CLINICAL INVESTIGATION

Prostate

SALVAGE RADIOTHERAPY FOR RISING PROSTATE-SPECIFIC ANTIGEN LEVELS AFTER RADICAL PROSTATECTOMY FOR PROSTATE CANCER: DOSE–RESPONSE ANALYSIS

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Purpose: To investigate the association between external beam radiotherapy (EBRT) dose and biochemical failure (BcF) of prostate cancer in patients who received salvage prostate bed EBRT for a rising prostate-specific antigen (PSA) level after radical prostatectomy.

Methods and Materials: We evaluated patients with a rising PSA level after prostatectomy who received salvage EBRT between July 1987 and October 2007. Patients receiving pre-EBRT androgen suppression were excluded. Cox proportional hazards models were used to investigate the association between EBRT dose and BcF. Dose was considered as a numeric variable and as a categoric variable (low, <64.8 Gy; moderate, 64.8–66.6 Gy; high, >66.6 Gy).

Results: A total of 364 men met study selection criteria and were followed up for a median of 6.0 years (range, 0.1–19.3 years). Median pre-EBRT PSA level was 0.6 ng/mL. The estimated cumulative rate of BcF at 5 years after EBRT was 50% overall and 57%, 46%, and 39% for the low-, moderate-, and high-dose groups, respectively. In multivariable analysis adjusting for potentially confounding variables, there was evidence of a linear trend between dose and BcF, with risk of BcF decreasing as dose increased (relative risk [RR], 0.77 [5.0-Gy increase]; p = 0.05). Compared with the low-dose group, there was evidence of a decreased risk of BcF for the high-dose group (RR, 0.60; p = 0.04), but no difference for the moderate-dose group (RR, 0.85; p = 0.41).

Conclusions: Our results suggest a dose response for salvage EBRT. Doses higher than 66.6 Gy result in decreased risk of BcF.

Biochemical failure, Dose response, Prostate bed, Prostate-specific antigen recurrence, Salvage.

INTRODUCTION

Randomized trials of definitive external beam radiotherapy (EBRT) for localized prostate cancer have shown that a higher radiation dose leads to improved prostate cancer outcomes (1–5). Kuban et al. (1) updated the M. D. Anderson experience of 301 men with T1b–T3 prostate cancer who were randomly assigned to receive 70 or 78 Gy of EBRT. Biochemical control was achieved in 76% of patients in the 70-Gy protocol vs. 83% of patients in the 78-Gy protocol, and the 8-year actuarial estimates of freedom from failure (biochemical or clinical) were 59% vs. 78%, respectively (p = 0.04). Similarly, Zietman et al. (2) evaluated 393 men with localized prostate cancer who were randomly assigned to receive 70.2 or 79.2 Gy of EBRT. Biochemical control at 5 years occurred in 79% of patients in the lower-dose protocol vs. 91% of patients in the higher-dose protocol; increasing the radiation dose improved local control from 48% to 67% (p < 0.001). A Mayo Clinic retrospective review by Vora et al. (6) reported 271 patients who received three-dimensional radiotherapy (3D-RT) with a median dose of 68.4 Gy (range, 66–71 Gy) and were compared with 145 patients who received intensity-modulated radiotherapy (IMRT) with a median dose of 75.6 Gy (range, 70.2–77.4 Gy). The 5-year biochemical control rate was 74.4% with lower-dose 3D-RT and 84.6% with higher-dose IMRT (p = 0.03).

The EBRT is also used after radical prostatectomy, either adjuvantly or as salvage therapy for a rising prostate-specific antigen (PSA) level, often referred to as biochemical failure (BcF). Swanson et al. (7) concluded that a rising PSA level postoperatively is most often attributable to the persistence of cancer in the prostate fossa. This view is supported by the observation that adjuvant EBRT reduces the risk of subsequent metastatic disease relapse (7). A reduction in
metastases and prostate cancer–related mortality was also noted by Trock et al. (8) when salvage EBRT was used in patients with an elevated postoperative PSA level. These observations suggest that the persistence postoperatively of prostate cancer in the prostate fossa results in a late wave of metastases in some patients, as has also been suggested after definitive EBRT (9).

Salvage EBRT may be used postoperatively in patients with a detectable PSA level, and several authors have reported results with this treatment (8, 10, 11). Although PSA levels decline after EBRT in a substantial proportion of patients, PSA levels may rise subsequently in some patients. This pattern of PSA decline, often to an undetectable level (11), with a delayed and steadily rising PSA profile suggests the possibility that cancer persisted in the prostate fossa despite salvage EBRT. It is a generally held view that lower doses of EBRT should be administered in the salvage setting, because the volume of cancer is presumed to be microscopic and because patients are less tolerant of EBRT postoperatively. However, Sella et al. (12) found that the prostate fossa mass averaged 1.4 cm (range, 0.8–4.5 cm) in diameter as measured by endorectal magnetic resonance imaging, and King and Kapp (13) suggested that the dose–response relationship of salvage and definitive EBRT are similar. To our knowledge, no randomized trials of dose escalation for salvage radiotherapy have been conducted.

Because the dose–response relationship of salvage EBRT has not been studied sufficiently, we evaluated a cohort of men treated at Mayo Clinic (14). The primary aim of this study was to investigate whether an association exists between EBRT dose and BcF of prostate cancer. In an exploratory analysis, we also examined whether the relationship between radiation dose and BcF is consistent for different pre-EBRT PSA levels. It remains to be seen whether a randomized trial will be conducted to study the question of whether there will be a benefit to dose escalation in patients with BcF postoperatively.

METHODS AND MATERIALS

This study was approved by the Mayo Clinic Institutional Review Board. Patients were seen from July 1987 through October 2007 for a detectable PSA level after radical prostatectomy. Information was collected retrospectively from medical records. Data were obtained from Mayo Clinic in Jacksonville, Florida (MCF), Mayo Clinic in Rochester, Minnesota (MCR), and Mayo Clinic in Phoenix/Scottsdale, Arizona (MCA). Items of interest were preoperative PSA level, pathologic tumor stage, Gleason score, DNA ploidy, surgical margin status, EBRT start date, patient age at EBRT start, pre-EBRT PSA level, neoadjuvant and/or concurrent androgen suppression (AS) associated with EBRT, EBRT prescribed dose, date of BcF, date of last follow-up, and Mayo Clinic site. Patients who received AS were excluded from this analysis.

The EBRT technique has been described previously (10). In summary, all patients were treated with EBRT using megavoltage (6- to 20-mV photons) linear accelerators at one of the three practice locations. EBRT treatment was planned and delivered to the estimated region of the prostate bed. EBRT to the estimated region of the seminal vesicle bed and remnants was done at the discretion of the treating physician. Five patients also received treatment to the pelvic lymphatic regions (45.0–50.4 Gy). The treatment volume was defined by skeletal landmarks with or without surgical clip location in the earlier years of treatment planning; by the mid 1990s, computed tomography–based treatment planning was performed on all patients. Retrograde urethrography was also performed in many patients. The median dose to the prostate bed was 64.8 Gy (range, 54.0–72.4 Gy).

A PSA value of 0.4 ng/mL and rising, as described by Amling et al. (15), is currently used at our institution to define BcF after surgery. We defined BcF after EBRT as a single PSA value of 0.4 ng/mL or higher, which had exceeded the post-EBRT nadir. The date of the defining PSA value was considered the date of BcF without backdating.

Numeric variables were summarized with the sample median, minimum, 25th percentile, 75th percentile, and maximum. The Kaplan-Meier method was used to estimate the cumulative rate of BcF after the start of EBRT, censoring at the date of death or date of last follow-up for patients who did not experience BcF. Cox proportional hazards models were used to investigate the association between EBRT dose and BcF; single variable Cox models were considered, as were multivariable models, adjusting for other possibly confounding variables (preoperative PSA level, pathologic tumor stage, Gleason score, margin status, patient age, and pre-EBRT PSA level) simultaneously. An interaction between EBRT dose and pre-EBRT PSA level was also considered in an analysis that should be considered exploratory because of the low power to detect such an interaction. Relative risks (RRs) and corresponding 95% confidence intervals (CIs) were estimated. We considered EBRT dose as a numeric variable to investigate a linear association with BcF and also as a three-level categorical variable (<64.8, 64.8–66.6, >66.6 Gy) to investigate a possible nonlinear association. Fisher’s exact test or a Kruskal-Wallis rank sum test was used to compare patient characteristics according to dose category. Preoperative PSA and pre-EBRT PSA levels were considered on the logarithm scale in all Cox proportional hazards models because of their skewed distributions. Statistical analyses were performed using SPLUS (version 8.0.1; Insightful Corporation, Seattle, Washington).

RESULTS

We identified 426 men who underwent salvage EBRT. A final sample size of 364 patients (198 MCF, 106 MCR, 60 MCA) was analyzed after patients who received AS (n = 62) were excluded. Patients were placed in three groups based on the EBRT dose: low dose (<64.8 Gy), moderate dose (64.8–66.6 Gy), and high dose (>66.6 Gy). Patient characteristics are shown in Table 1.

The median EBRT dose was 64.8 Gy (range, 54.0–72.4 Gy). The most common doses prescribed were 64.0 Gy (n = 92; 25%); 66.6 Gy (n = 67; 18%); and 70.2 Gy (n = 57; 16%). There were 154 men (42%) in the low-dose group, 124 men (34%) in the moderate-dose group, and 86 men (24%) in the high-dose group. Statistically significant differences in patient characteristics between radiation dose groups were noted for age, pathologic tumor stage, preoperative PSA level, pre-EBRT PSA level, and DNA ploidy (Table 1).

The median length of follow-up after the start of EBRT was 6.0 years (range, 0.1–19.3 years), with 196 patients (54%) experiencing BcF. Overall, the estimated cumulative
The rate of BcF at 1, 3, and 5 years after the start of EBRT was 20% (95% CI, 16–24%), 39% (95% CI, 33–44%), and 50% (95% CI, 44–55%), respectively (Fig. 1). At 5 years, the estimated cumulative rates of BcF for the low-, moderate-, and high-dose groups were 57%, 46%, and 39%, respectively (Fig. 2, Table 2). In single variable analysis (Table 2), there was strong evidence of a linear trend between EBRT dose and BcF, with the risk of BcF decreasing as the EBRT dose increased (RR, 0.70 [5.0-Gy increase]; 95% CI, 0.56–0.87; \( p \) = 0.002), when dose was considered as a numeric variable. In comparison with patients treated with a low dose, there was a trend, although not statistically significant, toward a decreased risk of BcF for patients treated with a moderate dose (RR, 0.76; 95% CI, 0.56–1.04; \( p \) = 0.08), whereas there was evidence of a decreased risk of BcF for patients treated with a high dose (RR, 0.60; 95% CI, 0.39–0.92; \( p \) = 0.02).

In the multivariable analysis (Table 2), adjusting for preoperative PSA level, pathologic tumor stage, Gleason score, margin status, patient age, and pre-EBRT PSA level, the observed linear trend between increasing EBRT dose and decreased risk of BcF weakened slightly but still remained (RR, 0.77 [5.0-Gy increase]; 95% CI, 0.59–1.01; \( p \) = 0.05), whereas the observed trend toward a decreased risk of BcF in patients treated with a high dose remained consistent (RR, 0.60; 95% CI, 0.39–0.92; \( p \) = 0.02). The trend toward a decreased risk of BcF in patients treated with a moderate dose still did not reach statistical significance (RR, 0.85; 95% CI, 0.58–1.25; \( p \) = 0.41). We did not adjust for DNA ploidy in the final multivariable analysis because information concerning this variable was missing in many patients (\( n \) = 96). However, in a sensitivity analysis adjusting for DNA ploidy in addition to the aforementioned variables, the associations between EBRT dose and BcF remained consistent when considering dose as a numeric variable (RR, 0.71 [5.0-Gy increase]; \( p \) = 0.04) and as a categoric variable (RR, 0.51 [high dose vs. low dose]; \( p \) = 0.04).

We also examined the association between EBRT dose and BcF for varying levels of pre-EBRT PSA by stratifying by the median pre-EBRT PSA value of 0.6 ng/mL (Fig. 3).

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low (&lt;64.8 Gy) (( n ) = 154)</th>
<th>Moderate (64.8–66.6 Gy) (( n ) = 124)</th>
<th>High (&gt;66.6 Gy) (( n ) = 86)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>68 (44, 79)</td>
<td>68 (46, 81)</td>
<td>65 (50, 85)</td>
<td>0.005</td>
</tr>
<tr>
<td>Pathologic tumor stage</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>T2</td>
<td>56 (37)</td>
<td>46 (38)</td>
<td>45 (53)</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>52 (34)</td>
<td>52 (43)</td>
<td>26 (31)</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>44 (29)</td>
<td>23 (19)</td>
<td>12 (14)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Margin</td>
<td></td>
<td></td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td>Positive</td>
<td>82 (54)</td>
<td>66 (54)</td>
<td>50 (59)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>71 (46)</td>
<td>57 (46)</td>
<td>35 (41)</td>
<td></td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>3–6</td>
<td>53 (43)</td>
<td>49 (42)</td>
<td>26 (31)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>52 (42)</td>
<td>44 (38)</td>
<td>41 (49)</td>
<td></td>
</tr>
<tr>
<td>8–10</td>
<td>18 (15)</td>
<td>23 (20)</td>
<td>16 (19)</td>
<td></td>
</tr>
<tr>
<td>Preoperative PSA (ng/mL)</td>
<td>13.6 (1.1, 219.0)</td>
<td>7.4 (2.3–57.5)</td>
<td>7.5 (1.9, 47.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-EBRT PSA (ng/mL)</td>
<td>0.8 (0.1, 15.3)</td>
<td>0.5 (0.1, 14.4)</td>
<td>0.5 (0.1, 20.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DNA ploidy</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>14 (11)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Diploid</td>
<td>58 (46)</td>
<td>62 (67)</td>
<td>30 (63)</td>
<td></td>
</tr>
<tr>
<td>Aneuploid</td>
<td>12 (9)</td>
<td>10 (11)</td>
<td>8 (17)</td>
<td></td>
</tr>
<tr>
<td>Tetraploid</td>
<td>43 (34)</td>
<td>21 (23)</td>
<td>9 (19)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EBRT = external beam radiotherapy; PSA = prostate-specific antigen.

The sample medium (minimum, maximum) is given for numeric variables. The \( p \) values result from Fisher’s exact test or a Kruskal-Wallis rank sum test. Information was unavailable for the following variables: pathologic tumor stage (\( n \) = 6), margin (\( n \) = 3), Gleason score (\( n \) = 42), preoperative PSA level (\( n \) = 32), and DNA ploidy (\( n \) = 96).

![Fig. 1. Estimated cumulative rate of biochemical failure (BcF) after the start of external beam radiotherapy (EBRT). Dotted lines represent 95% confidence intervals.](image-url)
There was no evidence of a difference in the relationship between dose and BcF for patients with a pre-EBRT PSA level less than the median value (low) and a pre-EBRT PSA level higher than the median value (high) ($p = 0.68$). However, although statistical significance was not approached, we did observe a stronger linear association between dose and BcF in patients with high pre-EBRT PSA levels (RR, 0.69 [5.0-Gy increase]; 95% CI, 0.47–0.99) compared with patients who had low pre-EBRT PSA levels (RR, 0.85 [5.0-Gy increase]; 95% CI, 0.57–1.28). Similarly, in comparison with patients receiving a low dose, in patients receiving a high dose, the decreased risk of BcF was more apparent in patients with high pre-EBRT PSA levels (RR, 0.39; 95% CI, 0.18–0.86) than in patients with a low pre-EBRT PSA level (RR, 0.84; 95% CI, 0.43–1.66). A larger sample size is needed to properly examine the effect of dose on BcF for varying pre-EBRT PSA levels.

**DISCUSSION**

Only a limited number of small retrospective studies have shown a benefit of salvage EBRT doses higher than 64.8 Gy (16–19); the largest of these studies included 122 patients (19). In contrast, a pooled multi-institutional analysis of 1,540 patients (11), including those from MCR, did not identify a dose–response relationship. However, Stephenson et al. (11) included patients treated with neoadjuvant and/or

### Table 2. Association between EBRT dose and BcF

<table>
<thead>
<tr>
<th>EBRT Dose, Gy</th>
<th>3-y Cumulative Rate, % (95% CI)</th>
<th>5-y Cumulative Rate, % (95% CI)</th>
<th>Single variable model</th>
<th>Multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numeric variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0-Gy increase</td>
<td>NA</td>
<td>NA</td>
<td>0.70 (0.56–0.87)</td>
<td>.002</td>
</tr>
<tr>
<td>Categoric variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low: &lt;64.8</td>
<td>47 (39–54)</td>
<td>57 (48–64)</td>
<td>1.00 (reference)</td>
<td>NA</td>
</tr>
<tr>
<td>Moderate: 64.8–66.6</td>
<td>35 (25–43)</td>
<td>46 (36–55)</td>
<td>0.76 (0.56–1.04)</td>
<td>.08</td>
</tr>
<tr>
<td>High: &gt;66.6</td>
<td>27 (16–37)</td>
<td>39 (25–51)</td>
<td>0.60 (0.39–0.92)</td>
<td>.02</td>
</tr>
</tbody>
</table>

*Abbreviations: BcF = biochemical failure; CI = confidence interval; EBRT = external beam radiotherapy; NA = not applicable; PSA = prostate-specific antigen; RR = relative risk.*

Estimated RR and $p$ values result from Cox proportional hazards models. Multivariable models were adjusted for preoperative PSA level, pathologic tumor stage, Gleason score, margin status, patient age, and pre-EBRT PSA level.
concurrent short-term AS in their study, and they acknowledged that the range of doses administered was relatively narrow. Nonetheless, the American Society for Therapeutic Radiology and Oncology Consensus Panel has recommended a dose “64 Gy or slightly higher” (20) for salvage EBRT, but the group also stated that “the highest dose of radiation therapy that can be given without morbidity is justifiable.”

To supplement current data and to potentially clarify the dose–response relationship, we evaluated a relatively large cohort of men treated with salvage EBRT for a rising PSA level after prostatectomy and also removed the potentially confounding factor of AS. We evaluated EBRT dose as

1. a numeric variable and
2. a three-level category on the basis of the commonly used doses of 64.8 and 66.6 Gy, allowing us to investigate linear and nonlinear associations with BcF.

In single variable analysis, we found strong evidence of a general decreasing risk of BcF as the EBRT dose increased. In evaluating low (<64.8 Gy), moderate (64.8–66.6 Gy), and high (>66.6 Gy) EBRT doses, we observed a decreased risk of BcF for patients receiving a high dose compared with those receiving a low dose, but we did not observe a difference in the risk of BcF between patients receiving low and moderate doses. These results remained consistent after adjusting for possible confounding factors in the multivariable analysis.

Anscher (21) suggested that 1 cm³ of prostate cancer volume would contain approximately 10⁸ to 10⁹ prostate cells. This number of cells would produce a serum PSA level of approximately 3.5 ng/mL. Therefore, a PSA level of 0.35 ng/mL after prostatectomy should represent the presence of 10⁷ to 10⁸ prostate cancer cells. Higher pre-EBRT PSA levels would suggest an increased volume of disease. This supposition, coupled with the endorectal magnetic resonance imaging findings of Sella et al. (12), supports the notion that the dose–response relationship of salvage and definitive EBRT are similar (13) and suggests that higher doses of radiation would then be needed to eradicate all the cancer cells. Although we did observe a stronger dose response in patients with a high pre-EBRT PSA level (>0.6 ng/mL) compared with other patients, this difference did not approach statistical significance. However, power to detect such an interaction was low in this study, and larger studies are needed to better explore a possible increased dose response in patients with a high pre-EBRT PSA level. These results, the overall results of the present study, and the results of similar investigations (16-19) provide evidence that the salvage EBRT dose recommendation needs to be revisited.

Research evaluating radiation treatment planning and delivery to minimize toxicity with dose escalation is ongoing, inasmuch as the tolerance of normal structures within or adjacent to the prostate fossa may limit the EBRT dose that may be given with minimal adverse effects. Feng et al. (22) observed a low rate of late genitourinary tract and gastrointestinal tract adverse events associated with adjuvant or salvage EBRT (median dose, 64.8 Gy) in 959 men treated between 1986 and 2004, a time when two-dimensional treatment planning and delivery predominated. Cozzarini et al. (23) found that rectal dose–volume parameters affect the development of hematochezia, and Fonteyne et al. (24) identified dose–volume constraints that may also provide useful guidance. These observations suggest that inversely planned, intensity-modulated EBRT, particularly with image-guided localization (25), may allow the safe delivery of higher EBRT doses. Indeed, this approach is already yielding promising results (26), and it should remain an avenue for active research.

The results of this study are not definitive; the study’s retrospective design may have introduced unforeseen biases. However, this study has longer-term follow-up, does not have the potentially confounding use of AS, and, to our knowledge, represents the largest patient cohort to show a benefit for higher doses of salvage EBRT. Considering the results of our study, we conclude that it is appropriate to consider doses higher than 66.6 Gy in the salvage setting when normal-tissue dose constraints are met (23, 24). The results of this study should be validated by others; the most meaningful future direction to assess these results would be a randomized clinical trial (13).

REFERENCES


21. Anscher MS. Adjuvant radiotherapy following radical prostatectomy is more effective and less toxic than salvage radiotherapy for a rising prostate specific antigen. *Int J Cancer* 2001;96:91–93.


