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Comparative effectiveness of treatments for high-risk prostate cancer patients

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Abstract

Background: To determine the comparative effectiveness of primary radical prostatectomy (RP) compared to external bean radiation therapy (EBRT) with androgen deprivation therapy (ADT), or EBRT plus brachytherapy (BT) with or without ADT among Medicare fee-for-service beneficiaries with high-risk prostate cancer, for 10-year, mortality (overall and prostate cancer-specific), complications, health service use, and cost.

Methods: This population-based cohort study used Surveillance, Epidemiology, and End Results − Medicare data. Eligible patients were men aged 66 or older and diagnosed with high-risk prostate cancer between 1996 and 2003. Outcomes evaluated were 10-year overall mortality and prostate cancer-specific mortality, complications, health service use, and cost. We used Cox regression, Poisson regression, and Generalized Linear Model (GLM) log-link models to assess the outcomes.

Main findings: The 10-year overall mortality of EBRT + ADT was comparable to that of the RP group (hazard ratio [HR] = 1.09, confidence interval [CI] = 0.72−1.66). The EBRT + BT ± ADT group had overall survival advantage compared to RP (HR = 0.47, CI = 0.31−0.73). Compared to the RP group, EBRT + ADT group had higher 10-year prostate cancer-specific mortality (HR = 2.19, CI = 1.92−5.21). Both EBRT + ADT and EBRT + BT ± ADT were associated with higher 10-year cost (odds ratio = 1.72, CI = 1.35−2.20; and odds ratio = 1.63, CI = 1.29−2.04), compared to RP group. Complications and health service use varied across 3 treatment groups and across phases of care.

Principal conclusions: Our results also demonstrate long-term overall survival benefits for EBRT + BT ± ADT, and greater bowel and bladder side effects over a decade, compared to RP. The RP group had advantage for long-term prostate-cancer specific mortality, compared to EBRT + ADT group. Thus, RP can provide superior cancer control with clear cost advantage for older men with high-risk disease. In terms of value proposition, our results support RP as preferred treatment option, compared to EBRT + ADT and EBRT + BT ± ADT for high-risk prostate cancer patients. © 2019 Elsevier Inc. All rights reserved.

Keywords: High-risk prostate cancer; SEER-Medicare elderly; Comparative effectiveness; Radical prostatectomy; Radiation therapy; Androgen deprivation therapy

1. Introduction

Radical prostatectomy (RP), external bean radiation therapy (EBRT) with androgen deprivation therapy (ADT), and EBRT with brachytherapy (BT), with or without ADT, are competing treatment modalities for high-risk prostate cancer (PCa). Between 20% and 30% of PCa patients have high-risk disease [1,2]. Due to the supposed increased risk of cancer recurrence and uncertain oncologic outcomes, surgical management was often excluded in high-risk individuals [3,4]. Since then, studies have shown comparable oncologic outcomes for RP relative to RT ± ADT for high-risk disease [3,5]. Use of RP in aggressive disease patients has increased

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over the last decade, thereby confirming its role as a reasonable treatment option in selected patients [3,5–7].

In the absence of prospective, randomized, comparative effectiveness studies of treatment modalities for high-risk PCa, observational studies can provide clinical and policy guidance [8]. Currently there is no consensus regarding optimal management strategy for high-risk PCa [8–11]. Guidelines (NCCN, AUA, and EAU) recommend EBRT + ADT, EBRT + BT, with or without ADT; and RP, for treating high-risk disease. The retrospective series to date comparing outcomes of RP and RT treatment high-risk PCa demonstrated widely disparate results, with some reporting improved outcomes after RP [12,13], or after RT [14], and a few noting equivalent efficacy [15]. These studies involved different definitions of high-risk PCa, evaluated disparate outcomes, and included smaller sample with short-term follow-up. Additionally, RP patients were younger and healthier than those receiving RT; these differences may further obscure the ability of these studies to establish the impact of treatment modality on outcomes [16–20].

A study using National Cancer Database reported that RP, and EBRT + BT ± ADT, had comparable survival, and EBRT + ADT had lower survival [16]. Another multicenter study reported that for PCa patients with Gleason score between 9 and 10, EBRT + BT + ADT was associated with significantly better PCa-specific mortality and longer time to distant metastasis compared with EBRT + ADT or RP [18]. While these results are important, comparative effectiveness of the treatment modalities related to complications, health service use, and cost over a long follow-up is unclear. The objective of our study was to analyze survival (overall and PCa-specific), health services use (emergency room [ER], inpatient and outpatient visits), complications, and cost between RP, EBRT + ADT, and EBRT + BT ± ADT, among fee-for-service Medicare enrollees with high-risk PCa.

2. Methods

2.1. Data sources

This retrospective cohort study used Surveillance, Epidemiology, and End Results (SEER) − Medicare data from the National Cancer Institute, which links SEER registries and Medicare enrollees with cancer residing in SEER regions. The SEER program collects data on cancer incidence, treatment, and mortality from 16 SEER sites and encompasses 26% of the US population [21].

Our cohort consisted of men aged ≥66 years, and diagnosed with PCa between 1996 and 2003. We excluded patients younger than 66 at diagnosis to ensure sufficient claims prior to PCa diagnosis for comorbidity calculation. We also excluded patients with low or intermediate PCa risk, Health Maintenance Organization (HMO) enrollees, and those without 13 months coverage prediagnosis and continuous Part A and B coverage, postdiagnosis. Institutional Review Board approved this study.

2.2. Measurement strategy

2.2.1. High-risk PCa cohort

High-risk, nonmetastatic PCa was defined as PCa with no evidence of metastasis (N0, M0) and at least one of the following criteria: Gleason score of ≥8, or clinical stage ≥T2c [3,22].

2.2.2. Dependent variables

Dependent variables were mortality (overall and PCa-specific), cost (reimbursements), complications, and health service use (ER, inpatient, and outpatient visits). From SEER's Patient Entitlement and Diagnosis Summary File (PEDSF), we obtained overall mortality data. Since SEER reports month/year of death, we assigned 15 as day of death to construct SEER date of death. We constructed Medicare date of death using Medicare day/month/year of death. We coded a patient as deceased if SEER and/or Medicare reported so. For overall mortality, those alive as of December 31, 2013 were censored. We obtained SEER reported PCa-specific mortality from PEDSF and censored it as of December 31, 2011. Three categories of complications, genitourinary (GU), gastrointestinal (GI), and erectile dysfunction (ED) were identified (see Supplementary eTable 1 for codes). We identified 3 phases of care, "treatment phase" (1-year postdiagnosis), "follow-up phase" (9 years after treatment phase), and "terminal phase" (1 year prior to death).

2.2.3. Covariates

Our analyses adjusted for demographic and socio-economic characteristics, disease severity, and comorbidity. Charlson comorbidity score was developed using inpatient, outpatient, and provider claims in the year prior to diagnosis [23]. We identified 3 mutually exclusive categories of treatment − RP, EBRT + ADT, and EBRT + BT ± ADT using PEDSF, inpatient, outpatient, and provider files (Supplementary eTable 1).

2.3. Analytical strategy

We tested for differences in baseline characteristics by treatment groups, using standard t tests and χ^2 tests. We used 3 models to analyze the effects of treatment. Model 1 estimated the unadjusted association of EBRT + ADT and EBRT + BT ± ADT with outcomes, with RP as reference category. Treatment of PCa can affect outcomes; however, treatment assignments are not random. Using multinomial logistic regression, for each patient we estimated the propensity of receiving either RP, EBRT + ADT, or EBRT + BT ± ADT based on age, race and ethnicity, geographic location, socioeconomic status, marital status, and comorbidity score [24]. Next, in Model 2, we modeled the associations between treatment group and outcomes, weighted by the inverse probability of propensity score (PS). In Model 3, we employed the economic technique of instrumental variable (IV) to address the

unmeasured treatment bias [25]. An appropriate IV is one that is associated with the exposure, but not with the outcome(s). It is possible that certain geographic regions use RP treatment more frequently, and therefore patients from these regions may be more likely to receive RP. Therefore, for each hospital referral region in our study, we determined the proportion of patients who received RP. We categorized hospital referral region regions as high/low treatment region using the median as cutoff and used this variable as an IV. We evaluated the strength of the IV using *F* statistic. The *F* statistic of a strong IV must be larger than 10 (ours was in excess of 10). We used Durbin-Wu-Hausman test of endogeneity to ensure that IV approach was essential for our model.

We used log-link Generalized Linear Models (GLM) models for analyzing cost and Cox models for analyzing survival. Poisson regression (zero inflated) was used to study the association between treatment groups and health services use and complications across phases of care. We used Statistical Analysis System, Version 9.4 (Statistical Analysis System Institute, Cary, NC) for analysis.

3. Results

3.1. Sample characteristics

Between 1996 and 2003, 6,296 PCa patients met our study criteria (Fig. 1). Of these, 677 received RP, 4,141 received EBRT + ADT, and 1,478 received EBRT + BT ± ADT. As seen from Table 1, a higher proportion of RP patients were aged 66 to 72, compared to EBRT + ADT (27%) and EBRT + BT ± ADT (46%) ($P< 0.0001$). The EBRT + BT ± ADT group had a higher proportion of whites (87%), compared to RP and EBRT + ADT (85% and 83% respectively, $P= 0.0015$). The RP group had a lower proportion of those with one or more comorbidity (28%), compared to EBRT + ADT and EBRT + BT ± ADT (37% and 32%, respectively, $P< 0.0001$). Comparison after PS weighing (Table 1) showed that except for age and race, other variables remained significantly different across groups.

3.2. Overall mortality

The EBRT + ADT group had higher hazard compared to RP, whereas the hazard for EBRT + BT ± ADT was comparable to RP (Table 2). After adjusting for PS and IV, the hazard of overall mortality was comparable between EBRT + ADT and RP (hazard ratio [HR] = 1.09, confidence interval [CI] =0.72, 1.66). The EBRT + BT ± ADT group had survival advantage compared to RP (HR = 0.47, CI = 0.31, 0.73). Survival curves Fig. 2A, for overall mortality cross near $S(t) = 0.9$ and $S(t) = 0.8$. A test of the proportional-hazards assumption yielded $\chi^2 = 65.8$, $P < 0.0001$. In the initial 2-year period, EBRT + ADT and EBRT + BT ± ADT had survival advantage over RP. The survival was higher for RP than EBRT + ADT between year 2 and 8, and for both radiation groups beyond year 8. Tests (log rank, Wilcoxon, Tarone, Peto, Modified Peto, and Fleming(1); all $P< 0.0001$), indicated significantly different effects of treatment groups.

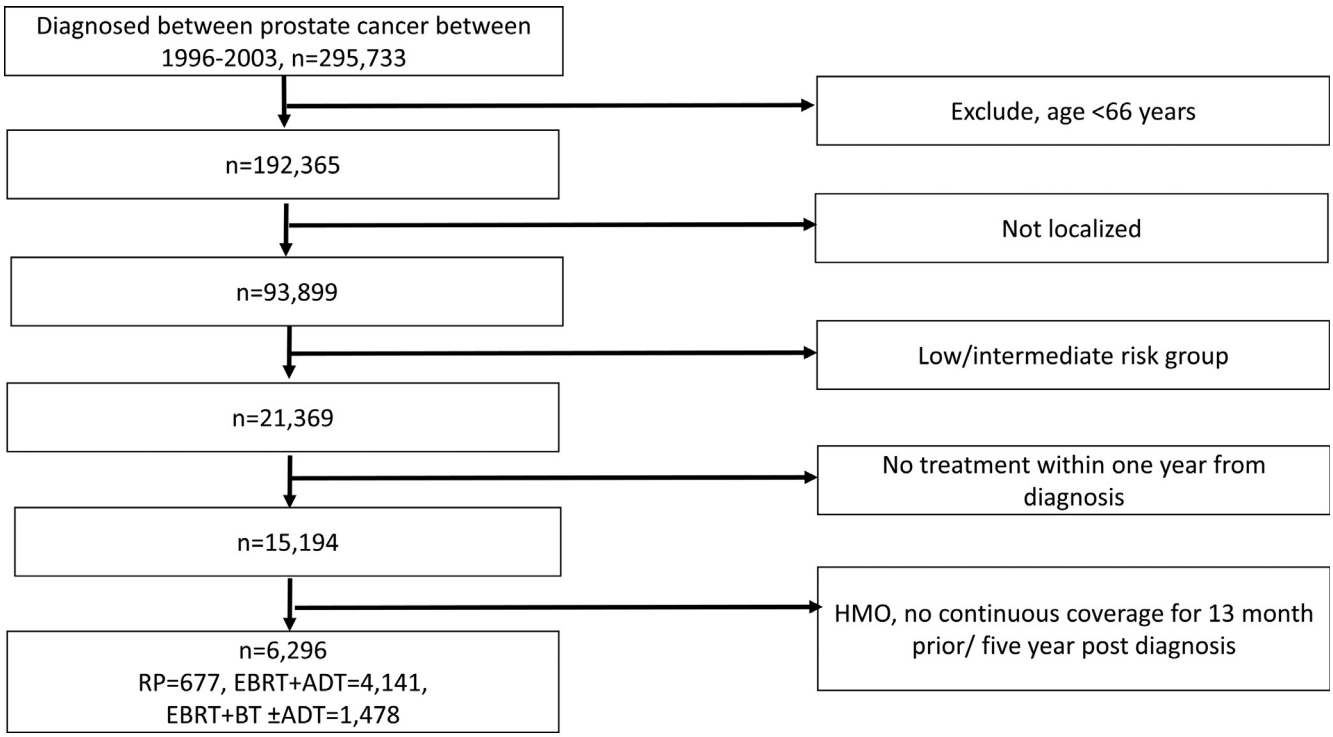

Fig. 1. Cohort selection process for prostate cancer patients diagnosed between 1996 and 2003.

Table 1
Personal and clinical characteristics of men aged ≥66 years, diagnosed with prostate cancer between 1996 and 2003 (n = 6,296).

Demographic	RP $n = 677$	EBRT + ADT $n = 4,141$	EBRT + BT ± ADT $n = 1,478$	Unadjusted P	Weighted P
Age in years, *n* (%)					
66–72	456 (67.36)	1,114 (26.90)	678 (45.87)	<0.0001	0.1769
73–77	120 (17.73)	1,313 (31.71)	538 (36.40)		
≥78	101 (14.92)	1,714 (41.39)	262 (17.73)		
Race, *n* (%)					
White	578 (85.38)	3,425 (82.71)	1,285 (86.94)	0.0015	0.9504
African American	66 (9.75)	432 (10.40)	126 (8.53)		
Asian	— *	138 (3.33)	22 (1.48)		
Hispanic	13 (1.95)	82 (1.98)	23 (1.56)		
Other	— *	64 (1.55)	22 (1.48)		
Geography, *n* (%)					
Metro	552 (81.54)	3,371 (81.41)	1,278 (86.17)	<0.0001	0.0119
Urban	20 (2.95)	74 (1.79)	20 (1.35)		
Rural	105 (15.51)	696 (16.81)	180 (12.18)		
Marital status, *n* (%)					
Married	531 (78.43)	2,605 (62.91)	1149 (77.74)	<0.0001	0.0248
Comorbidity score, *n* (%)					
0	489 (77.23)	2,580 (62.34)	1,010 (68.34)	<0.0001	0.0002
1	171 (25.26)	1,358 (32.79)	422 (28.55)		
≥2	17 (2.56)	203 (4.90)	46 (3.11)		
Socioeconomic status, *n* (%)					
High	350 (53.44)	2,021 (50.31)	846 (58.43)	<0.0001	0.0114
Medium	145 (22.14)	910 (22.65)	279 (19.29)		
Low	160 (24.43)	1,086 (27.04)	323 (922.31)		

ADT = androgen deprivation therapy; BT = brachytherapy; EBRT = external bean radiation therapy; RP = radical prostatectomy.
* Numbers not reported due to small cell size.

Table 2
Association between treatment groups and outcomes (n = 6,296).

	Overall mortality		Prostate cancer-specific mortality		Cost	
	HR	95%CI	HR	95% CI	OR	95% CI
Model 1: Unadjusted						
EBRT + ADT	2.07	1.81, 2.36	2.97	2.09, 4.22	1.29	1.20, 1.39
EBRT + BT± ADT	1.05	0.90, 1.22	1.49	1.01, 2.20	1.24	1.14, 1.34
Surgery alone (reference)						
Model 2: Propensity score IPTW adjusted						
EBRT + ADT	0.91	0.81, 1.02	1.58	1.21, 2.05	1.33	1.24, 1.43
EBRT + BT ± ADT	0.54	0.47, 0.61	0.81	0.59, 1.11	1.28	1.18, 1.39
Surgery alone (reference)						
Model 3: Instrumental variable adjusted						
EBRT + ADT	1.09	0.72, 1.66	2.19	1.92, 5.21	1.72	1.35, 2.20
EBRT + BT ± ADT	0.47	0.31, 0.73	1.15	0.41, 3.22	1.63	1.29, 2.04
Surgery alone (reference)						

ADT = androgen deprivation therapy; BT = brachytherapy; CI = confidence interval; EBRT = external bean radiation therapy; HR = hazard ratio; OR = odds ratio.

3.3. PCa-specific mortality

Unadjusted comparison (Model 1) showed that EBRT + ADT and EBRT + BT ± ADT had higher hazard of PCa-specific mortality, compared to RP (Table 2). After adjusting for PS and IV, EBRT + ADT had higher hazard of 10-year PCa-specific mortality (HR = 2.19, CI = 1.92, 5.21), compared to RP. Survival curves for PCa-specific mortality (Fig. 2C) cross at approximately year 2 and 4. A test of proportional-hazards assumption yielded $\chi^2 = 70.7$, $P < 0.0001$. For the first 2 years, RP had impaired survival, compared to both radiation groups. Survival advantage of RP began to improve at year 2, and was higher than both radiation groups after year 4, indicating better cancer

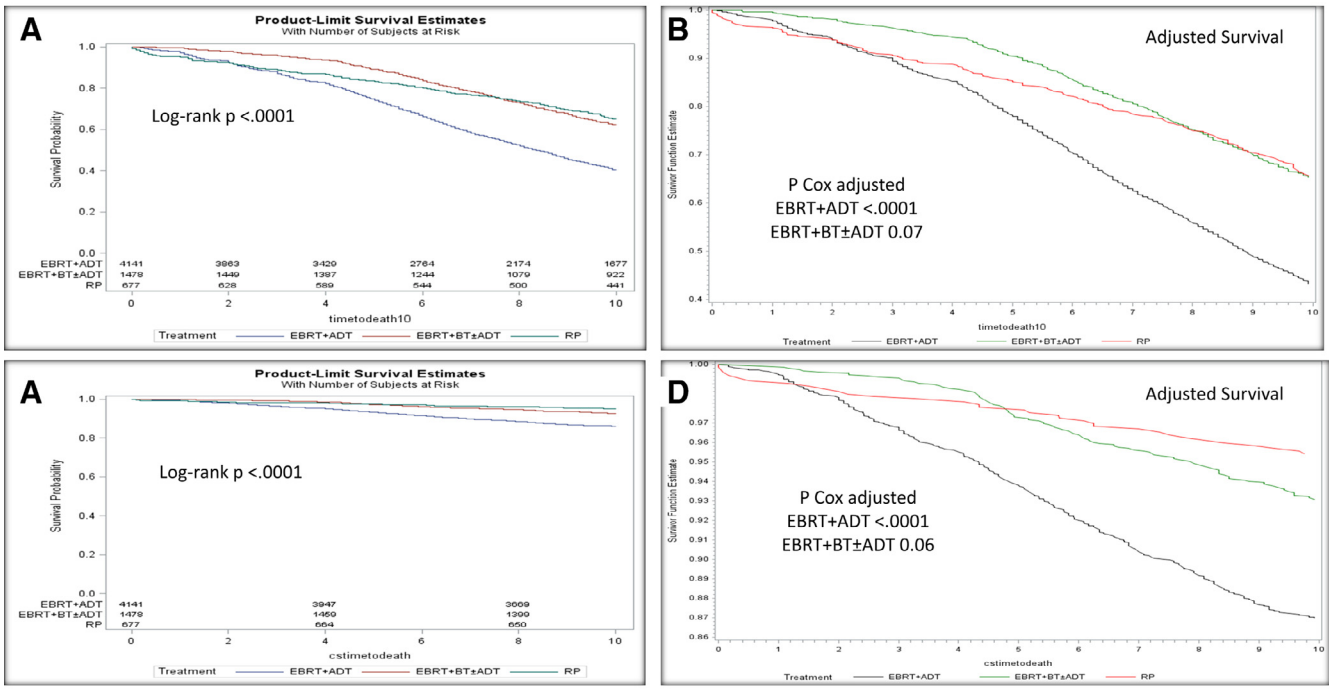

Fig. 2. Overall and PCa-specific survival. Kaplan-Meier curves for overall survival, unadjusted (A), adjusted (B); PCa-specific survival, unadjusted (C), adjusted (D); ADT=androgen deprivation therapy; BT=brachytherapy; CI=confidence interval; EBRT=external bean radiation therapy; HR=hazard ratio; PCa=prostate cancer; P=radical prostatectomy.

control. Tests (log rank, Wilcoxon, Tarone, Peto, Modified Peto, and Fleming(1); all $P< 0.0001$), indicated significantly different effects of treatment groups.

3.4. Cost of care

Compared to RP, EBRT + ADT, and EBRT + BT ± ADT groups had higher cost (Table 2). The PS adjustment showed that EBRT + ADT had 33% higher cost, and EBRT + BT ± ADT had 28% higher cost compared to RP. These numbers were 72% and 63%, respectively for IV models.

3.5. Phase-specific health service use

3.5.1. Emergency room visits

In the treatment phase, expected number of ER visits was not different for EBRT + ADT, and was 14% lower for EBRT + BT ± ADT, compared to RP (Table 3). In the follow-up phase, this number was higher for EBRT + ADT and EBRT + BT ± ADT groups (22% and 23%, respectively), compared to RP. In the terminal phase, compared to RP, ER visits were 62% higher for EBRT + ADT and 20% higher for EBRT + BT ± ADT. The PS and IV models yielded similar results.

3.5.2. Inpatient visits

During treatment phase, expected number of inpatient visits for both EBRT + ADT and EBRT + BT ± ADT groups was 71 % lower, compared to RP. In follow-up phase, this number was 48% higher for EBRT + ADT and 51% higher for EBRT + BT ± ADT, compared to RP. During terminal phase, compared to RP, inpatient visits were 60% higher for EBRT + ADT and 17% higher for EBRT + BT ± ADT.

3.5.3. Outpatient visits

In treatment phase, expected number of outpatient visits for EBRT + ADT and EBRT + BT ± ADT was higher (69% and 79%, respectively), compared to RP. During follow-up phase, this number was 20% higher for EBRT + ADT and 24% higher for EBRT + BT ± ADT, compared to RP. In terminal phase, compared to RP, outpatient visits were 86% higher for EBRT + ADT and 31% higher for EBRT + BT ± ADT.

3.6. Phase-specific complications

3.6.1. Genitourinary

In treatment phase, expected number of GU complications was 49% lower for EBRT + ADT, and 21% lower for EBRT + BT ± ADT, compared to RP (Table 3). In follow-up phase, this number was 28% higher for EBRT + BT ± ADT. In terminal phase, compared to RP, number of GU complications was 30% higher for EBRT + ADT.

3.6.2. Gastrointestinal

In treatment phase, expected number of GI complications was 20% higher for EBRT + ADT, and 31% higher

Table 3
Phase-specific Poisson regression for health service use and complications.

	Health resource utilization, OR (95% CI)			Complications, OR (95% CI)		
	ER	Inpatient	Outpatient	GU	GI	ED
Covariate adjusted						
Treatment phase						
EBRT + ADT	0.91 (0.81, 1.02)	0.29 (0.27, 0.31)	1.69 (1.62, 1.78)	0.51 (0.45, 0.57)	1.20 (1.01, 1.49)	0.29 (0.23, 0.36)
EBRT + BT ± ADT	0.86 (0.75, 0.98)	0.29 (0.26, 0.32)	1.79 (1.71, 1.88)	0.79 (0.71, 0.90)	1.31 (1.06, 1.62)	0.42 (0.34, 0.52)
Follow-up phase						
EBRT + ADT	1.22 (1.15, 1.29)	1.48 (1.39 1.58)	1.20 (1.18, 1.23)	1.08 (0.95, 1.20)	1.09 (1.01, 1.23)	0.55 (0.47, 0.64)
EBRT + BT ± ADT	1.23 (1.16, 1.31)	1.51 (1.41, 1.60)	1.24 (1.21, 1.27)	1.28 (1.13, 1.45)	1.24 (1.10, 1.39)	0.89 (0.77, 1.04)
Terminal phase						
EBRT + ADT	1.62 (1.46, 1.79)	1.60 (1.46, 1.76)	1.86 (1.17, 1.99)	1.30 (1.04, 1.63)	1.55 (1.22, 1.99)	1.12 (0.46, 2.71)
EBRT + BT ± ADT	1.20 (1.07, 1.35)	1.17 (1.06, 1.30)	1.31 (1.21, 1.42)	1.07 (0.84, 1.38)	1.23 (0.94, 1.61)	1.62 (0.65, 4.02)
Propensity score adjusted						
Treatment phase						
EBRT + ADT	0.81 (0.73, 0.89)	0.29 (0.26, 0.31)	1.71 (1.64, 1.79)	0.47 (0.42, 0.52)	1.14 (1.05, 1.36)	0.32 (0.26, 0.39)
EBRT + BT ± ADT	0.74 (0.65, 0.83)	0.29 (0.26, 0.31)	1.84 (1.76, 1.93)	0.73 (0.64, 0.81)	1.29 (1.06, 1.57)	0.49 (0.39, 0.63)
Follow-up phase						
EBRT + ADT	1.36 (1.29, 1.44)	1.68 (1.58 1.79)	1.38 (1.32, 1.38)	1.16 (1.03, 1.30)	1.27 (1.13, 1.42)	0.62 (0.53, 0.73)
EBRT + BT ± ADT	1.39 (1.32, 1.47)	1.74 (1.63, 1.86)	1.43 (1.40, 1.47)	1.40 (1.24, 1.59)	1.48 (1.31, 1.68)	1.05 (0.88, 1.24)
Terminal phase						
EBRT + ADT	1.49 (1.38, 1.63)	1.55 (1.43, 1.68)	1.62 (1.53, 1.72)	1.02 (0.86, 1.21)	1.48 (1.20, 1.83)	0.94 (0.43, 2.07)
EBRT + BT ± ADT	1.08 (1.07, 1.19)	1.11 (1.01, 1.22)	1.15 (1.07, 1.23)	0.79 (0.65, 0.97)	1.14 (0.89, 1.45)	1.50 (0.65, 3.46)
Instrumental variable adjusted						
Treatment phase						
EBRT + ADT	0.61 (0.31, 1.20)	0.33 (0.19, 0.59)	1.71 (1.36, 2.15)	0.17 (0.07, 0.38)	3.31 (2.06, 10.37)	0.14 (0.03, 0.62)
EBRT + BT± ADT	0.76 (0.40, 1.43)	0.38 (0.23, 0.62)	1.49 (1.21, 1.85)	0.75 (0.39, 1.42)	1.38 (0.50, 3.82)	0.34 (0.09, 1.22)
Follow-up phase						
EBRT + ADT	2.78 (2.05, 3.79)	2.46 (1.79 3.39)	1.88 (1.66, 2.12)	0.80 (0.39, 1.63)	1.62 (0.80, 3.27)	0.21 (0.07, 0.62)
EBRT + BT± ADT	1.88 (1.42, 2.49)	1.89 (1.41, 2.53)	1.03 (1.02, 1.15)	1.31 (1.11, 2.43)	1.42 (0.77, 2.63)	1.12 (0.45, 2.75)
Terminal phase						
EBRT + ADT	3.67 (2.18, 6.19)	4.65 (2.93, 7.37)	2.90 (2.09, 4.14)	3.83 (1.07, 3.67)	9.39 (2.37, 17.0)	0.49 (0.12, 1.41)
EBRT + BT± ADT	1.21 (0.76, 1.94)	1.87 (1.21, 2.87)	1.02 (1.01, 1.43)	0.67 (0.22, 2.05)	1.17 (0.37, 3.74)	2.14 (0.38, 12.05)

ADT = androgen deprivation therapy; BT = brachytherapy; CI = confidence interval; EBRT = external bean radiation therapy; ED = erectile dysfunction; ER = emergency room; GI = gastrointestinal; OR = odds ratio.

for EBRT + BT ± ADT, compared to RP. During follow-up phase, this number was 24% higher for EBRT + BT ± ADT. In terminal phase, compared to RP, number of GU complications was 55% higher for EBRT + ADT.

3.6.3. *Erectile dysfunction*

During treatment phase, expected number of ED complications was 71% lower for EBRT + ADT, and 58% lower for EBRT + BT ± ADT, compared to RP. In follow-up phase, compared to RP, this number was 45% lower for EBRT + ADT. In terminal phase, number of ED complications was comparable across groups.

4. Discussion

This study has several pertinent findings. In the elderly Medicare population, 10-year overall mortality was comparable between RP and EBRT + ADT. On the other hand, EBRT + BT ± ADT had overall survival advantage compared to RP that continued until year 8 of follow-up. RP was superior to EBRT + ADT for PCa-specific mortality between years 2 and 10 of follow-up. However, 10-year PCa-specific mortality was comparable between EBRT + BT ± ADT and RP. The 10-year cost analysis demonstrated that this clinical equivalence was associated with 30% to 70% lower overall cost for RP.

For phase-specific health services use, RP was associated with lower health service use during follow-up and terminal phases, compared to both radiation groups. Additionally, RP was associated with early (treatment phase) GU and ED complications, which emerged later for the radiation groups. This indicates opportunities for treatment-specific quality improvement initiatives as part of cancer survivorship care.

For high-risk patients unwilling to undergo surgery or those with at the most 10-years of life expectancy, RT could be a suitable treatment option. However, in localized PCa patients, RP was associated with a significant decline in PCa-specific mortality relative to RT and ADT [26]. A meta-analysis of published trials compared surgery and RT outcomes among PCa patients. Surgery had better overall

(49%) and cancer-specific survival (44%), compared to RT [19]. One cohort study observed higher incidence of secondary malignancies, and complications requiring hospital admissions, and open surgical procedures among those receiving RT [27]. Series analyzing effects of RP in high-risk PCa patients showed PCa-specific 10-year survival rates up to 92% (72%-92%) [28,29].

A population-based study found that after adjusting for disease aggressiveness, those receiving RP had a low rate of PCa mortality [2]. In another study, compared to high-dose RT, RP was associated with 65% risk reduction for metastasis [13]. The mortality outcomes that we observed are consistent with results from previous clinical trials and retrospective case studies [16–20,30]. Additionally, a recent study found that if appropriate radiation doses and 2 years of ADT were given, the apparent survival benefit of ADT + EBRT + BT compared to ADT + EBRT was removed [18].

This emphasizes the need for appropriate treatment strategies as the risk of morbidity, and complications are no worse for RP compared to EBRT + ADT [20,31].

4.1. Limitations

We note following limitations. Our study lacks intermediate outcomes like follow-up treatment, a measure of distant disease control that would support the association of RP with survival. Our study sample consists of Medicare beneficiaries aged ≥66 years, not enrolled in HMO, with continuous coverage and living in a SEER region. The SEER regions have a higher proportion of nonwhite persons, and SEER mortality rates may not be representative of national cancer mortality rates [21]. Earlier research has observed that 15% to 20% of high-risk cases were downgraded in the final pathological examination. However, our study does not address this issue. Another limitation is that a bias may exist as healthier patients are selected for surgery, and those with higher comorbidities are referred to RT. In our study, the RP group was younger with lower comorbidity, compared to the RT group. To address this issue, we determined the propensity of receiving specific treatment based on age, race and ethnicity, geographic location, socioeconomic status, marital status and comorbidity, and weighted our analysis by the inverse probability of PS. Finally, our study did not account for radiation doses. Current radiation practice uses higher doses than those used during our study period of 1996 to 2003, and may be more effective.

Despite these limitations, our study has several strengths. To our knowledge, ours is the first study that provides a comprehensive assessment of comparative effectiveness of three primary treatment modalities for high-risk PCa in terms of 10-year survival, cost, complications, and health service use using population-based data. In addition to SEER, we also used treatment data from Medicare claims to strengthen treatment identification. Our data supports advantage of RP in-terms of cost and health service use over 10-year follow-up. We demonstrate the trade-off between urinary, sexual, and GI complications, inpatient, outpatient and ER visits, and cost.

4.2. Conclusions

Conventionally, RP is infrequently considered a first line of therapy for high-risk PCa patients due to the high-risk of treatment failure. However, as our results indicate, RP can provide superior cancer control with clear cost advantage for high-risk patients.

Our results also demonstrate long-term survival benefits for EBRT + BT ± ADT, and greater bowel and bladder side effects over a decade, compared to RP. In terms of value proposition, our results support RP as preferred treatment option, compared to EBRT + ADT and EBRT + BT ± ADT among high-risk PCa patients.

Conflict of interest

None.

Acknowledgments

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. We acknowledge the efforts of the Applied Research Program, National Cancer Institute (NCI); the Office of Research, Development and Information, Centers for Medicare and Medicaid Services (CMS); Information Management Services; and the SEER program tumor registries in the creation of the SEER-Medicare database.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.06.005.

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