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Long-Term Survival After Radical Prostatectomy Versus External Beam Radiotherapy for Patients with High-Risk Prostate Cancer

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Abstract

BACKGROUND—We compared the long-term survival of patients with high-risk prostate cancer following radical prostatectomy (RRP) and external beam radiation therapy (EBRT) with and without adjuvant androgen deprivation treatment (ADT).

METHODS—We identified 1,238 patients who underwent RRP and 609 patients treated with EBRT (344 with EBRT + ADT and 265 with EBRT alone) between 1988–2004 who had a pretreatment prostate-specific antigen level (PSA) ≥ 20 ng/mL, biopsy Gleason score 8–10, or clinical stage $\geq T3$. Median follow-up was 10.2, 6.0, and 7.2 years after RRP, EBRT + ADT, and EBRT alone, respectively. The impact of treatment modality on systemic progression, cancer-specific, and overall survival was evaluated using multivariable Cox proportional hazard regression analysis and a competing risk-regression model.

RESULTS—Ten-year cancer-specific survival was 92%, 92%, and 88% following RRP, EBRT + ADT, and EBRT alone ($p=0.06$). After adjustment for case mix, no significant differences in the risks of systemic progression (hazard ratio, 0.78; 95% CI, 0.51 to 1.18; $p=0.23$) or prostate cancer death (hazard ratio 1.14; 95% CI, 0.68 to 1.91; $p=0.61$) were seen between patients treated with EBRT + ADT and patients who underwent RRP. The risk of all-cause mortality was, however, greater after EBRT + ADT than RRP (hazard ratio, 1.60; 95% CI, 1.25 to 2.05; $p=0.0002$).

CONCLUSIONS—RRP and EBRT + ADT provide similar long-term cancer control for patients with high-risk disease. Continued investigation into the differing impact of treatments on quality-of-life and non-cancer mortality are necessary to determine the optimal management approach for these patients.

Keywords

prostate cancer; radical prostatectomy; radiation therapy; androgen-deprivation therapy; prostate-specific antigen

INTRODUCTION

To assist with patient counseling and guide treatment selection, the National Comprehensive Cancer Network (NCCN) has recommended risk stratification of patients with newly-diagnosed prostate cancer according to prostate-specific antigen (PSA) level, biopsy Gleason score, and clinical stage.¹ Despite the fact that the widespread use of PSA testing has altered the clinical and demographic characteristics of men with newly-diagnosed prostate cancer,² men with what is characterized as high-risk disease continue to be encountered. Indeed, the management of these patients represents one of the most significant current challenges in prostate cancer treatment, as the optimal therapeutic strategy remains to be established.

Importantly, a number of studies have reported effective long-term cancer control for men with locally-advanced prostate cancer treated with external beam radiotherapy (EBRT), particularly when combined with adjuvant androgen deprivation therapy (ADT).^{3–8} At the same time, the role of surgery in the form of radical prostatectomy (RRP) for patients with high-risk disease has continued to be evaluated at select centers as well, and in fact durable survival outcomes following RRP for high-risk tumors have been reported.^{9–10} As such, given the lack of randomized trials comparing the efficacy of different therapeutic options for prostate cancer, treatment of these patients continues to be largely based upon individual physician experience and biases.¹¹

Interestingly, the retrospective series to date which have compared the outcomes after surgery and radiation for high-risk tumors have demonstrated widely disparate results, with several reporting improved outcomes following RRP,^{12–17} others finding better results following radiation,^{18–19} and a few,^{20–22} including a small prospective trial,²³ noting equivalent efficacy. However, these studies involved different definitions of high-risk prostate cancer, evaluated disparate outcome measures, and have included a relatively limited number of patients, often with short-term follow-up. Furthermore, men undergoing RRP have been shown to be younger and healthier in terms of comorbidity than men treated with radiation,^{11–24} differences which may have further obscured the ability of these studies to establish the impact of treatment modality on outcome.

Most recently, Zelefsky and colleagues compared the survival of patients with cT1–T3b prostate cancer treated at a single center with IMRT and RRP.¹⁵ After controlling for clinicopathologic variables, RRP was associated with a reduced risk of metastases and cancer-specific mortality.¹⁵ However, only 409 patients (17% of the overall cohort) with high-risk tumors were included in this study, which accounted for 19 deaths from prostate cancer at a follow-up of 5 years.¹⁵ At the same time, Cooperberg et al, in a primarily community-based dataset, likewise demonstrated decreased cancer-specific mortality after surgery versus radiation for patients with clinically-localized disease.¹⁶ Again, however, only 6.5% of patients undergoing RRP and only 24% of patients treated with EBRT in that series were in the highest risk category, and the median follow-up (3.9 years after RRP and 4.5 years after RT) was relatively short.¹⁶

Here, we compared the outcomes after RRP and EBRT for patients classified as having high-risk prostate cancer according to NCCN criteria.¹ Patients were treated at one of two high volume centers in a contemporary time period. With a robust dataset and long-term follow-up, we report the clinically-relevant endpoints of systemic progression (SP), death from prostate cancer, and overall mortality, controlling for case mix and patient variables.

MATERIALS AND METHODS

Study Population

After each center's Institutional Review Board approval was obtained, we reviewed the Mayo Clinic Prostatectomy Registry and the Fox Chase Cancer Center (FCCC) Radiation Oncology Database to identify 1,847 patients with high-risk prostate cancer who were treated with definitive local therapy in the form of RRP (Mayo Clinic) or EBRT (FCCC) between 1988–2004. High-risk disease was defined according to NCCN guidelines:1 PSA 20 ng/ml or clinical stage T3N0M0 or biopsy Gleason score 8–10. Tumors were classified according to the 2002 American Joint Committee on Cancer (AJCC),²⁵ and the Gleason system was used for grading. No patient had clinical evidence of pelvic lymph node disease on cross-sectional imaging or evidence of distant metastases on bone scan.

Surgical Treatment

In total, 1,238 patients underwent RRP for high-risk cancers. Patient demographics are presented in Table 1. Surgical procedures were performed by different surgeons using standardized techniques. No patient received ADT or radiation prior to RRP. All men included here were treated with an open retropubic approach. Adjuvant therapy was defined as treatment received within 90 days of RRP, and was given at the discretion of the treating physician. Medical hormone deprivation therapy was generally intended to be life long. However, given the retrospective nature of this study, it is uncertain whether patients discontinued treatment after a period of ADT. In total, 503 patients (40.6%) received adjuvant therapy after RRP, of whom 367 (29.6%) were treated with ADT, 85 (6.9%) with EBRT, and 51 (4.1%) with both. Salvage treatment, meanwhile, was defined as secondary therapy initiated greater than 90 days after RRP, and was likewise administered per individual physician. At last follow-up, 253 (20.4%) men had been treated with salvage EBRT, and 415 (33.5%) received salvage ADT. The median time from RRP to salvage treatment was 2.7 years (range 0.2–15.4) for salvage EBRT and 10.3 years (range 1.4–20.2) for salvage ADT.

EBRT

Clinical characteristics for the 609 patients treated with EBRT for high-risk cancers are listed in Table 1. Comorbidity status for these patients was assessed using the Charlson comorbidity score.²⁶ Radiation technique at FCCC evolved over the time period of the study, from conventional EBRT to 3-dimensional conformal (3DCRT) and more recently to intensity-modulated radiation therapy (IMRT). The techniques for treatment planning and delivery of each of these methods have been previously described.^{27,28} Overall, 564/609 (92.6%) patients received either conformal or IMRT. The median RT dose received was 72 Gy (range 5040–7900), which was administered in 2 Gy fractions. Pelvic lymph nodes were consistently included within the radiation portal for these patients. Patients were considered to have received adjuvant ADT with EBRT if they initiated any form of ADT within six months of the date of starting treatment with EBRT. A total of 344/609 (56.5%) patients treated with EBRT received adjuvant ADT. The median duration of adjuvant ADT in this group was 22.8 months (range 1–108). Of these patients, 57 (16.6%) subsequently received salvage ADT, at a median of 3.0 years (range 0.3–9.2) after initial treatment.

Outcome Assessment

Post-treatment assessments, including physical examination and serum PSA measurement, were done quarterly for the initial two years, semiannually for an additional two years, and annually thereafter. SP involved demonstrable metastases on radionuclide bone scan or on biopsies outside of the prostate/prostatic bed. Vital status was identified from death

certificates or physician correspondence. For patients followed elsewhere, the outcomes were monitored annually by correspondence.

Statistical Considerations

Comparison of patient clinicopathological variables between the treatment groups was performed using chi-square and Kruskal-Wallis tests, as appropriate. Survival times were defined from the day of surgery or the start of EBRT, as appropriate. Survival was estimated using the Kaplan-Meier method and compared with the log-rank test. Patients were censored at last follow-up or death if the end point of interest had not been attained. Cox proportional hazard regression models were used to analyze the impact of treatment approach on SP and survival, with adjustment for patient age, pretreatment PSA, and biopsy Gleason score (treated as continuous variables), as well as clinical tumor classification (treated as a categorical variable). Two additional methods were used to control for the baseline clinicopathological differences which have been documented in patients with prostate cancer undergoing surgery versus EBRT: 1) the analysis was restricted to include only EBRT patients with a Charlson comorbidity index of 0 or 1, and 2) a competing risk-regression model was used to account for competing causes of mortality.²⁹

All tests were two-sided, with a p value < 0.05 considered significant. Statistical analyses were done using the SAS version 9.1.3 software package (SAS Institute, Cary, North Carolina).

RESULTS

Consistent with previously-noted demographic trends in prostate cancer treatment, 1124 men treated with radiation here were significantly older than men who underwent surgery ($p < 0.0001$; Table 1), while patients in the EBRT + ADT cohort also had a significantly higher biopsy Gleason score ($P < 0.0001$) and more advanced tumor classification ($p < 0.0001$) than RRP patients. Median total pretreatment PSA, meanwhile, was highest in the EBRT alone cohort ($p = 0.02$).

At a median follow-up after RRP of 10.2 years (interquartile range 6.6, 14.0), 192 patients treated with surgery experienced SP, and 404 died, with 115 dying of prostate cancer. The median follow-up after EBRT + ADT and EBRT alone was 6.0 years (interquartile range 4.2, 8.7) and 7.3 years (interquartile range 4.5, 9.6), respectively. Twenty-seven and 35 patients treated with each of these modalities experienced SP and 90 and 108 died, including 19 and 25 who died from prostate cancer.

The estimated 10-year probability of freedom from SP was not significantly different among the treatments: 85% for RRP patients, 88% for EBRT + ADT patients, and 81% for EBRT alone patients ($p = 0.24$; Fig 1a). Ten-year cancer-specific survival was likewise equivalent for patients treated with surgery (92%) and EBRT + ADT (92%), and was modestly better than for patients who received EBRT alone (88%; $p = 0.06$; Fig 1b). The 10-year overall survival, however, was significantly improved for patients undergoing RRP (77%) than for patients treated with EBRT + ADT (67%) or EBRT alone (52%; $p < 0.001$; Fig 1c).

Table 2 depicts factors predictive of postoperative survival on the multivariable model, including the type of treatment. After controlling for patient age, year of treatment, pretreatment PSA, clinical T-classification, and biopsy Gleason score, patients who received EBRT alone had a significantly increased risk of SP (HR 1.53; 95% CI 1.05, 2.23; $p = 0.03$), death from prostate cancer (HR 2.14; 95% CI 1.35, 3.39; $p = 0.001$), and overall mortality (HR 2.04; 95% CI 1.62, 2.56; $p < 0.0001$) compared to patients who underwent RRP. EBRT + ADT, on the other hand, demonstrated similar cancer control to RRP, with a HR of 0.78

(95% CI 0.51, 1.18; $p=0.23$) for SP and 1.14 (95% CI 0.68, 1.91; $p=0.61$) for cancer-specific mortality. Nevertheless, receipt of EBRT + ADT was associated with a significantly increased risk of all-cause mortality compared to surgery (HR 1.60; 95% CI 1.25, 2.05; $p=0.0002$).

We further accounted for the baseline differences in patient age and comorbidity status among the treatment groups, factors which impact competing causes of mortality for patients with prostate cancer, in two ways. First, we repeated our analyses including only EBRT patients with a Charlson comorbidity index of 0 or 1. With this restriction, we found no appreciable change in our results (Fig 2), such that the estimated SP-free survival was again not significantly different between the three treatment groups, that patients treated with RRP or EBRT + ADT had a similar cancer-specific survival, and that patients who underwent RRP had the highest overall survival (77% at 10 years). Likewise, the associations of treatment modality with outcome did not change in the multivariate Cox model when only EBRT patients with a Charlson score of 0–1 were included (data not shown). We then also performed a competing risk-regression analysis, and again found no significant difference in the risk of SP (HR 0.71; 95% CI 0.47, 1.08; $p=0.11$) or death from prostate cancer (HR 0.99; 95% CI 0.60, 1.64; $p=0.97$) between patients treated with EBRT + ADT and patients who underwent RRP.

DISCUSSION

We evaluated two large institutional datasets of patients treated during the PSA era for high-risk prostate cancer as defined by common (NCCN) criteria. We found that both surgery and EBRT + ADT are associated with a 10-year disease-specific survival of 92%. EBRT alone was associated with decreased treatment efficacy compared to EBRT + ADT. Moreover, when controlling for case mix and patient variables, patients treated with EBRT + ADT had a significantly increased risk of all-cause mortality compared to patients who underwent RRP.

The outcomes for patients with high-risk prostate cancer managed with surgery and EBRT + ADT noted here are consistent with the results from previous clinical trials^{3–8} and retrospective case series.^{9,10} Indeed, the five-year mortality from prostate cancer of 3.2% for patients with locally-advanced tumors treated with EBRT and long-term ADT recently reported by Bolla and colleagues⁸ is nearly identical to our 4% rate death from prostate-cancer at five years. Furthermore, our data demonstrating improved survival with EBRT + ADT versus EBRT alone for high-risk cancers confirms prior reports which demonstrated a benefit of ADT with EBRT.^{3–6,8} It is important to note as well that the median radiation dose received by the patients in our study (72 Gy) and median duration of ADT in the EBRT + ADT group here (22.8 months) were suboptimal by modern practice standards. Indeed, patients with high-risk disease have been shown to derive a cancer-specific survival benefit from higher doses of radiation (78 Gy)³⁰ and longer courses (24–36 months)^{8,31} of ADT. Nevertheless, the radiation dosage here is similar to the doses (65–70 Gy) which have been utilized in a number of the prospective randomized trials evaluating EBRT for high-risk disease to date.^{3–8}

Meanwhile, the 10-year SP-free survival (85%) and cancer-specific mortality (8%) after RRP in the current study parallel the outcomes reported by Yossepowitch et al,¹⁰ while our 15-year prostate-cancer specific mortality of 15% after RRP is nearly identical to the findings of Stephenson and colleagues.³² One potential benefit to surgery for patients with high-risk disease is the ability to obtain pathological staging, which, as has been suggested previously,³³ may guide the selective application of secondary therapies. For example, Meng et al found that patients with high-risk prostate cancer treated with radiation therapy

were 3.5 times more likely to receive ADT than patients treated with RRP.¹¹ As increasing data have emerged on the adverse consequences of ADT on the quality of life³⁴ and non-cancer morbidity³⁵ of men with prostate cancer, the ability to delay if not avoid ADT may represent a potential advantage to surgery for these patients. The median time from RRP to salvage ADT here was 10.3 years. Although the timing of salvage ADT was at the discretion of the surgeon and is not an indicator of treatment success, this suggests that high-risk patients treated with surgery may have long intervals of ADT-free survival.

Interestingly, while RRP and EBRT + ADT were associated with nearly identical long-term cancer control, patients treated with EBRT + ADT had a significantly increased risk of all-cause mortality. One potential explanation for this finding may be an imbalance between RRP and EBRT + ADT cohorts in terms of medical comorbidities and unmeasured confounding variables. We attempted to account for selection bias with multivariable regression models and a competing risk-regression analysis. Nevertheless, the retrospective nature of this study prohibited our ability to completely account for baseline differences in clinicopathological demographics. As such, differences in age and comorbidity status may be responsible for the worse overall survival noted among patients treated with EBRT. In addition, comorbidity scores were not available for the surgical cohort, an acknowledged limitation of our current dataset, although a historical series from Mayo noted that only 11% of patient undergoing RRP at that time had a Charlson score of ≥ 2 .³⁶ Another explanation is that ADT adversely impacted men treated with EBRT. ADT has been associated with an increased risk of cardiac death, particularly in men with coronary artery disease.³⁷ While the exact mechanism of this interaction is unknown, the metabolic effects of ADT may contribute to the comorbidities and risk factors for cardiac death such as diabetes, hypercholesterolemia, and hypertension.³⁸ Patient selection based on these medical comorbidities may have resulted in treated with EBRT (versus RRP), and the addition of ADT may have potentiated the increased risk of cardiac mortality. Importantly, however, long-term hormone use was not associated with an increased risk of cardiac toxicity in a large, phase III randomized trial of patients treated with EBRT for locally-advanced prostate cancer.³¹

While a randomized trial from the pre-PSA era reported improved survival after surgery versus radiation,³⁹ the study involved only 97 patients and has been criticized for its methodology. A more recent trial demonstrated equivalent efficacy between the treatments, although only 95 patients were included, and all men received adjuvant ADT.²³ Given the lack of relevant outcome data from randomized trials comparing RRP and EBRT, then, observational studies such as the one here remain the primary means to currently evaluate the relative efficacy of local therapies for high-risk prostate cancer. However, the retrospective comparative series to date have been limited by relatively small numbers of high-risk patients included,^{12,19,23} and the frequent use of biochemical failure (BF) as an outcome measure.^{18–22} Indeed, given the variability in definitions for BF after EBRT,^{40,41} as well as the difficulty in comparing BF across treatments,⁴² we chose to focus on the endpoints of distant metastases, cancer-specific survival, and all-cause mortality. Determining the impact of prostate cancer treatments of outcomes other than BF remains clinically important, for as the natural history of PSA recurrence is variable, and usually prolonged, BF does not always translate into systemic progression and prostate cancer death.^{43–45}

We recognize that our study was limited by its retrospective nature, as well as by the disparate number of patients who were treated with RRP versus EBRT. Moreover, though considered in the life table methods, the differing lengths of follow-up between the surgery and EBRT patients could have impacted our long-term comparisons. We also acknowledge the lack of a centralized pathology review. In addition, we acknowledge the significant

heterogeneity of a risk group classification model as utilized here, although this model has not been previously found to limit the ability to discern the impact of treatment modality on survival.¹⁵ A further limitation of such a non-randomized study lies with the varied use of salvage therapies, specifically with regard to the choice, timing, and duration of treatment. However, we believe that the nonuniform application of secondary therapies reflect “real world” clinical practice, in which standardized guidelines for the management of failure after primary treatment do not presently exist.

Despite these factors, we demonstrated that patients with high-risk prostate cancer can achieve long-term cancer control after definitive primary therapy with surgery or EBRT + ADT. Indeed, the risk of prostate cancer-specific mortality at 10 years after primary treatment is relatively low (8%) in light of the aggressive features of these tumors. Continued investigation into the differing impact of treatments on quality-of-life measures³⁴ and non-cancer morbidities³⁵ will be necessary to help determine the optimal management approach for these patients. In addition, further study to identify more effective systemic therapies which may be integrated with local treatments will be required to improve patient outcomes.

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Figure 1. Outcome for patients with high-risk prostate cancer treated with RRP, EBRT + ADT, or EBRT alone. (A) Systemic progression-free survival. (B) Cancer-specific survival (C) Overall survival.

Figure 2. Outcome for patients with high-risk prostate cancer treated with RRP, EBRT + ADT, or EBRT alone. Analysis restricted to radiation patients with a Charlson comorbidity index of 0–1. (A) Systemic progression-free survival. (B) Cancer-specific survival (C) Overall survival.

Table 1

Patient demographics

Feature	Treatment			P
	RRP (n=1238)	EBRT + ADT (n=344)	EBRT alone (n=265)	
Median age at diagnosis, years (interquartile range)	66.0 (60.4, 70.3)	68.8 (62.9, 73.7)	69.3 (65.0, 73.9)	<0.0001
Year of treatment, no. (%)				<0.0001
1988–1993	433 (35)	57 (16.6)	134 (50.6)	
1994–1998	431 (34.8)	132 (38.4)	80 (30.2)	
1999–2004	374 (30.2)	155 (45)	51 (19.2)	
Median pretreatment PSA, ng/mL, (interquartile range)	20.5 (7.7, 30.1)	17.4 (8.1, 34.0)	22.0 (10.2, 33.0)	0.02
2002 AJCC tumor classification, no. (%)				<0.0001
cT1a–c	265 (21.4)	61 (17.8)	69 (26)	
cT2	562 (45.4)	136 (39.5)	114 (43)	
cT3–4	411 (33.2)	147 (42.7)	82 (31)	
Biopsy Gleason score, no. (%)				<0.0001
6	471 (38)	75 (21.8)	138 (52.1)	
7	303 (24.5)	105 (30.5)	74 (27.9)	
8–10	464 (37.5)	164 (47.7)	53 (20)	
Type of EBRT, no. (%)				<0.0001
Conventional	NA	5 (1.5)	40 (15.1)	
Conformal	NA	238 (69.2)	204 (77)	
IMRT	NA	101 (29.3)	21 (7.9)	
Charlson comorbidity index, no. (%)				0.12
0		230 (66.9)	183 (69.1)	
1		89 (25.9)	55 (20.8)	
2		25 (7.2)	27 (10.1)	

RRP indicates radical retropubic prostatectomy; EBRT, external-beam radiation therapy; ADT, androgen-deprivation therapy; PSA, prostate-specific antigen; AJCC, American Joint Commission on Cancer; IMRT, intensity-modulated radiation therapy

Table 2
Multivariable Cox Regression Analysis of Factors Associated with Outcome in Patients with High-Risk Prostate Cancer

Variable	Systemic Progression			Death from prostate cancer			Death from any cause		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age	0.98	0.96, 1.00	0.02	0.99	0.97, 1.01	0.34	1.05	1.04, 1.06	<0.0001
Year of treatment	0.96	0.93, 1.00	0.04	0.95	0.90, 1.00	0.03	0.97	0.94, 1.00	0.04
Log ₂ PSA	1.16	1.05, 1.28	0.002	1.17	1.03, 1.32	0.01	1.09	1.02, 1.17	0.008
Biopsy Gleason score	1.44	1.29, 1.62	<0.0001	1.60	1.39, 1.84	<0.0001	1.24	1.14, 1.34	<0.0001
2002 AJCC tumor classification (cT2 vs cT1c)	1.74	1.12, 2.69	0.01	1.97	1.09, 3.58	0.03	1.14	0.89, 1.45	0.30
2002 AJCC tumor classification (cT3/4 vs cT1c)	2.42	1.54, 3.79	0.0001	2.55	1.39, 4.70	0.003	1.20	0.93, 1.56	0.17
Treatment (EBRT vs RRP)	1.53	1.05, 2.23	0.03	2.14	1.35, 3.39	0.001	2.04	1.62, 2.56	<0.0001
Treatment (EBRT/ADT vs RRP)	0.78	0.51, 1.18	0.23	1.14	0.68, 1.91	0.61	1.60	1.25, 2.05	0.0002

HR indicates hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; AJCC, American Joint Commission on Cancer; RRP, radical retropubic prostatectomy; EBRT, external-beam radiation therapy; ADT, androgen-deprivation therapy.