Biochemical Outcome Following External Beam Radiation Therapy With or Without Androgen Suppression Therapy for Clinically Localized Prostate Cancer

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Treatment selection for men with clinically localized prostate cancer should be based on the results of carefully designed and well-conducted prospective randomized trials. Two randomized trials, one performed by the Radiation Therapy Oncology Group (RTOG) and the other by the European Organization for Research in the Therapy of Cancer (EORTC), have documented a benefit in cancer-specific survival for patients with locally advanced (T3, T4) prostate cancer who received a combination of external beam radiation therapy (RT) and short- (4 months) or long-term (3 years) androgen suppression therapy (AST), respectively, compared with RT alone. For men with clinically localized prostate cancer, 2 trials, one performed by the RTOG (RT with or without 4 months of AST) and the other by the Dana Farber Cancer Institute (RT with or without 6 months of AST), are expected to reach their target accruals during 2000.

Currently, however, no data exist regarding the relative efficacy of RT with or without AST for men with clinically localized disease. Therefore, our study was designed to provide early insight regarding the relative efficacy of RT and RT combined with 6 months of AST for men with clinically localized prostate cancer.

METHODS

Patient Selection

The study population comprised 1586 men treated with 3-dimensional con-
RT WITH OR WITHOUT ANDROGEN SUPPRESSION FOR PROSTATE CANCER

formal external beam RT with (n=276) or without (n=1310) AST at the Joint Center for Radiation Therapy, Boston, Mass, between January 1989 and August 1999 and who had prostate-specific antigen (PSA)–detected or clinically palpable prostate cancer. Selection of patients for administration of AST was determined by physician preference. Patients underwent a staging evaluation as described previously.3

Treatment
Radiation therapy was delivered using a 4-field technique and at least 10 mV photons to a total median dose of 70.2 Gy (range, 70.0-72.4) to the prostate gland after 95% normalization. Androgen suppression therapy was given for 6 months (2 months before, during, and after RT) and consisted of the combination of a luteinizing hormone–releasing hormone agonist and a non-steroidal antiandrogen.

Follow Up
Median follow-up time for patients stratified by treatment is listed in Table 1. Patients were seen 1 month after the end of RT, then at 3-month intervals for 2 years, every 6 months for 5 years, and annually thereafter. At each follow-up visit, a serum PSA was obtained prior to performing the digital rectal examination. All pretreatment PSA values were obtained within 1 month prior to initiation of therapy. No patients were lost to follow-up. Six men died of causes unrelated to prostate cancer and were censored at the time of their death because all were without evidence of prostate cancer recurrence.

Statistical Analysis
A Cox regression time to PSA failure analysis4 evaluating the ability of the treatment modality (RT with or without AST) to predict time to PSA failure was performed. The assumptions of the Cox model were met. Three risk groups had been previously established5 based on serum PSA level, biopsy Gleason score, and 1992 American Joint Commission on Cancer (AJCC) clinical tumor category. Low-risk patients had a PSA of 10 µg/L or less and Gleason score of 6 or less and 1992 tumor category T1c or T2a. Intermediate-risk patients had a PSA of 10.1 to 20 µg/L or a Gleason score of 7 or 1992 AJCC tumor category T2b. High-risk patients had a PSA of more than 20 µg/L or Gleason score of 8 or 1992 AJCC tumor category T2c. The relative risk (RR) of PSA failure and 95% confidence intervals (CIs) for men treated with RT plus AST vs men treated with only RT were calculated based on the coefficients from the Cox regression model for each risk group.

We defined PSA failure according to the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Statement.6 The definition required 3 consecutive rising PSA values, each obtained at least 3 months apart. Time of PSA failure was defined as the midpoint between the time of the first rise in PSA above the nadir and the PSA nadir. We used this definition while realizing that it may overestimate PSA failure6 in the group of men receiving RT plus AST given the known rebound in PSA following the withdrawal of AST in most men. Time 0 was defined as date of diagnosis.

Pairwise comparisons were made using a log-rank test. Estimates of PSA outcome were calculated using the Kaplan-Meier actuarial method.7 In the low-, intermediate-, and high-risk patient groups, sample size and number of events in the study were sufficient to detect a 10%, 11%, and 13% difference in PSA outcome, respectively, with 80% power at a .05 level of significance. This was calculated for a baseline PSA survival of 84%, 62%, and 43% at 5 years in the low-, intermediate-, and high-risk patients, respectively.

RESULTS
Prognostic Factor Comparison
Table 2 shows pretreatment clinical characteristics for the 1386 study patients stratified by treatment modality and clinical risk group. In the intermediate-risk group, there were more patients with a PSA of 10.1 to 20.0 µg/L (58% vs 47%; P=.03) and biopsy Gleason score of 7 (70% vs 54%; P=.001) in the RT plus AST than in the RT group. This imbalance could bias the results in favor of RT for patients in the intermediate-risk group.

Treatment Outcome Assessment
No significant difference between treatment groups was found for patients in the low-risk category (P=.09; relative risk [RR], 0.5; 95% CI, 0.3-1.1). Intermediate-risk and high-risk patients treated with RT plus AST had a 3-fold (RR, 0.2; 95% CI, 0.1-0.3) and 2.5-fold (RR, 0.4; 95% CI, 0.2-0.8) reduction in

Table 1. Patients Treated With Radiation or Radiation Plus Androgen Suppression Therapy Stratified Annually by Patient Risk Group∗

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Therapy</th>
<th>Median (Range) Follow-up, mo†</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>RT</td>
<td>23 (6-93)</td>
<td>100</td>
</tr>
<tr>
<td>Low</td>
<td>RT plus AST</td>
<td>27 (8-97)</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>RT</td>
<td>30 (6-94)</td>
<td>100</td>
</tr>
<tr>
<td>Intermediate</td>
<td>RT plus AST</td>
<td>28 (9-92)</td>
<td>0</td>
</tr>
<tr>
<td>High</td>
<td>RT</td>
<td>29 (6-98)</td>
<td>100</td>
</tr>
<tr>
<td>High</td>
<td>RT plus AST</td>
<td>23 (8-94)</td>
<td>0</td>
</tr>
</tbody>
</table>

*RT indicates radiation therapy; AST, androgen suppression therapy. The test for linear trend for the proportion of patients treated annually over the study period with RT plus AST is reported using a Pearson y² P value. Patients were assigned to treatment groups by physician preference.
†Median follow-up was calculated based on censorship at time of prostate-specific antigen (PSA) failure or last follow-up. Median (range) follow-up of all study patients including those who sustained PSA failure was 49 (8-100) and 51 (8-118) months in the RT and RT plus AST groups, respectively.

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risk of PSA failure, respectively, compared with patients treated with RT. Estimates of PSA outcome following RT with or without AST are shown in the Figure for patients in the low-risk (5-year PSA outcome, 92% vs 84%), intermediate-risk (5-year PSA outcome, 88% vs 62%), and high-risk (5-year PSA outcome, 68% vs 43%) groups.

**COMMENT**
Randomized studies\(^1,^2\) have documented a cancer-specific survival benefit for men with locally advanced prostate cancer (T3, T4) treated with RT plus AST compared with RT; studies evaluating treatments for patients with clinically localized disease (T1, T2) will complete accrual this year. In this retrospective cohort study, which controlled for the established prognostic factors, a significant benefit in 5-year PSA outcome was noted for men with clinically localized disease in the intermediate- and high-risk groups treated with RT plus 6 months of AST vs men treated with RT only.

Several items warrant further discussion. First, patients in the intermediate-risk group had a prognostic factor distribution favoring RT (Table 2). Second, given the known rebound in PSA following the withdrawal of AST and the use of the ASTRO consensus definition to define PSA failure, PSA failure may have been overestimated in patients treated with RT plus AST.\(^6\) However, because of a changing practice pattern in the United States beginning around 1996 toward RT plus AST, the median follow-up for patients in the intermediate- and high-risk groups treated with RT was longer by 2 to 6 months vs patients treated using RT plus AST (Table 1). While the difference in median follow-up favors the RT plus AST arm, the prognostic factor distribution and ASTRO definition of PSA failure favor the RT arm.

Next, based on the decreased positive surgical margin rates reported from a randomized trial\(^8\) of radical prostatectomy with or without neoadjuvant AST, the benefit in PSA outcome noted in this study may be largely the result of an improvement in local control. That low-risk patients generally have a lower intraprostatic tumor volume and a minimal risk of micrometastatic disease could explain why the difference in PSA outcome for low-risk patients receiving RT plus AST as compared with RT in this study did not reach statistical significance. Whether the improvement in PSA outcome noted from the randomized trial\(^9\) of high-dose (78 Gy) vs conventional-dose (70 Gy) 3-dimensional conformal external beam radiation therapy will translate into an additional benefit in PSA outcome for intermediate- and high-risk patients treated with high-dose RT plus AST as compared with high-dose RT needs to be studied.

Shortcomings of this retrospective study and all randomized studies ongoing in clinically localized prostate can-
...include the lack of an androgen suppression only control arm. Without such a control arm, it is difficult to ascertain whether any benefit was derived from the addition of RT to hormonal therapy. In addition, a small number of men may have remained castrate following the 6 months of AST, and this could improve PSA outcome in the combined treatment arm. Finally, the current study had a relatively short median follow-up and the median age of the patient population was 70 years, so that a significant risk of dying of other causes existed. Both of these issues may decrease the likelihood of detecting a future difference in cancer-specific survival as a result of the treatment. Realizing these potential limitations, PSA outcome, while not yet proven as a surrogate for cancer-specific survival, was used to assess clinical efficacy in this study.

However, recent studies lend credence to the use of PSA for prediction of cancer-specific survival. Specifically, the time to postoperative\(^1\) or post-\(^2\) PSA failure and a Gleason score of 8 or higher at biopsy for RT-managed patients or at prostatectomy for surgically managed patients were significant predictors of time to distant failure. The surgical study\(^10\) also concluded that time to distant failure was a significant predictor for death from prostate cancer. Therefore, given enough time left untreated, PSA failure in a patient who has undergone surgery or RT will lead to death from prostate cancer, and the time interval from PSA failure to death from prostate cancer will be shorter for men with poorly differentiated disease.

It will be several years before the results of the randomized trials evaluating the relative efficacy of RT with or without AST for patients with clinically localized prostate cancer will be available. In the interim, RT plus AST continues to be used to treat men with clinically localized prostate cancer despite the known toxicity\(^1\) (anemia, decreased bone density, impotence, decreased libido, mood swings, and decreased muscle mass) and unknown survival benefit compared with RT. Therefore, while no conclusions can be drawn from a nonrandomized retrospective comparison, our data provide physicians with information that may be used to counsel patients with clinically localized disease who have more aggressive prostate cancer (biopsy Gleason score $\geq 7$ or PSA $>10$ $\mu$G/L) than the clinical stage would suggest. The possibility exists that in these select men, the use of RT plus 6 months of AST may result in superior cancer control compared with the use of RT alone.

Author Contributions: Anthony V. D’Amico, MD, PhD, principal investigator and originator of concept; Delray Schultz, PhD, statistician for all Cox regression and Kaplan-Meier analyses; Marian Loffredo, RN, OCN, nurse protocol manager; Raymond Dugal, MD, Mark Hurwitz, MD, Irving Kaplan, MD, and Clair J. Beard, MD, enrolled and treated patients; Andrew A. Renshaw, MD, central pathology review; and Philip Kantoff, MD, coprincipal investigator.

REFERENCES