Localized prostate cancer: An analysis of the Centers for Disease Control and Prevention Breast and Prostate Cancer Data Quality and Patterns of Care study (CDC PoC-BP)

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Abstract

Introduction: Limited evidence exists on the comparative effectiveness of local treatments for prostate cancer (PCa) due to the lack of generalizability. Using granular national data, we sought to examine the association between radical prostatectomy (RP) and intensity-modulated radiation therapy (IMRT) treatment and survival.

Methods: Records were abstracted for localized PCa cases diagnosed in 2004 across seven state registries to identify patients undergoing RP (n=3019) or IMRT (n=667). Comorbidity was assessed by the Adult Comorbidity Evaluation-27 (ACE-27). Propensity score matching (PSM) was used to balance covariates between treatment groups. All-cause and PCa-specific mortality were primary endpoints. A subgroup analysis of patients with high-risk PCa (RP, n=89; IMRT, n=95) was conducted.

Results: Following PSM, matched patients (n=502 pairs) treated with either RP or IMRT were well-balanced with respect to covariates. With a median followup of 10.5 years (interquartile range [IQR] 9.9–11.0), the 11-year overall survival (OS) was 71.2% (95% confidence interval [CI] 66.9–75.8) for RP and 62.3% (95% CI 57.4–67.6) for IMRT. IMRT was associated with a 41% increased risk of all-cause mortality (hazard ratio [HR] 1.41, 95% CI 1.13–1.76) but not PCa-specific mortality (HR 1.75, 95% CI 0.84–3.64), as compared to RP. In patients with high-risk PCa, IMRT, as compared to RP, was not associated with a statistically significant difference in all-cause (HR 1.53, 95% CI 0.97–2.42) or PCa-specific mortality (HR 1.92, 95% CI 0.69–5.36).

Conclusions: Despite a low mortality rate at 10 years and possible residual confounding, we found a significantly increased risk of all-cause mortality but no PCa-specific mortality associated with IMRT as compared to RP in this population-based study.

Introduction

Radical prostatectomy (RP) and radiation therapy (RT) represent the most widely used and gold-standard definitive therapies for clinically localized prostate cancer (PCa). Randomized controlled trials comparing therapies for PCa are limited due to difficulties in patient accrual, leading to issues with generalizability and insufficient power to detect differences in mortality.[1-4] Moreover, the evolution of treatment technology and practice patterns outpace maturation of trial data, further complicating the generalizability of results because the tested treatment approaches may be obsolete prior to publication.

In the absence of contemporary randomized controlled trials comparing the efficacy of RP and modern RT, comparative effectiveness studies using observational data provide the next line of evidence.[5] This approach can be difficult since medical comorbidity is often unbalanced between patients receiving RT and those undergoing RP, with younger and healthier patients more likely to receive RP.[6] Previous observational studies using population-level data have shown RP is associated with improved survival compared to RT; however, these studies had variable followup, and many did not employ granular or detailed measures of comorbidity.[7-10] Importantly, RT has evolved since these studies were published and the impact of newer modalities remains unclear.

The Breast and Prostate Cancer Data Quality and Patterns of Care (PoC-BP) study, supported by the Center for Disease

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Control (CDC), facilitates examination of patterns of care for PCa treatment and the comparative effectiveness of RT and RP. This population-based cohort represents patients treated with contemporary external beam RT (EBRT) in the form of intensity-modulated RT (IMRT) as compared to earlier forms of RT examined in past observational studies.[10] Using granular data, including detailed patient comorbidity information captured by the Adult Comorbidity Evaluation-27 (ACE-27)[11] in the PoC-BP study, we sought to examine the association between RP and RT treatment and survival using a propensity score-matched analysis.

Methods

Study cohort

We used the CDC PoC-BP dataset of 8229 men diagnosed with histologically confirmed localized PCa in 2004 from seven state cancer registries funded by the CDC's National Program of Cancer Registries. The sampling methods employed have been previously described and included data abstraction from hospitals and non-hospitals (e.g. office and radiation facility) between 2007 and 2009.[12] State cancer registries provided vital status, date of death or last date of contact, and ICD codes for cause of death as of December 31, 2015.

Analysis was restricted to patients receiving definitive treatment within six months of diagnosis (57% of the cohort), as those receiving treatment after six months likely represents management with active surveillance. Further, we excluded patients treated with conservative therapies (active surveillance, expectant management, or primary androgen deprivation therapy [ADT]), combination brachytherapy ± IMRT, other forms of EBRT, ablation therapy, and other non-radical extirpative treatments. We identified 3019 patients who underwent RP (open and minimally invasive approaches, which have demonstrably comparable oncological outcomes[13]) and 667 patients treated with IMRT.

Patient, provider covariates

Patient demographics included cancer registry, age at diagnosis, race/ethnicity, marital status, socioeconomic status, insurance primary payer, and urban/rural location. Socioeconomic status and level of urbanization categorizations were based on patient's residence at diagnosis based on the 2000 U.S. census tract-specific data. Patient comorbidity was measured using the ACE-27 instrument, a chart-based comorbidity index validated in oncological outcomes research that grades the severity of multiple medical conditions (none, mild, moderate, or severe) with regard to how activities of daily living (ADL) are impacted, and algorithmically creates an index score for comparing degree of comorbidity in patients.[11] Conditions controlled with medications that do not limit ADLs and have not led to hospitalization are mild. Moderate conditions limit ADLs or require hospitalization or surgery. Severe comorbid conditions denote major complications, end-organ damage, uncontrollable symptoms, or debility requiring full ADL support. The ACE-27 comorbidity index has the most prognostic impact in patients with a high likelihood of cancer survival.[14]

Cancer clinical characteristics included Gleason score, serum prostate specific antigen (PSA) level, National Comprehensive Cancer Network (NCCN) risk group, and whether ADT was received. Practice and provider characteristics included physician medical school graduation year categorized by decade 1950–1990, practice type (solo vs. group), for-profit vs. non-profit, teaching status of facility, distance to treatment facility, and number of urologists per 100 000 men. We have previously described these provider variables, which are associated with the selection of RP or RT, and thus represent important variables to be included to reduce confounding.[12]

Prespecified subgroup analysis

We performed a prespecified subgroup analysis in patients with NCCN high-risk PCa treated with RP (n=89) and IMRT (n=95). This prespecified subgroup analysis was conducted given that prior studies have demonstrated heterogeneity in treatment effect with high-risk patients deriving greater survival benefit from surgery.[10] NCCN high-risk PCa is defined as clinical ≥T3a (American Joint Committee on Cancer Clinical Staging System, 6th edition), serum PSA >20 ng/ml, or Gleason grade group 4 or 5 based on transrectal ultrasound-guided prostate biopsy.

Statistical analysis

The primary endpoints were overall survival (OS) and PCa-specific survival (CSS). Propensity score matching (PSM) was performed using a multivariable logistic regression model to predict RP treatment vs. IMRT with covariates using 1:1 nearest-neighbor matching with a greedy algorithm (caliper 0.2 x propensity-score).[15] Standardized differences were within 0.1 between patients in RP and IMRT groups after PSM, ensuring well-balanced groups. PSM reduces selection bias by balancing covariates between groups[16] and has previously been employed to balance baseline covariates between treatment groups in clinical studies.[15] Any covariate unbalanced after PSM was adjusted for in our Cox proportional hazard models. Kaplan-Meier (KM) survival rates, with corresponding 95% confidence intervals (CI), were estimated from the propensity score-matched samples. Median followup was calculated using the reverse KM method. The reverse KM method to calculate median survival is the same calculation of KM with the event and censor indicator status switched. All-cause mortality was calculated from date of diagnosis to date of death or date of last followup. For PCa-specific mortality, deaths were identified from the ICD codes for PCa (C61, C619).

Marginal proportional hazard models were constructed to determine the association between OS or CSS and treatment modality, accounting for event clustering since matching inherently violates independence.[17] The cumulative incidence function was used to estimate absolute risks with PCa and non-PCa deaths as competing risks. Cause-specific hazard models estimated relative effects of treatment in the competing risk setting. A Fine-Gray test that accounted for clustering was used to test for differences between cumulative incidence functions.[18] Statistical significance was set at p<0.05 based on a two-tailed comparison. All analyses were performed using SAS Enterprise Guide 9.4 (SAS Institute Inc., Cary, NC, U.S.) and R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 3686 patients were analyzed, with 3019 receiving RP and 667 receiving IMRT (Table 1). Surgical patients in this unmatched cohort were more likely to be younger, with 45.5% of patients aged less than 60 years at the time of diagnosis compared to 58.8% being 70 years or older in the IMRT patients. Most patients were White (77.2% and 72.9% for surgery and IMRT, respectively) and married (79.7% and 75.4%, respectively). Patients who underwent RP were significantly more likely to be privately insured (74.0% compared to 45.5% in the IMRT patients). This is likely related to many RP patients being below the age to qualify for Medicare; 41.0% of patients receiving IMRT were covered by Medicare, compared with 15.5% of RP patients. Rural and urban locale of patients did not vary significantly between treatment groups. RP patients were healthier, with many having no comorbidities (42.0% vs. 26.7% for IMRT patients). Overall, patients were mostly healthy in both treatment groups, with 87.8% and 81.3% for RP and IMRT, respectively, having mild or no ACE-27 score. IMRT patients had higher PSA, and were also more likely to have received ADT (52.4% IMRT vs. 6.8% RP) and be in the NCCN high-risk group (19.7% IMRT vs. 12.6% RP). Practice type and facility ownership did not vary appreciably. IMRT patients tended to have a shorter distance to the treatment facility, while there was also a trend for surgery patients to have their care at teaching hospitals.

PSM was used to create a well-balanced cohort, defined in terms of standardized differences being 0.10 or less for the covariates in Table 1. This conventional benchmark was achieved for all variables except state registry, receipt of ADT, graduation year, practice type, facility ownership, teaching status, and distance to treatment facility. We identified 502 RP and 502 IMRT patients that we regarded as sufficiently well-balanced with respect to standardized differences (Table 1). The maximum followup was 11.9 years. The overall median followup for this analytic cohort was 10.5 years (interquartile range [IQR] 9.9–11.0). The median followup was 10.6 years (IQR 10.0–11.1) and 10.4 years (IQR 9.6–10.9) for the RP and IMRT cohorts, respectively. Over the duration of followup, there were 31 (3.1%) PCa-related deaths in the analytic cohort.

IMRT was associated with a 41% increased risk of all-cause mortality, compared to RP (hazard ratio [HR] 1.41, 95% CI 1.13–1.76) (Table 2). There was no significant difference in PCa-specific mortality between IMRT and RP (HR 1.75, 95% CI 0.84–3.64). Consistent with these findings, KM analyses demonstrated a significantly worse OS, but not CSS, in patients treated with IMRT as compared to RP (Figures 1, 2). Table 2 demonstrates the 11-year OS benefit for RP at 71.2% (95% CI 66.9–75.8) as compared to IMRT at 62.3% (95% CI 57.4–67.6). There was no statistically significant difference in 11-year CSS (95.5%, 95% CI 93.5–97.6 and 96.3%, 95% CI 94.0–98.7% for IMRT and RP, respectively).

We performed an a priori defined subgroup analysis of patients with NCCN high-risk PCa. IMRT, as compared to RP, was not associated with a statistically significant difference in all-cause mortality (HR 1.53, 95% CI 0.97–2.42) or PCa-specific mortality (HR 1.92, 95% CI 0.69–5.36) in the subset of patients with NCCN high-risk PCa (Table 2).

The 11-year cumulative incidence rates for overall, PCa-specific, and non-PCa specific mortality are shown in Table 3. The 11-year cumulative incidence rates were significantly higher for IMRT as compared to RP for overall and non-PCa-specific mortality, but not PCa-specific mortality (all-cause mortality 37.7%, 32.6–42.8 and 28.8%, 95% CI 24.4–33.3, p=0.003; non-PCa-specific mortality 33.8%, 28.9–38.9 and 25.7%, 21.6–29.9, p=0.011; and PCa-specific mortality 3.8%, 2.4–5.9) and 3.1%, 1.6–5.5, p=0.18, for IMRT and RP, respectively).

Discussion

In this observational study with granular comorbidity adjustment, we observed that among patients with localized PCa, IMRT was associated with a 41% increased risk of all-cause mortality as compared with RP, though there was no significant difference in PCa-specific mortality. In our a priori subgroup analysis of those patients with NCCN high-risk PCa, we did not observe statistically significant differences in all-cause or PCa-specific mortality.

In the absence of informative randomized data comparing modern approaches, comparative effectiveness studies

Table 1. Sociodemographic, clinical, and provider characteristics of surgery and IMRT treatment groups with standardized differences before and after propensity score matching

			Before propensity score matching			After propensity score matching		
Variable	**Total (%)[a]**	**Patients (n)[b]**	**Surgery n (%)[c]**	**IMRT n (%)[c]**	**Standardized difference**	**Surgery n (%)[c]**	**IMRT n (%)[c]**	**Standardized difference**
Total	**100**	**3686 (11 431)**	**3019 (83.9)**	**667 (16.1)**		**502 (50.7)**	**502 (49.3)**	
Registry					0.45			0.14
A	23.4	645 (2675)	558 (24.0)	87 (20.2)		81 (22.1)	74 (22.5)	
B	14.1	674 (1613)	462 (12.0)	212 (25.2)		139 (22.1)	128 (19.8)	
C	7.8	242 (892)	224 (8.6)	18 (3.7)		12 (3.1)	15 (4.0)	
D	8.6	651 (986)	537 (8.5)	114 (9.3)		94 (9.0)	91 (9.5)	
E	13.9	485 (1588)	402 (13.9)	83 (13.8)		51 (12.0)	60 (12.9)	
F	18.8	456 (2151)	377 (19.2)	79 (16.8)		76 (22.8)	68 (18.3)	
G	13.4	533 (1526)	459 (13.8)	74 (11.1)		49 (9.1)	66 (13.0)	
Age					1.27			0.06
<60	39.6	1471 (4528)	1405 (45.5)	66 (8.8)		50 (9.8)	66 (11.3)	
60–64	22.2	816 (2538)	719 (24.0)	97 (13.1)		101 (18.8)	96 (16.6)	
65–69	19.9	754 (2269)	606 (20.0)	148 (19.3)		180 (33.3)	132 (22.6)	
70–74	12.4	431 (1412)	246 (8.8)	185 (30.7)		139 (30.1)	141 (33.3)	
75+	6.0	214 (684)	43 (1.7)	171 (28.1)		32 (8.0)	67 (16.1)	
Race/ethnicity					0.13			0.09
Caucasian	76.5	2278 (8749)	1887 (77.2)	391 (72.9)		276 (72.5)	296 (72.8)	
African American	15.0	979 (1711)	771 (14.2)	208 (18.9)		170 (19.4)	152 (18.3)	
Hispanic	6.0	239 (683)	204 (6.1)	35 (5.4)		29 (5.4)	30 (6.2)	
API/AI/AN	2.5	190 (288)	157 (2.5)	33 (2.9)		27 (2.7)	24 (2.7)	
Marital status					0.20			0.04
Married	79.0	2873 (9030)	2386 (79.7)	487 (75.4)		373 (76.4)	381 (78.3)	
Single/divorced/separated/ widowed	16.9	671 (1928)	508 (15.8)	163 (22.5)		117 (20.6)	109 (19.7)	
Unknown	4.1	142 (474)	125 (4.5)	17 (2.1)		12 (3.0)	12 (2.0)	
Socioeconomic status					0.18			0.04
Low	11.4	645 (1298)	496 (10.7)	149 (14.7)		105 (13.8)	97 (13.0)	
Mid	17.0	680 (1941)	543 (16.5)	137 (19.7)		107 (18.6)	110 (20.5)	
High	71.6	2,350 (8165)	1971 (72.7)	379 (65.6)		290 (67.6)	295 (66.5)	
Insurance					0.68			0.06
None	1.5	64 (176)	53 (1.6)	11 (1.1)		8 (0.8)	9 (1.0)	
Medicaid	4.3	204 (492)	150 (4.1)	54 (5.6)		35 (5.7)	42 (5.8)	
Medicare or other public	19.6	765 (2237)	486 (15.5)	279 (41.0)		187 (37.0)	184 (37.3)	
Private	69.4	2503 (7935)	2218 (74.0)	285 (45.5)		247 (49.5)	245 (50.9)	
Unknown	5.2	150 (591)	112 (4.9)	38 (6.8)		25 (6.9)	22 (5.0)	
Urban/rural					0.07			0.04
Rural	12.5	522 (1430)	417 (12.2)	105 (14.2)		78 (12.5)	75 (13.2)	
Urban	50.6	1813 (5784)	1502 (51.1)	311 (48.1)		246 (52.3)	240 (49.2)	
Rural-urban mix	36.7	1340 (4191)	1091 (36.5)	249 (37.4)		178 (35.2)	187 (37.6)	
Unknown	0.2	11 (27)	9 (0.2)	2 (0.3)				
ACE-27 comorbidity score					0.36			0.09
None	39.5	1367 (4514)	1208 (42.0)	159 (26.7)		114 (22.5)	133 (29.4)	
Mild	47.2	1828 (5398)	1441 (45.8)	387 (54.6)		299 (58.3)	290 (54.7)	
Moderate	9.1	338 (1038)	253 (8.4)	85 (12.4)		60 (14.0)	53 (10.2)	
Severe	2.4	93 (270)	68 (2.2)	25 (3.4)		21 (4.0)	18 (3.4)	
Unknown	1.9	60 (212)	49 (1.6)	11 (2.9)		8 (1.2)	8 (2.3)	
Gleason					0.13			0.02
2–6	47.2	1712 (5399)	1396 (47.3)	316 (47.1)		246 (48.6)	241 (47.5)	
7	42.6	1603 (4865)	1339 (43.0)	264 (40.5)		197 (37.7)	202 (40.9)	
8–10	10.2	369 (1164)	283 (9.7)	86 (12.5)		59 (13.7)	59 (11.7)	

[a]Column percentages based on weighted number of patients. [b]Unweighted number of patients (weighted number in parenthesis). [c]Unweighted number of patients (weighted column percentages in parenthesis). [d]Low (T1-2a AND Gleason score ≤6 AND PSA <10 ng/mL), intermediate (T2b-T2c OR Gleason score 7 OR PSA 10–20 ng/mL), and high (≥ T3a OR Gleason score 8–10 OR PSA >20 ng/mL). ACE-27: Adult Comorbidity Evaluation-27; ADT: androgen deprivation therapy; IMRT: intensity-modulated radiation therapy; NCCN: National Comprehensive Cancer Network; PSA: prostate-specific antigen.

Table 1 (cont'd). Sociodemographic, clinical, and provider characteristics of surgery and IMRT treatment groups with standardized differences before and after propensity score matching

			Before propensity score matching			After propensity score matching		
Variable	Total (%)[a]	Patients (n)[b]	Surgery n (%)[c]	IMRT n (%)[c]	Standardized difference	Surgery n (%)[c]	IMRT n (%)[c]	Standardized difference
Total	**100**	**3686 (11 431)**	**3019 (83.9)**	**667 (16.1)**		**502 (50.7)**	**502 (49.3)**	
PSA					0.46			0.06
0–3.9	14.7	500 (1645)	452 (16.1)	48 (7.6)		45 (9.2)	44 (9.3)	
4–9.9	67.0	2363 (7486)	1977 (67.9)	386 (62.4)		317 (67.1)	313 (65.4)	
10–19.9	12.9	502 (1440)	364 (11.7)	138 (18.9)		99 (16.9)	96 (16.8)	
20+	5.4	226 (608)	136 (4.3)	90 (11.1)		41 (6.8)	49 (8.5)	
NCCN risk group[d]					0.25			0.03
Low	37.6	1316 (4295)	1106 (38.5)	210 (32.6)		167 (35.9)	166 (34.5)	
Intermediate	48.7	1842 (5565)	1532 (48.9)	310 (47.7)		246 (45.9)	241 (47.8)	
High	13.8	528 (1572)	381 (12.6)	147 (19.7)		89 (18.2)	95 (17.7)	
Receipt of ADT					1.22			1.12
No	85.5	2967 (9361)	2666 (93.2)	301 (47.6)		443 (91.3)	241 (50.1)	
Yes	14.5	560 (1585)	194 (6.8)	366 (52.4)		35 (8.7)	261 (49.9)	
Graduation year					0.25			0.21
1950–1969	10.4	279 (828)	243 (10.6)	36 (9.1)		47 (11.4)	26 (8.9)	
1970–1979	23.1	622 (1850)	472 (22.1)	150 (28.5)		92 (26.3)	110 (27.0)	
1980–1989	37.8	1008 (3020)	817 (37.4)	191 (39.8)		137 (37.0)	153 (40.6)	
1990+	28.7	791 (2293)	672 (29.9)	119 (22.6)		104 (25.3)	97 (23.5)	
Practice type					0.39			0.44
Solo practice	9.0	309 (720)	295 (10.2)	14 (3.0)		57 (12.8)	11 (3.3)	
Group practice	91.0	2391 (7271)	1909 (89.8)	482 (97.0)		323 (87.2)	375 (96.7)	
Ownership of facility					-0.16			-0.19
For-profit	9.8	325 (903)	296 (10.2)	29 (7.4)		53 (10.8)	21 (6.4)	
Non-profit/ government	90.2	2632 (8,296)	2250 (89.8)	382 (92.6)		388 (89.2)	295 (93.6)	
Teaching status					-0.10			0.11
Non-teaching	43.9	1323 (4035)	1121 (42.6)	202 (53.0)		237 (54.6)	152 (50.9)	
Teaching	56.1	1634 (5,164)	1425 (57.4)	209 (47.0)		204 (45.4)	164 (49.1)	
Distance to treatment facility					0.10			0.11
<5	29.2	884 (2760)	712 (28.5)	172 (32.9)		121 (30.0)	126 (31.1)	
5–9	23.3	702 (2199)	592 (23.3)	110 (23.1)		112 (27.0)	91 (24.9)	
10–14	12.5	370 (1179)	308 (12.6)	62 (11.6)		45 (11.6)	50 (11.8)	
15+	35.1	1092 (3315)	902 (35.6)	190 (32.3)		153 (31.4)	142 (32.1)	
Number of urologists per 100 000 men					0.19			0.05
0	13.7	559 (1347)	444 (13.5)	115 (14.9)		86 (14.0)	82 (13.8)	
>0–6	45.4	1160 (4,461)	988 (46.3)	172 (40.5)		154 (42.8)	143 (44.4)	
>6–10	23.7	765 (2325)	621 (23.6)	144 (23.8)		106 (25.3)	112 (22.7)	
10+	17.3	712 (1696)	559 (16.6)	153 (20.8)		105 (17.9)	105 (19.1)	

[a]Column percentages based on weighted number of patients. [b]Unweighted number of patients (weighted number in parenthesis). [c]Unweighted number of patients (weighted column percentages in parenthesis). [d]Low (T1-2a AND Gleason score ≤6 AND PSA <10 ng/mL), intermediate (T2b-T2c OR Gleason score 7 OR PSA 10–20 ng/mL), and high (≥ T3a OR Gleason score 8–10 OR PSA >20 ng/mL). ACE-27: Adult Comorbidity Evaluation-27; ADT: androgen deprivation therapy; IMRT: intensity-modulated radiation therapy; NCCN: National Comprehensive Cancer Network; PSA: prostate-specific antigen.

with observational data are helpful, although the latter are controversial due to residual confounding by comorbidities. Prior observational cohort studies have demonstrated that patients receiving RT have a greater comorbidity burden than those treated with surgery.[7,8] Comorbidity has been shown to be an independent prognostic factor in PCa outcomes,[6] and is an important component of shared decision-making. The ACE-27 score used in our study to evaluate comorbidity burden, like the Deyo-Charlson comorbidity index, has been shown to provide unique but significant prognostic information regarding comorbid illnesses.[19] To account for potential confounding from patient comorbidities, our study employed rigorous chart-based abstraction and assessment using the ACE-27 instrument to quantify risk.[11] Furthermore, comorbidity as assessed by ACE-27 was used for PSM to reduce selection bias in PCa treatment whereby patients with greater comorbidity are more likely to be treated with radiation over surgery. Indeed, our study represents the best methods for comparing effectiveness of treatments used for patients with very disparate baseline comorbidity burden.

A recent systematic review and meta-analysis of clinically localized PCa found that patients treated with RT had

Table 2. Eleven-year survival rates and hazard ratios of propensity score matched cohort and NCCN high-risk disease subgroup

	Treatment	n	Number of events	11-year survival rate (%) (95% CI)	HR (95% CI)	p
Propensity score matched cohort						
Overall survival	Surgery	502	128	71.2 (66.9–75.8)	1.00	0.004
	IMRT	502	164	62.3 (57.4–67.6)	1.41 (1.13–1.76)	
Prostate cancer survival	Surgery	502	12	96.3 (94.0–98.7)	1.00	0.12
	IMRT	502	19	95.5 (93.5–97.6)	1.75 (0.84–3.64)	
NCCN high-risk disease subgroup						
Overall survival	Surgery	89	32		1.00	0.07
	IMRT	95	42		1.53 (0.97–2.42)	
Prostate cancer survival	Surgery	89	6		1.00	0.20
	IMRT	95	10		1.92 (0.69–5.36)	

CI: confidence interval; HR: hazard ratio; IMRT: intensity-modulated radiation therapy; NCCN: National Comprehensive Cancer Network.

a greater risk of PCa-specific mortality (HR 2.08, 95% CI 1.76–2.47, p<0.00001) and all-cause mortality (HR 1.63, 95% CI 1.54–1.73, p<0.00001), compared to those treated with RP.[5] Our results are consistent with regard to all-cause mortality benefit for RP as compared to RT. However, we did not observe a significant difference in PCa-specific mortality between RP and RT. Many of the studies included in the previously mentioned systematic review and meta-analysis did not control for comorbidity; or, if they did, did not employ the type of rigorous statistical approach we adopted here. It has been previously demonstrated that comorbidity burden is greater in those men who undergo RT.[6] As such, confounding by inconsistent control for comorbidities may explain the increased all cause and PCa-specific mortality risk associated with RT in this meta-analysis. Recognizing the differences in comorbidity burden between PCa patients treated with RP or EBRT, a prior retrospective cohort study compared treatment outcomes in a cohort of men with no comorbidities as assessed using ACE-27 and Charlson comorbidity index. In this study, they found that EBRT was associated with increased PCa-specific mortality and overall mortality, compared to RP.[20] Unlike our study, this prior study did not attempt to adjust for age, thus their cohort RP patients were significantly younger than the RT patients (60 years vs. 66.8 years) which likely adds greater confounding possibly due to greater chance of developing comorbidity during followup.[20]

Limitations and strengths

Our study is limited by the retrospective, non-randomized nature of the cohort and challenges in inferring causality in a non-experimental setting. We considered as many covariates as possible to establish the propensity score and a well-balanced patient cohort. This reduced our small sample size after propensity score-matching and may have also adversely impacted statistical power. Although age and comorbidity burden at diagnosis were adjusted by PSM, we did not adjust for comorbidities that developed later. It is possible that advanced age or higher baseline comorbidity burden could be more likely to develop additional or worsening comorbidities during the followup period. Our study did not exclude those who were diagnosed with other primary

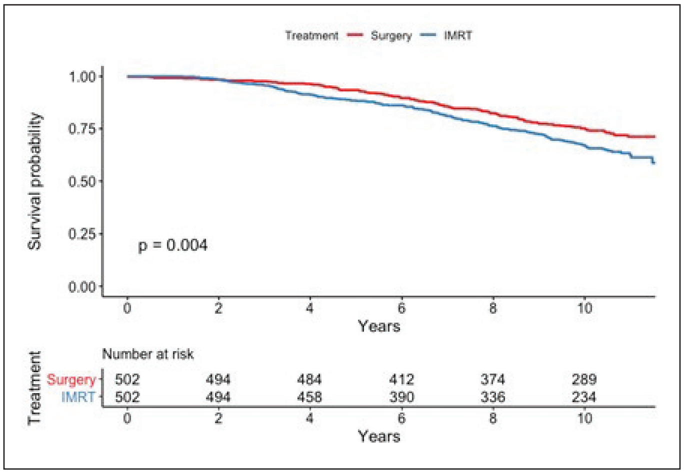

Figure 1. Overall survival of surgery and intensity-modulated radiation therapy (IMRT) treatment groups.

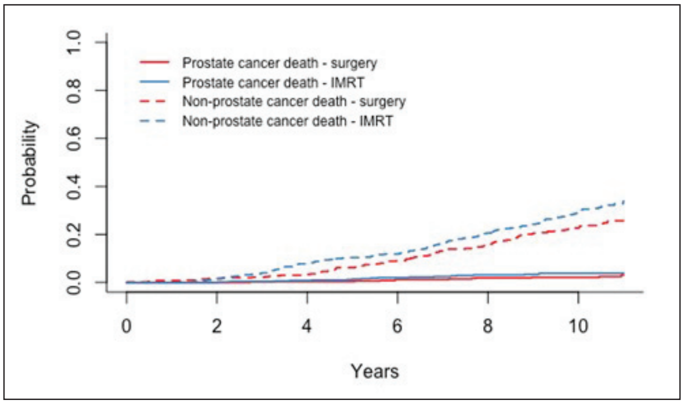

Figure 2. Cumulative incidence of prostate cancer and non-prostate cancer deaths in surgery and intensity-modulated radiation therapy (IMRT) treatment groups.

Table 3. Eleven-year cumulative incidence rates for all-cause, prostate cancer, and non-prostate cancer mortality rates in surgery and IMRT treatment groups

	11-year cumulative incidence (%)		
Treatment	All-cause mortality (95% CI)	Prostate cancer mortality (95% CI)	Non-prostate cancer mortality (95% CI)
Surgery	28.8 (24.4–33.3)	3.1 (1.6–5.5)	25.7 (21.6–29.9)
IMRT	37.7 (32.6–42.8)	3.8 (2.4–5.9)	33.8 (28.9–38.9)
p	0.003	0.18	0.011

CI: confidence interval; IMRT: intensity-modulated radiation therapy.

cancers; therefore, the survival time may be affected by other cancers. Our study does not include data on cancer recurrence and subsequent treatments, which may also impact survival. This is particularly important since bias may exist if there is preferential use of salvage therapies between the RP and RT (e.g., salvage RP or adjuvant/salvage RT). The observed association of treatment with a significant difference in all-cause but not PCa-specific mortality may reflect residual confounding that persists despite our best effort to control covariates. Conversely, underpowering due to low PCa deaths may explain why the difference in PCa-specific mortality did not reach statistical significance. Lastly, the treatment of localized PCa has continued to evolve with high-dose rate brachytherapy becoming increasingly used, but not included in our analysis.[21]

Despite these limitations, the major strength of our study is its generalizability, as it represents a population-based cohort created from the CDC National Program of Cancer Registries, which seeks to include all diagnosed cancer patients, regardless of age or insurance status. Thus, our cohort reflects the diversity of patients with localized PCa regarding comorbidity, age, race, and insurance status, as well as practice and provider characteristics. Observational studies may represent a complementary opportunity to study treatment effect in localized PCa given the challenges of performing randomized trials and rapidly evolving practice patterns. In order to guide patient selection in an environment of shared decision-making, ongoing followup of observational cohorts and completed randomized controlled trials will be needed.

Conclusions

We observed that in a population-based observational cohort of men with localized PCa that was well-balanced based on multiple covariates, including a robust index of comorbidity, IMRT was associated with a statistically significant increased risk of all-cause mortality but not PCa-specific mortality.

Competing interests: The authors do not report any competing personal or financial interests related to this work.

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This paper has been peer-reviewed.

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