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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 2, 2003 of Prostate Cancer Update consists of discussions with three research leaders on a variety of important issues, including timing and duration of total androgen blockade, PSA relapse, brachytherapy and several interesting case discussions.

Specific Learning Objectives for Issue 2

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

- Counsel patients about timing and duration of endocrine therapy based on currently available data.
- Describe the relative risks and benefits of total androgen blockade in the adjuvant and advanced disease setting.
- Describe and implement a treatment algorithm for patients with elevated PSA after radical prostatectomy.
- Counsel patients about the risks and benefits of brachytherapy versus external beam radiation.

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 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.

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Grants/Research Support/Speakers' Bureau: AstraZeneca Pharmaceuticals LP, TAP Pharmaceutical Products, Inc.
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Grants/Research Support: AstraZeneca Pharmaceuticals LP, Roche Laboratories, Inc., Genentech, Inc., Amgen, Inc., Cytyc Health Corporation, Sanofi-Synthelabo. Inc.

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Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information and comparison with recommendations of other authorities.

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
docetaxel	Taxotere®	Aventis Pharmaceuticals
estramustine phosphate	Emcyt®	Pharmacia Corporation, Inc.
goserelin	Zoladex®	AstraZeneca Pharmaceuticals LP
mitoxantrone	Novatrone®	Immunex Corporation
prednisone	—	Various

Editor's Note

A Day at the Clinic

Mark Soloway's annual "Challenging Cases in Urology" meeting held each year in Miami has truly set a new standard for education in the field over the last 13 years. His innovative use of interactive case discussions yields a vivid portrait of practice patterns. To give our listeners who were unable to attend the conference a glimpse into the some of the highlights, I asked Dr Soloway to bring to our interview session some of the more controversial cases he has discussed over the years.

However, he surprised me by pulling from his pocket a list of patients he had seen the day before. I appreciated the subtle point he was making — every patient with prostate cancer poses unique challenges. Not surprisingly, the cases Dr Soloway selected to discuss on the program are very provocative. If you have any comments or wish to tell him what you would have recommended to these men, please email me at NLove@med.miami.edu. We will select some of your responses to discuss when we follow-up the cases later this year.

— Neil Love, MD

Cases presented by Dr Soloway on the enclosed program

➔ **Case #1, Age 60.** Prior history of testicular cancer in 1977 treated with a right orchiectomy and retroperitoneal node dissection. In 1982, the patient was treated with a left orchiectomy and chemotherapy for a second testicular cancer. He currently receives testosterone replacement. Patient has a PSA of 5 ng/mL and Gleason 6 prostate cancer.

Key question: *Should a radical prostatectomy be performed in a patient with a prior retroperitoneal node dissection? Should the testosterone replacement be continued?*

Select publications

Colao A et al. **Effect of growth hormone (GH) and/or testosterone replacement on the prostate in GH-deficient adult patients.** *J Clin Endocrinol Metab* 2003;88(1):88-94. **Abstract**

Gerstenbluth RE et al. **Prostate-specific antigen changes in hypogonadal men treated with testosterone replacement.** *J Androl* 2002;23(6):922-6. **Abstract**

Guay AT et al. **Testosterone treatment in hypogonadal men: Prostate-specific antigen level and**

➔ **Case #2, Age 67.** 1993: radical prostatectomy, Gleason 4+3. Five years later: rising PSA, treated with and radiation therapy and androgen deprivation for 2 years. Currently: undetectable PSA.

Key question: *Is the patient cured?*

Select publications

Graefen M et al. **Validation study of the accuracy of a postoperative nomogram for recurrence after radical prostatectomy for localized prostate cancer.** *J Clin Oncol* 2002;20(4):951-6. **Abstract**

Palisaan RJ et al. **Assessment of clinical and pathologic characteristics predisposing to disease recurrence following radical prostatectomy in men with pathologically organ-confined prostate cancer.** *Eur Urol* 2002;41(2):155-61. **Abstract**

➔ **Case #3, Age 48.** PSA: 3.2 ng/mL, Gleason 3+3 in one of six biopsies. T1c. Other history: being treated successfully for HIV for several years.

Key question: *What is optimal primary therapy in view of the patient's HIV status?*

Select publications

Crum NF et al. **Increased risk of prostate cancer in HIV infection?** *AIDS* 2002;16(12):1703-1704. **No Abstract**

Guth AA. **Breast cancer and HIV: What do we know?** *Am Surg* 1999;65:209-211. **No Abstract**

Schwartz JD, Prince D. **Prostate cancer in HIV infection.** *AIDS* 1996;10:797-798. **No Abstract**

Smith C et al. **AIDS-related malignancies.** *Ann Med* 1998;30:323-344. **Abstract**

➔ **Case #4, Age 54.** 18 months s/p radical prostatectomy, Gleason 4+3, positive margin near the apex of the prostate. Currently: PSA fluctuating between 0.1 and 0.2 ng/mL.

Key question: *Has this man relapsed?*

Select publications

Grossfeld GD et al. **Predicting recurrence after radical prostatectomy for patients with high risk prostate cancer.** *J Urol* 2003;169(1):157-63. **Abstract**

Han M et al. **Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer.** *J Urol* 2003;169(2):517-23. **Abstract**

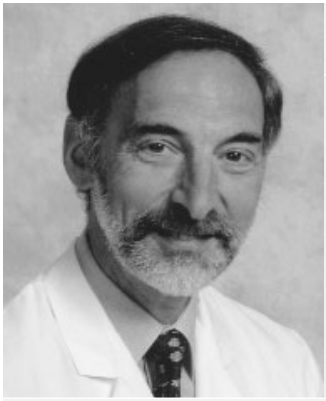
➔ **Case #5, Age 70.** 1997: T3 prostate cancer, Gleason 7, PSA 25 ng/mL. Treated with androgen deprivation (1 year) and external beam radiation therapy. 18 months ago: PSA progression. Patient lives in Ireland and was started on bicalutamide 150 mg daily. PSA has decreased from 8 to 0.8 ng/mL. Patient has moderate gynecomastia, no breast pain, no hot flashes and good sexual function.

Key question: *What therapy would this man have received in the United States?*

Select publications

Iversen P et al. **A randomised comparison of bicalutamide ('Casodex') 150 mg versus placebo as immediate therapy either alone or as adjuvant to standard care for early non-metastatic prostate cancer. First report from the Scandinavian Prostatic Cancer Group Study No. 6.** *Eur Urol* 2002;42(3):204-11. **Abstract**

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**



Mark S Soloway, MD

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Edited comments by Dr Soloway

CASE 1:
A 60-year-old man with Gleason 6 prostate cancer treated with long-term testosterone replacement after testicular cancer

HISTORY

This patient was in excellent health and presented with a PSA of 5 ng/mL. He had two positive biopsies, which revealed Gleason 6 prostate cancer. Interestingly, 25 years earlier, he had testicular cancer and was treated with an inguinal orchiectomy followed by a retroperitoneal lymph node resection. Five years later, he developed a second testicular tumor and had an orchiectomy followed by chemotherapy. He was cured of testicular cancer and has been taking intramuscular testosterone since that time.

His consulting surgeon was concerned that the retroperitoneal lymph node surgery may have caused adhesions that would make surgery too difficult. I don't believe his history would contraindicate surgery, so we're planning to perform a nerve-sparing radical prostatectomy.

DISCUSSION

The patient temporarily stopped taking testosterone upon diagnosis. But presuming he's receiving physiologic replacement, continuing it would be no different than in the average patient who has prostate cancer. If we find that his tumor is confined to the prostate and his PSA becomes zero postoperatively and remains zero, we will assume the tumor has been completely removed. We will then monitor the patient's PSA and re-institute the testosterone, which is important for his quality of life.

I realize the standard in breast cancer is to stop hormone replacement therapy when a woman is diagnosed. However, in the typical prostate cancer patient, we do not deplete testosterone after prostatectomy. In prostate cancer, I have a large database

CASE 1 *(Continued)*

to tell me that if the tumor was confined to the prostate — negative margins, no capsular penetrations, seminal vesicles and lymph nodes are negative — the patient has greater than a 90 percent chance that he's going to remain free of cancer.

It's a fascinating case and I'd be interested to learn what other physicians think about the issue of testosterone replacement after prostatectomy.

CASE 2: An apparently healthy 48-year-old man with HIV and a Gleason 6, T1c prostate cancer

HISTORY

This patient presented with a PSA of 3.2 ng/mL. One of the six ultrasound-guided biopsies was positive for a Gleason 6, 3+3, adenocarcinoma of the prostate. The clinical exam was totally normal. He has been HIV-positive for several years and takes a variety of medications, but he has no clinical sequelae of the disease. He had seen a radiation oncologist and two urologists before seeing me.

The radiation oncologist suggested that, given his age, his best chance for cure would be a radical prostatectomy. The message he got from the urologists was that they would not perform a nerve-sparing procedure on him, and I don't know the reason for that. He prefers surgery, and I recommended a nerve-sparing prostatectomy.

DISCUSSION

I believe radiation oncologists are divided on efficacy of radiation therapy versus surgery in young men. Some feel that beyond 10 years, the data favor radical prostatectomy. In addition, there is the controversial issue of second cancers. I have seen a number of men treated for prostate cancer with external beam radiation who, 7 to 12 years later, developed aggressive, muscle-invasive bladder cancer, which is within the radiation field. It may not be a factor to consider for someone over 70 years of age, but for a 50-year-old patient, I think it needs to be discussed.

The urologists this patient consulted were not prepared to perform a nerve-sparing procedure on him. I don't know whether that's because they didn't feel technically capable of doing the procedure, or whether they wanted to dissuade him from surgery because he was HIV-positive. They may have been concerned for themselves and/or the operating room team, or they may have genuinely felt the survival advantage would not be sufficient to put him through the procedure.

We must always consider whether a patient has a life expectancy sufficient to warrant a major operation. We know there are other treatments for prostate cancer that will allow someone to live 10 years — watchful waiting, initial androgen deprivation, delayed androgen deprivation and various forms of radiation therapy.

CASE 2 *(Continued)*

But for a patient of this age, the data would suggest that removing the prostate gives him the best chance that he will be free of cancer in 15 years. It's arguable, but that would be my philosophy based on the literature.

CASE 3:
A man with Gleason 7 prostate cancer and a rising PSA one and one-half years after treatment with androgen deprivation and external beam radiation

HISTORY

This 70-year-old man had a clinical T3 prostate cancer with a Gleason score of 7 and an initial PSA of 25 ng/mL. He received androgen deprivation and external beam radiation therapy with continued androgen deprivation for approximately one year. Three years later, his PSA began to rise and it was clear that this represented a recurrence.

I discussed different treatment options with the patient, including LHRH analogue, bilateral scrotal orchiectomy and bicalutamide 150 mg per day. Of interest, he lives most of the time in Northern Ireland where bicalutamide is approved for this indication. He was familiar with it because some of his friends are being treated with bicalutamide 150 mg.

FOLLOW-UP

The patient has taken bicalutamide 150 mg for a year and his PSA is 0.8 ng/mL, whereas previously it was approximately 8 ng/mL. He feels quite well, continues to have sexual activity and the only side effect he's experienced is gynecomastia, but it is not disfiguring or incapacitating.

DISCUSSION

The breast enlargement is noticeable, but he's not experiencing any breast pain or other side effects. Radiation therapy to prevent the gynecomastia is a possibility for someone we know is going to be on therapy for a period of time. There are not sufficient trials to know how successful it is, but if it is similar to when we used estrogens many years ago, it probably would be beneficial. My feeling is that he has fewer side effects than he would on an LHRH agonist — he doesn't have any hot flushes and his cognitive and sexual functions are excellent. Interestingly, if he were living here he would not be getting bicalutamide 150 mg because it's not available in the United States.

Trials comparing early versus late hormone therapy

Several important trials have addressed the question of when to initiate androgen deprivation in the treatment of advanced prostate cancer. The Medical Research Council (MRC) study compared early versus late hormone therapy in patients

with locally advanced or asymptomatic metastatic prostate cancer. The study was not perfect. Whereas we follow patients every three to four months, the study looked at patients only once a year.

Many patients experienced morbid events before they were started on hormone therapy, and some even died without ever receiving therapy. In addition, the "nonmetastatic" group included men with very high PSAs who almost certainly had metastases. The results showed that patients treated at diagnosis experienced fewer morbid events and survived longer than patients randomized to receive androgen deprivation therapy on progression.

Ed Messing and the Eastern Cooperative Oncology Group conducted a prospective randomized study of true adjuvant hormonal therapy. Although a limited study — only 100 patients — the results indicated that node-positive patients who had radical prostatectomy followed by immediate hormonal therapy had a lower mortality when compared to patients who did not receive hormonal therapy until progression.

The Bolla, or European Radiation Therapy, trial was the largest study to look at early versus later androgen deprivation therapy with sufficient follow-up. Patients were high risk with clinically localized prostate cancer, but it's likely many had metastases. They were randomized to receive either radiation therapy alone or radiation therapy followed by three years of androgen deprivation. There was a progression-free and an overall survival advantage for those who received the androgen deprivation therapy.

Oncologic principles supporting immediate versus delayed hormonal therapy

"Those who advocate limiting the use of ADT until advanced disease is seen believe that delayed therapy avoids long-term side effects, reduces cost and utilizes therapy when it is 'most needed.' We will defend the hypothesis that this approach is inappropriately nihilistic and ignores favorable preclinical and clinical evidence indicating that 'early' ADT is beneficial. Among the oncologic principles to consider is the clear demonstration that systemic treatment adjunctive to local therapy may improve survival. This is clearly the case in breast cancer where adjuvant hormonal therapy cures more patients as well as [in] colorectal, gastric cancer and melanoma where therapies with quite limited activity in advanced disease extend survival when used adjunctively."

SOURCE: Ahmed S, Trump DL. **The case for early androgen deprivation: The data should not be ignored.** *Urol Onc* 2002;7:77-80.

Mortality rates in landmark trials comparing immediate (diagnosis) versus deferred (progression) hormone treatment for advanced prostate cancer

Study (Median follow-up)	Patient Population	Protocol	Deaths from Prostate Cancer	
			With early hormonal therapy	Control
Medical Research Council Trial (Not reported)	Locally advanced or asymptomatic metastatic disease	Orchiectomy or LHRH analogue at progression vs at diagnosis	All patients: 203/469 (43%) M0 patients: 81/469 (17%)	All patients: 257/465 (55%) M0 patients: 119/465 (26%)
Bolla et al. (5.5 years)	T3-4, NO-2, MO	Radiotherapy at diagnosis vs radiotherapy plus goserelin	12/207 (6%)	42/408 (10%)
Granfors et al. (9.3 years)	T1-4, pNO-3, MO	Radiotherapy at diagnosis vs radiotherapy plus orchiectomy	12/45 (27%)	20/46 (44%)
Messing et al. (7.1 years)	≤ T2, positive nodes, MO	Orchiectomy or goserelin at progression vs at diagnosis	3/47 (6%)	16/51 (31%)

DERIVED FROM:

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;360:103-08.

Granfors T et al: **Combined orchiectomy and external radiotherapy versus radiotherapy alone for non-metastatic prostate cancer with or without pelvic lymph node involvement: A prospective randomized study.** *J Urol* 1998;159(6):2030-4. **Abstract**

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

Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: Initial results of the Medical Research Council Trial. *Br J Urol* 1997;79(2):235-46. **Abstract**

Early Prostate Cancer Trials: Adjuvant therapy with bicalutamide 150 mg

The best study to date addressing adjuvant hormone therapy is the Early Prostate Cancer (EPC) Trials program, which compares adjuvant bicalutamide 150 mg to placebo. I have no doubt that adjuvant bicalutamide will delay the time to PSA rise. Castration would have the same effect, but the side-effect profile is clearly in favor of bicalutamide, particularly in an otherwise healthy man. Adjuvant LHRH analogues or orchiectomy may not be appropriate or tolerable for many of our patients.

We simply have to wait for more events in the EPC trial to know with certainty whether bicalutamide will favorably impact time-to-progression and survival. Whether the relatively early data from the EPC should be presented to all men at this time is an important issue.

The timing of androgen deprivation after local treatment

The role and timing of androgen deprivation is a critical issue that urologists encounter on a regular basis. Unfortunately the available data are not

absolutely conclusive due to confounding factors. Few patients who had radiation therapy initially are candidates for a salvage radical prostatectomy, so hormonal therapy would be considered for approximately 95 percent of them. Based on their age, initial pathology and the time it took PSA to rise, patients who undergo radical prostatectomy as primary therapy might be candidates for adjuvant treatment or radiation therapy to the pelvis as salvage therapy. If local salvage treatment is not the primary option, the patient will be treated with hormonal therapy, but the question is when to initiate therapy.

Post-prostatectomy, a PSA rising above 0.4 ng/mL indicates the presence of prostate cancer, but we don't know if it would be better to wait until the PSA level is 3.0 ng/mL or 5.0 ng/mL. There won't be any clinical evidence of disease and you might spare the patient a year of side effects from androgen-deprivation therapy. Following radiation therapy, a PSA above 1.0 ng/mL would lead to a similar conclusion.

A patient-physician dialogue

In my editorial, *Timing of androgen deprivation for prostate cancer: Benefits versus side effects — A patient-physician dialogue*, I used the phrase "patient-physician dialogue" because I think it needs to be just that. Clinicians have a variety of issues they need to discuss with patients. One example is the implications of a slowly rising PSA. Some patients may not see that as a significant problem, while others will be upset that their cancer is not being treated. If it's going to adversely impact that patient 24 hours a day, then there may be a major benefit to treating the patient. But there are quality-of-life implications to treatment as well — some are minor, but some can be problematic such as hot flushes or diminished libido. It's important to discuss these issues with patients and ensure they understand the advantages and disadvantages of hormonal therapy, if it is presented as an option.

My own bias is not to initiate androgen deprivation as adjuvant therapy in high-risk patients because I like to be evidence-based in my practice. For the patient with a 50 percent chance of relapsing over the next two or three years, the available information suggests adjuvant hormonal therapy will delay clinical progression of their disease, but I do not know whether it will change their survival. On the other hand, by treating very early, it may suppress the tumor sufficiently so that they will never relapse. I do not think it will promote androgen independence early, as some have suggested. Those are the unknowns, and we do not have sufficient literature to compel me to present that information to all patients.

Patient preference in the timing of androgen deprivation therapy

It was clear from the Miami Patient Town Meeting that patients have a tremendous interest in being educated about their disease and participating in decision-making. It was also evident that patients are very focused on their PSAs. If asked specifically, many would opt for hormonal therapy relatively

early and very few would be willing to wait until their cancer metastasized. What we are seeing in clinical scenarios across the country is a high percentage of patients who receive androgen-deprivation therapy for clinically metastatic disease, but not as many receiving it for biochemical relapse.

Watchful waiting as an option for local prostate cancer

Increasingly, there is more information available to support watchful waiting as an option for appropriately staged individuals, given the caveat that the staging is not perfect. Watchful waiting may be appropriate in patients with a low tumor volume, low PSA and a low Gleason score—probably less than 7. Biopsies can provide misinformation, so if an intervention would be curative, a rebiopsy should be performed.

There was a paper from Johns Hopkins that indicated in appropriate patients with low-volume disease, untreated patients rarely will not be curable if they proceed to intervention at a later time. In this study, almost all of the cases had organ-confined or specimen-confined disease when they went on to have their prostate removed. This article provides important data about the safety of watchful waiting in appropriate cases. That's an important change that I've adopted in my clinical practice.

Monitoring the watchful waiting patient

In watchful waiting, the patient needs to understand that the cancer will not go away — that's not the point of this option. And he has to understand the biology of prostate cancer — that it probably takes months to years for a cancer to be clinically detectable — and it is unlikely that within six months or one year, his cancer will go from a from a curable to a noncurable stage.

Monitoring the patient consists of a digital rectal exam, PSA and biopsies every six months. The biopsies should consist of 10-12 biopsies, which shouldn't be uncomfortable procedures if performed with a periprostatic nerve block. No one has studied when to reduce the frequency of the biopsies, but common sense tells me if the second set of biopsies has either no cancer or a very low-volume cancer and the PSA remains unchanged, then one could go to one year, maybe even longer, between biopsies. The age of the patient would also be a factor.

Select publications

Boccardo F et al. **Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer: Updated results of a multicentric trial.** *Eur Urol* 2002;42(5):481-90. **Abstract**

Bolla M et al. **Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin.** *N Engl J Med* 1997;337:295-300. **Abstract**

Byar DP, Corle DK. **Hormone therapy for prostate cancer: Results of the Veterans Administration Cooperative Urological Research Group studies.** *NCI Monogr* 1988;7:165–70. **Abstract**

Carswell CI, Figgitt DP. **Bicalutamide: In early-stage prostate cancer.** *Drugs.* 2002;62(17):2473-81. **Abstract**

Eisenberger MA, Walsh PC. **Early androgen deprivation for prostate cancer?** *N Engl J Med* 1999;341(24):1837–8. No abstract available

Granfors T et al. **Combined orchiectomy and external radiotherapy versus radiotherapy alone for nonmetastatic prostate cancer with or without pelvic lymph node involvement: A prospective randomized study.** *J Urol* 1998;159(6):2030–4. **Abstract**

Grimm MO et al. **Clinical outcome of patients with lymph node positive prostate cancer after radical prostatectomy versus androgen deprivation.** *Eur Urol* 2002;41(6):628-34; discussion 634. **Abstract**

Iversen P et al. **A randomised comparison of bicalutamide ('Casodex') 150 mg versus placebo as immediate therapy either alone or as adjuvant to standard care for early nonmetastatic prostate cancer. First report from the Scandinavian Prostatic Cancer Group Study No. 6.** *Eur Urol* 2002;42(3):204-11. **Abstract**

Iversen P. **Antiandrogen monotherapy: Indications and results.** *Urology* 2002;60(3 Suppl 1):64-71. **Abstract**

Mazeman E, Bertrand P. **Early versus delayed hormonal therapy in advanced prostate cancer.** *Eur Urol* 1996;30 Suppl 1:40-3;discussion 49. **Abstract**

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

Milbank AJ et al. **Hormonal therapy for prostate cancer: Primum non nocere.** *Urology* 2002;60(5):738-41. **Full text**

Naito S. **Androgen deprivation in combination with radical prostatectomy for localized prostate cancer.** *Int J Urol* 2001;8(7):S19-21. **Abstract**

Pilepich MV et al. **Phase III Radiation Therapy Oncology Group (RTOG) Trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate.** *Int J Radiat Oncol Biol Phys.* 2001;50(5):1243-52. **Abstract**

Pilepich MV et al. **Phase III Radiation Therapy Oncology Group (RTOG) Trial 86-10 of androgen deprivation before and during radiotherapy in locally advanced carcinoma of the prostate. Proceedings of the American Society for Clinical Oncology (ASCO) Meeting, Los Angeles, CA (abstract).** *J Clin Oncol* 1998;17(suppl):308a. **Abstract**

Pilepich MV et al. **Phase III trial of androgen suppression using goserelin in unfavorable prognosis carcinoma of the prostate treated with definitive radiotherapy: Report of Radiation Therapy Oncology Group Protocol 85-31.** *J Clin Oncol* 1997;15(3): 1013–21. **Abstract**

Prostate Cancer Working Party Investigators Group. **Immediate versus deferred treatment for advanced prostatic cancer: Initial results of the Medical Research Council Trial.** *Br J Urol* 1997;79(2):235-46. **Abstract**

Schroder FH. **Endocrine treatment of prostate cancer—recent developments and the future. Part 1: maximal androgen blockade, early vs delayed endocrine treatment and side-effects.** *BJU Int* 1999;83(2):161-70. Review. No abstract available.

Soloway MS. **Timing of androgen deprivation for prostate cancer: Benefits versus side effects — A patient-physician dialogue.** *Urology* 2002;60:735-737. No abstract available

Soloway MS et al. **Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxMo prostate cancer: 5-year results.** *J Urol* 2002;167(1):112-6. **Abstract**

Studer UE et al. **Immediate vs deferred hormonal therapy for prostate cancer patients not suitable for curative local treatment (abstract).** *J Urol* 2002;167:303. **Abstract**

Walsh PC et al. **A structured debate: Immediate versus deferred androgen suppression in prostate cancer—evidence for deferred treatment.** *J Urol* 2001;166(2): 508–16. **Abstract**

Zagars GK et al. **Addition of radiation therapy to androgen ablation improves outcome for subclinically node-positive prostate cancer.** *Urology* 2001;58(2):233–9. **Abstract**

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

Richard Stock, MD

Professor and Chairman,
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Edited comments by Dr Stock

Real-time ultrasound-guided 3-D brachytherapy

Ultrasound is a superb tool that enables visualization of the prostate. We developed a real-time approach, which now goes even further and uses a computer that interacts with the ultrasound images to give us better seed placement and dose optimization.

There is a learning curve to performing brachytherapy, and radiation oncologists have not traditionally received much ultrasound training. Although urologists use ultrasound in their offices, they're not using it with the precision that is required to do an implant. Training also involves how to put the needles in properly and how to manipulate them, but ultrasound is one of the hardest things for physicians to master.

Combined-modality trial for men with high-risk prostate cancer

In 1993, there wasn't much data about the most important prognostic features. Initially we treated patients with seed implants as long as they did not have positive nodes or cancer in the seminal vesicles on biopsy. We were not giving external beam radiation along with brachytherapy at that time, and we found that those patients with high-grade cancers or high PSAs did not do well with just the seed implants.

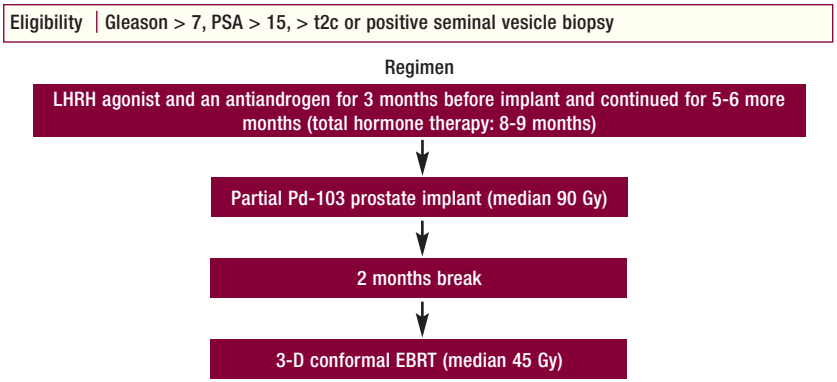
Since that was when many of the hormonal therapy trial results (RTOG trials and early Canadian trials) were coming out, we also began using hormones as both neoadjuvant and adjuvant therapy. I felt there was a group of patients who were very high risk — those with a Gleason score of 8 to 10, a PSA greater than 20 ng/mL and positive seminal vesicles.

Due to their high-risk features, those patients were more likely, as we know from the surgical series, to have extracapsular extension. Therefore, they probably would be better off receiving a combination of seed implant and external beam radiation.

That led us to design a trial in which we gave three modalities — a higher dose of external beam radiation (59 Gy), a lower dose of a seed implant and hormonal therapy. It started out as a Phase I/II trial, and we treated about 40 patients. Initially, we had superb outcomes, but we started to see increased rectal bleeding. So we began to lower our external beam radiation therapy dose.

Eventually, there were enough publications demonstrating that this was a safe way to deliver treatment. We began to give more standard doses of external beam radiation (45 Gy) and started to include more patients (i.e., those with Gleason scores of 7 or a PSA greater than 10 ng/mL). Since we were getting these outcomes in incurable patients, we decided to include more patients by expanding the inclusion criteria.

Biochemical outcomes following a multimodal regimen with radiation and hormonal therapy in high-risk, node-negative prostate cancer



Outcome: Median follow-up at 43 months following hormonal therapy demonstrated 89% overall freedom from biochemical failure

DERIVED FROM: Stock RG. **Hormonal therapy/brachytherapy & external beam radiation in HR localized prostate cancer. Presentation at Chemotherapy Foundation Symposium XX,** November 2002.

I think that the implant plus external beam gives a much higher intraprostatic dose than external beam radiation therapy alone. I'd love to take high-risk patients and compare this regimen to the best external beam radiation therapy alone, whether it is IMRT or 3-D conformal.

In more advanced disease, I think this regimen wins out because the outcomes are better. We even compared our own patients undergoing radical prostatectomies at Mount Sinai to those treated with this regimen. There were significant differences in the likelihood of being biochemically controlled — the rates were more than twice those with radical prostatectomy — because these patients are at risk of having extracapsular extension. Therefore, when the prostate is removed, cancer cells are left behind and there is a high PSA failure rate.

Adjuvant hormonal therapy

I wrote an editorial in favor of using hormonal therapy with brachytherapy for the journal *Brachytherapy*. There are certainly many who are opposed to the use of hormones, but there is overwhelming evidence that hormones are absolutely doing something.

The issue is how can you not offer hormonal therapy to high-risk patients when you treat them with an implant and external beam radiation or 3D conformal or IMRT? There may not be definitive data indicating that hormonal therapy works with IMRT or high-dose radiation, but we know that it improves outcomes with standard radiation.

Decision-making in patients with low-risk prostate cancer

For patients with low-risk prostate cancer, I let them know about the options. I tell them that with a seed implant, they are in and out of the hospital quickly, but they may have irritating symptoms. If they are the kind of person who couldn't care less, then the implant is the way to go. But if they will be bothered by a sudden strong urge to urinate, then maybe this is not the right procedure for them. Many urinary symptoms will become worse in the year following a seed implant.

In men with Gleason 6, low-risk prostate cancer, I tell them that the available data doesn't show any significant differences at this time between brachytherapy and external beam radiation. I explain what's involved with the implant, such as coming to the hospital and going home the same day. I also tell them that urinary symptoms can occur for a number of months to a year. With external beam radiation, the patient will have to come in every day, Monday through Friday, to receive treatment for eight and one-half weeks, and they may also have some urinary symptoms.

After six or seven years, 30 percent of fully potent men become impotent because of an implant and close to 40 percent to 50 percent become impotent because of external beam radiation therapy. I always tell patients there's no way to really know which treatment is better, in terms of potency, unless a randomized trial is conducted.

If having the cancer sit in their body even though it is irradiated will upset the patient, then surgery is probably a better option, as long as they understand the risks associated with radical prostatectomy. There are some patients for whom potency is not a real issue, and they may choose to have surgery.

Brachytherapy for young men with prostate cancer

There is the belief that the follow-up with brachytherapy is short. But, there is now 10-year outcome data. We have found that most patients fail within the first three to five years. After five years, if the patient has a very low PSA, the likelihood of failing is very small. For me, that is enough follow-up.

The patient's age makes no difference because there is almost no incidence of failure after 10 years. In fact, I think sexual function is much more important for the 45-year-old patient than for the older patient, and there is no question in my mind that the potency rate for radical prostatectomy is much lower than with the seed implant.

"PSA bounce" after brachytherapy

We check the PSA every six months. With brachytherapy, it can take a long time for the PSA to nadir — four or five years sometimes. Commonly, there can be a transient elevation in PSA or a "PSA bounce."

I wrote a paper for the *International Journal of Radiation Oncology* in which we found that PSA increases occur in approximately 40 percent of patients. We looked at the different definitions for "PSA bounce" that have been cited in literature — rises in PSA of 0.1 ng/mL or 0.4 ng/mL or anything greater than a 35 percent rise. Based on these definitions, there were different incidences of "PSA bounce." However, none of these different definitions predicted for failure.

When a patient's PSA rises, obviously, it could be the first step in a failure pattern, so the patient must be monitored. On the other hand, if the patient has low-risk prostate cancer and the implant was good, it is more likely to be a "PSA bounce" than a failure since 40 percent of patients have this benign bounce and in reality, only five to 10 percent will fail.

The most common time for a "PSA bounce" to occur is around 18 months. Perhaps with failure, the first elevation may be earlier. Once I've seen an elevation, I usually bring the patient back in three months. Most commonly there is only one elevation, but there can be two and, rarely, three. Then, the PSA goes back down.

Younger patients are more likely to have a "PSA bounce." So are patients with larger prostates because they probably have more prostatic epithelium. Therefore, they are more likely to have inflammation and transient rises.

Forty percent is not an insignificant number, and it is something that you must counsel patients about. The PSA does go down and, in the long term, the "PSA bounce" is not a predictor of failure. We are not sure about its mechanism, so we have to be very patient and give these men a lot of counseling.

Select publications

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Mitchell Benson, MD

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Edited comments by Dr Benson

Defining PSA failure after radical prostatectomy

The classic endpoint for radical prostatectomy has always been undetectable serum PSA following surgery. This came into question because of claims that a small subset of patients with low but detectable serum PSA following surgery may maintain this low level of PSA. The source of this PSA is debated.

The antibody for detecting PSA may cross-react with another protease in the serum — a false detection. Some claim that periurethral glands produce detectable levels of PSA. The explanation of greatest concern is that benign prostate was left behind at the time of radical surgery.

My clinical experience at Columbia University is that 98.7 percent of patients following radical prostatectomy achieve an undetectable PSA following their surgeries, and all patients not achieving undetectable PSA require additional therapy.

Total androgen ablation in patients with residual PSA

I am a very strong believer in total androgen ablation. In my practice, many patients who are on monotherapy had detectable PSA until an anti-androgen was added. This tells me that testosterone or other androgens in the serum secreted by the adrenals are not blocked by LHRH agonists. Removing the effects of those androgens causes PSA to decrease further.

Even the SWOG study of orchiectomy with or without anti-androgen therapy, which showed no difference in survival in the two groups, did show a difference in PSA response in the two groups.

The most recent meta-analysis also indicates that there's a statistically significant improvement in survival using combined androgen blockade over monotherapy. I believe anti-androgens do provide a benefit beyond blocking tumor flare.

Maximum androgen blockade in advanced prostate cancer: Conclusions from an overview of the randomised trials

"These results, which involve 98% of the worldwide randomised evidence, suggest that in advanced prostate cancer, the addition of an antiandrogen will improve the absolute 5-year survival by about 2% or 3%, with a range of uncertainty that runs from about 0% to about 5%.

One particular limitation is that most of the evidence was from patients who already had definite metastases when randomised, and some investigators have hypothesised that the benefits of MAB might be larger in other types of patients.

If, after AS in advanced prostate cancer, the addition of an antiandrogen for 2 or 3 years does produce an improvement of about 2% or 3% in overall survival, more effective hormonal regimens might produce somewhat greater absolute benefits, particularly if ways to identify the prostate cancers most likely to respond to prolonged hormonal treatment become available (as has happened with breast cancer)."

AS = androgen suppression

SOURCE: Prostate Cancer Trialists' Collaborative Group. **Maximum androgen blockade in advanced prostate cancer: An overview of the randomised trials.** *Lancet* 2000;355:1491–98. **Abstract**

Duration of androgen deprivation

Studies have shown that three to four months of androgen deprivation are inadequate, and we are awaiting data to tell us whether eight to nine months is sufficiently long.

The next data point that we have information on is from a European study looking at two years of androgen deprivation versus two years of androgen deprivation plus mitoxantrone in patients with metastatic disease or at high risk. Mitoxantrone was not efficacious in metastatic disease, but there was a statistically improved PSA failure-free survival in the group receiving combination therapy in an adjuvant setting.

Three years is the first time point showing a significant survival advantage from the Bolla paper published in the *New England Journal of Medicine*. Three years of MAB was both statistically and clinically significant in terms of long-term survival.

So three years is enough, two years might be enough, eight to nine months may be enough, but less than eight to nine months is clearly inadequate. We use two years of therapy with the hope that the preliminary mitoxantrone data will prove correct.

Five-year outcome for locally advanced prostate cancer patients treated with external beam radiation therapy and three years of adjuvant goserelin

	Combined radiation and hormonal therapy (n=207)	Radiation therapy only (n=208)
5-year overall survival	78%	62%
5-year disease-free survival	74%	40%
No. of patients with disease progression	13%	43%
Death due to prostate cancer	6%	10%
5-year rate of local control	98%	84%

DERIVED FROM: 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;360:103-08.

Adjuvant therapy for high-risk patients

Young patients who choose radical prostatectomy do so because they want to be cured. If they have an adverse pathology report or a detectable PSA after surgery, it is intellectually inconsistent to throw our hands up in the air. We have not achieved the desired result, and we cannot just stop there. That's not why they chose radical surgery. They bestow their trust upon us, and I am very aggressive in treating these patients.

In defense of those not using adjuvant therapy, those of us in academic urology have not borne our responsibility of enrolling these patients in clinical trials. However, we cannot wait for all the statistics before we start altering some of our concepts based on extrapolation from existing clinical trials.

I believe two years of androgen deprivation should be part of the standard approach in these patients. If adjuvant hormonal therapy for breast cancer can improve survival, there's no reason to conclude that it shouldn't improve survival in prostate cancer. Some argue that hormonal therapy only delays progression. But if two years of hormonal therapy can delay progression for five or six years, it's a benefit. The patient on androgen deprivation is happier than the patient who is progressing. It is a continuum.

We put many of our high-risk patients on the SWOG Intergroup study looking at adjuvant hormone therapy alone or with mitoxantrone and prednisone. This study uses two years of total androgen deprivation in both arms. Had the study been designed today, perhaps we would have chosen a docetaxel/estramustine phosphate regimen. The efficacy data for docetaxel in the metastatic setting seems stronger than the data for mitoxantrone, and there currently is a clinical trial trying to prove that.

Phase III Randomized Study of Adjuvant Androgen Deprivation Therapy with or without Mitoxantrone and Prednisone after Radical Prostatectomy in Patients with High-Risk Adenocarcinoma of the Prostate

Protocol IDs: SWOG-S9921, CLB-99904, CTSU

Eligibility	High-risk adenocarcinoma of the prostate s/p radical prostatectomy
ARM 1	goserelin sq q 12 weeks and bicalutamide po qd x 2 years
ARM 2	(goserelin sq q 12 weeks and bicalutamide po qd x 2 years) + (mitoxantrone iv on day 1 + prednisone po bid on days 1-21) q 3 weeks x 6

Patients may undergo XRT 5 days a week for 6.5-7.8 weeks beginning anytime (Arm I) or after completion of chemotherapy (Arm II), at the discretion of the physician.

Patients are followed q 6 months x 2 years and then annually for up to 13 years.

Study Lead Organizations:
Southwest Oncology Group
L. Michael Glode, MD, Protocol Chair
Ph: 303-315-4757; 1-800-473-2288

Cancer and Leukemia Group B
Nancy Ann Dawson, MD, Protocol Chair
Ph: 410-328-2565

SOURCE: NCI Physician Data Query, January 2003

Adverse pathologic findings to determine use of adjuvant therapy

Patients with Gleason 7 disease and positive margins or Gleason 8 through 10 disease or seminal vesicle involvement require adjuvant androgen deprivation. Adjuvant radiation therapy is more controversial. I'm not sure radiation therapy plays a role for the patient with negative margins, but any patient with positive margins for whom I consider adjuvant therapy will also receive radiation therapy to the bed of the prostate.

Keep in mind, however, that the Gleason scoring system does not take volume of cancer into account. It is uncommon but not impossible to have a patient with a Gleason 9 tumor with low-volume cancer. I don't treat all of those patients with adjuvant therapy. It is important to know and talk to your pathologist because not every pathologist does the same number of slices through a prostate. If a patient has truly low-volume, high-Gleason disease, depending upon the clinical circumstances, I might put them on surveillance.

Tolerability of endocrine therapy

If a patient's fear of dying is great, his tolerance for toxicity is also great. If his fear of dying is limited, his tolerance for toxicity is much more limited. Patients on two years of adjuvant androgen deprivation following radical prostatectomy at age 50 aren't happy, but patients with metastatic disease tolerate the side effects much better.

Some of the complaints in young men are obviously sexual, but God was kind when he made loss of libido go hand in hand with loss of ability. It's one thing to want something you can't have, but it's another thing not to want something you can't have. The major complaints have to do with energy changes, loss of

exercise performance and fatigue. The issue is more constitutional than sexual for many of these patients.

Patients on 150 mg bicalutamide monotherapy maintain more sexual function, so from the sexual standpoint, patients are very happy. High-dose bicalutamide may cause some gynecomastia and breast tenderness, but I haven't used a great deal of bicalutamide monotherapy in the adjuvant setting. I use total androgen blockade.

High-dose anti-androgen monotherapy

If you believe total androgen blockade is superior to monotherapy, it's hard to believe that high-dose bicalutamide will be superior to combination therapy because it's not a total blockade. But it may be enough. You may not need total blockade in the adjuvant setting.

Studies have shown that bicalutamide delays progression but the survival data are not mature. To say that this therapy is truly efficacious, we really need survival endpoints. I'm not a disbeliever in the concept of monotherapy, but there is not yet enough information to make me use it. I'd rather use two years of total blockade because I just don't know the survival benefit of bicalutamide 150 mg. Perhaps we'll be able to answer that question with longer follow-up.

Given the current data showing that bicalutamide delays progression, I believe it's very reasonable to present it as an option to a patient particularly unhappy with the side effects of androgen deprivation. But we have an obligation to say that we are not sure this will improve survival. In contrast, we know that total androgen blockade will delay progression, and there is evidence that it improves survival.

Continuous versus intermittent androgen deprivation

I believe that the gold standard for treating advanced prostate cancer remains continuous therapy. We have two open trials comparing intermittent therapy to continuous therapy. One is in the metastatic setting and one is for patients with PSA failure following radiation therapy.

Intermittent therapy only needs to be as good as — not necessarily better than — continuous therapy for it to become standard of care. Just as prostate cancer is a heterogeneous disease, patients themselves are heterogeneous. Intermittent therapy will be worse in some patients, neutral in others, and there may be some patients for whom intermittent therapy will be better. Our goal will be to identify which patients need which treatment.

ProstaScint® scans to guide therapy in patients with detectable PSA

In theory, the ProstaScint® scan is ideal. The downside is not the scan itself, but the fact that the antigen to which the antibody is made is an internal epitope. The prostate specific membrane antigen, which the antibody aims at, is a transmembrane protein. Half of the protein sticks out of the cell, and half

is inside. Unfortunately, the antibody used in this imaging study looks at the portion of the protein inside the cell. It becomes positive with cell death or cell breakdown antigen exposure. I would expect the results of imaging studies to be far superior if we aimed at the external epitope.

The ProstaScint® scan is most helpful in patients post-prostatectomy, because there is less background noise. It can be useful especially in those patients at high risk for micrometastatic disease and those with more aggressive cancers, which have faster growth rates leading to necrosis of prostate cells and exposure of the internal antigen. ProstaScint® scans may help dissect out patients with local disease versus micrometastatic disease in patients with Gleason 7 or 8 through 10 tumors following radical prostatectomy.

We've all seen false positives. But, in this country, we tend not to manage patients by statistics. If there is a one percent chance of success, we'll try it because we believe that human life is so valuable. As a result, ProstaScint® scans get utilized. They are helpful in some patients, but in many instances, this is not the sole means for making a decision — unless it's so overwhelmingly positive that we have a high reason to believe it's an accurate result.

Select publications

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Tyrrell CJ et al. **Comparison of an LH-RH analogue (Goeserelin acetate, 'Zoladex') with combined androgen blockade in advanced prostate cancer: Final survival results of an international multicentre randomized-trial. International Prostate Cancer Study Group.** *Eur Urol* 2000;37(2):205-11. **Abstract**

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

1. **The Medical Research Council (MRC) study comparing early versus late hormone therapy in patients with locally advanced or asymptomatic metastatic prostate cancer showed that patients treated early (at diagnosis) experienced fewer morbid events and survived longer than patients randomized to receive androgen deprivation therapy on progression.**
   a. True
   b. False

2. **Watchful waiting may be appropriate in patients with which of the following characteristics:**
   a. Low tumor volume
   b. Low PSA
   c. Low Gleason score
   d. All of the above

3. **According to Dr Soloway, monitoring the watchful waiting patient should consist of digital rectal exam and PSA every six months as well as:**
   a. Biopsies every six months
   b. Biopsies annually
   c. Biopsies every six months, then annually or less frequently if a second set of biopsies has either no cancer or low-volume cancer, and the PSA remains unchanged
   d. Biopsies annually, then every two years if a second set of biopsies has either no cancer or low-volume cancer, and the PSA remains unchanged

4. **In the Bolla paper published in *Lancet*, three years of endocrine therapy proved to be:**
   a. Statistically, but not clinically, significant in terms of long-term survival
   b. Statistically and clinically significant in terms of long-term survival
   c. Neither statistically nor clinically significant in terms of long-term survival

5. **According to Dr Stock, after six or seven years, 30 percent of fully potent men become impotent because of an implant and close to 40 percent to 50 percent become impotent because of external beam radiation therapy.**
   a. True
   b. False

6. **With 10 years of outcome data on brachytherapy, it has been shown that most failures occur within the first three to five years, and if the patient has a very low PSA after five years, the likelihood of failure is very small.**
   a. True
   b. False

7. **The most common time for a "PSA bounce" to occur is between:**
   a. Six months to one year
   b. One to two years
   c. Two to four years
   d. After four years

Post-test answer key:
1.a, 2.d, 3.c, 4.b, 5.a, 6.a, 7.b

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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 2

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

- Counsel patients about timing and duration of endocrine therapy based on currently available data. 5 4 3 2 1
- Describe the relative risks and benefits of total androgen blockade in the adjuvant and advanced disease setting. 5 4 3 2 1
- Describe and implement a treatment algorithm for patients with elevated PSA after radical prostatectomy. 5 4 3 2 1
- Counsel patients about the risks and benefits of brachytherapy versus external beam radiation 5 4 3 2 1

Effectiveness of the Individual Faculty Members

Speakers	Knowledge of Subject Matter	Effectiveness as an Educator
Mark S Soloway, MD	5 4 3 2 1	5 4 3 2 1
Richard Stock, MD	5 4 3 2 1	5 4 3 2 1
Mitchell Benson, MD	5 4 3 2 1	5 4 3 2 1

Overall Effectiveness of the Activity

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

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