Biochemical Outcome after Radical Prostatectomy or External Beam Radiation Therapy for Patients with Clinically Localized Prostate Carcinoma in the Prostate Specific Antigen Era

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BACKGROUND. To the authors’ knowledge, consensus is lacking regarding the relative long-term efficacy of radical prostatectomy (RP) versus conventional-dose external beam radiation therapy (RT) in the treatment of patients with clinically localized prostate carcinoma.

METHODS. A retrospective cohort study of 2635 men treated with RP (n = 2254) or conventional-dose RT (n = 381) between 1988–2000 was performed. The primary endpoint was prostate specific antigen (PSA) survival stratified by treatment received and high-risk, intermediate-risk, or low-risk group based on the serum PSA level, biopsy Gleason score, 1992 American Joint Commission on Cancer clinical tumor category, and percent positive prostate biopsies.

RESULTS. Estimates of 8-year PSA survival (95% confidence interval [95% CI]) for low-risk patients (T1c,T2a, a PSA level ≤ 10 ng/mL, and a Gleason score ≤ 6) were 88% (95% CI, 85, 90) versus 78% (95% CI, 72, 83) for RP versus patients treated with RT, respectively. Eight-year estimates of PSA survival also favored RP for intermediate-risk patients (T2b or Gleason score 7 or a PSA level > 10 and ≤ 20 ng/mL) with < 34% positive prostate biopsies, being 79% (95% CI, 73, 85) versus 65% (95% CI, 58, 72), respectively. Estimates of PSA survival in high-risk (T2c or PSA level > 20 ng/mL or Gleason score ≥ 8) and intermediate-risk patients with at least 34% positive prostate biopsies initially favored RT, but were not significantly different after 8 years.

CONCLUSIONS. Intermediate-risk and low-risk patients with a low biopsy tumor volume who were treated with RP appeared to fare significantly better compared with patients who were treated using conventional-dose RT. Intermediate-risk and high-risk patients with a high biopsy tumor volume who were treated with RP or RT had long-term estimates of PSA survival that were not found to be significantly different. [See editorials on pages 211–4 and 215–8, this issue. Cancer 2002;95: 281–6. © 2002 American Cancer Society. DOI 10.1002/cncr.10657

KEYWORDS: radical prostatectomy (RP), conventional dose radiation therapy (RT), prostate carcinoma, prostate specific antigen (PSA), survival.

Recommendations for the treatment of clinically localized adenocarcinoma of the prostate should be made using the results of evidence-based medicine. To our knowledge, to date there are no published large, prospective, randomized trials comparing radical prostatectomy (RP) with external beam radiation therapy (RT) for the treatment of prostate carcinoma during the prostate specific antigen (PSA) era. A single randomized study was performed in the pre-PSA...
era; however, the results of the study were inconclusive due to imbalances in the health, age, and lymph node assessment of the patients in the two treatment groups.2

The utility of the pretreatment PSA level, biopsy Gleason score, percent positive prostate biopsies, and the 1992 American Joint Commission on Cancer (AJCC) staging T category in predicting postradiation and postoperative PSA outcome has been well described previously. Therefore, to compare results between RP and RT in patients presenting during the PSA era, it is important to control for the values of these known predictive factors. In addition, the dose of RT also needs to be consistent among patients who receive RT because the RT dose has been reported to impact PSA outcome and toxicity, respectively, in prospective randomized trials.

Therefore, the purpose of the current study was to provide estimates of 8-year PSA outcome data stratified by the pretreatment PSA level, biopsy Gleason score, percent positive prostate biopsies, and the 1992 AJCC T category for patients with clinically localized prostate carcinoma who were treated with either RP or conventional-dose RT (i.e., 70 Grays [Gy]).

**MATERIALS AND METHODS**

**Patient Selection**

Between January 1988 and December 2000, 2635 men with clinically localized (category T1c, T2) prostate carcinoma underwent definitive local therapy. The local therapy received was either RP (n = 2254) at the Hospital of the University of Pennsylvania (HUP) or the Brigham and Women’s (BWH) Hospital, or conventional-dose RT (n = 381) at a single Harvard-associated community outreach facility. Patients underwent a staging evaluation as described previously based on the serum PSA level, biopsy Gleason score, and a biopsy Gleason score of 2a or 2a, a PSA level of or a biopsy Gleason score of or were defined as being at low risk. Intermediate-risk patients had either a PSA level or a biopsy Gleason score of or were considered to be at high risk. Further analysis of the intermediate-risk group was performed using a previously validated stratification using the percent positive prostate biopsies. Specifically, intermediate-risk patients with or were considered as having low and high biopsy tumor volume, respectively.

PSA failure was defined according to the American Society of Therapeutic Radiation and Oncology (ASTRO) 1996 consensus statement for patients treated with both RP and RT. The definition required that a patient had 3 consecutive rising PSA values, each obtained at least 3 months apart, before PSA failure was determined. The time of PSA failure was defined as the midpoint between the time of the PSA nadir value and the time of the initial rising PSA value. The limit of detection of PSA was 0.2 ng/mL. Follow-up intervals generally shortened once PSA failure was suspected.
but not achieved by the ASTRO definition, but PSA failure was scored only when the ASTRO criteria was satisfied. Time zero was defined as the date of diagnosis for all study patients. The median time interval from the time of diagnosis until RP or from diagnosis until the initiation of RT was 3 months (range, 2–7 months) and 3.2 months (range, 2.8–7 months), respectively. Pairwise comparisons were made using the log-rank test. For the purpose of illustration, estimates of PSA outcome were calculated using the actuarial method of Kaplan and Meier and displayed graphically. The 95% CIs for estimates of 8-year PSA survival were calculated using a bootstrapping procedure with 2000 replications.

RESULTS

Predictive Factors and Follow-Up Comparison

Patients treated with RT were more likely to be in the high-risk cohort (31% vs. 19%) and less likely to be in the low-risk cohort (24% vs. 49%) compared with patients treated with RP (P < 0.0001). Table 1 shows the pretreatment clinical characteristics for the 2635 study patients stratified by treatment modality and clinical risk group. There were no imbalances noted with regard to the pretreatment PSA level, biopsy Gleason score, or 1992 AJCC clinical T category among patients in the low-risk group, low biopsy tumor volume intermediate-risk group, and high biopsy tumor volume intermediate-risk group. There were more patients with a Gleason score of 7 versus 5-6 (P = 0.001) and clinical category T2b versus T1c or 2a disease (P = 0.03) who were treated with RT compared with RP in the high-risk group. This potentially could bias the results in favor of RP in the high-risk group. The median follow-up periods for patients treated with RP and patients treated with RT in each of the four clinical risk groups were not significantly different. Specifically, the median follow-up for those patients treated with RP versus those patients treated with RT were 4.3 years (range, 1–12.9 years) versus 3.9 years (range, 1–11.8 years), 4.2 years (range, 1.1–12.9 years) versus 3.9 years (range, 1.2–9.8 years), 2.9 years (range, 1.1–12.9 years) versus 3.3 years (range, 1.2–10.3 years), and 3 years (range, 1.2–11.5 years) versus 3.2 years (range, 1.3–12.9 years), respectively, in the low-risk, low biopsy tumor volume intermediate-risk, high biopsy tumor volume intermediate-risk, and high-risk groups, respectively.

Comparison of PSA Outcome

The 8-year estimates of PSA survival for low-risk patients treated with RP versus those treated with RT were 88% (95% CI, 85, 90) versus 78% (95% CI, 72, 83), respectively. The same values were 79% (95% CI, 73, 85) versus 65% (95% CI, 58, 72) for intermediate-risk patients with < 34% positive prostate biopsies who were treated with RP versus those treated with RT, respectively. These findings are illustrated in Figures 1 and 2, respectively. Conversely, intermediate-risk patients with ≥ 34% positive prostate biopsies and high-risk patients treated with RT had an initial reduction in PSA failure compared with patients treated with an RP. However, this reduction in PSA failure was not

<table>
<thead>
<tr>
<th>Pretreatment characteristic</th>
<th>RP (n = 2254)</th>
<th>RT (n = 381)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Low-risk group</td>
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<tr>
<td>PSA ≤ 4 ng/mL</td>
<td>1017 (45%)</td>
<td>1017 (45%)</td>
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<td>PSA &gt; 4–10 ng/mL</td>
<td>632 (28%)</td>
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<td>PSA &gt; 10–20 ng/mL</td>
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<td>Intermediate-risk and &lt; 34% positive prostate biopsies</td>
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<tr>
<td>PSA &gt; 10–20 ng/mL</td>
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<td>Gleason score of 5-6</td>
<td>142 (42%)</td>
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<tr>
<td>1992 AJCC T1c, 2a</td>
<td>234 (69%)</td>
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<tr>
<td>Intermediate-risk and ≥ 34% positive prostate biopsies</td>
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<td>High-risk group</td>
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<td>1992 AJCC T2b</td>
<td>47 (11%)</td>
<td>47 (11%)</td>
<td>0.23</td>
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</table>

RP: radical prostatectomy; RT: radiation therapy; PSA: prostate specific antigen; AJCC: American Joint Committee on Cancer. The P value represents the comparison of the proportion of patients with the given pretreatment predictive factor distribution treated with radical prostatectomy or radiation therapy using a chi-square metric. The risk groups were as defined in the “Statistical Methods” section.
maintained by 8 years, as noted in Figures 3 and 4. Specifically, 8-year estimates of PSA survival were 36% (95% CI, 27–44) versus 35% (95% CI, 12–55) for the high biopsy tumor volume intermediate-risk patients and 33% (95% CI, 27–39) versus 40% (95% CI, 28–52) for high-risk patients treated with RP versus those treated with RT, respectively.

**DISCUSSION**

The benchmark for selecting the treatment of patients with clinically localized prostate carcinoma should be large prospective randomized clinical trials. However, the two long-standing treatment options of either RP or RT to our knowledge have never been compared successfully for efficacy because of both patient preference and physician bias with respect to the perceived relative efficacy and toxicity of these two approaches. In the current study, PSA outcome up to 8 years after RP or conventional-dose (i.e., 70 Gy) RT was compared among patients who were matched on the basis of the known pretreatment predictors of PSA outcome.
The results of the current study revealed a modest (10–14%) and significant \( P \leq 0.05 \) benefit with RT compared with conventional-dose RT at 8 years after therapy for patients with low-risk or low biopsy tumor volume intermediate-risk disease. It is interesting to note that because of the protracted rate of failure in these patient subgroups, the benefit in PSA outcome did not emerge until 4–5 years after the completion of treatment, as noted in Figures 1 and 2. Conversely, there was an improvement in PSA outcome for RT compared with RP in intermediate-risk patients with high biopsy tumor volume disease and high-risk patients that was most notable during the first 3–6 years after treatment. However, this benefit was either lost or became insignificant by 8 years, as noted in Figures 3 and 4.

A possible explanation for the superior outcome of RP in the setting of low-risk disease and low biopsy tumor volume intermediate-risk disease is that an RT dose of 70 Gy may not be adequate to eradicate the disease completely in some low-risk or low biopsy tumor volume intermediate-risk patients. Support for this hypothesis came from a randomized dose escalation trial (78 Gy vs. 70 Gy)\(^{12}\) in which a benefit was noted in 5-year PSA outcome for all patients (78% vs. 68%; \( P = 0.03 \)) and, in particular, those patients with a pretreatment PSA level > 10–20 ng/mL (72% vs. 43%; \( P = 0.01 \)). This result is direct evidence to support the hypothesis that higher RT doses can improve PSA outcome.

The likely explanation of why PSA outcome was improved initially with RT compared with RP for in patients with high biopsy tumor volume intermediate-risk disease and high-risk patients was the use of the ASTRO consensus definition\(^{15}\) to define PSA failure. Specifically, despite utilizing the same definition of PSA failure (i.e., the ASTRO consensus definition\(^{15}\)) for both patients treated with RP and those treated with RT, those patients treated with RT are expected to have estimates of PSA outcome that will overestimate actual PSA control rates during the early years of follow-up. The reason for this phenomenon is that before a patient treated with RT can be considered a PSA failure he first must achieve a PSA nadir, which can take 1–2 years and occasionally longer,\(^{18}\) and then rise. Conversely, nearly all patients treated with RP will reach their nadir PSA level within 1–2 months postoperatively or sooner. As a result, a bias in favor of RT is introduced in studies when comparing the early results of PSA outcome. In the current study, this bias was observed in all patients but, as expected, it was particularly pronounced in the high biopsy tumor volume intermediate-risk patients (Fig. 3) and the high-risk patients (Fig. 4), in whom actual failure rates are intrinsically higher due to the presence of more extensive local and occult micrometastatic disease. Therefore, clinically meaningful and reliable results require longer follow-up periods, as provided in the current study, to overcome the initial bias favoring RT because of the relatively longer time to PSA nadir in patients treated with RT compared with those treated with RP. In addition, log-rank \( P \) values for overall comparisons of Kaplan–Meier estimates of PSA outcome may be significant due to early differences in PSA outcome between RP and RT as noted in Figures 3 and 4, despite the lack of a significant difference that becomes apparent with longer follow-up.

Two points deserve further consideration. First, patients with locally advanced (clinical category T3, T4) prostate carcinoma have been shown in a prospective randomized trial\(^{19}\) to have a survival benefit when androgen suppression therapy (AST) is added to RT. Second, this study suggested that RP and RT appear equally effective at 10 years in high-risk patients (Fig. 4) and high biopsy tumor volume intermediate-risk patients (Fig. 3) with clinically localized disease despite the higher proportion of RT-treated, high-risk patients with clinical category T2b and/or Gleason score of 7 disease (Table 1). Taken together, these two observations provide the basis on which to suggest that an improved outcome may exist with RT and AST compared with RT or RP alone in high-risk patients and high biopsy tumor volume intermediate-risk patients with clinically localized prostate carcinoma. However, a definitive answer requires a randomized study.

The main limitation of the current study is that it is retrospective and unknown confounding factors not accounted for in the pretreatment risk groups may make the comparisons of the treatment modalities less reliable. However, the overall sample size was large, which helps to reduce this type of confounding. Nevertheless, the current study is hypothesis-generating and awaits validation from a prospective randomized trial.

The results of the current study have provided evidence to support RT as opposed to conventional-dose RT in the treatment of patients with clinically localized low-risk or low biopsy tumor volume intermediate-risk prostate carcinoma. Further study utilizing a higher RT dose is needed and currently is ongoing in this patient population. In addition, evidence was presented to support the need for effective therapy that can provide tumor control beyond the prostate for high-risk patients and high biopsy tumor volume intermediate-risk patients, in whom PSA failure rates were reported to exceed 60% at 8 years and the impact of either local therapy on long-term PSA out-
come was not significantly different. For these patients, perhaps RT and AST should be considered.

REFERENCES


