2005 · Vol 1 · Issue 1

Patterns of Care in Cancer Medicine

Management of Prostate Cancer

Primary Therapy for Intermediate and High-Risk Disease

Rising PSA

Metastatic Disease

Editor

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A Case Survey Comparing Practices of Radiation Oncologists and Urologists

CME Certified

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Continuing Medical Education (CME) Information

STATEMENT OF NEED/TARGET AUDIENCE

It is important for physicians treating prostate cancer to be aware of similarities and differences between his or her practice patterns and those of their peers. It is also important for these physicians to recognize that heterogeneity exists both within and between the urology and radiation oncology communities, especially in clinical situations for which there is suboptimal research evidence.

This program focuses on the self-described practice patterns of randomly selected urologists and radiation oncologists on a variety of key clinical issues in prostate cancer. Also included is clinical investigator commentary and references addressing these issues. This CME program will provide physicians treating prostate cancer with information on national cancer patterns of care to assist with the development of clinical management strategies.

GLOBAL LEARNING OBJECTIVES FOR THE *PATTERNS OF CARE* SERIES

- Compare and contrast management strategies of urologists and radiation oncologists for the treatment of prostate cancer.
- Discuss prostate cancer management issues for which relative agreement and heterogeneity exist in patterns of care.
- Counsel cancer patients about multiple acceptable treatment options when they exist.

PURPOSE OF THIS ISSUE

The purpose of this issue of *Patterns of Care* is to support these objectives by comparing the perspectives of 100 randomly selected community urologists with those of 50 radiation oncologists, all interviewed in depth in September of 2005, and to offer in-depth commentary from faculty regarding their practice patterns in the management of prostate cancer.

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COMMERCIAL SUPPORT

This program is supported by an education grant from AstraZeneca Pharmaceuticals LP.

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Editor's Note: Quality-of-life implications of variations in practice patterns

Direct-to-consumer television ads for pharmaceuticals are supposed to target end users, but the truth of the matter is that any unassuming physician just trying to unwind in front of the tube is also a captive audience for these monotonous, hammering messages.

So it was this past Saturday that with my newly born son, Joseph Jacob (Neilly) Love, perched on my lap, I tried to enjoy the University of Miami's Titus Pullo-like football dismembering of the University of Virginia, while being buried by a video avalanche of PDE5 inhibitor-inspired "educational" ads related to erectile dysfunction.

Fortunately, TiVo® was on our side, and as we zipped through these and other mindless commercials without losing our focus on the U's ground game, I was struck, even in their rapid passing, by the sheer number of messages openly promoting what used to be a very private matter.

The integration of the "ED" concept into the Western psyche over the last few years is an awe-inspiring testimonial to the power of marketing, and it seems as though we have almost reached the point of accepting erectile dysfunction as just another "parts" defect that may require medical attention. But all ED is not created equal, and nowhere is this more apparent than with the currently accepted clinical management options for men with prostate cancer.

One of the great challenges of being a physician is utilizing therapies with significant side effects and toxicities, and in prostate cancer, we encounter perhaps the most provocative and personal set of downsides that exist in current cancer and maybe even noncancer medicine.

For localized disease, the patient experience is very different for men who have their prostates removed surgically compared to those who receive some variant of radiation therapy. During this very stressful waiting game, patients who choose surgery almost universally experience complete postoperative ED, and men lucky enough to have nerve-sparing procedures wait nervously for many months or longer to see whether functional recovery occurs.

Patients who sit under the beam or seed of their friendly radiation oncologist experience a reverse waiting process as gradual vascular compromise in some or most patients eventually results in ED.

The story is even more complicated when systemic therapy enters the equation. Chemical castration results in a highly toxic internal milieu with complex sequelae including ED and loss of libido, diminished muscle and bone mass, and uncomfortable vasomotor symptoms.

Bicalutamide monotherapy, which does not result in many of these problems but does cause gynecomastia, is a largely ignored therapeutic alternative, apparently because the existing clinical research database on this fascinating agent has not sufficiently impressed clinical investigators or the FDA to make it available to patients.

With this as background, let us consider the findings from our CME group's first national prostate cancer patterns of care study. With the expert input of Drs Adam Dicker and Mark Soloway, we designed a case-based telephone survey focused on intermediate and high-risk localized disease, PSA relapse and metastatic disease. (Our 2006 survey will be expanded to include low-risk localized disease.) In September 2005, we contracted the independent market research firm ReedHaldyMcIntosh to conduct this study, which randomly recruited 50 radiation oncologists and 100 urologists practicing in the United States.

As with our prior Patterns of Care studies in breast cancer and colorectal cancer (**www.PatternsofCare.com**), considerable heterogeneity is evident in the treatment recommendations made to men with prostate cancer.

What is unique about this variability is the profound difference in quality-of-life endpoints that exists with prostate cancer treatments compared to treatments for other tumors.

The findings obtained from this survey are probably not that surprising to physicians, who on a daily basis confront practice situations in which the available clinical research database does not clearly delineate the most favorable therapeutic option.

However, I predict that any patient or layperson seeing these data will take a deep breath or gasp and then strongly consider the importance of obtaining a second or third opinion when confronting this disease.

— Neil Love, MD
NLove@ResearchToPractice.net
December 8, 2005

The clinical investigator commentary in this book is from the Prostate Cancer Update *audio series* (**www.ProstateCancerUpdate.com**).

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Primary Therapy for Intermediate and High-Risk Disease

FIGURE 1

Clinically localized prostate cancer

- *Man in good general health*
- *PSA = 8.5, DRE normal, prostate size 40 g*
- *2/10 cores positive for adenocarcinoma (in right lobe: 20% and 30% of each core, respectively)*
- *Gleason Score = 7 (4 + 3) in both cores*

What local therapy, if any, would you most likely recommend for this patient?

	Age 48		Age 65		Age 78	
Observation/no local therapy	—	—	—	—	15% (2%)*	6% (2%)
Brachytherapy	4% (1%)	2%	13% (4%)	28% (10%)	36% (9%)	10% (2%)
External beam radiation	— (1%)	10% (4%)	2%	32% (18%)	33% (20%)	72% (32%)
Brachytherapy + external beam radiation	1%	8% (2%)	4% (2%)	10% (4%)	7% (5%)	6% (2%)
Radical prostatectomy (nerve sparing)	85% (2%)	80% (10%)	74% (2%)	28% (2%)	2%	4% (2%)
Radical prostatectomy (non-nerve sparing)	4% (1%)	—	2% (1%)	2%	—	2%
Laparoscopic prostatectomy	6%	—	5%	—	—	—
Cryosurgery	—	—	—	—	7% (3%)	—
What systemic therapy, if any, would you most likely recommend for this patient?						
LHRH agonist	4%	8%	8%	18%	31%	29%
LHRH agonist + bicalutamide (MAB)	—	4%	—	8%	3%	6%
LHRH agonist + bicalutamide (Flare)	1%	4%	1%	8%	5%	6%
No systemic therapy	95%	84%	91%	66%	61%	59%

* ***Note:*** Numbers in parentheses are percentage of physicians who use this local therapy combined with endocrine therapy.

Hormonal therapy combined with radiation therapy

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ANTHONY V D'AMICO, MD, PHD: The study we published in *JAMA* was a randomized trial with 206 men comparing 3D-conformal external beam radiation therapy (total dose of 70.35 Gray) with or without six months of combined hormonal blockade administered for two months before, two months during and two months after radiation therapy.

In the study, 57 percent of the patients had a PSA that was greater than 10 ng/mL, and 73 percent of the patients had a Gleason Score of seven or higher. This was a study of patients with high-grade cancer. For the most part, patients had T1c disease. More than half the patients had PSA-detected disease and about 50 percent had T2 or palpable tumors.

The primary endpoint of the trial was progression-free survival. Because the effect of hormonal therapy on cancer-related death was higher than expected, we saw a difference in overall survival, just like the Bolla trial. At five years, progression-free survival was 82 percent for the patients treated with hormonal therapy plus radiation therapy versus 57 percent for those treated with radiation therapy alone. This means the patients treated with radiation therapy alone had a PSA elevation and were on hormonal therapy 25 percent more frequently.

Cancer-specific mortality at five years was zero in the patients treated with hormonal therapy plus radiation therapy versus six percent in the patients treated with radiation therapy alone; overall survival demonstrated a 10 percent difference (88 percent versus 78 percent, respectively). The absolute number of deaths due to prostate cancer was six in the radiation therapy-only arm and zero in the hormonal therapy plus radiation therapy arm. Out of 206 patients, a six-event difference in prostate cancer deaths was enough to account for a survival difference, mainly because we initially screened patients for cardiovascular disease. The hazard ratio for overall

UROLOGISTS (N = 100) RADIATION ONCOLOGISTS (N = 50)

FIGURE 2

Clinically localized prostate cancer

- *Man in good general health*
- *PSA = 8.5, DRE normal, prostate size 40 g*
- *2/10 cores positive for adenocarcinoma (in right lobe: 20% and 30% of each core, respectively)*
- *Gleason Score = 8 (4 + 4) in both cores*

What local therapy, if any, would you most likely recommend for this patient?

	Age 48		Age 65		Age 78	
Observation/no local therapy	—	—	—	—	12% (8%)*	4% (2%)
Brachytherapy	3% (2%)	—	11% (7%)	4% (4%)	19% (10%)	6%
External beam radiation	4% (4%)	46% (40%)	10% (7%)	78% (70%)	45% (38%)	88% (76%)
Brachytherapy + external beam radiation	2% (2%)	8% (6%)	9% (5%)	8% (6%)	14% (9%)	2%
Radical prostatectomy (nerve sparing)	69% (10%)	44% (22%)	51% (8%)	10% (2%)	1%	—
Radical prostatectomy (non-nerve sparing)	15% (2%)	2% (2%)	12% (3%)	—	—	—
Laparoscopic prostatectomy	6%	—	5%	—	1%	—
Cryosurgery	1%	—	2%	—	8% (4%)	—
What systemic therapy, if any, would you most likely recommend for this patient?						
LHRH agonist	11%	46%	20%	52%	50%	54%
LHRH agonist + bicalutamide (MAB)	6%	16%	7%	22%	13%	18%
LHRH agonist + bicalutamide (Flare)	3%	8%	3%	8%	6%	6%
Other systemic therapy	2%	4%	3%	4%	1%	6%
No systemic therapy	78%	26%	67%	14%	30%	16%
If you recommend an LHRH agonist for this patient, which of the following is your most likely treatment scenario?						
Neoadjuvant	9%	9%	10%	8%	10%	—
Neoadjuvant and concurrent	9%	22%	35%	23%	24%	22%
Neoadjuvant, concurrent and adjuvant	37%	39%	25%	42%	28%	44%
Concurrent and adjuvant	36%	17%	25%	23%	22%	26%
Adjuvant	9%	13%	5%	4%	4%	4%
Sole treatment	—	—	—	—	12%	4%
For those who recommend an LHRH agonist: Would you recommend continuous or intermittent therapy?						
Continuous	90%	100%	90%	100%	87%	100%
Intermittent	10%	—	10%	—	13%	—

* ***Note:*** Numbers in parentheses are percentage of physicians who use this local therapy combined with endocrine therapy.

FIGURE 3

Clinically localized prostate cancer

- *Man in good general health*
- *PSA = 20, DRE normal, prostate size 40 g*
- *4/10 cores positive for adenocarcinoma (in right lobe: 20% and 30% of each core in both right and left lobes)*
- *Gleason Score = 7 (4 + 3) in all cores*

What local therapy, if any, would you most likely recommend for this patient?

	Age 48		Age 65		Age 78	
Observation/no local therapy	—	—	—	—	8%	4%
Brachytherapy	6%	2%	11%	2%	16%	4%
External beam radiation	4%	52%	21%	74%	54%	84%
Brachytherapy + external beam radiation	4%	10%	13%	14%	12%	4%
Radical prostatectomy (nerve sparing)	53%	30%	32%	8%	—	4%
Radical prostatectomy (non-nerve sparing)	27%	6%	19%	2%	1%	—
Laparoscopic prostatectomy	6%	—	3%	—	2%	—
Cryosurgery	—	—	1%	—	7%	—
What systemic therapy, if any, would you most likely recommend for this patient?						
LHRH agonist	20%	40%	31%	40%	49%	44%
LHRH agonist + bicalutamide (MAB)	12%	28%	15%	34%	19%	36%
LHRH agonist + bicalutamide (Flare)	5%	8%	7%	10%	9%	4%
Other systemic therapy	2%	2%	3%	2%	2%	2%
No systemic therapy	61%	22%	44%	14%	21%	14%
If you recommend an LHRH agonist for this patient, which of the following is your most likely treatment scenario?						
Neoadjuvant	15%	5%	—	5%	6%	5%
Neoadjuvant and concurrent	25%	25%	23%	25%	25%	32%
Neoadjuvant, concurrent and adjuvant	20%	45%	45%	45%	35%	32%
Concurrent and adjuvant	30%	25%	19%	25%	14%	22%
Adjuvant	10%	—	13%	—	8%	—
Sole treatment	—	—	—	—	12%	9%
For those who recommend an LHRH agonist: Would you recommend continuous or intermittent therapy?						
Continuous	87%	97%	85%	95%	83%	95%
Intermittent	13%	3%	15%	5%	17%	5%

survival was two, which means a twofold reduction in deaths in the men randomly assigned to combined hormonal therapy plus radiation therapy.

The validation that the combination of hormonal therapy and external beam radiation therapy provides a survival benefit compared to radiation therapy alone is an important clinical message.

A number of randomized studies have evaluated this comparison, particularly in men with localized high-risk disease.

UROLOGISTS (N = 100) RADIATION ONCOLOGISTS (N = 50)

FIGURE 4

Clinically localized prostate cancer

- *Man in good general health*
- *PSA = 20, DRE normal, prostate size 40 g*
- *4/10 cores positive for adenocarcinoma (20% and 30% of each core in both right and left lobes)*
- *Gleason Score = 7 (4 + 3) in all cores*
- *CT scan showed 2-cm enlarged node along the obturator fossa. Fine needle aspiration (FNA) indicates adenocarcinoma consistent with prostatic origin. Bone scan negative*

What local therapy, if any, would you most likely recommend for this patient?

	Age 48		Age 65		Age 78	
Observation/no local therapy	37%	8%	41%	12%	66%	26%
Brachytherapy	1%	2%	4%	6%	2%	2%
External beam radiation	33%	86%	42%	80%	27%	72%
Brachytherapy + external beam radiation	7%	2%	7%	2%	4%	—
Radical prostatectomy (nerve sparing)	13%	—	1%	—	1%	—
Radical prostatectomy (non-nerve sparing)	9%	2%	5%	—	—	—
What systemic therapy, if any, would you most likely recommend for this patient?						
LHRH agonist	30%	38%	30%	42%	30%	44%
LHRH agonist + bicalutamide (MAB)	54%	48%	53%	46%	48%	42%
LHRH agonist + bicalutamide (Flare)	6%	12%	8%	10%	10%	10%
Other systemic therapy	6%	—	8%	—	10%	2%
No systemic therapy	4%	2%	1%	2%	2%	2%
If you recommend an LHRH agonist for this patient, which of the following is your most likely treatment scenario?						
Neoadjuvant and concurrent	11%	5%	10%	5%	7%	—
Neoadjuvant, concurrent and adjuvant	19%	61%	18%	58%	14%	61%
Concurrent and adjuvant	23%	24%	21%	21%	17%	22%
Adjuvant	5%	5%	3%	5%	—	—
Sole treatment	42%	5%	48%	11%	62%	17%
For those who recommend an LHRH agonist: Would you recommend continuous or intermittent therapy?						
Continuous	80%	94%	82%	94%	82%	96%
Intermittent	20%	6%	18%	6%	18%	4%

"High risk" in this scenario is defined as a Gleason Score of seven or higher or a PSA level greater than 10 ng/mL.

The most recent study, published in *JAMA* in August 2004, demonstrated a 10 percent survival benefit at five years for men who received six months of hormonal therapy in combination with radiation therapy compared to men who received radiation therapy alone. Hormonal therapy consisted of flutamide with either leuprolide or goserelin.

Two questions remain in this scenario: (1) Is combined hormonal blockade necessary? and (2) Are six months of hormonal therapy adequate in patients with Gleason eight, nine or 10 disease, even if it is T1c or T2?

FIGURE 5

Clinically localized prostate cancer

- *Man in good general health*
- *PSA = 20, DRE with bilateral firmness; prostate size 40 g*
- *4/10 cores positive for adenocarcinoma (20% and 30% of each core in both right and left lobes)*
- *Gleason Score = 7 (4 + 3) in all cores*
- *MRI indicates invasion into the right seminal vesicle. Bone scan negative*

What local therapy, if any, would you most likely recommend for this patient?

	Age 48		Age 65		Age 78	
Observation/no local therapy	3%	—	5%	—	34%	4%
Brachytherapy	4%	—	4%	2%	3%	2%
External beam radiation	26%	80%	43%	86%	47%	92%
Brachytherapy + external beam radiation	13%	8%	16%	6%	12%	—
Radical prostatectomy (nerve sparing)	16%	8%	7%	4%	1%	2%
Radical prostatectomy (non-nerve sparing)	26%	2%	17%	—	1%	—
Other local therapy	12%	2%	8%	2%	2%	—

What systemic therapy, if any, would you most likely recommend for this patient?

LHRH agonist	27%	40%	36%	40%	41%	42%
LHRH agonist + bicalutamide (MAB)	32%	40%	34%	40%	36%	36%
LHRH agonist + bicalutamide (Flare)	8%	10%	10%	10%	9%	6%
Other systemic therapy	4%	2%	2%	2%	4%	6%
No systemic therapy	29%	8%	18%	8%	10%	10%

If you recommend an LHRH agonist for this patient, which of the following is your most likely treatment scenario?

Neoadjuvant and concurrent	28%	6%	27%	11%	11%	—
Neoadjuvant, concurrent and adjuvant	25%	61%	27%	58%	30%	56%
Concurrent and adjuvant	31%	33%	29%	31%	21%	38%
Adjuvant	11%	—	10%	—	5%	—
Sole treatment	5%	—	7%	—	33%	6%

For those who recommend an LHRH agonist: Would you recommend continuous or intermittent therapy?

Continuous	85%	98%	86%	100%	86%	100%
Intermittent	15%	2%	14%	—	14%	—

The studies preceding the trial published in *JAMA* were RTOG-9202 and the Bolla trial. The Bolla trial — an EORTC study — found that three years of hormonal therapy is better than no hormonal therapy. RTOG-9202 found that two years and four months was better than just four months of hormonal therapy. It was not an overall survival benefit but a cancer-specific survival benefit of 3.4 percent at five years.

The question still remains whether long-term hormonal therapy is necessary and safe. A European randomized study comparing three years to six months of hormonal therapy should answer the question more definitively. If long-term hormonal therapy truly is better, I sus-

FIGURE 6

Post-radical prostatectomy adjuvant therapy

- *Man in good general health*
- *Underwent radical prostatectomy and node dissection for Gleason Score 7 (4 + 3), PSA 8.5 prostate cancer*
- *PSA undetectable 6 weeks postsurgery*
- *Gleason Score = 7 (4 + 3), negative seminal vesicles, 2 positive margins (1 at apex, 1 posteriorly)*
- *0/5 nodes positive on right, 0/6 nodes positive on left*

What local therapy, if any, would you most likely recommend for this patient?

	Age 48		Age 65		Age 78	
Observation/no local therapy	61%	38%	66%	38%	80%	58%
External beam radiation	39%	62%	34%	62%	20%	42%

What systemic therapy, if any, would you most likely recommend for this patient?

LHRH agonist	8%	10%	7%	8%	6%	6%
LHRH agonist + bicalutamide	5%	2%	5%	2%	3%	2%
No systemic therapy	87%	88%	88%	90%	91%	92%

pect that older men (over 70 years of age), in whom occult cardiovascular disease can be prevalent, will benefit least, whereas younger men who don't have cardiovascular issues may benefit most.

Prostate Cancer Update 2005 (3)

ANTHONY L ZIETMAN, MD: RTOG-8610 and RTOG-9202 are maturing. Every time they're republished, the benefit from adjuvant androgen deprivation therapy seems to be confirmed. We now think about the use of adjuvant androgen deprivation with radiation therapy as follows: Patients with low-risk disease don't need it, and patients with high-risk disease do. We can probably use less hormonal therapy if the patient has a Gleason seven tumor and a PSA below 20 ng/mL. The patient needs more, maybe two or three years of hormonal therapy, if he has both a high Gleason Score and PSA.

The patients with intermediate-risk disease are an intriguing group. Anthony D'Amico published in *JAMA* 2004 the results from a randomized trial in which a little over 200 men with intermediate-risk prostate cancer were randomly assigned to receive radiation therapy alone or with six months of hormonal therapy. Combined androgen blockade was administered two months before, two months during and two months after conventional-dose radiation therapy. Not only did the trial show a disease-free survival advantage, but it has also shown an overall survival advantage at only five years.

Prostate Cancer Update 2005 (1)

ADAM P DICKER, MD, PHD: In radiation oncology, it's almost a mantra that if we don't achieve local control, we won't achieve distant control. This is not only true in prostate cancer; it's also true in breast cancer. Zietman published an article stating that the metastasis rate in prostate cancer is increased when local control is not achieved. Twenty years ago, everyone treated the whole pelvis with radiation to the nodes because it was believed that is where prostate cancer spreads; however, that practice was not based on any evidence. Roach's Phase III trial, RTOG-9413, comparing whole pelvic to prostate-only radiation therapy and neoadjuvant to adjuvant combined androgen suppression, was the first to demonstrate that large-field radiation therapy with neoadjuvant and concurrent hormonal therapy had a benefit as measured by PSA.

It appears radiation therapy will probably cure microscopic disease in the nodes, but only when combined with hormonal therapy. I don't anticipate that radiation therapy alone — at the dose we used, which was limited because of the small bowel — will cure micrometastatic disease. Some people believe hormonal therapy is synergistic with radiation. I've seen no evidence of that; rather, it probably has an additive effect.

I would not use the term "radiosensitizer" because hormonal therapy is active by itself, but it certainly augments radiation. I believe hormonal therapy plays a role, but how much of a role it plays locally is unclear. It's also not clear that the dose used in the Bolla study is sufficient to cure patients. A number of investigators are retrospectively examining their data from patients who received a Bolla-like therapy in various doses during different time periods to determine whether an increase in dose translates to decreased bony metastases and improved survival.

Prostate Cancer Update 2005 (4)

MACK ROACH III, MD: The CaPSURE database would suggest there's been a big

FIGURE 7

Post-radical prostatectomy adjuvant therapy

- *Man in good general health*
- *Underwent radical prostatectomy and node dissection for Gleason Score 7 (4 + 3), PSA 8.5 prostate cancer*
- *PSA undetectable 6 weeks postsurgery*
- *Gleason Score = 7 (4 + 3), margins negative, right seminal vesicle positive*
- *0/5 nodes positive on right, 0/6 nodes positive on left*

What local therapy, if any, would you most likely recommend for this patient?

	Age 48		Age 65		Age 78	
Observation/no local therapy	48%	40%	51%	38%	70%	52%
External beam radiation	52%	60%	49%	62%	30%	48%
What systemic therapy, if any, would you most likely recommend for this patient?						
LHRH agonist	15%	22%	13%	20%	12%	12%
LHRH agonist + bicalutamide	13%	8%	12%	8%	11%	6%
No systemic therapy	72%	70%	75%	72%	77%	82%

increase in the use of hormone therapy with radiation therapy — appropriate use, by and large, in the sense that patients with intermediate and high-risk disease are receiving it. Some individuals are probably still being treated inappropriately because they are receiving hormone therapy for low-risk disease. Some of those may be patients who were trying to decide what they wanted to do and were feeling nervous and wanted to try something because they didn't want to remain untreated. Some of the patients with low-risk disease may have received hormone therapy to shrink the prostate in preparation for brachytherapy.

However, I do suspect some physicians still utilize hormone therapy because they believe that hormone therapy and radiation therapy go hand in hand. Well, it turns out that in patients with low-risk disease, there's no benefit, and hormone therapy causes hot flashes, osteoporosis, fatigue, anemia and impotence. So if you were not going to benefit the patient in terms of biochemical control or survival, I wouldn't recommend it for patients with low-risk disease.

Duration and benefit of adjuvant hormone therapy

Prostate Cancer Update 2005 (2)

LEONARD G GOMELLA, MD: We generally recommend two to three years of adjuvant hormonal therapy when treating patients with locally advanced disease, based primarily on the data from recent trials. Bolla's EORTC trial showed superior outcomes in patients who received three years of hormonal therapy, and the RTOG-9202 showed that two years of hormonal therapy resulted in a survival advantage.

Admittedly, the duration of hormone therapy is controversial. Some institutional studies have suggested that as little as six months of hormonal therapy may be beneficial, and that's possible, but our recommendations rely on the larger multi-institutional trials with thousands of patients. While the prospective randomized trials all show this approach is effective, particularly in patients with high-risk disease, it's not advantageous for all patients. Patients with low-risk disease do not appear to benefit from the combination of hormones and radiation, and the side effects may detract from the patient's quality of life and overall outcome. In the RTOG-9202 trial, an overall survival advantage was seen in patients with high Gleason Scores; however, in the patients with lower-risk disease, although the combination may enhance PSA control, we don't see much improvement in survival.

Prostate Cancer Update 2005 (1)

DR DICKER: A couple of interesting recent research developments relate to the management of locally advanced prostate cancer. First, D'Amico et al reported results of a clinical trial that randomly assigned patients to receive radiation therapy with or without six months of total androgen suppression.

The group that received hormonal therapy demonstrated a survival advantage, which was surprising because the trial did not accrue a large number of patients. These data raise the question of whether six months of hormone therapy is adequate, or whether we need longer-duration therapy.

Another related article that touches on the duration of hormonal therapy is by a group in Finland who evaluated cognitive function in men — with an average age of 65 — before and after six and twelve months of hormonal therapy.

FIGURE 8

Post-radical prostatectomy adjuvant therapy

- *Man in good general health*
- *Underwent radical prostatectomy and node dissection for Gleason Score 7 (4 + 3), PSA 8.5 prostate cancer*
- *PSA undetectable 6 weeks postsurgery*
- *Gleason Score = 7 (4 + 3), margins negative, right seminal vesicle positive*
- *1/5 nodes positive on right, 0/6 nodes positive on left*

What local therapy, if any, would you most likely recommend for this patient?

	Age 48		Age 65		Age 78	
Observation/no local therapy	62%	32%	65%	36%	76%	46%
External beam radiation	38%	68%	35%	64%	24%	54%
What systemic therapy, if any, would you most likely recommend for this patient?						
LHRH agonist	33%	34%	36%	34%	39%	32%
LHRH agonist + bicalutamide (MAB)	34%	28%	34%	30%	26%	24%
LHRH agonist + bicalutamide (Flare)	7%	16%	7%	16%	7%	10%
Other systemic therapy	10%	8%	7%	6%	7%	8%
No systemic therapy	16%	14%	16%	14%	21%	26%
For those who recommend an LHRH agonist: Would you recommend continuous or intermittent therapy?						
Continuous	75%	93%	78%	93%	79%	94%
Intermittent	25%	7%	22%	7%	21%	6%

They found a significant decline in memory, time to process information, recall and visuomotor function associated with the decrease in testosterone. Their data do not directly connect hormonal therapy with the decline in psychomotor function, but it is clear to those who treat prostate cancer that long-duration therapy — more than one year — impacts patients' mental acuity.

Clinicians are interested in determining the maximally effective therapy that can be delivered with minimal side effects. When combined with radiation therapy, total androgen suppression may be equivalent to longer-duration therapy with an LHRH agonist alone for the treatment of clinically localized prostate cancer.

Prostate Cancer Update 2005 (4)

DR ROACH: The patients with high-risk disease who are treated with external beam radiotherapy have been shown to benefit from long-term hormone therapy. The question of how long they should be treated is controversial.

Although it's commonly done, no randomized trials have used one year of adjuvant hormone therapy. The shortest duration shown to improve survival was two years, and that was in RTOG-9202. The EORTC study reported by Bolla used three years of hormone therapy, and RTOG-8531 used hormone therapy for life.

In my opinion, recommending one year of adjuvant hormone therapy is experimental because it has not been proven. I think it may turn out that one year is as good as three years or four years, but in breast cancer, a longer duration of hormone therapy has been shown to be better than a shorter duration of hormone therapy. So in prostate cancer, I think patients with high-risk disease should be offered two years or more of adjuvant hormone therapy.

The most common duration of hormone therapy that I recommend for the typical patient who has T1/T2 disease and a PSA around 10 ng/mL is two years, although there are some patients with whom I do not feel comfortable stopping after two years. I have one patient whose PSA was in the thousands, and he had lymph node involvement. At present, he's doing fine. He's out three years, and his PSA is undetectable. However, I am afraid to discontinue his hormone therapy.

I suspect it's possible he'll be on hormone therapy for the rest of his life. But in the typical patient who's been screened, detected early and treated aggressively with local-regional therapy, including lymph node radiation, my standard use of adjuvant hormone therapy is for two years.

FIGURE 9

Post-radical prostatectomy adjuvant therapy

- *Man in good general health*
- *Underwent radical prostatectomy and node dissection for Gleason Score 7 (4 + 3), PSA 8.5 prostate cancer*
- *PSA = 0.7 six weeks postsurgery*
- *Gleason Score = 8, margins negative, right seminal vesicle positive*
- *0/5 nodes positive on right, 0/6 nodes positive on left*

What local therapy, if any, would you most likely recommend for this patient?

	Age 48		Age 65		Age 78	
Observation/no local therapy	32%	14%	34%	14%	60%	26%
External beam radiation	68%	86%	66%	86%	40%	74%
What systemic therapy, if any, would you most likely recommend for this patient?						
LHRH agonist	30%	28%	32%	28%	27%	30%
LHRH agonist + bicalutamide (MAB)	31%	16%	29%	16%	23%	16%
LHRH agonist + bicalutamide (Flare)	4%	10%	4%	10%	6%	6%
Other systemic therapy	4%	4%	4%	4%	7%	4%
No systemic therapy	31%	42%	31%	42%	37%	44%
For those who recommend an LHRH agonist: Would you recommend continuous or intermittent therapy?						
Continuous	85%	96%	85%	96%	84%	88%
Intermittent	15%	4%	15%	4%	16%	12%

Intermittent hormonal therapy

Prostate Cancer Update 2005 (2)

DR GOMELLA: Intermittent hormonal therapy is not considered the standard of care, but we do use it in select patients. The data on this therapy are conflicting — some preliminary European studies show that it doesn't adversely affect overall PSA recurrence or survival, whereas other studies report adverse outcomes in prostate cancer progression with intermittent therapy.

One of the challenges is that we are waiting for data on intermittent therapy from the large ECOG trial completed in the United States several years ago. The problem is that this trial evaluated intermittent therapy in patients with high PSA levels and metastatic disease. Most of us believe that intermittent therapy will probably be most effective in patients with a low disease burden and minimal PSA elevation.

In fact, we know from the Messing trial that some patients with micrometastatic disease receive hormonal therapy and never have a recurrence.

Certainly some patients who choose to discontinue hormonal therapy will not have disease relapse. This is anecdotal, but I have two young patients who had node-positive, micrometastatic disease with undetectable PSAs postoperatively.

After approximately three years of adjuvant hormonal therapy, they each asked me to take them off of hormonal therapy. They are now approaching almost 10 years since their diagnosis with no evidence of recurrence and they both have normal PSA levels.

What we really need are more studies on intermittent therapy for PSA-only recurrences with low levels. Because we don't have the data, we can't recommend intermittent therapy as a definitive treatment option; however, we can certainly discuss it with patients.

Neoadjuvant hormonal therapy trials

Prostate Cancer Update 2005 (3)

E DAVID CRAWFORD, MD: Years ago, studies of hormonal therapy administered prior to radical prostatectomy were conducted to determine if the positive surgical margin rate could be improved. Dr Soloway did a study in the United States, as did Dr Debruyne in Europe and Dr Gleave in Canada.

These studies showed that the use of hormonal therapy for three or eight months before surgery significantly decreased the positive margin rate. However, at three, five and even six years, no differences in the PSA failure rates were noted, which led people

FIGURE 10

Initial prostate biopsy

How many cores do you usually take when you first biopsy the prostate in a patient with an elevated PSA level? (median)

6 cores	8%
8 cores	20%
10 cores	19%
12-15 cores	50%
Other	3%

FIGURE 11

Frequency of diagnostic testing

How often do you request the following tests for newly diagnosed T1/T2 patients with Gleason Scores less than 7?

	Bone scan		CT scan		MRI	
Always	20%	6%	17%	14%	1%	—
Frequently	13%	4%	6%	12%	4%	—
Sometimes	19%	10%	13%	16%	14%	18%
Rarely	28%	42%	37%	20%	37%	30%
Never	20%	38%	27%	38%	44%	52%

FIGURE 12

Hormonal therapy for T1/T2 disease

In what percentage of patients with T1/T2 prostate cancer do you utilize adjuvant hormonal therapy?

Mean	23%	26%

In general, which LHRH agonist do you recommend? (check all that apply)

Leuprolide	84%	78%
Goserelin	18%	30%
Triptorelin	3%	—
Histrelin	2%	—

In general, which anti-androgen do you recommend? (check all that apply)

Bicalutamide	98%	98%
Flutamide	2%	8%
Nilutamide	1%	—

to believe that neoadjuvant hormonal therapy didn't do anything. These trials, however, were not powered with enough numbers and follow-up time.

My prediction is that with time, some of these studies will show a difference in the PSA failure rates. In patients with local prostate cancer, we're not going to obtain answers quickly. Sometimes it will take 10 or 15 years to observe a difference between the arms of a trial.

Adjuvant hormonal therapy in breast and prostate cancer

Prostate Cancer Update 2005 (1)

PROFESSOR SIR RICHARD PETO: Various reasons exist for the difference in the clinical research data between prostate cancer and breast cancer. First, breast cancer occurs in younger women while prostate cancer occurs in older men.

Obviously, a patient with a 40-year life expectancy is more interested in what happens in the long term than a patient with a 10-year life expectancy.

Second, the early hormonal treatments for prostate cancer were unpleasant. They consisted of castration and diethylstilbestrol (DES), which was discovered to be seriously cardiotoxic and would actually do more harm than good in terms of life expectancy. As soon as DES was no longer used and alternative means of turning off testicular function were discovered, trials began.

Hormonal therapy for prostate cancer substantially delays progression of the disease and moderately delays death from the disease. The effects of immediate hormonal treatment versus deferred hormonal treatment in a man with prostate cancer are comparable to the effects of five years of adjuvant tamoxifen in a woman with hormone-sensitive breast cancer. Additionally, hormonal therapy prevents a number of complications of metastatic disease, such as spinal metastases, ureteric obstruction and the need for further surgery.

The prostate cancer trials were not as large as the breast cancer trials, so the results were muddled by deaths from

FIGURE 13

Neoadjuvant hormonal therapy

When administering neoadjuvant hormonal therapy, how long do you usually continue treatment?

1 month	3%	4%
3 months	25%	50%
6 months	42%	30%
Other	24%	16%
I do not use neoadjuvant hormonal therapy	6%	—

FIGURE 14

Hormonal therapy combined with radiation therapy for locally advanced disease

In general, when you use hormonal therapy in combination with radiation therapy, how long do you continue hormonal therapy?

1 year	37%	22%
2 years	30%	60%
3 years	10%	8%
Indefinitely	4%	—
Other	19%	10%

other causes. The curves are similar, but the prostate trials have statistical noise from the large numbers of deaths that are unrelated to prostate cancer or its treatment. When patients are older, deaths from other causes confuse trial results.

The problem with evaluating hormone therapy for prostate cancer is that only a few thousand men with prostate cancer were being randomly assigned to therapy, compared to tens of thousands of women with breast cancer. That is why the evidence of benefit in breast cancer is so much better.

In breast cancer, we have seen impressive decreases in death rates in middle-aged women as a result of early use of tamoxifen and chemotherapy. I believe the effects of earlier treatment with hormonal therapy in prostate cancer over the next five or 10 years will be comparable to those produced by tamoxifen in breast cancer.

No good evidence indicates that bicalutamide treatment affects mortality from causes other than prostate cancer. Currently, the number of deaths from prostate cancer in the EPC trials is so limited that it is difficult to obtain any clear evidence of an effect on prostate cancer mortality. The question as to the effect on overall mortality is well worth asking, but it needs to be answered by separate analyses of prostate cancer mortality and nonprostate cancer mortality. One should ask, "Is there any evidence of hazard?" No. "Is there any evidence of benefit?" At some point, the answer to that question may well turn out to be "yes."

No good evidence indicates that bicalutamide increases the overall death rate from causes other than prostate cancer. If you have no overall evidence and you begin looking for subgroups of this and subgroups of that, you're almost bound to find a subgroup in which the results seem favorable and a subgroup in which the results seem unfavorable, but that is just statistical noise.

Role of combined hormonal blockade

Prostate Cancer Update 2005 (2)

DR D'AMICO: Off protocol, in patients with high-risk T1c or T2 disease, I use six months of combined hormonal blockade because that is what I used in the study I conducted.

In that study, about 27 percent of the patients did not complete the six months of flutamide, mainly because of elevations in their liver function tests (LFTs). They weren't necessarily having toxicities from the flutamide, but we had a rule: If the LFTs exceeded two times the upper limit of normal, we discontinued the drug for that patient. Despite that, the survival benefit was still seen.

It is an open question whether combined hormonal blockade is really necessary; however, without an answer from a randomized trial, I follow the randomized trial results we have.

When we designed that trial in 1994, bicalutamide wasn't available, so flutamide was used. Today, bicalutamide is used because it's a once-a-day drug and it doesn't have the same LFT issues.

In patients who have T3 or T4 disease by palpation, I use exactly what the RTOG utilized in their randomized study: two months of neoadjuvant combined hormonal blockade, two months of combined hormonal blockade concurrent with radiation therapy and two years of an LHRH agonist alone.

Prostate Cancer Update 2005 (4)

DR ROACH: We generally utilize monotherapy, because the trials have evaluated monotherapy in the adjuvant setting. However, the trial that studied two years of adjuvant hormone therapy used combined blockade for four months. The EORTC study, which looked at three years of hormone therapy, utilized combined blockade for one month. In RTOG-8531, in which they study adjuvant hormone therapy for life, they do

FIGURE 15

Combined hormonal therapy

When utilizing the combination of an LHRH agonist and an anti-androgen, which of the following best describes the purpose and how long do you continue to administer the anti-androgen?

	Adjuvant setting		Metastatic setting	
1 month to prevent flare	47%	52%	10%	38%
3 months to prevent flare	4%	4%	9%	2%
Indefinitely for maximum androgen blockade (MAB)	41%	38%	77%	50%
Other	7%	2%	3%	8%
I do not use combined androgen therapy	1%	4%	1%	2%

FIGURE 16

Neoadjuvant hormonal therapy

Would you recommend hormonal therapy for a newly diagnosed patient with clinically localized disease and a Gleason Score of 6 who, for personal or professional reasons, was required to postpone surgery for 6 months?

Yes	68%	44%
No	32%	56%

If so, which of the following would you generally recommend?

LHRH agonist alone	87%	68%
LHRH agonist with anti-androgen	12%	23%
Anti-androgen alone (bicalutamide 150 mg)	1%	9%

not utilize combined hormone blockade. Most patients would prefer to take combined androgen blockade for four months and two years of hormone therapy.

In 2000, we published a paper — the "meta-analysis" of the RTOG trials. We took all of the trials, pooled them together, and stratified them by their risk of death. We concluded that patients with low-risk disease did not benefit from hormone therapy. Patients with intermediate-risk disease — very much like Dr D'Amico's patients with intermediate-risk disease, except maybe a little bit higher risk — benefited from short-term hormone therapy (four months, for example), and patients with high-risk disease needed long-term hormone therapy.

SWOG-S9921: MAB with or without mitoxantrone/prednisone after prostatectomy

Prostate Cancer Update 2005 (3)

DR CRAWFORD: This ongoing trial, which is very important, randomly assigns men who have had a radical prostatectomy and are at high risk for recurrence to combined androgen blockade for two years with or without chemotherapy. We have almost 500 patients enrolled on this study, and we need about 1,400 to complete it. SWOG-S9921 sets out to define whether adding something to radical prostatectomy makes a difference.

Prostate Cancer Update 2005 (4)

IAN M THOMPSON, MD: Clearly, one of the two most important issues in early prostate cancer is how best to treat high-risk prostate cancer. This issue of adjuvant therapy sits kind of at bookends to the other important issue, which is how to determine clinically important prostate cancer. The issue of adjuvant treatment for high-risk cancer is the bookend that highlights the fact that some men clearly have bad prostate cancer for which monotherapy is inadequate. The question is, what should additional therapy include, be it radiation therapy, hormonal therapy, chemotherapy, biologic response modifiers, or combinations thereof?

If you look at the men in the SWOG-S9921 study, men tolerate treatment with mitoxantrone/prednisone extremely well. The task is explaining to the men that he needs additional therapy because he has high-risk disease and that he can expect to have some hot flashes while on two years of hormonal therapy. As urologists, we oftentimes think a cytotoxic is much worse than an LHRH. However, in our experience, once men understand the side-effect profile of the hormonal therapy and chemotherapy, the two therapies are seen as approximately equal in terms of side effects and toxicities.

Ongoing clinical trials evaluating docetaxel in patients with earlier-stage disease

Prostate Cancer Update 2005 (2)

FIGURE 17

Anti-androgen therapy

Have you ever prescribed bicalutamide 150 monotherapy?

No	63%	68%
Yes	37%	32%
For those answering "yes," in how many patients?		
Mean	16	18

FIGURE 18

Anti-androgen monotherapy

Have you ever utilized bicalutamide 150 mg as monotherapy in patients with clinically localized prostate cancer?

No	82%	92%
Yes	18%	8%
For those answering "yes," in how many patients?		
Mean	6	10

FIGURE 19

Anti-androgen therapy to prevent flare

What is the typical length of anti-androgen therapy you utilize when you prescribe it to prevent flare?

1 month	66%	68%
3 months	7%	14%
Other	24%	8%
I do not use anti-androgens to prevent flare	3%	10%

DR D'AMICO: We are conducting a trial in patients with high-risk disease. Patients are treated with radiation therapy and hormonal therapy with or without docetaxel. The chemotherapy will be administered for two cycles prior to the start of radiation therapy, concurrent with hormonal therapy and weekly during radiation therapy, so it's approximately four months of chemotherapy.

Dr Howard Scher is conducting a trial of hormonal therapy with or without docetaxel in patients with rapidly rising PSAs (eg, doubling times less than three to six months) following surgery or radiation therapy. Dr Mario Eisenberger will be conducting a postoperative adjuvant study in men with high-risk features at prostatectomy (ie, seminal vesicle invasion, Gleason Score of 8 to 10); patients will receive hormonal therapy and be randomly assigned to docetaxel or no further therapy.

It's important to select patients carefully for these studies. For example, the vast majority of patients with a PSA failure after local therapy don't die from prostate cancer. We know now that it's the rate of rise of the PSA — and not the PSA failure itself — that's important, so patients whose PSAs are rising quickly are the patients you want to enroll in these studies. The toxicity from chemotherapy occurs up front, and even younger men require some down time during the chemotherapy regimen. They have to be willing to accept an acute decrement in quality of life for a benefit that's not yet proven.

The study I'm conducting in men with high-risk disease is powered for a hazard ratio of 1.5, whereas the hazard ratio in our study with hormonal therapy was two. With the chemotherapy, we're hoping to see half the improvement that we saw with hormonal therapy. If we had a 10 percent benefit from hormonal therapy at five years, we'd be happy with a five percent benefit from chemotherapy. I'm powering the study for survival, pending the validation of a surrogate (eg, progression-free survival). We evaluated progression-free survival in the study of hormonal therapy and radiation therapy because, when that trial was designed in 1994, that endpoint was in vogue for hormonal therapy. The benefit from hormonal therapy was more than expected. We also saw a difference in survival; however, no data for chemotherapy in localized prostate cancer in a randomized setting indicate that progression-free survival can be used as an endpoint.

In our trial, prevention of bone metastases is a secondary endpoint that is clinically relevant. If you design a prostate cancer clinical trial powered for survival, you'll have plenty of power to go back and evaluate progression-free, disease-free and cancer-specific survival. But if you power the trial for an earlier endpoint, you may not have enough power to evaluate the ultimate endpoint. We expect this study will accrue in two years and be reported three to five years later.

Issues in radiation therapy

Prostate Cancer Update 2005 (3)

DR ZIETMAN: Every five years, the Patterns of Care Study (PCS) group surveys about 60 academic or community-based

FIGURE 20

PSA screening guidelines

Which of the following best describes at what age you recommend PSA screening?

40 for all patients	7%
40 only if African American, 50 for others	14%
40 only if family history of PCA, 50 for others	10%
40 only if African American with family history of PCA, 50 for others	18%
40 only if African American or family history of PCA, 50 for others	51%
50 for all patients	—

FIGURE 21

Use of postimplant CT scans

Do you perform postimplant CT scans?

Yes	94%
No	6%

FIGURE 22

Retreatment after brachytherapy

Have you ever had to re-treat a patient who received brachytherapy? If so, do you re-implant or use supplemental external beam?

Yes, generally re-implant	8%
Yes, generally use supplemental external beam	22%
Yes, use both re-implant and supplemental external beam	4%
No	66%

FIGURE 23

Type of external beam radiation utilized

In general, which form of radiation therapy do you use?

3-D conformal external beam	23%
Intensity modulated (IMRT)	71%
Other	6%

institutions across the United States. It reviews five to 10 randomly chosen patients from each institution to obtain a snapshot of what's going on nationally. In 2004, it reported the 1999 data and compared them to the 1994 data. Hormonal therapy is being used more frequently with radiation therapy in patients with localized prostate cancer, indicating the penetration of randomized trial data into clinical practice. When we break out hormonal therapy use by low-, intermediate- and high-risk prostate cancer, we find many men with low-risk disease who are receiving hormonal therapy with radiation therapy, a situation for which we have no randomized trial data showing any clear advantage.

High doses of radiation are now more frequently used. This trend is actually ahead of the randomized trial data. Both the PCS and the CaPSURE database are showing that external beam radiation therapy is being used less frequently and brachytherapy is being used more frequently in early-stage disease. In 1994, of the cases treated with radiation therapy in the United States, only three percent utilized brachytherapy.

By 1999, it was up to 36 percent, and I can assure you by now it's well above that. The CaPSURE database demonstrates that external beam radiation therapy is being used only a third as frequently in the sites they surveyed.

Prostate Cancer Update 2005 (1)

DR DICKER: Based on retrospective data from Richard Stock, we know that to achieve good biochemical control, 90 percent of the prostate should receive approximately 145 Gray with an I-125 prostate implant. That doesn't mean the patient won't be cured if only 85 percent of the prostate is treated, but if a postimplant CT dosimetry showed only 70 percent or less of the prostate was treated, I would have some concerns.

It doesn't matter whether the CT is performed on the day of the implant or one month later, but it's better to receive feedback as soon as possible after the implantation. It's difficult to remember problems you encountered in the operating room, especially if you performed multiple implants on the same day, and it's important to understand why one patient didn't receive a good dose.

When the prostate implant results in suboptimal coverage, I tell the patient we're not happy with what we achieved in the operating room and, assuming I

understand why things didn't go well and the situation can be corrected, my preference is to reimplant.

Others prefer supplemental external beam radiation therapy, but it is difficult to know what dose of radiation therapy to use. I've performed 500 to 600 implants in my career, and I've only had to reimplant twice. Assuming you didn't overdose the urethra or the rectum on the first implant, reimplantation shouldn't cause an increase in complications.

Prostate Cancer Update 2005 (3)

DR ZIETMAN: Two randomized trials have compared high-dose to conventional-dose external beam radiation therapy. The MD Anderson trial evaluated approximately 300 patients. For the patients with a PSA > 10 ng/mL, there was a clear advantage in terms of freedom from biochemical or disease failure at five years with high-dose radiation (78 Gray) compared to conventional-dose radiation (70 Gray). No advantage was seen for high-dose radiation in patients with a PSA ≤ 10 ng/mL.

The second randomized trial — the Massachusetts General Hospital/Loma Linda University trial — compared high-dose (79 Gray) to conventional-dose (70 Gray) radiation in men who mainly had low-risk disease. Of the 393 patients randomly assigned, approximately 250 had low-risk disease. The number of biochemical failure events at five years was halved for the patients with low-risk and intermediate-risk disease who were treated with high-dose radiation therapy.

Prostate Cancer Update 2005 (4)

DR ROACH: We have looked at our experience at UCSF in patients treated with implants versus those treated with external beam radiation therapy. If you use endorectal MR spectroscopy and look at what happens after external beam radiation therapy versus brachytherapy, there's a tendency for the abnormal spectra to normalize more quickly with brachytherapy.

If you look at time to complete metabolic atrophy — the prostate goes from being active metabolically, which is normal, to an atrophic state, it is significantly shorter with a permanent implant. In a study that observed patients treated with external beam radiation therapy versus brachytherapy, we saw about 70 percent of our patients treated with brachytherapy had complete metabolic atrophy, compared to approximately 20 percent of patients treated with external beam radiation therapy.

If you evaluate PSA decline and pick an arbitrary cutoff of PSA less than 0.5 ng/mL, 90 percent of our patients who were treated with brachytherapy had a PSA at follow-up of less than 0.5 ng/mL. Less than half of the patients who were treated with external beam radiation therapy never got to 0.5 ng/mL; the median PSA was around 0.9 ng/mL.

The metabolic response of the prostate is less dramatic with external beam radiation therapy. The PSA goes down to a lower level with an implant. This carries a number of implications. It doesn't prove that brachytherapy is more effective at curing cancer, but it does suggest that it's more effective at ablating the prostate and lowering PSA.

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FIGURE 24A

Rising PSA after postprostatectomy and external beam radiation therapy

- *Man in good general health*
- *Underwent radical prostatectomy and node dissection for Gleason Score 7 (3 + 4), PSA 8.5 prostate cancer*
- *Negative lymph nodes, seminal vesicles and surgical margins*
- *PSA nadir <0.1, then begins to rise, and the patient then receives external beam radiation*
- *PSA undetectable and then begins to rise as indicated in table*

Months post XRT	PSA
24	0.6
30	0.9
36	1.2
(12-month PSA doubling time)	

What systemic therapy, if any, would you most likely recommend for this patient?

	Age 48		Age 65		Age 78	
LHRH agonist	24%	24%	33%	26%	31%	28%
LHRH agonist + bicalutamide (MAB)	32%	22%	24%	22%	24%	18%
LHRH agonist + bicalutamide (Flare)	6%	6%	7%	6%	6%	8%
Bicalutamide 150 mg alone	6%	8%	5%	8%	—	2%
Other systemic therapy	15%	4%	12%	4%	9%	10%
No systemic therapy/observation	10%	16%	14%	16%	25%	22%
No recommendation/refer to oncologist	7%	20%	5%	18%	5%	12%
For those who recommend an LHRH agonist: Would you recommend continuous or intermittent therapy?						
Continuous	66%	78%	66%	79%	85%	86%
Intermittent	34%	22%	34%	21%	15%	14%

Use of PSA as an endpoint in clinical trials

Prostate Cancer Update 2005 (2)

ROBERT DREICER, MD: With each passing year, the number of patients with locally advanced prostate cancer — who are perhaps destined to do poorly relatively early — continues to decline as we detect disease earlier. This impacts our ability to perform adjuvant studies of chemotherapy. Currently, the FDA would not accept PSA failure as a clinical endpoint, so we have to wait for clinical progression or death. The FDA is actively considering these issues, and at least one forum was held last fall at the FDA, and another one is planned. Changes may be occurring in the agency's attitude toward PSA as an endpoint, but as of today, it's a dilemma. If we can only perform one study a decade, it will be a long time before we can answer the question about adjuvant chemotherapy in the treatment of prostate cancer.

As a clinical trial endpoint, PSA remains problematic in some settings. In patients with biochemical failure only, using PSA failure as a parameter of response remains unproven; however, in the adjuvant setting, I think most of us who take care of these patients would clearly accept time to PSA failure as an endpoint in patients undergoing radical prostatectomy — albeit not the only endpoint. Of course, reasonable assurances must be made to ensure that the PSA failures are real and not simply low levels of detectable PSA in patients who are not destined to progress. That's the optimal use of PSA in how we manage patients today, and it would be problematic to not use PSA failure as at least an intermediate endpoint.

Clearly, in studies of hormonal therapy, PSA failure would not be a useful endpoint. Biologic or targeted therapies are also potentially problematic unless we understand what these drugs do to PSA expression at the cellular level. With chemotherapy, we increasingly have reason to believe it would have validity in the postprostatectomy setting.

Time to delay of PSA failure is probably a good surrogate to activity. That's not to say you should end the trial based on that endpoint and not collect other data, but I believe it's an endpoint that will have some value and allow us to begin testing agents in the adjuvant setting without having to expose patients to Phase III investigations. It would allow us to perform hypothesis-genera-

FIGURE 24B

Rising PSA after radical prostatectomy and external beam radiation therapy

- *Man in good general health*
- *Underwent radical prostatectomy and node dissection for Gleason Score 7 (3+4), PSA 8.5 prostate cancer*
- *Negative lymph nodes, seminal vesicles and surgical margins*
- *PSA nadir <0.1, begins to rise, and the patient then receives external beam radiation*
- *PSA undetectable and then begins to rise as indicated in table*

What systemic therapy, if any, would you most likely recommend for this patient?

Months post XRT	PSA
24	0.6
27	0.9
30	1.2
(6-month PSA doubling time)	

	Age 48		Age 65		Age 78	
Surgical castration	—	—	—	—	10%	8%
LHRH agonist	21%	18%	29%	20%	33%	24%
LHRH agonist + bicalutamide (MAB)	42%	22%	39%	22%	30%	16%
LHRH agonist + bicalutamide (Flare)	4%	12%	4%	12%	5%	8%
Bicalutamide 150 mg alone	7%	6%	6%	4%	—	2%
Other systemic therapy	11%	6%	7%	6%	—	4%
No systemic therapy/observation	8%	8%	10%	8%	17%	12%
No recommendation/refer to oncologist	7%	28%	5%	28%	5%	26%
For those who recommend an LHRH agonist: Would you recommend continuous or intermittent therapy?						
Continuous	77%	81%	79%	81%	85%	88%
Intermittent	23%	19%	21%	19%	15%	12%

tion studies and select agents that make rational sense based on some of these early endpoints and then move on to formal Phase III studies.

Regarding the metastatic setting, Dr Crawford presented data at ASCO 2004 that were based on the preliminary analysis of the SWOG randomized trial S9916. These data suggested that a three-month change in PSA was, in fact, a surrogate for survival in the androgen-independent setting. Is it the same in the hormone-naïve environment? I don't know, and that's an important question.

Use of multiple clinical variables to predict disease recurrence

J Clin Oncol 2005

We developed a nomogram that estimates the probability of a positive bone scan at any time after biochemical failure before the administration of hormonal therapy based on commonly available data, including the results of pathologic analysis of the operative specimen (status of surgical margin, presence of extracapsular extension, seminal vesicle invasion, and Gleason sum at time of radical prostatectomy) as well as postoperative follow-up (tPSA [trigger PSA], PSA slope, and PSA velocity). The advantage of this approach is seen in the predictive ability of our model: bone scan results were predicted with a concordance index of 0.93.

— Zohar A Dotan, MD, PhD et al.
J Clin Oncol *2005;23(9):1962-8.*

JAMA 2005

A short PSA doubling time (PSADT) is associated with increased risk of clinical progression, metastasis, and prostate cancer–specific mortality. However, whether other clinical variables add information to PSADT is less clear. Using a cohort of patients all having biochemical recurrence after radical prostatectomy with prolonged follow-up, we identified 3 significant risk factors for prostate cancer–specific mortality: PSADT, pathological Gleason score, and time from surgery to biochemical recurrence. Using these variables, tables were constructed to estimate the 5-, 10-, and 15-year risk of prostate cancer–specific survival. …

…The 5-, 10-, and 15-year risk of prostate cancer survival for a patient not treated with early hormonal therapy with a PSADT in less than 3 months, recurrence 3 or more years after surgery, and a Gleason score between 8 and 10 was

FIGURE 25A

Rising PSA after primary external beam radiation therapy

- *Man in good general health*
- *Underwent external beam radiation for Gleason Score 7 (3 + 4), PSA 8.5 prostate cancer*
- *PSA nadir was 0.6 at 12 months, begins to rise as indicated in table*

What local therapy, if any, would you most likely recommend for this patient?

Months post XRT	PSA
24	0.6
30	0.9
36	1.2
(12-month PSA doubling time)	

	Age 48		Age 65		Age 78	
Observation/no local therapy	53%	56%	68%	62%	86%	86%
Brachytherapy	4%	6%	4%	8%	1%	4%
External beam radiation	3%	4%	2%	4%	2%	4%
Radical prostatectomy	16%	14%	3%	4%	1%	—
Cryosurgery	24%	20%	23%	22%	10%	6%
What systemic therapy, if any, would you most likely recommend for this patient?						
LHRH agonist alone	16%	22%	23%	28%	23%	28%
LHRH agonist + 50 mg bicalutamide (MAB)	18%	10%	15%	6%	18%	8%
LHRH agonist + 50 mg bicalutamide (Flare)	3%	2%	5%	2%	6%	2%
Bicalutamide 150 mg alone	2%	4%	3%	4%	—	—
Other systemic therapy	9%	4%	7%	4%	6%	4%
No systemic therapy/observation	50%	44%	45%	42%	46%	46%
No recommendation/refer to oncologist	2%	14%	2%	14%	1%	12%

50%, 1%, and less than 1%, respectively. For a similar patient but with a PSADT between 3.0 and 8.9 months, the 5-, 10-, and 15-year risk of prostate cancer survival was 78%, 19%, and < 1%, respectively. …Using the clinical variables of PSADT, Gleason score, and time to biochemical recurrence, patients could be stratified into groups with a varying risk of survival at year 15 of 94% vs < 1%, although the CIs for many of the subgroups were large. …

— Stephen J Freedland, MD et al. JAMA *2005;294(4):433-9.*

Management of PSA relapse

Prostate Cancer Update Special Edition 2005

GREGORY S MERRICK, MD: I'm relatively conservative in managing PSA recurrences. If we're going to treat those patients with hormonal therapy, I do not recommend the institution of androgen deprivation therapy until the PSA doubling time becomes less than 12 months. Once the doubling time is less than 12 months, I think we have to seriously consider it.

The big question then becomes continuous versus intermittent therapy. I have always been a proponent of intermittent because it allows a better quality of life. We like to leave a patient on therapy for nine to 12 months and, if the PSA becomes undetectable, to stop the androgen deprivation therapy until we once again see the PSA exceed some arbitrary point, whether it's 10 or 15 ng/mL.

I believe intermittent androgen deprivation is a marvelous way to approach patients with biochemical failures, especially those who are older, with concomitant medical problems. We've had great success with watching men along these lines. They all appear to respond to the subsequent second or third challenge of hormonal therapy. The one thing that you do note, however, is that with each cycle, the time off hormonal therapy tends to decrease.

Prostate Cancer Update Special Edition 2005

DR D'AMICO: In terms of PSA recurrence, one point that's become apparent across the specialties and now is coming into the community is that the rate of PSA rise dictates the time interval to a positive bone scan. For patients with PSA levels moving rather quickly, even men in their mid to late seventies, unless they

FIGURE 25B

Rising PSA after primary external beam radiation therapy

- *Man in good general health*
- *Underwent external beam radiation for Gleason Score 7 (3 + 4), PSA 8.5 prostate cancer*
- *PSA nadir was 0.6 at 12 months, begins to rise as indicated in table*

What local therapy, if any, would you most likely recommend for this patient?

Months post XRT	PSA
24	0.6
27	0.9
30	1.2
(6-month PSA doubling time)	

	Age 48		Age 65		Age 78	
Observation/no local therapy	60%	64%	69%	72%	87%	86%
Brachytherapy	4%	8%	5%	6%	2%	2%
External beam radiation	1%	4%	1%	4%	1%	4%
Radical prostatectomy	14%	6%	4%	—	—	—
Cryosurgery	22%	18%	21%	18%	10%	8%
What systemic therapy, if any, would you most likely recommend for this patient?						
LHRH agonist	17%	24%	28%	26%	26%	32%
LHRH agonist + bicalutamide (MAB)	25%	18%	19%	18%	21%	10%
LHRH agonist + bicalutamide (Flare)	4%	8%	6%	8%	6%	8%
Bicalutamide 150 mg alone	2%	4%	2%	4%	—	—
Surgical castration	—	—	—	—	4%	4%
Other systemic therapy	9%	4%	8%	4%	3%	6%
No systemic therapy/observation	41%	22%	35%	20%	39%	24%
No recommendation/refer to oncologist	2%	20%	2%	20%	1%	16%
For those who recommend an LHRH agonist: Would you recommend continuous or intermittent therapy?						
Continuous	68%	77%	73%	74%	74%	78%
Intermittent	32%	23%	27%	26%	26%	22%

have really significant comorbid illnesses that are going to take their life this year, I think it is important to carefully consider the hormonal therapy.

Another issue is this: When you use hormonal therapy for a man in the rising PSA setting, how long should you administer it? Forever? Intermittently? For a short course? This question is completely unanswered. A Portuguese study was presented at the AUA this year of intermittent versus continuous therapy for men with rising PSA or node-positive or metastatic disease. While the study only included 800 men, no difference was seen in overall survival between intermittent versus continuous treatment.

I will say that with 800 patients, the trial is likely not large enough to rule out a small benefit to continuous therapy. But this is the first small study of intermittent versus continuous therapy suggesting equality. Equality in this study however is probably limited to a five to seven percent difference. These trials have to be powered as equivalence studies, which means they need thousands of men. The SWOG study is such a study, but is not yet ready to report. So I don't think we're ready to say intermittent and continuous therapy are equivalent yet. But it is a big issue, because lifelong hormonal therapy in the rising PSA setting is not without consequence.

Defining the optimal time to initiate hormonal therapy

Prostate Cancer Update 2005 (1)

DANIEL P PETRYLAK, MD: Randomized trial data suggest that earlier hormone

FIGURE 26A

Rising PSA after primary androgen deprivation

- *Man in good general health*
- *Refuses local therapy*
- *Receiving an LHRH agonist and bicalutamide 50 mg for Gleason Score 7 (4 + 3), PSA 8.5 prostate cancer*
- *PSA nadir was 0.1 on hormonal therapy, begins to rise as indicated in table*

What systemic therapy, if any, would you most likely recommend for this patient?

Months post dx	PSA
24	0.6
30	0.9
36	1.2
(12-month PSA doubling time)	

	Age 48		Age 65		Age 78	
No recommendation/refer to oncologist	33%	38%	30%	38%	24%	34%
LHRH agonist	32%	26%	34%	28%	33%	26%
LHRH agonist + bicalutamide	12%	18%	11%	16%	12%	16%
Other systemic therapy/chemotherapy	12%	4%	13%	4%	12%	4%
No systemic therapy/observation	11%	14%	12%	14%	19%	20%

FIGURE 26B

Same case, shorter doubling time

- *Man in good general health*
- *Refuses local therapy*
- *Receiving an LHRH agonist and bicalutamide 50 mg for Gleason Score 7 (4 + 3), PSA 8.5 prostate cancer*
- *PSA nadir was 0.1 on hormonal therapy, begins to rise as indicated in table*

What systemic therapy, if any, would you most likely recommend for this patient?

Months post dx	PSA
24	0.6
27	0.9
30	1.2
(6-month PSA doubling time)	

	Age 48		Age 65		Age 78	
No recommendation/refer to oncologist	34%	40%	32%	40%	27%	36%
LHRH agonist	29%	24%	31%	26%	32%	30%
LHRH agonist + bicalutamide	12%	20%	11%	20%	11%	18%
Other systemic therapy	13%	14%	12%	12%	12%	10%
No systemic therapy/observation	12%	2%	14%	2%	18%	6%

therapy is beneficial at the point of PSA progression, but no data absolutely indicate benefit in the asymptomatic patient with a rising PSA. We know from studies of combination therapy that patients at high risk will benefit from early hormonal therapy plus radiation therapy. Ed Messing's trial randomly assigned patients who had positive lymph nodes after prostatectomy to immediate hormonal therapy versus delayed hormonal therapy. The trial demonstrated that earlier hormonal therapy was beneficial.

A number of important questions must be answered. Does a threshold value of PSA need to be defined for these patients? Does PSA doubling time depend on regional clinical characteristics? We need to investigate these questions.

Prostate Cancer Update 2005 (2)

DR DREICER: Earlier versus deferred hormonal therapy is a major breaking point in the GU community — particularly among the zealous believers in early androgen deprivation and the more nihilistic among us. In my own practice, because we see a large number of patients with biochemical failure, I have alternative, immunomodulatory investigational options. Putting that aside, PSA doubling time is increasingly useful to predict which patients are more likely to develop systemic progression in the hormone-naïve setting.

FIGURE 27

Hormonal therapy for the treatment of rising PSA level

When prescribing androgen deprivation therapy, what percentage of the time is it with each of the following?

	Adjuvant setting		Metastatic setting	
LHRH agonist	50%	45%	29%	34%
LHRH with anti-androgen (MAB)	21%	20%	44%	28%
LHRH with anti-androgen (Flare)	19%	25%	20%	25%

FIGURE 28

Intermittent hormonal therapy

Do you use or have you used intermittent androgen suppression?

	Adjuvant setting		Metastatic setting	
Yes	64%	29%	56%	45%
No	36%	71%	44%	55%

FIGURE 29

Rising PSA level

In general, in a patient with a rising PSA level, do you utilize either PSA doubling time or PSA velocity to determine when to initiate or recommend treatment?

Yes	90%	84%
No	10%	16%

I discuss the controversies of early androgen deprivation with patients and discuss why my colleagues are advocates of earlier therapy. When the patient asks me, ultimately, where I stand on the matter, I tell him that I respect the toxicity profile of androgen deprivation therapy. For a long time we have undersold the impact of androgen deprivation on quality of life.

I tend to advocate early androgen deprivation therapy for the motivated patient with a shortening PSA doubling time, which sometimes occurs after a relative period of stability. Now, is that correct? I don't know the answer to that question, but in my practice, that's the situation in which I talk to patients in a more proactive way.

RTOG-9601: Radiation therapy with or without bicalutamide 150 mg

Prostate Cancer Update 2005 (2)

DR GOMELLA: This Phase III randomized study is in patients with PSA relapse following radical prostatectomy. The study is closed to accrual, and we are anxiously awaiting the data. This will be one of the most exciting trials to be reported because it will determine whether it's beneficial to combine hormonal manipulation with radiation therapy in the salvage setting.

RTOG-8531 showed that patients who received radiation and hormones together after radical prostatectomy for unfavorable prostate cancer had a survival advantage over patients who only received radiation therapy. I believe RTOG-9601 will also be a positive study because we know the effectiveness of bicalutamide 150 mg in the adjuvant setting. Based on the Iverson and See data, it would be a stretch to think the combination would not be more effective than radiation therapy alone.

Bicalutamide 150 mg is approved in over 50 countries around the world; however, it has not received FDA approval in the United States. In Europe, bicalutamide is commonly used as step-up therapy in which patients receive oral agents, such as a 5-alpha reductase inhibitor, with a small dose of bicalutamide. The bicalutamide dose is then increased up to 150 mg before the patients are started on an LHRH analog as their definitive therapy.

Currently at our center, the medical oncologists' standard salvage regimen for patients whose disease is failing standard androgen ablation is bicalutamide 150 mg. We have seen responses to this regimen last for over a year and a half, so it appears to be reasonable salvage therapy and can be offered to patients. It does appear that a small percentage of men

FIGURE 30

Frequency of PSA testing

In general, how frequently do you test the PSA level in patients after initial local treatment?

Every 3 months	48%	38%
Every 4 months	15%	20%
Every 6 months	30%	38%
Every 12 months	4%	2%
Other	3%	2%

FIGURE 31

"PSA bounce"

What percentage of your patients who undergo radiotherapy for prostate cancer experience "PSA bounce"/benign rise?

<5%	18%	18%
6-25%	59%	56%
26-50%	15%	26%
>50%	8%	—

FIGURE 32

Benign rise in PSA level

How long do you wait after radiation therapy before evaluating the patient's PSA level?

<6 months	42%	62%
6 months	49%	36%
12 months	3%	2%
18 months	6%	—

may have an increased cardiac toxicity associated with the drug. The number of men who had adverse cardiac outcomes and the number of increased death rates in the low-risk arms of the EPC studies with bicalutamide 150 mg were low, but noticeable. These findings may have been statistical aberrations or statistical noise; nonetheless, they need to be further examined.

Although bicalutamide 150 mg is not currently approved for salvage therapy in the United States, I believe it's appropriate to discuss it with patients for whom it may be suitable, such as those who are sexually active and want to maintain their sexual functioning.

Bicalutamide can preserve sexual function, whereas a high percentage of men on an LHRH analog therapy experience significant sexual dysfunction. Quality of life and determining what's important to the patient have become central issues when considering treatment alternatives in prostate cancer.

Intermittent androgen deprivation therapy

Prostate Cancer Update 2005 (3)

LAURENCE KLOTZ, MD: I think the role of intermittent androgen deprivation therapy for patients with D2 disease is not that compelling. Of course, the more common situation is a rising PSA after the failure of local therapy, and the majority of these patients are being treated with hormonal therapy too early and aggressively. Many of them, such as a 75-year-old man who received radiation therapy five years ago and now has a PSA of 3 ng/mL, are probably not at risk of death from prostate cancer. Opinions vary, but my view is that many of these patients are not at risk. The data are clear that these patients do not need to be treated at that point.

If they are going to be treated, however, the less treatment the better, and intermittent androgen deprivation therapy is appropriate, even if the trials show a modest adverse effect on survival. I think the patients who are at risk of not doing well on intermittent androgen deprivation therapy are those with quite advanced, relatively rapidly progressing, life-threatening disease.

Impact of brachytherapy on PSA

Prostate Cancer Update 2005 (3)

DR ZIETMAN: We've learned that after brachytherapy, we have to sit on our hands for three or four years. If the PSA goes up, we need to ignore it. In fact, we could make a case for not checking the PSA at all in the first three years, which is hard to sell to patients. The median time to the PSA bounce is about 18 months, and it should be heading down again within the third or the fourth year. If it's not, something is probably wrong. The PSA after brachytherapy keeps going down, and at seven or eight years, the median PSA is lower than at four or five years.

FIGURE 33

"PSA bounce"

If you suspect "PSA bounce"/benign rise, do you treat the patient with either antibiotics or an anti-inflammatory?

Antibiotics and an anti-inflammatory	10%	10%
Antibiotics	3%	6%
Anti-inflammatory	6%	10%
I do not recommend antibiotics or an anti-inflammatory	81%	74%

FIGURE 34

"PSA bounce"

If you suspect "PSA bounce"/benign rise in a patient, when do you re-evaluate the PSA level?

1 month	2%	6%
2 months	7%	10%
3 months	60%	66%
4 months	10%	6%
6 months	21%	12%

FIGURE 35

Rising PSA level after local therapy

In general, after radical prostatectomy, what PSA level is your threshold to initiate or recommend some type of treatment?

≥0.2	22%	46%
≥0.4	39%	30%
Other	13%	16%
I base this decision on PSA doubling time/PSA velocity	26%	8%

FIGURE 36

Rising PSA level after local therapy

In general, in patients more than one year after radiation therapy, what PSA is your threshold to initiate or recommend some type of treatment?

≥1	19%	8%
≥1.5	24%	8%
Other	10%	20%
I base this decision on PSA doubling time/PSA velocity	47%	64%

Bicalutamide monotherapy for rising PSA

Prostate Cancer Update 2005 (3)

DR KLOTZ: Certainly, people talk about the benefit of bicalutamide 150 mg in terms of sparing libido, but I think the bone mineral density story is more compelling. Bicalutamide 150 mg actually increases bone mineral density because the high levels of testosterone are converted into estrogen, which is a bone mineral density-sparing hormone. To me, that is really the strong argument for its use.

There are two caveats, however. First is the question of whether bicalutamide 150 mg is equivalent in terms of duration of survival. The second issue is gynecomastia. A number of my patients who are on the bicalutamide EPC trial have had breast reduction surgery. They're quite happy, but this was definitely an issue for them.

I have not used much prophylactic radiation in these patients. I probably should use more of it, but it doesn't work in everyone, and it's radiation to the chest. The patients aren't too keen about it, so I haven't really employed it. There are studies using tamoxifen, but one of the problems is that if it's the estrogen that's contributing to the increase in bone mineral density, maybe by using tamoxifen to block gynecomastia, you're blocking the benefit to bone mineral density. From a theoretical perspective, it is possible tamoxifen will have an adverse effect.

Prostate Cancer Update 2005 (4)

HOWARD I SCHER, MD: Bicalutamide monotherapy does have some side effects, in terms of fatigue and gynecomastia, which can be significantly disfiguring. In the early 1990s when PSA was starting to be utilized, we were being referred patients from our surgical and radiation oncology colleagues with a rising PSA alone.

Recognizing that the toxicities of bicalutamide alone were different, we actually conducted a study and still have patients on it from 1993 using bicalutamide 200 mg, not the 150 mg dose, just trying to see if we could control the dis-

ease. We did observe that patients had disfiguring gynecomastia, in some cases requiring surgical reduction. But then again, of the original 50 patients who had a rising PSA, there were still eight on therapy in the year 2005. Almost an overwhelming majority had PSA responses. Again, this was a 200 mg dose. This is an option we bring up with patients.

In addition to discussing the gynecomastia with patients, we also have to discuss bicalutamide in the context of the randomized trials, which suggest that the outcomes may in fact be inferior to conventional hormones alone in patients with metastatic disease. What was of interest in the trial we conducted, and others as well, was that we've looked at the response in patients who've been on bicalutamide monotherapy and then cross to a GnRH analog.

The idea being, okay, we'll protect your bones. You'll be stronger while you're on bicalutamide, and then we'll add the conventional hormone later. It was only about 30 percent who responded with the crossover. So it's clearly a different drug. Again, we do discuss it, but I think pound for pound, it's probably not equivalent to more conventional hormones. That said, there are patients who will opt for it.

Role of chemotherapy in PSA relapse and locally advanced disease

Prostate Cancer Update 2005 (1)

DR DICKER: I usually refer patients with PSA relapse and no evidence of skeletal disease to medical oncologists who specialize in prostate diseases. I also encourage them to enroll in clinical trials that evaluate cytostatic therapy or some of the anti-androgen-type drugs. I believe most medical oncologists would be uncomfortable using cytotoxic therapy in a patient who does not have a positive scan. We don't have any evidence that simply reducing PSA in a patient with nonradiographic metastatic disease has an impact. Chemotherapy has the potential to harm patients, and we don't know the optimal duration for chemotherapy. We have preclinical data evaluating the anti-angiogenic effects of taxanes (both paclitaxel and docetaxel) in a variety of disease settings. I believe in the next year or two we'll see chemotherapy being combined more frequently with hormones and radiation therapy in the locally advanced disease setting. We all agree that a Gleason eight, nine or 10 is locally advanced disease, but we see plenty of tumors with lower Gleason scores and 15 out of 15 positive biopsies. I put those patients in a locally advanced disease category because if they have surgery they will have positive margins, and some will have seminal vesicle and lymph node involvement. It's a gray area, but patients with a Gleason seven, PSA less than 10 and appropriate performance status may benefit from hormones and chemotherapy.

Prostate Cancer Update 2005 (4)

DR SCHER: Regarding patients with a rapid PSA doubling time but with PSA-only disease, I'm not sure we fully know the natural history of that group. The tendency has been to use a second- and third-line hormone therapy first. Again, that will depend on the initial response, but I've seen situations where the second hormonal response exceeds the first. It doesn't make sense, but that's what has happened. There's a real debate as to when to play the chemotherapy card.

I could probably count on one hand the number of times I've actually recommended chemotherapy for this group. It's a not a curative treatment, so the real question is, when do you play that card? If it were curative, that would be a different story.

Prostate Cancer Update 2005 (4)

DR ROACH: Certain things make me nervous about not treating somebody with chemotherapy. If there are pretreatment high-risk features — a high-grade tumor, high Gleason score, high PSA, they were treated and now they've failed. The earlier they failed, the faster their PSA is rising; these are the issues that tend to make me want to be more aggressive with chemotherapy.

In patients who have low-risk features at the outset — the PSA and stage are not that high — and they have PSA-only failure, but their PSA is going up slowly, I would not recommend chemotherapy, although it's possible that they would benefit. The data for androgen-independent disease is primarily based on patients who had extensive experience with hormonal therapy and had been through multiple manipulations with hormone therapy; they also had metastatic disease, by and large, as opposed to PSA-only failure. There are studies that are being contemplated in the RTOG and other places, based on patients with PSA-only failure, in which the PSA doubling time is being incorporated into the eligibility to try and select out patients who are at higher risk for death.

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FIGURE 37

Metastatic disease: No prior therapy

- *Man in good general health*
- *PSA = 30*
- *6/10 cores positive for adenocarcinoma (20%, 30% and 30% of each core in both right and left lobes)*
- *Gleason Score = 7 (4 + 3)*
- *Bone scan reveals three areas of increased uptake in T12, L1, L2 consistent with metastases*
- *Patient is asymptomatic*

Would you recommend external beam radiation to the T12, L1, L2 region?

	Age 48		Age 65		Age 78	
Yes	19%	20%	21%	16%	16%	16%
No	81%	80%	79%	84%	84%	84%
What systemic therapy, if any, would you most likely recommend for this patient?						
Surgical castration	3%	—	5%	—	12%	—
LHRH agonist	15%	16%	17%	18%	15%	24%
LHRH agonist + bicalutamide (MAB)	49%	32%	45%	30%	38%	30%
LHRH agonist + bicalutamide (Flare)	19%	22%	21%	22%	24%	22%
Other systemic therapy	9%	10%	7%	10%	5%	2%
No systemic therapy/observation	1%	2%	1%	2%	2%	4%
No recommendation/refer to oncologist	4%	18%	4%	18%	4%	18%
For those who recommend an LHRH agonist: Would you recommend continuous or intermittent therapy?						
Continuous	91%	91%	92%	89%	90%	84%
Intermittent	9%	9%	8%	11%	10%	16%

Benefits of MAB with bicalutamide in patients with metastatic disease

Prostate Cancer Update 2005 (3)

DR KLOTZ: Our analysis integrated the results from trials with a common treatment arm in situations in which it's no longer feasible to conduct a placebo-controlled trial. Dr Schellhammer compared bicalutamide to flutamide with goserelin or leuprolide and demonstrated a 13 percent reduction in the risk of death for the patients receiving bicalutamide compared to those receiving flutamide.

We integrated those data with the results from the meta-analysis of the Prostate Cancer Trialists' Collaborative Group, which demonstrated a significant eight percent reduction in the risk of death for patients treated with flutamide plus castration compared to those treated with castration alone. The flutamide/castration arm can be cancelled out, and you end up with a comparison of bicalutamide plus castration to castration alone even though they have never been directly compared. This analysis demonstrated a 20 percent reduction in the risk of death for patients treated with bicalutamide plus castration.

Use of maximal androgen blockade

Prostate Cancer Update 2005 (1)

DR PETRYLAK: The survival data from the SWOG studies — particularly SWOG-8494, in which Dave Crawford was the principal investigator — showed approximately a three-month improvement in survival in favor of combined blockade compared to an LHRH agonist alone.

I use maximal androgen blockade. Certainly, we've treated patients with more aggressive therapy for less of a survival benefit. I believe it can't hurt. And if it can't hurt and has a possibility of

FIGURE 38

Metastatic disease: No prior therapy

- *Man in good general health*
- *PSA = 30*
- *6/10 cores positive for adenocarcinoma (20%, 30% and 30% of each core in both right and left lobes)*
- *Gleason Score = 7 (4 + 3)*
- *Bone scan reveals three areas of increased uptake in T12, L1, L2 consistent with metastases. MRI reveals no cord compression.*
- *Patient complains of back pain*

Would you recommend external beam radiation to the T12, L1, L2 region?

	Age 48		Age 65		Age 78	
Yes	81%	92%	80%	92%	77%	92%
No	19%	8%	20%	8%	23%	8%
What systemic therapy, if any, would you most likely recommend for this patient?						
Surgical castration	3%	—	4%	—	10%	—
LHRH agonist	11%	14%	13%	14%	12%	22%
LHRH agonist + bicalutamide (MAB)	46%	30%	43%	30%	41%	24%
LHRH agonist + bicalutamide (Flare)	23%	26%	24%	26%	23%	27%
Other systemic therapy	14%	8%	13%	8%	9%	2%
No systemic therapy/observation	—	2%	—	2%	1%	4%
No recommendation/refer to oncologist	3%	20%	3%	20%	4%	21%
For those who recommend an LHRH agonist: Would you recommend continuous or intermittent therapy?						
Continuous	91%	91%	92%	91%	91%	86%
Intermittent	9%	9%	8%	9%	9%	14%

improving survival, I will use the combined blockade with bicalutamide, which is the easiest drug for me to administer and for the patient to receive.

Intermittent versus continuous androgen deprivation

Prostate Cancer Update 2005 (3)

DR CRAWFORD: SWOG-S9346, which has been ongoing for a number of years, has accrued about 2,000 patients. Men with newly diagnosed, untreated metastatic disease receive combined androgen ablation. At nine months, if their PSA drops below 4 ng/mL, they are randomly assigned to continuous or intermittent therapy. With intermittent therapy, the patient resumes hormonal therapy when his PSA goes up to a predetermined level — usually half of the baseline level or 10 ng/mL.

The whole idea is to provide a hormonal therapy holiday to reduce toxicity and costs. Integrated in that trial is the use of bisphosphonates, particularly zoledronic acid, to evaluate their effects on bone disease.

We have enough data suggesting that intermittent therapy is probably not going to make the patient's scenario worse; at least that's what has been reported.

Whether it's going to be better is unknown. If the benefit is the same as for continuous therapy, it's a no-brainer that intermittent therapy would be the choice, since patients can have a drug holiday with fewer side effects and less expense.

Earlier integration of medical oncologists in management

Prostate Cancer Update 2005 (1)

DR PETRYLAK: In the community, urologists usually attempt a couple of hormonal manipulations and then send their patients to the oncologist. The optimal time to start chemotherapy is a bit of an art, and no FDA guidelines delineate the

FIGURE 39A

Metastatic disease: Prior therapy; 12-month PSA doubling time

- *Man in good general health*
- *Underwent external beam radiation therapy concurrent with LHRH agonist and bicalutamide 50 mg for Gleason Score 8 (4 + 4), PSA 12 prostate cancer*
- *PSA nadir was <0.1*
- *Bone scan now reveals three areas of increased uptake in T12, L1, L2 consistent with metastases*
- *Asymptomatic*
- *2.5 years post radiation the PSA is 1.5 and rises as indicated in table*

What systemic therapy, if any, would you most likely recommend for this patient?

Years post XRT	PSA
2.5	1.5
3.5	3.0
4.5	6.0
(12-month PSA doubling time)	

	Age 48		Age 65		Age 78	
LHRH agonist	34%	30%	34%	30%	35%	36%
LHRH agonist + bicalutamide (MAB)	15%	14%	16%	14%	12%	14%
LHRH agonist + bicalutamide (Flare)	6%	2%	6%	4%	6%	4%
Bicalutamide 150 mg alone	2%	2%	2%	2%	1%	2%
Docetaxel	3%	6%	3%	4%	1%	2%
Other systemic therapy	9%	4%	8%	4%	10%	6%
No systemic therapy/observation	—	6%	—	4%	5%	4%
No recommendation/refer to oncologist	31%	36%	31%	38%	30%	32%

proper time to start chemotherapy.

Not all patients with hormone refractory disease should start chemotherapy. I believe patients should see an oncologist initially, but they should never lose contact with their urologist. The urologist is the primary caregiver who diagnoses the disease and may have removed the prostate. These patients will continue to depend on their urologists when problems and complications develop from the prostate cancer, such as urinary tract obstruction, stinting and transurethral resections of the prostate.

Incorporating chemotherapy into the treatment of prostate cancer

Prostate Cancer Update 2005 (1)

DR DICKER: Two trials reported at ASCO 2004 demonstrated a survival advantage in patients with hormone-refractory disease receiving docetaxel-based therapy. Docetaxel is being extensively evaluated in clinical trials in patients with metastatic disease that is not hormone refractory. Various randomized trials are evaluating hormones with or without chemotherapy in the nonrefractory population. We don't know if chemotherapy — particularly docetaxel-based chemotherapy — combined with hormones is beneficial in patients with locally advanced disease. Chemotherapy regimens involving taxanes and estramustine have been evaluated, but estramustine has a number of side effects, including deep vein thrombosis. Those studies have been plagued with toxicities and haven't really moved forward.

Prostate Cancer Update 2005 (1)

DR PETRYLAK: Our first studies evaluating docetaxel with estramustine were performed in the laboratory in 1995. We were excited by what we saw in vitro and moved forward into a Phase I study that opened in February of 1996.

One of the old jokes about Phase I studies is that the first patient responds but then nobody else does. Well, the opposite happened in that study: The first patient didn't respond, but nearly every subsequent patient did. We saw promising responses in patients who were heavily pretreated. Median survival was close to 24 months, and that was the highest reported median survival of any study at that time.

This background provided the basis for SWOG-9916, which is a randomized trial comparing docetaxel/estramustine to mitoxantrone/prednisone in men with progressive androgen-independent prostate cancer and soft-tissue or bony metastases. These were not the asymptomatic patients with rising PSA only. They had to progress by one of three criteria: bone scan, CT or PSA. The trial opened in October 1999 and closed in January 2003. We demonstrated a 20 percent reduction in the rate of death in favor of those patients who received docetaxel/estramustine; however, estramustine-related toxicity was problematic

FIGURE 39B

Metastatic disease: Prior therapy; 6-month PSA doubling time

- *Man in good general health*
- *Underwent external beam radiation therapy concurrent with LHRH agonist and bicalutamide 50 mg for Gleason Score 8 (4 + 4), PSA 12 prostate cancer*
- *PSA nadir was <0.1*
- *Bone scan now reveals three areas of increased uptake in T12, L1, L2 consistent with metastases*
- *Asymptomatic*
- *2.5 years post-radiation the PSA is 1.5 and rises as indicated in table*

What systemic therapy, if any, would you most likely recommend for this patient?

Years post XRT	PSA
2.5	1.5
3.0	3.0
3.5	6.0
(6-month PSA doubling time)	

	Age 48		Age 65		Age 78	
LHRH agonist	31%	24%	32%	24%	33%	34%
LHRH agonist + bicalutamide (MAB)	12%	18%	12%	18%	10%	12%
LHRH agonist + bicalutamide (Flare)	5%	2%	5%	2%	5%	2%
Bicalutamide 150 mg alone	2%	2%	1%	2%	1%	4%
Docetaxel	3%	8%	3%	8%	3%	2%
Other systemic therapy	12%	6%	12%	6%	11%	6%
No systemic therapy/observation	3%	2%	3%	2%	5%	2%
No recommendation/refer to oncologist	32%	38%	32%	38%	32%	38%

and included deep venous thromboses, cardiovascular events and nausea.

A related and important trial was TAX-327, which compared docetaxel weekly or every three weeks plus prednisone to mitoxantrone/prednisone. Survival was improved with every three-week docetaxel. The data from both studies demonstrate for the first time that we have a chemotherapeutic agent — docetaxel — that results in prolonged survival for men with hormone-refractory prostate cancer.

Because the estramustine-related toxicity was problematic and the median survival and hazard ratios are similar for docetaxel/prednisone and docetaxel/estramustine, the FDA has recommended docetaxel/prednisone as the standard of care for hormone-refractory metastatic prostate cancer.

The FDA approved docetaxel for patients with hormone-refractory metastatic prostate cancer but didn't specify when it should be utilized. Hormone-refractory prostate cancer is a continuum. In general, the first sign of disease breakthrough is a rising PSA, and the patient is often asymptomatic. Generally, after seven to 12 months, we start seeing changes in scans, and patients become symptomatic. A window exists during which markers are going up and the patient is asymptomatic, yet the patient may want treatment.

Often physicians will try a second hormonal manipulation, such as ketoconazole, high-dose bicalutamide or nilutamide. All of these seem to have a 20 percent to 40 percent rate of response and a median time to progression of about four months, but no proven survival benefit.

An interesting observation gleaned from a subanalysis of TAX-327 data is that the hazard ratios for survival are similar whether patients are asymptomatic or symptomatic, and the difference of two months in median survival is conserved for both symptomatic and asymptomatic patients.

It is difficult to decide whether to utilize docetaxel in patients who are asymptomatic but have rising PSAs. It is important to evaluate how rapidly the disease is progressing. Clearly, if the PSA is not rising rapidly, you have time to try other manipulations. In my experience, by the time those manipulations fail, patients need chemotherapy.

In asymptomatic patients with rapidly rising or rapidly doubling PSA levels, progression of soft-tissue disease or progression on bone scan, I consider initiating chemotherapy. During the initial PSA rise, unless the patient has visceral disease, I'm not in favor of using chemotherapy. I would utilize an investigational agent or a secondary hormonal manipulation.

To use a baseball analogy, docetaxel can be saved as the "relief pitcher" for late innings, or you can use it earlier as your starting pitcher. Either way, we know that docetaxel has a high response rate

FIGURE 40A

Metastatic disease: Prior therapy; 12-month PSA doubling time

- *Man in good general health*
- *Underwent external beam radiation therapy concurrent with LHRH agonist and bicalutamide 50 mg for Gleason Score 8 (4 + 4), PSA 12 prostate cancer*
- *PSA nadir was <0.1*
- *Bone scan now reveals three areas of increased uptake in T12, L1, L2 consistent with metastases. MRI reveals no cord compression.*
- *Patient complains of bone pain*
- *2.5 years post-radiation the PSA is 1.5 and rises as indicated in table*

What systemic therapy, if any, would you most likely recommend for this patient?

Years post XRT	PSA
2.5	1.5
3.5	3.0
4.5	6.0
(12-month PSA doubling time)	

	Age 48		Age 65		Age 78	
LHRH agonist	26%	16%	26%	16%	28%	26%
LHRH agonist + bicalutamide (MAB)	11%	16%	11%	16%	10%	10%
LHRH agonist + bicalutamide (Flare)	1%	2%	1%	2%	1%	2%
Bicalutamide 150 mg alone	1%	4%	1%	4%	1%	2%
Docetaxel	3%	10%	3%	8%	3%	4%
Other systemic therapy	13%	10%	13%	10%	12%	14%
No systemic therapy/observation	—	2%	—	2%	1%	4%
No recommendation/refer to oncologist	45%	40%	45%	42%	44%	38%

and a proven survival benefit.

TAX-327: Docetaxel/prednisone versus mitoxantrone/prednisone

Prostate Cancer Update 2005 (3)

MARIO A EISENBERGER, MD: The patients enrolled in this trial had hormone-refractory metastatic prostate cancer and a testosterone level in the castrate range. Patients were allowed to have received only one prior chemotherapy treatment with estramustine and were withdrawn from anti-androgen therapy. The trial's endpoint was survival. We wanted to detect a hazard ratio of 0.75 for survival in favor of docetaxel.

The three treatment arms included: (1) docetaxel 75 mg/m^2 every three weeks plus prednisone, (2) docetaxel 30 mg/m^2 weekly for five out of six weeks plus prednisone and (3) mitoxantrone 12 mg/m^2 every three weeks plus prednisone. We enrolled 1,006 patients over two years, and the analysis occurred about three and a half years after the first patient was enrolled. Each treatment arm had more than 300 patients.

With a median follow-up of about 20.7 months, the median survival for patients treated with every three-week docetaxel and prednisone was 18.9 months, compared to a median survival of 16.5 months for those treated with mitoxantrone and prednisone. Forty-five percent and 48 percent of patients treated with every three-week and weekly docetaxel had a 50 percent decline in their PSA that lasted for at least three weeks, and 32 percent of the patients treated with mitoxantrone and prednisone had a 50 percent decline in their PSA, which was significantly different ($p < 0.001$).

About 30 percent of the patients in the docetaxel arms had a reduction in pain, compared to about 20 percent of the patients treated with mitoxantrone and prednisone. The difference in the reduction in pain between mitoxantrone plus prednisone and every three-week docetaxel plus prednisone was also significant ($p = 0.01$). Very few objective responses in soft tissue metastases were reported in all three arms.

The toxicity was as predicted with these compounds, mostly myelosuppression. Thirty-two percent of the patients treated with every three-week docetaxel and prednisone had myelosuppression (Grade III/IV neutropenia), but less than three percent had neutropenic fever, documented sepsis or death. Only 1.5 percent of the patients receiving weekly docetaxel and prednisone had myelosuppression (Grade III/IV neutropenia), compared to about 20 percent of the patients on mitoxantrone and prednisone. The incidence of febrile complications was very low and similar in all three treatment arms.

The other toxicities were minor (≤Grade II) and not dose limiting. There was some neuropathy, fatigue and edema in the patients treated with docetaxel,

FIGURE 40B

Metastatic disease: Prior therapy; 6-month PSA doubling time

- *Man in good general health*
- *Underwent external beam radiation therapy concurrent with LHRH agonist and bicalutamide 50 mg for Gleason Score 8 (4 + 4), PSA 12 prostate cancer*
- *PSA nadir was <0.1*
- *Bone scan now reveals three areas of increased uptake in T12, L1, L2 consistent with metastases. MRI reveals no cord compression.*
- *Patient complains of bone pain*
- *2.5 years post-radiation the PSA is 1.5 and rises as indicated in table*

What systemic therapy, if any, would you most likely recommend for this patient?

Years post XRT	PSA
2.5	1.5
3.0	3.0
3.5	6.0
(6-month PSA doubling time)	

	Age 48		Age 65		Age 78	
LHRH agonist alone	10%	14%	10%	14%	30%	22%
LHRH agonist + bicalutamide (MAB)	26%	18%	26%	18%	7%	12%
LHRH agonist + bicalutamide (Flare)	1%	—	1%	—	1%	—
Bicalutamide 150 mg alone	1%	4%	1%	4%	1%	4%
Docetaxel	4%	10%	4%	10%	2%	4%
Other systemic therapy	14%	10%	14%	10%	15%	14%
No systemic therapy/observation	—	2%	—	2%	2%	2%
No recommendation/refer to oncologist	44%	42%	44%	42%	42%	42%

FIGURE 41

Screening for metastatic disease

In general, do you order CT scans, bone scans and MRIs in the following patients to rule out metastatic disease? (percent responding yes)

	CT scans		Bone scans		MRIs	
In all patients prior to deciding on initial therapy	23%	36%	39%	38%	5%	6%
In patients at high risk prior to deciding on initial therapy	77%	78%	93%	98%	21%	18%
Patients with PSA relapse	59%	68%	87%	90%	13%	10%

FIGURE 42

Incidence of metastases on first diagnosis

What percentage of prostate cancer patients whom you evaluate present for the first time with metastatic disease?

Mean	8%	17%

FIGURE 43

Clinical use of bisphosphonates

In general, do you recommend bisphosphonates to each of the following groups of patients?

	Yes	Yes
Asymptomatic patients with bone metastases	48%	64%
Symptomatic patients with bone metastases	84%	84%
Patients on long-term androgen suppression (with low bone mineral density)	69%	66%
Patients on long-term androgen suppression (regardless of bone mineral density)	34%	40%

FIGURE 44

Sequencing of therapy in metastatic disease

In general, what is your sequence of systemic therapies for a patient in otherwise good health who received adequate local treatment for PSA 8.5, GS 6 (3 + 3) prostate cancer who later experiences a PSA rise with evidence of bone metastases? (Patient is experiencing pain. MRI reveals no spinal cord compression.)

	Age 48						Age 65						Age 78					
	1st		2nd		3rd		1st		2nd		3rd		1st		2nd		3rd	
Surgical castration	3%	—	—	—	—	—	2%	—	—	—	—	—	12%	2%	1%	—	1%	—
LHRH agonist alone	21%	16%	7%	2%	1%	—	21%	18%	6%	4%	1%	—	18%	14%	9%	8%	1%	—
LHRH agonist + bicalutamide	52%	46%	32%	18%	4%	2%	54%	48%	34%	18%	4%	2%	48%	48%	29%	14%	3%	—
LHRH antagonist	1%	2%	—	2%	1%	—	1%	2%	—	2%	1%	—	1%	2%	_	2%	1%	—
Bicalutamide 150 mg alone	—	—	—	4%	2%	—	—	—	—	4%	2%	—	—	—	—	4%	2%	—
Nilutamide	—	—	1%	—	2%	—	—	—	2%	—	2%	—	1%	—	2%	—	—	—
Docetaxel	—	2%	1%	6%	4%	6%	—	2%	1%	6%	4%	6%	—	—	1%	4%	3%	4%
Mitoxantrone + prednisone	—	—	—	2%	—	4%	—	—	—	2%	—	4%	1%	—	—	—	—	4%
Ketoconazole	—	—	2%	2%	2%	4%	—	—	2%	2%	2%	4%	—	—	1%	2%	3%	2%
Other	9%	4%	4%	4%	6%	6%	8%	4%	4%	2%	6%	4%	7%	4%	5%	2%	6%	4%
No systemic therapy	—	—	21%	30%	54%	62%	1%	—	20%	26%	53%	64%	—	2%	26%	34%	54%	70%
No recommendation/refer to oncologist	14%	30%	32%	30%	24%	16%	13%	26%	31%	34%	25%	16%	12%	28%	26%	30%	26%	16%

which is more toxic than mitoxantrone and prednisone, but the toxicities were quite reasonable. We had very few episodes of significant nausea and vomiting and some changes in liver function tests. Alopecia was reported more frequently with every three-week docetaxel, and changes in the nails and eyes were reported more with weekly docetaxel. About 16 percent of the patients on weekly docetaxel discontinued treatment because of an adverse drug reaction, compared to only 11 percent on every three-week docetaxel.

Comparing the results from SWOG-S9916 to those from TAX-327

Prostate Cancer Update 2005 (3)

DR CRAWFORD: We reported at a plenary session at ASCO 2004 and published in *The New England Journal of Medicine* our large Phase III trial headed up by Dan Petrylak from Columbia, which compared docetaxel and estramustine to mitoxantrone and prednisone.

This was the first trial in my history in the Southwest Oncology Group to show a survival benefit, and we've studied

FIGURE 45

Perceptions of chemotherapy for prostate cancer

For the following statement about chemotherapy for prostate cancer, please rate your level of agreement or disagreement.

	Strongly agree		Agree		Neutral		Disagree		Strongly disagree	
Chemotherapy is more effective in 2005 than 10 years ago.	37%	38%	45%	50%	10%	6%	5%	4%	3%	2%
Chemotherapy is better tolerated in 2005 than 10 years ago.	28%	34%	51%	50%	17%	14%	2%	2%	2%	—
Chemotherapy is safer and has fewer complications in 2005 than 10 years ago.	26%	26%	51%	46%	18%	24%	4%	4%	1%	—

FIGURE 46

Perceptions of chemotherapy for metastatic prostate cancer

In what percentage of the cases do you believe that chemotherapy can result in the following?

	Relieve the symptoms of metastatic prostate cancer		Shrink the size of tumors of metastatic prostate cancer	
Mean	40%	37%	37%	34%

FIGURE 47

Referrals to medical oncologists

What percentage of your overall patient population with prostate cancer do you refer to a medical oncologist at any point?

Mean	22%	25%

Approximately how many prostate cancer patients have you referred to a medical oncologist in the last year?

Mean	18	15

Of the patients with prostate cancer whom you refer to a medical oncologist, approximately what percentage of the time is their prostate cancer still potentially hormone sensitive?

Mean	14%	32%

every drug known to mankind. While the survival benefit in SWOG-S9916 was a couple of months, it's a big leap. The next leap, I think, is to use that as a basis for a platform to add new agents.

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DR EISENBERGER: The results from those two trials are very similar. In SWOG-S9916, survival for the patients treated with docetaxel plus estramustine was 17.5 months compared to 15.6 months for those on mitoxantrone plus prednisone. A PSA response occurred in 50 percent of the patients on docetaxel plus estramustine, compared to 27 percent of those on mitoxantrone plus prednisone.

The difference between the two trials was in the toxicities. Although no head-to-head comparison was conducted, estramustine plus docetaxel was more toxic than docetaxel plus prednisone. The most significant toxicities were cardiovascular or thrombotic. Halfway through SWOG-S9916, the protocol was amended to include prophylactic anticoagulation (ie, warfarin plus aspirin) for the patients treated with estramustine.

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DR D'AMICO: In 2004, results from two trials comparing docetaxel-containing regimens to mitoxantrone with prednisone in patients with hormone-refractory metastatic prostate cancer were published in *The New England Journal of Medicine* — one was SWOG-9916

FIGURE 48

Referrals to medical oncologists

What percentage of each type of patient with prostate cancer do you specifically refer to the following physicians at each point in the course of their disease?

	Radiation oncologist	Medical oncologist	
All patients prior to deciding on local therapy	43%	3%	5%
Patients with "low-risk" disease prior to deciding on local therapy	41%	2%	3%
Patients with "high-risk" disease prior to deciding on local therapy	53%	10%	17%
Patients with PSA relapse	34%	26%	36%
Patients with metastatic disease	27%	57%	59%

FIGURE 49

Familiarity with recent clinical trials of chemotherapy for prostate cancer

Please describe your level of familiarity with the following two studies evaluating docetaxel in metastatic disease.

	Totally unfamiliar		Relatively unfamiliar		Relatively familiar		Very familiar	
Tannock et al. **Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.** *N Engl J Med* 2004;351:1502-12.	15%	10%	32%	28%	32%	38%	21%	24%
Petrylak DP et al. **Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer.** *N Engl J Med* 2004;351:1513-20.	30%	22%	31%	34%	26%	22%	13%	22%

FIGURE 50

Consultations with medical oncologists for prostate cancer

In general, what percentage of your patients with prostate cancer do you recommend to have a consultation with a medical oncologist at the following time points?

Time point	Percentage of patients (mean)	
Initial therapy for localized low-risk disease	2%	3%
Initial therapy for localized high-risk disease	7%	16%
PSA-only progression	17%	29%
Asymptomatic metastatic disease	33%	55%
Symptomatic metastatic disease	63%	62%

FIGURE 51

Discussing the role of chemotherapy in prostate cancer

For each of the following disease types, which response best describes how often you discuss the role of chemotherapy in the management of each of the following groups of patients?

	Locally advanced disease		Rising PSA after initial treatment		Metastatic disease prior to or at the time of initiation of hormonal therapy		Androgen-independent metastatic disease	
Always	15%	4%	18%	2%	30%	18%	74%	70%
Usually	13%	8%	22%	12%	25%	22%	19%	24%
About half the time	13%	8%	20%	32%	21%	32%	5%	2%
Rarely	38%	42%	30%	30%	17%	14%	1%	2%
Never	21%	38%	10%	24%	7%	14%	1%	2%

FIGURE 52

Perceptions of chemotherapy for prostate cancer

Do you believe that research on chemotherapy for metastatic prostate cancer has demonstrated a favorable effect on survival?

Yes	59%	48%
No	12%	20%
Too early to know/insufficient data	29%	32%

FIGURE 53

Definition of hormone-refractory disease

Generally, how many hormonal therapies or changes to hormonal therapies will you try before you consider a patient to have hormone-refractory disease?

Mean	2	2

by Dr Dan Petrylak, and the other was TAX-327 by Dr Ian Tannock. Both studies demonstrated a survival benefit of about two months for the docetaxel-containing regimen.

One study combined estramustine with docetaxel, and the other evaluated docetaxel alone. Both studies showed a similar prolongation in survival, but because estramustine increased toxicity, it is not considered a necessary part of the regimen. Two dosing regimens for docetaxel were evaluated: every three weeks and weekly. The every three-week regimen appeared to be better, although the FDA and others are going to validate that in the future. The currently accepted regimen for docetaxel is 75 mg/m^2 every three weeks.

Patients whose performance status is good — such as men under 65 years of age — will tolerate docetaxel well. They come in, receive the infusion, go home, have a couple of days with some symptoms and then go back to their routine.

Toxic deaths are rare and few patients require hospitalization for complications.

Growth factors can be used to bring up blood counts if need be, and these patients must have their blood counts monitored. This is a new arena, not for medical oncologists, but for the urologists and radiation oncologists who deal with patients with prostate cancer.

Prostate Cancer Update 2005 (2)

DR GOMELLA: The new data showing a survival advantage with docetaxel-based chemotherapy in patients with hormone-refractory prostate cancer are provocative. The two large trials reported at ASCO in 2004 have made early chemotherapy a more viable option. The tolerability of docetaxel is also significantly better than the estramustine-based therapies that caused so much toxicity in the 1990s.

At this time, the average patient with a PSA recurrence who has not demonstrated metastatic disease is treated with hormonal therapy front line and, if that fails, another hormone intervention second line. My third-line treatment is chemotherapy, because I believe our best opportunity to intercede and have a favorable outcome is in the earliest stages of progression.

For example, we learned that salvage radiation therapy after radical prostatectomy is more effective when used earlier rather than later. We used to initiate salvage therapy when the patient's PSA reached 4 ng/mL, then 2 ng/mL, then

1.5 ng/mL. Now, for the best outcome, we initiate salvage radiation when the PSA reaches 1 ng/mL. I believe using chemotherapy earlier in the disease is reasonable to consider, although we don't have any good studies yet to say it should be utilized at the first evidence of PSA recurrence.

We are also seeing an emphasis on a multidisciplinary team approach and consulting with the medical oncologist earlier in the management of prostate cancer. Previously, we didn't have effective chemotherapy regimens to offer patients — nothing demonstrated a statistically significant advantage in large prospective randomized trials until mid-2004, when the two positive docetaxel studies were reported. I believe we will see an intrinsic change in the management of this disease as a result of these data. In addition, other compounds will be available in the next couple of years that may further redefine how patients with PSA recurrence or progressive prostate cancer are managed.

Prostate Cancer Update 2005 (2)

DR DREICER: Although I was obviously delighted to see the results of SWOG-S9916 and TAX-327, in effect, they've created many more questions than were answered. The majority of the patients enrolled in the two trials had androgen-independent metastatic disease, and many, but not all, were symptomatic. Until those data were available, chemotherapy in a noninvestigational setting was used to palliate patients; therefore, most patients, at least theoretically, were treated when they had disease-related symptoms.

The question now is, Does the patient who has asymptomatic metastatic disease need to be treated at that time, or later? That's a critical question to which we don't know the answer. In my practice, for asymptomatic patients with low-volume disease, I have a discussion about what we know about the trials. As an academician, I have clinical research opportunities for some of these patients and certainly would steer them in that direction. When a patient is not interested in participating in a clinical trial, I review the data with him and try to arrive at a reasonable decision based on his individual perspective.

Prostate Cancer Update 2005 (3)

DR KLOTZ: Among patients with metastatic disease, two trials have shown a survival benefit with docetaxel. This was widely acknowledged to be a huge step forward because, up to that point, chemotherapy provided just a quality-of-life benefit. A survival benefit is a major event. Of course, the size of that benefit was somewhere around two and a half months. The trials compared docetaxel against other chemotherapy regimens. Hence, it's definitely a significant event in the history of the management of prostate cancer.

Clearly, the standard of care is now docetaxel, and it should be offered to patients who have hormone-refractory metastatic prostate cancer. The controversy involves whether it should be offered earlier, and those studies are being conducted. If a patient has a rapidly rising PSA with hormone-refractory metastatic disease — whether he's symptomatic or not — I think it's reasonable to treat him with docetaxel. I use the PSA doubling time as a surrogate marker for symptomatic progression, because I know that the patient is going to have symptoms soon. If he has hormone-refractory disease without evidence of recurrence, I don't treat him.

Docetaxel is very well tolerated, and the mortality rate from toxicity is extremely low. I have been very impressed with the favorable toxicity profile of docetaxel. I also think that elderly patients tolerate it quite well. The toxicity associated with chemotherapy is acute, while the toxicity associated with hormonal therapy is chronic, long term and insidious. Patients receive chemotherapy for a much shorter period of time, as a rule.

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- Compare and contrast management strategies of urologists and radiation oncologists for the treatment of prostate cancer. 5 4 3 2 1
- Discuss prostate cancer management issues for which relative agreement and heterogeneity exist in patterns of care. 5 4 3 2 1
- Counsel cancer patients about multiple acceptable treatment options when they exist. 5 4 3 2 1

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Patterns of Care in Cancer Medicine

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This program is supported by an education grant from AstraZeneca Pharmaceuticals LP.

This program is supported by an education grant from
AstraZeneca Pharmaceuticals LP.

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Last review date: December 2005
Release date: December 2005
Expiration date: December 2006
Estimated time to complete: 2.0 hours