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# Prostate Cancer™ UPDATE

## Conversations with Urologic Oncology Leaders

### Bridging the Gap between Research and Patient Care

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# *Prostate Cancer Update*
## A Continuing Medical Education Audio Series

### STATEMENT OF NEED/TARGET AUDIENCE

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

### GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in prostate cancer screening, prevention and treatment and incorporate these data into management strategies in the local and advanced disease settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Inform prostate cancer patients about the specific risks and benefits of local and systemic therapies.
- Provide individualized counseling to patients regarding the choice and timing of endocrine therapy.
- Counsel appropriately selected patients in the high-risk or advanced disease settings about the risks and benefits of chemotherapy, including emerging data on taxane-based regimens.

### PURPOSE OF THIS ISSUE OF *PROSTATE CANCER UPDATE*

The purpose of Issue 1 of *Prostate Cancer Update* is to support these global objectives by offering the perspectives of Drs Soloway, Merrick, Stock and Ferrari on the integration of emerging clinical research data into the management of prostate cancer.

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## CONTENT VALIDATION AND DISCLOSURES

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**Dr Soloway —** Contracted Research: AstraZeneca Pharmaceuticals LP. **Dr Merrick —** No financial interests or affiliations to disclose. **Dr Stock —** Consulting Fees: Amersham plc, C R Bard Inc. **Dr Ferrari —** No financial interests or affiliations to disclose.

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## UPCOMING EDUCATIONAL EVENTS

American Society of Clinical Oncology 42nd Annual Meeting
June 2-6, 2006
Atlanta, Georgia
Event website: **asco.org**

RTOG Semiannual Meeting
June 22-25, 2006
Toronto, Ontario
Event website: **rtog.org**

ECOG Semiannual Meeting
June 23-25, 2006
Washington, DC
Event website: **ecog.org**

UICC World Cancer Congress 2006
July 8-12, 2006
Washington, DC
Event website: **2006conferences.org/u-index.php**

AUA Annual Review Course
July 20-23, 2006
Dallas, Texas
Event website: **auanet.org**

AUA Summer Research Conference
August 3-5, 2006
Madison, Wisconsin
Event website: **auanet.org**

ASTRO Translational Research in Radiation Oncology, Physics and Biology
September 8-10, 2006
Boston, Massachusetts
Event website: **astro.org**

31st ESMO Congress
September 29-October 3, 2006
Istanbul, Turkey
Event website: **esmo.org**

Second Annual Oncology Congress
October 19-21, 2006
New York, New York
Event website: **oncologycongress.com**

INTERVIEW

## Mark S Soloway, MD

Dr Soloway is Professor and Chair of the Department of Urology at Miller School of Medicine at the University of Miami in Miami, Florida.

### Tracks 1-14



## Select Excerpts from the Interview

### Track 2

**DR LOVE:** How do you think through the issue of local therapy for young patients with intermediate-risk disease?

**DR SOLOWAY:** I would generally perform a nerve-sparing prostatectomy on a young patient with intermediate-risk disease. In my own published data, no difference was apparent in biochemical recurrence rates among men of all ages who underwent nerve-sparing versus non-nerve-sparing prostatectomies (Sofer 2002).

So unless a finding at the time of surgery indicates that we should take the nerve bundle because the tumor is present right at the edge of the prostate, I try to perform a nerve-sparing procedure. More often than not, even in that situation, if you remove the nerve bundle, you still have a high chance that no cancer will be present. Leaving only one nerve bundle gives even a relatively young patient in his late forties a low likelihood of subsequent normal erections.

Another reason for performing a nerve-sparing procedure is that if the cancer is indeed localized and you have a positive margin or you monitor the PSA and intervene at the earliest sign of a biochemical recurrence, you have a second opportunity with external beam radiation therapy.

## Track 3

**DR LOVE:** What are your thoughts about using androgen deprivation therapy for patients with intermediate-risk disease treated with radiation therapy?

**DR SOLOWAY:** The Bolla study and subsequent RTOG studies have made an impact on practice. Based on these data, one could not disagree with the use of androgen deprivation in combination with radiation therapy (Bolla 2002; Hanks 2003; Lawton 2005; [1.1]). The optimal duration of androgen deprivation is still somewhat unclear. It may be one year, two years or longer. However, if I were to perform a prostatectomy, I would not add androgen deprivation.

**1.1**

### Radiation Therapy (RT) with Immediate Androgen Suppression versus Radiation Therapy with Delayed Androgen Suppression at Relapse for Patients with Node-Positive Prostate Cancer: Update on RTOG-8531

| | Arm I<br>RT +<br>immediate goserelin | Arm II<br>RT +<br>delayed goserelin |
|---|---|---|
| Biochemical control at five years<br>PSA < 1.5 ng/mL | 54% | 33% |
| Biochemical control at nine years<br>PSA < 1.5 ng/mL | 10% | 4% |

"Patients who received immediate hormone therapy (Arm I) had a statistically significant increase in PSA control compared with Arm II ($p < .0001$). This statistical difference in biochemical control is present for patients both with and without prostatectomy."

SOURCE: Lawton CA et al. *J Clin Oncol* 2005;23(4):800-7. **Abstract**

## Track 10

**DR LOVE:** How do you approach the issue of androgen deprivation for a patient with a postprostatectomy rise in PSA?

**DR SOLOWAY:** A trend toward earlier androgen deprivation has emerged. I believe this has been impacted by the Messing study of immediate postprostatectomy hormonal therapy in patients with positive lymph nodes (Messing 1999). Although it was a small study, it cannot be totally discounted. I believe a benefit exists with earlier, rather than later, androgen deprivation.

The PSA screening study in Tyrol, Austria provided diagnoses and initiated treatment. A reduction in prostate cancer mortality was seen within just a short number of years, so I believe the impact of hormone therapy did play a part (Bartsch 2001).

When we initiate androgen deprivation, one big issue is whether to administer it continuously or to provide the patient with the opportunity for intermittent therapy. I believe intermittent therapy is a reasonable approach.

I indicate to patients that we have yet to randomize trials indicating the two regimens are equivalent and that the standard has always been continuous androgen deprivation. But my own bias, depending on the patient's age, tolerance of the androgen deprivation and how long he's been on therapy, is that it is reasonable to stop it at some point and monitor the PSA.

## Track 11

**DR LOVE:** With regard to androgen deprivation, do you use an LHRH agonist alone or add an antiandrogen?

**DR SOLOWAY:** If a patient has overt metastatic disease, then I believe combined androgen deprivation offers some benefit. But in the setting of rising PSA, in which patients will be on androgen deprivation for many years, I'm unconvinced that the benefit is substantial enough to add bicalutamide. I use initial combined therapy for one month and then only the LHRH analog.

**DR LOVE:** Would you present maximal androgen blockade (MAB) therapy to a patient with a rising PSA as an option if he wanted to pay for it?

**DR SOLOWAY:** I would indicate to the patient that I do believe this approach provides a slight benefit. I am convinced by the studies and I would follow the data. I believe Laurence Klotz has best put that information together (Klotz 2001; Prostate Cancer Trialists' Collaborative Group 2000). I would counsel a patient that MAB therapy offers some small benefit, and if he accepts the additional expense, it is reasonable to administer it.

## Track 14

**DR LOVE:** What are your thoughts about trials evaluating docetaxel in the adjuvant setting?

**DR SOLOWAY:** A current strategy is to study a drug like docetaxel, which is currently in trials for high-risk, clinically localized prostate cancer, and determine whether we can use it to improve the efficacy of our current treat-

ments. Recently, when seeing a patient with high-risk Gleason eight prostate cancer, a resident asked me about enrolling such patients in trials evaluating docetaxel as neoadjuvant or adjuvant therapy based on the success of docetaxel for advanced, metastatic, hormone-refractory disease (Petrylak 2004; Tannock 2004; [1.2]).

One of the difficulties with docetaxel is that we see relatively few side effects until about six or eight months after we initiate treatment, and then we start seeing some significant side effects. When you have a patient who is likely to live seven to eight years, we should have convincing evidence that we're going to affect those years in a positive way before adding those side effects.

**1.2**

**Randomized Trials Comparing a Docetaxel-Containing Regimen to Mitoxantrone/Prednisone in Hormone-Refractory Metastatic Prostate Cancer**

| | SWOG-S9916[1] | | TAX-327[2]* | | |
|---|---|---|---|---|---|
| | D + E (n = 338) | M + P (n = 336) | D q3wk (n = 332) | D qwk (n = 330) | M (n = 335) |
| Median survival | 17.5 mo | 15.6 mo | 18.9 mo | 17.4 mo | 16.5 mo |
| Survival† | 36% | 30% | 50% | 43% | 40% |
| PSA response rate (≥50 percent decline) | 50% | 27% | 45% | 48% | 32% |
| Partial response rate | 17% | 11% | 12% | 8% | 7% |
| Decreased pain | — | — | 35% | 31% | 22% |
| Increased quality of life | — | — | 22% | 23% | 13% |

D = docetaxel; E = estramustine; M = mitoxantrone; P = prednisone

* All patients in TAX-327 received prednisone in addition to chemotherapy.
† Median follow-up 32 months for SWOG-S9916 and 20.7 months for TAX-327

SOURCES: [1] Petrylak DP et al. *N Engl J Med* 2004;351(15):1513-20. **Abstract**
[2] Tannock IF et al; TAX 327 Investigators. *N Engl J Med* 2004;351(15):1502-12. **Abstract**

**DR LOVE:** In the breast cancer model in adjuvant therapy, patients receive short-term chemotherapy, maybe four or six months, and then long-term hormone therapy. Prostate cancer in a patient with PSA-only disease is similar to early breast cancer in that there's no gross disease. Is it possible that four or six months of chemotherapy might be worth it in the long run?

**DR SOLOWAY:** I believe it might be. The question is, do we want to see the trials first or are we willing to take a leap of faith for our patients with Gleason eight, nine and 10 disease and say that because it works in metastatic disease, let's give the benefit to these patients while we're awaiting the trial data? Currently we don't do that, but I would not argue with someone who wanted to do so. It may provide a benefit, and it doesn't have a great deal of side effects. ■

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

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

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Tyrrell CJ et al; 'Casodex' Early Prostate Cancer Trialists Group. **Bicalutamide ('Casodex') 150 mg as adjuvant to radiotherapy in patients with localised or locally advanced prostate cancer: Results from the randomised Early Prostate Cancer Programme.** *Radiother Oncol* 2005;76(1):4-10. **Abstract**

INTERVIEW

## Gregory S Merrick, MD

Dr Merrick is Medical Director of the Schiffler Cancer Center at Wheeling Jesuit University in Wheeling, West Virginia.

### Tracks 1-16



## Select Excerpts from the Interview

### Track 2

**DR LOVE:** Would you discuss your treatment approach for a patient with low-risk prostate cancer who has a rapid PSA velocity?

**DR MERRICK:** It's been interesting to evaluate the influence of PSA velocity on the survival parameters — biochemical, cause specific and overall. Multiple studies have confirmed that a PSA velocity of greater than 2 ng/mL in the year prior to diagnosis significantly affects those survival outcomes (D'Amico 2005; [2.1]).

**DR LOVE:** How have you incorporated those data into your practice?

**DR MERRICK:** Until these data became available, rapid PSA velocity hasn't

been something that we have considered. For patients with low-risk disease, the cause-specific survival in our brachytherapy series is 99.5 percent at 10 years.

It's going to be difficult to alter that outcome by looking at any other parameters. What remains to be determined is how many patients fell into the cohort of this rapid PSA velocity. We have not yet examined that information.

Patients with low-risk disease are treated with monotherapy. Patients with high-risk disease receive combined-modality therapy. For patients with intermediate-risk disease, our prospective randomized trials are trying to prove that we can eliminate the supplemental external beam radiation.

**2.1** **Influence of PSA Velocity in the Year Prior to Diagnosis on the Seven-Year Estimates of Survival Following External Beam Radiation Therapy**

| Low-risk disease (n = 125) | PSA velocity >2 ng/mL/year (95% CI) | PSA velocity ≤2 ng/mL/year (95% CI) |
|---|---|---|
| PSA recurrence | 78% (57%-99%) | 54% (40%-69%) |
| Prostate cancer-specific mortality | 19% (2%-39%) | 0% |
| All-cause mortality | 53% (23%-81%) | 14% (5%-24%) |
| Higher-risk disease (n = 233) | | |
| PSA recurrence | 87% (74%-100%) | 60% (46%-74%) |
| Prostate cancer-specific mortality | 24% (12%-37%) | 4% (0%-11%) |
| All-cause mortality | 44% (29%-59%) | 31% (16%-46%) |

SOURCE: D'Amico AV et al. *JAMA* 2005;294(4):440-7. **Abstract**

## Track 8

**DR LOVE:** Would you describe your general algorithm for a patient with high-risk prostate cancer?

**DR MERRICK:** In our program, high-risk disease is defined as two or three adverse prognostic factors: a clinical stage greater than or equal to T2c, a PSA greater than 10 ng/mL and a Gleason score greater than or equal to seven. In our series, all of those patients receive pelvic radiation therapy along with a palladium boost. A high percentage of those men have also received androgen deprivation therapy.

Retrospectively, we have been able to show that the men who received androgen deprivation therapy have a statistically significant improvement in eight-year biochemical progression-free survival of approximately eight percent (Merrick 2005).

We will begin a prospective randomized trial in our Wheeling and Seattle group later this year, which will randomly assign patients with a Gleason score

of seven to nine and a PSA of 10 to 20 ng/mL to 45 Gray of pelvic radiation therapy and a palladium boost with or without nine months of androgen deprivation therapy. My expectation is that androgen deprivation therapy will improve biochemical outcome.

**DR LOVE:** Which specific androgen deprivation regimen do you use?

**DR MERRICK:** We're strong proponents of total androgen suppression. These patients will receive nine months of an LHRH agonist, either goserelin or leuprolide, along with four months of bicalutamide at 50 mg daily.

For all of my patients, I use total androgen suppression for four months. If the PSA is undetectable at that time, we continue the LHRH alone for the remainder of the treatment.

In the community, what we often see is an LHRH agonist with a short course of an antiandrogen to block the flare. I have not been a proponent of that approach. If you look at the RTOG studies, especially the studies that Mack Roach has conducted, they've all used total androgen suppression (Roach 2003; Hanks 2003).

**DR LOVE:** It seems that total androgen blockade is not used in the community as much as it's used in academia. Is that your impression?

**DR MERRICK:** It is. I believe the real key with prostate cancer treatment is to cure the patient up front. We can talk about treatment costs, but we know that if we treat a patient and cure him with a radical prostatectomy or brachytherapy or a similar combination, we're probably talking about a cost of $15,000 to $40,000.

Data have been published indicating that once a man experiences biochemical failure, from failure to death it costs the healthcare industry around $150,000 to $160,000. The curative treatment is always cheap in comparison to treating patients for the remainder of their lives in a palliative setting.

**DR LOVE:** Do you think financial issues are the main reason total androgen suppression is not used much?

**DR MERRICK:** This regimen does add cost for the patient. Therefore, often the choice to use it depends on whether the patient can financially afford it.

## Track 11

**DR LOVE:** How do you approach the management of PSA relapse?

**DR MERRICK:** I'm relatively conservative in managing PSA recurrences. If we're going to treat those patients with hormonal therapy, I do not recommend androgen deprivation therapy until the PSA doubling time becomes less than 12 months.

Once the PSA doubling time is less than 12 months, we have to seriously consider androgen deprivation.

The big question then is continuous versus intermittent treatment. I have always been a proponent of intermittent androgen deprivation therapy because of the better quality of life associated with it.

**DR LOVE:** Would you describe exactly how you use intermittent therapy?

**DR MERRICK:** We leave a patient on androgen deprivation therapy for nine to 12 months. If the PSA becomes undetectable, then we stop the androgen deprivation therapy until we see the PSA exceed some arbitrary PSA cut point, such as 10 or 15 ng/mL.

## Track 12

**DR LOVE:** What are your thoughts about the potential future role of chemotherapy earlier in the natural history of the disease?

**DR MERRICK:** This is a reasonable question to evaluate, but it has to be done in a prospective randomized trial. The studies that Dr Petrylak and Dr Tannock performed among patients with hormone-refractory disease were important for a large number of patients. However, it's also important to remember that the differences in overall survival were two months (Petrylak 2004; Tannock 2004). These weren't home runs we were hitting, but they were small steps, which doesn't minimize the importance of their work. However, I do think chemotherapy should, in select cases, be considered earlier, but it must be done in the setting of prospective randomized trials, not outside of a protocol. ■

## SELECT PUBLICATIONS


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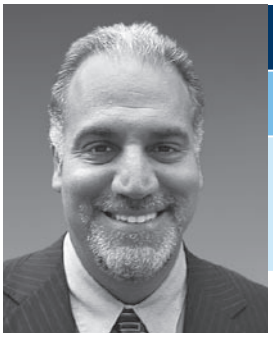
Tannock IF et al; TAX 327 Investigators. **Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.** *N Engl J Med* 2004;351(15):1502-12. **Abstract**



INTERVIEW

## Richard G Stock, MD

Dr Stock is Professor and Chair of the Department of Radiation Oncology at the Mount Sinai School of Medicine in New York, New York.

### Tracks 1-13



## Select Excerpts from the Interview

### Track 2

**DR LOVE:** Can you briefly provide an overview of the work you and your colleagues have done on the use of brachytherapy?

**DR STOCK:** We started treating patients with prostate brachytherapy in 1990, so now we have 15 or 16 years of data. We've put a lot of effort into following up on patients to see how they've done over time.

Our data set has matured and now shows us that the earlier outcomes we observed with our patients have held up.

One of the things we've seen with longer follow-up is that many of the early and late side effects of radiation that usually occur within the first five years of therapy are not more severe or different over time (Stone 2002). This finding was based on following our patients and asking them questions regarding their urinary function, continence rates and potency preservation. We found the

side effects patients were experiencing after five years held up over time, with no new side effects developing.

For example, we found that preservation of sexual function was maintained. This supported our earlier publications on potency preservation, in which we reported that approximately 60 percent of patients that were potent prior to brachytherapy maintained some form of potency after treatment (Stock 2001).

An interesting outcome we are finding with longer follow-up is that younger patients in particular are doing extremely well after treatment, with preservation of potency in the range of about 90 percent. This means that patients in the long term are doing well with brachytherapy as a treatment for prostate cancer.

We're finding similar results with the cancer control rate over time. We have determined that many of the patients who fail treatment in terms of biochemical recurrence do so within the first five years.

At longer follow-up, very few new or late recurrences of the cancer have been reported. Our results show a 90 to 95 percent biochemical control rate out to about 10 years (Kollmeier 2003; Stock 2006a; Stone 2005).

We don't have a data set to compare these brachytherapy outcomes with radical prostatectomy or external beam radiation therapy, but these outcomes seem to compare nicely to those reported by the major cancer centers.

## Track 3

**DR LOVE:** How do you approach patients with intermediate- or high-risk disease?

**DR STOCK:** We've always attempted to customize therapy, using different treatment approaches for different stages of disease.

For patients with low-risk disease, we primarily use an implant alone. For intermediate-risk disease, we usually use an implant combined with external beam radiation therapy or an implant combined with neoadjuvant or adjuvant hormonal therapy.

For our patients with high-risk disease, we use a combined approach that involves hormonal therapy, implant and external beam radiation therapy. Our outcomes with these treatment approaches have been successful (Stock 2006a).

We are particularly proud of the use of the combined approach for patients with high-risk disease, in which we use nine months of hormonal therapy, a radioactive seed implant and external beam radiation therapy. Recent analyses of this treatment approach show close to an 80 percent biochemical control rate at eight years for patients with high-risk disease (Stock 2004, 2006a), which is impressive.

For our patients with intermediate-risk disease, whom we treat either with an implant and hormonal therapy or an implant and external beam radiation therapy, we're achieving biochemical control rates in the high 80s and low 90s at 10 years (Stock 2006a).

## Track 5

**DR LOVE:** What are some of the clinical research reports that have been published in the last couple of years that you believe are important for radiation oncologists and urologists to be aware of?

**DR STOCK:** Some of the most important findings in radiation therapy in general have been the results of the prospective randomized studies that evaluate the use of hormonal therapy combined with external beam radiation therapy.

Two of the most important published trials are the RTOG-9202 study (Hanks 2003; [3.1, 3.2]) and the EORTC-22863 study (Bolla 2002 [4.1, 4.2, pages 20-21]), both of which evaluated long-term hormonal therapy for patients at high risk.

The RTOG trials, and in particular the RTOG-9202 trial that examined the use of two years of hormonal therapy with external beam radiation therapy, have shown the best biochemical control rates for high-risk disease (Hanks 2003).

These trials indicate that we may be able to treat high-risk microscopic metastatic disease in many patients with long-term hormonal therapy, so I'm excited by the data.

In an effort to extrapolate some of the positive outcomes of these trials from our own data, my colleagues and I are examining our data set of patients with particularly high-risk disease treated with combination therapy and trying to analyze the outcomes for those treated with longer-term hormonal therapy.

**3.1**

### Phase III Study Evaluating Long-Term Adjuvant Deprivation Therapy After Radiation Therapy in Locally Advanced Prostate Carcinoma

Protocol ID: RTOG-9202
Accrual: 1,554 (Closed)

**Eligibility**
Clinical stage T2c–T4 carcinoma of the prostate
No involved nodes
Karnofsky performance score > 70
Pretreatment PSA levels < 150 ng/mL

R

- Goserelin and flutamide two months before and during RT → no additional therapy
- Goserelin and flutamide two months before and during RT → goserelin x 2 years

SOURCES: Hanks GE et al. *J Clin Oncol* 2003;21(21):3972-8. **Abstract**; NCI Physician Data Query, April 2006.

## Track 7

**DR LOVE:** Would you discuss how you monitor the PSA after brachytherapy and other forms of radiation therapy and how you react to changes in PSA levels?

**3.2**

**Five-Year Treatment Efficacy Outcomes of RTOG-9202 Study of Long-Term Adjuvant Deprivation Therapy After Neoadjuvant Androgen Deprivation with External Beam Radiation Therapy for Locally Advanced Prostate Cancer**

| | STAD-RT | LTAD-RT | |
|---|---|---|---|
| Study endpoint* | Estimated rate (95% CI) | Estimated rate (95% CI) | *p*-value |
| Disease-free survival | 28.1% (24%-32%) | 46.4% (42%-50%) | <0.0001 |
| Overall survival | 78.5% (75%-82%) | 80% (76%-83%) | 0.73 |
| Cause-specific survival | 91.2% (89%-93%) | 94.6% (93%-96%) | 0.006 |
| Biochemical failure | 55.5% (51%-60%) | 28% (24%-32%) | <0.0001 |
| Distant metastasis | 17.0% (14%-20%) | 11.5% (8%-14%) | 0.0035 |
| Local progression | 12.3% (10%-15%) | 6.4% (4%-8%) | 0.0001 |

STAD-RT = short-term androgen deprivation with external beam radiation therapy
LTAD-RT = long-term androgen deprivation with external beam radiation therapy followed by goserelin

* Total patients assessed = 1,514

SOURCE: Hanks GE et al. *J Clin Oncol* 2003;21(21):3972-8. **Abstract**

**DR STOCK:** A couple of factors are important when following PSA in a patient treated by brachytherapy. One is that it takes about eight months to complete delivery of brachytherapy; radiation from an iodine-125 implant in the prostate will be emitted for about eight months.

The other factor is that it can take up to four or five years following brachytherapy for PSA to hit its nadir. The reason for this is that radiation therapy works by damaging the DNA, and even though cells may be genetically damaged from the radiation from either a seed implant or an external beam, the cells still may produce the PSA protein.

So I believe it's important to follow these patients carefully but at the same time not to jump to any immediate conclusions.

We also know that because these cells are still making PSA and because brachytherapy can be associated with some late inflammatory reactions, transient elevations in PSA during the follow-up period can occur.

People refer to this as a PSA bounce or PSA spike, which we see in about 30 percent of patients. It is interesting to note that we see this phenomenon more commonly in patients who receive good-quality implants and in young patients.

Therefore, it's important not to immediately start hormonal therapy in a young patient whose PSA goes up once or even twice after treatment. You have to be patient because many times the PSA levels go back down.

**DR LOVE:** What do you see in terms of the nadir of PSA with brachytherapy implants versus external beam radiation therapy?

**DR STOCK:** I believe a difference in PSA nadir is evident. Most of the patients that we treat with brachytherapy implants reach nadir at a level of 0.1 or less. When you cure a patient with external beam therapy and no evidence of biochemical recurrence appears, PSA levels will usually be in the range of about 0.5 to one.

So the difference between these two treatments is significant, and it points to the different biologic effect of dose between a brachytherapy implant and external beam radiation therapy, with an implant able to achieve a higher biologically effective dose compared to external beam radiation therapy.

**DR LOVE:** What defines a high-quality implant?

**DR STOCK:** One of the elements that defines a high-quality implant is the dose of radiation delivered to the prostate. One way to measure this is by using a dose-volume histogram, which measures the whole prostate as a volume and doses delivered as percentages of that volume.

Some of our early work at Mount Sinai was to define the D-90, which is the dose to 90 percent of the gland (Stock 2006b).

This method is now appreciated as a very good way of describing the dose delivered to the prostate. For iodine implants, for example, we think that doses, or D-90s, of more than 140 Gray are needed. For palladium, doses of more than 110 Gray are probably necessary.

**DR LOVE:** What are some of the common questions you hear from urologists and radiation oncologists?

**DR STOCK:** For many urologists, the major concern is long-term outcomes of brachytherapy. Even though we have data on radiation therapy approaching 15 years, urologists are still commonly concerned with late recurrences.

Radiation oncologists generally do not share that concern because they see the treatment results. They are concerned about how brachytherapy implants compare to the newer modalities of external beam radiation therapy in terms of morbidity, such as urinary symptoms, and how to reduce morbidity.

Therefore, when speaking to radiation oncologists, I often focus on the importance of the technique of implantation and the need to reduce the morbidity commonly associated with it. ■

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

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Hanks GE et al; Radiation Therapy Oncology Group. **Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: The Radiation Therapy Oncology Group Protocol 92-02.** *J Clin Oncol* 2003;21(21):3972-8. **Abstract**

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INTERVIEW

## Anna C Ferrari, MD

Dr Ferrari is Associate Professor and Director of the Genitourinary Cancer Program in the Division of Hematology/Oncology at the Derald H Ruttenberg Cancer Center of Mount Sinai School of Medicine in New York, New York.

### Tracks 1-11



## Select Excerpts from the Interview

### Track 3

**DR LOVE:** Would you discuss your clinical experience with docetaxel for the treatment of prostate cancer?

**DR FERRARI:** It is quite extensive. We have been using docetaxel or taxane-based chemotherapies since the late 1990s. Overall, my experience with this agent has been extremely positive.

I have seen many patients who are highly symptomatic, either with bone pain or obstructive symptoms. Some of them come into the office in a wheelchair or are hardly able to walk, and over the course of two to three months, you see remarkable changes both in their symptoms and in their overall sense of well-being and quality of life.

At times, as oncologists, we may be reluctant to start treatments for these patients because they are impaired in terms of their quality of life or their ability to move around, and we believe that the weakness or fatigue associated with chemotherapy could worsen their quality of life. But, not surprisingly,

because of the response rates that docetaxel elicits in the control of pain — not control of PSA progression — these patients' conditions reverse remarkably.

I could provide you many anecdotal stories, but I think the most significant aspect has been the overall experience and what the major studies ultimately showed (Petrylak 2004; Tannack 2004; [1.2, page 6]). Furthermore, it's not simply a PSA response or a 25 percent reduction in the size of the metastases; more than anything it's an improvement in their quality of life and the ability in many cases to return to their normal activities.

## Track 4

**DR LOVE:** What type of toxicity do you observe with docetaxel?

**DR FERRARI:** The side effects depend on the schedule you use. If we use the standard every three-week schedule — which is the schedule that has been approved by the FDA in combination with prednisone or estramustine — the higher doses cause hair loss. Generally it's not full baldness, but hair thinning and partial hair loss definitely occur.

Another symptom that we see is fatigue. Generally, most men describe fatigue within 72 hours or so after treatment. If I treat someone on a Wednesday or a Thursday, he might feel a bit more fatigued on Saturday or Sunday but not sufficient for that to carry over so he would not be able to go to work on Monday.

Perhaps the most common side effect is neutropenia. A decrease in the white cell count generally tends to occur anywhere between seven and 10 days post-treatment.

## Track 5

**DR LOVE:** Do you reserve chemotherapy for patients who have definite metastatic disease, or do you also offer it to a patient with PSA-only disease that has a rapid doubling time?

**DR FERRARI:** Although the docetaxel trials established the advantage of chemotherapy in men with definite metastatic disease, previous experience with other tumors tells us that an active combination of agents against androgen-independent cells is most likely to be effective earlier than later.

Prostate cancer is a heterogeneous disease. We will probably eliminate the tumor cells that are more sensitive early on, and cells that emerge subsequently or that survive this initial attack may be less sensitive to treatment.

All of the time that we gain is valuable, but I don't necessarily wait for the development of metastases. If the patient failed second- or third-line hormonal therapy and his PSA continued to rise, I think it would be time to initiate chemotherapy, even if he might be asymptomatic, because you know where he's heading. Once symptomatic metastatic prostate cancer is in place, it's much harder to achieve control of symptoms and complications from the metastases.

## Track 9

**DR LOVE:** Would you discuss the research data that have become available over the last couple of years examining various types of endocrine intervention?

**DR FERRARI:** The key trials that have been published are from the radiation therapy series and from the radical prostatectomy series. From the radiation therapy series, the milestone publication by Bolla (Bolla 1997) demonstrated that adjuvant hormonal therapy for three years in locally advanced prostate cancer offered a survival advantage (4.1, 4.2).

Subsequent studies that were conducted by the RTOG (Lawton 2001; Hanks 2003; [3.1, 3.2, pages 14–15) also showed that prolonged androgen suppression for two years offered a survival advantage and indicated a potential to cure a higher number of patients with high-risk localized disease. By now, the use of adjuvant hormonal therapy has widely become the standard of care for patients with high-risk features at presentation who have localized prostate cancer.

What is not yet completely defined is the duration of treatment. Certainly, the benefits of using adjuvant hormonal treatment for two and three years have been shown, but some data also show that six months of hormonal therapy may offer a benefit for patients with intermediate-risk disease (D'Amico 2004).

The risks of prolonged androgen deprivation for two and three years are not welcomed by anybody, and the chances of recovering potency and libido after two or three years of prolonged androgen suppression are extremely slim.

In the radical prostatectomy series of trials, the only data available are from the study by Messing (Messing 1999), showing that men with microscopic metastatic deposits in the lymph nodes at the time of radical prostatectomy who received hormonal therapy had improved overall survival compared to those who received no hormonal therapy. ■

**4.1**

### Phase III Study Comparing External Beam Radiation Therapy Alone or Combined with Androgen Suppression Therapy

Protocol ID: EORTC-22863
Accrual: 415 (Closed)

**Eligibility**
Clinical stage T1–2 carcinoma of the prostate
WHO Grade 3, or T3–4
N0–1 M0 tumors
Age < 80 years

R

- Pelvic irradiation (50 Gy) for 5 weeks, boost (20 Gy) for 2 weeks → no additional therapy
- Pelvic irradiation (50 Gy) for 5 weeks, boost (20 Gy) for 2 weeks → goserelin q4wk x 3 years

SOURCES: Bolla M et al. *Lancet* 2002;360(9327):103–6. **Abstract**; NCI Physician Data Query, March 2006.

**4.2**

## Five-Year Results of EORTC-22893: Randomized Trial of Radiation Therapy Alone or Radiation Therapy with Long-Term Goserelin in Patients with Locally Advanced Prostate Cancer

| Patient characteristics | Radiation therapy (n = 195) | Combined treatment* (n = 201) |
|---|---|---|
| Median age | 70 years | 71 years |
| Performance status 0 to 1 | 98% | 97% |
| Gleason score 7 to 10 | 36% | 33% |
| Unknown | 37% | 38% |
| T3 tumors | 82% | 82% |

| Efficacy | Radiation therapy (95% CI) (n = 195) | Combined treatment* (95% CI) (n = 201) | *p*-value |
|---|---|---|---|
| Five-year overall survival | 62% (52%-72%) | 79% (72%-86%) | 0.001 |
| Disease-free survival | 48% (38%-58%) | 85% (78%-92%) | <0.001 |

* Goserelin initiated on the first day of pelvic irradiation and continued for three years

SOURCE: Bolla M et al. *N Engl J Med* 1997;337(5):295-300. **Abstract**

## SELECT PUBLICATIONS


Bolla M et al. **Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin.** *N Engl J Med* 1997;337(5):295-300. **Abstract**

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Shipley WU et al. **Effect of a short course of neoadjuvant hormonal therapy on the response to subsequent androgen suppression in prostate cancer patients with relapse after radiotherapy: A secondary analysis of the randomized protocol RTOG 86-10.** *Int J Radiat Oncol Biol Phys* 2002;54(5):1302-10. **Abstract**

Tannock IF et al; TAX 327 Investigators. **Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.** *N Engl J Med* 2004;351(15):1502-12. **Abstract**

**QUESTIONS (PLEASE CIRCLE ANSWER):**

1. **Ongoing clinical trials will evaluate the role of docetaxel for men with earlier-stage prostate cancer.**
   a. True
   b. False

2. **A PSA velocity of _____ resulted in worse biochemical, cause-specific and overall survival compared to those with a lower PSA velocity.**
   a. Greater than 2 ng/mL in the year prior to diagnosis
   b. Greater than 4 ng/mL in the year prior to diagnosis

3. **Several RTOG studies incorporating hormonal therapy have used total androgen suppression.**
   a. True
   b. False

4. **The use of adjuvant hormonal therapy is now a standard of care for localized prostate cancer with high-risk features.**
   a. True
   b. False

5. **For patients with intermediate-risk prostate cancer, the role of external beam radiation therapy supplemental to brachytherapy is being evaluated in clinical trials.**
   a. True
   b. False

6. **In two randomized trials, the use of docetaxel for patients with hormone-refractory metastatic prostate cancer led to improvements in pain relief and quality of life in addition to overall survival.**
   a. True
   b. False

7. **In a milestone publication from Bolla and colleagues, patients with locally advanced prostate cancer who were treated for three years with adjuvant hormonal therapy had a five-year overall survival of _____ compared with 62 percent in those who received radiation therapy alone.**
   a. 65 percent
   b. 79 percent

8. **Data published by Soloway et al show _____ in biochemical recurrence rates among men with localized prostate cancer who underwent nerve-sparing versus non-nerve-sparing prostatectomies.**
   a. An increase
   b. A decrease
   c. No difference

9. **The RTOG-9202 trial randomly assigned patients with locally advanced prostate cancer to _____ for two years versus no additional therapy following neoadjuvant androgen deprivation and radiation therapy.**
   a. Flutamide
   b. Bicalutamide
   c. Goserelin
   d. Nilutamide

10. **In the RTOG-9202 trial there was a significant improvement in disease-free survival in patients who received long-term versus short-term androgen deprivation following neoadjuvant androgen deprivation and radiation therapy.**
    a. True
    b. False

11. **The SWOG-S9916 trial randomly assigned patients with hormone-refractory metastatic prostate cancer to mitoxantrone plus prednisone versus _____.**
    a. Mitoxantrone alone
    b. Prednisone alone
    c. Docetaxel alone
    d. Docetaxel plus estramustine

*Post-test answer key: 1a, 2a, 3a, 4a, 5a, 6a, 7b, 8c, 9c, 10a, 11d*

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- Critically evaluate the clinical implications of emerging clinical trial data in prostate cancer screening, prevention and treatment and incorporate these data into management strategies in the local and advanced disease settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Inform prostate cancer patients about the specific risks and benefits of local and systemic therapies. . . . . 5 4 3 2 1 N/A
- Provide individualized counseling to patients regarding the choice and timing of endocrine therapy. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients in the high-risk or advanced disease settings about the risks and benefits of chemotherapy, including emerging data on taxane-based regimens. . . . . 5 4 3 2 1 N/A

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|---|---|---|
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| Gregory S Merrick, MD | 5 4 3 2 1 | 5 4 3 2 1 |
| Richard G Stock, MD | 5 4 3 2 1 | 5 4 3 2 1 |
| Anna C Ferrari, MD | 5 4 3 2 1 | 5 4 3 2 1 |

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Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
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Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
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