Survival Among Men With Clinically Localized Prostate Cancer Treated With Radical Prostatectomy or Radiation Therapy in the Prostate Specific Antigen Era

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Purpose: Radical prostatectomy, external beam radiotherapy and brachytherapy are accepted treatments for localized prostate cancer. However, it is unknown if survival differences exist among treatments. We analyzed the survival of patients treated with these modalities according to contemporary standards.

Materials and Methods: A total of 10,429 consecutive patients with localized prostate cancer treated with radical prostatectomy (6,485), external beam radiotherapy (2,264) or brachytherapy (1,680) were identified. Multivariable regression analyses were used to model the disease (biopsy grade, clinical stage, prostate specific antigen) and patient specific (age, ethnicity, comorbidity) parameters for overall survival and prostate cancer specific mortality. Propensity score analysis was used to adjust for differences in observed background characteristics.

Results: The adjusted 10-year overall survival after radical prostatectomy, external beam radiotherapy and brachytherapy was 88.9%, 82.6% and 81.7%, respectively. Adjusted 10-year prostate cancer specific mortality was 1.8%, 2.9% and 2.3%, respectively. Using propensity score analysis, external beam radiotherapy was associated with decreased overall survival (HR 1.6, 95% CI 1.4–1.9, $p < 0.001$) and increased prostate cancer specific mortality (HR 1.5, 95% CI 1.0–2.3, $p = 0.041$) compared to radical prostatectomy. Brachytherapy was associated with decreased overall survival (HR 1.7, 95% CI 1.4–2.1, $p < 0.001$) but not prostate cancer specific mortality (HR 1.3, 95% CI 0.7–2.4, $p = 0.5$) compared to radical prostatectomy.

Abbreviations and Acronyms

3DCRT = 3-dimensional conformal external beam radiotherapy

ADT = androgen deprivation therapy

BCR = biochemical recurrence

bGS = biopsy Gleason score

c-index = concordance index

CCI = Charlson comorbidity index

EBRT = external beam radiotherapy

IMRT = intensity modulated external beam radiotherapy

PCa = prostate cancer

PCSM = prostate cancer specific mortality

PSA = prostate specific antigen

RP = radical prostatectomy

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Conclusions: After adjusting for major confounders, radical prostatectomy was associated with a small but statistically significant improvement in overall and cancer specific survival. These survival differences may arise from an imbalance of confounders, differences in treatment related mortality and/or improved cancer control when radical prostatectomy is performed as initial therapy.

Key Words: prostatic neoplasms, prostatectomy, radiotherapy, brachytherapy, treatment outcome

RADICAL prostatectomy, external beam radiotherapy and brachytherapy are accepted treatment options for localized prostate cancer. Unfortunately there is no conclusive evidence that any treatment is superior in terms of quantity or quality of life. Prior randomized trials have been limited by methodological flaws, premature closure due to poor accrual and inferior radiation therapy techniques.[1–3] As such, treatment decisions are based largely on patient preference and/or physician bias.

Retrospective studies have demonstrated similar biochemical recurrence rates when stratified by serum PSA, clinical stage and biopsy Gleason score.[4–6] However, comparisons using BCR are problematic due to differences in posttreatment PSA kinetics and different definitions of BCR.[7,8] In addition, the frequent use of ADT with radiation therapy can significantly influence the time to BCR. Lastly, BCR does not uniformly lead to clinical metastases or death.[9] Therefore, BCR is not a valid comparator of treatments, and is an imprecise proxy for overall survival and PCSM. To investigate if differences in overall survival or PCSM exist among treatments, we analyzed a cohort of patients treated with RP, EBRT and brachytherapy according to contemporary treatment standards in the later PSA era.

METHODS

Patients

Between 1995 and 2005, 10,429 consecutive men with clinically localized PCa were treated at Barnes-Jewish Hospital (St. Louis, Missouri) or Cleveland Clinic (Cleveland, Ohio) with RP (6,485), EBRT (2,264) or brachytherapy (1,680). Information on patient (race, age and comorbidity) and disease specific parameters (PSA, bGS and clinical stage) as well as treatment related details was obtained from prospective databases (table 1). At Barnes-Jewish Hospital comorbidity was prospectively recorded through medical record review using the ACE-27 (Adult Comorbidity Evaluation 27) index.[10] At Cleveland Clinic comorbidity was recorded through retrospective review of the medical record using the Charlson comorbidity index.[11] All prostate biopsy specimens were reviewed by genitourinary pathologists at the respective institutions.

Survival Analysis

Information on survival was obtained through a review of the medical record, patient correspondence and the Social Security Death Index. The coding of parameters for analysis was done a priori without knowledge of the association with survival. Serum PSA was modeled with restricted cubic splines because of suspected nonlinear effects. bGS was modeled as 2–6, 7 and 8–10. Since different comorbidity instruments were used at each institution, we categorized CCI on a 4-point scale (none, mild, moderate or severe) based on scores of 0, 1, 2 to 3, or 4 or greater. This categorization of CCI was selected a priori as analysis of the raw data revealed a similar proportion of patients at the Cleveland Clinic with CCI scores of 2 to 3 and 4 or greater compared with patients at Barnes-Jewish Hospital, with moderate and severe comorbidity by ACE-27.

Radical prostatectomy was performed with the retropubic or laparoscopic approach. At Barnes-Jewish Hospital EBRT consisted of 3DCRT from 1995 to 1999 and intensity modulated EBRT (IMRT) from 1999 to 2005. At Cleveland Clinic it consisted of 4-field conventional EBRT in 1995 only, 3DCRT from 1995 to 1997 and IMRT in all patients since 1998. The median EBRT dose at Barnes-Jewish Hospital and Cleveland Clinic was 7,400 cGy (IQR 7,070 to 7,544) and 7,800 cGy (IQR 7,400 to 8,000), respectively. Overall 456 patients received less than 7,400 cGy (176 low, 154 intermediate, 126 high risk), and 16 deaths from PCa and 124 deaths from competing causes were observed among these patients. Brachytherapy was delivered using intraoperative treatment planning with ultrasound guidance. Overall 1,348 (34%) patients treated with EBRT and brachytherapy received neoadjuvant, concurrent and/or adjuvant ADT, including 12% (244 of 1,966, median 6 months [IQR 3 to 6]), 45% (521 of 1,169, median 6 months [IQR 6 to 6]) and 82% (583 of 709, median 6 months [IQR 6 to 12]) of patients classified as low, intermediate and high risk by D'Amico criteria.

Statistical Analysis

The primary end point was overall survival and PCSM was the secondary end point. Overall survival and PCSM were estimated using the Kaplan-Meier and cumulative incidence methods, respectively. Multivariable Cox proportional hazards regression analysis was used to determine the association of baseline patient and disease specific parameters with overall survival. Fine and Gray competing risk regression analysis was used to determine the association of clinical parameters with PCSM. In an attempt to address imbalances in the distribution of covariates among treatment groups, we used propensity scores to minimize bias from nonrandom assignment of treatments.

For the multivariable models internal validation using tenfold cross-validation was performed to obtain an unbiased measure of their performance. Discrimination was quantified using the c-index, and calibration was assessed by visual inspection of plots comparing observed and predicted outcomes.[12] All statistical analyses were performed using R v2.8.1 software (R Foundation for Statistical Com-

Table 1. *Baseline and treatment characteristics of patients*

	Cleveland Clinic (5,811)						Barnes-Jewish Hospital (4,618)					
	RP		EBRT		Brachytherapy		RP		EBRT		Brachytherapy	
No. pts	2,843		1,638		1,330		3,642		626		350	
Median age, (IQR)	60	(56–65)	69	(63–73)	68	(62–72)	61	(55–66)	70	(65–75)	69	(63–73)
Median ng/ml PSA (IQR)	5.9	(4.6–8.2)	8.9	(6.0–15.9)	6.1	(4.8–8.0)	5.4	(4.1–7.8)	6.8	(4.7–10.7)	5.2	(3.8–6.8)
No. African-American ethnicity (%)	310	(11)	434	(27)	149	(11)	334	(9)	101	(16)	31	(9)
No. comorbidity index (%):												
None	2,307	(81)	1,084	(66)	809	(61)	2,157	(59)	220	(35)	163	(47)
Mild	377	(13)	317	(19)	322	(24)	1,213	(33)	277	(44)	123	(35)
Moderate	150	(5)	241	(12)	179	(14)	237	(7)	107	(17)	56	(16)
Severe	9	(0.3)	39	(3)	20	(1)	35	(1)	22	(3)	8	(2)
No. bGS (%):												
2–6	1,980	(70)	789	(47)	1,080	(81)	2,774	(76)	390	(61)	313	(89)
7	745	(26)	606	(37)	247	(18)	710	(20)	172	(29)	36	(10)
8–10	118	(4)	243	(16)	13	(1)	158	(4)	64	(10)	1	(1)
No. clinical stage (%):												
T1ab	15	(0.5)	25	(2)	7	(0.5)	40	(1)	7	(1)	0	
T1c	2,074	(73)	883	(54)	1,036	(83)	2,921	(80)	396	(62)	265	(76)
T2a	554	(20)	351	(22)	211	(16)	364	(10)	112	(19)	66	(19)
T2b	124	(4)	158	(10)	9	(1)	250	(7)	54	(9)	17	(5)
T2c	48	(2)	92	(6)	7	(0.5)	49	(1)	20	(3)	2	(1)
T3	28	(1)	129	(8)	0		18	(0.5)	37	(6)	0	
No. D'Amico risk group (%):[4]												
Low	1,669	(59)	479	(29)	932	(70)	2,297	(63)	283	(44)	272	(78)
Intermediate	945	(33)	619	(37)	370	(28)	1,049	(29)	207	(35)	73	(21)
High	229	(8)	540	(34)	28	(2)	296	(8)	136	(21)	5	(1)
Median cGy dose (IQR)	Not applicable		7,800	(7,400–8,000)	14,400		Not applicable		7,400	(7,070–7,544)	14,500	
No. deaths (%):	196		429		147		271		161		52	
PCa	34	(17)	79	(18)	8	(5)	42	(15)	15	(9)	4	(8)
Cardiopulmonary disease	45	(23)	140	(33)	46	(31)	47	(17)	43	(27)	12	(23)
Non PCa	76	(39)	112	(26)	53	(36)	104	(38)	43	(27)	18	(35)
Other causes	25	(13)	60	(14)	21	(14)	52	(19)	28	(17)	7	(13)
Unknown, not PCa	5	(3)	21	(5)	7	(5)	8	(3)	14	(9)	6	(12)
Unknown	11	(6)	17	(4)	12	(8)	18	(7)	18	(11)	5	(10)
Median mos followup (IQR)	59	(33–93)	74	(44–102)	51	(36–73)	72	(49–99)	70	(51–93)	70	(51–89)

puting) with additional packages (Design and cmprsk) added.

RESULTS

Median followup among survivors was 67 months (IQR 43 to 96) and 1,550 (11%) had a followup of 10 years or longer. Overall 1,256 patients died, including 467 (7%), 590 (26%) and 199 (12%) treated with RP, EBRT and brachytherapy, respectively. The unadjusted 10-year overall survival after RP, EBRT and brachytherapy was 87.0% (95% CI 85.5–88.3), 63.2% (95% CI 60.0–66.1) and 59.8% (95% CI 52.2–66.5), respectively, and the adjusted 10-year overall survival was 88.9% (95% CI 87.5–90.1), 82.6% (95% CI 79.8–85) and 81.7% (95% CI 78.7–84.4), respectively (fig. 1, *A*).

On multivariable analysis adjusting for propensity score, patients treated with EBRT (HR 1.6, 95% CI 1.4–1.9) and brachytherapy (HR 1.7, 95% CI 1.4–2.1) had a significantly decreased survival compared to those treated with RP ($p < 0.001$, table 2). There was no significant difference in overall survival between brachytherapy and EBRT (HR 0.9, 95% CI 0.8–1.1). The internally validated c-index of this model was 0.74 and showed good calibration at the 10-year point (data not shown). Similar results were observed when comparing patients receiving 3DCRT-IMRT to those treated with RP during the same period (HR 1.5, 95% CI 1.2–1.8). When analyzed by D'Amico risk group, RP was associated with improved overall survival (table 3).

Overall 182 patients died of PCa. Death from PCa was observed in 76 (1.2%), 94 (4.2%) and 12 (0.7%) patients treated with RP, EBRT and brachytherapy, respectively. The unadjusted 10-year PCSM was 2.2% (95% CI 1.6–2.8), 6.1% (95% CI 4.7–7.5) and 2.4% (95% CI 0.6–4.2), and the adjusted 10-year prostate cancer specific mortality was 1.8% (95% CI 1.6–2.1), 2.9% (95% CI 2.6–3.3) and 2.3% (95% CI 2.0–2.6), respectively (fig. 1, *B*).

On multivariable competing risk regression analysis adjusting for propensity score, treatment modality was not a significant predictor of PCSM ($p = 0.13$, table 2). However, EBRT was associated with in-

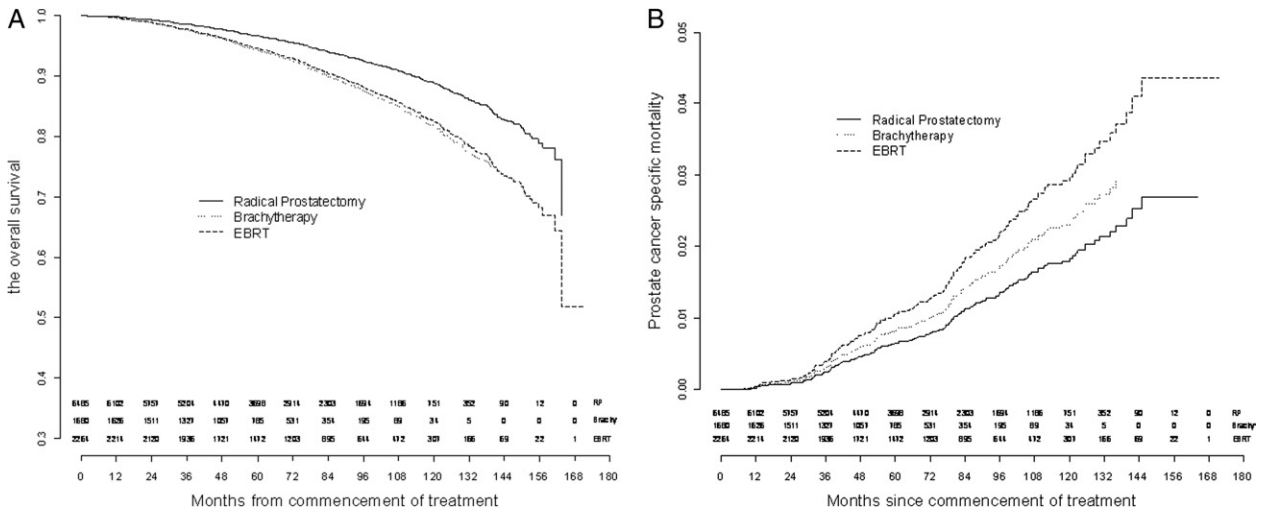

Figure 1. Adjusted overall survival (*A*) and prostate cancer specific mortality (*B*) stratified by treatment modality

creased prostate cancer specific mortality compared to RP (HR 1.5, 95% CI 1.0–2.3, p = 0.041). No significant difference in PCSM was observed comparing brachytherapy and RP (HR 1.3, 95% CI 0.7–2.4, p = 0.5) or brachytherapy and EBRT (HR 1.2, 95% CI 0.6–2.4). The internally validated c-index of a model containing these parameters was 0.81 and the model showed good calibration at the 10-year point (data not shown). Similar results were observed when comparing patients receiving 3DCRT-IMRT to those treated with RP during the same period (HR 1.8, 95% CI 1.4–1.9). Within each D'Amico risk group significant differences in PCSM among treatments were not observed, although the statistical power was limited by subgroup analyses (table 3).

To further quantify the impact of treatment modality on overall survival and PCSM, we assessed the internally validated c-index, and predicted outcomes of the multivariable models that included and excluded this parameter. For overall survival and PCSM the inclusion of treatment modality resulted in a slight increase in predictive accuracy (c-index 0.736 vs 0.731 and 0.810 vs 0.807). The inclusion of treatment modality in the base model resulted in different probabilities of overall survival (fig. 2, *A*) and PCSM (fig. 2, *B*) compared to those predicted by the base model for most patients, and this difference was consistent based on treatment modality. If the inclusion of treatment modality contained no predictive information, predictions for patients using the

Table 2. *Multivariable analysis of parameters associated with overall survival and PCSM*

	Overall Survival		PCSM	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Treatment:				
RP	1.0 (referent)	<0.001	1.0 (referent)	0.13
EBRT	1.6 (1.4–1.9)		1.5 (1.0–2.3)	
Brachytherapy	1.7 (1.4–2.1)		1.3 (0.7–2.4)	
Pt age	2.2 (1.7–2.9)	<0.001	0.8 (0.5–1.3)	0.065
African-American ethnicity	1.5 (1.2–1.8)	<0.001	0.7 (0.4–1.2)	0.18
Comorbidity:				
None	1.0 (referent)	<0.001	1.0 (referent)	0.4
Mild	1.6 (1.4–1.8)		1.2 (0.8–1.7)	
Moderate	3.3 (2.8–3.9)		1.4 (0.9–2.3)	
Severe	5.0 (3.6–7.0)		0.7 (0.2–2.9)	
Pretreatment PSA	1.5 (1.3–1.7)	<0.001	1.7 (1.1–2.5)	0.017
bGS:				
2–6	1.0 (referent)	<0.001	1.0 (referent)	<0.001
7	1.4 (1.2–1.6)		2.9 (1.8–4.5)	
8–10	2.2 (1.8–2.8)		11.1 (6.5–18.9)	
Clinical stage:				
T1c	1.0 (referent)	0.002	1.0 (referent)	0.12
T1ab	1.4 (0.8–2.4)		0.3 (0.1–1.0)	
T2a	1.3 (1.1–1.6)		0.4 (0.1–1.5)	
T2b	1.3 (1.0–1.6)		0.5 (0.1–1.6)	
T2c	1.3 (0.9–1.8)		0.5 (0.1–1.7)	
T3	2.3 (1.5–3.3)		0.8 (0.2–2.9)	

Table 3. *Overall survival and PCSM for RP, EBRT and brachytherapy according to D'Amico risk classification on univariable analysis*

	Overall Survival		PCSM	
Risk Classification	HR (95% CI)	p Value	HR (95% CI)	p Value
Low:				
EBRT vs RP	1.7 (1.3–2.1)	<0.001	1.8 (0.5–6.2)	0.4
Brachytherapy vs RP	1.7 (1.4–2.2)	<0.001	2.3 (0.8–6.9)	0.14
Intermediate:				
EBRT vs RP	1.5 (1.2–1.9)	0.001	1.8 (0.8–3.8)	0.13
Brachytherapy vs RP	1.5 (1.1–2.1)	0.019	0.6 (0.1–2.7)	0.5
High:				
EBRT vs RP	1.7 (1.3–2.3)	0.001	1.3 (0.8–2.1)	0.2
Brachytherapy vs RP	3.1 (1.7–5.9)	<0.001	1.6 (0.4–6.6)	0.5

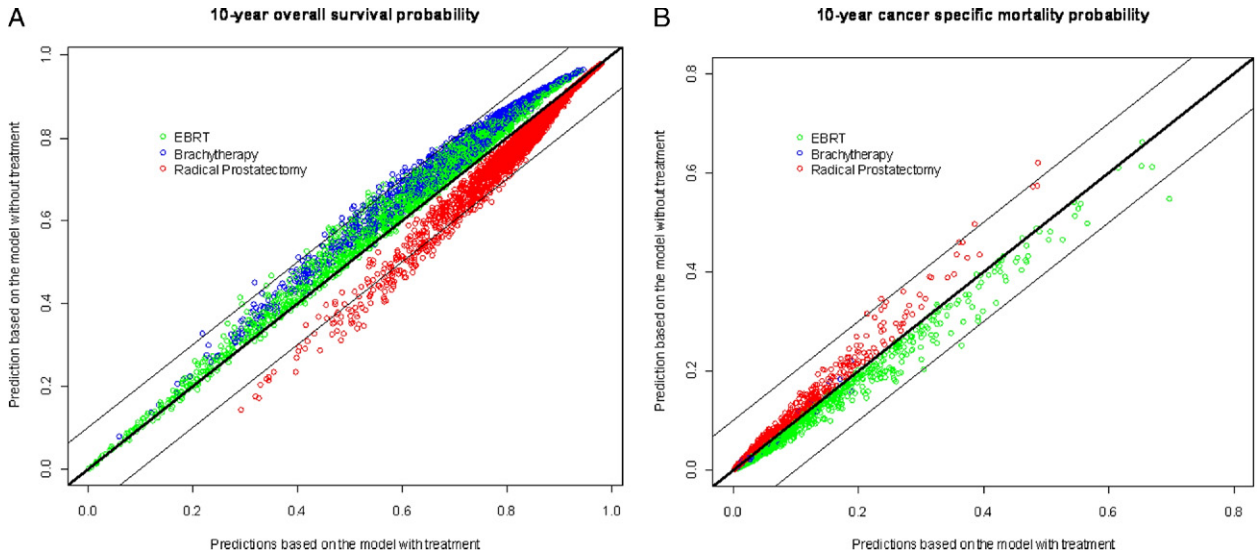

Figure 2. Predicted overall survival (*A*) and prostate cancer specific mortality (*B*) based on multivariable model that does (x-axis) and does not (y-axis) include treatment modality.

enhanced and base models should correspond perfectly and align on the 45-degree line.

DISCUSSION

A man with clinically localized PCa is faced with a challenging process of selecting the optimal treatment. He must choose between radical therapy and surveillance for a cancer that may pose an uncertain threat to his longevity or quality of life.[13] If he chooses treatment, none has been proven superior in terms of quantity or quality of life. In the absence of data from randomized trials, one must rely on observational studies, although these may be biased. In this study, to our knowledge the largest comparative analysis of contemporary patients treated according to current treatment standards, RP was associated with improved overall survival compared to EBRT and brachytherapy after adjusting for major confounders, and improved PCSM compared to EBRT. However, the differences in adjusted survival among treatment modalities at 10 years were small, particularly for PCSM.

In the only published United States randomized trial RP was associated with improved metastasis-free survival compared to EBRT.[1] However, the relevance of this trial is limited to contemporary patients as it was performed in the pre-PSA era according to historical treatment standards and had methodological flaws. A randomized trial from Japan failed to demonstrate an improvement in overall survival or PCSM, although the sample size was small (95).[2] Two large United States randomized trials comparing RP and radiation therapy were closed prematurely due to poor accrual.[3] The ProtecT (Prostate Testing for Cancer and Treatment) trial is evaluating BCR, clinical progression and quality of life differences among men randomized to RP, EBRT and surveillance.

Four observational studies have reported improved PCSM and/or overall survival among patients treated with RP compared to EBRT.[14–17] Merglen et al reported a 2.3-fold increased PCSM in men treated with EBRT vs RP.[14] However, few of these cancers were detected by screening, the majority of men (79%) did not receive local therapy, detailed information on the treatments received was not available and no adjustments were made for comorbidity. Albertsen et al analyzed PCSM among 1,618 men in the Connecticut Tumor Registry diagnosed in the early PSA era (1990 to 1992), adjusting for D'Amico risk classification and comorbidity.[15] Men treated with EBRT had a 2.2-fold increased PCSM compared to RP during a median followup of 13 years. In a third study of 256 men with bGS 8–10 cancers, Tewari et al reported a 54% and 49% lower all cause and prostate cancer specific mortality, respectively, for those treated with RP compared to EBRT.[16] In a single institution, retrospective study Zelefsky et al reported a significantly improved 8-year freedom from distant metastasis and PCSM in 1,318 men treated with RP compared to 1,062 who received IMRT adjusting for disease related parameters.[17]

Our study is consistent with these prior observations and expands on these findings. All men in our study were treated after 1995, when the stage migration caused by screening appears to have

stabilized.[18] The majority of men received high dose EBRT using conformal techniques, and the majority of intermediate and high risk patients received neoadjuvant, concurrent and/or adjuvant ADT, which has been shown to improve outcomes.[19,20] Information on PSA, bGS and clinical stage was available for all patients, and was obtained from prospectively maintained databases. Comorbidity was assessed by a chart based review using validated indices.[10,11] In addition, propensity score analysis was used to control for potential known confounders and bias in treatment selection. Lastly our primary end point was overall survival, which is likely to be the outcome of greatest importance. PCSM is a problematic end point to compare treatments due to the difficulty in attributing cause of death in men with PCa, and the potential for inaccurate and even biased assignments of cause of death in vital statistics for patients with PCa.[21]

Differences in PCSM between RP and external beam radiotherapy may be related to a superior ability to achieve local control and/or improved delivery of effective secondary therapy for local recurrence/persistence. Regarding the former, there is no conclusive evidence that RP alone achieves superior local control compared to EBRT or brachytherapy. However, by enabling a pathological assessment of the primary tumor and regional lymph nodes, RP defines the extent of disease more accurately and, therefore, improves the selection of candidates for adjuvant treatment. Clinical staging of PCa is imprecise and upwards of 16% of low risk patients have adverse pathological features.[22] Postoperative radiotherapy has been proven to reduce the risk of disease recurrence, distant metastasis and all cause mortality.[23] Adjuvant ADT was associated with improved survival in a small randomized trial in men with pathologically positive lymph nodes treated with RP.[24] In terms of salvage therapy for BCR, salvage radiotherapy is frequently used for men with biochemical recurrence after RP. Since any detectable PSA 4 to 6 weeks after surgery usually signals the presence of recurrent cancer,[7] treatment is given earlier in the disease process, which translates to improved cancer control.[25] In contrast, local salvage therapy is seldom considered for patients with BCR after radiation therapy and in most disease has progressed beyond the point where local salvage therapy would be effective due to the difficulty in interpreting early post-irradiation PSA changes.[17] Thus, the early implementation of secondary therapy on the basis of the pathological findings at RP or early postoperative PSA changes may contribute to the improved survival we observed with RP.

Alternatively we may not have fully adjusted for all confounders that contribute to survival. This issue is germane to our analysis as there is a bias for EBRT among men with locally advanced features and/or limited life expectancy. However, using patient age, ethnicity and comorbidity, we were able to discriminate among patients with reasonable accuracy for competing causes of mortality (c-index 0.78, model not shown). A second possibility is that deaths were related to treatment. A higher rate of ADT use was observed for men in our study treated with EBRT and brachytherapy, and this has been linked to cardiovascular mortality and fracture risk (although it has not been confirmed in prospective randomized trials).[26] In addition, an increased risk of secondary pelvic malignancies has been reported among men receiving EBRT for PCa but not brachytherapy.[27] However, the potential for treatment related mortality related to ADT or radiation therapy is not likely to account fully for the magnitude of survival differences observed.

Our study has several limitations worth noting, the most obvious being the lack of randomization. While systematic reviews have demonstrated that well designed observational studies do not systematically overestimate or underestimate the magnitude of the effects of treatment, a randomized trial is the superior method to compare treatments.[28] Another limitation is the imbalance of confounders among treatment groups. On average, patients treated with EBRT were older, and had higher comorbidity scores and more adverse disease related features. Thus, our models for overall survival and PCSM may not adjust completely for these imbalances despite our efforts to control for them using appropriate methodology. Our study evaluated overall survival and PCSM within 10 years of treatment, but men with localized PCa appear to be at risk for death from PCa for up to 20 years.[29] While we believe the treatments received in our study reflect contemporary standards, treatment guidelines are in constant evolution. Thus, it is difficult to have a cohort of patients with sufficiently mature followup (more than 10 years) that has received therapy that represents the current standard of care. In particular, the ADT duration and the radiation dose for many patients treated with EBRT would be considered insufficient by current standards. Lastly we only considered survival differences among treatments and we did not consider effects on quality of life.

In summary, after adjusting for major confounders, RP was associated with improved overall survival compared to EBRT and brachytherapy. In addition, radical prostatectomy was associated with improved PCSM compared to EBRT. However, the absolute improvement in overall and PCSM among groups at 10 years was modest. These survival differences may arise from an imbalance of patient or

disease related confounders despite our efforts to adjust for them, from improved cancer control when RP is performed as initial therapy, and/or from differences in treatment related mortality.

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