Predominant Treatment Failure in Postprostatectomy Patients Is Local: Analysis of Patterns of Treatment Failure in SWOG 8794

Gregory P. Swanson, Michael A. Hussey, Catherine M. Tangen, Joseph Chin, Edward Messing, Edith Canby-Hagino, Jeffrey D. Forman, Ian M. Thompson, and E. David Crawford

ABSTRACT

Purpose
Southwest Oncology Group (SWOG) trial 8794 demonstrated that adjuvant radiation reduces the risk of biochemical (prostate-specific antigen [PSA]) treatment failure by 50% over radical prostatectomy alone. In this analysis, we stratified patients as to their preradiation PSA levels and correlated it with outcomes such as PSA treatment failure, local recurrence, and distant failure, to serve as guidelines for future research.

Patients and Methods
Four hundred thirty-one subjects with pathologically advanced prostate cancer (extraprostatic extension, positive surgical margins, or seminal vesicle invasion) were randomly assigned to adjuvant radiotherapy or observation.

Results
Three hundred seventy-four eligible patients had immediate postprostatectomy and follow-up PSA data. Median follow-up was 10.2 years. For patients with a postsurgical PSA of ≤ 0.2 ng/mL, radiation was associated with reductions in the 10-year risk of biochemical treatment failure (72% to 42%), local failures (20% to 7%), and distant failures (12% to 4%). For patients with a postsurgical PSA between higher than 0.2 and ≤ 1.0 ng/mL, reductions in the 10-year risk of biochemical failure (80% to 73%), local failures (25% to 9%), and distant failures (16% to 12%) were realized. In patients with postsurgical PSA higher than 1.0, the respective findings were 94% versus 100%, 28% versus 9%, and 44% versus 18%.

Conclusion
The pattern of treatment failure in high-risk patients is predominantly local with a surprisingly low incidence of metastatic failure. Adjuvant radiation to the prostate bed reduces the risk of metastatic disease and biochemical failure at all postsurgical PSA levels. Further improvement in reducing local treatment failure is likely to have the greatest impact on outcome in high-risk patients after prostatectomy.

J Clin Oncol 25:2225-2229. © 2007 by American Society of Clinical Oncology

INTRODUCTION

Two large randomized studies evaluating the role of post-radical prostatectomy (RP) adjuvant radiation have now been completed.1,2 Patients with high risk for treatment failure were randomly assigned to postprostatectomy radiation or no immediate treatment. Both studies showed that adjuvant radiation reduces the biochemical treatment failure rate. In the Southwest Oncology Group (SWOG) study, this reduction was 48% at 5 years, and in the European Organisation for Research and Treatment of Cancer (EORTC) study it was 40%. Only the SWOG study had long enough follow-up to report 10-year outcomes, and biochemical failure was reduced by 35% with immediate radiation. These studies provide important information on the patterns of postprostatectomy treatment failure. Both studies showed that the predominant pattern of treatment failure is local, with only a modest risk of metastatic disease. We evaluated the data from SWOG 8794 to try to gain additional insight into failure patterns as related to prostate-specific antigen (PSA) and effect on long-term control.

PATIENTS AND METHODS

SWOG 8794 was a prospective randomized study designed to address whether high-risk postprostatectomy patients benefited from immediate radiation therapy to
the prostate fossa. High risk was defined as extracapsular tumor extension, positive surgical margins, or seminal vesicle involvement. To be eligible, patients had to have histologically negative lymph nodes (although toward the end of the study, lymphadenectomy was not required for certain low-risk patients) and a negative bone scan. Patients with total urinary incontinence, intraoperative rectal injury, persistent urinary extravasation, or pelvic infection were excluded. No previous radiotherapy or chemotherapy for prostate cancer was allowed.

Patients had to be registered within 16 weeks after surgery. They were then randomly assigned to immediate radiation or no treatment, and treatment was to begin within 10 working days.

PSA first became widely available at the time the study opened (1988), and although not an initial requirement, the protocol was amended to mandate its collection. Most patients had longitudinal PSA data. There was no restriction on PSA level at enrollment.

Radiation therapy was directed at the prostate fossa. A four-field or arch technique was allowed. On the four-field approach, this was defined as a 9 × 9 cm or 10 × 10 cm antero-posterior and postero-anterior portal. The only additional requirement on the lateral portals was an attempt to block at least part of the rectum. The prescribed dose was 60 to 64 Gy. The radiation data was reviewed for dosimetric and volumetric compliance.

Follow-up visits were scheduled every 3 months for 1 year, every 6 months for 2 years, and annually thereafter. At each visit, a PSA was obtained as were additional staging studies (eg, bone scan) as clinically indicated.

**Statistical Methods**

The primary study end point was metastasis-free survival, defined as the time from random assignment to first evidence of metastatic disease or death due to any cause. The study design details have been previously published. Additional secondary end points included PSA failure-free interval, which was defined for men with a postsurgical PSA of 0.4 ng/mL or lower as the time to first occurrence of a PSA higher than 0.4 ng/mL. Recurrent disease was defined as any evidence of measurable or assessable (eg, bone lesions) disease, but excluding isolated PSA failure, and recurrence-free survival was defined as the first evidence of any objective recurrence (not including PSA) or death due to any cause. Patients without the event of interest were censored at their last contact date (last PSA assessment date for PSA failure). The methods of Kaplan and Meier were used to generate the time-to-event curves (Figs 1 to 4).

Counts and percentages of local failures and metastases were calculated and are presented in Table 1. The proportions were calculated by treatment arm for all patients with an available postprostatectomy PSA value, as well as in subgroups of patients defined by these PSA values.

**RESULTS**

Patient characteristics have been previously reported. Four hundred twenty-five patients were eligible and had PSA levels obtained on follow-up, with 374 having immediate postprostatectomy PSA data. Median follow-up was 10.2 years. A 25% reduction in metastasis-free survival was observed in patients randomly assigned to the radiation arm and this result was close to statistical significance (hazard ratio [HR], 0.75; 95% CI, 0.55 to 1.02; P = .063). Thirty-five (17%) of 211 patients in the observation arm had distant metastasis compared with 17 (8%) of 214 on the radiation arm, which was found to be statistically significant (P < .01). The overall PSA recurrence results were based on the subset of patients whose postprostatectomy PSA was undetectable (PSA ≤ 0.2 ng/mL), and radiation reduced the risk of PSA recurrence by 57% (P < .001). Overall, radiation therapy decreased the risk of clinical recurrence (local or metastatic) or death by 38% (P = .001). A total of 111 (52.6%) of 211 patients on the
observation arm suffered a recurrence of their disease or death with a median reached at 9.9 years compared with 84 (39.3%) of 214 subjects with a median reached at 13.8 years who received adjuvant radiotherapy.

For patients that had a recorded postprostatectomy PSA (374 patients), 14 (7%) of 190 patients in the radiation group were observed to have detectable distant metastases, compared with 30 (16%) of 184 in the observation group. In addition, adjuvant radiation reduced the risk of PSA failure from 64% to 41% at 5 years and from 77% to 55% at 10 years. The median time to PSA failure in the radiation group was 9.2 years and 2.2 years in the observation group.

Of the 184 patients in the observation arm with a preradiation PSA, 122 (66%) had a PSA of ≤ 0.2 ng/mL (undetectable), 44 (24%) had a PSA higher than 0.2 ng/mL and ≤1.0 ng/mL, and 18 (10%) had a PSA higher than 1.0 ng/mL. In the 190 radiation patients, the numbers were 122 (64%), 57 (30%), and 11 (6%), respectively. The PSA failure-free interval estimates (stratified by treatment arm and postprostatectomy PSA group) are shown in Figures 1 and 2. For the observation patients with a postoperative PSA of ≤0.2 ng/mL, the PSA failure rate at 10 years was high (72%) and was not appreciatively different from the PSA failure rate at 10 years for observation patients with a postoperative PSA higher than 0.2 ng/mL and ≤ 1.0 ng/mL (80%). For patients on the radiation arm with a PSA ≤ 0.2 ng/mL, the results were much better (10-year PSA failure, 42%). In radiation patients with a PSA higher than 0.2 and ≤ 1.0 ng/mL, the 10-year PSA failure was 73%. In both the observation and radiation groups, the patients with a postoperative PSA higher than 1.0 did not do well.

Among patients with postoperative PSA of ≤0.2 ng/mL, the HR of experiencing PSA treatment failure was much lower for patients receiving radiation compared with observation (HR, 0.35). In patients with a postoperative PSA between higher than 0.2 ng/mL and ≤ 1.0 ng/mL, the HR was estimated to be 0.67. The HR comparing radiation with observation for the higher than 1.0 ng/mL group was found to be 0.51. Despite the observed differences in HRs between the subgroups, there was no statistical evidence that the HR comparing radiation with observation differed between the post-RP PSA subgroups (P = .12).

As presented in Table 1, radiation reduced the percentage of patients with metastasis from 16% to 7% and the percentage of patients with clinical local treatment failures from 22% to 8%. As noted earlier for biochemical failure, similar effects on reduction of metastatic disease were seen in patients across all subgroups of postoperative PSA levels.

Thirty-three percent (n = 70) of the patients in the observation group subsequently received radiation after PSA failure. Fifty-six of these had an available post-RP PSA, date of beginning salvage RT, and available postsalvage RT PSA measurements (Table 2). Median time to salvage RT was 2 years postrandomization. Time to second PSA treatment failure (postsalvage RT) was calculated as the time from start of salvage radiation to occurrence of a PSA measurement ≥ 0.4 ng/mL. Thirty-four patients with a postprostatectomy PSA level of ≤ 0.2 ng/mL received salvage radiation for a rising PSA and/or local treatment failure. The percentage of patients free from PSA failure at 5 years after having salvage radiation was 38%, and the median time to further PSA failure was 2.8 years. Seventeen patients with a nadir of higher than 0.2 and ≤ 1.0 ng/mL underwent subsequent radiation and 5-year PSA failure-free rate after salvage radiation was 18%, with a median time to further failure of 1 year. In comparison, for the patients that received immediate adjuvant radiation with a post-prostatectomy PSA ≤ 0.2 ng/mL, the 5-year PSA failure-free rate was 77%, and for patients with a PSA higher than 0.2 and ≤ 1.0 ng/mL, the rate was 34%.

The impact of radiation on PSA treatment failure was also examined by Gleason sum subgroups in the 338 patients with an available Gleason sum at baseline. It should be noted that a proportional hazards analysis revealed some evidence that freedom from PSA

---

**Table 1. Percentages of Patients With Local Recurrence or Metastasis by Post-RP PSA Subgroup**

<table>
<thead>
<tr>
<th>Group</th>
<th>Observation No. of Patients</th>
<th>LF</th>
<th>%</th>
<th>Mets</th>
<th>%</th>
<th>LF and Mets</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with post-RP PSA†</td>
<td>184</td>
<td>40</td>
<td>22</td>
<td>30</td>
<td>16</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Post-RP PSA ≤ 0.2</td>
<td>122</td>
<td>24</td>
<td>20</td>
<td>15</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>0.2-1.0</td>
<td>44</td>
<td>11</td>
<td>25</td>
<td>7</td>
<td>16</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>18</td>
<td>5</td>
<td>28</td>
<td>8</td>
<td>44</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients with post-RP PSA†</td>
<td>190</td>
<td>15</td>
<td>8</td>
<td>14</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Post-RP PSA ≤ 0.2</td>
<td>122</td>
<td>9</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0.2-1.0</td>
<td>57</td>
<td>5</td>
<td>9</td>
<td>7</td>
<td>12</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>11</td>
<td>1</td>
<td>9</td>
<td>2</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RP, radical prostatectomy; PSA, prostate-specific antigen; LF, local failure; Mets, distant metastasis. †For patients with LF then metastasis, numbers are included in both “LF” and “Mets” categories.

†Three hundred seventy-four patients with available post-RP PSA.
treatment failure differed between patients who had an available Gleason sum and those who did not ($P = .02$). Radiation therapy was observed to decrease the hazard of a PSA treatment failure in each of the subgroups defined by Gleason sum $\leq 6$ (HR, 0.54), sum of 7 (HR, 0.37), and sum $\geq 8$ (HR, 0.64). Figures 3 and 4 present the Kaplan-Meier estimates of freedom from PSA recurrence by Gleason sum. The test of the interaction between treatment and Gleason sum verified that there is no evidence that the HR comparing radiation with observation differed significantly by Gleason sum subgroup ($P = .36$).

**DISCUSSION**

SWOG 8794 and EORTC 22911 convincingly showed that adjuvant radiation can reduce the risk of biochemical treatment failure in men with positive pathologic findings found at the time of RP for prostate cancer. Most informative are the patterns of treatment failure in these two studies. One of the surprising findings of SWOG 8794 is that even out to 10 years, the risk of metastatic disease is extremely low (only 16% in the untreated group). There was some thought at the time SWOG 8794 was initiated that the study would not be positive because the primary risk of treatment failure in these patients was thought to be systemic, not local. Both randomized studies have proved exactly the opposite. In the EORTC study, for the observation group, the rate of clinical local treatment failure was four times the rate of systemic failure. In the SWOG study, it was 30% higher (16% distant metastasis vs 24% local failure occurrence). This was for gross local treatment failure, so while demonstrative of the pattern of treatment failure, likely underestimates the number of patients that harbor locally persistent cancer in the form of microscopic disease. This premise is supported by the strongly positive response to local radiation and the relatively low number of systemic treatment failures in this study as well as the uniformly positive response to local radiation in salvage series. In this study, by improving the local control, adjuvant radiation was associated with a reduction in the proportion of patients with metastases (from 16% to 7%).

The significant local response to radiation is somewhat remarkable considering that the radiation doses used (60 to 64 Gy) are suboptimal by today’s standards (which is closer to 70 Gy). That the results were still significantly positive indicates that further improving local control (ie, with higher radiation doses or adding other adjuvant treatment) would likely offer further improvement in the results. With these studies giving strong evidence that the primary risk of treatment failure is local and not distant, studies treating these patients solely with systemic therapy are probably misguided.

Other than just increasing the radiation dose, some attempts have been made to improve the efficacy of radiation in post-prostatectomy patients. In patients with a rising PSA, the Radiation Therapy Oncology Group randomly added bicalutamide to salvage radiation with the hope that it might improve results. The premise was that bicalutamide might act as a radiation potentiator and also reduce systemic treatment failure. Those results are pending. Subsequently, SWOG proposed a study (S0611) for rising PSA that randomly assigned patients receiving radiation to concomitant docetaxel. This is primarily for its radiosensitizing properties, although docetaxel alone is an effective agent against prostate cancer, so there may be some potential systemic effects also. At this time, the National Cancer Institute has chosen instead to support further research with radiation and androgen ablation in patients with a rising post-prostatectomy PSA.

Another observation from these data is that the preradiation (postprostatectomy) PSA levels predicted subsequent outcomes. The EORTC mandated an undetectable ($\leq 0.4$ ng/mL) PSA for participation. Their 5-year PSA failure-free rate in radiation patients was 74%. In the SWOG study, for patients with an undetectable PSA ($\leq 0.2$ ng/mL) the 5-year PSA failure-free rate was very similar at 77% (compared with 59% for the entire radiation cohort). Also, in the SWOG study, radiation patients with a post-prostatectomy PSA of more than 0.2 and $\leq 1.0$ ng/mL had a PSA failure-free rate of 34% at 5 years (compared with 77% for the $\leq 0.2$ ng/mL group). Because the ultimate risk of metastasis was only slightly higher (8% absolute difference) in the higher than 0.2 to $\leq 1.0$ ng/mL group than in the $\leq 0.2$ ng/mL group, this 43% difference in biochemical control between the higher and lower PSA groups would indicate less efficacy in eradicating local disease. Because PSA is representative of cancer bulk, this would indicate that the radiation was not able to completely eradicate all the residual disease in patients with higher PSA on a consistent basis. This impacts the fundamental question as to whether radiation can be delayed until the PSA starts to rise or needs to be given immediately. In the observation arm, at 10 years, 23% patients had not experienced treatment failure, indicating that adjuvant radiation would not likely have helped them. If radiation can be safely delayed and given only to those with a rising PSA, then the subgroup that would not have experienced treatment failure will have avoided unnecessary treatment. We evaluated, in an exploratory fashion, the effect of delaying radiation until the PSA rose. For the more favorable patients in the observation arm (preradiation PSA $\leq 0.2$ ng/mL), when given salvage radiation at the time of subsequent rising PSA, the 5-year PSA failure-free rate postradiation was 38% (Table 2). Within the limitations of a small subgroup analysis, this appears less than the same group given immediate radiation (77%), but is very similar to the patients with a higher PSA of 0.2 to 1.0 ng/mL that received immediate radiation (34% 5-year PSA failure-free rate). That their control rate was similar to the immediate radiation patients with a higher starting PSA would suggest the control rate is not so much directly dependent on the timing of the radiation as it is with the microscopic bulk of tumor (as represented by PSA level). A reasonable premise is that with higher doses of radiation, eradication of even bulkier tumors is likely, so with the higher doses used currently, there may be no detriment to waiting for the PSA rise before...
starting radiation as long as it is started fairly early (ie, at first rise). Clearly, this can only be determined by clinical trials.

In conclusion, patients with high-risk features at prostatectomy experience a high rate of biochemical and clinical treatment failure. That treatment failure is now documented to be primarily in the area of the prostate fossa, and adjuvant radiation reduces both biochemical and clinical treatment failure. Patients with high-risk prostate cancer after prostatectomy should be offered adjuvant radiation as standard treatment. Further studies should evaluate optimizing local control as that appears to be the best opportunity for cure.

The authors indicated no potential conflicts of interest.

REFERENCES


