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LAUNCH ISSUE

Prostate Cancer™ UPDATE

Conversations with Urology Leaders

Bridging the Gap between Research and Patient Care

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2 audio tapes

2 audio CDs

Print supplement

CME Certified

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 1, 2002 of Prostate Cancer Update consists of discussions with five research leaders on a variety of important issues, including nerve-sparing radical prostatectomy, brachytherapy, the use of bisphosphonates to prevent skeletal events, early versus delayed hormonal therapy, adjuvant bicalutamide and second- and third-line hormonal therapies.

Educational objectives

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

- Discuss the risks and benefits of nerve-sparing radical prostatectomy.
- Review the risks and benefits of early versus delayed hormonal therapy in men with prostate cancer.
- Summarize the study design and results from the Early Prostate Cancer (EPC) trials, which evaluated bicalutamide as immediate or adjuvant therapy in men with prostate cancer.
- Examine the emerging role of bisphosphonates in men with prostate cancer.
- Evaluate the long-term outcomes associated with brachytherapy.
- Discuss potential second- and third-line hormonal therapies for men with prostate cancer.

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 and takes responsibility for the content, quality and scientific integrity of this CME activity.

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.

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How to use this supplement

This monograph supplements the audio program and contains edited comments, clinical trial schemas, graphics and references. **Prostatecancerupdate.net** includes a full transcription of the audio program and an easy-to-use representation of each page of this booklet, allowing users to link immediately to relevant full-text articles, abstracts, trial information and other web resources indicated throughout this guide in **red underlined text**.

Editor's Note

Clinical decision-making in the absence definitive research data

> *"There are always periods of uncertainty in the evolution of science and medicine."*
>
> — Michael Baum, ChM, FRCS
> Chairman, Cancer Research Campaign Breast Cancer Trials Group

Dr Mark Soloway and I shared the same elevator for more than a decade, and on occasion, we would exchange updates on our respective fields of prostate and breast cancer. One such encounter last fall particularly piqued my interest. Mark mentioned the preliminary results from the massive Early Prostate Cancer trials that evaluated the immediate use of the antiandrogen, bicalutamide. He was curious about medical oncologists' reactions in the 1980s to similar evolving data on the adjuvant use of the antiestrogen, tamoxifen, in breast cancer.

In a series of subsequent lunch discussions, I reviewed with Mark the fascinating history of this paradigm-breaking oncologic research. My interest in adjuvant tamoxifen began as a faculty member in the division of medical oncology at the University of Miami. However, I gained a much different and unique perspective on this subject matter through a series of in-depth interviews with breast cancer research leaders that were part of a nationally distributed, continuing education audio series that I initiated in 1988. The production of Breast Cancer Update allowed me to observe firsthand both investigators and community physicians struggle in their attempt to apply what were often ambiguous trial results to daily patient care.

One of my first interviews was with Dr Michael Baum, a self-described "iconoclastic Brit," who conducted several of the original tamoxifen studies. In the early 1980s, a number of individual trials demonstrated that tamoxifen reduced the recurrence rate when given immediately after primary surgery in women without evidence of distant disease. But at that time, no survival benefit was evident for tamoxifen, and oncologists hesitated to prescribe this intervention. Baum and others argued that the delay in appearance of metastases alone was sufficient reason to use this relatively nontoxic therapy and that the lack of a survival advantage was the result of insufficient events (deaths) in the database.

In 1985, Dr Baum and Oxford statistician, Richard Peto, conducted an international meta-analysis of all the existing randomized adjuvant tamoxifen trials. Now with sufficient events (deaths) to analyze, this meta-analysis clearly demonstrated that adjuvant tamoxifen led to a significant reduction in mortality. In 2002, adjuvant tamoxifen is the standard of care for most women with invasive breast cancer. Peto — who later was knighted for this groundbreaking research — recently estimated that in the United States alone there are approximately 10,000 fewer breast cancer deaths each year, mainly as a result of the widespread use of this treatment approach.

Dr Soloway was surprised to learn that 5 years of adjuvant tamoxifen has now been demonstrated to reduce the risk of developing metastases by about 50% and has been associated with about a one-third reduction in mortality. One obvious critical question

in prostate cancer is whether immediate endocrine therapy may eventually prove to have similar benefits. Clearly, breast and prostate cancer are different diseases with some similarities, and the role of early endocrine therapy is only one of numerous prostate cancer management questions that urologists and radiation therapists struggle with every day.

Having lived through the challenges of conducting the classic randomized trials comparing lumpectomy to mastectomy, I admire and empathize with investigators launching the American College of Surgeons' SPIRIT trial that will compare radical prostatectomy to interstitial radiation therapy. To answer another key question challenging the urology and radiation oncology community, large cooperative group trials are randomizing high-risk patients to adjuvant androgen deprivation with or without chemotherapy. Certainly, breast cancer research has established that large-scale, well-designed and conducted randomized clinical trials are critical elements to cancer control. Most oncologists attribute the recent 22% reduction in breast cancer mortality to the widespread implementation of the modest but humanly important benefits that have been defined by randomized studies.

In the interim, during this "period of uncertainty," prostate cancer patients and their physicians must make decisions about both local and systemic therapy based on what are often provocative but less than definitive clinical trial results. Through our conversations, Mark and I began to see the potential benefit of launching an audio series like Breast Cancer Update that would provide urologists and radiation oncologists access to the opinions and experiences of prostate cancer research leaders. The success of our breast cancer audio series — more than 75% of oncologists are regular listeners — is based on the interest we all have in hearing research "mavens" describe new frontiers in cancer treatment and provide insights into what these strategies mean to patient care. Through Prostate Cancer Update, it is our intent to provide balanced perspectives and insights from clinical investigators at the cutting edge of this exciting field.

This inaugural issue reflects our interest in addressing not only the science but also the art of prostate cancer decision-making. Dr Paul Schellhammer — a faculty member who was invited because of his many contributions to prostate cancer clinical research and patient care — shares with us his own personal experience with the disease. Dr Schellhammer's comments reflect what we all know — that it is very challenging for a healthcare professional to understand the thoughts and feelings of a cancer patient. In future issues of this audio series, a research initiative on the perspectives of prostate cancer patients will be described. At that time, Mark and I will solicit your participation in this innovative project.

Looking back at the evolution of breast cancer clinical research, we can predict that in perhaps ten years there will be clear-cut answers to the current controversies in prostate cancer management such as the role of radical prostatectomy compared to interstitial radiation, the best time to use hormonal therapy and the role of chemotherapy. Until that time, clinicians and patients will struggle every day to arrive at optimal individualized decisions. Eventually, today's difficult choices will be replaced with a new generation of controversies in the continuous cycle that defines contemporary cancer medicine.

— Neil Love, MD

Mark Soloway, MD

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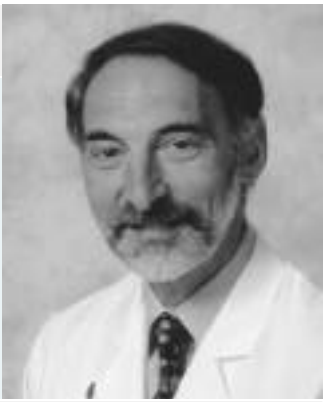

Edited comments by Dr Soloway

CHALLENGING CASE 1: 41-year-old man with a Gleason 6, T1 tumor

Clinical History

This healthy young man decided to check his PSA during a routine medical check-up while he was evaluating his cholesterol. His PSA was 15 ng/mL. DRE was negative, but biopsy revealed 3/6 positive core biopsies.
The patient elected treatment with radical prostatectomy.

Key Management Question

Should bilateral nerve-sparing surgery be performed?

Follow-up

Bilateral nerve-sparing prostatectomy was performed. Subsequently, the patient has maintained full potency and continence. Six years later, PSA is undetectable, and there is no clinical evidence of disease.

Case Discussion

Most physicians, including radiation oncologists, would recommend prostatectomy for a man of this age. Whether to perform nerve-sparing surgery is the key issue. Since cancer eradication is the most important objective, one thought would be to not compromise that goal. On the other hand, if the fascia on the prostate can be left intact and the nerves preserved, there is a very small chance of compromising that goal. Since erections are very important to quality of life and failure is most likely to be systemic as opposed to local, I performed a bilateral nerve-sparing prostatectomy.

Many urologists do not perform nerve-sparing prostatectomy for fear of compromising cancer control. In a rare patient, nerve-sparing surgery may compromise local tumor control or cure. However, if you have one or both of the neurovascular bundles totally removed, erectile function is diminished. I perform nerve-sparing prostatectomies in 70% to 80% of men with good prognostic factors (cT1c, Gleason Score $\leq$ 7 or non-palpable disease). Age, preoperative potency, time after prostatectomy, the number of nerves involved and the use of sildenafil (Viagra®) will determine a man's postoperative potency. Our study of my own series — published in the Journal of Clinical Oncology — retrospectively compared men with or without nerve-sparing procedures. The curves for PSA recurrences are superimposable in men with or without nerve-sparing procedures. There may be a small group of men who experience a local recurrence because of a nerve-sparing prostatectomy. However, I tend to agree with Dr Patrick Walsh and other research leaders that the probability is less than 10%.

CHALLENGING CASE 2: 66-year-old man with 4/9 positive nodes at prostatectomy

Clinical History

The patient had a history of ulcerative colitis that was asymptomatic. He complained of a decrease in ejaculate volume, nocturia and hesitancy. DRE revealed an asymmetric, moderately enlarged prostate (~35 grams), with the right side being firmer than the left. Biopsy revealed 8/8 positive cores, and his Gleason score was 7. CT and bone scans were negative. Radical prostatectomy revealed 4/9 positive lymph nodes on the right, bilateral seminal vesicle involvement, positive surgical margins and pathologic Gleason score of 9. Postoperatively, the PSA was undetectable.

Key Management Question

Should adjuvant endocrine therapy be implemented?

Follow-up

LHRH-agonist therapy was initiated, and the patient's PSA has remained undetectable. He is fully continent but experiences some hot flashes as well as severely diminished libido and erectile function.

Case Discussion

This gentleman is not likely to be cured with local therapy alone. In the operating room, we encountered enlarged lymph nodes containing adenocarcinoma of the prostate. Intraoperatively, the question was, "Should a prostatectomy be performed?" Some urologists would stop the procedure and give hormone therapy alone or radiation therapy in combination with hormone

therapy. In men with diploid tumors, the Mayo Clinic advocates prostatectomy. Even though we did not know this patient's ploidy, I proceeded with a radical prostatectomy in the hope of performing the operation with minimal morbidity. Perhaps, removing the prostate may minimize local problems at the time of relapse. At the time of progression, 10% to 15% of men with intact prostates will develop local problems such as bleeding or ureteral obstruction.

In light of the data from the Eastern Cooperative Group (ECOG) trial by Dr Messing, I initiated androgen deprivation with an LHRH-agonist and an antiandrogen. Since this man is not a good candidate for intermittent therapy, I have also recommended a bilateral orchiectomy.

CHALLENGING CASE 3: 57-year-old man with Gleason 9 tumor on TURP

Clinical History

This otherwise healthy patient had a 2-3 year history of prostatitis, consisting of perineal discomfort and voiding problems. Transrectal biopsy x 3 was negative. His PSA increased from 0.6 to 1.3 ng/mL in one year. TURP was performed, and Gleason 9 prostate cancer was diagnosed. Subsequent DRE revealed palpable disease. CT and bone scans were negative.

Key Clinical Question

Should neoadjuvant chemotherapy and/or endocrine therapy be utilized?

Follow-up

The patient was enrolled on a clinical trial consisting of neoadjuvant estramustine phosphate, etoposide (VP-16), paclitaxel and an LHRH-agonist for 5 months followed by a radical prostatectomy. At surgery, the margins were negative, but bilateral seminal vesicle invasion was observed. The Gleason score was 9 and nodes were negative.

The patient continues to receive an LHRH-agonist. His PSA is undetectable, and he is fully continent.

Case Discussion

Since this man was young, healthy and had a low PSA, we suggested an investigational approach that included chemotherapy and hormone therapy for several months prior to his definitive local treatment. If this man had not enrolled on a clinical trial, the choices would have included androgen deprivation followed by prostatectomy or prostatectomy alone.

CHALLENGING CASE 4: 75-year-old man in excellent health with a Gleason 6, cT2 tumor

Clinical History

A PSA that increased from 4.9 to 6.7 ng / mL in 3 years led to a biopsy that revealed a single focus of prostate cancer. DRE was asymmetrical (cT2, 65 grams), and Gleason score was 6.

Key Clinical Question

Should the patient be managed with local and / or systemic therapy?

Follow-up

The initial plan was for androgen deprivation to be later followed with external beam radiation therapy and interstitial brachytherapy.

However, after 9 months of androgen deprivation with an LHRH-agonist, the patient decided to continue on hormone therapy and not proceed with the radiation. After another 3 months on the LHRH-agonist, his PSA was 0.1 ng / mL. At that time, about 3 years ago, the LHRH-agonist was discontinued, and he remains asymptomatic with a PSA of 4.5 ng / mL.

Case Discussion

There were several good choices for this type of patient — interstitial brachytherapy, external beam radiation with or without interstitial brachytherapy, intermittent androgen deprivation and observation alone. Very few urologists would have removed his prostate. He is now 79 years old and asymptomatic, and we can say that he has had a reasonable treatment.

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Paul Schellhammer, MD, FACS

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Trustee, American Board of Urology

Edited comments by Dr Schellhammer

Editor's note:

After a distinguished career in prostate cancer clinical research, in 2000 Dr Schellhammer was diagnosed with the disease and treated with a radical prostatectomy. Now, 18 month later, his PSA is rising and he is contemplating various treatment options.

A personal perspective on prostate cancer

I attend to men with prostate cancer in situations very similar to mine, and I try to calm their emotional upheaval. It did not work in reverse. At first diagnosis, I was upset and fearful. I was afraid — not of the treatment — but of the consequences of subsequent failure such as a rising PSA, bone metastases and death.

Three of 25 biopsies were positive with a high Gleason score (7-9). My surgery went very well, and my prostate was removed without any positive margins, seminal vesicle or lymph node involvement. If the Gleason score had been one core of 3+3, then I may have considered interstitial radiation. However, with a higher grade, the best current algorithms would indicate interstitial radiation plus external beam radiation plus hormonal therapy. I did not feel comfortable with that combination.

At six weeks after surgery, I developed leg pain, fever and chills. A CT scan revealed a psoas abscess — a rare complication associated with radical prostatectomy — which was drained and treated with antibiotics.

From the Mayo Clinic series of patients with high-grade disease, I predicted a 40% to 60% chance of developing progression within 2 to 3 years. Throughout the first postoperative year, my PSA was zero. At the one-year anniversary, my PSA was minimally elevated at 0.09 ng/mL. Since then, my PSA has slowly gone up to 0.2-0.25 ng/mL. In the next couple of months, I will be receiving a short course (6-9 months) of androgen deprivation (LHRH-agonist and bicalutamide), radiation therapy and a taxane-based chemotherapy regimen.

I have never recommended chemotherapy to a patient in my situation. Now that I have thought about it, rather than recommend — because we don't have the data — I now introduce chemotherapy as a possible option. I suggest that the patient consult a medical oncologist for at least a discussion. But that's a new wrinkle in my patient interaction.

In essence, I changed my practice as a result of this experience. What made me change was the difference between actual reality and the hypothetical situation. The hypothetical situation that I was in before as a physician advising patients did not "put the rubber to the road." When you think about the issue personally — I won't say day in and day out — but every day, you learn a little bit more.

Adjuvant hormonal therapy

Nine months after my surgery, results from the bicalutamide Early Prostate Cancer (EPC) trials were announced. I asked, "If the results are true for patients starting bicalutamide within one month of surgery, what about patients who are within 6 to 9 months of surgery?"

The medical oncologists claimed that one could not make that extrapolation, and I decided not to initiate therapy. Had the results of the delay in bone-scan progression been available at the time of my surgery, I probably would have initiated bicalutamide 150 mg.

Gynecomastia was the major problem in the 100 men we enrolled on the EPC trial. Those men in whom it was bothersome had liposuction. There was no significant downside that would have precluded me from taking bicalutamide, and the delay in bone-scan progression would have been a worthwhile and significant end point.

Although the data is not yet mature, intuitively and hypothetically, adjuvant bicalutamide may also affect mortality. In women with breast cancer, adjuvant tamoxifen trials have demonstrated that survival differences may take a long time to emerge.

I am now discussing the option of adjuvant hormonal therapy with high-risk men with newly diagnosed prostate cancer similar to my own.

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Edited comments by Dr Messing

Adjuvant hormonal therapy for men with node-positive disease

Unquestionably, I advise men with positive lymph nodes at the time of their prostatectomy to strongly consider adjuvant endocrine therapy. I refer to my study and mention that it was a small study, which has been criticized. Since the trial evaluated an LHRH-agonist, I usually prescribe either leuprolide or goserelin in combination with a brief course of an antiandrogen. When potency and libido are an issue, I may consider 150 mg of bicalutamide monotherapy and breast irradiation.

If I personally had been diagnosed with node-positive prostate cancer, I would want adjuvant endocrine therapy. Before the results of my study, I would have done the exact opposite. We did everything possible to the data to attempt to disprove the survival difference in our trial, but there was no question that it was present. Surprisingly, few urologists in the community are initiating adjuvant hormonal therapy in men with node-positive prostate cancer. They usually wait until the PSA becomes detectable to start hormonal therapy. In contrast to breast or colorectal surgeons, urologists do not think of using adjuvant therapy with surgery. That may be the wrong approach.

Management of patients with positive surgical margins at prostatectomy

There are 3 potential alternatives for this type of patient: observation until the PSA becomes detectable, radiation therapy to the prostatic bed or hormonal therapy. In men with low-grade tumors, I would favor external beam radiation therapy in order to save hormonal therapy until later. For those with high-grade tumors, radiation therapy alone may not be effective since there is a possibility of systemic disease. Although no real data exist, I

would lean towards hormonal therapy for high-grade tumors. When libido or potency is not an issue, I recommend standard chemical castration with an LHRH-agonist. If the patient were potent, I would consider bicalutamide almost exclusively. I rarely use orchiectomy. Most, but not all, men will accept hormonal therapy. If I were the patient in this situation, I would probably choose an LHRH-agonist unless I thought my nerves had been preserved. Then, I would choose bicalutamide.

The Early Prostate Cancer (EPC) trials in clinical practice

In the Early Prostate Cancer (EPC) trials, immediate bicalutamide resulted in about a 40%-50% reduction in bone metastases irrespective of the primary treatment — radical prostatectomy, radiation therapy or watchful waiting. High-risk men — those with a 50% chance of failing within a few years after prostatectomy — should consider adjuvant bicalutamide. Men with high Gleason-grade tumors, positive surgical margins and a large volume of disease have an increased risk of PSA failure within 2 years. Since their course is pretty obvious, treating those men would be worthwhile.

Management of patients with postprostatectomy PSA failure

According to the radiation therapy literature, men should be treated before their postprostatectomy PSA reaches 1 ng / mL. I usually offer radiation therapy to a man whose PSA is rising at a measurable rate. Since radiation decreases the chance of regaining continence, I am more reluctant to radiate a patient who is incontinent. In the high-risk patient with node-positive or high-grade disease (Gleason grade ≥ 7), where the likelihood of systemic disease is increased, hormonal therapy may be preferred over radiation therapy.

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Edited comments by Dr See

The Early Prostate Cancer (EPC) trials

Study design

The study was designed for a pooled analysis of 3 individual trials — the North American trial (Canada and US), the Capri trial (Europe, South Africa, Central America and Australia) and the SPCG trial (Scandinavia). Objective disease progression and survival were the 2 primary endpoints. The 3 trials included men with localized or locally advanced prostate cancer that was not metastatic.

Cultural variations in the treatment of prostate cancer led to differences in the 3 trials. In Scandinavia, watchful waiting was the preferred approach. These watchful waiting patients will provide meaningful data about early hormonal therapy in men not receiving primary therapy of curative intent. In North America, watchful waiting was not routine, and those patients were excluded from the trial.

In contrast to the North American trial, the Capri and SPCG trials allowed the inclusion of men with node-positive disease. The men were randomized to immediate bicalutamide 150 mg daily or placebo. In the North American trial, the average PSA at randomization was 7 ng / mL. In contrast, the average PSA in the SPCG trial was more than double. These were very different populations in terms of extent of disease. The North American trial had the best risk population, which reflects the earlier detection of prostate cancer in this country.

THE EARLY PROSTATE CANCER (EPC) TRIALS: A COMPARISON OF THE INDIVIDUAL STUDIES

Trial	N	Location	Tumor Stage	Standard Care	Duration of Adjuvant Bicalutamide
North American	3,292	U.S.,Canada	T1b, T1c, T2,T3, pT4,N0-X,M0	RP and RT	2 years
Capri	3,603	Europe, South Africa, Israel,Mexico, Australia	T1b, T1c, T2,T3, T4, **any N**, M0	RP, RT, and **WW**	5+ years
SPCG	1,218	Scandinavia	T1b, T1c, T2,T3, T4, **any N**, M0	RP, RT, and **WW**	Until progression

RP = Radical Prostatectomy, RT = Radiation Therapy, WW = Watchful Waiting

Progression

Since the North American trial enrolled patients with the lowest risk, no demonstrable difference in the risk of objective progression has emerged for adjuvant bicalutamide. Conversely, in the SPCG and Capri trials, immediate bicalutamide significantly reduced the risk of objective progression compared to placebo. When data from the three trials were pooled, here was a benefit associated with bicalutamide in all treated patients irrespective of their primary treatment modality (radical prostatectomy, radiation therapy or watchful waiting), nodal status, extent of local disease, Gleason score or PSA level (> 4).

Although we do not yet see a difference in objective progression for the North American trial, there is a significant difference in the risk of PSA doubling. If PSA is a predictor of outcome, the curves for objective progression may eventually separate.

Survival

Approximately 5% of the patients in the trials have died. We have a long time until we reach the median survival. Therefore, we continue to follow these patients for objective progression and survival. In the future, we hope to know the impact of bicalutamide on survival.

THE EARLY PROSTATE CANCER (EPC) TRIAL RESULTS

- Immediate bicalutamide significantly reduces the risk of objective progression for all primary treatment modalities (RP, RT and WW).
- Immediate bicalutamide reduces the risk of PSA progression.
- Too early to determine the impact of immediate bicalutamide on survival – trial is ongoing.
- Predominant adverse events associated with bicalutamide are gynecomastia and breast pain.
- Bicalutamide has a minimal effect on libido and erectile function.

RP = Radical Prostatectomy, RT = Radiation Therapy, WW = Watchful Waiting

Tolerability of bicalutamide

Gynecomastia/breast pain

There appeared to be cultural differences in the tolerance of drug-related adverse events. In the North American trial, about 17% of the men on bicalutamide withdrew because of an adverse event. In contrast, only 3% of the men on bicalutamide in the SPCG trial withdrew due to an adverse event.

The predominant adverse events leading to withdrawal were gynecomastia and breast pain. Up to 70% of the men treated with bicalutamide experienced gynecomastia. Since antiandrogens block the pituitary hypothalamic perception of testosterone levels, there is an increased production of LH and increased testicular synthesis of testosterone. The liver and fat, in turn, convert the excess testosterone into estrogenic compounds. Hence, the estrogenic compounds stimulate estrogen-sensitive tissue and produce gynecomastia and breast pain.

Breast pain, which is described as sensitivity in the areolar tissue, is reversible when bicalutamide is discontinued. On the other hand, gynecomastia persists in 50% to 60% of men when therapy is discontinued. Breast irradiation may be effective in the prevention of gynecomastia. Chris Tyrrell is currently studying the efficacy of single-fraction radiation therapy for the prevention of gynecomastia. Men were generally more tolerant of breast pain than gynecomastia.

Libido

The SPCG trial evaluated sexual function with a questionnaire. Relative to placebo, bicalutamide was associated with a small reduction in sexual interest. This change in libido was less than what would be expected with an LHRH-agonist.

Bone mineral density

Unlike the LHRH-agonists, preliminary data indicate there are no changes in bone mineral density associated with the use of bicalutamide 150 mg. The circulating levels of testosterone related to bicalutamide may protect the bone.

Counseling patients about the EPC data

The proper thing is to have a discussion and let the patient fit the data into their own personalized risk-benefit ratio. I would tell a patient, “You have had a primary therapy, either prostatectomy or radiation, which carries some risk of treatment failure. In your case, the risk of failure might be X. We have new data suggesting that adjuvant bicalutamide may reduce the risk of objective progression and PSA doubling, but we do not know what this means in terms of overall survival. The majority of men on bicalutamide will develop gynecomastia and breast pain.”

In the absence of survival data, should we be talking to our patients about this? Fifteen years ago, we had a similar situation in breast cancer. Adjuvant tamoxifen, an antiestrogen, was known to reduce the risk of progression, but at that point, there was no known effect on survival. Today we know that

adjuvant tamoxifen does reduce mortality significantly. Obviously, there is some uncertainty, but we are compelled to inform men about the data and allow them to make their own decision about therapy.

Quality of life considerations in delaying PSA failure

In my clinical practice, I dread the discussion with men when their PSA rises after definitive therapy. Since patients can be devastated emotionally from this experience, there may be value to delaying a rise in PSA. There may potentially be situations where survival is not affected, yet the period of illness or disability may be decreased. The Medical Research Council (MRC) trial, for example, evaluated early versus delayed hormonal therapy in men with advanced prostate cancer. Clearly, there was a reduction in the risk of pathologic fracture and cord-compression with early hormonal therapy.

Early versus delayed hormonal therapy in men with prostate cancer

There has been much debate over the use of early versus delayed hormonal therapy in prostate cancer. Ten years ago, I was in favor of delayed hormonal therapy. During the last decade, however, evidence has suggested that earlier intervention may be associated with survival advantages. Support comes from the Messing trial, which found adjuvant androgen deprivation to significantly improve survival in men with node-positive prostate cancer undergoing radical prostatectomy. The Bolla trial, in men with clinically advanced prostate cancer undergoing radiation therapy, demonstrated that 3 years of adjuvant hormonal therapy not only reduced the risk of progression but also improved survival. These data are prompting a reassessment of our historic stance on the timing of androgen deprivation. Personally, I have shifted towards earlier, rather than delayed, hormonal therapy with the recognition that the optimal timing is unknown.

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Prostate Cancer Journal Club

Pamidronate prevents bone loss associated with androgen deprivation therapy

Smith MR et al. *N Eng J Med* 2001;345:948-55.

In this trial, men with nonmetastatic prostate cancer were randomized to leuprolide plus pamidronate (every 3 months) or leuprolide alone. All of the patients also received bicalutamide for the first 4 weeks. In the men treated with leuprolide alone, there was a significant decrease in bone mineral density. On the other hand, the men treated with leuprolide plus pamidronate did not have a significant loss in bone mineral density relative to their baseline.

Although men who are treated with androgen deprivation therapy have decreased bone mineral density, it is not known whether they will be at risk for fractures. The emerging data suggests that we could potentially prevent significant fractures if we avoid a decrease in bone mineral density. This is an important study supporting the early use of bisphosphonates in men on androgen deprivation therapy for prostate cancer. In my practice, I am moving in the direction of supporting the use of bisphosphonates in all men on androgen deprivation therapy.

Zoledronic acid prevents skeletal-related adverse events in men with metastatic hormone refractory prostate cancer

Saad F et al. *American Urological Association Meeting*; June 2, 2001.

In a large, multi-institutional, double-blind trial — presented only in abstract form — men with hormone refractory prostate cancer that had metastasized

to the bone were randomized to zoledronic acid — a more potent bisphosphonate than pamidronate — or placebo. Skeletal-related events, such as pathological fractures, occurred less frequently in the men treated with zoledronic acid. These results were the basis for the recent FDA approval of zoledronic acid for the prevention of skeletal-related events in men with bone metastases from prostate cancer. Another ongoing, randomized, placebo-controlled trial will evaluate the efficacy of zoledronic acid in preventing bone metastases in men with PSA-only hormone refractory prostate cancer. I believe that we should be initiating bisphosphonate therapy in men with known bone metastases.

Ten-year follow-up of low-risk prostate cancer treated with brachytherapy

Grimm PD et al. *Int J Radiation Oncology Biol Phys* 2001;51:31-40.

The paucity of data on the long-term outcomes associated with brachytherapy relative to other treatment modalities is frequently discussed. Finally, the report by Grimm et al provides long-term follow-up demonstrating that brachytherapy is an effective treatment for men with low-risk prostate cancer (PSA <10, Gleason Sum = 2-6, T1-T2b). Of the 125 consecutively treated men, 87% had no evidence of disease and only 12% had biochemical failure at 10 years. This is an important paper to consider when counseling men about the local treatment options and their outcomes.

RTOG 8531: Long-term adjuvant androgen deprivation following radiation therapy improves survival in men with Gleason 8-10 prostate cancer

Lawton CAet al. *Int J Radiation Oncology Biol Phys* 2001;49:937-46.

RTOG 8531 randomized nearly 1,000 men to radiation therapy alone or radiation therapy plus long-term adjuvant androgen deprivation with goserelin. Although long-term adjuvant goserelin delayed time to progression, time to PSA progression and the development of metastases, there was no improvement in overall survival. In the update to the trial by Lawton et al, adjuvant goserelin improved the survival of men with Gleason scores of 8 to 10. In counseling men with high-risk disease, the improved survival associated with the addition of adjuvant androgen deprivation to radiation therapy should be discussed.

Bicalutamide as immediate therapy in prostate cancer reduces the risk of disease progression

Wirth M et al. *Urology* 2001;58:146-51.

Wirth et al reported results from one of the Early Prostate Cancer (EPC) trials — an international, multicenter, randomized, placebo-controlled study that evaluated bicalutamide 150 mg as immediate therapy in men with localized or locally advanced prostate cancer. This is the first large trial to investigate

whether adjuvant hormonal therapy improves the outcomes of men with prostate cancer. Men receiving bicalutamide had a delay in the time to PSA doubling and a significant reduction in the risk of objective progression. The trial is still immature and there have not been enough deaths to analyze survival.

If one considers a delay in time to progression an important endpoint, then this study supports early hormonal therapy. If one is only concerned about survival, this study suggests that we need to stay tuned because more information will follow. I hope the delay in time to progression will lead to an improvement in survival, but I will need to stay tuned as well.

To decide whether a delay in time to progression is worthwhile, individual men should be informed of these results and the potential toxicities associated with bicalutamide. The majority of men treated with bicalutamide experienced gynecomastia and breast tenderness or pain. Some patients may decide that these potential side effects are tolerable in order to delay progression and the onset of metastases.

Other comments

Management of patients with a rising PSA

In men with a PSA elevation postprostatectomy or postradiation therapy, there are no clinical trials demonstrating that early hormonal therapy will improve survival. But the Medical Research Council (MRC), Bolla and Messing trials — none of which included men with PSA elevations postprostatecomy / radiation therapy — all demonstrated that early hormonal therapy was better in terms of survival. In the MRC trial, early hormonal therapy improved overall and prostate cancer-free survival for men with asymptomatic locally advanced prostate cancer. Additionally, early hormonal therapy reduced the development of spinal cord compressions and fractures. In the Bolla trial, adjuvant hormonal therapy improved survival in men with localized prostate cancer who were treated with radiation therapy. In the Messing trial, adjuvant hormonal therapy improved survival in men undergoing prostatectomy for node-positive prostate cancer.

Many men watch their PSAs very closely, and they panic when it is elevated. For those men, preventing a PSA elevation would positively impact their quality of life. An Intergroup trial is being designed to compare hormonal therapy with or without chemotherapy in men with a rising PSA. Presently, the standard of care for a rising PSA is hormonal therapy.

CHALLENGING CASE 5: 58-year-old man with Gleason 9 prostate cancer

Clinical History

This man had high-risk disease, with bilateral involvement of the prostate. DRE revealed an enlarged prostate with a nodular left lobe. PSA was 11 ng / mL. Biopsy resulted in 2 / 3 and 3 / 3 positive cores on the right and

left sides, respectively, with a Gleason score of 9. CT and bone scans were negative.

Key Management Question

What is the optimal systemic therapy for this patient: chemotherapy and/or hormonal therapy?

Follow-up

The patient was enrolled on a pilot trial evaluating external beam radiation therapy plus brachytherapy followed by adjuvant chemotherapy (weekly docetaxel) and 2 years of hormonal therapy (LHRH-agonist).

After 1.5 years, his PSA is undetectable. He is feeling well and working full time. He has resolving urinary frequency related to the brachytherapy and impotence due to the hormonal therapy, which is being treated with sildenafil.

Case Discussion

This man had high-risk disease, with bilateral involvement of the prostate. Since capsular penetration was likely, I did not recommend prostatectomy. If he had elected prostatectomy, I would have encouraged him to enroll in the Intergroup trial which randomizes men to 2 years of adjuvant hormonal therapy (goserelin/bicalutamide) plus or minus 6 cycles of chemotherapy (mitoxantrone/prednisone). Both groups are randomized to receive 2 years of hormonal therapy. The Intergroup trial will evaluate the benefit of adding chemotherapy to hormonal therapy in the adjuvant setting. This patient was also given the option of enrolling in a University of Maryland pilot trial to evaluate external beam radiation therapy and brachytherapy followed by adjuvant chemotherapy (weekly docetaxel) and 2 years of hormonal therapy (LHRH-agonist). Since the Bolla trial demonstrated that the addition of hormonal therapy to radiation therapy improved survival, the nonprotocol option for this man would have been radiation therapy in combination with hormonal therapy.

CHALLENGING CASE 6: 80-year-old man with multiple responses to hormonal therapy

Clinical History

When the patient was 70 years old, DRE revealed a hard nodule on the right lobe of his prostate (cT3). His PSA was 30 ng/mL, and his Gleason score was 7. CT and bone scans were negative. He was treated with external beam radiation therapy. Two years later, he began a succession of endocrine therapies for PSA elevation (goserelin, orchiectomy, bicalutamide and ketoconazole/hydrocortisone), all of which resulted in PSA responses. Currently, he has progressive PSA elevation while receiving ketoconazole/hydrocortisone.

Date	PSA (ng/mL)	Therapy
2/91	30.0	external beam radiation therapy
9/91	11.8	
8/93	26.0	goserelin
11/94	0.1	goserelin
1/96		elective bilateral orchiectomy
2/97	9.0	bicalutamide 50 mg (1 year)
8/99	71.0	ketoconazole & hydrocortisone
8/01	<1.0	ketoconazole & hydrocortisone
2/02	12.0	

Key Clinical Question

What therapeutic strategy should be utilized in an elderly man with a rising PSA, who responded to prior hormonal therapies?

Follow-up

I have now switched him to DES 1 mg.

Case Discussion

I use the combination of ketoconazole and hydrocortisone as second-line hormonal therapy after LHRH agonists and bicalutamide. Ketoconazole inhibits both testicular and adrenal androgenesis; whereas, hydrocortisone prevents adrenal insufficiency as well as having an antitumor effect. As second-line hormonal therapy, ketoconazole plus hydrocortisone has a 60% chance of reducing the PSA. He was started on ketoconazole/hydrocortisone, and his PSA dropped to less than 1 ng/mL. When that regimen failed, I utilized DES.

He still remains metastases-free, and his PSA on DES has decreased to 5. If he progresses again, other therapies to consider would include PC-SPES, aminoglutethimide, tamoxifen or perhaps an aromatase inhibitor.

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Wirth M et al. **Bicalutamide (Casodex) 150 mg as immediate therapy in patients with localized or locally advanced prostate cancer significantly reduces the risk of disease progression.** *Urol* 2001;58:146-51. **Abstract**

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
bicalutamide	Casodex®	AstraZeneca Pharmaceuticals, LP
ketoconazole	Nizoral®	Janssen Pharmaceuticals
diethylstilbestrol (DES)	Stilphostrol®	Bayer Corporation
pamidronate	Aredia®	Novartis Pharmaceuticals
sildenafil	Viagra®	Pfizer Labs
zoledronic acid	Zometa®	Novartis Pharmaceuticals
estramustine phosphate	Emcyt®	Pharmacia & Upjohn
etoposide (VP-16)	VePesid®	Bristol-Myers Oncology
paclitaxel	Taxol®	Bristol-Myers Oncology
finasteride	Proscar®	Merck & Co., Inc.
leuprolide	Lupron®	TAP Pharmaceuticals
goserelin	Zoladex®	AstraZeneca Pharmaceuticals, LP
docetaxel	Taxotere®	Aventis Pharmaceuticals
mitoxantrone	Novantrone®	Immunex Corporation
prednisone	—	Various
hydrocortisone	—	Various
tamoxifen	Nolvadex®	AstraZeneca Pharmaceuticals,LP
aminoglutethimide	Cytadren	Ciba-Geigy

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

1. Which of the following factors help determine a man's potency postprostatectomy?

a. Age b. Time after prostatectomy c. Preoperative potency
d. All of the above e. None of the above

2. Which of the following statements is/are true about the Messing study?

a. Adjuvant androgen deprivation improved survival in men undergoing radical prostatectomy for node-positive prostate cancer.
b. Adjuvant androgen deprivation did not influence survival in men undergoing radical prostatectomy for node-positive prostate cancer.
c. Adjuvant androgen deprivation reduced the risk of recurrence in men undergoing radical prostatectomy for node-positive prostate cancer.
d. a and c
e. b and c

3. The primary endpoints for the Early Prostate Cancer (EPC) trials were:

a. Survival b. PSA progression c. Objective disease progression
d. All of the above e. a and c

4. The EPC trial was comprised of 3 individual trials — the North American trial,the Capri trial and the SPCG trial. Which of the following differences existed in the design of the 3 trials?

a. The inclusion of watchful waiting as a treatment option
b. The inclusion of men with node-positive prostate cancer
c. The duration of bicalutamide therapy
d. All of the above
e. None of the above

5. Which of the following statements is/are true?

a. In the EPC trials,bicalutamide was associated with a reduction in the risk of objective disease progression.
b. In the EPC trials,bicalutamide was associated with a reduction in the risk of death.
c. None of the above
d. a and b

6. In the EPC trials,the most common adverse events associated with bicalutamide included:

a. Bone fractures b. Gynecomastia c. Breast pain d. b and c e. All of the above

7. Which of the following has not yet been demonstrated with regard to the emerging role of bisphosphonates in men with prostate cancer?

a. Pamidronate decreases the bone loss associated with androgen deprivation therapy in men with nonmetastatic prostate cancer.
b. Zoledronic acid decreases skeletal-related events,such as pathologic fractures,in men with hormone refractory prostate cancer that has metastasized to the bone.
c. Zoledronic acid decreases bone metastases in men with PSA-only hormone refractory prostate cancer.
d. a and c
e. All of the above

8. True/False: A recent study by Grimm et al reported on the long-term outcomes associated with brachytherapy in men with low-risk prostate cancer. Of the 125 men treated with brachytherapy, 87% had no evidence of disease at 10 years.

a. True

b. False

9. True/False: An update to RTOG 8531 by Lawton et al reported improved survival with the addition of androgen deprivation to radiation therapy in men with Gleason 2-4 prostate cancer.

a. True

b. False

10. Which of the following hormonal therapies may be considered second- or third-line approaches in men with prostate cancer?

a. Bicalutamide monotherapy
b. Ketoconazole
c. Aminoglutethimide
d. None of the above
e. All of the above

Exam Answer Key: 1. D, 2. D, 3. E, 4. D, 5. A, 6. D, 7. C, 8. True, 9. False, 10. E

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PCU1 2002

Conversations with Urology Leaders

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Extent to which program activities met the identified objectives

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

- Discuss the risks and benefits of nerve-sparing radical prostatectomy 5 4 3 2 1
- Review the risks and benefits of early versus delayed hormonal therapy in men with prostate cancer 5 4 3 2 1
- Summarize the study design and results from the Early Prostate Cancer (EPC) Trial,which evaluated bicalutamide as immediate or adjuvant therapy in men with prostate cancer 5 4 3 2 1
- Examine the emerging role of bisphosphonates in men with prostate cancer 5 4 3 2 1
- Evaluate the long-term outcomes associated with brachytherapy 5 4 3 2 1
- Discuss potential second- and third-line hormonal therapies for men with prostate cancer. 5 4 3 2 1

Overall effectiveness of the activity

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

Related to my practice needs 5 4 3 2 1

Will influence how I practice 5 4 3 2 1

Will help me improve patient care 5 4 3 2 1

Stimulated my intellectual curiosity 5 4 3 2 1

Overall quality of material 5 4 3 2 1

Overall, the activity met my expectations 5 4 3 2 1

Avoided commercial bias or influence 5 4 3 2 1

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

___Yes ___No

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

_____

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Degree:

q MD q DO q PharmD q RN q PA q BS q Other _____

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