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Brachytherapy improves outcomes in young men (≤60 years) with prostate cancer: A SEER analysis

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ABSTRACT

PURPOSE: The aim of the study was to compare prostate cancer–specific mortality (PCSM) in young men with clinically localized prostate cancer treated by either external beam radiation (EBRT) alone or brachytherapy with or without external beam radiation.

METHODS AND MATERIALS: Utilizing the Surveillance, Epidemiology and End Results database, 15,505 patients ≤60 years of age diagnosed with prostate cancer between 2004 and 2009 and treated with radiation therapy alone were identified. Incidence of PCSM was determined for both groups and compared using competing risk models.

RESULTS: The overall 8-year PCSM for the study population was 1.9% (95% confidence interval [CI]: 1.6–2.2). For patients treated with EBRT or brachytherapy with or without external beam, the 8-year PCSM was found to be 2.8% (CI: 2.2–3.4) and 1.2% (CI: 0.9–1.6), respectively ($p < 0.001$). Univariable analysis demonstrated that brachytherapy was associated with lower PCSM risk (hazard ratio = 0.40; CI: 0.30–0.54; $p < 0.001$). High Gleason risk category, black race, higher Tumor (T) stage, and higher grade were all associated with greater mortality risk ($p < 0.01$). On multivariable analysis, brachytherapy continued to be associated with a significantly lower mortality risk (hazard ratio = 0.65; CI: 0.47–0.89; $p = 0.008$). Subgroup analyses found that among those with Gleason score ≥8, younger patients had increased risk of PCSM ($p = 0.001$).

CONCLUSIONS: In men ≤60 years of age with prostate cancer, radiation therapy continues to offer excellent outcomes. After adjusting for relevant variables, the use of brachytherapy was associated with reduced PCSM compared to treatment with EBRT alone.

Keywords: Brachytherapy; Prostate cancer; SEER; Outcomes

Introduction

The most effective definitive treatment for clinically localized prostate cancer in young men (aged ≤60 years) has been the subject of much debate within the clinical and research community. Traditionally, there has been a bias toward a recommendation of radical prostatectomy in this patient population due to a perception that radiation therapy produced poorer clinical outcomes and higher relapse rates attributable to their longer life expectancy (1). Current research, however, is demonstrating that age may not be a significant prognostic factor for either biochemical failure or prostate cancer–specific mortality (PCSM) in men who receive radiotherapy alone for prostate cancer (2, 3).

Research is now focusing on the specific role radiation can play as monotherapy for prostate cancer treatment. Recent studies, including the ASCENDE-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy) trial, have compared outcomes between external beam radiotherapy alone or combined with a brachytherapy boost and found that brachytherapy

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resulted in a significant improvement in relapse-free survival and PCSM when compared to external beam radiation (EBRT) alone (4–6). The influence of age on these outcomes, however, has not been fully investigated.

Given this current research context, the purpose of this study therefore was to compare the PCSM in young men (≤60 years of age at the time of diagnosis) with clinically localized prostate cancer treated by either EBRT alone or brachytherapy with or without external beam radiation (BRT ± EBRT). In so doing, we hope to explore the role radiation therapy can play in the treatment of this disease and the impact of age on outcomes in these patients.

Methods and materials

Patients meeting this study's eligibility criteria were identified using the Surveillance, Epidemiology and End Results (SEER) Database (7). This database contains incidence and survival statistics from 18 population-based cancer registries (1973–2010), representing approximately 28 percent of the U.S. population. Even though all SEER database information remains deidentified, institutional review board approval was obtained before performing the analyses (approval #569264).

The study population included men 60 years old or younger who were diagnosed with prostate adenocarcinoma between 2004 and 2009. International Classification of Diseases for Oncology code 8140/3 was used when selecting histological type. Patients were selected who were treated with radiation therapy, including EBRT only or BRT ± EBRT. Patients who had received radical prostatectomy at any point during treatment were excluded, as were patients with unknown radiation type. A total of 15,505 patients met these criteria and were included in the overall analysis.

Demographic data retrieved from the SEER database included subject age, race, marital status, age at the time of diagnosis, and geographic location. Age was analyzed as both a continuous variable as well as a categorical variable (≤45 years and >45–60 years). Race was categorized as black or other (white, American Indian/AK Native, Asian/Pacific Islander), based on SEER coding. Location was divided into north central, north east, south, and west regions.

Treatment type was categorized as either EBRT or BRT ± EBRT. Pathologic data included SEER classification of tumor grade (I or II, III or IV, NA), Gleason risk category (low risk ≤ 7 or high risk ≥8), and tumor (T) (TNM) stage (T1 or ≥T2). No patients with positive nodes or metastatic disease were included.

Survival time was calculated starting at the date of diagnosis to the date of death. If death was not observed, patients were censored at the date of last followup. Cause of death was determined using SEER site-specific death codes and categorized as being due to prostate cancer or other causes.

Statistical analysis

Demographic and pathologic data were extracted for the entire cohort. Continuous variables were presented as a median (interquartile range) and tested with Kruskal–Wallis tests. Categorical variables were presented as N (%) and tested using χ^2 tests. Given that the brachytherapy only and the brachytherapy with external beam radiation groups behaved similarly on statistical analysis and that the number of patients in each cohort was small, these groups were combined and compared to those who received EBRT only. All-cause mortality (ACM) and PCSM were estimated for each treatment modality using Fine and Gray's subhazard regression methods for competing risks. Plots of cumulative incidence were created to visually depict the association between treatment and mortality. Eight-year cumulative incidence rates were estimated and compared using Wald-based tests. Univariable and multivariable subhazard regression methods were also performed within select subgroups. All statistical tests were two sided with statistical significance evaluated at the 0.05 alpha level and confidence intervals (CIs) presented at the 95% level. All analyses were performed using R v3.2.3 (R Development Core 2008).

Results

Our population included 15,505 men. Of those, 6555 (43.5%) had undergone EBRT only, and 8500 (56.5%) had received brachytherapy (BRT ± EBRT). The median followup time for the entire study population was 5.7 years (interquartile range: 4.25–7.1 years).

Patient demographic information and clinical characteristics are listed in Table 1, and the frequency of events by radiation type and followup stratified by survival status can be seen in eTable 1. Patients who received EBRT only tended to have higher grade disease (Grade III or IV) (47.1% vs. 30.1%), higher Gleason risk category (≥8) (12.3% vs. 4.9%), and a larger percentage were black (30.1% vs. 22.7%) ($p < 0.001$).

The overall 8-year cumulative incidence of PCSM for the study population was 1.9% (CI: 1.6–2.2), whereas the cumulative incidence of ACM was 8.3% (CI: 7.7–9.0). For patients treated with EBRT or BRT ± EBRT, the cumulative 8-year PCSM incidence was found to be 2.8% (CI: 2.2–3.4) and 1.2% (CI: 0.9–1.6), respectively ($p < 0.001$) (Fig. 1).

Univariable analysis examining PCSM (Table 2) demonstrated that brachytherapy was associated with lower PCSM risk (hazard ratio [HR] = 0.40; CI: 0.30–0.54; $p < 0.001$). Within the group aged 35–59 years, older age was numerically associated with a reduction in PCSM, but this result was not statistically significant (HR = 0.98; CI: 0.94–1.01; $p = 0.200$). High Gleason risk category, black race, higher TNM stage, and higher grade were all associated with greater PCSM risk ($p < 0.01$). On multivariable analysis (controlling for high Gleason risk category, age, race, marital

Table 1
Demographic and tumor characteristics of study population (n = 16,605)

Characteristic	EBRT (%)	BRT ± EBRT (%)	p-Value	Overall (%)
Overall	8081 (48.7)	8524 (51.3)		16,605
Outcome			<0.001	
Alive	7382 (91.4)	8099 (95.0)		15,481 (93.2)
Dead—prostate	172 (2.1)	65 (0.8)		237 (1.4)
Dead—nonprostate	527 (6.5)	360 (4.2)		887 (5.3)
Months of followup	66 (50, 84)	70 (53, 87)	<0.001	68 (51, 85)
Months of followup among survivors	68 (51, 86)	70 (54, 87)	<0.001	69 (53, 86)
Age (median [IQR])	56 (53, 58)	56 (53, 58)	0.002	56 (53, 58)
Age (mean ± SD)	55.1 ± 3.6	55.0 ± 3.7	0.002	55.1 ± 3.6
Age categorical			0.025	
≤45 years	134 (1.7)	183 (2.1)		317 (1.9)
46–60 years	7947 (98.3)	8341 (97.9)		16,288 (98.1)
Grade			<0.001	
III/IV	4344 (53.8)	2538 (30.1)		6912 (41.6)
NA	0 (0.0)	1 (0.0)		1 (0.0)
Gleason—risk category			<0.001	
Low risk = 6/7	6826 (84.5)	8104 (95.1)		14,930 (89.9)
High risk = 8+	1255 (15.5)	420 (4.9)		1675 (10.1)
Marital status			<0.001	
Married	4973 (61.5)	5964 (70.0)		10,937 (65.9)
Nonmarried	2563 (31.7)	2095 (24.6)		4658 (28.1)
NA	545 (6.7)	465 (5.5)		1010 (6.1)
Race			<0.001	
Black	2244 (27.8)	1932 (22.7)		4176 (25.1)
Other	5725 (70.8)	6510 (67.4)		12,235 (73.7)
NA	112 (1.4)	82 (1.0)		194 (1.2)
Region			<0.001	
North central	959 (11.9)	572 (6.7)		1531 (9.2)
Northeast	1399 (17.3)	1286 (15.1)		2685 (16.2)
South	1822 (22.5)	2926 (34.3)		4748 (28.6)
West	3901 (48.3)	3740 (43.9)		7641 (46.0)
Tumor (T) stage[a]			<0.001	
T1	5196 (64.3)	5969 (70.0)		11,165 (67.2)
T2+	2885 (35.7)	2555 (30.0)		5440 (32.8)

EBRT = external beam radiation therapy; BRT ± EBRT = brachytherapy with or without external beam; IQR = interquartile range.
Categorical variables present count (percent), whereas continuous measures present median (interquartile range) unless otherwise stated.
[a] N+, M1 were excluded.

status, TNM stage, and grade), brachytherapy continued to be associated with a significantly lower mortality risk (HR = 0.65; CI: 0.47–0.89; p = 0.008) (Table 3). Sensitivity analysis using propensity scores with these same predictors revealed identical results. Univariable and multivariable analyses examining ACM can be seen in eTable 2.

Subsequent univariable and multivariable analyses exploring PCSM stratified by Gleason risk group continued to show a reduction in mortality in each of these subgroups (Tables 4 and 5). Age was not associated with risk of PCSM among those with Gleason score ≤7, but among those with Gleason score ≥8, older patients had a significantly lower mortality risk (HR = 0.91; CI: 0.86–0.96; p = 0.001). Interaction terms between age and treatment were not significant, suggesting no differences in benefit across subgroups (eTable 3).

Discussion

Prostate cancer provides a unique situation in which several treatment modalities are available, but there is a lack of randomized studies to assist patients in choosing the treatment that is right for them. Because of this, young men often face difficult decisions regarding the management of their illness, and the inherent treatment risks, side effects, and quality of life implications become extremely important in their choice of treatment. These are some of the reasons why the best treatment for localized prostate cancer in young men continues to be strongly debated. This investigation sought to analyze PCSM in young men with clinically localized prostate cancer treated with EBRT only or BRT ± EBRT. In so doing, we hope to add to the debate regarding treatment options in this population of patients.

Our results demonstrated a statistically significant decrease in 8-year PCSM with the use of brachytherapy (BRT ± EBRT) when compared to EBRT alone (1.2% [CI: 0.9–1.6] and 2.8 [CI: 2.2–3.4]; $p < 0.001$). Furthermore, our univariable data showed that brachytherapy was associated with lower PCSM risk (HR = 0.40; CI: 0.30–0.54; $p \leq 0.001$) with an even more pronounced effect seen on multivariable analysis (HR = 0.65; CI:

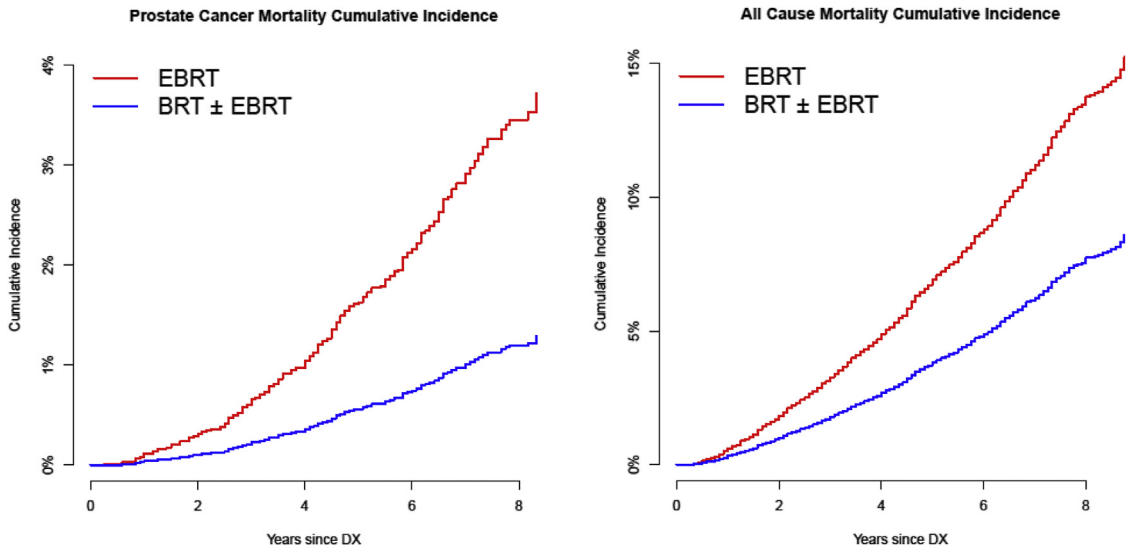

Fig. 1. Cumulative incidence curves for prostate cancer–specific mortality and all-cause mortality by treatment modality. BRT = brachytherapy; EBRT = external beam radiation.

0.47–0.89; $p = 0.008$). These results are consistent with those seen by Hoskin *et al.* (5) in their Phase III clinical trial exploring outcomes with dose escalation using an high-dose-rate (HDR) brachytherapy boost. They were able to demonstrate 5-, 7-, and 10-year relapse-free survival rates of 75%, 66%, and 46% for the boost group compared to 61%, 48%, and 39% for EBRT alone ($p = 0.04$, log-rank test), suggesting that an improvement in relapse-free survival can be realized with brachytherapy.

Clinical evidence demonstrates that escalated radiation dose strongly impacts biochemical outcomes in prostate cancer, with the best outcomes seen when doses of 75 Gy or higher are used (8–11). The challenge becomes achieving these high doses of radiation without exceeding the limits of tissue tolerance for the surrounding structures, particularly the bladder and rectum. Brachytherapy is a realistic means of achieving this balance. Martinez *et al.* (12) treated 207 patients with 46 Gy pelvic EBRT and increasing HDR brachytherapy boost doses (5.5–11.5 Gy/fraction) and were able to demonstrate improved 5-year biochemical control rates in the high-dose group (87% vs. 52%; $p < 0.001$). Grade 3 gastrointestinal and genitourinary complication rates were 0.5–9%. In a similar study, Zwahlen *et al.* (13) examined outcomes with dose escalation using HDR brachytherapy and three-dimensional conformal external beam radiotherapy (3DCRT), compared to treatment with 3DCRT alone. They found 5- and 7-year biochemical control rates of 82.5% and 80.3%, respectively, for the 3DCRT + BRT group and 81.3% and 71%, respectively, for 3DCRT alone. Grade 3 late urinary and

Table 2
Univariable analysis examining prostate cancer–specific mortality using the Fine and Gray proportional subhazards model for competing risks

Variable	HR (95% CI)	*p*-Value
Radiation type (vs. EBRT)		
BRT ± EBRT	0.34 (0.26.0–0.46)	<0.001
Gleason (vs. ≤7)		
High risk ≥ 8	9.96 (7.72–12.85)	<0.001
Age at diagnosis		
Years	0.98 (0.95–1.02)	0.330
Race (vs. non-black)		
Black	1.33 (1.01–1.75)	0.045
Marital status (vs. married)		
Unmarried	1.21 (0.92–1.60)	0.170
TNM stage (vs. T1)		
T2+	2.04 (1.58–2.63)	<0.001
Grade (vs. I/II)		
III/IV	8.34 (5.88–11.84)	<0.001

HR = hazard ratio; CI = confidence interval; EBRT = external beam radiation therapy; BRT ± EBRT = brachytherapy with or without external beam.

Table 3
Multivariable analysis examining prostate cancer–specific mortality using the Fine and Gray proportional subhazards model for competing risks

Variables	HR (95% CI)	*p*-Value
Radiation type (vs. EBRT)		
BRT ± EBRT	0.65 (0.48–0.89)	0.006
Gleason (vs. ≤7)		
High risk ≥ 8	4.68 (3.48–6.29)	<0.001
Age at diagnosis		
Years	0.98 (0.94–1.01)	0.200
Race (vs. non-black)		
Black	1.22 (0.90–1.64)	0.190
Marital status (vs. married)		
Unmarried	1.10 (0.82–1.47)	0.530
TNM stage (vs. T1)		
T2+	1.30 (0.99–1.70)	0.059
Grade (vs. I/II)		
III/IV	3.74 (2.46–5.70)	<0.001

HR = hazard ratio; CI = confidence interval; EBRT = external beam radiation therapy; BRT ± EBRT = brachytherapy with or without external beam.

Table 4
Multivariable analysis examining prostate cancer–specific mortality using the Fine and Gray proportional subhazards model for competing risks with interactions between Gleason risk category and treatment modality

Variables	HR (95% CI)	*p*-Value
Radiation type (vs. EBRT)		
BRT ± EBRT	0.99 (0.62–1.56)	0.950
Gleason (vs. = 7)		
Low risk ≤ 6	0.49 (0.20–1.19)	0.120
High risk ≥ 8	5.66 (3.97–8.07)	<0.001
Age at diagnosis		
Years	0.98 (0.94–1.01)	0.180
Race (vs. non-black)		
Black	1.18 (0.88–1.60)	0.270
Marital status (vs. married)		
Unmarried	1.11 (0.83–1.49)	0.470
Grade (vs. I/II)		
III/IV	1.50 (0.70–3.22)	0.300
Interactions		
BRT ± EBRT and low risk ≤6	0.45 (0.20–1.05)	0.064
BRT ± EBRT and high risk ≥8	0.54 (0.27–1.07)	0.075

HR = hazard ratio; CI = confidence interval; EBRT = external beam radiation therapy; BRT ± EBRT = brachytherapy with or without external beam.

Table 5
Univariable and multivariable analyses examining prostate cancer–specific mortality stratified by Gleason risk category using the Fine and Gray proportional subhazards model for competing risks

Variables	HR (95% CI)	*p*-Value
Univariable		
Low risk ≤ 7		
Radiation type (vs. EBRT)		
BRT ± EBRT	0.55 (0.38–0.80)	0.002
High risk ≥ 8		
Radiation type (vs. EBRT)		
BRT ± EBRT	0.50 (0.30–0.83)	0.007
Multivariable		
Low risk ≤ 7		
Radiation type (vs. EBRT)		
BRT ± EBRT	0.60 (0.40–0.89)	0.011
Age at diagnosis		
Years	1.02 (0.97–1.08)	0.370
Race (vs. non-black)		
Black	1.50 (0.97–2.33)	0.067
Marital status (vs. married)		
Unmarried	1.22 (0.80–1.86)	0.350
TNM stage (vs. T1)		
T2+	1.83 (1.26–2.67)	0.002
High risk ≥ 8		
Radiation type (vs. EBRT)		
BRT ± EBRT	0.53 (0.32–0.88)	0.014
Age at diagnosis		
Years	0.94 (0.90–0.99)	0.010
Race (vs. non-black)		
Black	1.11 (0.74–1.68)	0.610
Marital status (vs. married)		
Unmarried	1.02 (0.68–1.53)	0.920
TNM stage (vs. T1)		
T2+	1.06 (0.73–1.53)	0.760

HR = hazard ratio; CI = confidence interval; EBRT = external beam radiation therapy; BRT ± EBRT = brachytherapy with or without external beam.

rectal morbidity rates were 7.1% and 0%, respectively. As such, the combination of brachytherapy with eternal beam radiation not only achieves the escalated doses required for favorable outcomes but does so with minimal toxicity (14, 15).

Recent research, however, has suggested that high-risk prostate cancer represents a heterogeneous disease with variable outcomes dependent on the number of risk factors. Joniau *et al.* (16) developed a pretreatment prognostic model for prostate cancer–specific survival in which high Gleason risk disease was stratified into three prognostic subgroups: good, intermediate, and poor. They were able to demonstrate that overall survival, clinical progression-free survival, and histopathologic outcomes significantly worsened as you advanced from good to poor prognosis subgroups. Building on this work and the premise that some patients with high Gleason risk disease may benefit from less aggressive therapy, Muralidhar *et al.* (17) examined the PCSM in stratified high-risk prostate cancer patients treated with either EBRT alone or EBRT with a brachytherapy boost (EBRT + BT). They were able to establish similar 5-year PCSM in patients with favorable high-risk disease regardless of whether they were treated with EBRT + BT or EBRT alone (1.6% vs. 1.8%; $p = 0.258$). Their results also showed that those with an unfavorable prognosis had a significantly reduced rate of PCSM at 5 years if treated with EBRT + BT compared to EBRT alone (3.9% vs. 5.3%; $p = 0.022$). This not only supports the theory of the heterogeneous nature of high-risk prostate cancer but also supports the use of a brachytherapy boost in patients with unfavorable prognosis. A well-designed prospective randomized trial would be required to definitively determine the benefit or harm of a brachytherapy boost in these subsets of high-risk disease.

The question of age as an important predictor of PCSM is a significant one. This has become even more crucial due to the routine implementation of prostate specific antigen screening and increased public awareness of prostate cancer which has resulted in greater numbers of younger patients being diagnosed with this disease (18). Age is a significant contributing factor in decision-making and often dictates the treatments that are offered to patients. In fact, one population-based study established not only that young men comprise an increasingly large proportion of patients with newly diagnosed prostate cancer, but also that physicians showed a strong bias toward treatment with radical prostatectomy in this subset of patients (19). Furthermore, younger men treated with radiation therapy may be more likely to receive higher doses of radiation than older men, and as previously mentioned, escalated radiation dose has been shown to be associated with improved outcomes. These age-related differences in approach stem from the perception that younger patients have more aggressive disease and that radiation therapy may produce poorer clinical outcomes and higher relapse rates attributable to longer life expectancy (1).

Our results showed no statistically significant association between age and PCSM on univariable and multivariable analyses. However, those diagnosed at a younger age and with a Gleason score ≥8 had poorer prostate cancer–specific survival than older patients with Gleason score ≥8 ($p = 0.001$). Furthermore, interaction terms between age and treatment were not significant and thus do not suggest that a particular age range showed a greater difference between outcomes in the two groups studied. Patients would therefore benefit equally from radiation therapy regardless of age.

This is in keeping with the results seen in the published literature. Shapiro *et al.* (20), in their study of the long-term outcomes in younger men (<60 yrs) following permanent prostate brachytherapy, found that age was not a significant predictor of outcome. They demonstrated, via a subgroup analysis, that younger patients showed similar biochemical recurrence rates to that of older patients and concluded that brachytherapy can be used as definitive first-line treatment option for men of all ages. They suggested, however, that age can be used as a unique surrogate of other strongly associated, coexisting factors. Other recent studies have drawn similar conclusions (3, 21).

The lack of age-related differences in outcomes may be explained by the fact that when dose-escalated ranges of radiation are used, outcomes are equivalent between younger and older patients. This had previously been discussed by both Zelefsky *et al.* (22) and Klayton *et al.* (2) who concluded that biochemical control is equivalent across age groups once appropriate doses of radiation are used.

Our study specifically looked at patients who received EBRT vs. BRT ± EBRT. We made no distinction between patients receiving brachytherapy as monotherapy and those who received dose escalation utilizing a brachytherapy boost. We also made no differentiation between low-dose-rate and HDR brachytherapy. These are limitations of our study and restrict the interpretation of our results.

Our study has other inherent limitations. Although the SEER database remains the definitive resource for cancer incidence and survival data in the United States, there are potential shortcomings to its use that warrant discussion. Although it contains retrospective information on over six million *in situ* and invasive cancer cases (7), its coverage is limited to only 28% of the total U.S. population, and minority groups and urban communities tend to be overrepresented. This compromises the generalizability of results. In addition, data regarding particular clinicopathologic factors of prognostic significance, including information regarding tumor recurrence, late metastasis, prostate specific antigen readings, hormonal therapy, and specifics of radiation therapy (such as technology, dose, isotope used, and dose rate), are not readily available. Information on toxicity and quality of life parameters were also not obtainable. Furthermore, because data are gathered from centers all across the country, quality assurance and the standardization of treatment among patients cannot be guaranteed (23). Finally, advances in radiotherapy protocols ensure that current treatments are vastly superior to those offered a decade ago, and as a result, data may not accurately reflect the outcomes and risks for men treated in the 21st century. In the 1990s, the predominant treatment technique was conventional EBRT to a median dose of 65–70 Gy. Since that time, the availability of 3D conformal radiation treatment planning and the introduction of intensity-modulated radiation therapy have radically improved outcomes and minimized long-term toxicity when compared to conventional EBRT (9). Notwithstanding these deficiencies, this analysis remains pertinent as it directly reflects practice patterns in the United States and allows for a baseline comparison of outcomes in prostate cancer.

Conclusions

In men ≤60 years of age with prostate cancer, radiation therapy continues to offer excellent outcomes. After adjusting for relevant variables, the use of brachytherapy was associated with reduced PCSM compared to treatment with EBRT alone. There were no differences in this association across Gleason risk category or age, suggesting that these groups would benefit equally from radiation therapy.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brachy.2016.12.010.

References

[1] Rosser CJ, Chichakli R, Levy LB, *et al*. Biochemical disease-free survival in men younger than 60 years with prostate cancer treated with external beam radiation. *J Urol* 2002;168:536–541.
[2] Klayton TL, Ruth K, Horwitz EM, *et al*. Young age under 60 years is not a contraindication to treatment with definitive dose escalated radiotherapy for prostate cancer. *Radiother Oncol* 2011;101:508–512.
[3] Burri RJ, Ho AY, Forsythe K, *et al*. Young men have equivalent biochemical outcomes compared with older men after treatment with brachytherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2010;77:1315–1321.
[4] Morris WJ, Tyldesley S, Pai HH, *et al*. ASCENDE-RT: a multicenter, randomized trial of dose-escalated external beam radiation therapy (EBRT-B) versus low-dose-rate brachytherapy (LDR-B) for men with unfavorable-risk localized prostate cancer. *J Clin Oncol* 2015;33(Suppl 7):3.
[5] Hoskin PJ, Rojas AM, Bownes PJ, *et al*. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012;103:217–222.
[6] Xiang M, Nguyen PL. Significant association of brachytherapy boost with reduced prostate cancer-specific mortality in contemporary patients with localized, unfavorable-risk prostate cancer. *Brachytherapy* 2015;14:773–780.
[7] Surveillance, Epidemiology, and End Results (SEER) Program (Available at: www.seer.cancer.gov) Research Data (1973-2010), National Cancer Institute, DCCPS, Surveillance Research Program,

Surveillance Systems Branch, released April 2013. Accessed July 30, 2013.

[8] Pollack A, Zagars GK, Starkschall G, *et al*. Prostate cancer radiation dose response: results of the M.D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53:1097−1105.

[9] Zelefsky MJ, Fuks Z, Hunt M, *et al*. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *J Urol* 2001;166:876−881.

[10] Hanks GE, Hanlon AL, Pinover WH, *et al*. Dose selection for prostate cancer patients based on dose comparison and dose response studies. *Int J Radiat Oncol Biol Phys* 2000;46:823−832.

[11] Lyons JA, Kupelian PA, Mohan DS, *et al*. Importance of high radiation doses (72 Gy or greater) in the treatment of stage T1−T3 adenocarcinoma of the prostate. *Urology* 2000;55:85−90.

[12] Martinez AA, Gustafson G, Gonzalez J, *et al*. Dose escalation using conformal high-dose-rate brachytherapy improves outcome in unfavorable prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;53:316−327.

[13] Zwahlen DR, Andrianopoulos N, Matheson B, *et al*. High dose-rate brachytherapy in combination with conformal external beam radiotherapy in the treatment of prostate cancer. *Brachytherapy* 2010;9:27−35.

[14] Duchesne GM, Williams SG, Das R, *et al*. Patterns of toxicity following high-dose-rate brachytherapy boost for prostate cancer: mature prospective phase I/II study results. *Radiother Oncol* 2007;84:128−134.

[15] Eulau SM, Van Hollebeke L, Cavanagh W, *et al*. High dose rate 192Iridium brachytherapy in localized prostate cancer: results and toxicity with maximum follow-up of 10 years. *Int J Radiat Oncol Biol Phys* 2000;48:149.

[16] Joniau S, Briganti A, Gontero P, *et al*. Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study. *Eur Urol* 2015;67:157−164.

[17] Muralidhar V, Xiang M, Orio PF, *et al*. Brachytherapy boost and cancer-specific mortality in favorable high-risk versus other high-risk prostate cancer. *J Contemp Brachytherapy* 2016;8:1−6.

[18] Post PN, Stockton D, Davies TW, *et al*. Striking increase in incidence of prostate cancer in men aged < 60 years without improvement in prognosis. *Br J Cancer* 1999;79:13−17.

[19] Lin DW, Porter M, Montgomery B. Treatment and survival outcomes in young men diagnosed with prostate cancer: a population based cohort study. *Cancer* 2009;115:2863−2871.

[20] Shapiro EY, Rais-Bahrami S, Morgenstern C, *et al*. Long-term outcomes in younger men following permanent prostate brachytherapy. *J Urol* 2009;181:1665−1671.

[21] Tward JD, Lee CM, Pappas LM, *et al*. Survival of men with clinically localized prostate cancer treated with prostatectomy, brachytherapy, or no definitive treatment: impact of age at diagnosis. *Cancer* 2006;107:2392−2400.

[22] Zelefsky MJ, Marion C, Fuks Z, *et al*. Improved biochemical disease-free survival of men younger than 60 years with prostate cancer treated with high dose conformal external beam radiotherapy. *J Urol* 2003;1705:1828−1832.

[23] Spencer BA, Miller DC, Litwin MS, *et al*. Variations in quality of care for men with early-stage prostate cancer. *J Clin Oncol* 2008;26:3735−3742.