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Mortality After Prostate Cancer Treatment with Radical Prostatectomy, External-Beam Radiation Therapy, or Brachytherapy in Men Without Comorbidity

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Abstract

Background—Medical comorbidity is a confounding factor in prostate cancer (PCa) treatment selection and mortality. Large-scale comparative evaluation of PCa mortality (PCM) and overall mortality (OM) restricted to men without comorbidity at the time of treatment has not been performed.

Objective—To evaluate PCM and OM in men with no recorded comorbidity treated with radical prostatectomy (RP), external-beam radiation therapy (EBRT), or brachytherapy (BT).

Design, setting, and participants—Data from 10 361 men with localized PCa treated from 1995 to 2007 at two academic centers in the United States were prospectively obtained at diagnosis and retrospectively reviewed. We identified 6692 men with no recorded comorbidity on a validated comorbidity index. Median follow-up after treatment was 7.2 yr.

Intervention—Treatment with RP in 4459 men, EBRT in 1261 men, or BT in 972 men.

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Outcome measurements and statistical analysis—Univariate and multivariate Cox proportional hazards regression analysis, including propensity score adjustment, compared PCM and OM for EBRT and BT relative to RP as reference treatment category. PCM was also evaluated by competing risks analysis.

Results and limitations—Using Cox analysis, EBRT was associated with an increase in PCM compared with RP (hazard ratio [HR]: 1.66; 95% confidence interval [CI], 1.05–2.63), while there was no statistically significant increase with BT (HR: 1.83; 95% CI, 0.88–3.82). Using competing risks analysis, the benefit of RP remained but was no longer statistically significant for EBRT (HR: 1.55; 95% CI, 0.92–2.60) or BT (HR: 1.66; 95% CI, 0.79–3.46). In comparison with RP, both EBRT (HR: 1.71; 95% CI, 1.40–2.08) and BT (HR: 1.78; 95% CI, 1.37–2.31) were associated with increased OM.

Conclusions—In a large multicenter series of men without recorded comorbidity, both forms of radiation therapy were associated with an increase in OM compared with surgery, but there were no differences in PCM when evaluated by competing risks analysis. These findings may result from an imbalance of confounders or differences in mortality related to primary or salvage therapy.

Keywords

Prostatic neoplasms; Prostatectomy; Radiation therapy; Comorbidity; Comparative effectiveness research

1. Introduction

Preexisting medical comorbidity is of paramount importance in prostate cancer (PCa) treatment decision making. A selection bias exists among cancer specialists for preferring radiation therapy (RT) for patients with significant comorbid illness who are felt not to be candidates for surgery [1,2]. In addition to influencing treatment choice, medical comorbidity influences mortality after the diagnosis of localized PCa [3,4] directly through competing causes of death or indirectly by exacerbating underlying disease states [5]. Several groups have reported that underlying medical comorbidity can influence overall mortality (OM) after PCa treatment [6–9].

In the absence of randomization, this imbalance of medical comorbidity makes valid comparisons among treatment options difficult. Several comparisons of PCa treatment options have either ignored medical comorbidity because the information was not collected [10] or have attempted to control for measured comorbidity using statistical methods [11–15]. However, concerns remain that unmeasured factors could still bias results.

Statistically adjusting for comorbidity in observational studies assumes that comorbidity severity is accurately assessed and that measurement error does not result in incomplete statistical adjustment. Experts in the methodology of comparative effectiveness literature have recommended restriction analysis as an alternative to statistical adjustment to minimize the effect of confounding bias [16]. For this reason, we sought to compare mortality among treatments for men with no medical comorbidity. Our objective was to evaluate for any differences in mortality—either PCa mortality (PCM) or OM in patients treated in the prostate-specific antigen (PSA) era with radical prostatectomy (RP), external-beam RT (EBRT), or brachytherapy (BT).

2. Patients and methods

From 1995 to 2007, 10 361 men underwent treatment (RP, EBRT, or BT) for localized PCa at the Cleveland Clinic (Cleveland, OH, USA) or Barnes-Jewish Hospital (St. Louis, MO, USA) and were prospectively entered into institutional databases. As part of each institutional database, pretreatment medical comorbidity was measured by two validated comorbidity indexes—retrospectively with the Charlson comorbidity index [17] at the Cleveland Clinic and prospectively at the time of diagnosis by the Adult Comorbidity Evaluation Index-27 (ACE-27) [18] at Barnes-Jewish Hospital—that have been reported to have similar mortality prediction [19]. The Charlson index evaluates the presence of 19 comorbid ailments, and the ACE-27 includes 26 comorbid ailments and a comorbidity score (none, mild, moderate, and severe). Of 10 361 men, 6692 (64.6%) were retrospectively identified with an ACE-27 assessment of none or a Charlson index of zero (Table 1); these patients formed the study cohort. Treatment consisted of RP, EBRT, or BT. RP was performed by way of an open retropubic or minimally invasive approach. EBRT dosage was consistent with the standard of care at the time of treatment, with doses gradually escalated from 68.4 to 79.2 Gy. BT was administered with intraoperative ultrasound guidance. Patient demographic (age at time of treatment, race) and clinical information (pretreatment PSA, clinical stage, biopsy Gleason grade) were reviewed and compared among treatments using analysis of variance for continuous data and the χ^2 test for categorical data.

PCM and OM were assessed by a combination of chart review, correspondence, and query of the National Death Index. Ten-year mortality estimates for PCM and OM for the entire cohort were obtained by the Kaplan-Meier method.

Analysis with the univariate Cox proportional hazards model identified variables associated with PCM or OM at a level of significance of $p < 0.10$. Significant covariates were incorporated into multivariate Cox proportional hazards models for PCM and OM to compare the hazard ratio (HR) for EBR and BT, with RP as the reference group with an HR of 1.0. Adjusted mortality graphs for PCM and OM were made based on the Cox models. We additionally controlled for selection bias not controlled for by multivariable methods by using propensity adjustment using logistic regression modeling similar to the method described by Mangano et al [20] for the three different treatments. A propensity score for treatment (EBRT relative to RP, BT relative to RP) was developed using clinical and disease information (age, race, PSA, biopsy Gleason grade, clinical stage), and the propensity score was then included in the model for PCM and the model for OM. We additionally evaluated PCM using a Fine and Gray competing risks analysis, which has been suggested to improve accuracy by adjusting for the competing risk of other-cause mortality [21].

A p value of <0.05 was considered statistically significant. Statistical analysis was performed with SAS 9.2 (SAS Institute Inc., Cary, NC, USA), SPSS 17 (IBM Corp., Armonk, NY, USA), and Stata (StataCorp., College Station, TX, USA). Institutional review board approval was obtained.

3. Results

In the cohort of men without measured medical comorbidity, treatment groups differed with respect to age, race, PSA, clinical stage, and biopsy Gleason grade (Table 2). Median follow-up after treatment was 7.2 yr, while 2397 of 6692 men (35.8%) had evaluation to either death or follow-up for >10 yr. Mortality occurred in 664 men (9.9%), which was classified as PCM in 123 men and other-cause mortality in 541 men. By the Kaplan-Meier method, the 10-yr PCM was 2.6% and the 10-yr OM was 13.3%.

Univariate and multivariate Cox proportional hazards models are displayed for PCM in Table 3. EBRT was associated with an increase in PCM compared with RP (HR: 1.66; 95% confidence interval [CI], 1.05–2.63); for BT there was also an elevated hazard ratio (HR: 1.83) for PCM compared with RP, but it was not statistically significant (95% CI for HR, 0.88–3.82) (Fig. 1). When covariates for propensity score analysis were included in the analysis of PCM, the relationships on multivariable analysis remained similar, with EBRT associated with an increase in PCM compared with RP (HR: 1.64; 95% CI, 1.05–2.55; $p = 0.03$) and a similar HR for PCM with BT compared with RP (HR: 1.63; 95% CI, 0.77–3.45).

PCM was additionally evaluated using Fine and Gray competing risks analysis (Table 3). When using a competing risks model, there was no statistically significant increase in PCM for EBRT compared with RP (HR: 1.55; 95% CI, 0.92–2.60) or for BT compared with RP (HR: 1.66; 95% CI, 0.79–3.46).

Results for OM are shown in Table 4. In comparison with RP, both EBRT (HR: 1.71; 95% CI, 1.40–2.08) and BT (HR: 1.78; 95% CI, 1.37–2.31) were associated with increased OM (Fig. 2). When using the propensity adjustment method in the multivariable analysis of OM, the relationships remained similar, with an increase in OM with EBRT (HR: 1.67; 95% CI, 1.37–2.04; $p < 0.0001$) and with BT (HR: 1.69; 95% CI, 1.30–2.19; $p < 0.0001$) compared with RP.

4. Discussion

In an effort to minimize the confounding due to underlying medical comorbidity, we evaluated mortality after PCa treatment in men with no documented medical comorbidity at the time of PCa treatment. In this patient cohort, PCM was infrequent. A Cox proportional hazards statistical analysis identified that EBRT was associated with an increase in PCM compared with RP, even when adjusting for differences in patient demographics and cancer severity. However, the association of EBRT with increased PCM was no longer statistically significant when evaluated with a competing risks model. This association, of similar magnitude with either model, raises speculation that the treatment efficacy of historical RT may have been diminished compared with surgery during the same time period; however, lack of a statistically significant effect does not allow a definitive conclusion. The lack of a difference in PCM with BT may be related to the use of BT in lower-risk patients and avoidance in high-risk patients, as it is known that mortality from low-risk PCa is a relatively infrequent occurrence, to the extent that some low-risk patients may not even warrant active treatment. In addition, the number of patients treated with BT was relatively lower, which is reflected in the wider confidence interval and lower certainty of the findings.

With respect to OM, both forms of RT were associated with an increase in OM compared with surgery. The finding of increased OM after RTs could potentially be due to treatment toxicity. Speculative reasons for increased mortality after irradiation include a clinically significant increased rate of secondary malignancy after irradiation [22,23] or secondary toxicity from androgen-deprivation therapy (ADT), which is used more commonly with irradiation than surgery. However, the link between androgen deprivation and cardiovascular toxicity remains controversial [24,25].

The fact that the differences in OM with radiation treatment modalities compared with surgery were more pronounced than in PCM has several possible explanations. PCM during our cohort was relatively low, so the small number of events limits our ability to evaluate the relationship. In addition, cause-of-death data from death records can be unreliable [26]. Therefore, patients whose recorded death was from other causes may have in fact died of PCa; however, it is not known if this error would differ based on treatment modality. We

attempted to minimize this error by reviewing all available records and not solely depending on death certificate data. Our evaluation relied on retrospective observational data to compare the mortality outcomes of treatment options for localized PCa. The reliance on observational data is necessary because randomized controlled trials are lacking. Other groups have attempted to use observational data to compare treatment outcomes with varying methods to evaluate and control for comorbidity. Adbollah et al [14] used Surveillance Epidemiology and End Results (SEER) data and concluded that RP provided more favorable survival rates compared with RT with median follow-up of 4.3 yr. However, a limitation of SEER data is the lack of any information on medical comorbidity. Using the SEER cancer registry data linked to Medicare, which allowed attempted statistical adjustment for comorbidity but was limited to patients >65 yr, Abdollah [14] recently reported improved outcomes with surgery compared with irradiation for PCa, as had Liu et al (median follow-up was not reported) [27]. Another population-based evaluation in a Canadian province, which included attempted statistical control for medical comorbidity, also reported increased mortality after RT compared with surgery [28].

Kutikov et al recently reported on a nomogram using data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) that reported on multivariate analysis that treatment with irradiation was associated with increased risk of PCa and non-PCa death [29]. Previously, Cooperberg et al had used data from CaPSURE and, after statistically adjusting for Charlson comorbidity, concluded that surgery was associated with a significant and substantial reduction in mortality relative to RT. Cooperberg et al reported that this finding was unlikely due to unmeasured confounding, as statistical adjustments and sensitivity analysis did not affect the results [15]. Our analysis differed, as we restricted our evaluation to men with no measured comorbidity in an attempt to minimize unmeasured confounding bias. In a two-institution evaluation of high-risk PCa, Boorjian et al [13] reported that PCM was similar for RP and EBRT (follow-up of 10.2 and 6–7.2 yr, respectively); however, OM was increased after EBRT if patients received ADT. In an effort to minimize confounding, Boorjian et al also reported that when restricting this analysis to the subset of patients with a Charlson comorbidity index of 0 or 1, this relationship was unchanged. Our analysis differed, as we attempted to include only healthy patients and excluded patients with Charlson comorbidity of 1, which can include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disorder, ulcer disease, mild liver disease, and diabetes without end organ damage [17].

A primary concern in any evaluation comparing different treatment options for PCa is the possibility that unmeasured confounding differences exist between men who chose to receive irradiation compared with surgery. The RT group had higher stage, grade, and PSA and was older and more likely to be African American. It is likely that additional unmeasured variables exist between the two groups. We attempted to minimize the potential for confounding by restricting our analysis to men with no measured pretreatment medical comorbidity, which would be a presumptively healthy group, and statistically controlling for differences between treatment groups in age, race, PSA, biopsy Gleason grade, and clinical stage.

This nonrandomized observational evaluation has limitations. While the comorbidity indexes used in our study identified and excluded men with measured pretreatment medical comorbidities, there are other possible unmeasured treatment differences between groups. For instance, morbid obesity (body mass index ≥38) and hypertension are captured by the ACE-27 comorbidity index; however, these factors are not assessed in the Charlson comorbidity index. A history of smoking, hypercholesterolemia, or socioeconomic status are also not assessed by either comorbidity index and may have differed by treatment group.

The possibility also exists that when suggesting treatment modality, clinicians may be able to identify differences in patients that are not accurately assessed by comorbidity indexes. Whether the impact of these unmeasured factors is influential enough to explain our findings remains unknown, and further research will be needed to elucidate whether and how much of a mortality difference exists in healthy patients undergoing treatment of PCa.

We restricted our analysis to men with no measured comorbidity, so the results of our analysis are best applied to that population and not generalized to all men with PCa. There is debate about who should be treated (with any modality) for PCa. Given that patients with no comorbidity have longer life expectancies, our analysis addresses the population most likely to benefit from treatment and therefore of greatest interest. In our study, median follow-up was >7 yr; further follow-up is necessary, however, as PCM can occur years after treatment.

The RT given was consistent with the standard of care at the time, but dose escalation has occurred over time, and the effect on mortality of contemporary doses of RT cannot be evaluated in this study. The use of ADT could not be controlled for in the statistical model because surgical patients did not receive ADT at the time of treatment. The administration of ADT in the context of EBRT was predicated on the standard of care at the time treatment was delivered [12]. More recently, the adoption of ADT in men with unfavorable-risk PCa has been reported to improve survival in patients treated with EBRT [30,31] and potentially could affect results in a more contemporary cohort. In addition, detailed information on the receipt of salvage therapies was not available for the entire cohort.

While our results suggested a survival benefit for prostatectomy in men with no measured comorbidity, patient choice remains important, as treatment choice incorporates not only available data on cure rates but also concerns about the adverse effects of primary treatment. Other factors such as quality of life, continence, and erectile function also affect treatment decisions [32,33] and were not evaluated in this report. Finally, our study did not include an active surveillance cohort, and active surveillance is an option for low-risk PCa [34].

5. Conclusions

In a large multicenter series of men without recorded comorbidity, both forms of RT were associated with an increase in OM compared with surgery. These findings may result from differences in cancer control, mortality related to primary or salvage therapy, or an imbalance of confounders.

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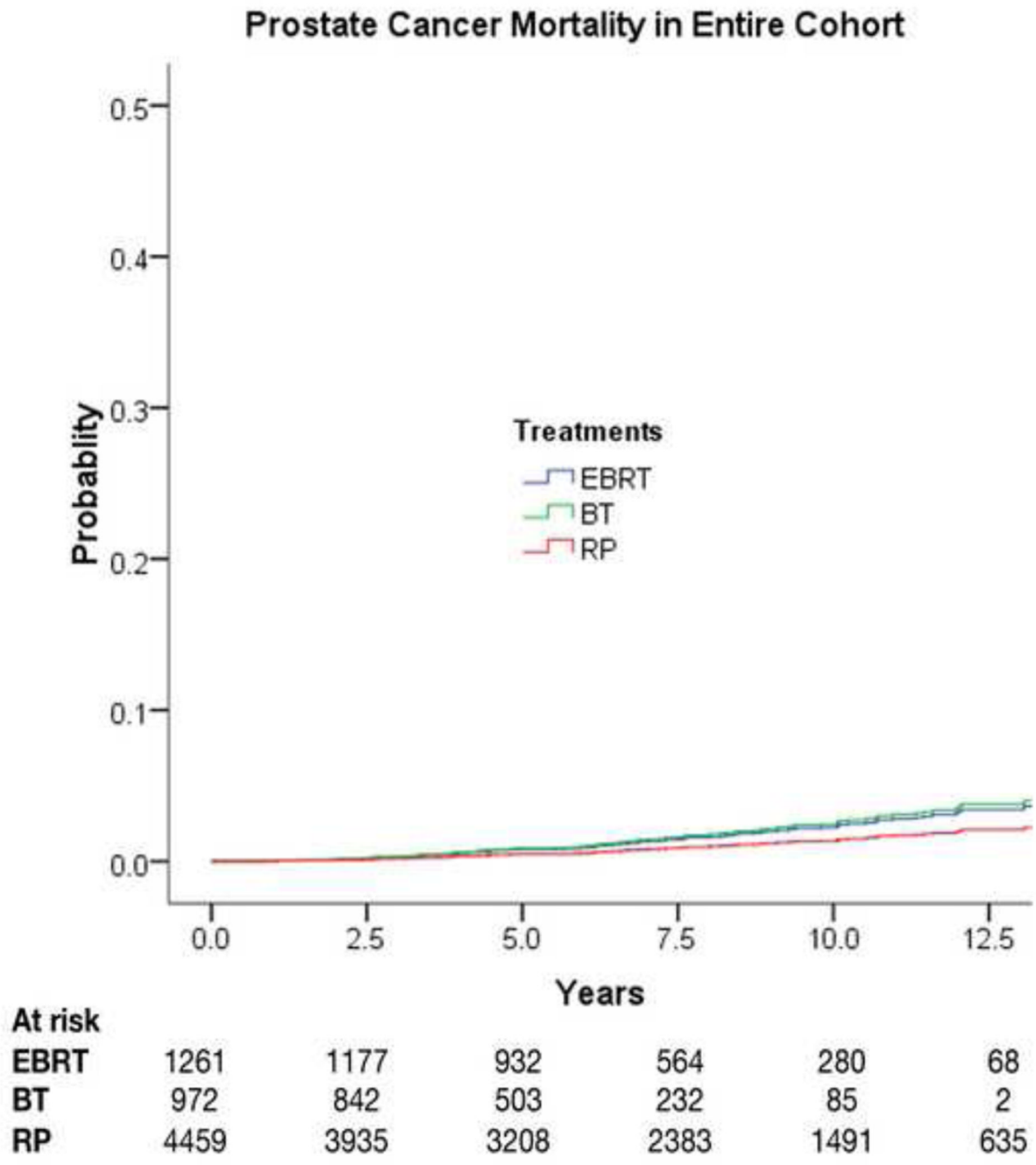

Fig. 1.

Prostate cancer mortality by treatment type, adjusting for covariates in multivariate Cox proportional hazards model. EBRT = external-beam radiation therapy; BT = brachytherapy; RP = radical prostatectomy.

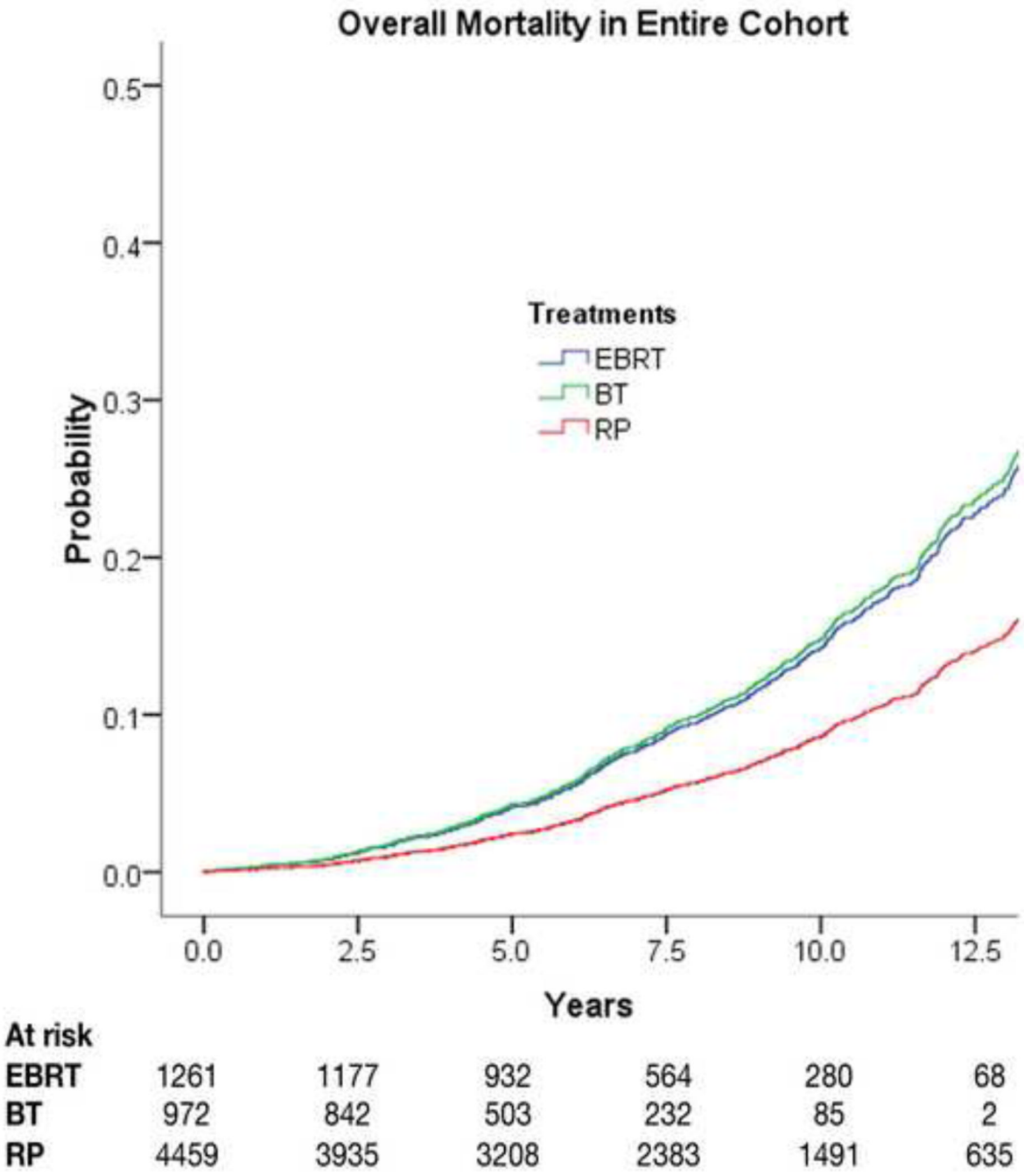

Fig. 2.

Overall mortality by treatment type, adjusting for covariates in multivariate Cox proportional hazards models. EBRT = external-beam radiation therapy; BT = brachytherapy; RP = radical prostatectomy.

Table 1

Medical comorbidity of all 10 361 men treated for localized prostate cancer*

Medical comorbidity	Overall, *n* = 10361	RP, *n* = 6477	EBRT, *n* = 2204	BT, *n* = 1680
None, no. (%)	6692 (65)	4459 (69)	1261 (57)	972 (58)
Mild, no. (%)	2615 (25)	1587 (25)	583 (26)	445 (26)
Moderate, no. (%)	922 (9)	387 (6)	300 (14)	235 (14)
Severe, no. (%)	132 (1)	44 (1)	60 (3)	28 (2)

RP = radical prostatectomy; EBRT = external-beam radiation therapy; BT = brachytherapy.

* The Adult Comorbidity Evaluation Index-27 comorbidity index groups patients into *none*, *mild*, *moderate*, and *severe*. Charlson comorbidity index: 0 = none; 1 = mild; 2–3 = moderate; ≥4 = severe.

Table 2

Characteristics of 6692 men with no comorbidity treated for localized prostate cancer

	RP, *n* = 4459	EBRT, *n* = 1261	BT, *n* = 972	*p* value
Age, yr, median	60	68.3	66.8	<0.001
Race, African American, no. (%)	366 (8)	260 (21)	107 (11)	<0.001
PSA, median	6.96	11.11	6.66	<0.001
Biopsy Gleason score, no. (%)				<0.001
5–6	3316 (74)	696 (55)	805 (83)	
7	976 (22)	414 (33)	162 (17)	
8–10	167 (4)	151 (12)	5 (0.5)	
Clinical stage, no. (%)				<0.001
T1	3480 (78)	743 (59)	798 (82)	
T2	951 (21)	446 (35)	174 (18)	
T3	28 (0.6)	72 (6)	0 (0)	
D'Amico risk group, no. (%)				<0.001
Low	2807 (63)	452 (36)	707 (73)	
Intermediate	1331 (30)	463 (37)	248 (26)	
High	(321 (7)	346 (27)	17 (2)	

RP = radical prostatectomy; EBRT = external-beam radiation therapy; BT = brachytherapy; PSA = prostate-specific antigen.

Table 3

Univariate and multivariate models for prostate cancer mortality

	Univariate		Multivariate Cox proportional hazards model		Multivariate competing risks model	
	HR	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age	1.03	0.03	1.00 (0.98–1.03)	0.84	1.00 (0.97–1.02)	0.82
Race compared with non-African American	1.55	0.09	0.95 (0.56–1.61)	0.85	0.94 (0.55–1.63)	0.83
PSA	**1.08**	**<0.001**	**1.03 (1.01–1.05)**	**0.002**	**1.03 (1.01–1.05)**	**0.002**
Biopsy Gleason score compared with 5–6						
7	**1.72**	**0.005**	**2.62 (1.65–4.18)**	**<0.001**	**2.55 (1.60–4.08)**	**<0.001**
8–10	**11.25**	**<0.001**	**10.47 (6.42–17.08)**	**<0.001**	**10.11 (6.23–16.42)**	**<0.001**
Clinical stage compared with T1	**5.79**	**0.02**	1.29 (0.86–1.93)	0.22	1.28 (0.84–1.95)	0.25
T2	**11.52**	**<0.001**	**2.63 (1.40–4.92)**	**0.003**	**2.66 (1.30–5.46)**	**0.008**
T3						
Treatment compared with RP	**3.27**	**<0.001**	**1.66 (1.05–2.63)**	**0.03**	1.55 (0.92–2.60)	0.10
EBRT	0.78	0.48	1.83 (0.88–3.82)	0.11	1.66 (0.79–3.46)	0.18
BT						

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen; RP = radical prostatectomy; EBRT = external-beam radiation therapy; BT = brachytherapy.

Table 4

Univariate and multivariate models for overall mortality

	Univariate		Multivariate	
	HR	***p* value**	**HR (95% CI)**	***p* value**
Age	1.10	<**0.001**	1.07 (1.06–1.08)	<0.001
Race compared with non-African American	1.80	**<0.001**	**1.34 (1.08–1.66)**	**0.008**
PSA	**1.04**	**<0.001**	**1.01 (1.00–1.02)**	**0.02**
Biopsy Gleason score compared with 5–6	**1.54**	**<0.001**	**1.38 (1.15–1.65)**	**<0.001**
7	**3.10**	**<0.001**	**2.52 (1.96–3.23)**	**<0.001**
8–10				
Clinical stage compared with T1	**1.31**	**0.001**	1.06 (0.89–1.26)	0.50
T2	**3.76**	**<0.001**	**1.65 (1.13–2.41)**	**0.01**
T3				
Treatment compared with RP				
EBRT	**3.16**	**<0.001**	**1.71 (1.40–2.08)**	**<0.001**
BT	**1.58**	**<0.001**	**1.78 (1.37–2.31)**	**<0.001**

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen; RP = radical prostatectomy; EBRT = external-beam radiation therapy; BT = brachytherapy.