PCU | 2003 VOL 2 | ISSUE 1

Prostate Cancer™ UPDATE

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

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2 Audio Tapes
2 Audio CDs
Monograph

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 urology. Published results from clinical trials lead to the emergence of new surgical and radiation therapy techniques and therapeutic agents, along with changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing urologist and radiation oncologist must be well informed of these advances. To bridge the gap between research and patient care, Prostate Cancer Update utilizes one-on-one discussions with leading urologic oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists urologists and radiation oncologists in the formulation of up-to-date clinical management strategies.

Global Learning Objectives

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

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

Issue 1, 2003 of Prostate Cancer Update consists of discussions with four research leaders on a variety of important issues, including the role of lymph node dissection in radical prostatectomy, selection of endocrine therapy, defining PSA relapse, chemotherapy in metastatic disease, and high dose brachytherapy.

Specific Learning Objectives for Issue 1

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

- Determine and implement an evaluation and management algorithm for patients with a rising PSA after their initial therapy for prostate cancer
- Counsel patients on the risks and benefits of antiandrogen therapy, LHRH agonist therapy and maximum androgen blockade
- Describe the clinical implications of current research in radiation therapy of prostate cancer, including interpretation of PSA results

Accreditation Statement

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

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The Postgraduate Institute for Medicine designates this educational activity for a maximum of 3 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only credits that he/she actually spent in the activity.

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The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor.

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
bicalutamide	Casodex®	AstraZeneca Pharmaceuticals, LP
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
doxorubicin	Adriamycin®, Rubrex®	Pharmacia Corporation
estramustine phosphate	Emcyt®	Pharmacia & Upjohn
etoposide (VP-16)	– various	Bristol-Myers Oncology
goserelin	Zoladex®	AstraZeneca Pharmaceuticals, LP
paclitaxel	Taxol®	Bristol-Myers Oncology
samarium		
strontium - 90		
tamoxifen	Nolvadex®	AstraZeneca Pharmaceuticals, LP
vinblastine	Velbane®	Eli Lilly & Co

Editor's Note

Evidence Base

Every physician likes to remember the patient that defied the odds and experienced an unexpectedly favorable outcome, but in the enclosed program, Thomas Keane challenges us to consider cases where radical prostatectomy failed to achieve tumor control. I was particularly struck by the second patient, a man who entered the Early Prostate Cancer adjuvant trial randomizing between two years of bicalutamide 150 mg and placebo. The patient experienced a biochemical relapse one year after completing adjuvant therapy, and when the blinded trial code was broken, it was revealed that the patient had received bicalutamide. This man has now responded to maximal androgen blockage, but my medical oncology background in breast cancer makes me wonder if the relapse would have occurred if adjuvant therapy had been utilized for a longer duration.

When tamoxifen was first utilized as post-operative adjuvant therapy of breast cancer, the standard duration — following the model of chemotherapy — was only one year. Women who relapsed following treatment were routinely retreated with tamoxifen, and often the tumors responded. Gradually, the duration of adjuvant therapy was extended, and clinical trials randomizing between one and two years of tamoxifen revealed a survival advantage for longer treatment (Figure 1). Eventually, an optimal duration of five years was established through randomized studies, but it took about a decade to determine this.

Figure 1: Relative reduction in rates of recurrence and death with adjuvant tamoxifen in patients with ER-positive breast cancer

	Relative Reduction	
	Recurrence	Mortality
1 year	21% +/-5	14% +/-5
2 years	28% +/-3	18% +/-4
5 years	50% +/-4	28% +/-5

SOURCE: Early Breast Cancer Trialists' Collaborative Group. **Tamoxifen for early breast cancer: An overview of the randomised trials.** *Lancet* 1998;351:1451–67. **Abstract**

I am generally very cautious about drawing analogies between breast and prostate cancer, but often the similarities are undeniable. It's gratifying to encounter other physicians with interests in both endocrine-related tumors, and this issue of Prostate Cancer Update includes an interview with radiation oncologist, Frank Vicini, who has done sentinel research in both fields.

One of the curiosities I find with prostate cancer is that the approach to adjuvant androgen deprivation differs based on the primary local treatment. Specifically, it appears that high-risk men treated with primary radiation therapy are more likely to receive adjuvant endocrine therapy than men at the same risk who are treated with radical prostatectomy.

In breast cancer, adjuvant therapy is recommended based on the risk of systemic relapse, whether the primary local therapy is lumpectomy / radiation therapy or mastectomy. When I have asked prostate cancer research leaders about this, most have commented that the adjuvant trials conducted by the radiation oncology cooperative groups have demonstrated benefit, but the post-surgical trials have been less convincing. Dr Vicini, who is very familiar with the breast cancer literature, had another perspective: specifically, that the surgical clinical trials have utilized a shorter duration of adjuvant treatment and thus resulted in less benefit.

In an emerging era of evidence-based medicine, we are often left with less-than-perfect evidence, which is where clinical judgment becomes critical. Another of Dr Keane's cases is a 52-year-old man with a PSA of 12 and a Gleason 8 tumor with seminal vesicle invasion on radical prostatectomy.

What interested me most about this case discussion was the very active role the patient and his wife had in sorting through the available clinical trial data with Dr Keane. These discussions resulted in an individualized decision that encompassed the entire biopsychosocial panorama of this man's life.

Many of the key clinical decisions in cancer treatment must be made based on clinical trial results that are not definitive. This series is intended to provide the perspectives of research leaders on the strategic integration of these data into discussions with patients and, also, insights into how evolving research will address these issues in the future. Dr Keane's cases demonstrated that many key issues require much more randomized trial data to allow more evidence-based decisions.

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Edited comments by Dr Chodak

Reserving lymph node dissection for patients at high risk

I don't believe we should do lymph node dissection unless the probability of lymph node metastases is significant. Peter Carroll published a mathematical decision analysis several years ago in which it was determined that unless the risk of lymph node metastases was greater than 15%, it wasn't worthwhile to remove the lymph nodes. More than 80% of patients diagnosed today have less than a 10% probability of lymph node metastases, and they can be spared lymph node dissection. There is a small, but real, complication rate. It prolongs the surgery, increases the cost, and in a low-risk subset of patients, the chance of benefit is small.

We still have no proof that removing lymph nodes involved with cancer improves survival. To me, it is a diagnostic test that tells us whether to proceed with prostatectomy. In a high-risk patient — a man with a PSA over 10, Gleason score of 7 or higher and a palpable tumor — I would ask the patient before going to the operating room what he would like to do if there is cancer in the lymph nodes. I generally remove the lymph nodes, do a frozen section and only proceed with prostatectomy if the results are negative. But, the patient has to make the decision because I cannot tell him for sure that there is no benefit from prostatectomy. I can only say there is no scientific proof of a benefit. If he wants to be very aggressive and do the prostatectomy anyway, I would not even do a frozen section.

Early endocrine therapy in men with positive lymph nodes

I am guided by two randomized trials. Ed Messing did a study in men who had radical prostatectomy, who were randomized to receive either early or late hormone therapy, showing a survival benefit for early hormone therapy. Although there are some valid criticisms of that study, it is the only

randomized trial addressing this question. A study by Granfors looked at men who had a lymph node dissection and received radiation with or without supplemental hormone therapy. This study also showed a significant survival benefit in the group receiving the combination of radiation and hormones.

Neither study tells us whether or not local therapy was beneficial, but both trials support the concept that earlier hormone therapy in the face of lymph node metastases improves survival compared to delayed therapy. If I do a lymph node dissection and find positive nodes, I recommend that the patient receive hormone therapy.

Bicalutamide 150 mg versus castration in non-metastatic disease

In a study of men with metastatic prostate cancer, bicalutamide was inferior by about 42 days in average survival compared to castration. However, in patients with non-metastatic disease, there was no significant survival difference between castration and bicalutamide. I think that offering bicalutamide is reasonable in these patients, particularly those who are concerned with libido and sexual function. Men undergoing castration are far more likely to be impotent and have problems with their libido than those receiving bicalutamide.

Endocrine therapy in patients with PSA relapse

In counseling patients regarding antiandrogens versus castration, the conversation centers on the side-effect profiles. Bicalutamide is associated with better libido and better sexual function, but therapy is associated with breast tenderness and enlargement. Patients undergoing castration have hot flashes, sexual dysfunction and decreased sex drive, weight gain and decreased energy.

In terms of comparing efficacy, there's just not enough data to answer that question. I am very careful to let science drive the information and not just give my gut feeling. To the best of our information available, one could extrapolate and say that, "I think that there may not be a difference," but we do not know for sure.

Treatment of high-risk patients after local therapy

As we treat patients earlier, the side effects go on for a longer and longer period of time. For example, in patients undergoing castration, we are increasingly worried about bone de-mineralization and fractures. There is also some question about whether castration has a deleterious effect on mentation. As we use these therapies for longer periods of time, we may run into added side effects that we're not completely aware of.

With regard to efficacy, I tell these patients that there is a potential to delay progression with both castration and bicalutamide, but comparing them isn't easy. We don't have any scientific data to guide us; therefore, we have to

make a philosophical choice whether to be conservative or aggressive. Patients usually have a general feeling about how aggressive they want to be. If they are fearful of dying of their disease and want to do everything possible to decrease that probability, then you take an aggressive approach, which includes hormone therapy — whether it's castration or an antiandrogen — and possibly radiation therapy.

Informing patients about specific risks and benefits of treatments

It is important to be sure that patients choose therapy based on the information that we have available. Every patient needs to know the status of our knowledge in terms of his chance of recurrence, his chance of benefiting from a therapy and the chance of having a side effect.

If we talk about local therapy, patients should be given the complication rates of the doctor treating them rather than the complication rates across the country. We keep data on outcomes that we relay back to patients. I can say, "In my practice in your age group, here are the complications and here are the probabilities of benefiting from the treatment."

Impact of earlier endocrine treatment on mortality

We started using PSA extensively for screening in about 1990. Prostate cancer mortality began declining in about 1993. Many people believe that screening is the cause for the change, but the long natural history of prostate cancer would make it very difficult for a mortality reduction to occur so soon after PSA testing began. The disease just doesn't progress that rapidly. So, we need a better explanation.

What's a better explanation? I believe it is earlier hormone therapy. Over the last 10 years since the development of PSA, we are alerted to people progressing after primary therapy much earlier than ever before. Many of these patients went on hormone therapy before they developed metastatic disease, when there were fewer hormone-independent cells. There were more cells capable of responding to the primary hormone therapy. Although those people weren't cured, they did have a delay in disease progression and death.

Selecting patients for maximum androgen blockade

I believe that maximum androgen blockade (MAB) remains an option for patients with metastatic disease. The meta-analysis has flaws that preclude a clear conclusion that you shouldn't use MAB, and I think there is a subset of patients who may receive a significant benefit. Other men may derive little or no benefit. We can't select which patients fall into each group; therefore, I believe that it is an option for the patient who wants to be aggressive. There is scientific data that supports it in terms of improving survival, but there is a trade-off.

Approaching decision-making with the prostate cancer patient

It is important to review the side effects and the probability of experiencing those side effects for the treatment options that are available. I then attempt to understand how important it is for that patient to avoid a specific side effect, and that discussion helps guide their therapy.

It is really a matter of first obtaining a sense of what they're willing to accept, and then trying to offset that with the gain they are likely to receive from the therapy. If I can't tell them that they're going to live longer, what can I tell them? Oftentimes, there is a lot of missing information, and patients have to struggle with the uncertainty. They have to understand that there is not a clear direction, and that it isn't possible for me to make the choice for them.

Importance of presenting patients with information

Even if we as physicians don't agree with a treatment, we have an obligation to present randomized study information to patients. We must consider the implications if several years from now a patient progresses and finds out there was a treatment you never even discussed with them. If there is no randomized trial data, it becomes more equivocal, but if there is a randomized study addressing a particular clinical situation, I think we are obligated to share that information with our patients.

Patients know that a rising PSA is a bad thing, and preventing that is clearly their goal. A rising PSA is psychologically traumatic even though it doesn't mean they're going to die or suffer from their cancer. Patients select primary therapy because they want to avoid progression, and that continues along every step of the way. The difference is the price they're willing to pay for that. Depending on their age and their quality of life, they may trade off differently at different times in their life.

You ultimately want your patient to feel that you gave them the best information and did the best thing for them. Although you can't guarantee they're going to have a good outcome, you can at least guarantee that you're giving them the best information.

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Zincke H et al. **Role of early adjuvant hormonal therapy after radical prostatectomy for prostate cancer.** *J Urol* 2001;166(6):2208-15. **Abstract**

Thomas E Keane, MBBCh

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Edited comments by Dr Keane

CASE 1:
52-year-old man with Gleason 8 prostate cancer and seminal vesicle invasion

HISTORY

This very fit accountant owned his own business, played tennis and had excellent sexual function. His wife was in her mid-forties, and they had three children. His PSA had risen from 4 ng/mL, one year ago, to 12 ng/mL. A biopsy revealed Gleason 7 prostate cancer in both lobes, with a nodule on the right side. A bone scan and CT scan were both negative.

He decided to have a radical perineal prostatectomy and lymph node sampling. The lymph nodes were negative, but the final pathology revealed Gleason 8 prostate cancer with right seminal vesicle invasion.

FOLLOW-UP

The perineal prostatectomy — which was non-nerve-sparing — went very well, and he had an excellent postoperative recovery with a PSA of zero at four weeks. He elected to receive adjuvant radiation therapy in combination with goserelin and bicalutamide. Two years later, his PSA is still zero. He has occasional hot flashes that used to bother him, but not anymore. He tires more easily and does not play as much tennis. He did not develop gynecomastia.

DISCUSSION

Selection of primary local therapy

I did not feel brachytherapy was an option because of the questionable results in patients with Gleason 7 prostate cancer. Although he was a candidate for external beam radiation therapy, I pointed out that most of the data for conformal radiation therapy has, at best, 12 to 13 years of follow-up.

I felt he would do fine over the next number of years and that he needed a treatment with more long-term data. If all the margins and nodes were negative when we removed his tumor, he had a very good chance of remaining disease-free. I did, however, point out that a Gleason 7 is not a Gleason 6, and that it has a poorer prognosis.

The primary focus for the patient and his wife was in curing the disease; that was the main driving force for their decision. Given what they had told me, I felt the best option was to approach it as aggressively as possible by sampling the lymph nodes and removing the prostate.

Since he had cancer in both lobes of the prostate, my advice was not to have a nerve-sparing prostatectomy. I told him that if potency was paramount to his existence, then he should have radiation therapy, because it would certainly preserve potency longer than a non-nerve-sparing radical perineal prostatectomy. They were an extremely close couple and despite the fact that their physical activity would or might be curtailed, they were willing to accept it.

Postprostatectomy options

The seminal vesicle invasion was very upsetting. I told him that most patients with seminal vesicle involvement ultimately develop metastatic disease. I felt that cure was unlikely and that he had two major options at that point. One was to observe and the other was to accept the fact that he probably still had the disease present and to offer him — once his continence returned — radiation therapy plus hormones.

Adjuvant radiation therapy and hormone therapy

I was extrapolating from the Bolla data, which demonstrated a survival advantage for external beam radiation therapy plus three years of hormone therapy over radiation therapy alone in advanced local disease. I told him that we did not know if he would do as well with just hormone therapy alone. That is the focus of a study that is being conducted, but it is not accruing well.

He elected radiation therapy and hormone therapy. The plan was to keep him on treatment for three years. He asked about maximum androgen blockade (MAB), and after a long conversation, he went on goserelin plus bicalutamide.

We discussed the pros and the cons of MAB. I told him that at this stage of the disease, we did not know if MAB was necessary, since in the absence of documented metastatic disease, we do not know if blocking flare is an issue. However, there was a possibility that the testosterone surge might make the disease more aggressive. He said, "I want to be as careful as I can, so I think I will go on the combination and stay on the combination for the three years."

Duration of adjuvant hormonal therapy

I have set three years as my target in this man, because the only study that has shown an absolute survival advantage for all stages of the disease was the Bolla study. There is a trial by Hanks (RTOG 9202) evaluating a combination of neoadjuvant plus adjuvant hormone

therapy given for 24 months. In a subgroup analysis, that study did show a survival advantage for the patients with the higher Gleason grades. So, it may be that you only need 24 months of treatment. But, I tend to go with the Bolla data.

The real issue will arise after three years of hormonal therapy. I intend to tell him to stop treatment, but I don't know if he will want to. Judging from my last conversation, he is going to say, "Well, what are we going to do to follow this? Can I go on intermittent androgen ablation?"

Adjuvant bicalutamide monotherapy

Had the results from the Early Prostate Cancer (EPC) trial been available at the time of this man's surgery, he would certainly have been a candidate for bicalutamide 150 mg. He had poor-prognosis prostate cancer with a PSA of zero, and he was interested in some form of hormonal therapy.

The EPC trial is a combination of three different studies — Scandinavian, European and American. The results from the Scandinavian study, which consists primarily of patients on watchful waiting, have been impressive. The initial data indicate that for the group on bicalutamide 150 mg, there is a significant decrease in objective progression in terms of changes on the bone scan. So, the Scandinavian study may turn out to be a study of early antiandrogen therapy compared to watchful waiting in localized prostate cancer. With regards to the American trial, it is still very early. It was a two-year analysis, and there have been very few events.

CASE 2:
60-year-old man with a T1c, Gleason 6 prostate cancer

HISTORY

This man presented with a PSA of 8 ng/mL, T1c disease and Gleason 3+3 in both lobes of the prostate. He was potent and continent. In 1998, he underwent a nerve-sparing radical perineal prostatectomy. His margins were negative, and his postoperative PSA dropped to $\leq$ 0.02 ng/mL, our lowest limit of normal. He then entered the EPC trial and we later found out that he was randomized to bicalutamide. He had minimal effects on his breasts, but he did notice some tingling.

FOLLOW-UP

In 2001, over one year after completing two years of therapy with bicalutamide 150 mg, he was potent, continent and his PSA was 0.25 ng/mL. Two months later, his PSA was 0.3 ng/mL, and three months after that it had risen to 0.5 ng/mL. His bone scan was negative, and his ProstaScint® scan was negative in the pelvis but positive in the para-aortic and mesenteric areas. He was started on MAB. His PSA went back down to undetectable, and he had no great alteration in his symptoms.

CASE 2 *(Continued)*

DISCUSSION

When his PSA began to rise, I went back immediately and looked at his presenting pathology. I looked at his postoperative pathology, which was Gleason 3+3, and the margins, which were all negative. I looked at the timing of this event — three years after initial surgery. So, we were trying to define what caused this recurrence. Was it local or metastatic disease?

Based on the Gleason grade and the PSA, one would be tempted to say it was local. However, his PSA was doubling in less than six months. The timing was right on the cusp, between two to three years. If it were five years, it would more likely be local recurrence. If it were two years, it would more likely be metastatic disease. This man fell right in between where we would say probably local and probably metastatic.

Had the ProstaScint® scan been positive in the mesentery alone, I would have been worried, because there have been reports of false positives in the mesenteric area. But this patient had a rising PSA, which was doubling quite fast, and activity in the mesenteric and the para-aortic lymph nodes. In view of those findings, I put him on hormonal therapy with MAB.

Response to castration after bicalutamide monotherapy

We were able to find out that his initial randomization on the EPC trial was to bicalutamide rather than placebo, but the PSA increase occurred a year after completing therapy on the trial. There is relatively minimal data available on response rates to castration after antiandrogens, but we know that these do occur, and this man did respond to MAB.

Response to secondary androgen deprivation following antiandrogen monotherapy

"Of the 23 patients who had follow-up PSA determinations, 19 (83%) showed a subsequent PSA decline. Median survival following secondary therapy was 22 months in the 14 patients whose decline was 50% or greater; survival was 17 months in the 9 patients whose PSA either rose or declined by less than 50%."

SOURCE: Fabozzi SJ et al. **PSA response to secondary androgen deprivation following failed treatment of metastatic prostate cancer with the antiandrogen Casodex.** *Urol Oncol* 1995;1:64-66. **Abstract**

CASE 3:
64-year-old man with Gleason 7 prostate cancer, a positive margin and extracapsular penetration

HISTORY

This patient presented with a PSA of 7 ng/mL and a clinical stage T2a, Gleason 6 prostate cancer. He underwent a nerve-sparing, radical perineal prostatectomy. The subsequent pathology revealed a Gleason score of 7, a positive margin at the left base and extracapsular penetration. Postoperatively, his PSA went to zero. He declined participation in the bicalutamide EPC trial and also decided not to receive radiation therapy.

FOLLOW-UP

Three years later, his PSA was 0.3 ng/mL. Then two months after, it was 0.7 ng/mL. His bone scan and rectal exam were both negative. His ProstaScint® scan was negative in the pelvis, but there were three different sites in the chest that were positive. CT scan of his chest demonstrated several pulmonary nodules, and we confirmed by biopsy that this was recurrent prostate cancer. He was treated with maximum androgen blockade, and his PSA went down to zero. A CT scan has yet to be repeated.

DISCUSSION

Initially, I told this man he had about a 50% or greater chance of progression because of the pathology. It was a definite positive margin and there was extracapsular spread. Therefore, I felt that he needed to do something.

With regards to the radiation therapy that I recommended, he specifically asked, "Am I going to hurt myself by waiting and not receiving radiation therapy immediately?" I told him I did not really think he would hurt himself, if we watched his PSA very carefully and made sure to move quite quickly before the PSA reached 1.5 to 2 ng/mL. Radiation oncologists tell us that is the point at which one is more likely to have a favorable response in terms of normalizing the PSA. Of course, they also tell us that there is no evidence that intervening at that point is going to result in a survival advantage.

I also offered him participation in the EPC trial randomizing between bicalutamide and placebo, to which we were accruing patients at that time. However, he preferred delaying both radiation and hormonal therapy until a PSA indicated that there was disease activity.

Using the ProstaScint® scan to determine the pattern of recurrence

I think the ProstaScint® scan is much better than CT or MRI in certain situations. I still think there are too many false negatives and false positives with it though. However, when I am trying to determine whether a patient with a rising PSA has local disease, I'll use the ProstaScint® scan to help guide my decision.

If the ProstaScint® scan indicates activity in the prostate itself, I will usually use local treatment. If there is no activity anywhere and the other factors add up to the recurrence being local, I'll also give local treatment. But if the ProstaScint® scan is positive outside of the pelvis, I will usually not give radiation therapy.

Select publications

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William Beaumont Hospital

Clinical Associate Professor,
University of Michigan

Clinical Professor,
Oakland University

Edited comments by Dr Vicini

William Beaumont Hospital brachytherapy dose-escalation trial

We have evaluated high-dose brachytherapy as a means of dose escalation for prostate cancer in a series of Phase II dose escalation trials starting in 1992. The patients had to have a tumor stage of T2b or greater, PSA of 10 ng / mL or greater, or a Gleason score of 7 or greater. The dose-limiting structure is the rectum, but we've reached the highest planned dose level and not seen serious rectal complications. The real question is how much dose you need, and it appears that optimal biochemical local control may peak between 950 and 1050 Rad.

During this trial, studies have been published suggesting that in these locally advanced patients, some of the subsets benefit from adjuvant androgen deprivation therapy, and so the trial was set-up to allow patients to receive endocrine therapy.

Currently, we treat these patients with either 3D conformal therapy or on our high-dose brachytherapy boost protocol, where instead of eight weeks of external beam treatment they receive five weeks of therapy, but they have the two implants interdigitated during the five weeks of treatment. These patients also generally receive hormonal therapy for two years, and my preference is for complete androgen blockade.

I believe that the reason the radiation therapy trials have demonstrated a benefit for adjuvant androgen deprivation therapy, whereas most of the surgical trials have not, is that the radiation trials used more prolonged treatment.

ASTRO criteria for biochemical relapse after radiation therapy

This is in the process of being redefined. Through the years, we have seen problems with the definition of three consecutive rises. One issue is follow-up and the intervals of testing. Too short of a follow-up can give a false impression of the true efficacy of the therapy. Probably the largest research concern has been the backdating issue, in that failure is defined as the mid-point between the nadir and the first of three consecutive rises. Early in a trial, this gives a false impression that a particular therapy is better than it really is. In other words, instead of saying the patient failed when they've reached the third PSA increase, you backdate it and say they failed at the mid-point between the nadir and first consecutive rise. We've also found that it has the opposite effect as the years go on. In other words, it may overestimate the benefits of radiation early on, but it underestimates the benefits later on.

Another issue is the clinical impact. If the PSA is not doubling very quickly, you may be able to just monitor the patient for many years. Our group looked at more than 40 different modifications of the ASTRO Consensus Panel definition, and we found that the definition of the nadir plus 2 ng/mL is very accurate in defining when a patient has truly failed, but more importantly, this predicted for clinical significance. I believe the ASTRO consensus panel will convene again, taking all of this information into consideration and refine the definition.

Transient false-positive rises in PSA after radiation therapy ("PSA bounce")

This even applies to external beam radiation therapy. Any time you have a very aggressive therapy, like brachytherapy, you can see a fairly rapid drop in the PSA of some patients. You can have something as simple as prostatitis, such as inflammation from riding an exercise bicycle for an extended period, that in effect massages the prostate and causes a false blip in the PSA. That is one of the problems with the biochemical failure definitions — these spikes in the PSA may have nothing to do with the prostate cancer. They may just be irritation to the prostate.

Fortunately, these elevations are usually transient, but in some cases they can last for an extended period of time. Generally if it's a very small increase that only lasts about three to four months, it's of no practical or clinical significance, but beyond that, it's really hard to say what to do with the PSA rises. Essentially, you need to monitor these patients, but not assume that they've failed treatment because of a very small increase in the PSA.

Advantages of high-dose-rate brachytherapy

With high-dose-rate brachytherapy, the patient is radioactive only during the actual time the seeds are temporarily implanted. Also, by placing the needles directly into the gland under ultrasound guidance, you can control the dose

much more precisely than with the permanent seed implant.

With the permanent seed implant, the prostate can swell after the implant is performed, and the seeds can migrate after treatment. With high-dose-rate brachytherapy, what you implant is what you treat. The gland is impaled, and the actual radiation dose distribution that is calculated is actually received by the prostate. If you're going to dose escalate, high-dose-rate brachytherapy offers the best means of tailoring the dose precisely to the gland.

Quality control: Tracking prostate gland movement during radiation therapy

There are quality control issues with both brachytherapy and 3D-conformal external beam radiation therapy. With 3D-conformal external beam radiation therapy, generally you're treating a static image of the prostate before a treatment. Unless you monitor the prostate over the course of treatment and how the patient sets up from day to day, you may not necessarily be treating the same volume each day. The radiation therapy has to be adapted to how the prostate changes over time and how the patient moves over time. The prostate does change shape even though the patient is immobilized. Subtle changes in the motion of the prostate gland means changes in the rectum as well. So you have to be very careful because you're right on the edge of the dose tolerance.

At our institution, we do serial CT scans during the first week of treatment to track the motion and shape of the prostate. We track how the patient moves on the table, and we are even learning how the prostate moves upon breathing. This is one of the most interesting areas of investigation right now.

Surgical Prostatectomy versus Interstitial Radiation Intervention Trial (SPIRIT)

Accrual to the SPIRIT trial will be challenging. About 90% of my patients have already decided on their choice of therapy by the time I see them. It's the rare patient with early-stage prostate cancer who will be subjected to randomization between prostatectomy and brachytherapy.

The trial will give us useful information, but I'm concerned about interpreting the data. How will we tease out the subtle differences in the manner in which permanent seed implants are performed and how prostatectomies are performed? Differences in the quality of the procedures could "wash out" potential differences between the actual procedures themselves. These are low-risk patients, so to detect any differences in outcome will require large numbers of patients.

Select publications

Phase III Randomized Study of Radical Prostatectomy Versus Brachytherapy in Patients with Stage II Prostate Cancer **Open Protocol**

Protocol ID: ACOSOG-Z0070

Accrual: 1,980 patients within 5.5 years

Eligibility	Patients with Gleason ≤ 6, PSA ≤ 10, T1c, prostate volume < 60cc and T2a N0 M0 disease

ARM 1	Radical prostatectomy
ARM 2	Brachytherapy

Study Contact: Paul H Lange, Chair, Ph: 206-543-3918
American College of Surgeons Oncology Group
Source: NCI PDQ, December 2002

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Kestin LL et al. **Practical application of biochemical failure definitions: What to do and when to do it.** *Int J Radiat Oncol Biol Phys* 2002;53(2):304-15. **Abstract**

Martinez AA et al. **Dose escalation using conformal high-dose-rate brachytherapy improves outcome in unfavorable prostate cancer.** *Int J Radiat Oncol Biol Phys* 2002;53(2):316-27. **Abstract**

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William Kevin Kelly, DO

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Memorial Sloan-Kettering Cancer Center

Edited comments by Dr Kelly

CASE 4:

69-year-old man with metastatic disease following initial primary treatment with brachytherapy and external beam radiation therapy

HISTORY

On a routine visit in 11/98, the patient had a PSA of 7.3 ng/mL and normal exam. Prostate biopsy revealed adenocarcinoma in both lobes of the prostate, Gleason 3+4 in seven out of 10 cores on the right and Gleason 3+5 in one out of six cores on the left. CT and bone scans were negative. He was treated with a combination of brachytherapy and external beam radiotherapy.

In 11/99, his PSA nadired to 1.38 ng/mL. His next PSA in 5/01 was 85.15 ng/mL, and the staging workup revealed metastatic disease to the liver, multiple osseous metastases and extrinsic compression of the rectum.

The patient was treated with combined androgen blockade, his PSA decreased to 0.35 ng/mL, and his rectal obstruction lessened. Within nine months his PSA rose to 5.49 ng/mL. The antiandrogen was stopped and re-staging revealed progressive disease in the liver and bone. He also had an asymptomatic femoral vein thrombosis observed on CT, and we anticoagulated him. At this point he was very fatigued, had right upper quadrant pain and his performance status was 70% to 80%. We talked about treatment options — palliation versus chemotherapy versus an investigational approach. He wanted active treatment, and we treated him with estramustine, paclitaxel and carboplatin, which he tolerated very well. He's now off pain medication, more active and his quality of life has improved dramatically. After completing his first two cycles of therapy, he had a 50% regression in liver lesions.

CASE 4 *(Continued)*

DISCUSSION

Patients with metastatic prostate cancer often respond well to palliative chemotherapy, but typically these tumors come back very quickly. This patient had significant improvement in his quality of life after treatment.

We use a platinum-based regimen in patients like this with high-grade tumors, because many of these high-grade tumors have neuroendocrine features, which respond well to this regimen. Patients with visceral metastases, particularly liver metastases; low tumor burdens relative to PSA; and a short hormonal response often have tumors with neuroendocrine features.

Paclitaxel, estramustine and carboplatin for metastatic prostate cancer

We recently reported results of this regimen, which was generally well-tolerated and showed significant anti-tumor activity. The major complication was thromboembolic disease — usually deep venous thrombosis — which occurred in approximately 25% of the patients. Most of these patients were anticoagulated and continued on therapy with no subsequent sequelae.

Nineteen of 24 patients who were being treated for severe pain were able to discontinue narcotics. About two-thirds of the patients had at least a 50% decline in PSA, and 45% of the patients had measurable disease regression.

Select grade 3 & 4 adverse events in Phase I and II studies of paclitaxel, estramustine phosphate and carboplatin in patients with advanced prostate cancer

Toxicity	% Patients
Thrombosis/embolism	
Deep vein thrombosis, requiring anticoagulant therapy	21%
Embolic event, including pulmonary embolism	4%
Hyperglycemia	
Serum blood sugar 250 - 500 mg/dL	38%
Serum blood sugar >500 mg/dL; or acidosis	0%
Hypophosphatemia	
1.0 - 2.0 mg/dL	38%
<1.0 mg/dL	4%
Leukopenia	
WBC 1000 - 2000/mm^3	18%
WBC <1000/mm^3	4%
Vomiting	
≥ 6 episodes in 24 hrs over pretreatment or need for IV fluids	4%
Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse	2%

DERIVED FROM: Kelly WK et al. **Paclitaxel, estramustine phosphate, and carboplatin in patients with advanced prostate cancer.** *J Clin Oncol* 2001;19(1):44-53.

Chemotherapy for advanced prostate cancer

In a generally healthy man, my first-line chemotherapy choice is usually an estramustine-taxane-based regimen — either estramustine-paclitaxel or estramustine-docetaxel. These regimens are well tolerated, and there is a lot of latitude in adjusting the dose if necessary.

There are toxicities so you have to select your patients carefully. In patients who have severe cardiac disease or other comorbidities, some of these regimens may not be optimal. On the other hand, response to second-line chemotherapy in advanced prostate cancer is not very good, and I usually try an investigational therapy at that point.

Multi-institutional chemotherapy trials of estramustine-taxane combinations in androgen-independent prostate cancer patients

First Author	Chemotherapy Regimen	Number of Patients	PSA Level Decrease ≤ 50%	Measurable Disease Response
Hudes	96-hour continuous infusion paclitaxel + EMP	34	53%	44%
Smith	EMP + VP-16 + paclitaxel	40	65%	45%
Kreis	EMP + docetaxel	17	82%	17%
Petrylak	EMP + docetaxel	34	63%	28%
Savarese	EMP + docetaxel	40	69%	19%
Kelly	paclitaxel +EMP + carboplatin	56	67%	45%

EMP=estramustine phosphate; VP-16=etoposide

DERIVED FROM: Kelly WK et al. **Paclitaxel, estramustine phosphate, and carboplatin in patients with advanced prostate cancer.** *J Clin Oncol* 2001;19(1):44-53.

Trial randomizing to doxorubicin versus doxorubicin plus samarium

There were 103 patients who received induction chemotherapy and were then randomized to doxorubicin alone versus doxorubicin plus samarium, using samarium for bone consolidation. Samarium was chosen because it targets the bone and, subsequently, can target additional cells that are within the bone stroma.

The results showed there was significant benefit in the patients who received the bone-targeted therapy. The median survival was increased from 16.8 months to 27.7 months. This was a significant finding because we hadn't seen any studies that actually showed improvement in overall survival. Unfortunately, this is a small study, but it's interesting that we're starting to use combined modality therapies to treat prostate cancer, actually targeting the end organs.

Chemotherapy regimens result in responses in about 70% of the patients, but typically when the chemotherapy is stopped, the disease recurs in three to four months. Often I'll use this bone consolidation approach after a patient's had a response to chemotherapy, looking for a way to stabilize the response. There are two radioisotopes that can be used — strontium-89 and samarium. I'll use either, but samarium may be preferable because it has less bone marrow toxicity than strontium. Repeated doses of strontium-89 result in myeloablation, making it very difficult to treat the patient with further chemotherapy.

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Smith DC et al. **Phase II trial of oral estramustine, oral etoposide, and intravenous paclitaxel in hormone-refractory prostate cancer.** *J Clin Oncol* 1999;17(6):1664-71. **Abstract**

Post-test

Questions ***(please circle answer)***

1. What was the duration of adjuvant hormonal therapy in the Bolla trial?
   a. 6 months
   b. 12 months
   c. 18 months
   d. 24 months
   e. 36 months

2. In the EPC trials, the Scandinavian study demonstrated a significant decrease in objective progression in the patients treated with bicalutamide 150 mg. The Scandinavian study consisted mainly of patients managed by:
   a. Watchful waiting
   b. Radical prostatectomy
   c. External beam radiation therapy
   d. Brachytherapy
   e. Cryotherapy

3. Which of the following are helpful in determining the pattern of recurrence (local or distant) in patients with a rising PSA after initial therapy for prostate cancer?
   a. Original surgical pathology
   b. Time to recurrence
   c. PSA doubling time
   d. ProstaScint® scan
   e. All of the above

4. **True/False:** Clinical trials have demonstrated that lyphadenectomy improves survival in patients with lymph node metastases.

5. **True/False:** In Messing's trial of early versus delayed endocrine therapy, there was a survival benefit for those men receiving early hormonal therapy.

6. **True/False:** The ASTRO definition for the date of PSA relapse/failure is the mid-point between the PSA nadir and the first of three consecutive PSA rises.

7. The SPIRIT trial will address which of the following?
   a. External beam radiation versus brachytherapy
   b. Radical prostatectomy versus external beam radiation
   c. Radical prostatectomy versus brachytherapy
   d. None of the above

8. Which of the following is not a known side effect of bicalutamide monotherapy?
   a. Decreased cognition
   b. Breast tenderness
   c. Breast enlargement
   d. All of the above are side effects
   e. B and C

9. **True/False:** In the trial of paclitaxel, estramustine and carboplatin for metastatic prostate cancer conducted by Dr Kelly, the major complication was thromboembolic disease, which occurred in approximately 25% of the patients.

10. **True/False:** When samarium was added to chemotherapy, survival in metastatic disease was increased.

Evaluation Form

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Conversations with Urologic Oncology Leaders

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Please answer the following questions by circling the appropriate rating:

5 = ***Outstanding*** 4 = ***Good*** 3 = ***Satisfactory*** 2 = ***Fair*** 1 = ***Poor***

Global Learning Objectives

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

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

Specific Learning Objectives for Issue 1

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

- Determine and implement an evaluation and management algorithm for patients with a rising PSA after their initial therapy for prostate cancer. 5 4 3 2 1
- Counsel patients on the risks and benefits of antiandrogen therapy, LHRH agonist therapy and maximum androgen blockade. 5 4 3 2 1
- Describe the clinical implications of current research in radiation therapy of prostate cancer, including interpretation of PSA results. 5 4 3 2 1

Effectiveness of the Individual Faculty Members

Speakers	Knowledge of Subject Matter	Effectiveness as an Educator
Neil Love, MD	5 4 3 2 1	5 4 3 2 1
Gerald W Chodak, MD	5 4 3 2 1	5 4 3 2 1
Thomas E Keane, MBBCh	5 4 3 2 1	5 4 3 2 1
Frank A Vicini, MD	5 4 3 2 1	5 4 3 2 1
William Kevin Kelly, DO	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

Will the information presented cause you to make any changes in your practice?

___Yes ___No

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

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This program was supported by an educational grant from AstraZeneca Pharmaceuticals, LP.

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