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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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How to use this monograph

This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program and the website, ProstateCancerUpdate.net, where you will find a full transcription of the audio program and 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. This is a CME activity that 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.

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 as well as 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 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 physicians in the formulation of up-to-date clinical management strategies.

Issue 3, 2002 of Prostate Cancer Update consists of discussions with four research leaders about several patient management scenarios and a variety of important topics including selecting local therapy for younger patients, therapeutic options for patients with intermediate-risk prostate cancer, the clinical utility of postoperative nomograms, ongoing prostate cancer prevention clinical trials and bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer.

Learning Objectives

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

- Distinguish patients with prostate cancer for whom radiation plus hormonal therapy is appropriate.
- Evaluate issues regarding the timing and selection of hormonal therapy for prostate cancer patients who have undergone definitive local therapy.
- Differentiate the risks and benefits of hormonal therapies including antiandrogen therapy and medical or surgical castration.
- Identify patient perspectives in therapy decision-making in order to more effectively counsel patients about the risks and benefits of various therapy choices available to them.
- Understand the impact of biochemical failure on patients in order to assist them in making decisions about available therapeutic options.
- Understand the clinical utility of using postoperative nomograms in order to counsel patients about the potential value of adjuvant therapy.

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.

Designation Statement

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

Faculty Disclosure Statements

The Postgraduate Institute for Medicine has a conflict of interest policy that requires course faculty to disclose any real or apparent commercial financial affiliations related to the content of their presentations/materials. It is not assumed that these financial interests or affiliations will have an adverse impact on faculty presentations; they are simply noted in this supplement to fully inform participants.

Editor's Note

Visiting Professors

Most of the research leaders interviewed for this series spend a day at our conference center at the University of Miami. These visits include a guest lecture and hours of intensive query by the Prostate Cancer Update team of clinicians. The sessions are very much a give and take. Our renowned guests share with us their unique perspectives and expertise, while we impart our experiences in cancer education, and our sincere interest in making an important impact on patient care by functioning as an interface to doctors caring for prostate cancer patients and their families. We usually interview these visiting professors for the audio portion of our program at the end of this long day. Sometimes the trust that we engender has interesting consequences, as these leaders often not only discuss clinical research data and trials but also more personal perspectives on what this all means to patient care.

For example in this issue, oncologist Mary-Ellen Taplin — in addition to discussing management of patients with rising PSAs — shares her personal experiences as the wife of a patient with a brain tumor. Dr Taplin notes that she and her husband visited four major medical centers and received four different opinions on optimal management. A recurring theme in prostate cancer is the lack of clear-cut, evidence-based standards of care for many situations, and Dr Taplin eloquently elaborates on the feelings of patients and families when confronted with this type of dilemma.

Every physician understands the challenge of empathizing with a person with a life-threatening disease, and yet it is interesting that in spite of our best efforts, it often takes a real life event to truly comprehend what our patients think and feel. In the first issue of this series, urologist, Dr Paul Schellhammer, shared his experience as a prostate cancer patient and noted how different his perspective is now when he sees patients in his clinic. When Dr Schellhammer first arrived at our center, we were unaware of his own personal history of the disease, and we were truly moved when he unhesitatingly agreed to share it with a national audience of physicians.

Recently, our team hosted another group of "visiting professors" — members of a local Man-to-Man prostate cancer support group and their spouses. These courageous men and women agreed to participate in video interviews, which will be utilized to stimulate discussion at our first "Prostate Cancer Town Meeting" being held in Hollywood, Florida, on September 22, 2002. In future issues of this audio series, we will share with you the deliberations of this unique workshop, which is seeking to have patients, families and physicians develop ideas and suggestions for new initiatives in patient education and support. The following, is an excerpt of one of the premeeting video interviews.

— Neil Love, MD

A candid account of the impact of prostate cancer: A 52-year-old man's experience

Being diagnosed with prostate cancer is earth-shattering — your life changes in an instant. I was a basket case for six months. It was a very difficult experience to go through. As a person in his fifties, I cannot even conceive of my own mortality. It was unbelievably shocking, and I was just devastated.

My urologist is a real "people person." He related to me as a human being rather than as a statistic. I wanted to know every detail about surgery before I went in, and he spent two hours walking me through it with graphs and charts and discussions about what would happen.

I felt like I had a partner who was going to fight along with me. I was very pleased with him. But, the house officers who I worked with didn't have a clue. They were amazingly insensitive. They didn't understand the impact of their words.

One thing for which I was not fully prepared was the incontinence afterward. I have never had a catheter, and 12 days of that was just horrible. Afterwards, I was relieved for about 10 minutes, until I found that I had to wear a diaper. It took almost three months to get out of diapers, and I was absolutely petrified that it was going to last forever.

Hormone therapy set me back a little bit in terms of energy level and the ability to maintain a true lifestyle. My libido was completely absent, and I gained a lot of weight. I wish someone had warned me to take some proactive measures to avoid so much weight gain.

The entire experience has been an emotional roller coaster. I don't know if it was the hormone therapy or the stress after the diagnosis, but I was crying all the time, and anything set me off, even a sad song. I did things that were not typical for me, I wanted to cuddle all the time. I never used to do that. I wanted to hold hands sitting on the couch watching TV with my wife, with whom I've been married for 24 years.

I have a huge support system, which has been critical in adapting to this. My wife has always been less active in our relationship. I was always the one who took charge of everything. But she suddenly got this incredible energy and took charge of the whole thing, and it kind of flipped the relationship. I was helpless for the first time.

So, with her taking charge and people in my network of family and friends providing support, it made a big difference. I had a lot of input and support. I also found other men who had prostate cancer with whom to talk, which was very comforting.

I know that with a Gleason 8 tumor, there is the potential that I am going to have a recurrence, but from what I can see, maybe something else will get me first.

Adam P Dicker, MD, PhD

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Edited comments by Dr Dicker

CASE 1:
64-year-old man with a T1c Gleason 7 (3+4) prostate cancer

History

This man, employed as a cabinetmaker, was in a very stable marriage and had adult children. His previous PSA had been within the age-adjusted normal range, but during the current evaluation his PSA was 12 ng/mL. A prostate biopsy revealed a Gleason 7 (3+4) prostate cancer in two cores on the left and one core on the right, with 20-40% involvement in each core.

Follow-up

He elected a combination of external beam radiation therapy with brachytherapy. Towards the end of the external beam radiation, he experienced more frequent bowel movements, indicating rectal irritation. As he was healing from that, we did a permanent radioactive seed implant. He developed a lot of annoying urinary side effects.

Six months after the implant, his PSA is 0.5 ng/mL, and it has been dropping very steadily. His urinary symptoms have persisted, and he wakes up two to three times a night to urinate, despite being on an alpha-blocker.

Case discussion

A Gleason 3+4 prostate cancer clearly behaves differently than lower grade prostate cancer. In surgical or radiation series where those patients were treated with a single modality, there was an inferior outcome in terms of cure. How to improve the cure rate for these patients is a subject of much investigation. From the urology perspective, it is a question of whether neoadjuvant hormonal therapy or postoperative radiation therapy might be of benefit. In the radiation oncology community, the questions have centered on escalating the radiation dose,

CASE 1 *(Continued)*

combining external beam radiation therapy with brachytherapy or the use of adjuvant hormonal therapy.

I am very uncomfortable — at least intellectually — about what the right answer is for this type of patient. Although I am biased toward brachytherapy and I actually think external beam radiation therapy with brachytherapy is a way to increase the dose to the prostate, no data suggests that external beam radiation therapy plus brachytherapy is superior to external beam radiation therapy alone.

This patient was interested in brachytherapy. He did not, however, appreciate that Gleason 7 prostate cancer is more aggressive than favorable-risk prostate cancer. I had the unpleasant task of informing him that he would not be an appropriate candidate for brachytherapy alone. It is not the standard of care to treat an intermediate-risk prostate cancer patient (PSA = 12 ng/mL, Gleason score = 7) with brachytherapy alone.

Urologists who counsel patients with intermediate-risk prostate cancer must caution them about their increased risk of positive margins, and they should also discuss the available treatment options for positive margins or extracapsular extension. Had he elected surgery, his chance of having positive margins was 40% to 50%. Positive margins do not always equal a death sentence. Clearly, there are patients with positive margins who do not have a PSA recurrence. There is also considerable controversy about who should receive adjuvant therapy in this situation.

Adjuvant hormonal therapy

There are very few adjuvant hormonal therapy trials in prostate cancer. In patients with node-positive disease, studies have demonstrated a benefit for adjuvant hormonal therapy. There is also a large trial — the Early Prostate Cancer (EPC) trial — that looked at prostate cancer patients with localized disease, locally advanced disease and those undergoing watchful waiting.

In the EPC trial, patients were randomized to adjuvant bicalutamide 150 mg or placebo. Clearly, patients with intermediate-risk and locally advanced disease benefited from adjuvant therapy. For the patients with favorable-risk prostate cancer, the follow-up in the EPC trial is not long enough to know whether adjuvant therapy is beneficial.

I think there are a group of patients with intermediate-risk disease — a very broad category — who would benefit from adjuvant therapy, and a group who would not. It also depends on the local therapy utilized and whether there are subsequent local therapies.

In the United States, bicalutamide 150 mg is not FDA-approved, and it is not part of my armamentarium. The role for adjuvant LHRH therapy is also not yet defined in patients with intermediate-risk prostate cancer.

Re-implantation of radioisotope seeds for a suboptimal implant

Earlier in my career, I had two patients in whom I was not satisfied with the results of the postoperative CT scan, and they required re-implantation. In those days, I did the postoperative CT scan on the day of the implant, so I knew immediately whether the seed distribution was adequate. The patients were re-implanted one month later, and both have been fine.

It is very complicated to re-implant the prostate, both technically and from a medical physics standpoint. We are actually writing up these cases for publication. Re-implantation is not addressed in the literature, because it is a very difficult situation to manage.

"PSA bounce" after radioactive seed implant

It has been observed that one and a half to two years after an implant, patients may suddenly have their PSA double or triple from its nadir of less than 1 ng/mL. After another few weeks, the PSA can go up to 5, 10 or even as high as 12 ng/mL. PSA bounce may also occur three or four years after an implant and is not limited to the year and a half window, although that is the most common time period.

It occurs in as many as 20% of patients treated with brachytherapy. Many of these patients have urinary symptoms, which are reminiscent of the first month or two after the implant.

At first, it was thought that it might be caused by a urinary tract infection, but that did not pan out. I believe "PSA bounce" is related to some nonspecific inflammatory event in the prostate, which we do not understand, but provides a great deal of anxiety to the patient and the doctor.

It is difficult to differentiate a "PSA bounce" from tumor recurrence. In a favorable-risk patient, however, tumor recurrence does not usually occur a year and a half after external beam radiation therapy or brachytherapy. Usually, patients with favorable-risk prostate cancer fail about two to three years, or sometimes later, after treatment. Patients with intermediate-risk and locally advanced disease fail earlier. During these PSA bounces, patients require considerable reassurance.

Commentary on the update of the Bolla trial

A paper, recently published in *The Lancet*, substantiates the 1997 report in the *New England Journal of Medicine* of the benefit of hormonal therapy in patients receiving radiation. The long-term cure rates are significantly improved with hormonal therapy, and patients with the worse disease are the ones who benefit the most from hormonal therapy added to radiation therapy.

It is not yet known whether three years of hormonal therapy is required. The EORTC is currently comparing six months to three years of total androgen blockade.

A major criticism of the trial is whether the radiation therapy is actually necessary. Some of these patients may have been cured by hormonal therapy alone. However, it is very difficult to compare hormonal therapy alone to radiation therapy alone and hormonal therapy plus radiation therapy. From a patient's perspective, all the arms are not equally balanced.

CASE 2:
65-year-old man with Gleason 8, cT2a prostate cancer

History

This very active attorney had been getting his PSA checked about every other year. His PSA was generally in the 3.5 to 4 ng/mL range. For reasons that were unclear, he missed his physical exam. When it was finally rescheduled, his PSA was 15 ng/mL and he had an abnormal rectal exam with induration on the right.

A transrectal ultrasound-guided biopsy revealed Gleason 4+4 prostate cancer in 70% of two cores on the right. A bone and CAT scan did not reveal any evidence of osseous disease or lymphadenopathy.

Follow-up

He opted for a combination of hormonal therapy and radiation therapy. Because his gland was somewhat bulky, he was treated with three to four months of hormonal therapy before the radiation therapy. He continued on hormonal therapy during the radiation therapy, and he has been on it now for two and a half years. My goal is for him to receive three years of hormonal therapy. Then, he will continue to be monitored.

After three weeks on hormonal therapy, he noticed a loss of libido. He was not happy about it, but he was in a stable relationship and his wife was extremely supportive. After a couple of months, he started experiencing hot flashes, which he did not find too bad. Then after about a year and a half, he noticed a 10-pound weight gain around his midsection that, despite all attempts to exercise and diet, still remains.

Case discussion

Although this may appear to be a very simple case, it is not necessarily straightforward. Had the patient opted for surgery, his probability of having positive margins was high.

Some physicians believe that it is best to debulk the prostate by removing it and then follow with postoperative radiation therapy. Another group of doctors believes that if the patient will have positive margins, the probability of failing is high and some other forms of local therapy, such as radiation therapy, might provide similar benefits without removing the prostate.

Based on a number of studies from the Radiation Therapy Oncology Group (RTOG) and the EORTC, hormonal therapy plus radiation therapy is superior to radiation therapy alone in patients with locally advanced disease. Although the EORTC trial, with three years of hormonal therapy, is the only one demonstrating a survival benefit, it is the best data we have now.

My philosophy is that this man had a systemic element to his disease. Although local control is important, it is not sufficient for a cure. Some physicians would order a ProstaScint® scan in this group of patients. If it showed disease in the supraclavicular fossa, that could make an impact on the selection of therapy. Others may use the ProstaScint® scan to decide whether to treat the pelvis with radiation.

In a younger patient, some physicians might recommend a laparoscopic node dissection. If the nodes were positive, then the patient might get radiation or hormonal therapy. The hormonal therapy would be given indefinitely, similar to the Messing trial.

For this patient, I recommended long-term androgen suppression and radiation therapy. I felt

that was the standard of care. If the patient wanted to try to do something beyond radiation therapy with hormonal therapy, it would be in the context of a clinical trial evaluating the role of chemotherapy in addition to hormonal therapy and radiation therapy. This patient, however, felt that the potential benefits of chemotherapy did not outweigh the potential toxicity, and he did not want to pursue that avenue.

Without hormonal therapy, this man's chance of relapse was 50% to 60%. The risk of recurrence would probably be reduced by 15% to 20% with the addition of hormonal therapy. He reluctantly accepted the hormonal therapy.

He was not thrilled to hear that hormonal therapy would result in decreased libido and erectile dysfunction — effects that can persist even after the hormonal therapy is discontinued. With two or three years of hormonal therapy, there is a 5% to 10% chance that libido and sexual function may never return.

Had bicalutamide 150 mg been available, he might have been more interested in that option. Bicalutamide 150 mg does not have the same negative impact on muscle mass, libido and erectile function. The patient would have had to balance the side-effect profile of bicalutamide relative to an LHRH agonist. I am in favor of patients having more, not less, options.

The EPC trial evaluated the role of bicalutamide 150 mg in the truly adjuvant setting. On the other hand, the Bolla study and the RTOG studies gave concurrent and continued hormonal therapy. We need trials comparing the positive arm of the Bolla trial to bicalutamide 150 mg.

It is important to counsel patients who will be on hormonal therapy for a long period of time about the potential side effects, including hot flashes and weight gain. They should also be informed that what they experience in the first few months of hormonal therapy might not be the same as after two years. They should feel free to bring up these side effects on their visits.

Select publications

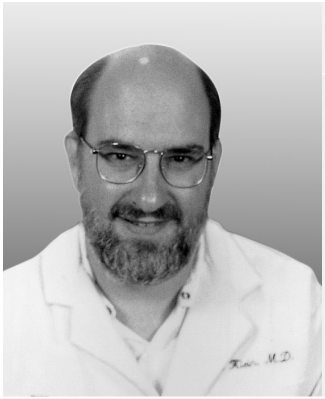
Blasko JC et al. **Prostate specific antigen based disease control following ultrasound guided 125iodine implantation for stage T1/T2 prostatic carcinoma.** *J Urol* 1995;154(3):1096-9. Abstract

Bolla M et al. **Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial.** *Lancet* 2002;360(9327):103-6. Abstract

Critz FA et al. **Prostate specific antigen bounce after radioactive seed implantation followed by external beam radiation for prostate cancer.** *J Urol* 2000;163(4):1085-9. Abstract

Pollack A et al. **Prostate cancer radiation dose response: Results of the M.D. Anderson phase III randomized trial.** *Int J Radiat Oncol Biol Phys* 2002;53(5):1097-105. Abstract

Smathers S et al. **Temporary PSA rises and repeat prostate biopsies after brachytherapy.** *Int J Radiat Oncol Biol Phys* 2001;50(5):1207-11. Abstract



Eric A Klein, MD

Head of Urologic Oncology
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The Cleveland Clinic

Co-director,
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Edited comments by Dr Klein

Cleveland Clinic prostate cancer database

We developed a localized prostate cancer database in which we have almost 5,000 patients treated in the PSA era for localized prostate cancer with either external beam radiation therapy or surgery.

We have been able to demonstrate in a prospective fashion that the biochemical failure rates between those two treatments are equal at about ten years. My gut feeling is that well-selected patients will respond favorably to either therapy and that the differences in outcome and quality of life are relatively minor.

Equivalent efficacy of radical prostatectomy and external beam radiation therapy for localized prostate cancer in the PSA era

"Eight-year biochemical failure rates were identical between RT and RP in any subgroup. Outcome is determined mainly by pretreatment PSA levels, bGS, clinical T stage and, for RT patients, radiation dose. . . ."

. . . One major criticism of comparisons between radiation and surgery for localized prostate cancer has been the use of two different end point definitions. Using the more stringent definition of reaching and maintaining a PSA level < 0.5 ng/mL in both RP and RT patients did not change the ultimate conclusion that there were no differences in outcome between the two modalities that could not be accounted for by differences in patient selection."

EXCERPT FROM: Kupelian PA et al. **Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: A large single-institution experience with radical prostatectomy and external-beam radiotherapy.** *J Clin Oncol* 2002;20:3376-3385. Abstract

Prostate cancer treatment decisions

There are a couple of pieces of information I share with every patient. First, they will have some side effects irrespective of the therapy they choose, although the side effects will be specific for each treatment. Second, based upon our observations, they cannot make a wrong choice — any therapy is likely to give them good cancer cure for the first ten years.

The real anxiety for both the physician and the patient is associated with the younger men with prostate cancer, who are more difficult in some ways and easier in others. Preservation of potency and continence is an important issue postprostatectomy. In all major series, younger patients have a better chance of having their potency and continence preserved.

The main reason urologists limit the use of radiation therapy in younger patients is the theoretical possibility that the local failure rate will be higher with anything that preserves the primary organ. If you look at other tumors, both urologic and nonurologic, that is probably correct. However, in our localized prostate cancer database, the local recurrence rate is the same at ten years for surgery and radiation therapy.

For the youngest patients (40 to 50 years old), I think radical prostatectomy is the preferred treatment option. The reasons are twofold. First is the theoretical chance of a lower local recurrence rate. If the prostate is left in place and the patient lives another 20 or 25 years, some of the normal epithelial cells in the prostate can survive and form a second tumor.

The other incontrovertible advantage to a radical prostatectomy is the pathology report, which provides powerful prognostic information, such as the grade of the tumor, the percentage of Gleason 4 cancer and the presence of extracapsular extension or positive margins.

Since there are patients who are upgraded from a Gleason score of 6 to 7 based on the surgical pathology, a pathology report is a better prognosticator than pretreatment characteristics. There are also occasional patients who clinically have organ-confined disease, but may actually have seminal vesicle invasion. When prognosticating for a patient, the pathology report is better than the pretreatment parameters.

Ongoing adjuvant chemotherapy trials

We are currently enrolling patients in two adjuvant chemotherapy trials. The first study is a phase III Southwest Oncology Group (SWOG-9921) trial, which is evaluating combined androgen blockade for two years with or without mitoxantrone/prednisone for six months. The second study, a phase II feasibility trial, is evaluating docetaxel alone for up to six months.

Counseling node-positive prostate cancer patients about adjuvant therapy

In counseling patients, I tell them, “Mr. Jones, you have an aggressive cancer.

And our experience over the last decade has taught us that you're not likely to be cured by a single treatment. I don't really know what the best treatment is, whether that's radiation or surgery or a combination of radiation and hormones or chemotherapy and surgery, but I am absolutely convinced that you need more than one treatment." Then, I present all the options. Ultimately, I let the patient decide what appeals to him the most. Probably half of my patients with node-positive prostate cancer who are not eligible for a clinical trial decide to go on adjuvant hormonal therapy. Two factors drive that decision. First, patients have a morbid fear of having positive lymph nodes — they know it is a bad thing. Second, the Messing trial received a lot of press, and patients specifically ask about it.

Prostate Cancer Journal Club

Validation study of the accuracy of a postoperative nomogram for recurrence after radical prostatectomy for localized prostate cancer.

Graefen M et al. *J Clin Oncol* 2002;20(4):951-6. **Abstract**

Mike Kattan, a statistician first at Baylor and then at Memorial Sloan-Kettering, developed a series of nomograms for predicting the likelihood of cure after treatment with surgery, radiation therapy or brachytherapy. They are an evolution from the prior nomograms, particularly the Partin tables, which actually predict for pathologic stage and extracapsular extension as a surrogate for cure.

Kattan retrospectively reviewed large databases of prostate cancer patients treated with surgery, radiation therapy or brachytherapy. He then determined the likelihood of biochemical failure at a given time point, either five or seven years after therapy.

There are preoperative, postoperative, preradiation therapy and prebrachytherapy nomograms. These nomograms are available in a software package that can be downloaded onto a hand-held PDA.

The nomogram in this paper by Graefen et al is a postoperative nomogram. In patients electing prostatectomy because of favorable preoperative characteristics, the nomogram can predict the likelihood of being disease-free seven years postprostatectomy. Based on that prediction, a decision can be made as to whether or not adjuvant therapy might be appropriate.

This paper was based on the worldwide experience of almost 3,000 patients who underwent radical prostatectomy. The original nomogram was based on a single surgeon's series, Peter Scardino, from Baylor and Memorial Sloan-Kettering.

To order prostate nomograms

http://www.mskcc.org/mskcc/html/5796.cfm

CASE 3:
48-year-old man with a family history of prostate cancer

History

This man had a normal rectal exam, and his first PSA was 2.6 ng/mL. Since his father was diagnosed with prostate cancer at age 62, he sought advice about whether to undergo a prostate biopsy.

Follow-up

He had a prostate biopsy that was positive for prostate cancer. He was treated with radical prostatectomy, which revealed organ-confined disease.

Case discussion

Based on the early screening studies, a prostate biopsy would not have been indicated until the PSA reached a level of 4 ng/mL, despite this patient's positive family history. Recently, Catalona and others have reported a 20% incidence of prostate cancer when the PSA is between 2.5 and 4 ng/mL. Given the relatively low morbidity associated with a prostate biopsy and a 20% chance of having prostate cancer, I recommended a prostate biopsy for this individual. There is data, which has not always been interpreted in a uniform fashion, suggesting that the lower the PSA at diagnosis, the greater likelihood of having organ-confined disease. This is not true in every case. For example, some very high-grade tumors (Gleason of 8 to 10) do not produce much PSA.

But for lower-grade tumors, there is a linear relationship between PSA at diagnosis and the likelihood of having organ-confined disease. If one accepts that early treatment is going to lower the mortality rate for prostate cancer, again recognizing the controversy, it makes sense to biopsy younger men with PSAs below 4 ng/mL.

In 1995, Phil Gann published in JAMA a follow-up to the Physicians Health Study in which he looked at the risk of developing prostate cancer based on a bank of serum PSAs. He found that PSA predicted the likelihood of developing a clinically significant Gleason ≥ 7 prostate cancer with about 5.5 years of lead time. Even those men with a PSA below 4 ng/mL, but above 1 ng/mL, had a greater likelihood of having prostate cancer than those with a PSA below 1 ng/mL.

Even within the "normal" range, PSA stratifies risk. That was another reason to consider a biopsy in this gentleman. Furthermore, even though it is unlikely this man has a true hereditary form of prostate cancer, a positive family history in a first-degree relative doubles the risk of being diagnosed with prostate cancer.

Prostate Cancer Prevention Trial (PCPT)

In 1993, the Prostate Cancer Prevention Trial (PCPT) was initiated on the basis of the hypothesis that cumulative androgen exposure increases the risk of prostate cancer.

The PCPT randomized 18,000 men to either placebo or finasteride for seven years. At the end of seven years, a prostate biopsy will be performed and the

rates of prostate cancer will be compared in the placebo and finasteride groups. The last biopsies will be done in 2003. Therefore, we ought to have some data by late 2003 or early 2004.

CASE 4: 52-year-old man with high-grade prostatic intraepithelial neoplasia (PIN)

History

This man had a normal rectal exam, a PSA of 5.1 ng/mL and a sextant biopsy that revealed high-grade prostatic intraepithelial neoplasia (PIN).

Follow-up

This patient had another biopsy, which was negative for both cancer and high-grade PIN. He is being followed at six-month intervals with a PSA level and a DRE. He has not been rebiopsied.

Case discussion

PIN is considered a precancerous condition that has a 10% to 30% chance of ultimately becoming prostate cancer.

In a man with a normal rectal exam and PSA between 4 and 10 ng/mL, the likelihood of finding cancer with six biopsies is probably about 20%. If you do a second set of six biopsies, the likelihood rises to around 35%. It is now possible to combine the second set of sextant biopsies with the first set. The use of local anesthesia in the office has aided our ability to do more biopsies.

Obtaining 8 to 12 biopsies in the first sitting, one can detect all of the cancers that used to require two sets of sextant biopsies. Initially, this patient did not have an adequate biopsy sampling. Currently, the standard recommendation for high-grade PIN is to rebiopsy the prostate to make sure a cancer was not overlooked because of sampling error.

There is no standard recommendation for patients who do not have PIN or cancer on re-biopsy. Generally, I follow those patients with a rectal exam and a PSA level at six-month intervals. When either changes in some significant fashion, a rebiopsy is indicated.

The Southwest Oncology Group (SWOG-9917) is studying patients who have had two sets of biopsies, in which at least one demonstrates high-grade PIN. The SWOG trial is a randomized comparison of placebo and selenium taken daily for three years followed by a repeat biopsy. I try to encourage these patients to enter this SWOG trial.

Selenium and Vitamin E Cancer Prevention Trial (SELECT)

The hypotheses behind SELECT are two separate epidemiologic observations. First, the Clark trial — designed to determine whether selenium prevented nonmelanoma skin cancer in 1,300 men — found a marked reduction in the incidence of prostate cancer in those who took selenium.

Second, the ATBC trial evaluated whether beta-carotene or vitamin E (alone or

in combination) in 29,000 Finish smokers could reduce the risk of lung cancer. There was a marked reduction both in the incidence and mortality due to prostate cancer associated with vitamin E.

The primary objective of SELECT is to determine whether selenium or vitamin E, alone or in combination, can prevent prostate cancer. It is a four-arm trial randomizing 32,400 men to vitamin E plus a placebo, selenium plus placebo, vitamin E plus selenium or two different placebos.

We need long-term exposure to these agents that are hypothesized to act as antioxidants. There will be five years of accrual, and the trial will end seven years after the last participant is enrolled. Therefore, the first individual enrolled will be on therapy for 12 years, and the last individual enrolled will be on therapy for seven years. The average exposure to treatment will be a little over eight and a half years.

An end-of-study prostate biopsy is not required. The end point will be the clinical diagnosis of prostate cancer as discovered by routine clinical care (i.e., an annual rectal exam and PSA level).

If you look at ATBC and the Clark trial, the risk reductions were pretty marked, 40% better. SELECT was powered with more conservative risk reduction estimates of 25% for each agent alone and about 44% for both together.

Select publications

Clark LC et al. **Decreased incidence of prostate cancer with selenium supplementation: Results of a double-blind cancer prevention trial.** *Br J Urol* 1998;81(5):730-4. Abstract

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Edited comments by Dr McLeod

Local therapy decision-making: The case of a retired US Army General

General Norman Schwarzkopf has publicly disclosed information about his prostate cancer experiences, so I am not violating patient confidentiality by discussing his case. After returning from Desert Storm in 1994, he had a routine DRE, which revealed a prostatic nodule. His PSA was low — approximately 1.2 ng/mL. Prostate biopsy demonstrated organ-confined disease, with areas of Gleason 4 and Gleason 6 prostate cancer.

When I met with him, a paramount concern of his was the risk of urinary incontinence due to local therapy. He was a relatively young, very active man, who wanted to maintain his lifestyle. He had prior consultations at a number of medical centers with specialists in prostate cancer, and he knew all of the treatment options. His perspective was consistent with his military experiences. He knew that he could never gather "perfect intelligence." He had to evaluate information from physicians, friends and family and make a decision with the data that was available.

He elected to have a radical prostatectomy, and seven years postsurgery, he has no evidence of recurrent disease and is continent.

Multimodality therapy

Some urologists believe that prostate cancer can be cured through prostatectomy alone, without reliance upon adjuvant therapy. However, dependent upon which prostatectomy series you read, 30-50% of patients will have extracapsular disease, and the location of the prostate limits the margin width that can realistically be accomplished. In the past, prostatectomy was

followed by adjuvant radiation therapy. Presently, we have shifted to simply monitoring the PSA, and urologists are reluctant to utilize adjuvant therapy.

Prostate Cancer Journal Club

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.

See WA et al. *J Urol* 2002;168(2):429-35. **Abstract**

Status of the EPC trials

The EPC trial — evaluating bicalutamide 150 mg versus placebo — is the largest prostate cancer study ever conducted. There is a misconception that the trial is completed. It is still ongoing and data are still being collected and analyzed. This will be an extremely valuable prostate cancer database, which will allow us to stratify patient and disease characteristics and determine the patients with greatest risk/benefit ratio for bicalutamide.

Physicians want to know whether bicalutamide will result in an improvement in mortality, but currently there have not been enough deaths to evaluate this endpoint. In the North American trial, there is only about two years of follow-up. However, evidence is accumulating that time to progression is reduced by bicalutamide 150 mg.

First analysis of the Early Prostate Cancer program

"Treatment with bicalutamide provided a highly significant reduction of 42% in the risk of objective progression compared with standard care alone (9.0% versus 13.8%, hazards ratio 0.58; 95% confidence interval 0.51, 0.66; p<< 0.0001). . . . Reductions in the risk of disease progression were seen across the entire patient population, irrespective of primary treatment or disease stage. Overall survival data are currently immature and longer follow up will determine if there is also a survival benefit with bicalutamide."

EXCERPT FROM: 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**

Optimal duration of 150 mg adjuvant bicalutamide

This is an important question to be addressed in randomized trials. In the adjuvant breast cancer trials, five years of tamoxifen was better than two years. That was the rationale for why this trial was designed to be a pooled

analysis and evaluate bicalutamide for five or more years in Europe and two years in the United States.

Preliminary efficacy results of bicalutamide 150 mg versus placebo in patients managed with no local therapy ("watchful waiting")

In the Scandinavian trial — which was predominantly watchful waiting — 29% of the patients on placebo had objective progression as opposed to 16% who were on bicalutamide 150 mg — almost a 50% reduction in objective progression for patients receiving bicalutamide. This will be one of the critical results from the trial.

The value of delaying time to biochemical failure

Patients are emotionally devastated after PSA relapse. Several years earlier, they made an emotional and physical investment in primary local therapy. PSA recurrence is as if they are being told that they have cancer again, and many patients want to be treated for a rising PSA.

The Pound article demonstrated that, on average, there is a 13-year interval from PSA rise until the patient dies of metastatic disease. However, that is a mean — for some patients it will be shorter, for others a longer period until death.

Also, delaying the time until a patient develops metastases is clinically meaningful. Some of the adverse side effects of an LHRH agonist can be avoided with a therapy such as bicalutamide 150 mg. I take into consideration comorbid illnesses, life goals, sexual and social functioning, etcetera when deciding on whether to treat these patients.

Quality-of-life advantage of bicalutamide 150 mg compared to medical or surgical castration

LHRH agonists may have debilitating side effects. Even with intermittent therapy, testosterone does not necessarily return to normal levels and alleviate symptoms. Additionally, osteoporosis may be an important issue in 60-year-old men treated with castration. There are preliminary studies that suggest that bicalutamide 150 mg does not have an adverse impact on bone density.

One trial demonstrated that bicalutamide was equivalent to medical or surgical castration in M0 disease, but with fewer side effects — anemia, osteoporosis, muscle-wasting, hot flashes, etcetera.

In terms of the expected side effects from bicalutamide 150 mg, I tell patients, "You have a 75% chance of having breast pain and/or nipple tenderness." In all probability it will be a nuisance, and most patients will plateau. The breast tenderness typically resolves after therapy is completed. It does not become a major impediment to their lifestyle.

Gynecomastia can be managed with low-dose radiation prior to beginning

treatment with bicalutamide. If a patient does develop breast enlargement, it typically plateaus after one year. If the gynecomastia is disturbing to the patient, then a mastectomy or liposuction can be performed, with cosmetically favorable results.

Resolution of gynecomastia and breast pain after cessation of therapy

"Gynecomastia and breast pain improved or resolved in 70% and 90% of patients, respectively, who withdrew from therapy with these events ongoing. The resolution rate for breast pain at 1 year after cessation of therapy was 84%. The resolution rate for gynecomastia was dependent on the duration of therapy, with resolution rates at 1 year after cessation of therapy ranging from 64% for patients who had taken bicalutamide for less than 6 months to 29% for those who had received greater than 18 months of bicalutamide therapy."

EXCERPT FROM: 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

Select publications

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Edited comments by Dr Taplin

CASE 5:
57-year-old man with a rising PSA two years after external beam radiation therapy

History

This man was initially diagnosed in March 1999. At that time, he had some induration on his rectal exam and a PSA of 7.3 ng/mL. A biopsy confirmed Gleason 7 to 9 prostate cancer.

He enrolled in a clinical trial of external beam radiation therapy in conjunction with hyperthermia. He received a somewhat lower dose of radiation, 67 Gy, than we routinely use today. In addition, he received six months of hormone therapy with an LHRH agonist and bicalutamide.

He had a good response with a nadir PSA of 0.2 ng/mL. The radiation caused nocturia, some frequency during the day, and impotence. The six months of hormone therapy caused fatigue, a reduction in mental clarity and memory impairment.

About two years after his primary therapy, his PSA had risen to 1.8 ng/mL. Over the next six months, it rose to 2.8 ng/mL. His radiation oncologist referred him for further evaluation. On physical exam he had a palpable prostate nodule, and a biopsy revealed recurrent prostate cancer.

Follow-up

I presented him with the options of standard hormonal therapy (i.e., orchiectomy or an LHRH agonist), intermittent hormonal therapy or testosterone-sparing hormonal therapy with bicalutamide 150 mg. At that time, cryotherapy was not available in our institution. He chose bicalutamide 150 mg.

He also received low-dose prophylactic breast irradiation, and he has not experienced any

gynecomastia or nipple tenderness. After one year of therapy, he has not had any side effects other than infrequent, mild nausea. He has also been able to maintain his libido. His PSA decreased from 2.8 to 0.2 ng/mL.

I see him every three months. Patients who are on bicalutamide 150 mg are followed regularly, as if they were on an LHRH agonist, with visits every three or four months.

Case discussion

For several reasons, I felt it was important to consider early hormonal therapy for this patient. His PSA doubling time was less than a year, and he had biopsy-proven tumor at the prostatic bed, which could cause urinary retention in the future.

He probably could have been considered for cryotherapy. We now have a couple of urologists in our area who are doing cryotherapy. However, a recent report in the *Journal of Clinical Oncology* suggests that patients with Gleason 9 and 10 prostate cancer do not do well with cryotherapy. This patient had a Gleason 9 tumor, so cryotherapy may not have changed the natural history of his disease.

Factors affecting selection of patients for salvage cryotherapy after XRT failure

"We believe that cryotherapy is not an optimal therapeutic option for all patients with locally recurrent PCa after XRT. On the basis of our current study, salvage cryotherapy is more likely to fail in patients who have locally recurrent androgen-independent PCa, a PSA level of greater than 10 ng/mL, a Gleason score of 9 and 10 for the recurrent PCa, or a pre-XRT clinical stage greater than T2. What is not known is whether these patients would receive a significantly greater benefit from another therapy with curative intent, namely, salvage prostatectomy, or other noncurative approaches such as early or late androgen-deprivation therapy."

EXCERPT FROM: Izawa JI et al. **Salvage cryotherapy for recurrent prostate cancer after radiotherapy: Variables affecting patient outcome.** *J Clin Oncol* 2002;20(11):2664-71. Abstract

Since he was actively working and playing golf, the patient was interested in a type of therapy that would keep his quality of life as close to normal as possible. The side effects most often associated with bicalutamide 150 mg are breast enlargement and nipple tenderness.

Given that he still had libido, he was interested in maintaining it. Men without erectile function are still interested in keeping their libido intact. It seems to be important for their sense of self, how they feel about life and for their spouses.

Although bicalutamide 150 mg is not FDA-approved in this country for this use, we have a lot of experience with bicalutamide 50 mg in combination with a LHRH agonist. I have done

CASE 5 *(Continued)*

studies using the higher dose and treated about 50 patients with bicalutamide 150 mg, so I feel comfortable with its side-effect profile.

The studies done in Europe suggest that the efficacy of bicalutamide 150 mg approaches that of standard hormone therapy, although it may not be as durable. In most cases, at the time of PSA progression, the majority of patients respond to an LHRH agonist.

If he progresses, I probably will treat him with an LHRH agonist. I could also offer him orchiectomy. But since he did not like how he felt on his initial hormonal therapy, orchiectomy would not provide the opportunity for intermittent therapy. I probably would continue the bicalutamide at 50 mg a day for a month after the first dose of the LHRH agonist.

A small study in about 23 patients suggests that approximately 82% of patients with a rise in PSA while on bicalutamide monotherapy can have a reduction in their PSA with secondary androgen deprivation (medical or surgical castration). The duration of that secondary response appears durable.

This gentleman seems to be handling his relapse well, psychologically. He does not appear to be focused on death. Some patients ask about their life expectancy every time they see me. But he does not, and he seems to be living his life in a healthy, productive way with his disease.

Tolerability of bicalutamide and LHRH agonists

My overall impression is that muscle strength is better on bicalutamide 150 mg than an LHRH agonist, and anemia may not be as much of a problem. Most patients on an LHRH agonist have a reduction in their hematocrit to about 36% to 39%.

Generally, there is not much of a physiologic effect from the reduction in hematocrit, but it may be a problem for patients with concomitant conditions. In patients with anemia of chronic disease, the addition of an LHRH agonist may take a hematocrit of 36% or 37% down to 32%. I think then it does become a practical issue.

Genetic counseling for men with prostate cancer

During the initial visit, I take a family history to determine who in the family has cancer and what types of cancer they have, paying specific attention to prostate cancer. I find out how many sons these men have and their sons' ages. I strongly recommend screening, starting at the age of 40, for the sons of men with prostate cancer. I emphasize that screening requires both a blood test and a digital rectal exam.

In families with multiple generations of prostate cancer victims (i.e., grandfather, father and son), we certainly stress screening as strongly as possible. The more relatives in the family with prostate cancer, the higher the risk. The brothers and fathers of men with prostate cancer should also be screened.

The impact of personal experience with illness on clinical practice

I do not usually share this information with my patients, but six years ago my husband was diagnosed with a low-grade brain tumor. I have firsthand experience with how illness and difficult decisions about surgery, radiation and medicine affect people, relationships and outlook on life. Although I have been a practicing oncologist for 10 or 12 years, I felt ill equipped to handle these burdens. Through a variety of different avenues I have learned to deal with these issues, and it has improved my skills as a clinical oncologist incredibly.

I am willing to take more time to listen to patients. Before, I made assumptions about who they were and what they needed. Now, I hear and empathize with them better. I also have a much better perception that the patient and his family often view this disease and its treatments very differently. It is a cliché, but prostate cancer affects an entire network of lives. Nobody teaches you these things in fellowship or residency. The focus is always on the patient, the surgery and the medicine.

Until you have confronted these burdens personally, it is easy for a doctor to say, “You should do this” or “You should do that." However, once you have lived with compromise, you realize that there is no right or wrong. It was amazing to me that we went to four different major medical centers and received four different recommendations. It is difficult for patients to figure that out.

Instead of telling patients what they should do, it is incredibly important to provide information by telling them, "This is what we know, and this is what we do not know. I can’t tell you what to do, but you need to decide what makes the most sense to you." Patients do not want to hear that there is not a correct answer. They want decisions to be black and white, yes or no. Unfortunately, the issues are too complex for that to be a realistic option.

Select publications

Fabozzi SJ et al. **PSA response to secondary androgen deprivation following failed treatment of metastatic prostate cancer with the antiandrogen Casodex.** *Urol Oncol* 1995;1:64-6. Abstract

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Valeri A et al. **Targeted screening for prostate cancer in high-risk families: Early onset is a significant risk factor for disease in first-degree relatives.** *J Urol* 2002;168(2):483-7. Abstract

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
bicalutamide	Casodex®	AstraZeneca Pharmaceuticals, LP
docetaxel	Taxotere®	Aventis Pharmaceuticals
finasteride	Proscar®	Merck & Co., Inc.
mitoxantrone	Novantrone®	Immunex Corporation
prednisone	—	Various
tamoxifen	Nolvadex®	AstraZeneca Pharmaceuticals, LP

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

1. **Which of the following would be a considered reason to recommend prostatectomy for prostate cancer patients in their 40s and 50s?**
   a. There is longer follow-up data for patients treated with radical prostatectomy.
   b. There is a theoretical risk of the local failure rate being higher with radiation therapy.
   c. The pathology report can provide significant prognostic information.
   d. All of the above.

2. **Patients with Gleason 7 prostate cancer are excellent candidates for brachytherapy as a single modality.**
   a. True
   b. False

3. **During which time period after a radioactive seed implant is a PSA bounce most likely to occur?**
   a. 1 – 3 months b. 1.5 – 2 years c. 3 – 4 years d. 5 – 10 years

4. **It has been demonstrated that the biochemical failure rate for external beam radiation therapy and prostatectomy are comparable at ten years.**
   a. True b. False

5. **The nomograms developed and published by Michael Kattan from Memorial Sloan-Kettering can predict the likelihood of biochemical failure after:**
   a. Prostatectomy b. Radiation therapy c. Brachytherapy d. All of the above

6. **Which of the following statements is false about prostatic intraepithelial neoplasia (PIN)?**
   a. It is a precancerous condition with a 10% to 30% chance of becoming prostate cancer.
   b. Low-grade PIN has the same prognostic significance as high-grade PIN.
   c. A sextant biopsy is inadequate.
   d. The standard recommendation when high-grade PIN is detected is to rebiopsy the prostate to assure a cancer was not overlooked because of sampling error.

7. **Which of the following in a large randomized trial are being evaluated for their ability to prevent cancer in SELECT?**
   a. Vitamin E b. Selenium c. Saw palmetto d. a and b e. a and c

8. **Prostate cancer screening should be encouraged for which of the following family members of a patient with prostate cancer?**
   a. Sons b. Brothers c. Fathers d. All of the above

9. **A recent report suggests that patients with Gleason 9 and 10 prostate cancer do well when treated with cryotherapy.**
   a. True b. False

10. When comparing the side effects of bicalutamide monotherapy and an LHRH agonist, which of the following statements is false?

a. Bicalutamide monotherapy is associated with gynecomastia.

b. Bicalutamide monotherapy is associated with breast tenderness.

c. Patients treated with an LHRH agonist are usually able to maintain erectile function.

d. Patients treated with an LHRH agonist experience a loss of libido.

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

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Conversations with Urologic Oncology Leaders

Bridging the Gap between Research and Patient Care

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Please answer the following questions by circling the appropriate rating:

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

Extent to which program activities met the identified objectives

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

- Distinguish patients with prostate cancer for whom radiation plus hormonal therapy is appropriate 5 4 3 2 1
- Evaluate issues regarding the timing and selection of hormonal therapy for prostate cancer patients who have undergone definitive local therapy 5 4 3 2 1
- Differentiate the risks and benefits of hormonal therapies including antiandrogen therapy and medical or surgical castration 5 4 3 2 1
- Identify patient perspectives in therapy decision-making in order to more effectively counsel patients about the risks and benefits of various therapy choices available to them 5 4 3 2 1
- Understand the impact of biochemical failure on patients in order to assist them in making decisions about available therapeutic options 5 4 3 2 1
- Understand the clinical utility of using postoperative nomograms in order to counsel patients about the potential value of adjuvant therapy 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.

_____

_____

Degree:

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

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