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Association between Radical Prostatectomy and Survival in Men with Clinically Node-positive Prostate Cancer

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Abstract

Evidence supporting radical prostatectomy (RP) for men with clinically node-positive (cN+) prostate cancer (PC) is limited. In a US national database, we identified 741 men with cN+ nonmetastatic PC diagnosed during 2000–2015 who underwent definitive local therapy with RP (n = 78), radiotherapy (RT) with neoadjuvant androgen deprivation therapy (ADT) (n = 193), or nondefinitive therapy with ADT alone (n = 445) or observation (n=25). We compared PC-specific mortality (PCSM) and all-cause mortality (ACM) using multivariable Fine-Gray competing risk regression and Cox regression, respectively. Compared to nondefinitive therapy, RP was associated with significantly better PCSM (subdistribution hazard ratio [SHR] 0.32, 95% confidence interval [CI] 0.16–0.66; p = 0.002) and ACM (HR 0.36, 95% CI 0.21–0.61; p < 0.001). Compared to RT, RP was not associated with a significant difference in PCSM (SHR 0.47, 95% CI 0.19–1.17; p = 0.1) or ACM (HR 0.88, 95% CI 0.46–1.70; p = 0.71). These data suggest that RP is associated

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Study concept and design: Sarkar, Rose.

Acquisition of data: Sarkar, Rose, Bryant, Murphy.

Analysis and interpretation of data: Sarkar, Rose.

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with favorable survival outcomes that appear to be superior to those for patients who did not receive definitive therapy and comparable to those for patients receiving definitive ADT/RT. Randomized trials of surgery with multimodal therapy are needed.

Patient summary: We found that in clinically node-positive prostate cancer, radical prostatectomy was associated with a cancer-specific and overall survival benefit compared to nondefinitive therapy. Randomized clinical trials are required to determine the best treatment approach in this patient population.

Keywords

Clinically node-positive; Multimodal therapy; Prostate cancer; prostate cancer– specific mortality; Radical prostatectomy

Evidence supporting radical prostatectomy (RP) for men with clinically node-positive (cN+) prostate cancer (PC) is limited [1–3]. Guidelines differ on the utility of RP. The National Comprehensive Cancer Network does not recommend RP, whereas the European Association of Urology only recommends RP for highly selected patients as a component of multimodal therapy [4,5]. There is a critical need for additional data to clarify the role of RP in men with cN+ PC.

We and others have previously demonstrated that radiotherapy (RT) with androgen deprivation therapy (ADT) improves outcomes compared to ADT alone [6–8]. We assessed survival among men with cN+ disease who underwent RP and compared outcomes to those for men who received ADT/RT and nondefinitive therapy.

The Veterans Affairs Informatics and Computing Infrastructure (VINCI) platform offers access to tumor registry data from US veteran's hospitals gathered by trained registrars according to standard protocols issued by the American College of Surgeons [9]. We identified 1072 veterans diagnosed between 2000 and 2015 with cN+ nonmetastatic PC and treated with no therapy, ADT, ADT/RT, or RP with or without additional therapy. Node-positive status was determined from cancer registry data reflecting the American Joint Committee on Cancer staging criteria. We excluded 75 patients with >6 mo between diagnosis and the start of ADT or between the start of ADT and the start of RT. We also excluded six patients who received palliative radiation and 166 patients with missing covariate data. Since the ADT/RT and RP groups are subject to immortal-time bias, we used a "landmark analysis" approach whereby we excluded 84 patients who died within 1 yr of diagnosis, leaving us with 741 patients.

Covariates included clinical tumor stage, pretreatment prostate-specific antigen (PSA), age, race, diagnosis year, Gleason score, employment, marital status, body mass index (BMI), and zip code–level education and median income.

The primary outcomes were PC-specific mortality (PCSM), non-cancer mortality (NCM), and all-cause mortality (ACM). Cause of death was obtained from the National Death Index [10]. Patients were censored at last follow-up. We compared baseline covariates among groups using a χ^2 test, *t* test, or Wilcoxon rank-sum test. We evaluated mortality differences using multivariable Fine-Gray competing risk regression and Cox regression for

PCSM/ACM and ACM, respectively. All tests of significance were two-sided and were performed using SAS (SAS Institute, Cary, NC, USA).

The cohort included 741 men, of whom 470 underwent nondefinitive therapy (ADT = 445; no upfront treatment = 25), and 271 underwent definitive local therapy (RP = 78; ADT/RT = 193). The median follow-up was 4.3 yr overall (nondefinitive 3.9 yr, ADT/RT 5.0 yr, RP 5.3 yr) and 5.13 yr among surviving patients. There were 318 deaths (nondefinitive 245, ADT/RT 57, RP 16), of which 180 were due to PC (nondefinitive 138, ADT/RT 34, RP 8). Of patients receiving RP, 36 received ADT, nine received RT, and 41 received no additional therapy. Patients receiving definitive local therapy were younger and had higher BMI and lower median pretreatment PSA compared to the nondefinitive treatment group (13.7 vs 32.0; $p < 0.001$) There were no significant differences in clinical T stage, Gleason score, or comorbidity between the groups. Of the 78 cN+ RP patients, eight (10%) were found to have pathologically node-negative disease (Supplementary Table 1). ADT/RT patients received a median radiation dose of 75.6 Gy (interquartile range [IQR] 73–78). RP patients who received RT had a median cumulative radiation dose of 66.6 Gy (IQR 64.9–67.8). Among RP patients the median number of lymph nodes examined was 11 (IQR 7–17) and the median number of positive lymph nodes was 1 (IQR 1–2).

Compared to patients who received nondefinitive therapy, RP patients had lower PCSM ($p < 0.001$) and ACM ($p < 0.001$) on univariable analysis (Fig. 1A,C). In multivariable models, RP patients had better PCSM (subdistribution hazard ratio [SHR] 0.32, 95% confidence interval [CI] 0.16–0.66; $p = 0.002$) and ACM (HR 0.36, 95% CI 0.21–0.61; $p < 0.001$) compared to patients receiving nondefinitive treatment (Table 1).

Compared to ADT/RT, RP was not associated with a significant difference in the risk of PCSM ($p = 0.13$) or ACM ($p = 0.16$) on univariable analysis (Fig. 1B,D). In multivariable models, there was no significant difference in PCSM (SHR 0.47, 95% CI 0.19–1.17; $p = 0.1$) or ACM (HR 0.88, 95% CI 0.45–1.7; $p = 0.71$) between the RP and ADT/RT groups (Table 1). However, power calculations revealed that although our sample size was sufficiently powered to detect differences in cancer mortality between RP and nondefinitive therapy, it was not sufficiently powered to detect differences in cancer mortality between RP and ADT/RT.

In multivariable models we did not detect a significant difference in NCM between RP and nondefinitive therapy or between RP and ADT/RT (Supplementary Table 2). To allay concerns regarding model overfitting for the RP and ADT/RT PCSM comparison (with 42 prostate cancer deaths and 13 variables), a simpler model is presented in Supplementary Table 3.

Our results suggest that RP is associated with favorable survival outcomes that appear to be superior to those for patients who did not receive definitive therapy and comparable to outcomes for patients receiving definitive ADT/RT. In addition, the RP cohort had relatively low utilization of multimodal therapy including postoperative RT and ADT, which might further improve outcomes [11]. Thus, inclusion of RP as a reasonable treatment strategy in

national guidelines should be considered and the optimal treatment strategy should be further explored in randomized trials.

Out study builds on a recent National Cancer Data Base (NCDB) study that showed that local therapy (RP or RT) was associated with better mortality outcomes [3]. However, the study by Seisen and colleagues [3] did not directly assess the impact of RP versus no local therapy on PCSM or overall survival. Consequently, this is the first study to demonstrate the value of RP in cN+ PC for both PCSM and ACM. Like Seisen et al we did not detect a difference in mortality between RP and ADT/RT, although the low utilization of multimodal therapy after RP, the small sample size, and the lack of statistical power limit this comparison. Another interesting feature of our study is that >10% of cN+ men who underwent RP were found to be pN0, indicating that RP provides important diagnostic information that is superior to standard imaging studies [12]. Thus, standard imaging alone may lead to the withholding of potentially curative treatment in a substantial proportion of men. However, it is important to note that improvements in imaging may change the cN+ landscape [13].

Our study has potential limitations. While we controlled for comorbidity, age, income, and other demographic factors, and though VINCI provides more granular information on confounders than the Surveillance, Epidemiology and End Results database or NCDB, there may be residual selection bias for healthier patients for the definitive treatment arms. While reliable, the NDI may misclassify a proportion of prostate cancer deaths, potentially limiting the PCSM comparisons [14]. In addition, we were unable to control for the number of positive clinical lymph nodes and patients with many involved pelvic lymph nodes would be less likely to receive definitive local therapy.

Despite these limitations our data suggest that RP may be a reasonable treatment strategy for cN+ PC. However, randomized clinical trials are needed to determine the best treatment approach in this group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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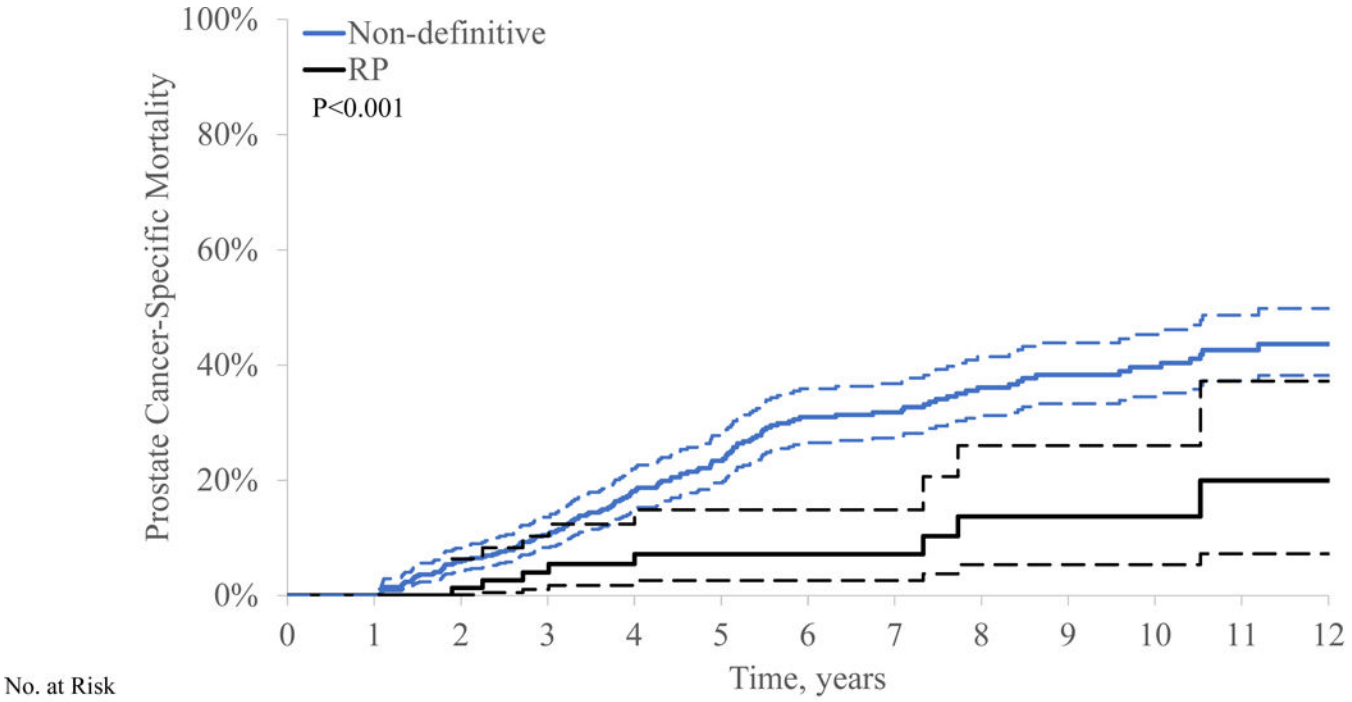
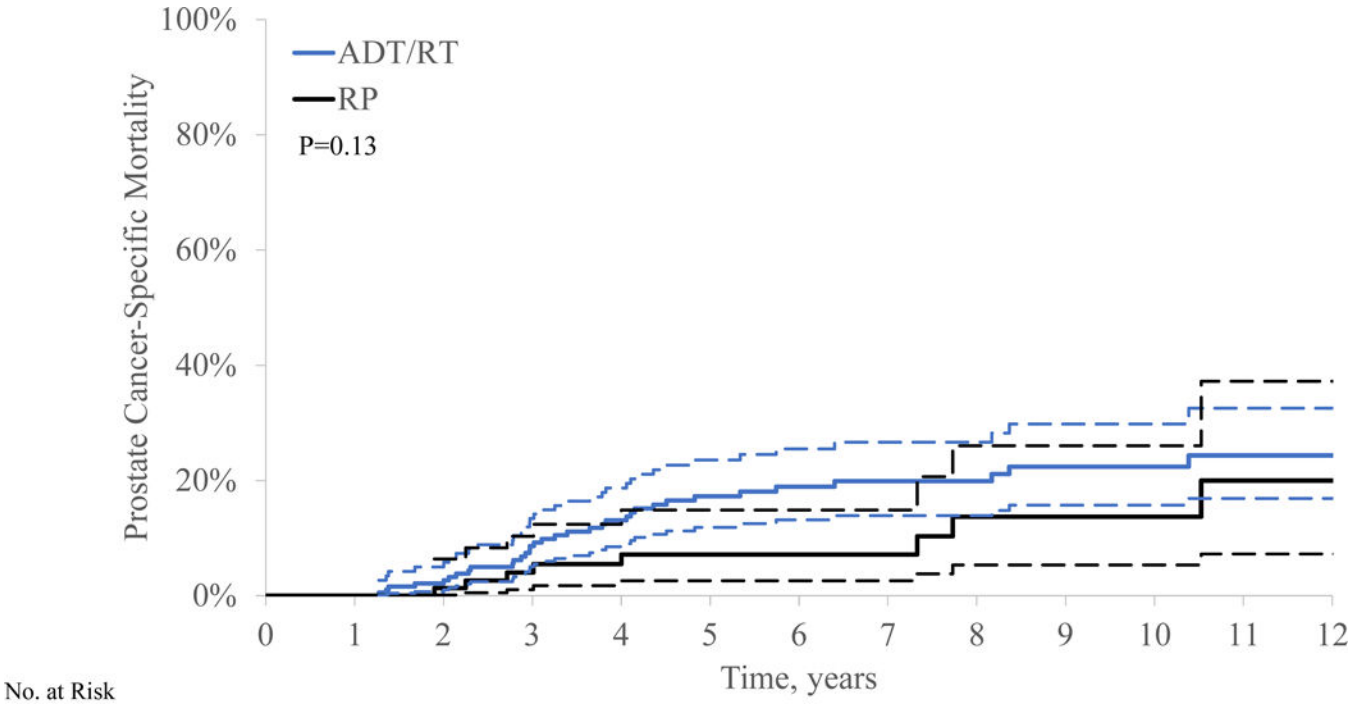
Our results suggest that radical prostatectomy is associated with favorable survival outcomes in clinically node-positive prostate cancer that appear to be superior to outcomes for patients who did not receive definitive therapy and comparable to outcomes for patients receiving definitive radiotherapy. Thus, inclusion of radical prostatectomy as a reasonable treatment strategy for clinically node-positive prostate cancer in national guidelines should be considered and the optimal treatment strategy should be further explored in randomized trials



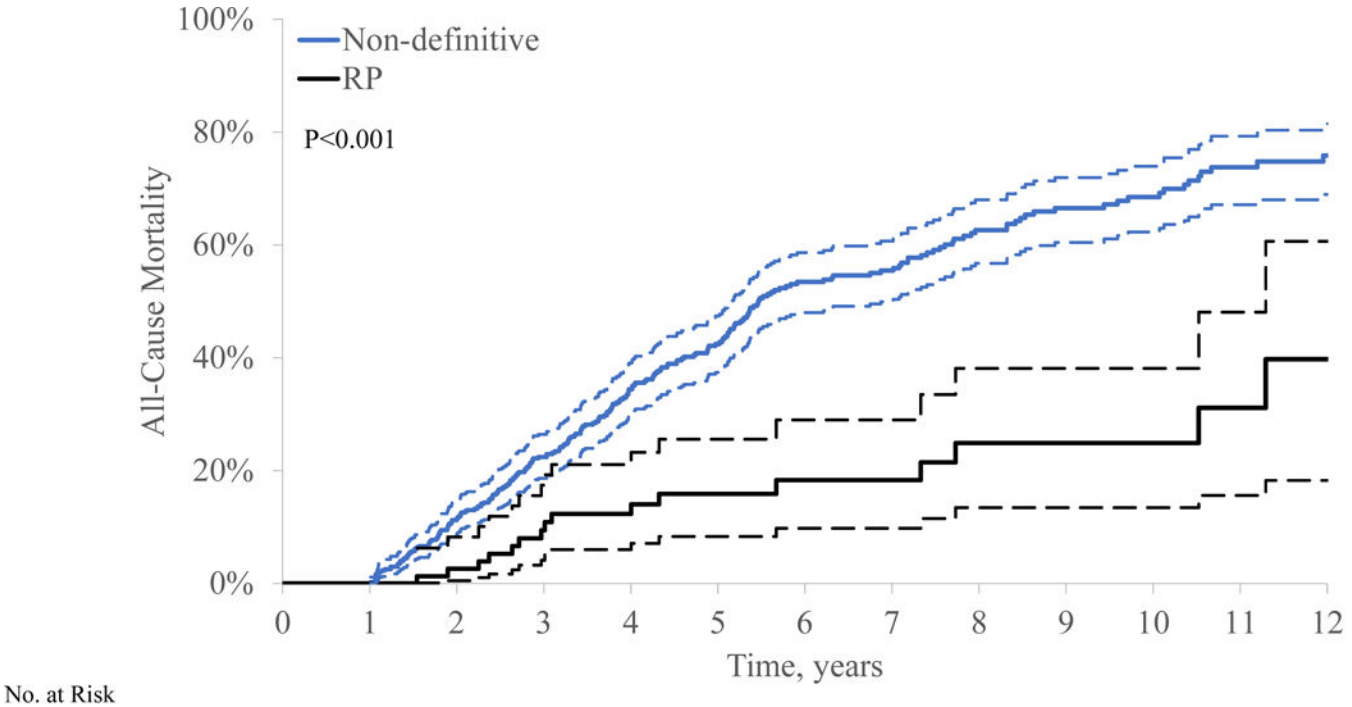
No. at Risk

Non-definitive	470	470	400	312	225	175	124	101	71	56	44	30	22
RP	78	78	74	63	52	44	31	26	19	16	12	9	5



No. at Risk

ADT/RT	193	193	168	144	122	98	77	64	57	41	31	28	20
RP	78	78	74	63	52	44	31	26	19	16	12	9	5



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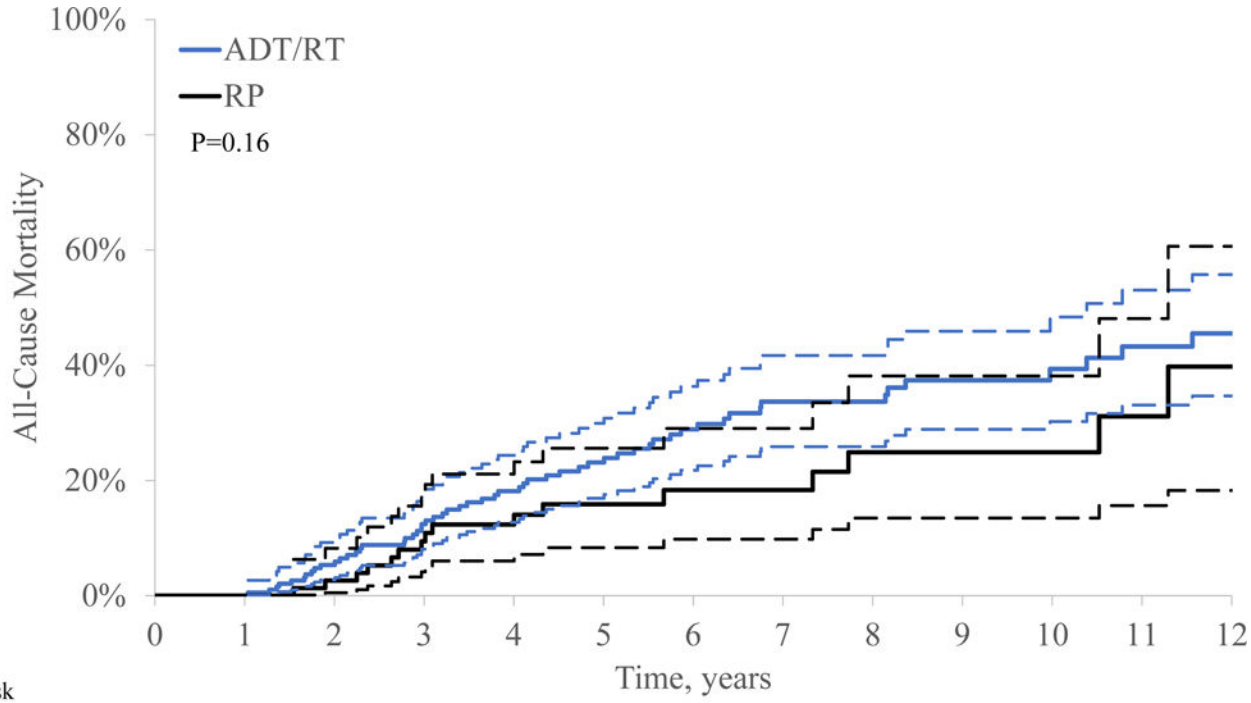

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ADT/RT	193	193	168	144	122	98	77	64	57	41	31	28	20
RP	78	78	74	63	52	44	31	26	19	16	12	9	5

Fig. 1 –.

Unadjusted curves for cumulative prostate cancer–specific and all-cause mortality. Prostate cancer–specific mortality for (A) nondefinitive therapy versus radical prostatectomy (RP) and (B) androgen deprivation therapy (ADT)/radiotherapy (RT) versus RP. All-cause mortality for (C) nondefinitive therapy versus RP and (D) ADT/RT versus RP. Gray's test for equality of cumulative incidence functions was used to calculate the *p* values. Dashed lines indicate the confidence intervals.

Table 1 –

Results of multivariable Fine Gray competing risk regression for PCSM and Cox regression for ACM for RP versus nondefinitive therapy and ADT/RT

	RP versus nondefinitive treatment				RP versus ADT/RT			
	PCSM		ACM		PCSM		ACM	
	SHR (95% CI)	*p* value	HR (95% CI)	*p* value	SHR (95% CI)	*p* value	HR (95% CI)	*p* value
Treatment								
RP	0.32(0.16–0.66)	0.002	0.36(0.21–0.61)	<0.001	0.47(0.19–1.17)	0.1	0.88(0.46–1.7)	0.71
Non-RP	Reference		Reference		Reference		Reference	
Black race								
Yes	0.62(0.4–0.98)	0.039	0.85(0.62–1.17)	0.33	0.8 (0.27–2.35)	0.69	0.83(0.42–1.67)	0.6
No	Reference		Reference		Reference		Reference	
Age	1 (0.82–1.22)	0.97	1.25(1.07–1.44)	0.004	1.17(0.71–1.93)	0.53	1.73(1.25–2.4)	0.001
BMI	0.8 (0.69–0.94)	0.005	0.93(0.83–1.05)	0.23	0.77(0.57–1.05)	0.1	0.87(0.69–1.08)	0.21
Median income	1.04(0.93–1.17)	0.49	1.02(0.94–1.11)	0.61	0.93(0.79–1.1)	0.42	1.05(0.95–1.17)	0.35
HSG	0.88(0.67–1.14)	0.32	0.94(0.79–1.12)	0.5	0.96(0.53–1.73)	0.89	0.85(0.6–1.2)	0.35
Married								
Yes	0.92(0.65–1.29)	0.63	0.89(0.69–1.15)	0.36	0.46(0.24–0.86)	0.015	0.46(0.28–0.76)	0.003
No	Reference		Reference		Reference		Reference	
Employment								
Yes	1.12(0.62–2.03)	0.71	1.18(0.73–1.91)	0.51	1.26(0.42–3.77)	0.68	2.05(0.87–4.79)	0.1
No	Reference		Reference		Reference		Reference	
Diagnosis year								
2000–2005	Reference		Reference		Reference		Reference	
2006–2010	0.74(0.51–1.06)	0.1	1.01(0.77–1.32)	0.96	1.67(0.78–3.56)	0.19	1.48(0.83–2.66)	0.19
2011–2015	0.5 (0.27–0.92)	0.03	0.36(0.22–0.59)	<0.001	0.43(0.13–1.41)	0.16	0.45(0.18–1.11)	0.08
CCI								
0	Reference		Reference		Reference		Reference	
1	1.13(0.71–1.8)	0.6	1.51(1.07–2.12)	0.019	1.44(0.57–3.62)	0.44	1.29(0.68–2.44)	0.44
≥2	0.65(0.32–1.34)	0.24	1.63(1.12–2.39)	0.012	0.23(0.03–2.17)	0.2	0.85(0.31–2.29)	0.74
PSA	1.07(0.95–1.2)	0.26	1.01(0.93–1.11)	0.77	1.34(1.01–1.78)	0.05	1.44(1.17–1.77)	<0.001
cT stage								

	RP versus nondefinitive treatment				RP versus ADT/RT			
	PCSM		ACM		PCSM		ACM	
	SHR (95% CI)	*p* value	HR (95% CI)	*p* value	SHR (95% CI)	*p* value	HR (95% CI)	*p* value
3–4	1.74(1.24–2.45)	0.002	1.23(0.94–1.6)	0.14	1.51(0.72–3.17)	0.27	0.87(0.51–1.48)	0.6
1–2	Reference		Reference		Reference		Reference	
Gleason score								
≥8	1.65(1.12–2.45)	0.012	1.28(0.97–1.7)	0.08	3.04(1.23–7.5)	0.016	1.5 (0.85–2.63)	0.16
≤7	Reference		Reference		Reference		Reference	

RP = radical prostatectomy; PSA= prostate–specific antigen (log transformed); BMI = body mass index; ADT = androgen deprivation therapy; RT = radiotherapy; CCI = Charlson comorbidity index; HR = hazard ratio; SHR = subdistribution HR; CI = confidence interval; HSG = high school graduation.