Metastasis After Radical Prostatectomy or External Beam Radiotherapy for Patients With Clinically Localized Prostate Cancer: A Comparison of Clinical Cohorts Adjusted for Case Mix

Michael J. Zelefsky, James A. Eastham, Angel M. Cronin, Zvi Fuks, Zhigang Zhang, Yoshiya Yamada, Andrew Vickers, and Peter T. Scardino

Abstract

Purpose
We assessed the effect of radical prostatectomy (RP) and external beam radiotherapy (EBRT) on distant metastases (DM) rates in patients with localized prostate cancer treated with RP or EBRT at a single specialized cancer center.

Patients and Methods
Patients with clinical stages T1c-T3b prostate cancer were treated with intensity-modulated EBRT (≥ 81 Gy) or RP. Both cohorts included patients treated with salvage radiotherapy or androgen-deprivation therapy for biochemical failure. Salvage therapy for patients with RP was delivered a median of 13 months after biochemical failure compared with 69 months for EBRT patients. DM was compared controlling for patient age, clinical stage, serum prostate-specific antigen level, biopsy Gleason score, and year of treatment.

Results
The 8-year probability of freedom from metastatic progression was 97% for RP patients and 93% for EBRT patients. After adjustment for case mix, surgery was associated with a reduced risk of metastasis (hazard ratio, 0.35; 95% CI, 0.19 to 0.65; \(P = .001\)). Results were similar for prostate cancer–specific mortality (hazard ratio, 0.32; 95% CI, 0.13 to 0.80; \(P = .015\)). Rates of metastatic progression were similar for favorable-risk disease (1.9% difference in 8-year metastasis-free survival), somewhat reduced for intermediate-risk disease (3.3%), and more substantially reduced in unfavorable-risk disease (7.8% in 8-year metastatic progression).

Conclusion
Metastatic progression is infrequent in men with low-risk prostate cancer treated with either RP or EBRT. RP patients with higher-risk disease treated had a lower risk of metastatic progression and prostate cancer–specific death than EBRT patients. These results may be confounded by differences in the use and timing of salvage therapy.

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Introduction
The eradication of local disease in patients with clinically localized prostate cancer has been shown to decrease the risk of tumor dissemination and prostate cancer mortality. In the Scandinavian Prostate Cancer Group Study,1 patients with clinically localized prostate cancer treated with surgery less often developed symptomatic local cancer progression, had a lower likelihood of metastatic progression, and suffered fewer prostate cancer–related deaths than men randomly assigned to watchful waiting. In a recent report from our institution,2 among those with negative post-treatment biopsies obtained several years after external beam radiotherapy (EBRT), a decreased likelihood of distant metastases (DM) and prostate cancer–related deaths was observed. Taken together these data indicate that local control of prostate cancer favorably alters the risk of DM and reduces prostate cancer–specific mortality.

Radical prostatectomy (RP) and EBRT represent standard treatment interventions for managing clinically localized prostate cancer. During the past two decades, there have been substantial improvements in surgical techniques resulting in a reduced incidence of positive surgical margin rates and better cancer control, especially among experienced surgeons with high-volume practices. In addition, improved radiotherapy delivery systems in the form of...
three-dimensional conformal radiotherapy and intensity-modulated radiotherapy (IMRT) have facilitated the delivery of high EBRT dose levels to the prostate.4,5 Based on randomized trials,6-9 higher radiation doses are recognized as critical for achieving improved cancer control rates and successful long-term outcomes. Because there are no outcome data from randomized trials comparing RP and EBRT, definitive conclusions cannot be reached regarding the relative effectiveness of these two interventions for achieving long-term cancer control, outside of retrospective comparative studies.10-15

Here we report a retrospective study comparing RP and EBRT for localized prostate cancer. Patients were treated by a limited number of highly experienced clinicians; all EBRT patients received ≥ 81 Gy IMRT. We used DM and prostate cancer–specific mortality as end points to ensure clinical relevance. The use of a clinical data set, which provides for robust data on tumor characteristics, allowed for evaluation and control of case mix differences between groups.

PATIENTS AND METHODS

Patient Cohort

The study cohort consisted of 2,380 patients with clinical stages T1c-T3b biopsy-proven adenocarcinoma of the prostate treated with either open RP at the Baylor College of Medicine (BCM) or Memorial Sloan-Kettering Cancer Center (MSKCC) or with IMRT to dose levels of ≥ 81 Gy at MSKCC between January 1, 1993, and June 30, 2002. Patients were treated by one of two experienced surgeons (J.A.E., MSKCC; P.T.S., MSKCC and BCM) or experienced radiation oncologists (all MSKCC). The final data set included 1,318 RP patients and 1,062 EBRT patients.

Surgical Treatment

Table 1 presents the clinical characteristics of patients undergoing open RP. No patient in this cohort was treated with androgen-deprivation therapy (ADT) before surgery. In general, men ≥ 70 years, and those with serious comorbid medical conditions were encouraged to consider EBRT, although 6% (79 of 1,318) of the surgical patients in this sample were ≥ 70 years. Surgical treatment included bilateral pelvic lymphadenectomy removing the external iliac, obturator, and hypogastric lymph nodes. Frozen section examination of the lymph nodes was not performed, and all men underwent RP. On pathologic assessment, 4% of RP patients (52 of 1,318) had positive lymph nodes. Patients treated with adjuvant or salvage radiotherapy after RP were included in this cohort (n = 79; 6%). In addition, immediately after surgery, 17 patients (1%) were treated with indefinite ADT due to high-risk pathologic features.

EBRT

Table 1 presents the clinical characteristics of these 1,062 patients. The techniques for treatment planning and delivery for IMRT have been previously described.4,5 The pelvic lymph nodes were not included within the radiation portal. A prescription dose of 81 Gy was given to 839 patients (79%); 223 patients (21%) received 86.4 Gy. Short-course (3 to 6 months) ADT was given to 35 were treated with salvage ADT/RP, although the working definitions used by the clinicians at the time. For both RP and EBRT patients, salvage therapy was used to treat biochemical or locoregional failure before the manifestation of DM. Salvage therapy included salvage EBRT, which was defined as a course of radiotherapy delivered after 12 months from RP. In general, salvage radiotherapy was delivered via IMRT to a median dose of 70.2 Gy prescribed to the planning target volume which generously encompassed the prostatic bed region. Salvage RP was performed after radiotherapy failure in selected patients. In some patients with failure, salvage ADT and chemotherapy was given alone or in combination with salvage RT. Salvage treatment with ADT or chemotherapy initiated fewer than 6 months from the primary therapy was considered a salvage treatment event, provided that the patient experienced a prostate-specific antigen (PSA) recurrence before initiation of secondary treatment. For this study, biochemical recurrence after RP was defined as two consecutive rises in serum PSA ≥ 0.2 ng/mL and for EBRT patients using the American Society for Therapeutic Radiology and Oncology definition (three consecutive rising values from the nadir PSA) as these were the working definitions used by the clinicians at the time.

Salvage Therapies for Relapsing Disease

Characterization of salvage therapy. For both RP and EBRT patients, salvage therapy was used to treat biochemical or locoregional failure before the manifestation of DM. Salvage therapy included salvage EBRT, which was defined as a course of radiotherapy delivered after 12 months from RP. In general, salvage radiotherapy was delivered via IMRT to a median dose of 70.2 Gy prescribed to the planning target volume which generously encompassed the prostatic bed region. Salvage RP was performed after radiotherapy failure in selected patients. In some patients with failure, salvage ADT and chemotherapy was given alone or in combination with salvage RT. Salvage treatment with ADT or chemotherapy initiated fewer than 6 months from the primary therapy was considered a salvage treatment event, provided that the patient experienced a prostate-specific antigen (PSA) recurrence before initiation of secondary treatment. For this study, biochemical recurrence after RP was defined as two consecutive rises in serum PSA ≥ 0.2 ng/mL and for EBRT patients using the American Society for Therapeutic Radiology and Oncology definition (three consecutive rising values from the nadir PSA) as these were the working definitions used by the clinicians at the time.

Salvage therapy. Salvage therapy was given to 107 (76%) of 141 RP patients who developed biochemical recurrence. Of these, salvage radiotherapy was given to 59 (42%), of whom 35 were treated with salvage ADT/chemotherapy as well. Salvage ADT or chemotherapy without radiotherapy specific death was 5.0 years for radiation and 5.1 years for surgery. The database was closed for analysis on September 30, 2006.

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>-----------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Median age at surgery, years</td>
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<tr>
<td>Interquartile range</td>
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<tr>
<td>Median total PSA, ng/mL</td>
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<tr>
<td>Interquartile range</td>
</tr>
<tr>
<td>Median preoperative 5-year Kattan nomogram-free probability</td>
</tr>
<tr>
<td>Interquartile range</td>
</tr>
<tr>
<td>Clinical stage</td>
</tr>
<tr>
<td>T1c</td>
</tr>
<tr>
<td>T2a</td>
</tr>
<tr>
<td>T2b</td>
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<tr>
<td>T2c</td>
</tr>
<tr>
<td>T3a</td>
</tr>
<tr>
<td>T3b</td>
</tr>
<tr>
<td>Biopsy Gleason score*</td>
</tr>
<tr>
<td>≤ 6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>≥ 8</td>
</tr>
<tr>
<td>Year of treatment</td>
</tr>
<tr>
<td>1993-1995</td>
</tr>
<tr>
<td>1996-1997</td>
</tr>
<tr>
<td>1998-2000</td>
</tr>
<tr>
<td>2001-2002</td>
</tr>
<tr>
<td>Positive surgical margins</td>
</tr>
<tr>
<td>Extracapsular extension</td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
</tr>
<tr>
<td>Lymph node involvement</td>
</tr>
</tbody>
</table>

NOTE. All differences in clinical characteristics between treatment groups were statistically significant (P < .001).

Abbreviations: PSA, prostate-specific antigen; NA, not applicable.

*Biopsy Gleason score was missing for 188 surgery patients. For these patients, we estimated biopsy Gleason score using pathologic Gleason score.

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was given to an additional 48 patients (34%) who subsequently developed biochemical recurrence.

For the EBRT cohort, salvage ADT (defined as the administration of ADT starting > 6 months after primary therapy) was given to 88 (43%) of 207 patients with rising PSA profiles or documented biochemical recurrence (74 of 207 with a documented PSA relapse). Four patients underwent salvage RP for documented biochemical recurrence and local relapse within the prostate gland.

RP patients treated with salvage therapy received such treatments more quickly after recurrence than patients treated with primary EBRT (median time to secondary therapy after recurrence was 13 months vs 69 months for RP and EBRT patients, respectively).

### Statistical Considerations

Survival times were defined from the day of surgery or the start of EBRT, as appropriate. For the outcome of DM-free survival, patients without documented DM were censored at their date of last follow-up. Of note, no patients died of prostate cancer without documented evidence of a positive bone scan. A Cox proportional hazards regression was used to evaluate the association between treatment and outcome, with adjustment for pretreatment tumor characteristics known to be associated with relapsing disease, treatment year, and age. Two methods were used to control for pretreatment tumor characteristics: the Kattan pretreatment nomogram risk probability and the National Comprehensive Cancer Network (NCCN) risk group classification (www.nccn.com). Low risk is defined as patients with clinical stages T1-T2a, Gleason scores 2 to 6, and PSA lower than 10 ng/mL. Intermediate risk is classified as patients with any T2b-T2c, Gleason 7, or PSA value of 10 to 20 ng/mL. High-risk disease is defined as clinical stage T3, Gleason 8 to 10, or PSA higher than 20 ng/mL. Both approaches account for pretreatment serum PSA levels, clinical stage, and biopsy Gleason score. The nomogram probability was entered into the models as a continuous variable, and the NCCN risk group classification was categorized as low or intermediate risk versus high risk.

Since radiotherapy patients were on average older than surgery patients, and therefore more likely to die from other causes, we repeated all analyses using a competing risk-regression model. All statistical analyses were performed using Stata 9.2 (Stata Corp, College Station, TX) and R (R Foundation for Statistical Computing, www.r-project.org) with the `cmprsk` statistical package.

### RESULTS

#### Baseline Differences Between Groups

As expected, patients treated with EBRT were significantly older than men undergoing RP (median 69 vs 60 years; Table 1). Patients treated with EBRT also had significantly higher serum PSA levels, clinical stages, and biopsy Gleason scores ($P < .001$). The median 5-year biochemical recurrence-free probability predicted by the Kattan nomogram was 84% for RP patients and 80% for EBRT patients.

#### DM-Free Survival Outcomes

A total of 69 patients, 21 in the RP group and 48 in the EBRT cohort, developed DM. The 8-year probability of freedom from metastatic progression was 97% for RP patients (95% CI, 95% to 98%) and 93% for EBRT patients (95% CI, 90% to 95%; Fig 1). After adjustment for the Kattan preoperative nomogram risk probability, age, and treatment year, surgery was associated with a reduced risk of metastasis (hazard ratio [HR], 0.33; 95% CI, 0.19 to 0.65; $P < .001$). Using NCCN risk category as a covariate did not affect results (HR, 0.33; 95% CI, 0.19 to 0.63; $P = .001$), nor did entering serum PSA level, clinical stage, and Gleason score in the model instead of the nomogram (HR, 0.35; 95% CI, 0.19 to 0.64; $P < .001$). The most significant variable associated with metastatic progression was risk group (high vs lower risk groups) followed by treatment (surgery vs radiotherapy; Table 2).

Figure 2 shows the outcome differences between RP and EBRT according to the baseline prognostic risk using the Kattan preoperative nomogram; there was no significant interaction between Kattan preoperative risk and treatment in the whole cohort ($P = .3$) or in the subset with $\leq 50\%$ predicted risk of recurrence within 5 years ($P = .15$). Given a constant relative risk, the absolute difference between groups was greater for patients with higher-risk cancers. The adjusted absolute difference in DM-free survival rates was similar for men with low-risk cancer (1.9% difference in 8-year metastasis-free survival); for men with intermediate-risk cancer a small difference was observed (3.3% difference in 8-year metastasis-free survival); and for high-risk patients, the difference in survival was more substantive (7.8%).

The results using a competing risk-regression analysis instead of a Cox regression analysis were similar: the HR for DM among surgery patients compared with EBRT patients was 0.36 (95% CI, 0.19 to 0.68; $P = .002$). In this analysis the use of short-term neoadjuvant ADT was not significantly associated with DM (HR, 0.78; 95% CI, 0.39 to 1.55; $P = .45$).

It is possible that the apparently decreased rates of DM in RP patients may be related to differences in the use or timing of salvage therapy among the RP versus RT cohorts after documented biochemical failure. However, a time-dependent covariate analysis controlling for salvage therapy led to similar results as our main analysis (HR, 0.27; 95% CI, 0.15 to 0.48; $P < .0005$).

### Table 2. Multivariable Cox Regression Model for the Outcome of Distant Metastases From Prostate Cancer

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at treatment*</td>
<td>0.98</td>
<td>0.95 to 1.02</td>
<td>.3</td>
</tr>
<tr>
<td>Year of treatment*</td>
<td>0.97</td>
<td>0.87 to 1.07</td>
<td>.5</td>
</tr>
<tr>
<td>NCCN risk (high vs intermediate/low)</td>
<td>6.37</td>
<td>3.89 to 10.5</td>
<td>&lt; .0005</td>
</tr>
<tr>
<td>Treatment (surgery vs radiotherapy)</td>
<td>0.35</td>
<td>0.19 to 0.63</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviation: NCCN, National Comprehensive Cancer Network.

*Hazard ratio estimates are given for a 1-year increase.
Several important findings were observed. Metastatic recurrence is rare in patients with prostate cancer with NCCN low-risk disease treated by surgery or radiotherapy; accordingly, absolute differences between treatments are of questionable clinical relevance in this low-risk group, which comprises 40% (952 of 2,380) of the patients in our cohort and the majority of newly diagnosed patients. For patients with intermediate-risk cancer, a small increase of 3% in the rate of DM was observed which may be clinically relevant. In high-risk patients, our data highlight the most significant difference between the groups.

The differences in DM-free survival cannot be explained by inferior EBRT outcomes relative to other reports in the literature. Our results for high-risk patients treated with IMRT appear to be at least comparable to other reported EBRT results.18,19 Our data suggest that even EBRT doses of ≥ 81 Gy are not always sufficient to eradicate completely local cancer leading to a higher likelihood of DM. We have previously demonstrated the important influence local cancer control has on the dissemination of distant disease in prostate cancer.2 Others have also suggested that, in particular, for patients with bulky locally advanced tumors, dose levels of 80 Gy delivered with EBRT may be insufficient for optimal local cancer control.20

Further improvement in outcomes for our high-risk patients treated with radiotherapy could possibly have been achieved with the routine use of elective nodal irradiation (ENI) and/or longer duration of ADT. Although patients at our institution with high-risk disease are currently treated with ENI using IMRT techniques and longer courses of ADT, the patients included in this report were only treated with high radiation doses, with ENI and adjuvant ADT not routinely administered. Randomized phase III studies demonstrating improved survival benefits for the treatment of lymph nodes and longer courses of ADT were conducted only in the setting of low radiation doses.21-26 It is plausible that similar improvements could have been demonstrated with higher doses. We believe that in the absence of randomized data, patients with high-risk prostate cancer opting for treatment with EBRT should be treated with ENI and a longer course of ADT to maximize their cancer-control outcomes.

Dose levels administered with EBRT using current techniques may not be sufficiently tumoricidal for adequate and complete eradication of large-volume cancer. In such patients combined brachytherapy with IMRT may be more favorable, and is associated with the delivery of significantly higher biologic equivalent dose levels far beyond those achieved with 81 to 86 Gy IMRT. Several reports have observed a low incidence of DM at 5 years and longer for high-risk patients treated with combined brachytherapy and conformal radiotherapy techniques.27,28

The incidence of DM in our high-risk RP cohort appears to be lower than other surgical reports30-33 which may contribute to the

### DISCUSSION

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### Table 3. Unadjusted Actuarial Probabilities of Prostate Cancer Death According to Treatment Group by NCCN Risk Group

<table>
<thead>
<tr>
<th>NCCN Risk</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Kaplan-Meier Probability of Prostate Cancer Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 Year</td>
</tr>
<tr>
<td>Low</td>
<td>952</td>
<td>1</td>
<td>0.0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1,019</td>
<td>10</td>
<td>0.0</td>
</tr>
<tr>
<td>High</td>
<td>409</td>
<td>19</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Abbreviation: NCCN, National Comprehensive Cancer Network.
differences in the RP and EBRT groups. Yossepowitch et al.\textsuperscript{2} recently reported the distant metastases outcomes in 5,960 men treated between 1985 and 2005 with surgery at MSKCC and BCM. That report, from our institution, included outcomes of all high-risk patients and was not restricted to patients treated by the most experienced surgeons. The probability of DM at 10 years was 22% for the 938 high-risk NCCN patients in that cohort, treated in an earlier era between 1985 and 2002, compared with 8% at 8 years reported here. The improved results in the current report could be explained by better surgical technique used by the highly experienced surgeons in the present series,\textsuperscript{3} specifically, wider excision of periprostatic tissues with lower rates of positive surgical margins and more extensive pelvic lymph node dissection. The differences may also be due to chance, since this cohort of high-risk NCCN patients is smaller. The favorable outcomes for high-risk patients in this report may not be applicable to less experienced surgeons or those employing more limited resection techniques.

Limitations of this report include its design as a nonrandomized retrospective comparison with a relatively short median follow-up (5 years). Despite significant efforts made using statistical methods to address selection bias, the treatment groups were not completely balanced. Older patients and patients with higher biopsy Gleason score were preferentially treated with EBRT. Another potential limitation of a retrospective study is unmeasured confounding. EBRT patients might have had more aggressive cancers than RP patients similar by treatment year, age, stage, grade, and PSA. However, the difference between treatment groups was large (HR, 0.35). As an exploratory analysis, we assumed an unmeasured confounder sufficiently potent to reclassify all Gleason 6 radiotherapy patients as Gleason 7. Differences between groups remained large (HR, 0.54) with a trend toward statistical significance ($P = 0.061$).

Furthermore, the administration of salvage radiotherapy and/or ADT was earlier and more prevalent in the RP group, which confounds the interpretation of metastasis-free survival and cause-specific survival outcomes. In this series, more patients who biochemical failure were treated with salvage therapy after RP than after EBRT, and secondary therapy was begun much earlier (median 13 v 69 months), reflecting the ease of detection of recurrent cancer after RP. The differences in late metastatic rates may reflect differences in the effects of salvage therapy as much as differences in local control achieved with primary treatment of localized prostate cancers. Outcomes in high-risk cancers treated with EBRT could be further improved with the earlier administration of salvage therapy, local or systemic.

The higher rate of DM and prostate cancer death in the high-risk radiotherapy group could be related to the more abbreviated course of adjuvant ADT (<1 year) and omission of ENI in our series. In addition, 81 to 86 Gy of EBRT may be insufficient to achieve local disease eradication in high-risk prostate cancer, leading to higher risks of subsequent DM. For high-risk patients, we now favor combined brachytherapy and IMRT approaches which effectively deliver much higher radiation dose levels to the prostate or surgery followed by adjuvant radiotherapy in selected patients to achieve maximal tumor control. Our results also suggest a need for a surgical arm in future trials of therapy for high-risk cancers. Ultimately, for cancers with aggressive phenotypes and high metastatic potential, the integration of more effective systemic therapies with optimal local treatments will be necessary to optimize cause-specific outcomes.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The author(s) indicated no potential conflicts of interest.

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Collection and assembly of data: Michael J. Zelefsky, James A. Eastham, Angel M. Cronin, Andrew Vickers, Peter T. Scardino

Data analysis and interpretation: Michael J. Zelefsky, James A. Eastham, Angel M. Cronin, Zvi Fuks, Zhigang Zhang, Andrew Vickers, Peter T. Scardino

Manuscript writing: Michael J. Zelefsky, James A. Eastham, Andrew Vickers, Peter T. Scardino

Final approval of manuscript: Michael J. Zelefsky, James A. Eastham, Angel M. Cronin, Zvi Fuks, Zhigang Zhang, Yoshiya Yamada, Andrew Vickers, Peter T. Scardino

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