 1):72-7; discussion 77-8. **Abstract**

Slevin ML et al. **Attitudes to chemotherapy: Comparing views of patients with cancer with those of doctors, nurses, and general public.** *BMJ* 1990;300(6737):1458-60. **Abstract**

Taylor KL et al. **Impact of undergoing prostate carcinoma screening on prostate carcinoma-related knowledge and distress.** *Cancer* 2002;95(5):1037-44. **Abstract**

Wegner RE. **Deciding on radical prostatectomy: A patient's perspective.** *Semin Urol Oncol* 2000;18(3):192-9. **Abstract**

Edited comments by Peter R Carroll, MD

Recent trends in prostate cancer

A significant stage migration has occurred over the last five years. Urologists, radiation oncologists and others treating patients with prostate cancer should be mindful of this dramatic stage migration. According to data from Europe, 30 to 50 percent of the currently detected prostate cancers may be clinically insignificant. In other words, small and low-grade cancers that may not be a risk to the patient are being overdetected.

In addition, extended-pattern biopsies — even after controlling for PSA — result in an even greater number of lower-volume cancers being overdetected. PSA screening and the extended-pattern biopsies both contribute to the overdetection of prostate cancer. As clinicians, we must understand that some cancers currently being detected may not need immediate treatment. I'm hopeful that the use of watchful waiting will actually increase.

Watchful waiting in patients with low-risk features

Each year, our group treats about 750 new patients with prostate cancer — primarily with surgery and radiation. The most rapidly growing population for us right now is the patient treated with watchful waiting. Currently, we have about 160 men on watchful waiting, and that number is rapidly increasing. We have a number of clinical trials for these patients, because they're an ideal population in which to evaluate at novel therapies.

In the younger man with low-risk features, we're very cognizant of not compromising their ability to be cured, so their PSA and Gleason score must be low and they must have had an extended-pattern biopsy. At the present time, most patients will have between 10 and 18 biopsies, which results in less grade and stage miscalculations. Interestingly, the percent-free PSA tends to predict the likelihood of progression. Patients with a free PSA greater than 10 percent — usually between 15 and 20 percent — are candidates for watchful waiting.

According to our data in patients with low-risk disease on watchful waiting, between 30 and 50 percent will require treatment over the next three to five years. Patients most likely to require treatment are those who are younger or have a rising serum PSA. Patients with a low percent-free PSA generally will receive treatment.

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For patients on watchful waiting, our ability to effectively treat them does not appear to be compromised; they tend to stay in the same risk category. I always advise patients that I cannot assure them 100 percent that watchful waiting will not compromise their ability to be effectively treated, but patients with low-risk disease tend to do well.

Management of patients with intermediate- or high-risk disease

The outcomes of treatment in men with intermediate-risk disease (PSA = 10-20 ng/mL, Gleason 7 and palpable cancer) are widely disparate. In patients with intermediate- and high-risk disease, well-validated nomograms should be used to identify their risk, because some patients with high-risk disease behave more like patients with intermediate-risk disease and vice versa. Patients with very high-risk disease (high grade, high T stage, high PSA) should be considered for clinical trials with hormonal therapy, chemotherapy, dendritic cell therapy, surgery, radiation, etcetera.

Randomized trial data suggest that hormonal therapy should be used along with radiation therapy in patients with intermediate- or high-risk disease. National trends from the last 10 years demonstrate an increased use of neoadjuvant and adjuvant hormonal therapy, but not all men are being appropriately treated. Some patients with high-risk disease who would benefit from combination therapy are not receiving it.

This may not be the case in patients with intermediate-risk disease because those randomized trial data are more recent. For example, the RTOG trial led by Mack Roach demonstrated a benefit from short-term hormonal therapy and radiation therapy to the prostate and pelvis in patients with intermediate-risk disease.

In a nonprotocol setting, patients with intermediate- or high-risk disease who are being treated with radiation therapy should also receive hormonal therapy. In patients with intermediate-risk disease, short-term hormonal therapy — four to six months — should be prescribed. Patients with high-risk disease may benefit from both neoadjuvant and adjuvant hormonal therapy for at least two years.

Early versus delayed hormonal therapy

The timing of hormonal therapy after a PSA relapse is now a matter of much debate. Many trials, such as Ed Messing's trial published in the *New England Journal of Medicine* demonstrate a benefit from early hormonal therapy. In our data set, we found that hormonal therapy delivered early at PSA relapse after prostatectomy appears to be associated with a decreased risk of prostate cancer death. We are currently trying to determine in which patients the risk is reduced, because some of the patients with low-risk disease might not benefit. However, it's becoming clear that the early use of hormonal therapy may be very important for patients with high-risk disease.

In the immediate postprostatectomy period in a patient with high-risk disease, we evaluate the postoperative hypersensitive PSA and the status of the margins,

seminal vesicles and lymph nodes. Then, we treat these patients selectively. Patients with high-grade organ-confined tumors, negative margins and lymph nodes, and undetectable PSA will be watched. Patients with positive margins, depending on the extent and grade, may or may not receive radiation therapy. Patients with higher-risk features — seminal vesicle invasion, lymph node involvement — will be considered for a clinical trial of hormonal therapy with or without chemotherapy.

We are observing a relatively high use of hormonal therapy. According to the bulk of the data, hormonal therapy will impart a survival advantage in patients at very high risk. The questions are: How high a risk and when should it be instituted? In patients with a very long life expectancy, we have to be careful that we don't expose them to treatment-associated side effects rather than benefit.

Select publications

Publications discussed by Dr Carroll

Berger AP et al. **Early detection of prostate cancer with low PSA cut-off values leads to significant stage migration in radical prostatectomy specimens.** *Prostate* 2003;57(2):93-8. **Abstract**

Cooperberg MR et al. **National practice patterns and time trends in androgen ablation for localized prostate cancer.** *J Natl Cancer Inst* 2003;95(13):981-9. **Abstract**

Harlan SR et al. **Time trends and characteristics of men choosing watchful waiting for initial treatment of localized prostate cancer: Results from CaPSURE.** *J Urol* 2003;170(5):1804-7. **Abstract**

Meng MV et al. **Predictors of treatment after initial surveillance in men with prostate cancer: Results from CaPSURE.** *J Urol* 2003;170(6 Pt 1):2279-83. **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**

Ornish D et al. **Can lifestyle changes reverse prostate cancer?** *Proc AUA* 2003;**Abstract 286**.

Peto R, Dalesio O. **Breast and prostate cancer: 10-year survival gains in the hormonal adjuvant treatment trials.** *Eur J Cancer* 2003;1(Suppl 5):101;**Abstract 328**.

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

Thompson IM et al. **The influence of finasteride on the development of prostate cancer.** *N Engl J Med* 2003;349(3):215-24. **Abstract**

Edited comments by Matthew R Smith, MD, PhD

Osteoporotic fractures associated with androgen deprivation therapy

Gonadal steroids regulate bone metabolism in men and women. Androgen deprivation therapy — gonadotropin-releasing hormone (GnRH) agonists and bilateral orchiectomy — dramatically decreases gonadal steroid levels resulting in accelerated bone loss, osteoporosis and fractures. Retrospective studies, the best data available, demonstrate very high fracture rates in men treated with androgen deprivation therapy.

It's also important to note that osteoporotic fractures are common in older men not being treated with androgen deprivation therapy. Even though the baseline fracture rate in older men is lower than the rate in postmenopausal women, the rates of clinical fractures in men on androgen deprivation therapy are several-fold higher. We may only be observing the tip of the iceberg because the patterns of hormonal therapy utilization have changed dramatically in the past decade, and the late consequences of early androgen deprivation therapy are only beginning to be observed.

Although not particularly common, hip fractures are the most feared and dangerous consequence of osteoporosis; they are associated with high rates of mortality. Vertebral body fractures are more common. They can be asymptomatic, but more commonly they cause pain and the characteristic body habitus changes associated with osteoporosis — loss of height and kyphoscoliosis.

Impact of androgen deprivation therapy on bone metabolism

Both testosterone and estrogen are important for the homeostasis of the skeleton in men; however, estrogen appears to be the dominant regulator of bone metabolism. Estrogen occurs in men as a result of the metabolism of testosterone; therefore, estrogen deficiency is the primary culprit for bone loss related to androgen deprivation therapy. Older men not receiving treatment for prostate cancer have estrogen levels that are in between the levels seen in pre- and postmenopausal women. Estrogen levels in men treated with androgen deprivation therapy are immeasurable — substantially lower than in postmenopausal women.

With a GnRH agonist, testosterone levels fall by more than 95 percent, and estradiol levels also fall by a corresponding amount. This results in an abrupt,

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dramatic and long-lasting decline in both testosterone and estrogen levels. The rate of bone loss in men treated with androgen deprivation therapy is several-fold higher than in women in early menopause.

Originally, it was believed that the high rate of initial bone loss would be followed by a more gradual loss. However, we've observed that these higher rates of bone loss persist even after years of androgen deprivation therapy. This is consistent with the observation that gonadal steroid deficiency is markedly different from the one associated with menopause. The addition of an antiandrogen to medical or surgical castration does not appear to worsen bone loss.

Impact of antiandrogen monotherapy on bone metabolism

Antiandrogen monotherapy does not lower gonadal steroid levels. Through a central feedback mechanism, bicalutamide monotherapy increases the serum concentrations of testosterone and estradiol. Testosterone is blocked by the antiandrogen; therefore, the net effect is somewhat elevated and unopposed estrogen levels, which accounts for the typical side effects of breast tenderness and enlargement. That endocrine profile probably spares the bone in men treated with bicalutamide monotherapy.

In a cross-sectional study of men treated with bicalutamide monotherapy or a GnRH agonist (Figure 1.1), we've evaluated bone turnover markers — a surrogate for bone loss and fractures. Men receiving a GnRH agonist had high rates of bone turnover, and men receiving antiandrogen monotherapy had a bone turnover rate that was consistent with the rate in normal men.

Figure 1.1

Cross-Sectional Study of Bone Turnover During Bicalutamide 150 mg Monotherapy for Prostate Cancer

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

*Elevations correlate with increased rates of bone loss and predict fractures independent of bone mineral density.
**BCE = bone collagen equivalents

SOURCE: Smith MR et al. **Cross-sectional study of bone turnover during bicalutamide monotherapy for prostate cancer.** *Urology* 2003;61(1):127-31.**Abstract**

EPC trials of adjuvant bicalutamide monotherapy

According to results from the adjuvant bicalutamide monotherapy trial (Figure 1.2), a high-risk population will have improved progression rates and survival with sufficient follow-up. In these men with high-risk disease, adjuvant hormonal therapy with castration may also provide a benefit.

If patients were presented with a summary of the quality-of-life, survival and our newer physiologic data, the choice between antiandrogen monotherapy and castration would be clear. They would choose antiandrogen monotherapy. If physicians were asked which they preferred, they would have the same answer, unless they had bone metastases which may result in a modest inferiority in outcome.

Figure 1.2

Objective clinical progression in the Early Prostate Cancer Trial

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

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

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

A comparison of the side-effect profiles of bicalutamide monotherapy and an LHRH agonist

In terms of the quality of life associated with bicalutamide monotherapy and an LHRH agonist, we have data from completed randomized trials, and the differences are fairly striking. Quality-of-life experts are struck by the magnitude of the differences between those two treatments. For a number of domains — physical capacity, sexual interest, fatigue — bicalutamide monotherapy is statistically better than medical or surgical castration, and the differences are quite large.

For sexual function, the differences are also quite dramatic. Men on androgen deprivation therapy have little or no libido and few, if any, have the ability to maintain an erection. Although bicalutamide monotherapy is not neutral, most men maintain their libido and many, if not most, men who have erectile function are able to maintain it while on therapy.

Medical or surgical castration has a dramatic effect on body composition. After one year, men on androgen deprivation therapy have a 10 percent increase in fat mass and about a three percent loss in lean body mass. The effects of bicalutamide monotherapy on body composition have not been adequately studied.

Two randomized trials are looking at this issue, and the data should be available soon. The fact that bicalutamide monotherapy preserves physical capacity suggests that it also has less adverse effects on physiologic outcomes. Hence, it may cause less fat accumulation and less muscle loss.

The differences in vasomotor symptoms are also striking. Hot flashes occur in the majority of men receiving androgen deprivation therapy, whereas they are nearly nonexistent with bicalutamide monotherapy.

We are also only just beginning to understand the impact of treatment on cognitive function, which is very challenging to measure in aging men because changes occur over time. I believe androgen deprivation therapy does affect cognitive function. In select cases, patients have noticed that their creative, mathematical and writing abilities were altered while on therapy.

Another side effect associated with androgen deprivation therapy is fatigue, which fully impacts on cognitive ability. Men treated with bicalutamide report less fatigue than men receiving androgen deprivation therapy. The superior outcomes with bicalutamide may reflect fewer sleep disturbances related to a lack of vasomotor symptoms, less adverse body composition and less anemia.

Breast effects associated with bicalutamide

The dominant side effects associated with bicalutamide monotherapy are breast tenderness and enlargement, which are probably best managed with either prophylactic breast irradiation, antiestrogens or aromatase inhibitors — all of which have been evaluated for the prevention of the breast effects. A comparative study has been conducted, but the data have yet to be published. My suggestion is to carefully look at the impact of those interventions on other outcomes, like bone and body composition changes.

Some of the advantages associated with bicalutamide monotherapy in the bone relate to the fact that it elevates estrogen levels. Therefore, strategies designed to mitigate the breast tenderness and enlargement may also alter the other effects. For example, an aromatase inhibitor in a man on bicalutamide monotherapy would lower his estrogen levels. This would probably prevent or reduce breast tenderness and enlargement but at the same time contribute to bone loss.

Hormone therapy for PSA relapse

If I personally experienced a PSA relapse, I'd choose antiandrogen monotherapy. There is no evidence that androgen deprivation therapy is better than antiandrogen monotherapy in that setting, and the adverse effects are less with antiandrogen monotherapy.

Antiandrogen monotherapy provides the opportunity to preserve quality of life and effectively treat the disease. For patients in my practice who experience PSA relapse, I point out the known differences between the treatments and the gaps in the data. While the use of bicalutamide 150 mg is considered off label, the use of a GnRH agonist in that setting is also off label.

In the setting of a PSA relapse, I refer to the similarity in survival outcomes in men with nonmetastatic prostate cancer treated with bicalutamide monotherapy and medical or surgical castration. For men who choose (or I intend to treat with) a GnRH agonist, I'll briefly discuss the addition of an antiandrogen and the meta-analyses suggesting a modest survival advantage. My firm medical recommendation is that they take it — at least initially — to prevent the potential for flare. Some but not all patients continue it long term.

Select publications

Publications discussed by Dr Smith

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**

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

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

Smith MR et al. **Cross-sectional study of bone turnover during bicalutamide monotherapy for prostate cancer.** *Urology* 2003;61(1):127-31. **Abstract**

Smith MR et al. **Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer.** *J Urol* 2003;169(6):2008-12. **Abstract**

Smith MR et al. **Changes in body composition during androgen deprivation therapy for prostate cancer.** *J Clin Endocrinol Metab* 2002;87(2):599-603. **Abstract**

Smith MR et al. **Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer.** *N Engl J Med* 2001;345(13):948-55. **Abstract**

Edited comments by Arif Hussain, MD

Treatment approaches for PSA relapse

A PSA recurrence can precede clinical progression by several months to years. No standard treatment exists for these patients, in terms of when to intervene and with what therapy.

Hormone ablation therapy

One approach is hormone ablation therapy, which is the standard treatment for men diagnosed with metastatic disease based on imaging studies. Hormone ablation therapy works in over 80 percent of men with metastatic disease, but it invariably fails over time. Men with PSA-only relapse after surgery or radiation therapy and negative imaging studies have a much lower tumor burden. Therefore, it makes sense to use a therapy that works well in patients with metastatic prostate cancer.

In the community, urologists often use hormonal therapy when the PSA starts rising. Hormonal therapy is likely to provide excellent PSA control, but it is unlikely to be curative in PSA-only failures. Like patients with metastatic disease, hormonal therapy eventually fails in patients with PSA-only recurrence. However, it may take longer to fail because the amount of disease burden is much lower.

Chemotherapy

Traditionally, chemotherapy has been used in men with hormone-resistant metastatic prostate cancer. However, hormone-resistant prostate cancer is also chemotherapy resistant. Two-thirds of men with hormone-resistant prostate cancer have increased Bcl-2, which is involved in the apoptotic pathway.

Bcl-2 expression is associated with resistance to a variety of cytotoxic drugs. Chemotherapy drugs might be useful in patients with hormone-sensitive prostate cancer before they are exposed to hormonal therapy.

Sequential chemohormonal therapy for PSA relapse

We conducted a pilot study in 39 patients who experienced PSA recurrence (Figure 2.1). Prior to trial entry, imaging studies (e.g., CAT scans and bone scans) were obtained. Thirty-two of the 39 patients had negative imaging studies. In

Dr Hussain is an Associate Professor of Medicine at the University of Maryland Greenebaum Cancer Center in Baltimore, Maryland.

contrast, seven of the 39 patients had metastatic disease; amazingly the PSA levels in these men were in the teens. This underscores the heterogeneity of prostate cancer. PSA levels don't necessarily predict the extent of disease.

We treated all of these hormone-naive men with up-front chemotherapy — single-agent docetaxel every three weeks for four to six cycles — followed by hormone ablation therapy for 12 to 20 months. We administered four months of total androgen suppression (LHRH agonist and bicalutamide) in the 32 patients with negative imaging studies, and 12 months of total androgen suppression in six patients with positive imaging studies. One patient dropped out of the study. Then, we administered an additional eight months of peripheral androgen blockade (finasteride and bicalutamide).

Figure 2.1

PSA Response

• After Docetaxel	n=35
↓PSA ≥ 40%	23 (65.7%)
↓PSA ≥ 50%	17 (48.5%)
↓PSA ≥ 75%	7 (20%)
• After LHRH + Bicalutamide x 4 mos	n=33
Median PSA (range)	0.1 (0.1 – 7.5 ng/mL)
• After Finasteride + Bicalutamide	n=32
Median PSA (range)	0.1 (0.1 – 3.2 ng/mL)

SOURCE: Hussain A. Presentation, 2003 Chemotherapy Foundation.

Of the 33 men followed for a median of 20 months after the end of treatment, 25 have had a rise in their PSA, but eight have maintained their PSA at less than 0.1 ng/mL. Of those eight men, three previously had metastatic soft tissue disease and are now in complete remission based on imaging studies. In these three men, imaging studies performed after treatment with docetaxel revealed a greater than 50 percent reduction in tumor size. After four months of total androgen suppression, the tumors had completely disappeared.

Clearly, a subgroup of men exists in which long-term disease control is possible, even in metastatic disease. It is hard to predict *a priori* those groups of men. This approach is similar to the strategies with adjuvant systemic therapy in early breast cancer. In prostate cancer, we are behind in terms of integrating chemotherapy with hormonal therapy.

Case history: A 54 year-old man with PSA progression

Ten years ago this man had a prostatectomy for a Gleason 7 prostate cancer with negative margins, seminal vesicles and lymph nodes. His preoperative PSA was about 7 or 8 ng/mL, and his postoperative PSA was less than 0.1

ng/mL. Three years postprostatectomy, at the age of 54, his PSA began to rise to about 1.5 or 1.8 ng/mL. He underwent salvage radiation therapy, and his PSA became less than 0.1 ng/mL. After another four or five years, his PSA began to rise again to 3, 4, 7, and then 8 ng/mL.

Follow-up

He was referred to me by a urologist. The patient continued with observation until his PSA was 11 ng/mL; then he wanted to participate in our trial. On prestudy imaging evaluations, the bone scan was negative but the CAT scan revealed multiple bilateral pulmonary nodules, which I thought represented prostate cancer metastases. He underwent a lung biopsy, which proved to be recurrent prostate cancer.

I treated him with single-agent docetaxel for six cycles, and he had a 78 percent reduction in his PSA. At that point, most, but not all, of his pulmonary nodules had disappeared. Then he received one year of total androgen suppression. After four months of total androgen suppression, the residual pulmonary nodules had completely disappeared. I continued the hormonal therapy and treated him with peripheral androgen blockade. While on chemotherapy, this patient was able to work four out of the five days and, in fact, insisted on going to the gym. He developed neutropenia but did not develop any infections. He also experienced Grade II fatigue.

Discussion

This man had failed radical prostatectomy and salvage radiation therapy. His options included hormone ablation therapy but he knew that it eventually would fail, so he elected to enroll in our trial. He received single-agent docetaxel and had a greater than 50 percent response in his pulmonary nodules, which completely disappeared after hormonal therapy. I have followed him for a year — all his CAT scans are negative, his PSA is less than 0.1 ng/mL and his testosterone levels are noncastrate. He is my success story.

Select publications

Publications discussed by Dr Hussain

Hussain A et al. **Docetaxel followed by hormone therapy after failure of definitive treatments for clinically localized/locally advanced prostate cancer: Preliminary results.** *Semin Oncol* 2001;28(4 Suppl 15):22-31. **Abstract**

Oh WK et al. **Neoadjuvant docetaxel followed by radical prostatectomy in patients with high-risk localized prostate cancer: A preliminary report.** *Semin Oncol* 2001;28(4 Suppl 15):40-4. **Abstract**

Picus J et al. **Efficacy of peripheral androgen blockade on prostate cancer: Initial results of CALGB 9782.** *Proc ASCO* 2002;**Abstract 727**.

Taplin ME et al. **Docetaxel (D), estramustine (E) and short term androgen withdrawal for patients with a rising PSA after definitive local therapy of prostate cancer.** *Proc ASCO* 2003;**Abstract 1609**.

Post-test: *Prostate Cancer Update*, Issue 1, 2004

Conversations with Urologic Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The CaPSURE™ database reported a decline in the use of watchful waiting since its peak in the mid-1990s.

a. True
b. False

2. Randomized trial data suggest that hormonal therapy should be used in conjunction with radiation therapy in patients with _____.

a. low-risk prostate cancer
b. intermediate-risk prostate cancer
c. high-risk prostate cancer
d. a and b
e. b and c

3. Which of the following factors can assist in selecting therapy for a postprostatectomy PSA relapse?

a. Pathology report
b. Time from surgery to PSA relapse
c. PSA kinetics
d. All of the above
e. None of the above

4. Both testosterone and estrogen are important for the homeostasis of the skeleton in men; however, estrogen appears to be the dominant regulator of bone metabolism.

a. True
b. False

5. Androgen deprivation therapy (i.e., gonadotropin-releasing hormone [GnRH] agonists or bilateral orchiectomy) dramatically decreases gonadal steroid levels, which results in:

a. Accelerated bone loss
b. Increased risk of osteoporosis
c. Increased risk of fractures
d. All of the above
e. None of the above

6. Zoledronic acid is FDA-approved for

a. The treatment of patients with hypercalcemia of malignancy
b. The treatment of patients with bone metastases from any solid tumor or multiple myeloma
c. The prevention of osteoporosis related to androgen deprivation therapy
d. a and b
e. a and c

7. In patients treated with androgen deprivation therapy, pamidronate and zoledronic acid were both found to prevent bone loss and increase bone mineral density.

a. True
b. False

8. When compared to an LHRH agonist, bicalutamide monotherapy has advantages in the following areas:

a. Quality of life
b. Sexual function
c. Vasomotor symptoms
d. Fatigue
e. All of the above

9. Which of the following strategies have been evaluated for the prevention of the breast effects associated with bicalutamide?

a. Prophylactic breast irradiation
b. Antiestrogens
c. Aromatase inhibitors
d. All of the above
e. None of the above

10. Chemotherapy is commonly utilized in men with hormone-sensitive metastatic prostate cancer.

a. True
b. False

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

Evaluation Form: *Prostate Cancer Update*, Issue 1, 2004

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

Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Peter R Carroll, MD	5 4 3 2 1	5 4 3 2 1
Matthew R Smith, MD, PhD	5 4 3 2 1	5 4 3 2 1
Arif Hussain, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

Evaluation Form: *Prostate Cancer Update*, Issue 1, 2004

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

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

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

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