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European Association of Urology

Prostate Cancer

Long-term Prostate Cancer–specific Mortality After Prostatectomy, Brachytherapy, External Beam Radiation Therapy, Hormonal Therapy, or Monitoring for Localized Prostate Cancer

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Article info

Article history:
Accepted September 28, 2023

Associate Editor:
Alberto Briganti

Keywords:
Active surveillance
Androgen deprivation therapy
Cancer of the Prostate Strategic Urologic Research Endeavor
Comparative effectiveness research
Prostate cancer
Radical prostatectomy
Radiotherapy
Survival

Abstract

Background: The optimal treatment of localized prostate cancer (PCa) remains controversial.
Objective: To compare long-term survival among men who underwent radical prostatectomy (RP), brachytherapy (BT), external beam radiation therapy (EBRT), primary androgen deprivation therapy (PADT), or monitoring (active surveillance [AS]/watchful waiting [WW]) for PCa.
Design, setting, and participants: This is a cohort study with long-term follow-up from the multicenter, prospective, largely community-based Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry. Men with biopsy-proven, clinical T1–3aN0M0, localized PCa were consecutively accrued within 6 mo of diagnosis and had clinical risk data and at least 12 mo of follow-up after diagnosis available.
Outcome measurements and statistical analysis: PCa risk was assessed, and multivariable analyses were performed to compare PCa-specific mortality (PCSM) and all-cause mortality by primary treatment, with extensive adjustment for age and case mix using the Cancer of the Prostate Risk Assessment (CAPRA) score and a well-validated nomogram.
Results and limitations: Among 11 864 men, 6227 (53%) underwent RP, 1645 (14%) received BT, 1462 (12%) received EBRT, 1510 (13%) received PADT, and 1020 (9%) were managed with AS/WW. At a median of 9.4 yr (interquartile range 5.8–13.7) after treatment, 764 men had died from PCa. After adjusting for CAPRA score, the hazard ratios for PCSM with RP as the reference were 1.57 (95% confidence interval [CI] 1.24–1.98; $p < 0.001$) for BT, 1.55 (95% CI 1.26–1.91; $p < 0.001$) for EBRT, 2.36 (95% CI 1.94–2.87; $p < 0.001$) for PADT, and 1.76 (95% CI 1.30–2.40; $p < 0.001$) for AS/WW. In models for long-term outcomes, PCSM differences were negligible for low-risk disease and increased progressively with risk. Limitations include the evolution of diagnostic and

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https://doi.org/10.1016/j.eururo.2023.09.024

therapeutic strategies for PCa over time. In this nonrandomized study, the possibility of residual confounding remains salient.

Conclusions: In a large, prospective cohort of men with localized PCa, after adjustment for age and comorbidity, PCSM was lower after local therapy for those with higher-risk disease, and in particular after RP. Confirmation of these results via long-term follow-up of ongoing trials is awaited.

Patient summary: We evaluated different treatment options for localized prostate cancer in a large group of patients who were treated mostly in nonacademic medical centers. Results from nonrandomized trials should be interpret with caution, but even after careful risk adjustment, survival rates for men with higher-risk cancer appeared to be highest for patients whose first treatment was surgery rather than radiotherapy, hormones, or monitoring.

1. Introduction

Approximately 34 700 men will die from prostate cancer (PCa) in the USA in 2023, making this disease the second leading cause of cancer-related death among men [1]. For men with organ-confined disease, multiple treatment options including radical prostatectomy (RP), brachytherapy (BT), external beam radiation therapy (EBRT), and monitoring (active surveillance [AS] or watchful waiting [WW]) are available, although uncertainty persists surrounding the relative long-term effectiveness and benefits of each modality [2–4]. In some cases, androgen deprivation therapy (ADT) is used as primary monotherapy (PADT), but its benefit in terms of better overall or cancer-specific survival has not been well established [5,6]. Treatment choices may be influenced heavily by individual health status, life expectancy, and patient preferences [2–4]. The intended benefits of intervention must also be balanced against the risks of long-term treatment-related adverse events, which may negatively impact health-related quality of life [7].

Owing to the protracted natural history of PCa [8], long-term PCa-specific mortality (PCSM) and all-cause mortality (ACM) are more appropriate when comparing the survival benefits of these treatment modalities rather than biochemical recurrence–free or clinical recurrence–free survival. Biochemical recurrence should not be used to compare RP and radiation modalities [9], and clinical recurrence is heavily driven by the intensity of monitoring and the treatment era.

The landmark ProtecT randomized controlled trial (RCT) comparing the effectiveness of RP, EBRT + ADT, and prostate-specific antigen (PSA)-based active monitoring for initial treatment of localized PCa showed no statistically significant differences in PCSM among the three arms at 15 yr, but enrolled nearly exclusively men with low- to intermediate-risk PCa (according to the risk parameters available at diagnosis) and more time is needed for the data to mature given the low event rates reported to date [10,11].

Observational data can provide important insights complementary to RCTs, but are vulnerable to selection bias and other sources of both measured and unmeasured confounding. Prior cohort studies [12–16] vary in quality, often involving short follow-up, low event rates, inadequate risk adjustment, selective treatment inclusion, and/or problematic biochemical outcomes. Very few studies have reported on primary BT and, so far, none has reported on PADT and WW/AS in the same cohort [17].

In this study, we analyzed PCSM and overall mortality outcomes after RP, BT, EBRT, PADT, or AS/WW as the primary treatment, with careful risk adjustment and extended follow-up allowing modeling of outcomes at 20 yr, for men diagnosed with localized PCa in the national, multicenter, prospective, mostly community-based Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry.

2. Patients and methods

2.1. CaPSURE registry

Participants were enrolled in the CaPSURE prospective cohort study of biopsy-proven, localized PCa. Beginning in 1995, the CaPSURE registry accrued clinical and patient-reported data for more than 15 000 patients from 45 urology practices, largely community-based, across the USA [18]. Up to 1998, accrual was both retrospective and prospective; after 1999, all accrual was prospective. Participating urologists at each site consecutively recruited men within 6 mo of diagnosis, reporting their clinical, treatment, and outcome data. Patients self-reported demographic, comorbidity, and quality-of-life data at baseline and regular follow-up intervals. Comorbidities were assessed using the Charlson comorbidity index [19]. All CaPSURE participants provided written informed consent under supervision of local and central institutional review boards [18].

Treatments were planned and initiated according to usual practices at participating sites and patients were followed until withdrawal from the study or death. Clinicians reported mortality, which was subsequently verified via death certificate review. PCSM was defined as PCa listed as a primary, secondary, or tertiary (in terms of chain of causality) cause of death on the certificate with no other malignancy listed as a higher-order cause. The National Death Index was queried periodically (most recently in June 2022) for the date and cause of death for patients who were lost to follow-up or whose death certificate was unavailable. Perioperative mortality and death due to complications of radiation and/or ADT contributed to ACM but not to PCSM.

2.2. Statistical analysis

Patient demographic data (age at diagnosis, race/ethnicity, number of comorbidities) and clinicopathologic characteristics (PSA, clinical T stage, Gleason grade, and percentage of positive biopsy cores) were

compared between treatment groups using χ^2 and Mantel-Haenszel χ^2 tests for categorical and categorized continuous variables, respectively, and Student *t* test and analysis of variance for continuous variables.

Granular clinical PCa risk at diagnosis was assessed using two widely used, well-validated pretreatment instruments to broaden the applicability of our risk-adjusted analyses: the pretreatment nomogram published by Stephenson et al. [20] and the UCSF-Cancer of the Prostate Risk Assessment (CAPRA) score [21]. Both instruments assess risk on the basis of PSA, Gleason score, clinical stage, and number or percent of positive biopsy cores; CAPRA also includes age. The CAPRA score was imputed if there was exactly one missing variable. For our nomogram-based analyses, risk was expressed as the Stephenson score subtracted from 100 (100 − nomogram), with higher numbers indicating higher risk.

Primary treatments included RP, BT, EBRT, PADT, and AS/WW. The RP group included patients receiving RP monotherapy or RP with adjuvant/salvage EBRT. Men who received combination low-dose-rate or high-dose-rate BT with EBRT were classified as receiving primary BT. The use of bilateral orchiectomy or luteinizing hormone–releasing hormone agonists/antagonists ± antiandrogens without subsequent local definitive therapy was classified as PADT. We combined AS and WW into a single group owing to variability in eligibility and monitoring practices across CaPSURE sites and over time.

Outcomes of interest were PCSM and ACM. Kaplan-Meier time-to-event curves stratified by treatment were compared using the log-rank test. Follow-up was counted from the date of primary treatment, and patients were censored at the date of their last PSA test or office visit. Risk-adjusted Weibull parametric regression analyses were used to evaluate each outcome event. Clinical CAPRA risk and 100 −nomogram were used in place of the component variables, adjusted for age, comorbidities, and primary treatment. For each endpoint, the hazard ratio (HR) with 95% confidence interval (CI) was calculated for BT, EBRT, PADT, and AS/WW in comparison to RP. Model covariates were assessed for inter-item correlations. For sensitivity analyses, we used competing-risks regression to evaluate survival and conducted a landmark analysis among men with at least 5 yr of cancer-specific survival after primary treatment.

To further explore the outcome difference between RP and EBRT and to reflect the propensity for treatment assignment and any imbalances in censoring, we built a weight-adjusted censoring inverse probability weighted regression adjustment (IPWRA) model (*stteffects* package in Stata), with CAPRA score as the major independent predictor of outcome. CAPRA, age, and comorbidity were included as predictors of treatment selection, and age and comorbidity as predictors of censoring.

Despite careful risk adjustment, we recognize that confounding by indication and other unmeasurable confounding may affect our results. We therefore calculated E-values—which serve as a means of quantifying a boundary on how strong unmeasured confounding factors would need to be to negate the results [22]—for the HRs between RP and EBRT using both the CAPRA and 100 − nomogram-adjusted models. Finally, as a thought experiment to further quantify how extensive unmeasured confounding would need to be to alter our primary findings with respect to RP and EBRT, we artificially increased the 100 − nomogram in progressive 5-point increments for EBRT patients to estimate the extent of unmeasured confounding that would need to be assumed to nullify the results [16]. All statistical tests were two-sided and analyses were performed using Stata version 16 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Patient cohort

In total, 15 332 men were enrolled in CaPSURE. The last patient was accrued in October 2017 (Supplementary Fig. 1), with the most recent follow-up recorded in June 2022. Of these, 406 were excluded for metastatic (cN1 and/or cM1) and 170 for locally advanced (cT3b or cT4) disease at diagnosis. Of the remaining 14 756 men, 13 498 received RP, BT, EBRT, PADT, or AS/WW as their primary treatment. Men with <12 mo of follow-up after primary treatment (n = 757) or more than one missing risk parameter at diagnosis (n = 877) were excluded. Thus, 11 864 men comprised the final cohort (Fig. 1).

3.2. Baseline patient demographics and clinical characteristics

In the final cohort, 6227 men (53%) underwent RP, 1645 (14%) received BT, 1462 (12%) underwent EBRT, 1510 (13%) received PADT, and 1020 (9%) were managed with AS/WW. Baseline patient demographics and clinical characteristics stratified by primary treatment group are summarized in Table 1. All patient demographics and clinical characteristics differed between the treatment groups (p < 0.001). Men who underwent RP were younger and had fewer comorbidities than patients undergoing other treatments. A higher proportion of men who underwent AS/WW had Gleason grade ≤6 at biopsy, ≤10% positive biopsy cores, and clinical stage T1 in comparison to the other treatment groups. Patient age, CAPRA score, and 100 − nomogram at diagnosis were highest for men treated with PADT. CAPRA scores and 100 − nomogram were very highly correlated (Pearson's r = 0.84; p < 0.001). Among RP patients, 5.4% received postprostatectomy RT at any point (3.8%, 6.6%, and 11.2% of those with CAPRA score 0–2, 3–5, and 6–10 tumors, respectively; Supplementary Table 1). The median EBRT dosage was 72 Gy (interquartile range [IQR] 69–76). Rates of neoadjuvant/adjuvant ADT were 31%, 48%, and 66% for men undergoing EBRT, and 28%, 43%, and 59% for men undergoing BT for CAPRA score 0–2, 3–5, and 6–10 tumors, respectively. Fewer than 1% of radiation patients received any subsequent local therapy. By contrast, 32.4% of AS/WW patients eventually received treatment. The median follow-up for men not dying from PCa was 87 mo (IQR 45–149), with 3849 patients surviving for at least 10 yr and 1577 for at least 15 yr.

3.3. PCSM and ACM outcomes

During extended follow-up, 5793 deaths were reported, of which 764 were attributed to PCa as the cause. PCSM risk increased consistently with increasing CAPRA score across all treatments (Supplementary Fig. 1). An unadjusted cumulative hazard plot for PCSM by treatment is presented in Figure 2. There were statistically significant differences in survival rates across treatment types (log-rank test,

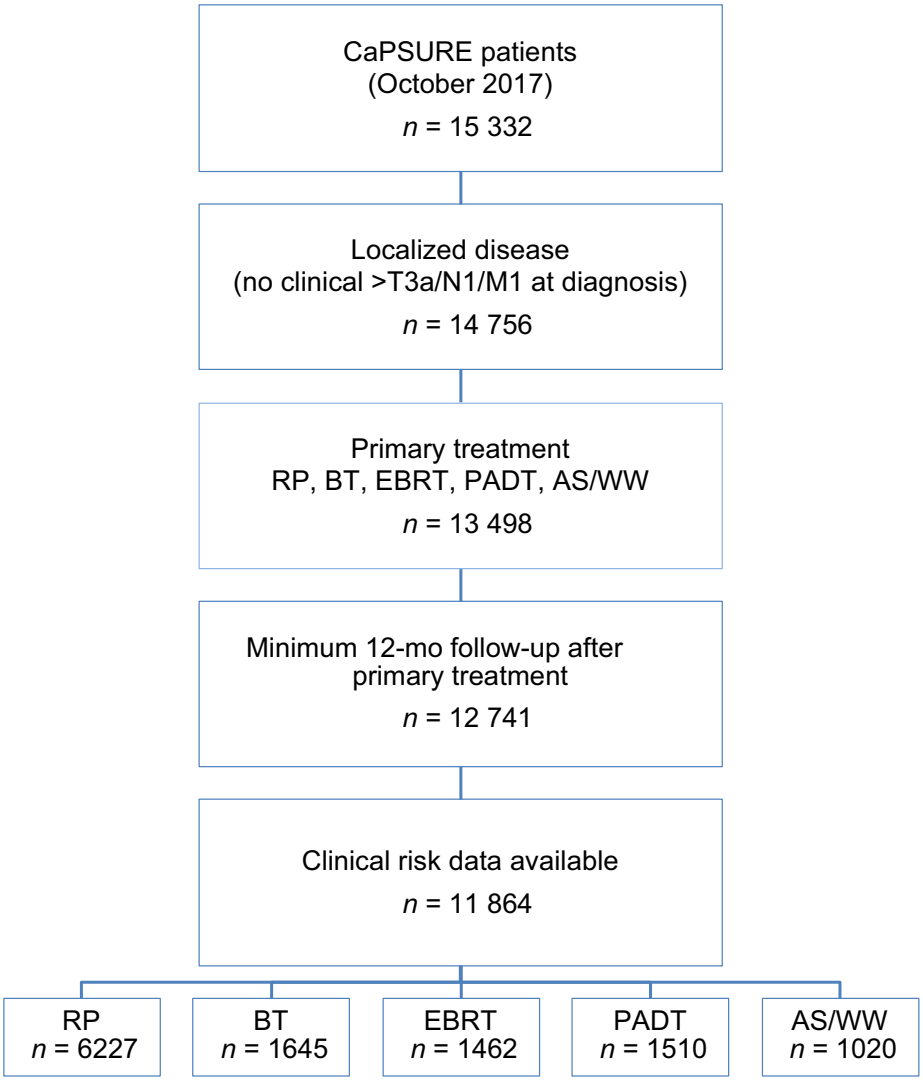

Fig. 1 – Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the study cohort. CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor; RP = radical prostatectomy; BT = brachytherapy; EBRT = external beam radiation therapy; PADT = primary androgen deprivation therapy; AS = active surveillance; WW = watchful waiting.

$p < 0.001$). Univariate cumulative hazard plots for PCSM by CAPRA risk group are presented in Supplementary Figure 2.

The risk-adjusted analysis results are presented in Table 2. After adjustment for clinical CAPRA score, the HR for PCSM was 1.57 (95% CI 1.24–1.98; $p < 0.001$) for BT, 1.55 (95% CI 1.26–1.91; $p < 0.001$) for EBRT, 2.36 (95% CI 1.94–2.87; $p < 0.001$) for PADT, and 1.76 (95% CI 1.30–2.40; $p < 0.001$) for AS/WW in comparison to RP. Figure 3 and Supplementary Table 2 present model predictions for 20-yr PCSM by risk for each treatment. Survival differences are minimal for men with lower-risk disease, but increase at higher levels of risk. The use of 100 – nomogram yielded similar HRs of 1.66 (95% CI 1.30–2.13; $p < 0.001$) for BT, 1.73 (95% CI 1.38–2.17; $p < 0.001$) for EBRT, 2.40 (95% CI 1.94–2.97; $p < 0.001$) for PADT, and 1.88 (95% CI 1.36–2.60; $p < 0.001$) for AS/WW in comparison to RP (Table 2). In our landmark analysis with minimum follow-up of 5 yr, we again observed higher PCSM risk with other treatments in comparison to RP, with HRs (adjusted for CAPRA) of 1.66 (95% CI 1.29–2.14; $p < 0.001$) for BT, 1.64 (95% CI 1.31–2.04; $p < 0.001$) for EBRT, 2.21 (95% CI 1.77–2.76; $p < 0.001$) for PADT, and 1.83 (95% CI 1.31–2.55; $p < 0.001$) for AS/WW.

After adjustment for age, comorbidity, and clinical CAPRA score, the HRs for ACM were 1.39 (95% CI 1.26–1.52) for BT, 1.32 (95% CI 1.20–1.44) for EBRT, 1.79 (95% CI 1.62–1.98) for PADT, and 1.50 (95% CI 1.34–1.68) for AS/WW in comparison to RP (all $p < 0.001$). After adjustment for 100 – nomogram, comparable results were obtained, with HRs of 1.36 (95% CI 1.23–1.51) for BT, 1.34 (95% CI 1.21–1.49) for EBRT, 1.77 (95% CI 1.59–1.97) for PADT, and 1.51 (95% CI 1.33–1.71) for AS/WW in comparison to RP (all $p < 0.001$; Table 2).

Competing-risk analysis again showed that all other treatment groups in comparison to RP were associated with greater ACM after adjustment for age and clinical CAPRA score, with HRs of 1.33 (95% CI 1.04–1.70; $p = 0.021$) for BT, 1.42 (95% CI 1.13–1.77; $p = 0.003$) for EBRT, 1.79 (95% CI 1.42–2.25; $p < 0.001$) for PADT, and 1.45 (95% CI 1.05–2.00; $p = 0.023$) for AS/WW (Table 2). After adjustment for age and 100 – nomogram, similar HRs for ACM were

Table 1 – Patient demographics and clinical characteristics at diagnosis by primary treatment group

Parameter	RP (n = 6227)	BT (n = 1645)	EBRT (n = 1462)	PADT (n = 1510)	AS/WW (n = 1020)	p value
Median age, yr (IQR)	62 (57–67)	69 (63–74)	71 (66–75)	74 (68–79)	72 (65–77)	<0.001
Race/ethnicity, n (%)						<0.001
Caucasian	5482 (88)	1452 (88)	1215 (83)	1202 (80)	912 (89)	
African American	537 (8.6)	120 (7.3)	202 (14)	237 (16)	72 (7.1)	
Other	208 (3.3)	73 (4.4)	45 (3.1)	71 (4.7)	36 (3.5)	
Comorbidities, n (%)						<0.001
0 comorbidities	1090 (18)	141 (8.6)	152 (10.4)	114 (7.6)	104 (10)	
1 comorbidity	1525 (25)	305 (18.5)	261 (17.9)	206 (14)	163 (16)	
2 comorbidities	1209 (19)	333 (20.2)	296 (20.3)	267 (18)	195 (19)	
3 comorbidities	658 (11)	237 (14.4)	193 (13.2)	255 (17)	144 (14)	
>3 comorbidities	423 (6.8)	183 (11.1)	214 (14.6)	236 (16)	162 (16)	
Data missing	1322 (21)	446 (27)	346 (24)	432 (29)	252 (25)	
Median PSA, ng/ml (IQR)	5.9 (4.5–8.7)	6.1 (4.6–8.7)	8.4 (5.5–14.6)	10.7 (6.4–23)	6 (4.4–8.5)	<0.001
PSA category, n (%)						<0.001
0–6 ng/ml	3192 (51)	795 (48)	415 (28)	318 (21)	507 (50)	
6.01–10 ng/ml	1721 (28)	515 (31)	428 (29)	370 (25)	310 (30)	
10.01–20 ng/ml	839 (14)	224 (14)	354 (24)	352 (23)	135 (13)	
20.01–30 ng/ml	163 (2.6)	38 (2.3)	88 (6)	140 (9.3)	26 (2.6)	
>30 ng/ml	135 (2.2)	33 (2)	131 (9)	286 (19)	19 (1.9)	
Data missing	177 (2.8)	40 (2.4)	46 (3.2)	44 (2.9)	23 (2.3)	
Bx Gleason grade, n (%)						<0.001
2-6	4029 (65)	1135 (69)	713 (49)	663 (44)	825 (81)	
7 (3 + 4)	1163 (19)	261 (16)	307 (21)	272 (18)	94 (9.2)	
7 (4 + 3)	498 (8)	135 (8.2)	177 (12)	208 (14)	48 (4.7)	
8–10	424 (6.8)	98 (6)	215 (15)	329 (22)	23 (2.3)	
Data missing	113 (1.8)	16 (1)	50 (3.4)	38 (2.5)	30 (2.9)	
Median PPBC, % (IQR)	30 (17–50)	25 (14–44)	41.7 (20–68)	42.9 (17–75)	16.7 (10–33)	<0.001
PPBC, n (%)						<0.001
≤10%	685 (11)	281 (17)	109 (7.5)	141 (9.3)	252 (25)	
11–33%	2331 (37)	693 (42)	391 (27)	386 (26)	416 (41)	
34–50%	1695 (27)	413 (25)	418 (29)	374 (25)	168 (17)	
51–75%	642 (10)	117 (7.1)	198 (14)	183 (12)	31 (3)	
>75%	585 (9.4)	115 (7)	270 (19)	319 (21)	65 (6.4)	
Data missing	289 (4.6)	26 (1.6)	76 (5.2)	107 (7.1)	88 (8.6)	
Clinical T stage, n (%)						<0.001
cT1	3183 (51)	800 (49)	629 (43)	595 (39)	601 (59)	
cT2a	1242 (20)	387 (23.5)	307 (21)	268 (18)	216 (21)	
cT2b	457 (7.3)	63 (3.8)	122 (8.3)	124 (8.2)	52 (5.1)	
cT2c	1099 (18)	285 (17)	298 (20)	367 (24.3)	84 (8.2)	
cT3a	67 (1.1)	13 (0.8)	58 (4)	90 (6)	12 (1.2)	
Data missing	179 (2.9)	97 (5.9)	48 (3.3)	66 (4.4)	55 (5.4)	
Median CAPRA score (IQR)	2 (1–4)	2 (1–3)	3.5 (2–5)	4 (3–7)	2 (1–3)	<0.001
CAPRA risk group, n (%)						<0.001
Low (0–2)	3436 (55)	955 (58)	435 (30)	390 (26)	664 (65)	
Intermediate (3–5)	2298 (37)	555 (34)	669 (46)	592 (39)	301 (30)	
High (6–10)	493 (7.9)	135 (8.2)	358 (25)	528 (35)	55 (5.4)	
Median 100-nomogram score (IQR)	15 (9–23)	15 (9–22)	21 (14–39)	30 (16–54.5)	11 (8–18)	<0.001
PCa deaths (n)	263	94	150	208	49	

RP = radical prostatectomy; BT = brachytherapy; EBRT = external beam radiation therapy; PADT = primary androgen deprivation therapy; AS = active surveillance; WW = watchful waiting; IQR = interquartile range; PSA = prostate-specific antigen; CAPRA = Cancer of the Prostate Risk Assessment (score from 0 to 10); Bx = biopsy; PPBC = percentage positive Bx cores; PCa = prostate cancer.

obtained (Table 2). On exclusion of patients who received delayed local therapy, the HR for AS/WW was higher at 2.67 (95% CI 1.83–3.88). In the IPWRA analysis adjusted for factors associated with treatment assignment and with censoring, EBRT was associated with a 3.3-yr (95% CI 0.3–6.4; p = 0.034) earlier time to PCSM in comparison to RP.

The E-values associated with the HRs of 1.55 and 1.73 for EBRT versus RP in the CAPRA-adjusted and 100 − nomogram-adjusted models were 2.48 ± 1.84 and 2.85 ± 2.10, respectively, indicating that in order to explain the HRs observed, residual unmeasured confounding factors would need to be associated with both treatment and outcome by at least 2.5-fold [22]. Finally, in our thought experiment in which 100 − nomogram values were artificially increased for patients who underwent EBRT, the difference in PCSM between RP and EBRT remained statistically significant until the increase was 20 points, and the HR did not cross 1.0 until the scores were increased by ≥25 points (Supplementary Table 3). This indicates that in order for the results to be explained by residual confounding, unmeasured risk factors equivalent to a 25-point increase in 100 − nomogram would need to be consistently present among EBRT patients.

4. Discussion

The optimal treatment for localized PCa has remained controversial over the years because of inconclusive results from observational studies and the few RCTs on this topic. In fact, a report on comparative effectiveness research (CER) from the Institute of Medicine identified localized PCa among the top 25 national priority areas for improvements in CER [23]. Our current long-term outcomes analysis

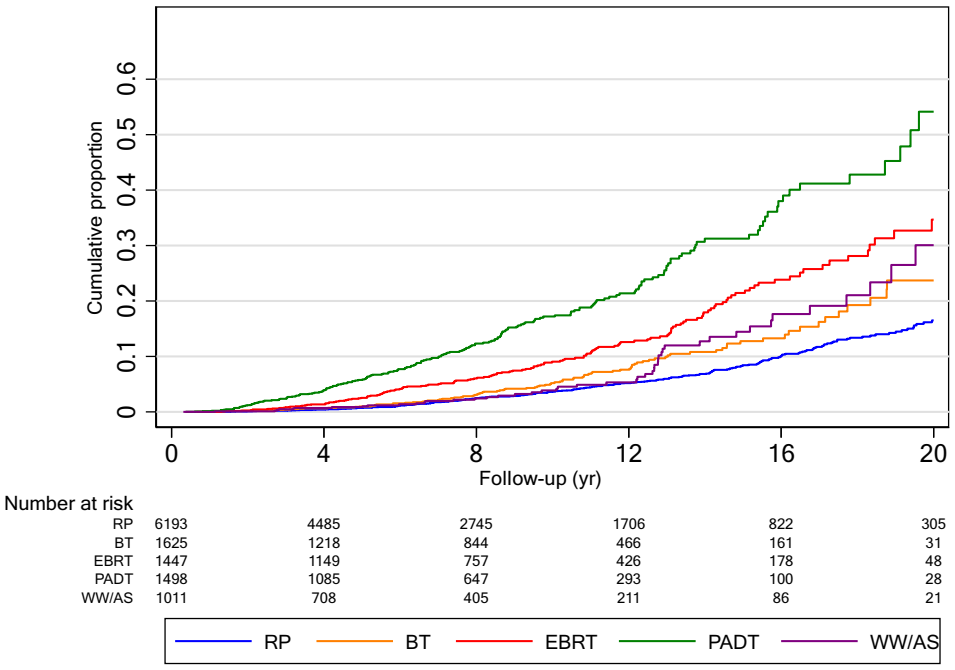

Fig. 2 – Unadjusted Kaplan-Meier curves demonstrating the likelihood of prostate cancer–specific mortality by type of primary treatment. The 95% confidence intervals are presented as dashed lines for each treatment. Outcomes varied statistically significantly by primary treatment ($p < 0.001$, log-rank test). RP = radical prostatectomy; BT = brachytherapy; EBRT = external beam radiation therapy; PADT = primary androgen deprivation therapy; AS = active surveillance; WW = watchful waiting.

further supports the conclusions from our earlier 2010 study of risk-adjusted mortality outcomes after primary treatment, this time with substantially longer follow-up, and now also including BT and AS/WW as management strategies [16].

We were able to confirm again statistically significant and clinically meaningful differences in ACM and PCSM rates across primary treatments when controlling closely for tumor risk factors and other clinical parameters. Differences across treatment arms were particularly distinct with increasing risk. Survival among men with low-risk tumors, regardless of treatment or observation, was very high, and our results certainly support the use of AS or WW for most low-risk and many intermediate-risk tumors. By contrast, among men with higher-risk disease, those who received local therapy had better survival outcomes than those managed more conservatively, and in our models the best survival outcomes for higher-risk disease were observed for men whose first treatment was RP.

These findings are largely consistent with a meta-analysis by Wallis et al [17] with input from both urology and radiation oncology experts that revealed better survival following initial RP than after initial RT across ten studies, with HRs of 1.63 (95% CI 1.54–1.73) for overall mortality and 2.08 (95% CI 1.76–2.47) for PCSM [17]. In comparison to most of the studies included in that meta-analysis, however, our analysis includes much more granular and detailed risk adjustment, substantially longer follow-up, and inclusion of men managed with all the major treatment strategies. Our findings are consistent across a range of analytic and sensitivity strategies. Moreover, while residual confounding due to selection bias is a potential concern in any nonrandomized study, the thought experiment we performed raising 100 – nomogram for EBRT patients indicates that to fully explain our observations about RP vs. EBRT, such confounding would have to be present to a very high degree and consistency. Likewise, the E-values calculated indicate that there would need to be an implausibly large degree of residual confounding (equivalent to a HR >2.5) to explain away the results.

While RCTs remain the gold standard for comparisons between treatment options for PCa, they face challenges related to high costs associated with long-term follow-up, technical innovations during the course of a trial, and crossover after randomization. One contemporary RCT, the ProtecT trial, recently reported 15-yr PCSM and ACM data from a cohort of 1643 men with localized PCa randomized to either active monitoring, RP, or EBRT [10]. The incidence of both clinical progression and metastases was lower in the groups receiving either definitive treatment, and the incidence of biochemical progression was lower after RP than after EBRT, but there were no differences in mortality rates among the three groups [10].

ProtecT was a remarkably successful trial, but enrolled men largely with low- or intermediate-risk PCa at diagnosis (71%, 26%, and 2% for CAPRA scores of 0–2, 3–5, and 6–10, respectively) [24,25]. Even the 15-yr median follow-up is too short to assess mortality endpoints in low- and intermediate-risk PCa; only 45 PCSM events have accrued to date [17]. As of the 10-yr analysis, PCSM events attributed to the RP arm disproportionately affected men who did not receive the intended treatment; only two of five men who died of PCa in the RP arm actually received RP, versus four of four men in the RT arm [11]. The 15-yr results so far have only been presented on an intent-to-treat basis, so it is too soon to know whether differences between RP

Table 2 – Weibull regression analysis of PCSM and ACM and Fine-Gray competing-risk analysis of ACM with radical prostatectomy as the reference

	Weibull regression analysis						Fine-Gray competing-risk analysis			
	PCSM				ACM[a]		ACM[b]			
	CAPRA score		100 − nomogram		CAPRA score		100 − nomogram		CAPRA score		100 − nomogram	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
BT	1.57 (1.24–1.98)	<0.001	1.66 (1.30–2.13)	<0.001	1.39 (1.26–1.52)	<0.001	1.36 (1.23–1.51)	<0.001	1.33 (1.04–1.70)	0.021	1.42 (1.09–1.84)	0.008
EBRT	1.55 (1.26–1.91)	<0.001	1.73 (1.38–2.17)	<0.001	1.32 (1.20–1.44)	<0.001	1.34 (1.21–1.49)	<0.001	1.42 (1.13–1.77)	0.003	1.52 (1.18–1.95)	0.001
PADT	2.36 (1.94–2.87)	<0.001	2.40 (1.94–2.97)	<0.001	1.79 (1.62–1.98)	<0.001	1.77 (1.59–1.97)	<0.001	1.79 (1.42–2.25)	<0.001	1.78 (1.37–2.30)	<0.001
AS/WW	1.76 (1.30–2.40)	<0.001	1.88 (1.36–2.60)	<0.001	1.50 (1.34–1.68)	<0.001	1.51 (1.33–1.71)	<0.001	1.45 (1.05–2.00)	0.023	1.52 (1.08–2.14)	0.017
CAPRA score	1.39 (1.35–1.44)	<0.001			1.08 (1.07–1.10)	<0.001			1.36 (1.32–1.41)	<0.001		
100 − nomogram			1.03 (1.02–1.03)	<0.001			1.01 (1.00–1.01)	<0.001			1.03 (1.02–1.03)	<0.001

PCSM = prostate cancer-specific mortality; ACM = all-cause mortality; CAPRA = Cancer of the Prostate Risk Assessment; HR = hazard ratio; CI = confidence interval; RP = radical prostatectomy; BT = brachytherapy; EBRT = external beam radiation therapy; PADT = primary androgen deprivation therapy; AS = active surveillance; WW = watchful waiting.

[a] Adjusted for age and comorbidity.

[b] Adjusted for age.

and RT will emerge from further analyses. Longer follow-up in ProtecT, and another ongoing RCT focused on higher-risk tumors (SPCG-15) [26], will be critically important, but data are not yet available. In the meantime, carefully adjusted observational studies may shed complementary light on this important clinical question.

In one notable exception to the general finding of superior survival for RP among men with high-risk disease, Kishan et al [27] retrospectively compared oncologic outcomes for men with high-grade Gleason 9–10 PCa who underwent RP, EBRT, or EBRT + BT at multiple large tertiary care centers. The adjusted 5-yr PCSM rate was lower with EBRT + BT (3%, 95% CI 1–5%) in comparison to RP or EBRT alone (12%, 95% CI 8–17%). Overall survival also favored EBRT + BT, but only until 7.5 yr of follow-up, after which the survival advantage did not persist [27]. Possible explanations for these results, which are not concordant with most other studies, include very high-dose radiation (91 Gy equivalent in the EBRT + BT group), inclusion only of men treated in tertiary care centers, shorter median follow-up, and restriction of the analysis to a very high-risk subset of men (Gleason 9–10 tumors account for only 391 [3.4%] of the men in our present analysis).

Limitations of our analysis need to be acknowledged. CaPSURE practice sites do not reflect a random sample of the overall PCa population in the USA. However, we have previously demonstrated that CaPSURE patients are largely similar to those represented in the Surveillance, Epidemiology and End Results database [21]. Second, central pathology review has never been performed for CaPSURE and older cases have not been regraded to contemporary standards. Third, other paradigms for the diagnostic work-up for PCa have evolved over time. Within this cohort, most patients did not undergo multiparametric magnetic resonance imaging with subsequent fusion-targeted biopsy at diagnosis or during active surveillance, or pretreatment prostate-specific membrane antigen positron emission tomography staging. Thus, it is very likely that the absolute mortality estimates from our model presented in Figure 3 substantially overestimate the absolute risk for contemporary patients and do not apply to men diagnosed today. However, there is no reason to believe that these changes would affect the relative differences observed between primary treatment modalities.

Fourth, we only have radiation dose data for a subset of men in CaPSURE and the dose was generally lower than the current standard among those for whom we have data. Improvements in radiation dose and technique over the past decades have evolved, potentially driving better outcomes today although it has been shown that these largely improve biochemical outcomes and not necessarily PCSM or overall survival [28], and are relatively unlikely to explain the magnitude of differences we observe. CaPSURE includes few men treated with proton-beam therapy or stereotactic body radiation therapy; however, neither of these emerging modalities has been shown to improve mortality outcomes compared to other forms of EBRT.

Neoadjuvant ADT improves survival outcomes for men with higher-risk PCa treated with EBRT [29]. Neoadjuvant ADT rates for EBRT patients in CaPSURE track closely with

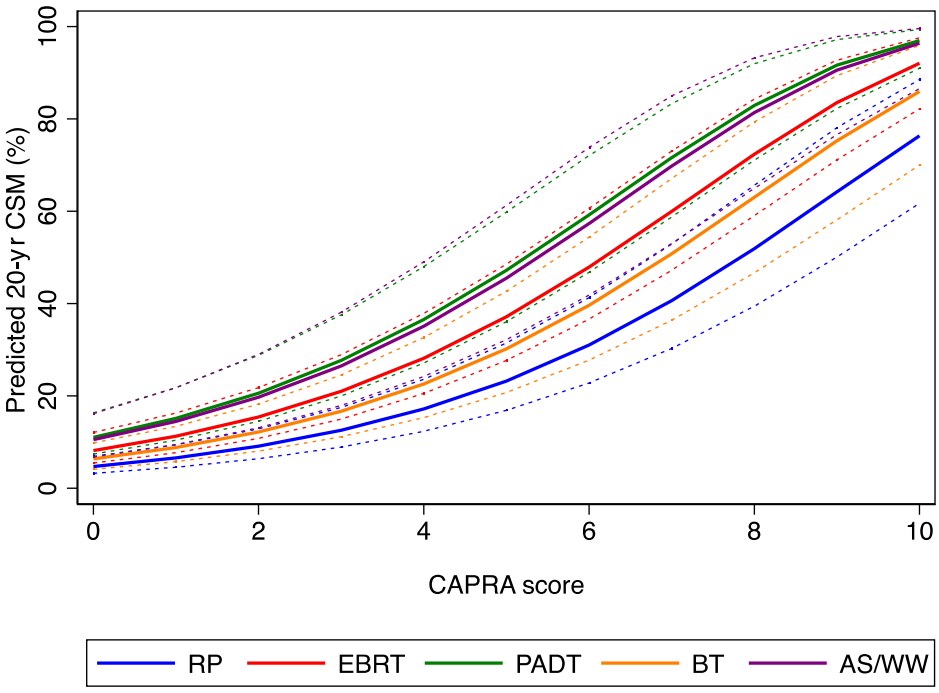

Fig. 3 – Predicted 20-yr CSM by type of primary treatment. The 95% confidence intervals are presented as dashed lines for each treatment. CSM = cancer-specific mortality; RP = radical prostatectomy; EBRT = external beam radiation therapy; PADT = primary androgen deprivation therapy; BT = brachytherapy; AS = active surveillance; WW = watchful waiting; CAPRA = Cancer of the Prostate Risk Assessment.

risk, and mostly increased over the accrual period. The mean treatment duration was 5 mo; relatively few patients received ≥2 yr of ADT [30]. Underuse of ADT for EBRT patients, while not a negligible concern, is unlikely to fully explain the large survival differences we observed. Rates of post-prostatectomy RT (either adjuvant or salvage) were also quite low relative to what would be expected for higher-risk disease in current contemporary practice, which would reduce the survival benefit associated with primary RP.

Fifth, we are not able to definitively differentiate patients undergoing AS from those on WW, which could affect the mortality rates depending on the relative contribution of healthier AS patients versus patients with greater comorbidity who may have been managed with WW rather than active treatment or AS. Rates of secondary treatment after initial AS/WW were higher than after other treatments, although not as high as observed in, for example, ProtecT; without such crossover, mortality differences between AS/WW and local therapy would be higher, as indicated in our subset analysis excluding patients undergoing delayed intervention.

Finally, as this was not a randomized trial, the possibility certainly remains that residual or unmeasured confounding may explain the differences observed between treatment arms. However, our E-value analyses and risk-shifting thought experiment both indicate that such confounding would have to be both large and pervasively consistent, which does not seem likely given the extent to which we are able to control closely for tumor risk and other patient variables.

Particular strengths of our study, as noted above, include the representation of a variety of practice locations, sizes, and treatment strategies in CaPSURE, mostly reflecting PCa patients managed in a community setting; better granularity of risk stratification details; longer follow-up; fewer missing data; and greater inclusion of varied treatment approaches. We report one of the largest extant subcohorts of men dying of PCa. We would emphasize that long-term mortality is only one consideration for men diagnosed with PCa; different treatment options are associated with differential toxicities and risks to short- and long-term quality of life, as has been well-documented via long-term studies in CaPSURE [7] and many other cohorts. Shared decision-making should reflect patient priorities with respect to both length and quality of life.

5. Conclusions

In a large, prospective, multicenter, community-based cohort of men with localized PCa, PCSM was lowest following surgery and highest following PADT and AS/WW. Differences were minimal for low-risk disease. A greater difference in PCSM between treatment groups was noted for the group of patients with higher-risk disease, for whom RP as the first treatment was associated with better PSCM. These findings were stable across a range of sensitivity analyses, and might support a greater role for surgery in higher-risk disease. We stress that in these cases, RP is often appropriately the first phase in a multimodal strategy that also includes secondary RT and/or ADT. PADT should not be used as monotherapy for localized disease, whether high-risk PCa or otherwise. Many caveats apply to the interpretation of retrospective analyses, particularly with respect to unmeasured confounding, and we await further follow-up from long-term RCTs to help in further elucidating differences in survival across these treatment modalities.

Author contributions: Matthew R. Cooperberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Herlemann, Cooperberg.
Acquisition of data: Cowan, Broering, Carroll, Cooperberg.
Analysis and interpretation of data: Herlemann, Cowan, Cooperberg.
Drafting of the manuscript: Herlemann, Cooperberg.
Critical revision of the manuscript for important intellectual content: Herlemann, Cowan, Washington, Wong, Broering, Carroll, Cooperberg.
Statistical analysis: Carroll, Cooperberg.
Obtaining funding: Carroll, Cooperberg.
Administrative, technical, or material support: Carroll.
Supervision: Cooperberg, Carroll.
Other: None.

Financial disclosures: Matthew R. Cooperberg certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This work was supported by the US Department of Defense Prostate Cancer Research Program W81XWH-13-2-0074. The sponsor played a role in the design and conduct of the study and in data collection.

Peer Review Summary

Peer Review Summary and Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2023.09.024.

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