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Observation, Radiotherapy, or Radical Prostatectomy for Localized Prostate Cancer: Survival Analysis in the United States

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Purpose: Contemporary treatment strategies for localized prostate cancer (PCa) have been evolved over time. However, there is little data regarding survival outcomes based on initial treatment by risk group in this new era. This study aims to evaluate survival outcomes among men who underwent observation, radiotherapy, or radical prostatectomy for localized PCa using a population-based cohort.

Materials and Methods: The Surveillance, Epidemiology, and End Results (SEER) prostate with watchful waiting dataset (2010–2016) was used. We included men diagnosed with localized PCa and clinical stage T1c-2cN0M0. Other inclusion criteria were age 50–79 years, prostate-specific antigen (PSA) ≤50 ng/mL, and initial treatment with observation (active surveillance/watchful waiting), radiotherapy, or radical prostatectomy. PCa risk was assessed using the D'Amico classification. The primary endpoint was overall survival. Secondary endpoints included PCa-specific survival. Inverse probability of treatment weighting (IPTW)-adjusted Cox proportional hazard regression and competing risk analysis were performed to assess outcomes.

Results: After IPTW-adjusting, pseudo-population comprised 521,656 men (observation: 170,428, radiotherapy: 175,628, radical prostatectomy: 175,600) at a median 36.5 month follow-up. Observation demonstrated the lowest 5-year overall survival rate (91.6%) after IPTW-adjusting in comparison to radiotherapy (92.4%) and radical prostatectomy (96.1%, p<0.001). Men who underwent radical prostatectomy had the lowest cumulative PCa-specific and all-cause mortality (p<0.001). Compared to observation, radiotherapy (sub-distribution hazard ratio [sHR], 0.89; 95% CI, 0.81–0.97; p=0.012) and radical prostatectomy (sHR, 0.46; 95% CI, 0.41–0.52; p<.001) had a lower risk of PCa-specific mortality in competing risk analysis after adjustment for all other factors and other-cause death.

Conclusions: Intermediate-term mortality risk in men with localized PCa were lower with active treatments compared to observation - especially for intermediate- and high-risk disease. However, observation represents a safe management strategy in men within the low-risk group.

Keywords: Observation; Prostatectomy; Prostatic neoplasms; Radiotherapy; Survival

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INTRODUCTION

Previous studies have been unable to conclusively determine if prostate cancer-specific mortality (PCSM) outcompetes the risk of other-cause mortality (OCM) in clinically - localized disease. Available treatment modalities include observation (active surveillance [AS] or watchful waiting [WW]), radiotherapy (RT), or radical prostatectomy (RP), and each modality is performed in approximately 20%-40% of localized prostate cancer (PCa) cases [1], highly dependent on patient preferences and individual clinician practices [2,3]. The preferred treatment option of men with localized PCa, especially for intermediate- and high-risk disease, remains controversial due to its often protracted behavior.

Three randomized controlled trials (RCT), SPCG-4, PIVOT, and ProtecT were conducted through the late 1990s to early 2000s to compare observation *versus* active treatment in men with localized PCa [4-6]. However, these trials have limitations making it difficult to generalize their findings to widespread clinical practice: SPGC-4 was conducted before the prostate-specific antigen (PSA) era. The PIVOT trial, performed in the early era of PSA testing, suffered low enrollment and statistical power, as well as high rates of crossover, and of non-PCa related mortality. The ProtecT trial only enrolled a small number of men with high-risk disease, and the monitoring group was based on PSA follow-up only which does not represent the current standard; furthermore the event rate published to date is extremely low and again subject to substantial crossover [7].

Several large population-based observational studies have attempted to address this gap by reflecting 'real-life situations' [8-12]. However, most of the data utilized in these studies do not accurately differentiate patients undergoing observation (AS or WW) from other non-active treatments, such as androgen-deprivation therapy and instead, used the data code "monitoring or conservative management" for both [2].

In this study, we evaluate survival outcomes after observation, RT, or RP in a large, contemporary, population-based sample of men with localized PCa from the Surveillance, Epidemiology, and End Results (SEER) prostate with watchful waiting (SEER-WW) database between 2010 and 2016, which provides a validated explicit indicator for observation. We aimed to examine whether significant survival differences exist according to initial treatment type and risk subgroups (low-, intermediate-, and high-risk) after rigorous adjustment in real-world data (RWD).

MATERIALS AND METHODS

1. Study design and population

This is a retrospective population-based cohort study. Initially, we identified 248,372 men diagnosed with localized PCa and clinical stage T1c-2cN0M0 from the SEER-WW dataset using imputations for missing data [2,3,13]. The SEER-WW dataset includes a dichotomous variable for observation (AS or WW, either yes or no/unknown) as an initial treatment plan. Men were aged 50–79 years with a PSA ≤50 ng/mL, and initial treatment with observation, RT, or RP.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [14].

2. Measurements and outcomes

The primary endpoint was overall survival. Secondary endpoints included PCa-specific and OCM. We also captured race/ethnicity, health insurance, marital status, SEER registry, PSA, clinical T stage, biopsy grade group, D'Amico risk group, and initial treatment.

3. Statistical analyses

Descriptive statistics were reported as mean, standard deviation (SD), median and interquartile range (IQR) for continuous variables. Frequency and percentage were presented for categorized variables. We used the χ^2 test and analysis of variance to compare differences of categorical and continuous variables among groups, respectively.

To adjust for selection bias, we used the propensity score-based weighting method. As we compared multiple–not binary - treatments, multinomial propensity scores were estimated using generalized boosted models for receiving each treatment [15]. All patient characteristics significantly different by treatment were used in the generalized boosted models as covariates. They included age at diagnosis, race, health insurance, marital status, SEER registry, PSA, clinical T stage, and biopsy grade group. The inverse probability of treatment weighting (IPTW) using propensity score for each patient was calculated to balance observable characteristics among groups. For IPTW-adjusting, we used twang

package version 1.5 in R. We constructed and tested 13 models using different settings for parameters and variables, then finally selected the best-balanced model. In this model, we set a maximum number of iterations as 30,000, 3-way interaction, which estimated as the average treatment effect on the population, and stop method as the mean of effect size. The balance in covariates among groups was assessed by the standardized difference before and after weighting.

Kaplan–Meier curves were presented according to initial treatment types, and a log-rank test was used to compare curves before and after IPTW-adjusting. Unadjusted and IPTW-adjusted standardized cumulative PCa-specific and all-cause mortalities according to initial treatments were calculated per 1,000 person-yr.

Then, univariate and multivariable Cox proportional hazard regression analyses to predict overall survival and PCa-specific survival were performed to calculate IPTW-adjusted hazard ratios (HRs), respectively. All significant variables in univariate regression analyses were used in multivariable models. Fine and Gray competing risk analyses were used to adjust for death from other-cause and IPTW-adjusted sub-distribution hazard ratios (sHRs) predicting for death from PCa by initial treatments were estimated [16]. In this way, we could avoid a common potential violation of proportional hazards assumption, and quantify PCSM after accounting for OCM. Subgroup analyses by D'Amico risk group were repeated for all regression models.

E-values for IPTW-adjusted HRs of PCa-specific survivals and IPTW-adjusted sHRs were calculated to evaluate how strong the unmeasured confounding would has to negate the observed results as sensitivity analysis [17,18]. The E-value is the minimum strength of association on the HR that an unmeasured confounder would need to have with both the exposure and the outcomes, conditional on the measured covariates, to fully explain away a specific exposure-outcome association [18].

A two-sided p-value <0.05 was considered statistically significant for all analyses. All statistical analyses were performed using R version 3.6 (http://www.r-project.org/) and SAS® 9.4 (SAS Institute).

4. Ethics statement

The Seoul National University Hospital Institutional Review Board deemed this study exempt from review and informed consent (approval number: 2112-100-1284) because patient information in these databases was completely de-identified and publicly available. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [14].

RESULTS

1. Study cohort

We identified 176,456 eligible patients from 248,372 men with localized PCa (clinical T1c-2cN0M0). The clinical characteristics at the time of the initial treatment are presented in Supplement Table 1. All variables differed significantly among groups (all p-value <0.001). After IPTW-adjustment, the patient number of the pseudo-population increased to 521,656 at a median 36.5 months (IQR, 18.9–54.0 months) follow-up. Table 1 shows the same baseline characteristics in the pseudo-

Table 1. Patient characteristics according to initial treatments in the inverse probability of treatment weighted cohort (n=521,656)

Variable	Observation (n=170,428)	Radiotherapy (n=175,628)	Radical prostatectomy (n=175,600)	p-value	SMD
Age, y	65.1±7.1 65.0 (60.0–70.0)	64.9±6.9 65.0 (59.0–70.0)	64.0±6.6 64.0 (59.0–70.0)	<0.001	0.103
Age group, y				0.302	0.017
50–59	44,533 (25.0)	44,685 (25.4)	45,068 (25.7)		
60–69	83,302 (48.9)	86,450 (49.2)	86,428 (49.2)		
70–79	44,593 (26.2)	44,493 (25.3)	44,105 (25.1)		
Race				0.556	0.011
White	133,189 (78.1)	136,915 (78.0)	137,082 (78.1)		
Black	26,284 (15.4)	26,778 (15.2)	26,581 (15.1)		
Others/unknown	10,955 (6.4)	11,935 (6.8)	11,937 (6.8)		

Table 1. Continued 1

Variable	Observation (n=170,428)	Radiotherapy (n=175,628)	Radical prostatectomy (n=175,600)	p-value	SMD
Health insurance				0.916	0.006
Insured	160,045 (93.9)	164,750 (93.8)	164,803 (93.9)		
Medicaid	7,804 (4.6)	8,332 (4.7)	8,208 (4.7)		
Uninsured	2,580 (1.5)	2,546 (1.4)	2,589 (1.5)		
Marital status				0.265	0.011
Married	128,839 (75.6)	133,829 (76.2)	134,030 (76.3)		
Unmarried	41,589 (24.4)	41,799 (23.8)	41,570 (23.7)		
SEER registry				0.997	0.025
Alaska Natives	17 (0.0)	35 (0.0)	41 (0.0)		
Atlanta (Metropolitan)	6,883 (4.0)	7,030(4.0)	7,002 (4.0)		
California excluding SF/SJM/LA	35,998 (21.1)	36,303 (20.7)	36,310 (20.7)		
Connecticut	8,543 (5.0)	8,699 (5.0)	8,760 (5.0)		
Detroit (Metropolitan)	10,193 (6.0)	10,881 (6.2)	10,855 (6.2)		
Greater Georgia	13,257 (7.8)	13,660 (7.8)	13,597 (7.7)		
Hawaii	1,574 (0.9)	1,995 (1.1)	1,988 (1.1)		
Iowa	7,146 (4.2)	7,209 (4.1)	7,280 (4.1)		
Kentucky	8,259 (4.8)	8,302 (4.7)	8,394 (4.8)		
Los Angeles	13,365 (7.8)	13,847 (7.9)	13,959 (7.9)		
Louisiana	10,461 (6.1)	11,251 (6.4)	11,300 (6.4)		
New Jersey	22,016 (12.9)	22,995 (13.1)	22,934 (13.1)		
New Mexico	2,510 (1.5)	2,792 (1.6)	2,771 (1.6)		
Rural Georgia	326 (0.2)	401 (0.2)	354 (0.2)		
San Francisco-Oakland SMSA	9,569 (5.6)	9,631 (5.5)	9,539 (5.4)		
San Jose-Monterey	5,124 (3.0)	5,320 (3.0)	5,253 (3.0)		
Seattle (Puget Sound)	10,404 (6.1)	10,365 (5.9)	10,349 (5.9)		
Utah	4,781 (2.8)	4,913 (2.8)	4,914 (2.8)		
PSA, ng/mL	7.9±5.6 6.3 (4.8–9.0)	8.0±6.0 6.3 (4.7–9.0)	7.8±5.8 6.1 (4.7–8.9)	<0.001	0.018
PSA, ng/mL				0.322	00.022
≤4	22,064 (12.6)	23,473 (13.4)	23,512 (13.4)		
4.1–10	115,111 (67.5)	117,836 (67.1)	117,699 (67.0)		
10.1–20	26,668 (15.6)	26,584 (15.1)	26,692 (15.2)		
20.1–50	6,586 (3.9)	7,735 (4.4)	7,697 (4.4)		
Clinical T stage				0.547	0.014
T1c	121,609 (71.4)	124,534 (70.9)	124,301 (70.8)		
T2a	24,238 (14.2)	24,639 (14.0)	24,632 (14.0)		
T2b-c	24,581 (14.4)	26,455 (15.1)	26,667 (15.2)		
Biopsy grade group				0.687	0.022
1	77,326 (45.4)	77,621 (44.2)	77,707 (44.3)		
2	50,332 (29.5)	52,114 (29.7)	51,994 (29.6)		
3	21,388 (12.5)	22,714 (12.9)	22,639 (12.9)		
4	14,482 (8.5)	15,193 (8.7)	15,308 (8.7)		
5	6,901 (4.0)	7,986 (4.5)	7,953 (4.5)		
D'Amico risk group				0.130	0.025
Low risk	85,881 (49.5)	56,256 (31.9)	52,136 (29.6)		
Intermediate risk	61,110 (35.2)	81,427 (46.2)	83,892 (47.6)		
High risk	26,413 (15.2)	38,557 (21.9)	40,072(22.8)		

Table 1. Continued 2

Variable	Observation (n=170,428)	Radiotherapy (n=175,628)	Radical prostatectomy (n=175,600)	p-value	SMD
Follow-up duration, mo	33.3±20.5 31.0 (16.0–50.0)	39.1±20.3 41.0 (23.0–56.0)	38.3±20.5 40.0 (21.0–56.0)	<0.001	
Survival				<0.001	
Alive	161,333 (94.7)	167,293 (95.3)	171,267 (97.5)		
Other cause death	8,232 (4.8)	7,480 (4.3)	3,913 (2.2)		
Disease specific death	863 (0.5)	854 (0.5)	420 (0.2)		

Continuous variables are expressed as mean±standard deviation or median (interquartile range) and categorical variables are expressed as frequency (percentage).
PSA: prostate-specific antigen, SEER: Surveillance, Epidemiology, and End Results, SF/SJM/LA: San Francisco/San Jose–Monterey/Los Angeles, SMD: standardized mean difference, SMSA: standard metropolitan statistical area.

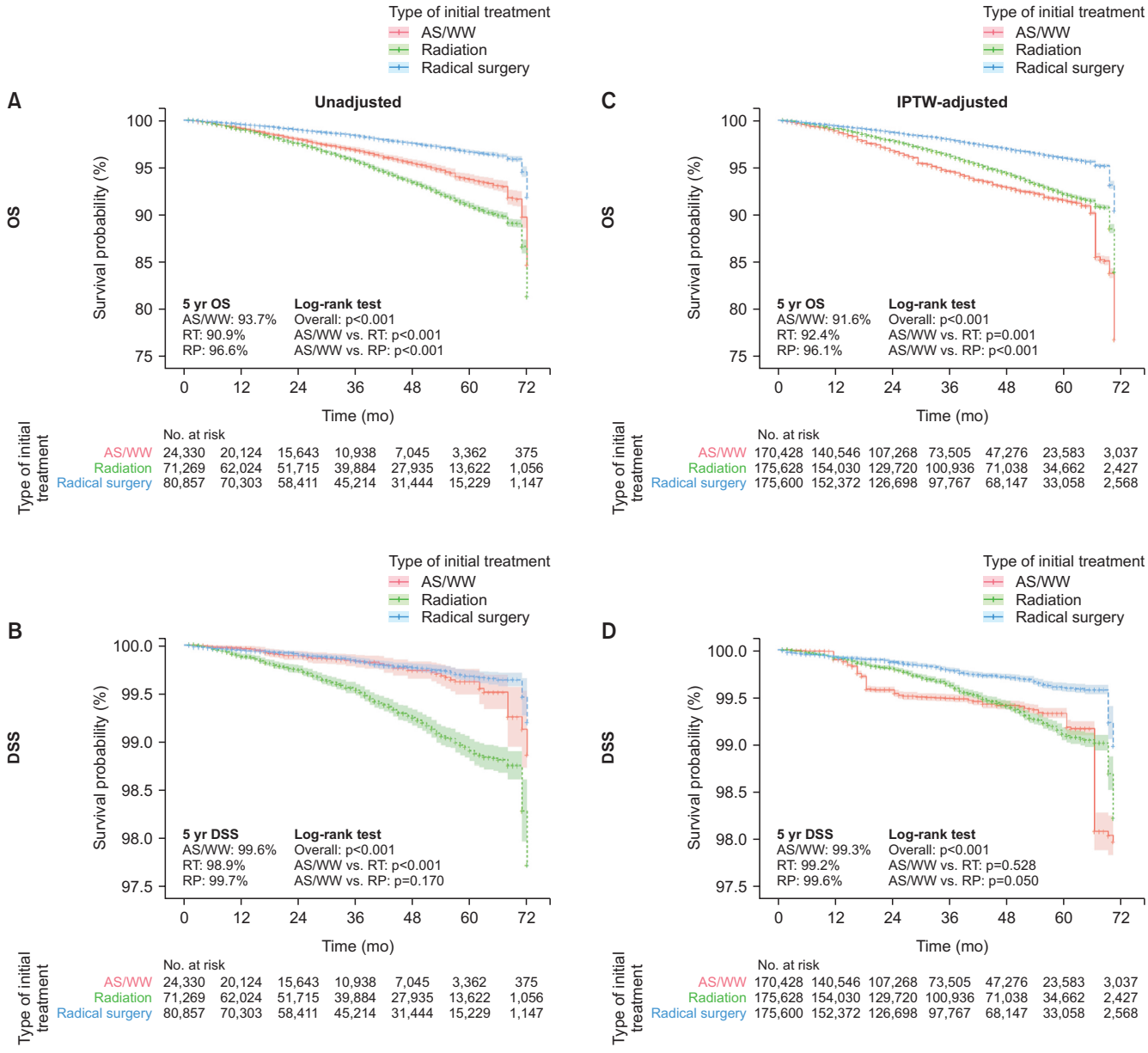

Fig. 1. Kaplan–Meier survival curves before and after IPTW-adjustment. OS (A) and DSS (B) before IPTW-adjustment. OS (C) and DSS (D) after IPTW-adjustment. AS/WW: active surveillance/watchful waiting, DSS: disease specific survival. IPTW: inverse probability of treatment weighting, OS: overall survival, RP: radical prostatectomy, RT: radiotherapy.

population after this adjustment. All standardized mean differences in baseline characteristics were well-balanced with an absolute standardized difference ≤0.1. Standardized mean differences before and after adjustment are visualized in Supplement Fig. 1.

2. Cumulative mortality

Supplement Table 2 describes unadjusted and IPTW-adjusted cumulative mortality by initial treatments. The lowest PCa-specific and all-cause mortality rates were observed after RP. Before adjustment, men who had RT had the lowest PCa-specific and overall survival; however, after IPTW-adjustment men managed with observation (AS/WW) had the lowest survival rates by Kaplan–Meier analyses (Fig. 1). Cumulative mortalities by D'Amico risk group are summarized in Supplement Table 3.

3. Cox proportional hazard regressions and competing risk analyses in IPTW-adjusted cohorts

All variables were significantly associated with all-cause and PCSM using univariate Cox proportional hazard regression. Multivariable Cox regression models are presented in Fig. 2. Notably, RT (HR, 0.77; 95% confidence interval [CI], 0.75–0.80; p<0.001) and RP (HR, 0.42; 95% CI, 0.40–0.43; p<0.001) were significantly associated with a lower risk for death from any cause compared to observation. Additionally, both treatments showed lower HRs in terms of death from PCa com-

			Death from any cause		Death from prostate cancer	
Variable		N	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Initial treatment	AS/WW	24,330	Reference		Reference	
	Radiation therapy	71,269	0.77 (0.75, 0.80)	<0.001	0.86 (0.78, 0.95)	0.002
	Radical prostatectomy	80,857	0.42 (0.40, 0.43)	<0.001	0.44 (0.39, 0.49)	<0.001
Age, yr	50-59	45,142	Reference		Reference	
	60-69	86,757	1.67 (1.60, 1.74)	<0.001	2.00 (1.73, 2.32)	<0.001
	70-79	44,557	2.90 (2.78, 3.03)	<0.001	2.64 (2.27, 3.07)	<0.001
Race	White	137,457	Reference		Reference	
	Black	26,896	1.18 (1.14, 1.23)	<0.001	1.20 (1.06, 1.35)	0.004
	Others/uknown	12,103	0.60 (0.55, 0.64)	<0.001	0.30 (0.21, 0.41)	<0.001
Clinical T stage	T1c	124,841	Reference		Reference	
	T2a	24,772	1.03 (0.99, 1.07)	0.091	1.21 (1.13, 1.43)	<0.001
	T2b-c	26,843	1.12 (1.08, 1.16)	<0.001	1.15 (1.03, 1.28)	0.014
PSA, ng/mL	≤4	23,665	Reference		Reference	
	4.1-10	118,248	1.02 (0.97, 1.06)	0.443	0.70 (0.61, 0.80)	<0.001
	10.1-20	26,729	1.30 (1.24, 1.37)	<0.001	0.82 (0.70, 0.96)	0.015
	20.1-50	7,814	1.34 (1.25, 1.44)	<0.001	1.09 (0.90, 1.31)	0.392
Biopsy grade group	1	78,067	Reference		Reference	
	2	52,249	1.33 (1.28, 1.37)	<0.001	1.35 (1.17, 1.56)	<0.001
	3	22,833	1.41 (1.35, 1.47)	<0.001	2.42 (2.08, 2.82)	<0.001
	4	15,294	1.53 (1.46, 1.61)	<0.001	4.26 (3.68, 4.93)	<0.001
	5	8,013	3.69 (3.53, 3.86)	<0.001	15.10 (13.25, 17.21)	<0.001
Medical insurance	Insured	165,360	Reference		Reference	
	Medicaid	8,428	1.16 (1.09, 1.23)	<0.001	0.85 (0.70, 1.04)	0.119
	Uninsured	2,668	1.22 (1.10, 1.35)	<0.001	0.61 (0.39, 0.98)	0.041
Marital status	Married	134,466	Reference		Reference	
	Unmarried	41,990	1.29 (1.26, 1.33)	<0.001	1.28 (1.16, 1.41)	<0.001
SEER registry	California excluding SF/SJM/LA	36,350	Reference		Reference	
	Alaska Natives	47	1.85 (0.69, 5.00)	0.224	0.00 (-Inf, Inf)	0.974
	Atlanta (metropolitan)	7,071	1.50 (1.40, 1.61)	<0.001	0.88 (0.70, 1.10)	0.260
	Connecticut	8,764	0.88 (0.81, 0.94)	<0.001	1.34 (1.13, 1.58)	<0.001
	Detroit (metropolitan)	10,926	1.34 (1.26, 1.42)	<0.001	1.58 (1.35, 1.85)	<0.001
	Greater Georgia	13,659	1.58 (1.49, 1.66)	<0.001	0.52 (0.42, 0.63)	<0.001
	Hawaii	2,020	0.92 (0.79, 1.08)	0.327	0.32 (0.15, 0.70)	0.004
	Iowa	7,284	1.24 (1.16, 1.33)	<0.001	0.56 (0.43, 0.72)	<0.001
	Kentucky	8,387	1.54 (1.45, 1.64)	<0.001	0.81 (0.65, 1.00)	0.049
	Los Angeles	13,981	0.98 (0.92, 1.05)	0.592	0.75 (0.62, 0.91)	0.003
	Louisiana	11,344	1.55 (1.46, 1.64)	<0.001	1.10 (0.92, 1.31)	0.283
	New Jersey	23,057	1.17 (1.12, 1.23)	<0.001	0.39 (0.32, 0.47)	<0.001
	New Mexico	2,790	1.19 (1.07, 1.31)	0.001	0.56 (0.39, 0.80)	0.001
	Rural Georgia	405	1.00 (0.71, 1.40)	0.986	0.24 (0.04, 1.60)	0.141
	San Francisco-Oakland SMSA..	9,648	1.06 (0.99, 1.14)	0.095	0.93 (0.76, 1.15)	0.516
	San Jose-Monterey	5,357	1.05 (0.96, 1.15)	0.309	0.68 (0.49, 0.94)	0.018
	Seattle (Puget Sound)	10,404	1.13 (1.06, 1.20)	<0.001	0.63 (0.51, 0.77)	<0.001
	Utah	4,962	1.07 (0.98, 1.17)	0.121	0.45 (0.31, 0.65)	<0.001

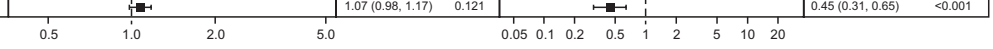

Fig. 2. Forest plots for multivariable Cox proportional hazard regression models in the IPTW-adjusted cohort. AS/WW: active surveillance/watchful waiting, IPTW: inverse probability of treatment weighting, PSA: prostate-specific antigen, SEER: Surveillance, Epidemiology, and End Results, SF/SJM/LA: San Francisco/San Jose–Monterey/Los Angeles. SMSA: standard metropolitan statistical area.

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pared to observation (HR, 0.86; 95% CI, 0.78–0.95; p=.002 and HR, 0.44; 95% CI, 0.39–0.49; p<.001, respectively). HRs of initial treatment by subgroups are presented in Table 2. Active treatment did not confer a PCa-specific survival benefit in men with low-risk disease. RT improved PCa-specific survival only in the high-risk group, whereas RP was significantly associated with improved PCa-specific survival in both the intermediate- (HR, 0.43; 95% CI, 0.35–0.54; p<0.001) and high-risk (HR, 0.36; 95% CI, 0.31–0.42; p<0.001) groups compared to observation.

Adjusted sHRs of initial treatments to predict PCa mortality estimated by Fine and Gray competing risk analysis are summarized in Table 3. Compared to observation, RT (sHR, 0.89; 95% CI, 0.81–0.97; p=0.012) and RP (sHR, 0.46; 95% CI, 0.41–0.52; p<0.001) showed lower risks of PCSM, after adjustment for all other factors and other-cause death. This PCa-specific survival benefit was noted for men with high-risk disease but not D'Amico low-risk. In intermediate-risk disease, only RP had a significantly lower sHR (0.44; 95% CI, 0.36–0.55; p<0.001) compared to observation.

E-values for IPTW-adjusted HRs in terms of death from PCa in men who underwent RT and RP com-

Table 2. IPTW-adjusted HRs of initial treatments by D'Amico risk group

Variable	Death from any cause		Death from prostate cancer	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Low-risk				
Observation	-		-	
Radiotherapy	1.09 (1.02–1.17)	0.009	1.68 (1.22–2.31)	0.001
Radical prostatectomy	0.64 (0.60–0.69)	<0.001	0.79 (0.54–1.14)	0.204
Intermediate-risk				
Observation	-		-	
Radiotherapy	0.80 (0.77–0.84)	<0.001	0.90 (0.75–1.07)	0.230
Radical prostatectomy	0.40 (0.38–0.43)	<0.001	0.43 (0.35–0.54)	<0.001
High-risk				
Observation	-		-	
Radiotherapy	0.57 (0.55–0.60)	<0.001	0.68 (0.60–0.77)	<0.001
Radical prostatectomy	0.32 (0.30–0.34)	<0.001	0.36 (0.31–0.42)	<0.001

CI: confidence interval, HR: hazard ratio, IPTW: inverse probability of treatment weighting.

Table 3. IPTW-adjusted sHRs predicting death from prostate cancer by initial treatments according to D'Amico risk group

Variable	sHR (95% CI)	p-value
Entire cohort		
Radiotherapy *vs.* observation	0.89 (0.81–0.97)	0.012
Radical prostatectomy *vs.* observation	0.46 (0.41–0.52)	<0.001
Low-risk patients		
Radiotherapy *vs.* observation	1.69 (1.23–2.32)	0.001
Radical prostatectomy *vs.* observation	0.80 (0.55–1.16)	0.232
Intermediate-risk patients		
Radiotherapy *vs.* observation	0.91 (0.76–1.08)	0.273
Radical prostatectomy *vs.* observation	0.44 (0.36–0.55)	<0.001
High-risk patients		
Radiotherapy *vs.* observation	0.72 (0.63–0.82)	<0.001
Radical prostatectomy *vs.* observation	0.39 (0.33–0.46)	<0.001

CI: confidence interval, IPTW: inverse probability of treatment weighting, PSA: prostate-specific antigen, SEER: Surveillance, Epidemiology, and End Results, sHR: sub-distribution hazard ratio.
Adjusted for age, race, medical insurance, marital status, SEER registry, clinical T stage, PSA, and biopsy grade group.

pared to observation were 1.60 and 3.97, respectively. E-values for IPTW-adjusted sHRs for both active treatments were 1.50 and 3.77, respectively.

DISCUSSION

In our analysis, after rigorous adjustment, active treatments showed a significantly lower risk of overall and PCSM compared to observation, especially in intermediate- and high-risk disease. AIn comparison to our RWD study, three RCTs (SPCG-4, PIVOT, and ProtecT) showed different mortality rates by the initial treatment which may be partially explained by the periods of study, study design, quality of enrollment, the evolution of diagnostic and therapeutic approaches, and variable lengths of follow-up. Additionally, patients in clinical practice commonly differ from those enrolled in RCTs and thus, RCTs can have limited generalizability in some clinical settings or cohorts. Even the most recent RCT, the ProtecT trial, only included a small subset of high-risk patients (3%) [19] compared to 22.3% in our study, which better reflects the contemporary population at diagnosis [20]. ProtecT also mainly included men identifying as white (ProtecT 99% *vs.* 78% in our study) which does not adequately represent the general population in the United States. ProtecT trial was limited with inadequate for the sample size [7], but our RDW study had enough sample size overcoming the shorter follow-up.

Population-based cohort studies allowed real-world evidence-based treatment strategies for men with localized PCa in the absence of generalizable RCT data. Indeed, many cohort studies have used the SEER database for competing-risk analysis [9,21], despite its limitations, including usage of "observation" as a proxy for both AS/WW and non-active treatments due to the absence of separate codes, or the risk of selection bias. In order to overcome this, Wong et al [11], used the quintiles of the estimated propensity score to balance observed covariates between treatment and observation groups, and concluded a better oncological outcome after RP - a finding which has been confirmed by other groups as mentioned above. However, the clinical T stage was not matched, and the absence of competing risk analyses made it challenging to draw the appropriate conclusion in terms of PCSM. In addition, men who underwent RT as primary treatment were excluded for analysis. Only three studies performed propensity score matching and competing risk analysis sequentially. Abdollah et al [8,12] performed two studies using SEER database (1992–2005), including a total of 44,694 patients. However, even after matching, the standardized difference of age was relatively high between the two groups (9.0 y *vs.* 0.1 y in our study). Furthermore, the exclusion of RT patients and the lack of risk stratification and/or PSA adjustment were substantial limitation of the study. In another study by Albertsen et al [22] using data from the Connecticut Tumor Registry, the authors concluded that men undergoing surgery for localized PCa may have an advantage in PCSM compared to those undergoing RT or observation. In this study, risk adjustment was not performed in this small cohort. Additionally, the authors acknowledged that their results may not be applicable to contemporary men as most men in this study were diagnosed between 1990 and 1992. This is an issue for many studies utilizing the SEER database before the 2010s, as mentioned above. Collectively, previous population-based research studies could not avoid the potential problem of patients' risk adjustment or account for the effect of OCM. In most of the studies, traditional statistical methods, such as propensity score matching did not allow for a valid comparison among the three different treatment groups. Thus the RT group was usually excluded, despite it accounts for one-third of men with localized PCa [23]. In this study, we used recently-a SEER-WW data (2010–2016), which has a newly created variable clearly defined as "AS/WW". Unlike previous SEER databases, this new variable enables more accurate treatment group classification. To overcome the potential limitations of any observational study, we used the IPTW method which is one of the most advanced statistical adjustments, which provides flexible and valid three-way matching. In addition, IPTW-weighted competing risk analysis provides an unbiased estimate of the risk of PCSM in the presence of OCM. By rigorous adjustment for confounding factors and performing additional competing risk analysis using Fine and Gray method in this large study population, we could increase the statistical power in a more balanced way used before.

Since D'Amico et al [24] developed a combined modality staging system by stratifying patients into groups with a low-, intermediate-, and high-risk PCa in 1998, there has been a constant push for risk-based management of men with localized PCa [25]. For low-risk men,

observation as initial treatment has increased from around 30% to 60% from the early 2000s to 2010s, while RT rates trended down and surgery rates remained constant [1,3]. For high-risk groups, on the contrary, treatment selection among RT, RP, and observation has remained relatively constant since the 2000s. Overall, between the early 2000s to 2010s, there has been a significant trend towards observation and surgery while decreasing RT decreased in localized PCa. Cumulative incidence rates of initial therapy for localized PCa stratified by risk group demonstrated that RP is performed more often in men with intermediate- and high-risk disease compared to low-risk (48%, 45%, and 10% for intermediate-, high-, and low-risk group, respectively) [1]. These findings are supported by our final competing risk analysis showing improved survival rates after RP for intermediate- and high-risk patients (RP *vs.* observation: sHR [95% CI] 0.44 [0.36–0.55] for intermediate-risk and 0.39 [0.33–0.46] for high-risk). Meanwhile, RT was chosen as primary treatment in 30%–40% of men irrespective of risk classification in real-world clinical practice [1]. Based on our study findings, RT did not confer a survival benefit in low-risk patients similar to RP. While high-risk patients were noted to have a significant survival benefit from RT compared to observation, there was no significant survival benefit in the intermediate-risk group.

There are several limitations that must be acknowledged. First, our observational study is inherently limited by lack of randomization and this may have biased survival outcomes. Despite every effort to control for all measurable parameters, it is still possible that insufficient balancing may occur due to unmeasured factors, leading to selection bias affecting the observed survival rates. This possibility was higher in RT *vs.* observation (E-value for sHR 1.5). However, it is not likely that unmeasured factors would have a greater effect on PCa mortality than by having a sHR exceeding 3.77 in RP *vs.* observation. Second, the median follow-up period was relatively short (36.5 mo). In particular, the relatively shorter follow-up period in the observation group may have led to a lower cumulative cancer mortality rate compared to RT. To overcome this limitation, we attempted to increase statistical power through a large-sized IPTW-adjusted pseudo-population, with a more than 300-fold sample-sized cohort compared to previous RCTs. Third, for men in the observation group, we could not distinguish between WW or AS. Fourth, further information on treatment side effects, complications, comorbidity, and pathologic subtypes could not be taken into account, thereby limiting a comprehensive interpretation.

Despite these limitations, our analysis has several strengths. First, this study is performed in the contemporary era of PSA testing and treatment strategies. Second, this study is based on population-based RWD, which more accurately represents a real practice, contemporary patient distribution, especially in terms of racial/ethnic diversity, age range, risk groups, and geographic variation. Third, this is the first study of IPTW-based rigorous adjustment and competing risk analysis, demonstrating the association between initial treatment and survival outcomes supported by strong statistical power. Additionally, SEER-WW database analysis made study interpretation more precise by using a new, improved classification of the observation group (AS/WW) compared to prior SEER survival analyses, followed by the comparison of three independent treatment groups (observation, RT, and RP). Although the relatively short follow-up may limit a completely accurate assessment of survival outcomes for men with indolent, low-risk PCa, the large IPTW-adjusted sample size in this study leads to a more precise estimate of survival benefit in men undergoing active treatment.

CONCLUSIONS

After rigorous adjustment, active treatments including surgery, showed a significantly lower risk of overall and PCSM compared to observation in men with localized PCa - particularly in intermediate- and high-risk groups. However, observation (AS/WW) represents a safe option in men with low-risk PCa and should be the preferred treatment option in this subgroup.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: CWJ, AH, MRC. Data curation: All authors. Formal analysis: JHH, AH, CWJ. Funding acquisition: AH, CWJ. Investigation: All authors. Methodology: All authors. Project administration: PRC, MRC. Resources: PRC, MRC. Software: PRC, MRC. Supervision: CWJ, PRC, MRC. Validation: All authors. Visualization: All authors. Writing–original draft: JHH, AH, CWJ. Writing–review & editing: All authors.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.220151.

Data Sharing Statement

The data analyzed in this study were derived from public resources and are openly available at locations cited in the reference section.

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