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Prostate Cancer™ UPDATE

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

SPECIAL EDITION

Proceedings from a "Think Tank" held at the 2004 American Urological Association Meeting

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

Prostate Cancer Update
A CME Audio Series and Activity

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

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

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

PURPOSE OF THIS ISSUE OF *PROSTATE CANCER UPDATE*:
The purpose of Issue 4 of *Prostate Cancer Update* is to support these global objectives by offering the perspectives of prostate cancer research leaders present at a Think Tank meeting on the integration of emerging clinical research data into the management of prostate cancer.

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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
alfuzosin hydrochloride	Uroxatral™	Sanofi-Synthelabo Inc
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
aspirin	Various	Various
bicalutamide	Casodex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
cisplatin	Platinol®	Bristol-Myers Squibb Company
clopidogrel bisulfate	Plavix®	Sanofi-Synthelabo Inc Bristol-Myers Squibb Company
DES	Discontinued	Discontinued
doxazosin mesylate	Cardura®	Pfizer Inc
finasteride	Proscar®	Merck & Company Inc
fluorouracil (5-FU)	Various	Various
flutamide	Eulexin®	Schering-Plough Corporation
goserelin acetate	Zoladex®	AstraZeneca Pharmaceuticals LP
irinotecan	Camptosar®	Pfizer Inc
leucovorin calcium	Various	Various
leuprolide acetate implant	Viadur™ Lupron Depot®	ALZA Corporation TAP Pharmaceuricals Inc
megestrol acetate	Megace®	Bristol-Myers Squibb Company
nilutamide	Nilandron®	Aventis Pharmaceuticals Inc
tamoxifen citrate	Nolvadex®	Astrazeneca Pharmaceuticals LP
tamsulosin hydrochloride	Flomax®	Boehringer Ingelheim
trastuzumab	Herceptin®	Genentech BioOncology
vinorelbine	Navelbine®	GlaxoSmithKline

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Editor's Note

San Francisco experiment

Innovation in one's work prevents boredom but also can be stressful. Just prior to the two-day audio recording that led to this program, I questioned my judgment in attempting to effectively moderate the dozen loquacious clinical research leaders who gamely agreed to participate in our Second Annual *Prostate Cancer Update* Think Tank, held in May during the American Urological Association meeting in San Francisco.

Most of the attendees had already participated in our *Prostate Cancer Update* audio series; however, that format is much more controlled and after 16 years of interviewing research leaders one-on-one, I pretty much know what to expect.

Recording and editing a Think Tank was a totally different story and something our group has never done before. Since only one faculty member could speak at a time, I was quite nervous that these esteemed leaders would feel muzzled and I would quickly resemble a frantically waving police person on a wild Italian traffic circle.

Fortunately, technology was on my side. Faculty members were provided with networked laptop computers, granting them the opportunity to constantly input comments while others spoke. This also helped me to direct traffic and "green light" those who typed provocative comments.

The edited audio result of this educational endeavor is divided into three segments:

1. Adjuvant endocrine therapy for men with high-risk localized tumors

Bill See presented an update of the most important evolving research database on this question: the Early Prostate Cancer Trials of high-dose bicalutamide. To continue the theme of data that isn't as straightforward as we would like it to be, the Scandinavian portion of this mega-trial showed improved survival in men with high-risk tumors treated with bicalutamide, but decreased survival in men with low-risk tumors. Statistical fluke? That doesn't seem likely, but time will tell.

The group also watched a web replay of Richard Peto's presentation from the "Best of Oncology" session of the last ECCO meeting in Belgium.* During this

*http://oncology.fecs.be/conferences/ecco12/virtualmeetings.shtml

compelling lecture, the renowned and recently knighted Oxford statistician (affectionately known to friends as "Sir Richard") compared his unpublished international meta-analysis of adjuvant endocrine therapy for prostate cancer to a series of similar analyses in breast cancer, and concluded that the treatment benefits are about the same.

Peto notwithstanding, tamoxifen and other endocrine therapies are utilized routinely in the adjuvant breast cancer setting but relatively infrequently in men treated with radical prostatectomy. Yes, PSA is available to allow early therapy at relapse, but as Judd Moul so eloquently stated, we have no data to tell us that treating at early PSA progression results in the same survival benefit as it does immediately post-op.

Ed Messing — the only Think Tank member besides me to attend Peto's closed 2003 Oxford meeting where he first unveiled these data — re-presented to the group his oft-quoted ECOG trial in node-positive patients. That study demonstrated a persuasive survival benefit to adjuvant castration, although patient accrual was very modest. One of his key conclusions is that no data are available to determine if the same benefit would have been observed if therapy had been delayed until PSA progression.

2. Management of PSA-only relapse

Judd Moul started the debate by noting his embarrassment that virtually no prospective randomized trial evidence exists to support physicians and patients facing this challenging situation. While retrospective data he presented from his CPDR database suggests that earlier endocrine therapy in these men results in delayed clinical progression, survival data are not mature enough to draw conclusions.

The Think Tankers seemed to uniformly support Judd's risk-stratified approach to decision-making for biochemical progression, but they also agreed that, to a great extent, clinicians are "flying by the seat of their pants" when managing these patients.

Laurence Klotz further complicated the discussion by presenting a new analysis suggesting that maximal androgen blockade may be more effective than previously believed, if the antiandrogen utilized is bicalutamide.

3. Chemoprevention

Ian Thompson presented the somewhat ambiguous data from his trial using finasteride, which was published in the *New England Journal of Medicine* last year. The good news is that fewer prostate cancers were diagnosed in patients treated with finasteride; the bad news is that more high-grade tumors were also observed in these men.

Listeners to our series often comment in emails that they enjoy hearing the experts squirm in their seats when I ask what research data like this means to patient care. Ian and the other attendees seem to conclude that in a man with a

BPH indication or semi-indication for finasteride, these data suggest you can "kill two birds with one stone" with finasteride, assuming potential sexual dysfunction is not a major concern.

Sex or no sex, I don't know how comforting these data will be to men at high risk. Thank God that Eric Klein and the SELECT gang got that study done. Hopefully, when those data are mature, we will have a better option (or options).

With all these controversies and data glitches, our educational experiment at times felt more like stop-and-go traffic than a smooth country ride, but embedded within the back-and-forth are a number of audio nuggets that I believe will assist in patient care. If nothing else, perhaps this program will further motivate us to enroll more patients in clinical trials so that we can obtain answers to these critical questions.

For this print supplement to our program, we have included an edited version of four of the most provocative presentations in the meeting. The PowerPoint slide files of these lectures are enclosed on the first CD and **www.ProstateCancerUpdate.net**.

Needless to say, we would very much like to know whether the enclosed program resonates with our loyal listeners, and your feedback on the Think Tank educational concept is welcomed and appreciated.

— Neil Love, MD
NLove@ResearchToPractice.net

Select publications

Iversen P et al; Casodex Early Prostate Cancer Trialists' Group. **Is the efficacy of hormonal therapy affected by lymph node status? Data from the bicalutamide (Casodex) Early Prostate Cancer program.** *Urology* 2004;63(5):928-33. **Abstract**

Messing EM et al. **Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer.** *N Engl J Med* 1999;341(24):1781-8. **Abstract**

Moul JW et al. **Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy.** *J Urol* 2004;171(3):1141-7. **Abstract**

Peto R. **Breast and prostate cancer: 10 year survival gains in the hormonal adjuvant treatment trials.** Presentation, Best of Oncology, European Cancer Conference 12, 2003. No abstract available

See W et al. **Immediate treatment with bicalutamide 150mg as adjuvant therapy significantly reduces the risk of PSA progression in early prostate cancer.** *Eur Urol* 2003;44(5):512-7. **Abstract**

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

Think Tank Presentation 1

Overview of Adjuvant and Neoadjuvant Endocrine Therapy for Prostate Cancer

Leonard G Gomella, MD

1.1

Risk and 5-Year Outcome

- Low risk: <25% PSA failure — <T2a, Gleason ≤ 6, PSA ≤10 ng/mL
- Intermediate risk: 25–50% PSA failure — T2b, Gleason = 7, PSA >10-20 ng/mL
- High risk: >50% PSA failure — T2c, Gleason scores 8-10, PSA >20 ng/mL

SOURCE: D'Amico AV et al. *JAMA* 1998;280:969-974. **Abstract**

SLIDE 1.1 While we tend to focus on PSA recurrence rate, unless adequately treated with localized therapy, prostate cancer can be a lethal disease. This was elegantly described by Peter Albertson several years ago: If you evaluate a series of men from 55 to 74 years of age, the chance of dying from prostate cancer, managed conservatively, is quite high in patients with higher Gleason scores. Clearly, we're not just talking about the potential for PSA progression. These cancers can be lethal if not treated properly.

The turning point in this area was brought forth by Anthony D'Amico and his colleagues at the University of Pennsylvania, who published a paper in *JAMA* about four years ago in which they specifically evaluated risk stratification in patients with localized prostate cancer treated with curative intent. They evaluated the outcomes of patients treated with monotherapy using radical prostatectomy, external beam radiation therapy or implant therapy. Some patients were treated with combined therapy.

Based on PSA progression, those patients with low-risk disease who were treated with monotherapy, did fairly well. However, the patients with high-risk features — high Gleason score, high PSA, advanced clinical stage — regardless of the treatment but particularly those treated with monotherapy, uniformly did poorly based on PSA progression. Patients at low risk were defined as those who had less than a 25 percent risk of PSA failure at five years.

These patients had low clinical stages, Gleason scores of six or less and PSAs less than 10 ng/mL. The troubling cases are those patients who have greater than a 50 percent progression rate based on PSA failure, and those with more bulky tumors and higher Gleason scores, particularly in the range of 8 to 10.

1.2

Risk Stratification and Prostate Cancer Outcome

- Patients at low risk appear to have similar outcomes with any monotherapy
- Patients at high risk do not usually do well with monotherapy
- Combination therapies are appropriate to improve outcomes

SLIDE 1.2 The bottom line in risk stratification today is that patients at low risk appear to have similar outcome with any monotherapy, but it's the patients at high risk who tend not to do well with monotherapy, and combination therapies may be appropriate to consider at this point in time.

We're moving forward rapidly in this area, and we're getting more and more sophisticated and more and more specific with how we can assess risk in an individual patient with prostate cancer. By doing risk assessment of an individual patient, we may be able to tailor treatment for them more precisely and improve their final outcome.

1.3

Prostate Cancer Risk/Outcome Assessment

- Partin tables
- Center for Prostate Disease Research (CPDR, www.CPDR.org)
- Roach, D'Amico formulas
- Artificial neural networks
- Kattan nomograms: preoperative, postoperative, XRT (external radiation therapy) and brachytherapy

SOURCE: *Semin Urol Oncol* 2002;20 (series).

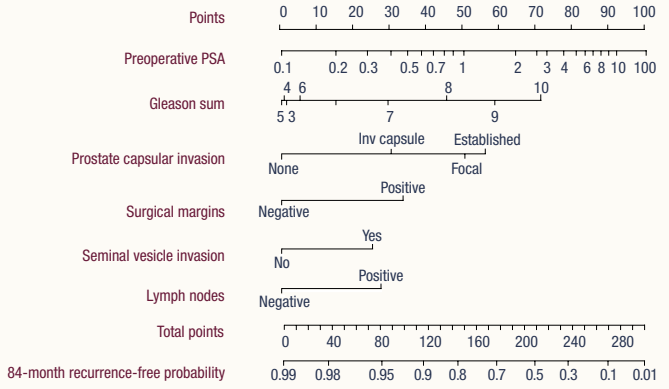
SLIDE 1.3 Most urologists are familiar with the Partin tables. Dr Moul's group at the Center for Prostate Disease Research in Washington has a website that can be used to enter multiple parameters.

Dr Roach and Dr D'Amico developed their own formulas. David Crawford, Dr Gamito and others have been active in the area of artificial neural network. Mike Kattan, who started this work when he was in Texas and is continuing at Sloan-Kettering in New York, has developed a whole series of nomograms, which are particularly useful for a variety of patients, both preoperatively and postoperatively.

The nomograms have been expanded to assess risk of patients treated by external beam radiation therapy, 3-D conformal therapy, and brachytherapy.

1.4

Post-op Nomogram for Prostate Cancer Recurrence

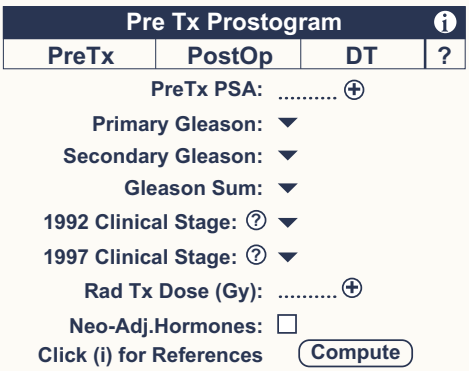


SOURCE: Kattan MW et al. Reprinted with permission from the American Society of Oncology. *J Clin Oncol* 1999;17:1499-507. **Abstract**

SLIDE 1.4 This is an example of one of the early postoperative nomograms in manual format that everyone has become familiar with. Individual parameters are each assigned a point, and the points are added together for a seven-year recurrence-free probability. These can be customized for each patient and are very specific for the unique parameters of the individual patient.

1.5

Nomograms.org



SLIDE 1.5 Nomograms are now available via the Internet at nomograms.org, where anyone can log in and receive instructions on how to download a Palm-friendly, Windows-CE-friendly or desktop-friendly format. Users can enter specific criteria and determine the risk of a patient having progression after definitive local therapy.

1.6

Common Options for High-Risk Disease

Radical prostatectomy
+ Neoadjuvant hormonal therapy (NHT)
+ Adjuvant HT (AHT)
+ Adjuvant radiation therapy
+ Chemohormonal therapy

Radiation therapy
+ NHT
+ AHT
+ NHT and AHT
+ Chemohormonal therapy

SLIDE 1.6 After having developed all of these very sophisticated tools, we face our next challenge. After we identify a patient at higher risk of progression or failure after definitive local therapy, what do we do for them? This is an evolving and rapidly progressing area of research. The improved outcomes, particularly when it comes to survival in prostate cancer, may be due to some of new multimodality therapies that are being applied to patients with high-risk disease.

If we identify a patient with high-risk disease, performing a radical prostatectomy (RP) is an option, but we will focus on combined therapy, evaluating neoadjuvant hormonal therapy (NHT) and adjuvant hormonal therapy (AHT) to improve the outcome of these patients. Adjuvant radiation therapy (RT) and chemohormonal therapy are also options, but the focus of our discussion will be endocrine manipulations. If you plan on treating a patient at high risk with radiation therapy, the hormonal approaches — other than dose escalation, which has been proven to help a little bit — include neoadjuvant or adjuvant hormonal therapy. In radiation therapy the approach receiving the most attention and the most positive outcome is the combination of neoadjuvant and adjuvant hormonal therapy.

1.7

NHT and AHT Rationale

- Documented progression rates after high-risk RP and RT
- Safe, reversible forms of castration
- Sensitivity of soft tissue prostate cancer to androgen ablation
- RT and HT synergy
- NHT effective in other tumors (lung, ENT)
- Survival advantage of immediate versus deferred HT

SLIDE 1.7 The rationale for combined neoadjuvant and adjuvant hormonal therapy is that we have documented progression rates in patients with high-risk disease treated with monotherapy by radical prostatectomy (RP) and radiation therapy. Safe, reversible forms of castration are now available to us. We know that soft-tissue prostate cancer appears to be much more responsive to androgen ablation than bony metastatic disease. The synergy between radiation therapy and hormonal therapy (HT) has been well documented in animal studies and in several important clinical trials.

The concept of neoadjuvant hormonal therapy has been proven to be efficacious in other tumor systems, such as in lung and head and neck cancers. Evidence strongly suggests that in patients with high-risk localized disease, immediate hormone therapy offers an absolute survival advantage over deferred hormonal therapy.

1.8

NHT and AHT Disadvantages

- Adverse effects of androgen blockade
  - Libido/hot flashes/mood swings/cost
  - Antiandrogen side effects (liver, diarrhea, gynecomastia)
  - Potency effects
- Desmoplastic reaction: may make RP and nerve sparing difficult
- Alters RP pathologic evaluation
- Androgen resistant clones might develop but unlikely based on Ki-67 and PCNA

SLIDE 1.8 Having said that, are there any downsides to neoadjuvant and adjuvant hormonal therapy? Certainly, we have to realize it is a double-edged sword, and we may have some problems with these treatments. The adverse effects of androgen blockade may include problems with libido, hot flashes and mood swings, and these therapies are more costly. Antiandrogens, either as monotherapy or combined therapy, have a unique side-effect profile involving liver toxicity. Some agents have the potential to cause diarrhea or gynecomastia. Occasionally, neoadjuvant monotherapy causes a very pronounced desmoplastic reaction that may make a nerve-sparing prostatectomy more challenging. Neoadjuvant therapy before radical prostatectomy significantly alters the final pathologic evaluation, and that must always be considered.

A theoretical concern exists that treating patients who have localized disease with androgen ablation may cause or stimulate the development of androgen-resistant clones; however, based on extensive basic science studies of Ki-67 and PCNA assays, at least in the short term, it's unlikely that using these approaches causes the development of androgen resistance.

1.9

Early Experience with NHT

- Vallett 1944
  - Castration followed by perineal 70 days later
- Colston 1944
  - Stilbesterol prior to perineal regression
  - "...perioperative estrogens will allow permanent extirpation of the whole disease... with excellent chance for long-term cure..."
- DES/orchiectomy extensive favorable literature through 1980s

SLIDE 1.9 Neoadjuvant and adjuvant hormonal therapy are concepts that are over 60 years old. The very first description of neoadjuvant

hormonal therapy dates back to 1944, when Drs Vallet and Colston and other surgeons reported using castration or estrogens before perineal prostatectomy with fairly favorable outcomes. DES and orchiectomy were used extensively through the 1980s, but more advances in this area really occurred in the 1990s.

1.10

High-Risk Prostate Cancer: RP + NHT

- 3 months NHT: 7 Phase III studies in 1990s
  - 50% reduction in positive margins
  - 30% to 50% size reduction
  - Pathology altered (Gleason invalid)
  - PSA recurrence: no change at 3 to 4 years
- CUOG 3 versus 8 months NHT study
  - PSA recurrence: no change at 4 years
  - Reduced PSA recurrence in intermediate-risk patients only in high volume centers

SOURCES: Klotz L et al. *Mol Urol* 2000;4:233-7. **Abstract** Soloway MS et al. *J Urol* 2002;167:112-6. **Abstract** Gleave ME et al. AUA Annual Meeting, 2003;**Abstract 690**.

SLIDE 1.10 In the 1990s, at least seven Phase III trials evaluating neoadjuvant hormonal therapy and radical prostatectomy were reported, and all demonstrated a 50 percent reduction in positive margins in general. They confirmed that the pathology was significantly altered, and the Gleason score would not be valid if neoadjuvant monotherapy was utilized.

The bottom line of these studies was that no change in PSA recurrence was observed. One thought was that perhaps these three-month studies were of insufficient duration to provide the full androgen-withdrawal effect on the prostate.

The Canadian Urologic Oncology Group (CUOG), after some pilot studies, performed a study of a three versus eight months that was reported last year by Dr Gleave. A small cohort of patients at intermediate risk who were treated at high-volume centers had a reduced incidence of PSA recurrence at four years follow-up, but overall no significant change in PSA recurrence was observed. We're waiting to see more follow-up from this study.

1.11

RP + AHT (LHRH, Antiandrogens)

- Prayer-Galetti
  - Gion M et al. *Eur Urol* 2000;37:460-9.
- Wirth
  - Wirth M et al. *Br J Urol* 1997.
  - Wirth M, Froehner M. *Eur Urol* 1999;36:14-19.
- Messing/ECOG study
  - HT versus observation in N + RP
- Bicalutamide EPC (early prostate cancer) trial
  - 2 years bicalutamide versus placebo for all RP

SLIDE 1.11 What about performing radical prostatectomies and adjuvant hormonal therapy? A series of studies exist. Some of the key studies include Dr Messing's ECOG study and Dr See's bicalutamide early prostate cancer trial, which suggest that using adjuvant hormonal therapy with radical prostatectomy offers some significant advantages.

1.12

RT with NHT and with or without AHT

- Early trials
  - RTOG-8307 (DES/megestrol acetate)
  - RTOG-8531 (XRT + LHRH agonist)
- Bolla/EORTC
- RTOG-8610 (T3 disease)
- RTOG-9202 (T2 NHT versus maintenance hormone therapy)
- RTOG-9413 (high-risk for nodes, combination XRT/NHT)
- Bicalutamide EPC trial

DES = diethylstilbestrol

SLIDE 1.12 What about radiation therapy with neoadjuvant or adjuvant hormonal therapy? The radiation oncologists have been very progressive in this area and have been conducting trials for over 20 years. They have brought forward some significant, large, prospective, randomized clinical trials of combination therapy, including trials of patients with T3 disease, T2 disease and patients at high risk for having positive nodes. Bicalutamide has also been evaluated in the EPC trial, along with radiation therapy.

1.13

Early Hormone Use Improves Survival: Sir Richard Peto

- Meta-analysis prostate cancer trials early versus late hormone therapy (HT)
- 5,000 men age 65-74
- 10-year survival ↑ 12%-20%
- Death rates per 100,000 men
  - Europe: 106 (1990), 87 (2000)
  - United States: 124 (1990), 83 (2000)
- Combined therapy often uses early HT

SOURCE: Prostate Cancer Trialists Collaborative Group. 12th Annual European Cancer Conference (ECCO), Copenhagen, September 2003;**Abstract 328**.

SLIDE 1.13 Sir Richard Peto performed a meta-analysis in which he examined a large number of patients treated with early versus late hormonal therapy. The bottom line was that he believed the significant increase in the 10-year survival rates, both in Europe and in the

United States during the 1990s — an increase of anywhere from 12 to 20 percent in absolute survival —could possibly be from the early use of hormone therapy.

1.14

NHT and AHT Take-Home Points

- Assess and risk-stratify each patient
- Review all treatment options and consider combined therapy in high-risk disease
- Most trials show advantage for combined HT approaches; RP/NHT conflicting
- Attempt to place patients on open randomized trials
- Early HT (NHT/AHT) may be responsible for improved survival in prostate cancer

SLIDE 1.14 As we move forward with neoadjuvant and adjuvant hormonal therapy, it is very important to assess the risk of progression in each patient treated for localized disease. It's important to review all the treatment options with the patient and, if you have a patient with high-risk disease, consider some type of combined therapy that may or may not include hormones or radiation therapy. Most randomized trials have demonstrated an advantage for combined hormonal therapy. As we noted, the radical prostatectomy/neoadjuvant hormonal data is conflicting. It's very important to always try to enroll patients on open randomized clinical trials. Lastly, it is possible that the early use of hormonal therapy — neoadjuvant and adjuvant hormonal therapy — may be responsible for the improvement that we're seeing in prostate cancer survival over the last decade.

Select publications

D'Amico AV et al. **Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer.** *JAMA* 1998;280(11):969-74. **Abstract**

Gleave M et al. **Randomized comparative study of 3 vs 8 months of neoadjuvant hormonal therapy prior to radical prostatectomy: 3 year psa recurrence rates.** *Proc AUA* 2003;**Abstract 690**.

Kattan MW et al. **Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer.** *J Clin Oncol* 1999;17(5):1499-507. **Abstract**

Klotz L et al. **Neoadjuvant hormone therapy: The Canadian trials.** *Mol Urol* 2000;4(3):233-7. **Abstract**

Peto R, Dalesio O. **Breast and prostate cancer: 10-year survival gains in the hormonal adjuvant treatment trials.** *European Journal of Cancer Supplements* 2003;1(5):S101;**Abstract 328**.

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**

Think Tank Presentation 2

Management of PSA Relapse: Early versus Late Androgen Deprivation

Judd W Moul, MD, FACS

2.1

PSA Relapse

New prostate cancer cases per year	231,000
3/4 who receive localized disease treatment annually	173,250
35% who may experience PSA-only recurrence per year	60,600
More men are younger and healthier at time of PSA-only recurrence	

SOURCE: Based on SEER statistics, 2004.

SLIDE 2.1 Depending on how you define it, rising PSA may be the most common stage of advanced prostate cancer. Certainly, the quality of life slips when PSA rises after prostatectomy, brachytherapy or external beam radiation.

2.2

PSA Relapse: Arguments for Early HT

- Most common presentation of "advanced" prostate cancer
- Relatively easy-to-define clinical condition
- Likely to impact natural lifespan for many contemporary patients
- Survival advantage to early hormonal therapy for advanced disease becoming more clear
- "Watchful waiting" not acceptable for many men

SLIDE 2.2 Several arguments exist for early hormonal therapy: PSA relapse is the most common presentation in advanced disease, it's a relatively easy-to-define clinical condition, and it's likely to impact the natural life span of many contemporary patients. Early hormonal therapy for advanced disease offers a survival advantage that is becoming more clear, and watchful waiting is not acceptable to many of our patients.

2.3

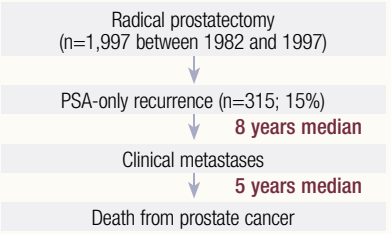
PSA Relapse: Arguments Against Early HT

- Long natural history of rising PSA before clinical metastases and death for most men
- No randomized, controlled clinical trials to address this issue
- Side effects of hormonal therapy
- Cost of hormonal therapy

SLIDE 2.3 Arguments against early hormonal therapy include the long natural history of a rising PSA before clinical metastases and death for most men. Additionally, no randomized clinical trials have been conducted to address this issue, which is a major problem. Finally, the side effects and cost of hormonal therapy are not inconsequential.

2.4

PSA Relapse: Natural History of Untreated Men



SOURCE: Pound CR et al. *JAMA* 1999;281:1591-7. **Abstract**

SLIDE 2.4 The Pound article from Johns Hopkins describing the well-known eight-year median time from PSA recurrence to clinical metastases is based on the Hopkins' definition of 0.2 ng/mL. At the time of clinical metastases, most of those men began hormonal therapy and had a median survival of five years from initiation of therapy until death, so the average survival after PSA recurrence was 13 years.

2.5

Journal of Urology March 2004

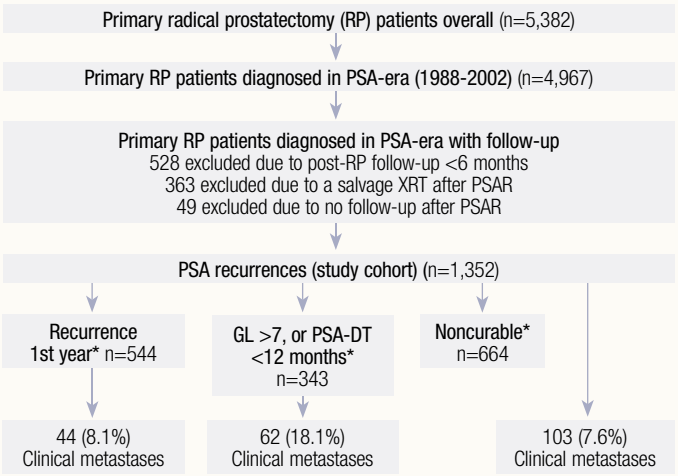
Early versus Delayed Hormonal Therapy for Prostate Specific Antigen Only Recurrence of Prostate Cancer After Radical Prostatectomy

Judd W Moul, Hongyu Wu, Leon Sun, David G McLeod, Christopher Amling, Timothy Donahue, Leo Kusuda, Wade Sexton, Keith O'Reilly, Javier Hernandez, Andrew Chung and Douglas Soderdahl

SLIDE 2.5 A study we conducted through the Center for Prostate Disease Research (CPDR) was published in the March 2004 issue of the *Journal of Urology*. We examined the CPDR database in an attempt to determine what was happening to patients with PSA-only recurrences in the military healthcare system.

2.6

Study Cohort Diagram Illustrating Exclusion and Inclusion of Patients



*Groups not mutually exclusive

SOURCE: With permission from Moul JW et al. **Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy.** *J Urol* 2004;171:1141-7. **Abstract**

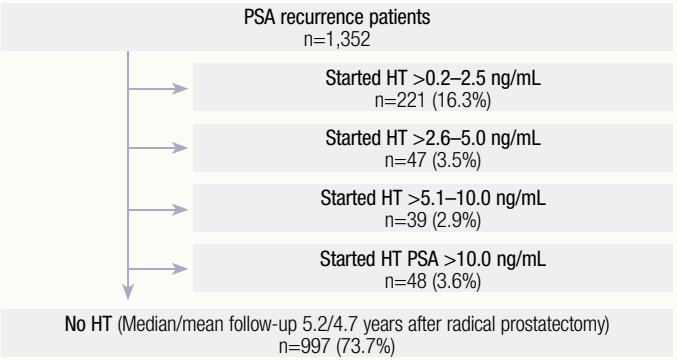
SLIDE 2.6 The database included 5,382 patients who underwent primary radical prostatectomy, of which 4,967 occurred during the PSA era — 1988 to 2002. We excluded 528 patients due to inadequate postradical prostatectomy follow-up (less than six months) and 363 patients due to salvage radiation therapy after a PSA recurrence. We could argue whether that was valid or not, but we were trying to duplicate the Pound study, which excluded patients who underwent salvage radiation therapy. An additional 49 patients were excluded due to lack of follow-up after the PSA recurrence.

Defined by the Pound criteria of a PSA greater than 0.2 ng/mL, 1,352 patients had PSA recurrences. We also performed some subset analyses, evaluating the subgroup of 544 patients who had a recurrence in the first year, the subgroup of 343 patients at high risk who had a Gleason greater than seven in their radical specimen, or a PSA doubling time less than 12 months and a third subgroup analysis of noncurable patients defined by the Hopkins' definition of noncurable.

Overall, of these 1,352 patients, 103 had clinical metastases, which was the endpoint for the study. In the high-risk group of 343 patients, 62 had clinical metastases. Of the patients with recurrence in the first year, 44 had clinical metastases. The average follow-up was about four years after PSA recurrence.

2.7

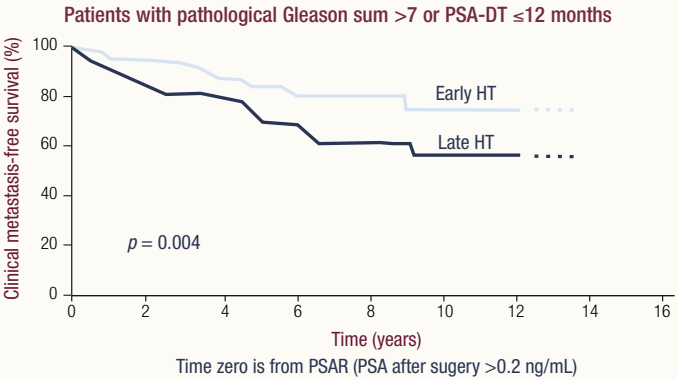
PSA Only Recurrence Cohort to Illustrate PSA at Initiation of HT



SOURCE: With permission from Moul JW et al. **Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy.** *J Urol* 2004;171:1141-7. Abstract

2.8

Early HT Administered at PSA ≤5 ng/mL Affects Clinical Metastasis-Free Survival



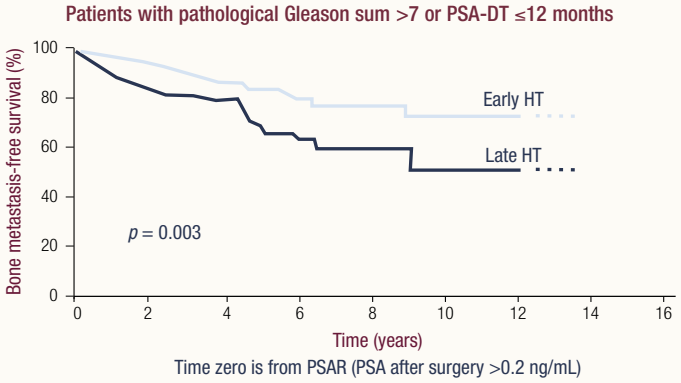
SOURCE: With permission from Moul JW et al. **Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy.** *J Urol* 2004;171:1141-7. Abstract

SLIDE 2.7 Breaking down these 1,352 PSA recurrences, 221 patients started hormone therapy for a PSA greater than 0.2 ng/mL but less than 2.5 ng/mL; 47 patients for a PSA between 2.6 ng/mL and 5 ng/mL; 39 patients for a PSA between 5 ng/mL and 10 ng/mL; and then 48 patients for a PSA greater than 10 ng/mL but before clinical metastases. The remaining 997 patients, with a median follow-up of almost five years after radical prostatectomy, received no hormonal therapy.

SLIDE 2.8 Early hormonal therapy conferred a clinical metastasis-free survival benefit in the group of patients with a pathologic Gleason's sum greater than seven or a PSA doubling time 12 months or less in men who started hormonal therapy before their PSA reached 5 ng/mL.

2.9

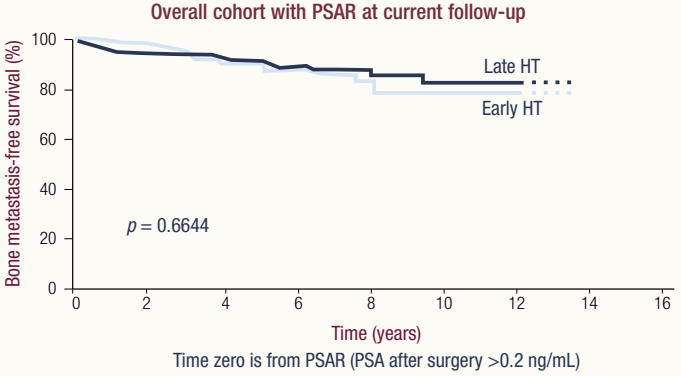
Early HT Administered at PSA ≤10 ng/mL Affects Clinical Metastasis-Free Survival



SOURCE: With permission from Moul JW et al. **Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy.** *J Urol* 2004;171:1141-7. **Abstract**

2.10

Early HT Administered at ≤5 ng/mL Did Not Affect Clinical Metastasis-Free Survival



SOURCE: With permission from Moul JW et al. **Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy.** *J Urol* 2004;171:1141-7. **Abstract**

SLIDES 2.9, 2.10 Patients who had a PSA less than 10 ng/mL, as opposed to less than 5 ng/mL, had similar benefit from early hormonal therapy, although whether you started at less than 5 ng/mL or less than 10 ng/mL, in this type of database analysis we couldn't demonstrate a benefit for patients at high risk. In the overall cohort of over 1,300 patients, however, there was no clinical metastasis-free survival benefit from early versus delayed hormonal therapy.

2.11

PSA Relapse: Arguments for Early HT

Good News:

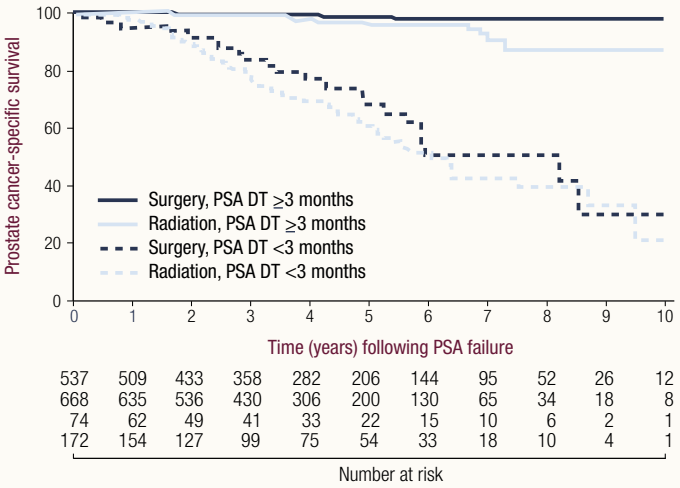
- First study to show clinical DFS benefit from early HT for PSA relapse
- Emphasizes the importance of "Risk Stratification" in PSA relapse
- Supports that men with high grade disease (Gleason 8-10) and quick PSA-DT (<12 months) are at high risk of clinical failure

Bad News:

- Not a randomized controlled trial
- Overall, early HT provided no benefit
- Database study is a "moving target" and results may change over time
- Follow-up too short to determine overall survival impact

2.12

CPDR/CaPSURE/Harvard PSA-DT Study



SOURCE: Reprinted with permission from Oxford University Press. D'Amico AV et al. **Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy.** *J Natl Cancer Inst* 2003;95:1376-83. Abstract

SLIDE 2.11 The good news is this is the first study to show a clinical disease-free survival benefit from early hormonal therapy for PSA recur-

rence. I'm almost embarrassed to say that we should have a randomized trial in this group of patients, and this retrospective database study is really the first such paper in the literature. The findings emphasize the importance of risk stratification in patients with PSA relapse and tend to support that men with high-grade disease and a short PSA doubling time are at high risk for clinical failure.

The bad news is this was not a randomized, controlled trial. Overall, if we look at all 1,300 patients with PSA recurrence, early hormonal therapy showed no benefit. This is a database study and is a moving target.

The results may change over time as the patients are followed and more of those nonhormonal therapy patients switch to hormonal therapy. Currently, the follow-up is too short to determine if an overall survival impact exists.

In the last couple of slides, I want to emphasize the importance of risk stratification in patients with biochemical recurrence.

SLIDE 2.12 Anthony D'Amico, Peter Carroll and I combined our databases to evaluate PSA doubling time and demonstrate that a PSA doubling time of less than three months was a surrogate for death from prostate cancer. Among the factors we examined, PSA doubling time definitely seems to be an endpoint we should be using as we design future clinical trials.

2.13

Take Home Messages

- PSA relapse is very common
- No randomized controlled trials to guide our clinical decisions
- Our recent work (Moul et al. *J Urol* March 2004) emphasizes that we take a "risk stratified" approach to PSA relapse
- Men with high-grade disease (Gleason 8-10) and those with short PSA-DT (<12 months) have delayed clinical metastases if they receive early HT
- Unknown if early HT for PSA relapse will improve cancer-specific or overall survival

SLIDE 2.13 The take-home message is: PSA relapse is very common and no randomized controlled trial data exist to guide our clinical decisions. Our recent work emphasizes that we must take a risk-stratified approach to PSA relapse. Men with high-grade disease and those with a short PSA doubling time appear to have delayed clinical metastases if they receive early hormonal therapy. It's unknown whether early hormonal therapy for PSA relapse will improve cancer-specific or overall survival. That will require longer follow-up in the CPDR database.

Select publications

Cannon GM Jr et al. **Prostate-specific antigen doubling time in the identification of patients at risk for progression after treatment and biochemical recurrence for prostate cancer.** *Urology* 2003;62 Suppl 1:2-8. **Abstract**

D'Amico AV et al. **Determinants of prostate cancer specific survival following radiation therapy during the prostate specific antigen era.** *J Urol* 2003;170(6 Pt 2):S42-6. **Abstract**

D'Amico AV et al. **Intermediate end point for prostate cancer-specific mortality following salvage hormonal therapy for prostate-specific antigen failure.** *J Natl Cancer Inst* 2004;96(7):509-15. **Abstract**

D'Amico AV et al. **Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy.** *N Engl J Med* 2004;351(2):125-35. **Abstract**

D'Amico AV et al. **6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial.** *JAMA* 2004;292(7):821-7. **Abstract**

D'Amico AV et al. **Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy.** *J Natl Cancer Inst* 2003;95(18):1376-83. **Abstract**

Dreicer R. **Controversies in the systemic management of patients with evidence of biochemical failure following radical prostatectomy.** *Cancer Treat Rev* 2002;28(4):189-94. **Abstract**

Eastham JA et al; **Polyp Prevention Trial Study Group. Variation of serum prostate-specific antigen levels: An evaluation of year-to-year fluctuations.** *JAMA* 2003;289(20):2695-700. **Abstract**

Johnstone PA et al. **The 100-day PSA: Usefulness as surrogate end point for biochemical disease-free survival after definitive radiotherapy of prostate cancer.** *Prostate Cancer Prostatic Dis* 2004;7(3):263-7. **Abstract**

Kessler B, Albertsen P. **The natural history of prostate cancer.** *Urol Clin North Am* 2003;30(2):219-26. **Abstract**

Loberg RD et al. **Prostate-specific antigen doubling time and survival in patients with advanced metastatic prostate cancer.** *Urology* 2003;62 Suppl 1:128-33. **Abstract**

Moul JW. **Variables in predicting survival based on treating "PSA-only" relapse.** *Urol Oncol* 2003;21(4):292-304. **Abstract**

Moul JW et al. **Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy.** *J Urol* 2004;171(3):1141-7. **Abstract**

Pollack A et al. **Biochemical failure as a determinant of distant metastasis and death in prostate cancer treated with radiotherapy.** *Int J Radiat Oncol Biol Phys* 2003;57(1):19-23. **Abstract**

Pound CR et al. **Natural history of progression after PSA elevation following radical prostatectomy.** *JAMA* 1999;281(17):1591-7. **Abstract**

Roobol MJ et al. **Prostate-specific antigen velocity at low prostate-specific antigen levels as screening tool for prostate cancer: Results of second screening round of ERSPC (ROTTERDAM).** *Urology* 2004;63(2):309-13. **Abstract**

Think Tank Presentation 3

Antiandrogens are Androgen Receptor Antagonists: Clinical Implications for the Use of Maximal Androgen Blockade

Laurence Klotz, MD

3.1

Combined Androgen Blockade: Accepted Myths

- The antiandrogens are basically equivalent, other than side-effect profile
- Their main function is to block adrenal androgens
- There might be a miniscule survival benefit, but it isn't clinically significant
- The cost is excessive

SLIDE 3.1 The accepted myths about combined androgen blockade (CAB) are basic. "The antiandrogens are equivalent, other than their side-effect profiles." Their main function is to block adrenal androgens, so the term "antiandrogen" is a misnomer and I'll come back to that. There might be a miniscule survival benefit, but it isn't clinically significant, and the cost is excessive. Hopefully, I'll dissuade you about each one of these myths.

3.2

Combined Androgen Blockade: A Second Look

- In the castrate patient, it's about blocking androgen-independent activation of the androgen receptor (not adrenal androgens)
- There are important differences between the antiandrogens
- The survival benefit is significant
- The cost is modest relative to many other analogous interventions

SLIDE 3.2 Why is CAB worth a second look? Four reasons exist. In the castrate patient, whom I'm talking about, the adrenal androgens are almost certainly not the major issue. It's androgen-independent activation of the androgen receptor that's antagonized by the nonsteroidal antiandrogens that's important. A lot of work has been done in these last few years that's not well known, and I'll review it very briefly.

The nonsteroidal antiandrogens have quite different actions in terms of the degree to which they block androgen-independent activation. The survival benefit is significant, and there's a new analysis I'm going to show with bicalutamide, which demonstrates that it's probably much more significant than has been recognized. The cost is modest relative to other analogous interventions.

3.3

Total Androgen Blockade Timeline

- 1982: Small clinical series suggesting efficacy
- 1982-1988: 26 randomized controlled trials
- 1989: Final analysis of NCI study (daily leuprolide with or without flutamide) shows 26% survival benefit
- 1989: Overview analysis planned
- 1990: Confirmatory SWOG study of orchiectomy with or without flutamide opens (n=1,250)
- Early 1990s: Other publications showing mixed results; most studies too early and/or too small relative to effect size in NCI study

SLIDE 3.3 The timeline for CAB is well known, going back to 1979 and the first publications by Labrie. This is the single most-studied question in urology, as far as I know, with 26 randomized controlled trials. The NCI study, with a 26 percent survival benefit, changed clinical practice. Everyone started using CAB, and in the late 1980s the Overview analysis under Richard Peto's direction was planned. The SWOG study was powered based on the expectation of finding a 25 percent survival benefit. In the 1990s, clinical trials had mixed results.

3.4

All Nonsteroidal Antiandrogens Are Not Created Equal

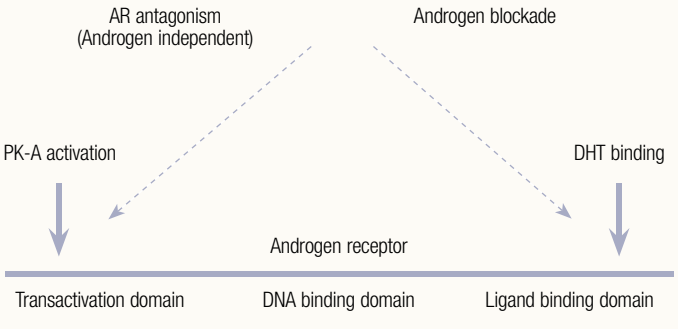
Important differences in:

- AR binding affinities
- Inhibition of ligand-independent AR activation
- Toxicity profile
- Survival benefit in sole head-to-head comparison
- Second- and third-line response to changing antiandrogen in hormone refractory disease

SLIDE 3.4 So, where are we today? All nonsteroidal antiandrogens are not created equal. Differences exist in binding affinities, inhibition of ligand-independent AR activation, the toxicity profiles, survival benefits in the sole head-to-head comparison, and second- and third-line responses to changing antiandrogen therapy in patients with hormone refractory disease.

3.5

Two Mechanisms of Action: In Absence of Androgens, AR Antagonism is Critical



SLIDE 3.5 If these drugs were the equivalent of the alpha blockers — alfuzosin versus doxazosin versus tamsulosin — you wouldn't expect to see the second-line responses, where patients taken off one antiandrogen responded to another. A lot of evidence exists that they do have different actions. So, the term "antiandrogen" is a misnomer. These agents really are androgen receptor antagonists, meaning they not only competitively block ligand binding at the ligand binding domain, but they also block androgen-independent activation.

This is mediated by protein kinase A, and there's a whole slew of cytokines — IL12, IL8, TGF beta — that can activate the androgen receptor in the absence of the ligand. And this is blocked by the antiandrogens. They also interact with co-activators and co-suppressors of the androgen receptor, and the ideal antagonist would inhibit co-activators and activate co-repressors. So, these are just two pieces of laboratory data demonstrating differences in the androgen-independent activation blockade.

3.6

Antiandrogens: Evidence for Differential Efficacy

- 2 x 2 design of leuprolide versus goserelin and flutamide versus bicalutamide
- 813 patients with D2 disease, median follow-up 160 weeks
- The combination of leuprolide plus flutamide was significantly inferior to the other three groups (goserelin/bicalutamide, goserelin/flutamide, leuprolide/bicalutamide) ($p = 0.008$)
- Bicalutamide was superior to flutamide (HR = 0.87)

SOURCE: Sarosdy MF et al. *Urology* 1998;52(1):82-88. **Abstract**

SLIDE 3.6 Finally, the single head-to-head comparison of flutamide and bicalutamide was first published about six years ago with 800 patients

who had D2 disease, and the median follow-up was approximately three years. The population in this study was very comparable to the patients who were entered on the earlier MAB versus monotherapy studies — D2 and advanced disease. The study demonstrated leuprolide plus flutamide was inferior to the other three groups, and bicalutamide was superior to flutamide.

In this two-by-two study, if you pull out the bicalutamide and flutamide arms plus LHRH, there is a significant overall survival benefit for the bicalutamide compared to the flutamide. That's only one study, but it was a large and well-conducted study.

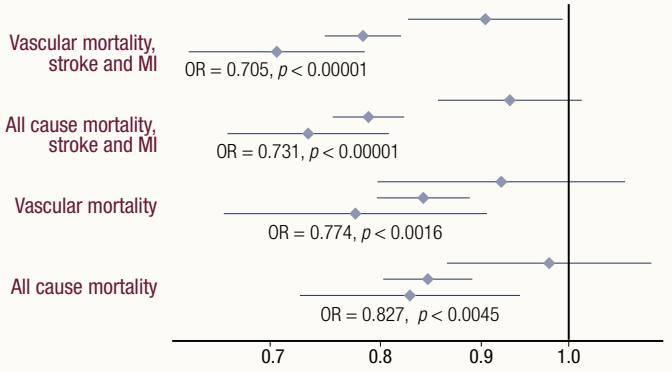
3.7

The 'X > Y and Y > Z, Therefore X > Z' Model

- Rothmann M et al. Design and analysis of noninferiority mortality trials in oncology. *Stat Med* 2003;22:239-64.
- Capecitabine (Xeloda®) versus 5-FU plus leucovorin (LV)
- Meta-analysis of trials comparing 5-FU plus LV to 5-FU alone
- Conclusion: Capecitabine superior to 5-FU

3.8

Active-Control Trials: How Would a New Agent Compare with Placebo? A Method Illustrated with Clopidogrel, Aspirin and Placebo



SOURCE: Reprinted from *American Heart Journal* vol 141, Fisher L et al. **Active-control trials: How would a new agent compare with placebo? A method illustrated with clopidogrel, aspirin, and placebo.** pp 26-32, 2001, with permission from Elsevier.

SLIDES 3.7, 3.8 So, the question is: Can you somehow integrate this data with all the MAB data to draw conclusions about the benefit of bicalutamide compared to monotherapy? Well, you wouldn't think so. The conventional wisdom is you can't compare data from different trials, but it turns out it can be done. Biostatisticians have attempted

to define models to allow these comparisons, and several reports in the literature exist where drugs actually received FDA approval based on the demonstration of benefit from these models. This type of modeling demonstrated that drug X is greater than drug Y and drug Y is greater than drug Z from earlier clinical trials, therefore it can be concluded that drug X is superior to drug Z.

The problem we face in this setting, where no hormone-naïve D-2 patients are available to study anymore, is analogous to other situations in medicine where you have comparisons that were done five or ten years ago that are no longer possible. In one example, capecitabine compared to 5-FU plus leucovorin showed a survival benefit, and the question was: Is capecitabine superior to 5-FU alone? Studies demonstrated 5-FU plus leucovorin was superior to 5-FU alone. So, this was submitted to the FDA, and capecitabine was approved as being superior to 5-FU alone, even though it had never been directly compared.

Another example involves a comparison of the platelet antagonist clopidogrel to placebo. Clopidogrel was shown to be superior to aspirin. Aspirin is superior to placebo in terms of recurrence, cardiovascular mortality and survival benefit. To make a long story short, it can be seen that clopidogrel was superior to placebo, even though they've never been directly compared, and yet this kind of analysis was accepted. The basic posit is that the patients have to be comparable, and the mathematics are complex in terms of figuring out the confidence limits.

3.9

Pieces of the Jigsaw Puzzle

- From Trial US0001 we know
  - HR (bicalutamide/flutamide) = 0.87
- From the PCTCG meta-analysis we know
  - HR (flutamide/castration) = 0.92
- Simple mathematics
  - (bicalutamide/flutamide) x (flutamide/castration) = bicalutamide/castration
  - HR of 0.87 x 0.92 = 0.80
- Balance of evidence suggests the HR for bicalutamide + castration versus castration alone is 0.80

SLIDE 3.9 In the Schellhammer trial, comparing bicalutamide to flutamide, the hazard ratio was 0.87, and in the PCTCG meta-analysis, comparing flutamide to castration, the hazard ratio was 0.92. The mathematics of a hazard ratio of 0.87 multiplied by 0.92 is 0.80, which is based on randomized trials. The D2 patients in the Schellhammer trial are comparable to the D2 patients in the MAB analysis, and to my mind, there's no reason they would respond differently to MAB than the patients in the earlier trial. So, the balance of evidence suggests the hazard ratio for bicalutamide plus castration versus castration alone is 0.8. That's a significant survival benefit by anyone's standard.

3.10

Cost Per Month of Survival Gained with Antiandrogen versus Lung/Colon Cancer

Comparison of cost per month survival gain for CAB in advanced prostate cancer with new treatments for advanced NSCLC and metastatic colorectal cancer

	Advanced prostate cancer	Advanced non-small cell lung cancer
Reference regimen	Castration (orchiectomy or LH-RHa)	Cisplatin
New regimen	Castration + NSAA	Cisplatin + vinorelbine
Difference in median overall survival*	3.7 mo to 7.3 mo	2.0 mo
Median time to progression for new regimen	21.2 mo and 16.5 mo	4 mo
Dosing schedule	NSAA† 50 mg/d	Vinorelbine 25 mg/m^2/wk
Cost	NSAA† $193.20/mo	Vinorelbine 50 mg = $172.38
Cost per month survival gain	$437-$1,107	$1,241

* Difference in median overall survival equals overall survival with new regimen minus overall survival with reference regimen; $p < 0.05$ for new regimen compared with reference regimen.
† Costs and dosing regimen of bicalutamide used for calculations.
LH-RHa = luteinizing hormone releasing hormone analogue; NSAA = nonsteroidal antiandrogen
[Citations omitted]

SOURCE: Aprikian A et al. *Canadian Journal of Urology* 2003;10(5):1986-94. **Abstract**

SLIDE 3.10 What about the cost of therapy? A report by Armen Aprikian and colleagues in the October 2003 issue of the *Canadian Journal of Urology* compared the cost of MAB with flutamide, using the survival benefit from the PCTCG meta-analysis of three to seven months compared to other interventions for advanced small-cell lung cancer, metastatic colon and breast cancer. The interventions included vinorelbine, irinotecan, trastuzumab, and anastrozole.

Basically, in terms of cost per month of survival gain — even if you accept it's three to six months, much less six to 12 months, which one would expect for D2 prostate cancer — the conservative assessment would be $500 per month versus up to $11,000 with irinotecan and $5,000 with trastuzumab. So, the cost compared to other interventions that are used by medical oncologists is relatively modest.

3.11

Bicalutamide as Second-Line Therapy (After Biochemical Progression)

- 23% of men have >50% fall in PSA with bicalutamide as second-line therapy
- Median duration of response is four months (Joyce, 1998)
- Effect likely small

SLIDE 3.11 So, the question that arises is why not just use MAB as second-line therapy? Why not just treat when patients progress and get the same effect? The point is that the second-line responses tend to be short, and roughly only one in four patients will derive more than a 50 percent PSA response with bicalutamide with a median response duration of four months. So, you're unlikely to see a very significant overall survival benefit with these agents used as second-line therapy.

3.12

Bottom Line

- Antiandrogens nilutamide and flutamide demonstrate a modest survival benefit with MAB
- Bicalutamide is a more potent androgen receptor antagonist, has fewer side effects and produced improved survival compared to flutamide in the only comparative trial
- Cost is less than other cancer therapies producing comparable benefit
- Reasonable to conclude that MAB with bicalutamide is of benefit in patients at risk for prostate cancer death

SLIDE 3.12 The bottom line is a modest survival benefit conferred by the older drugs. Bicalutamide is a more potent androgen receptor antagonist, with fewer side effects and improved survival in the only comparative trial. The cost is less than other cancer therapies and results in comparable benefits. It's reasonable to conclude that MAB with bicalutamide will benefit patients at risk for prostate cancer death, and patients who aren't at risk of death shouldn't be treated.

Select publications

Aprikian AG et al. **An oncology perspective on the benefits and cost of combined androgen blockade in advanced prostate cancer.** *Can J Urol* 2003;10(5):1986-94. **Abstract**

Fisher LD et al. **Active-control trials: How would a new agent compare with placebo? A method illustrated with clopidogrel, aspirin, and placebo.** *Am Heart J* 2001;141(1):26-32. **Abstract**

Sarosdy MF et al. **Comparison of goserelin and leuprolide in combined androgen blockade therapy.** *Urology* 1998;52(1):82-8. **Abstract**

Think Tank Presentation 4

The Prostate Cancer Prevention Trial Revisited

Ian M Thompson, MD

4.1

Rationale for Prevention

- Obviates the problem of overdiagnosis
- Would have an enormous impact on health
- For every 1% reduction in disease, 2,000 patients are not treated for cancer
- Prostate carcinogenesis in many cases appears to occur over a period of years
- Most deaths occur later in life
- You don't necessarily have to prevent the disease — if you can delay its manifestation, you will almost certainly decrease mortality

SLIDE 4.1 Why prevent prostate cancer? Prevention certainly has a number of advantages, one of which is that it obviates the issue of overdetection and overdiagnosis, and has an enormous impact on health. Every one percent reduction in prostate cancer prevalence reduces treatment for prostate cancer by 2,000 patients a year in the United States.

Another favorable aspect of prevention is that in many cases the carcinogenesis appears to occur over a period of decades. Most prostate cancer-related deaths occur late in life, so you don't necessarily have to prevent the disease — if you can delay it, perhaps by five to seven years, you may actually cut mortality in half.

4.2

Rationale for Hormonal Prevention of Prostate Cancer

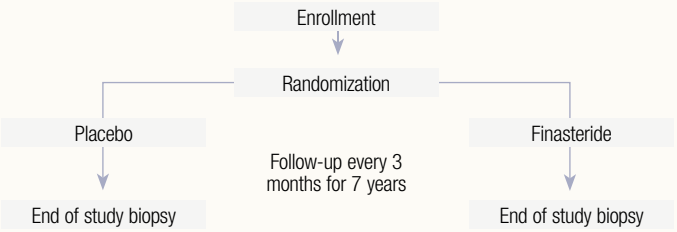
- Without androgenic stimulus, multiple stigmata of prostate disease is reduced
- Many animal models of prostate cancer require supraphysiologic levels of androgens
- Clinical and epidemiologic observations:
  - SNPs/variations in androgen pathway linked with prostate cancer
    - Androgen receptor CAG repeats
    - SNPs of SRD5A2, CYP 17, HSD3B2, etc
- Ethnic/geographic variations in diet (isoflavenoids)
- 5AR variations in populations

SLIDE 4.2 Why hormonal prevention? We know that androgenic stimuli are associated with prostate disease and carcinogenesis. Preclinical models frequently require supraphysiologic levels of androgens. The EPI data suggest that anything that makes the androgen receptor see more stimulation leads to a higher risk of prostate cancer. A large body of evidence indicates that variations among ethnic groups by diet or by behavior is related to risk and binding with the androgen receptor.

Certainly, before the development of 5-alpha-reductase inhibitors, we really didn't have a good preventative approach — other than perhaps switching to an Asian diet — to reduce one's risk of disease. The development of 5-alpha-reductase inhibitors provided us with new opportunities.

4.3

PCPT Schema



SOURCE: Thompson I et al. *N Engl J Med* 2003;349(3):215-24. **Abstract**

SLIDE 4.3 The PCP trial was designed in 1992 and began enrollment shortly thereafter. The target accrual was 18,000 men over a period of three years, who would then be followed annually with rectal examinations and PSA tests. Due to the impact of finasteride on PSA, a biopsy was to be performed at the end of the study, which is probably the most interesting aspect of the trial.

4.4

Recommendations of PCPT DSMC Received March 3, 2003

- The primary objective has been met
- Treatment effects sufficiently large as to be unlikely to be affected by further endpoint determinations
- Results should be released as soon as reasonably possible
- End-of-study biopsies are no longer required
- Written information should be sent to participants and investigators

SOURCE: Thompson I et al. *N Engl J Med* 2003;349(3):215-24. **Abstract**

SLIDE 4.4 The Data and Safety Monitoring Committee of PCPT met in early 2003, and the results of their deliberations were released in March. The trial was closed approximately 15 months early because the primary objective, which was a reduction in the prevalence of prostate cancer, had been met. Additional biopsies were unnecessary. Participants and investigators were notified, and the results were published in the July 2003 issue of the *New England Journal of Medicine*.

4.5

PCPT Overall Results

	Finasteride	Placebo	*p*-value
Total biopsies included[1]	4,368	4,692	
Prostate cancer	803	1,147	$p < 0.001$
For-cause biopsy/procedure[2]	1,639	1,934	
Prostate cancer	435	571	$p = 0.05$
End-of-study biopsy[3]	3,652	3,820	
Prostate cancer	368	576	$p < 0.001$

[1] Participants may have had a negative for-cause biopsy and an end-of-study biopsy
[2] Biopsy or other procedure (eg, TURP, cystoprostatectomy)
[3] Excludes end-of-study biopsies for-cause

SOURCE: Thompson I et al. *N Engl J Med* 2003;349(3):215-24. **Abstract**

SLIDE 4.5 A 25 percent reduction in prostate cancer prevalence was observed over the course of the trial. We wanted to analyze two sets of biopsies — the for-cause prostate diagnoses, which were prompted by an abnormal rectal examination or a PSA above 4 ng/mL, and the end-of-study biopsies, which is this kind of anomalous category of prostate cancer that we didn't know existed.

4.6

Seven-Year Period Prevalence

	Finasteride	Placebo
Known prostate cancer status	4,368	4,692
Prostate cancer	803 (18.4%)	1,147 (24.4%)
Relative risk reduction* (95% CI) 24.8% (18.6% - 30.6%)		

* Risk reduction of finasteride compared to placebo

SOURCE: Thompson I et al. *N Engl J Med* 2003;349(3):215-24. **Abstract**

SLIDE 4.6 A significant reduction in prostate cancer occurred in both groups, and we diagnosed prostate cancer in a fair number of patients to whom we would routinely say, "You don't have prostate cancer."

4.7

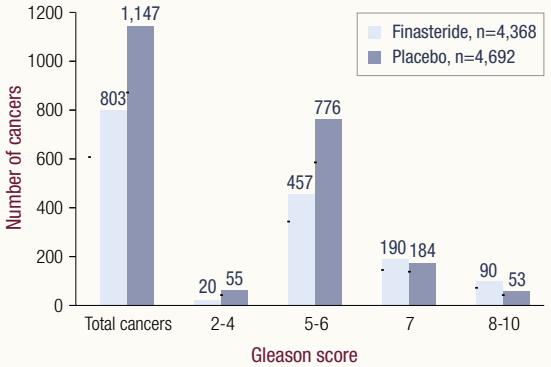
Biopsy Technique

	Finasteride	Placebo
Prostate volume (cm^3) (median)	25.5	33.6
Percent with six cores	81.5%	81.0%

SOURCE: Thompson I et al. *N Engl J Med* 2003;349(3):215-24. **Abstract**

4.8

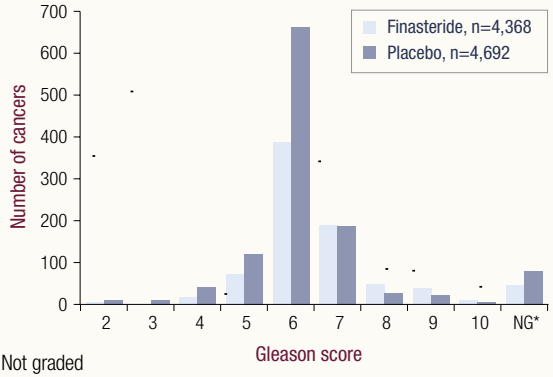
Gleason Score Total Number of Cancers



SOURCE: Thompson I et al. *N Engl J Med* 2003;349(3):215-24. **Abstract**

4.9

Gleason Score: All Cancers



* NG = Not graded

SOURCE: Thompson I et al. *N Engl J Med* 2003;349(3):215-24. **Abstract**

SLIDES 4.7 – 4.9 The biopsy technique required a minimum of six cores. The trial was designed in 1992, and we anticipated a bias would exist as a result of that, because of the volume reduction in the finasteride arm and potential overdetection in the finasteride arm.

In fact, four or five years ago we asked ourselves, "Should we require more biopsies in the placebo arm to equalize detection?" We decided that would introduce another bias, and we assumed that any bias would be against the finasteride arm and any beneficial effect observed would be potentially greater.

One of the most interesting anomalies in this trial was a substantial reduction in Gleason 5 and 6 prostate cancer, which were the predominant numbers, but effectively not much change in Gleason 7, and 47 more cases of Gleason 8-10 cancer in patients who received finasteride.

Approximately 50 percent of all prostate cancer diagnosed in the United States today is Gleason 6. If you examine the individual Gleason scores, you see substantial reductions in Gleason 6 cancer — more than 300 fewer cases — and a slight increase in Gleason 8, 9 and 10 cancers.

4.10

The 'Grade Effect'

- Was it 'real' or artifact?
- If real, it is a serious concern
- The increase in tumor grade could considerably dilute any advantage vis a vis survival.
  - 354 fewer Gleason 1-6 tumors versus 6 more Gleason 7 tumors and 47 more Gleason 8-10 tumors
  - 354 fewer intermediate/low-grade versus 54 more high-grade...

4.11

"Cancer Grade after Therapy is Unvalidated, of No Practical Value, and Should Not Be Used"

(WHO expert panel. *Cancer* 1996;78:376.)

SLIDES 4.10, 4.11 The real question is whether the differential effect on grade is real or an artifact? If it's real, then it's a serious concern because it could dilute any survival benefit. The real issue is that finasteride is associated with 350 fewer cases of Gleason 2-6 prostate cancer, six more cases of Gleason 7, and 37 more cases of Gleason 8-10. How do you balance that out? I must admit, I don't know.

A WHO-NCI-American Cancer Society panel came together and stated that grade should not be used after therapy. In fact, we've been criticized for publishing Gleason scores in the study because we were using a hormonal agent.

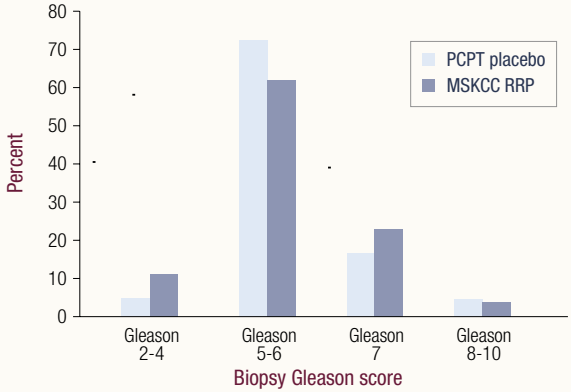
4.12

Status

- I don't think we know for sure where we stand today
- What do you do when the intervention affects your prognostic marker?
- Answer: Use another validated surrogate marker of prognosis
- The problem: There isn't one

4.13

Were the Tumors Averted Clinically Significant? Compare with RRP



SOURCE: Hull GW et al. *J Urol* 2002;167(2 pt 1):528-34. **Abstract**

4.14

'Clinical Significance' Placebo Arm Only

Cancer bilateral	44.1%
Perineural invasion	15.3%
Percent positive cores	43.5%
Gleason score increased at radical prostatectomy	28.4%
pT3 disease	44.4%

SOURCE: Thompson I et al. *N Engl J Med* 2003;349(3):215-24. **Abstract**

SLIDES 4.12 – 4.14 What do you do when the intervention may affect the marker for prognosis? The answer is you have to use another validated prognostic marker, but one doesn't exist. Several thousand potential prognostic factors are available in prostate cancer, but none are validated.

The other discussion that often arises is, "This group is at low risk and had PSA levels less than 3 ng/mL at the outset. Obviously, the tumors prevented have no clinical importance." However, patients in practices with the same grade of prostate cancer are often offered radical prostatectomy.

In terms of clinical significance, these are preliminary data. In the placebo arm only — which includes a mix of biopsy and radical prostatectomy — bilateral disease occurred in 44 percent, perineural invasion in 15 percent, positive cores in 43 percent.

Gleason score increased at radical prostatectomy in 28 percent of patients, and pT3 disease occurred in 44 percent. This pattern closely mimics the type of disease we would consider to be clinically or biologically consequential.

4.15

Functional Variability in SRD5A2 Polymorphisms

Polymorphism	V_{max} (T → DHT)	Relative sensitivity to finasteride
Normal	1.9	60
P30L	0.5	420
A49T	9.9	180
V89L	1.1	113
F194L	2.2	7
R227Q	0.06	260
Fold-difference	198	60

SOURCE: Juergen Reichardt, University of Southern California.

SLIDE 4.15 Where are we going in the future? We know the hypothesis that finasteride competitively inhibits 5-alpha-reductase type 2. Of interest, the gene that codes for that has a number of polymorphisms that code for variance of the enzyme. They have different abilities to make dihydrotestosterone (DHT) and different sensitivity to finasteride.

It may very well be, for example, from the least to most active in combination, there is a 300-fold variation in the activity of finasteride. If you've ever wondered why an individual comes in to be treated for benign prostatic hyperplasia (BPH) and has an immediate response, it is perhaps related to this phenomenon, although that's never been investigated. It's just a hypothesis that we're investigating as part of a program project grant.

4.16

A More Compelling Rationale for Prostate Cancer Prevention

- Our early detection efforts may be off-the-mark
- Among men with prostate cancer who undergo treatment
  - 30% or more will require adjuvant therapy within 5 years
  - One *could* argue that mortality has changed little since 1975
- Yet our diagnostic rate has exploded

SLIDE 4.16 The more compelling rationale for the prevention of prostate cancer has to do with all the issues discussed here, because I have very serious concerns that our early detection efforts may be off the mark.

For example, based on Medicare data in men who have prostate cancer and undergo treatment, approximately 30 percent or more will require adjuvant therapy within five years. These are patients with rising PSAs, seminal vesicle invasion, positive margins and so forth. Using SEER data from 1976 to 2000, one could argue that mortality has not changed much in the United States and yet our diagnostic rate has exploded.

4.17

Potential Problems with Current Detection Methods

- Data from initial PCPT *NEJM* article
- Of prostate cancers detected in the study, 48% were detected at end-of-study
- These were in men with a normal DRE and a PSA <4.0 ng/mL
- In placebo group, 15% had cancer and 15% of these had high grade cancer

SLIDE 4.17 According to the original publication from last year, of the patients with prostate cancer detected in the study, about 48 percent were detected at the end of the study and were in men with a normal digital rectal exam (DRE) and a normal PSA, or at least a PSA less than 4 ng/mL. In the placebo group, approximately 15 percent of these men had cancer, and about 15 percent had high-grade disease.

Select publications

Hull GW et al. **Cancer control with radical prostatectomy alone in 1,000 consecutive patients.** *J Urol* 2002;167(2 Pt 1):528-34. **Abstract**

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

Post-test:
Prostate Cancer Update — Issue 4, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. According to the Pound study, what is the average survival time after PSA recurrence following radical prostatectomy?
   a. 2 years
   b. 5 years
   c. 8 years
   d. 10 years
   e. 13 years

2. Clinical metastasis-free survival benefit is seen when early hormonal therapy is administered to patients with PSA relapse and pathologic Gleason's sum greater than 7 or a PSA doubling time less than 12 months in men who started hormonal therapy before their PSA reached 5 ng/mL.
   a. True
   b. False

3. A PSA doubling time of < 3 months after PSA relapse following radiation therapy or radical prostatectomy is a surrogate for death from prostate cancer.
   a. True
   b. False

4. In the Prostate Cancer Prevention Trial, men who were > 55 years old with a PSA level of < 3.0 ng/mL were randomly assigned to treatment with finasteride or placebo for seven years.
   a. True
   b. False

5. The data from Ian Thompson's finasteride trial, which was published in the July 2003 issue of the *New England Journal of Medicine*, suggests that finasteride:
   a. Prevents the appearance of prostate cancer.
   b. Delays the appearance of prostate cancer.
   c. Resulted in reduced risk of urinary problems.
   d. Was associated with an increased risk of high-grade prostate cancer.
   e. All of the above

6. Sir Richard Peto's meta-analysis of CAP trials on early versus late hormonal therapy demonstrated that an increase in absolute survival may be associated with the early use of hormone therapy.
   a. True
   b. False

7. Randomized controlled trial data clearly supports the use of early hormonal therapy in all men with PSA relapse.
   a. True
   b. False

8. A study by Sarosdy reported in *Urology* demonstrated a survival advantage for bicalutamide plus an LHRH compared to flutamide plus an LHRH in patients with D2 disease.
   a. True
   b. False

9. What tools are available for conducting individual risk/outcome assessment for prostate cancer?
   a. Partin tables
   b. Kattan nomograms
   c. CPDR website
   d. Roach and D'Amico formulas
   e. All of the above

10. Several Phase III trials, which evaluated neoadjuvant hormonal therapy and radical prostectomy in the 1990s, demonstrated which of the following?
    a. 50% reduction in positive margins
    b. No change in PSA recurrence
    c. a and b

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

Evaluation Form:
Prostate Cancer Update — Issue 4, 2004

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

Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

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

OVERALL EFFECTIVENESS OF THE FACULTY MEMBERS

To what extent do you feel the faculty members' comments were helpful or not helpful?

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

Evaluation Form:
Prostate Cancer Update — Issue 4, 2004

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature:..... Date:.....

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:

.....

What other topics would you like to see addressed in future educational programs?

.....

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

.....

Degree:

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

FOLLOW-UP

As part of our ongoing, continuous, quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes, I would be willing to participate in a follow-up survey.

☐ No, I'm not willing to participate in a follow-up survey.

Additional comments about this activity:

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Prostate Cancer™ UPDATE

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SPECIAL EDITION

Prostate Cancer™

UPDATE

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