





Survival after radical prostatectomy versus radiation therapy in clinical node-positive prostate cancer

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Abstract

Aim: To compare overall mortality (OM), cancer-specific mortality (CSM), and other cause mortality (OCM) rates between radical prostatectomy (RP) versus radiotherapy (RT) in clinical node-positive (cN1) prostate cancer (PCa).

Materials and Methods: Within Surveillance, Epidemiology, End Results (SEER) (2004–2016), we identified 4685 cN1 PCa patients, of whom 3589 (76.6%) versus 1096 (24.4%) were treated with RP versus RT. After 1:1 propensity score matching (PSM), Kaplan–Meier plots and Cox regression models tested the effect of RP versus RT on OM, while cumulative incidence plots and competing-risks regression (CRR) models addressed CSM and OCM between RP and RT patients. All analyses were repeated after the inverse probability of treatment weighting

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(IPTW). For CSM and OCM analyses, the propensity score was used as a covariate in the regression model.

Results: Overall, RT patients were older, harbored higher prostate-specific antigen values, higher clinical T and higher Gleason grade groups. PSM resulted in two equally sized groups of 894 RP versus 894 RT patients. After PSM, 5-year OM, CSM, and OCM rates were, respectively, 15.4% versus 25%, 9.3% versus 17%, and 6.1% versus 8% for RP versus RT (all $p < 0.001$) and yielded respective multivariate hazard ratios (HRs) of 0.63 (0.52–0.78, $p < 0.001$), 0.66 (0.52–0.86, $p < 0.001$), 0.71 (0.5–1.0, $p = 0.05$), all favoring RP. After IPTW, Cox regression models yielded HR of 0.55 (95% confidence interval [CI] = 0.46–0.66) for OM, and CRR yielded HRs of 0.49 (0.34–0.70) and 0.54 (0.36–0.79) for, respectively, CSM and OCM, all favoring RP (all $p < 0.001$).

Conclusions: RP may hold a CSM advantage over RT in cN1 PCa patients.

KEYWORDS

clinical node positive, external beam radiotherapy, prostate cancer, radical prostatectomy

1 | INTRODUCTION

Clinically lymph-node-positive (cN1) prostate cancer (PCa) represents approximately 12% of PCa cases at initial diagnosis¹ and represents a challenging clinical dilemma with respect to treatment selection between radical prostatectomy (RP) versus radiation therapy (RT). A recent systematic review suggested an advantage in terms of both overall survival (OS) and cancer-specific mortality (CSM) for men with cN1 PCa receiving local treatment.² However, to date, only a few studies have compared cancer control outcomes between RP versus RT in cN1 PCa patients.^{3–5} Specifically, Seisen et al.⁴ tested the effect of RP ($n = 751$) versus RT ($n = 1236$) on OS and found no statistically significant differences (HR = 0.54, 95% CI = 0.19–1.52, $p = 0.2$). However, they could not address CSM. Similarly, Sarkar et al.⁵ did not identify a statistically significant differences in CSM (hazard ratio [HR] = 0.47, 95% confidence interval [CI] = 0.19–1.17; $p = 0.1$) or OS (HR = 0.88, 95% CI = 0.46–1.70; $p = 0.71$) between RP ($N = 78$) versus RT ($N = 445$). It is of note that in both studies RP effect trended towards a survival benefit versus RT. Moreover, Jang et al.³ showed that men clinically node-positive PCa treated initially with RP + adjuvant RT had a lower risk of CSM and improved OS when compared to those men treated with RT + androgen deprivation therapy, but experienced higher rates of erectile dysfunction and urinary incontinence. Based on a limited amount of data examining these two alternative treatment modalities, we initiated a contemporary analysis addressing CSM according to RP versus RT in cN1 PCa patients, after adjustment for OCM, which may mask the effect of local treatment in patients at low CSM but an elevated OCM risk. Our analysis relied on the Surveillance, Epidemiology, and End Results (SEER) database (2004–2016). We hypothesized that no overall mortality (OM), CSM, or OCM differences exist between RP versus RT.

2 | MATERIALS AND METHODS

2.1 | Study population

The SEER database samples 26% of the United States and approximates the United States in terms of demographic composition, as well as cancer incidence.⁶ Within SEER database 2004–2016, we identified and included all patients ≥ 18 years old with histologically confirmed nonmetastatic, cN1 adenocarcinoma of the prostate, diagnosed at biopsy (International Classification of Disease for Oncology [ICD-O-3] code 8140 site code C61.9). Patients with missing vital status, unknown prostate-specific antigen (PSA), unknown clinical T-, N-, M-stages, unknown biopsy Gleason Grade Group (GGG) were excluded. Moreover, we excluded autopsy or death certificate only cases and all patients with treatment other than RP or RT.

CSM was defined as deaths attributable to PCa. Conversely, other cause mortality (OCM) was defined as deaths attributable to other causes than PCa. Follow-up was defined as the time from diagnosis to the end of the study period, loss to follow-up, CSM, or OCM.

2.2 | Statistical analyses

Statistical analyses were based on six steps. First, we tested for differences in OM, CSM, and OCM rates in the unmatched population of RP versus RT. For OM analysis, we relied on multivariable Cox regression models, after adjustment for age, biopsy GGG, clinical T stage, and race. For CSM and OCM analysis, we relied on competing risks regression (Fine-Gray).⁷ Second, we matched RT cN1 patients with RP cN1 patients, in a 1:1 fashion, according to age, biopsy Gleason score, clinical T stage, PSA (in 5 ng/ml intervals), and repeated OM, CSM, and OCM analyses. Finally, as previous analyses relied on inverse probability of treatment weighting (IPTW) instead of PSM,⁴ we repeated all OM, CSM, and OCM

analyses in RP versus RT after IPTW (according to a year of diagnosis, age, region, rural versus urban, marital status, socioeconomic status, biopsy GGG, clinical T stage, and PSA). The IPTW is computed by inverting the probability of treatment received. Specifically, it was computed as $1/(\text{propensity score})$ for those who received RP, and $1/(1-\text{propensity score})$ for RT patients. Applying IPTW in Fine and Gray's method is not well developed at the R software level. However, according to previously defined methodology,⁸ we included the propensity score as an independent variable inside of the regression as a proxy. Specifically, we estimated cumulative incidences and proportional sub-hazards of cancer-specific mortality accounting for other-cause mortality (and vice versa) in the IPTW-adjusted groups. Equality of the cumulative incidence curves was tested by a modified log-rank test. For all statistical analyses, R software environment for statistical computing and graphics (version 3.4.3) was used. All tests were two-sided with a level of significance set at $p < 0.05$.

3 | RESULTS

3.1 | Study population characteristics

We identified 4685 cN1 PCa patients. Of those, 3589 (76.6%) underwent RP versus 1096 (24.4%) RT. In general, RT patients were older, harbored higher PSA values, higher clinical T stage, and higher biopsy GGG (Table 1 and Figure 1). Specifically, median (interquartile ranges [IQR]) age was 63 (57–67) in RP-treated patients versus 67 (61–73) in those treated with RT. Median PSA was 10.1 (6.3–18.7) versus 22 (10.1–54) ng/ml for RP versus RT, respectively. Moreover, clinical T stage (cT)1, cT2, cT3, cT4, and cTx stages were, respectively, 44.7% versus 23.4%; 41.4% versus 32%; 11.5% versus 33.5%; 1.3% versus 10.1%; and 1% versus 0.9% in RP versus RT. Finally, rates of GGG 1, GGG 2, GGG 3, GGG 4, GGG 5, and unknown GGG between RP versus RT were, respectively, 4.5% versus 3.6%; 19.4% versus 8.7%; 21.6% versus 11.8%; 20.9% versus 27%; 29.1% versus 44.3%; and 4.5% versus 4.7%.

3.2 | Survival analyses (OM, CSM, OCM) before propensity score matching (PSM)

Before PSM, in the overall cohort of cN1 patients ($N = 4685$), 5-year OM rates were 11.7% versus 26.8% ($p < 0.001$) for, respectively, RP versus RT (Figure 2A), which translated into an HR of 0.58, 95% CI = 0.49–0.70, $p < 0.001$, after multivariable adjustment for PSA, biopsy GGG, cT stage, age, and race (Table 2).

Moreover, cumulative incidence plot-derived 5-year CSM rates were 7.1% versus 17.9% ($p < 0.001$) for, respectively, RP versus RT (Figure 2B), which translated into an HR of 0.62 (95% CI = 0.49–0.78, $p < 0.001$), after multivariable adjustment for PSA, biopsy GGG, cT stage, age, and race (Table 2).

Finally, cumulative incidence plot-derived 5-year OCM rates were 4.6% versus 8.9% ($p < 0.001$) for, respectively, RP versus RT (Figure 2B), which translated into an HR of 0.64 (95% CI = 0.48–0.84,

TABLE 1 Descriptive characteristics of 4685 nonmetastatic cN1 patients within the Surveillance, Epidemiology and End Results (2004–2016) database, stratified according to treatment type (RP vs. EBRT)

	Overall (N = 4685)		p value
	RP (N = 3589)	RT (N = 1096)	
Age at diagnosis (years), median (IQR)	63 (57–67)	67 (61–73)	<0.001
PSA (ng/ml), median (IQR)	10.1 (6.3–18.7)	22 (10.1–54)	<0.001
Clinical T stage (n, %)			<0.001
cT1	1606 (44.7)	257 (23.4)	
cT2	1485 (41.4)	351 (32)	
cT3	414 (11.5)	367 (33.5)	
cT4	47 (1.3)	111 (10.1)	
cTx	37 (1)	10 (0.9)	
Biopsy Gleason Grade Group (n, %)			<0.001
1	160 (4.5)	39 (3.6)	
2	697 (19.4)	95 (8.7)	
3	777 (21.6)	129 (11.8)	
4	750 (20.9)	296 (27)	
5	1045 (29.1)	485 (44.3)	
Unknown	160 (4.5)	52 (4.7)	
Race (n, %)			<0.001
Caucasian	2557 (71.2)	744 (67.9)	
African American	483 (13.5)	181 (16.5)	
Asian	143 (4)	74 (6.8)	
Hispanic	406 (11.3)	97 (8.9)	

Abbreviations: cN1, clinical node-positive; EBRT, external beam radiotherapy; IQR, interquartile range; PSA, prostate-specific antigen; RP, radical prostatectomy.

$p < 0.001$), after multivariable adjustment for PSA, biopsy GGG, cT stage, age, and race (Table 2).

3.3 | PSM (1:1)

To address population differences, 1:1 PSM according to age, biopsy GGG, cT stage, and PSA (at 5 ng/ml intervals) was applied to the entire cohort of patients ($N = 4685$), of whom 3589 underwent RP versus 1096 RT. PSM resulted in two equally sized groups of 894 RP versus 894 RT patients (Table S1 and Figure S1).

3.4 | Survival analyses (OM, CSM, OCM) after PSM

Kaplan–Meier plot (Figure 3A) depicting OM at 5 years of follow-up revealed 15.4% versus 25% rates for, respectively, RP versus RT

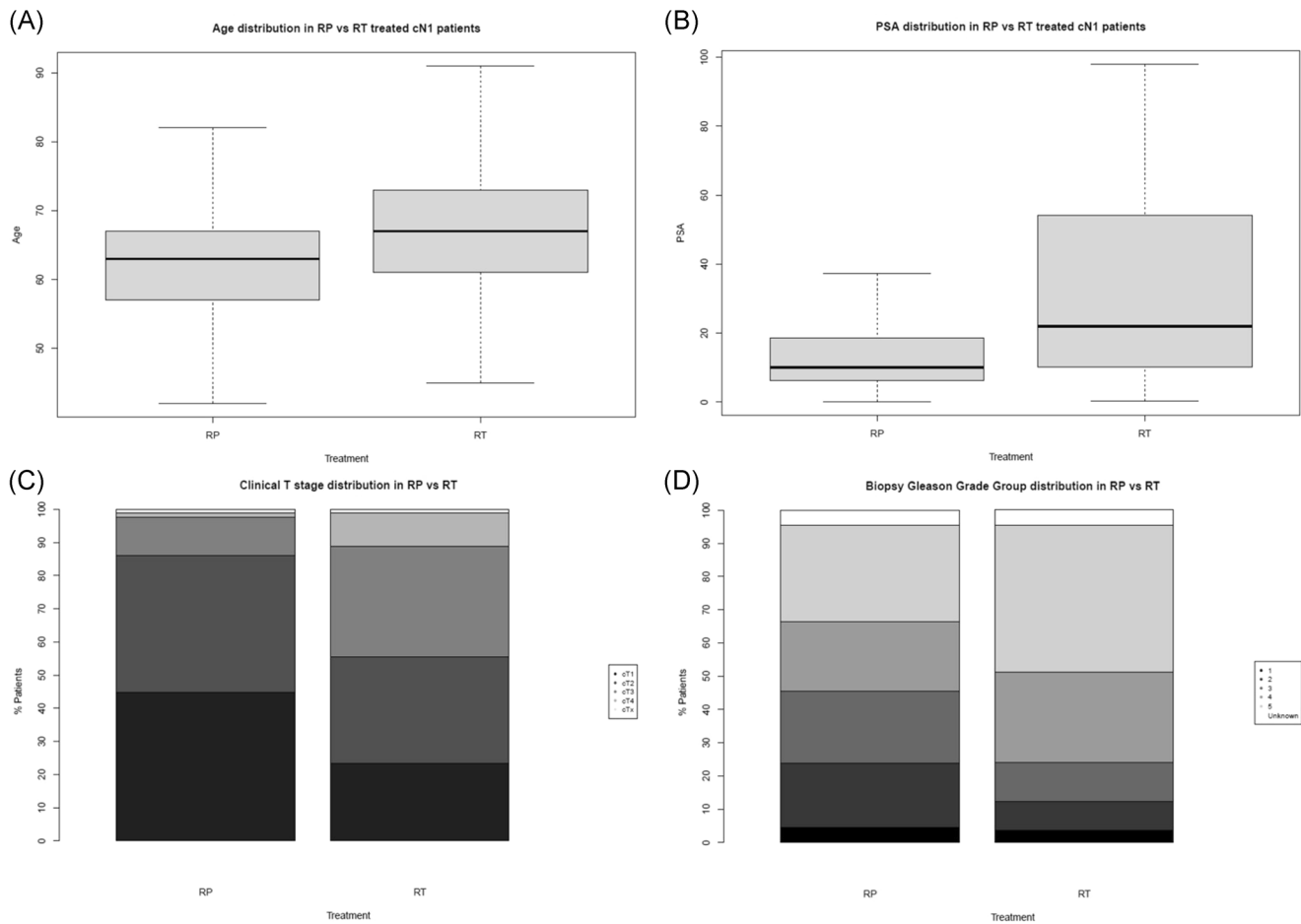


FIGURE 1 Barplots depicting distributions of (A) age, (B) PSA, (C) clinical T stage, (D) biopsy Gleason Grade Group in clinical node-positive patients treated with RP versus RT. cN1, clinical node-positive; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy

($p < 0.001$). The latter translated into a multivariate Cox regression hazard ratio (HR) of 0.63 (95% CI = 0.52–0.78, $p < 0.001$) favoring RP, after adjustment for PSA, cT stage, biopsy GGG, age, and race (Table 3).

Cumulative incidence plots (Figure 3B) depicting CSM at 5 years of follow-up revealed 10.4% versus 16.2% rates for respectively RP vs. RT ($p < 0.01$). The latter translated into a multivariate competing-risks HR of 0.66 (95% CI = 0.52–0.86, $p < 0.001$) favoring RP, after adjustment for OCM and additional multivariable adjustment for PSA, cT stage, biopsy GGG, age, and race (Table 3).

Cumulative incidence plots (Figure 3B) depicting OCM at 5 years of follow-up revealed rates were 5.0% versus 8.2% rates for, respectively, RP vs. RT ($p = 0.01$). The latter translated into a multivariate competing-risks HR of 0.71 (95% CI = 0.5–1.0, $p = 0.05$) favoring RP, after adjustment for CSM and additional multivariable adjustment for PSA, cT stage, biopsy GGG, age, and race (Table 3).

3.5 | Survival analyses (OM, CSM, OCM) after IPTW

IPTW adjusted for differences according to the year of diagnosis, age, region of residence, rural versus urban, marital status, socioeconomic status, biopsy GGG, clinical T stage, and PSA, which might have influenced assignment to either RP or RT.

After IPTW (Figure S2), Kaplan Meier plots depicting OM (Figure 4A), and cumulative incidence plots depicting CSM and OCM (Figure 4B) at 5 years of follow-up revealed rates of 13% versus 22.1%, 8.4% versus 15.3%, and 4.6% versus 6.8%, respectively, for RP versus RT (all $p < 0.001$). After IPTW, multivariable Cox regression model for OM (Table 4) yielded HR of 0.55 (95% CI = 0.46–0.66, $p < 0.001$) favoring RP, while multivariable competing risks regression models yielded HRs of 0.49 (0.34–0.70, $p < 0.001$) and 0.54 (0.36–0.79, $p < 0.001$) for, respectively, CSM and OCM, all favoring RP, after further adjustment for race (Table 4).

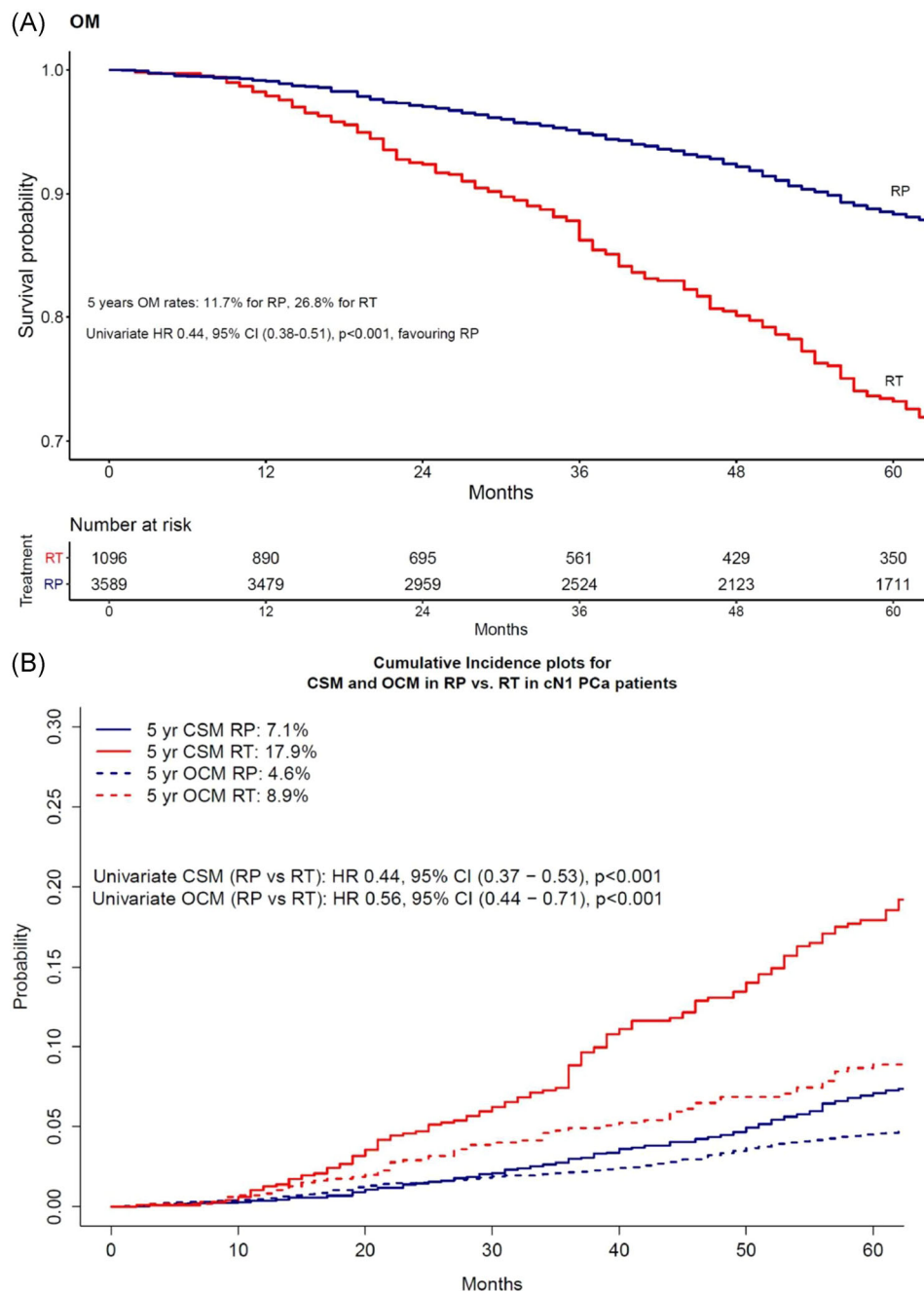


FIGURE 2 (A) Kaplan–Meier plots and (B) cumulative incidence plots depicting (A) overall mortality (OM), and (B) cancer-specific mortality (CSM) and other cause mortality (OCM) before propensity score matching or IPTW in RP versus RT in clinical node-positive prostate cancer patients. CI, confidence interval; cN1, clinical node-positive; HR, hazard ratio; PCa, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

We hypothesized that no differences exist in CSM and OCM rates of cN1 patients treated with RP versus RT. We tested this hypothesis within a large, contemporary, population-based sample of cN1 patients treated with RT versus RP. Our study resulted in several noteworthy observations.

First, we observed very important differences in age, PSA, clinical stage, and biopsy GS characteristics of RP patients, relative to their RT counterparts. Specifically, RT patients were older and had a more aggressive disease. These findings are in accordance with those of Seisen et al.,⁴ who also reported older age, and higher PSA, clinical T stages, and biopsy Gleason scores in cN1 patients treated with RT versus RP. Based on these very

TABLE 2 Multivariable Cox and competing risks regression models testing for the differences in OM, CSM, and OCM in between RP versus EBRT, within the Surveillance, Epidemiology and End Results (2004–2016) database in 4685 nonmetastatic clinical node-positive PCa patients

	Cox regression		Competing risks regression			
	OM HR (95% CI)	p value	CSM HR (95% CI)	p value	OCM HR (95% CI)	p value
Treatment (RT as ref)	0.59 (0.42–0.70)	<0.001	0.62 (0.49–0.78)	<0.001	0.64 (0.48–0.84)	<0.001
Age	1.02 (1.01–1.03)	<0.001	1.01 (0.99–1.02)	0.2	1.05 (1.03–1.06)	<0.001
Race (Caucasian as ref)						
African American	0.88 (0.72–1.10)	0.3	0.86 (0.64–1.15)	0.31	0.99 (0.7–1.39)	0.95
Asian	0.60 (0.41–0.87)	0.008	0.74 (0.48–1.14)	0.18	0.48 (0.23–0.98)	0.04
Hispanic	0.79 (0.62–1.00)	0.05	0.8 (0.58–1.1)	0.16	0.83 (0.56–1.23)	0.35
PSA (ng/ml)	1.00 (1.00–1.01)	0.01	1 (1–1.01)	0.02	1 (1–1.01)	0.71
Clinical T stage (cT1 as ref)						
cT2	1.05 (0.90–1.24)	0.5	1.06 (0.86–1.31)	0.6	1.09 (0.85–1.39)	0.49
cT3	0.98 (0.79–1.22)	0.9	1.07 (0.81–1.41)	0.64	0.86 (0.61–1.22)	0.4
cT4	1.61 (1.17–2.21)	0.004	2.06 (1.39–3.05)	<0.001	0.79 (0.4–1.56)	0.5
cTx	0.52 (0.19–1.40)	0.2	0.85 (0.31–2.34)	0.76	0 (0–0)	<0.001
Biopsy Gleason Grade Group (GGG 1 as ref)						
GGG 2	1.24 (0.79–1.95)	0.3	1.78 (0.79–4.02)	0.16	0.97 (0.56–1.67)	0.9
GGG 3	1.42 (0.91–2.21)	0.1	2.6 (1.18–5.74)	0.02	0.86 (0.5–1.5)	0.6
GGG 4	1.66 (1.08–2.56)	0.02	3.56 (1.63–7.75)	<0.001	0.77 (0.45–1.32)	0.35
GGG 5	2.79 (1.84–4.24)	<0.001	6.08 (2.83–13.07)	<0.001	1.09 (0.66–1.82)	0.73
Unknown GGG	2.55 (1.58–4.11)	<0.001	5.29 (2.33–12)	<0.001	1.15 (0.61–2.17)	0.67

Abbreviations: CI, confidence interval; CSM, cancer-specific mortality; EBRT, external beam radiotherapy; GGG, Gleason Grade Group; HR, hazard ratio; OCM, other cause mortality; OM, overall mortality; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy.

important differences, meaningful comparisons without the strictest statistical adjustment may potentially result in severely biased results. In consequence, we applied PSM and additional multivariable adjustments to control for such differences. The use of PSM reduced the RT population from 1096 to 894 patients and, even more importantly, the RP population from 3589 to 894 patients. This attrition emphasizes the existence of very strong case-mix differences between RP versus RT. These differences might be too pronounced for correction with multivariable adjustment methods alone; instead, they should ideally be addressed with PSM or IPTW, as was done in the current analysis, as well as in that of Seisen et al.⁴ and Jang et al.,³ but not in that of Sarkar et al.⁵ The degree of attrition of assessable patients after matching (1096 to 894 for RT versus 3589 to 894 for RP) also emphasizes the lack of comparability between a large proportion of RP patient's versus RT counterparts. Therefore, despite PSM allowing head-to-head comparison between RP- and RT-treated patients, incidence rate estimates after PSM should be interpreted with caution, as the after-matching population is not representative of the real-life scenario. The attrition phenomenon only applies to PSM, but not to IPTW, where instead each original

observation is kept within the analytic cohort after adjustment of its weight. In consequence, Seisen et al. who relied on IPTW were able to address a bigger population than that of our propensity score-matched analysis. To ensure comparability, we also applied IPTW.

In the second part of our analyses, we focused on OM, CSM, and OCM differences between RP versus RT cN1 patients before PSM or IPTW. The resulting 5-year OM, CSM, and OCM rates were invariably lower in RP versus RT patients and RP was associated with respective multivariable HRs of HR of 0.58 ($p < 0.001$), 0.62 ($p < 0.001$), and 0.64 ($p < 0.001$). Since such results without PSM or IPTW may be biased, we repeated analyses of OM, CSM, and OCM after PSM as well as IPTW. As IPTW in Fine and Gray's method is not well developed at the R software level, we included the propensity score as an independent variable inside of the regression as a proxy. However, according to previously defined methodology.⁸ Here, the resulting 5-year OM, CSM, and OCM rates invariably favored RP versus RT patients and RP was invariably associated with protective multivariable HRs (HR for OM, CSM, and OCM 0.63 [$p < 0.001$], 0.66 [$p < 0.001$], 0.71 [$p = 0.05$] after PSM; and 0.55, 0.49, 0.54 [all $p < 0.001$], after IPTW).

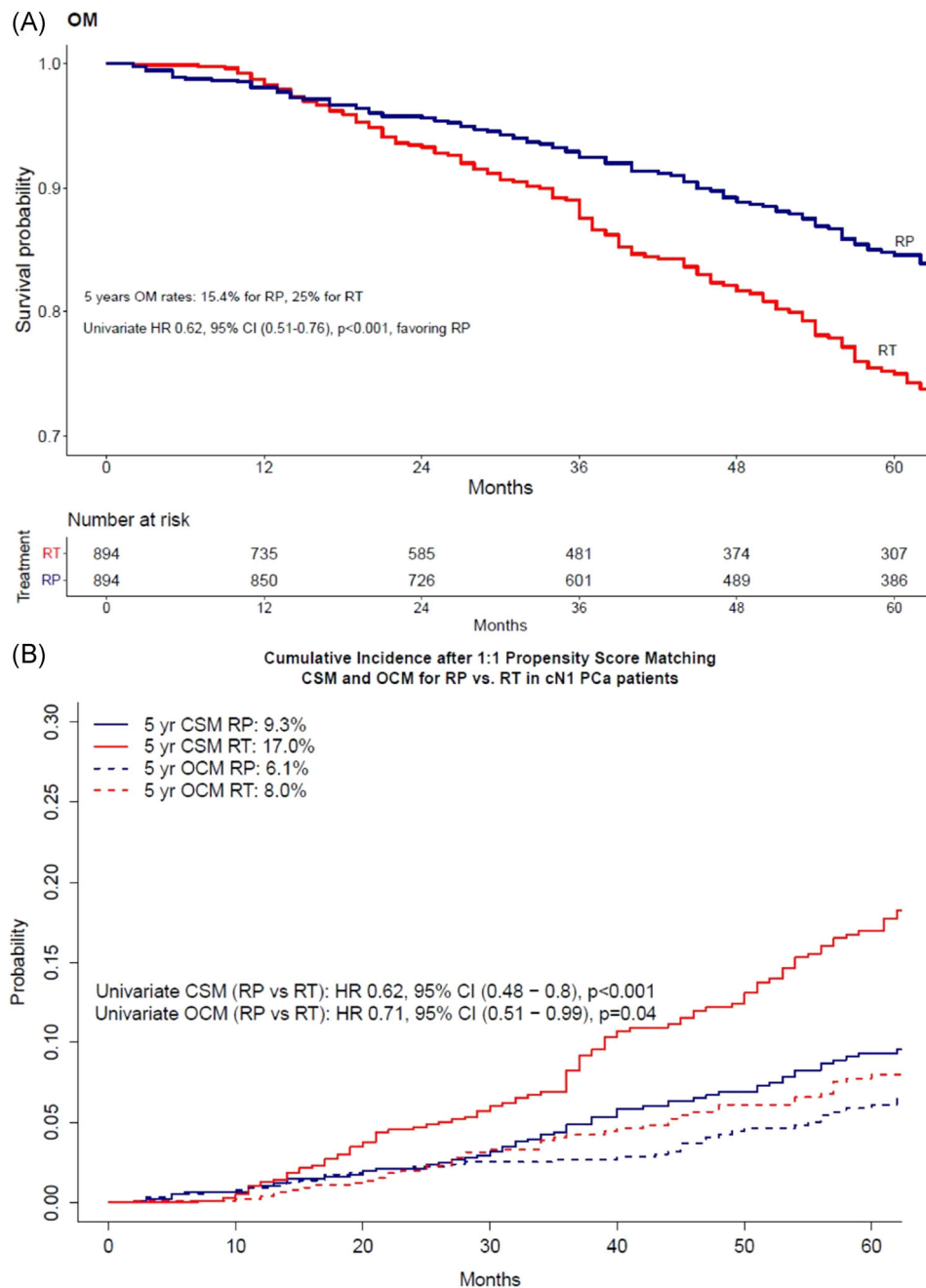


FIGURE 3 (A) Kaplan–Meier and (B) cumulative incidence plots after 1:1 propensity score matching depicting (A) overall mortality (OM), and (B) cancer-specific mortality (CSM) and other cause mortality (OCM) in RP versus RT in clinical node-positive prostate cancer patients. CI, confidence interval; HR, hazard ratio; RP, radical prostatectomy; RT, radiotherapy [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.com)]

Taken together, our observations invariably indicate that RP cN1 patients exhibit lower OM, CSM, and OCM rates. This benefit in CSM and OM may originate from better RP cancer control. This can be partly explained by the fact that the use of RT for cN1 PCa could be highly limited by the absence of accurate pathological pelvic staging that only a meticulous lymph node dissection can provide. Therefore, the cytoreductive^{9,10} or

abscopal¹¹ effect related to the local treatment of the primary tumor might be reduced for RT patients. Finally, the observed OCM benefit is usually interpreted as a selection bias and it is most likely operational in the current analysis to the same extent as in other SEER analyses.

Our findings are novel and add to the results of Seisen et al.⁴ who exclusively focused on OM as an endpoint due to the absence of

TABLE 3 Multivariable competing risks regression models testing for the differences in CSM and OCM between RP versus EBRT, after 1:1 propensity score matching (according to age, biopsy Gleason score, clinical T stage, PSA) within the Surveillance, Epidemiology and End Results (2004–2016) database in 1788 nonmetastatic clinical node positive PCa patients

	Cox regression		Competing-risks regression			
	OM		CSM		OCM	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Treatment (RT as ref)	0.63 (0.52–0.78)	<0.001	0.66 (0.51–0.86)	<0.001	0.71 (0.5–1)	0.05
Age	1.03 (1.02–1.04)	<0.001	1.01 (0.99–1.03)	0.26	1.05 (1.03–1.08)	<0.001
Race (Caucasian as ref)						
African American	0.98 (0.72–1.34)	0.9	1.08 (0.73–1.6)	0.72	0.86 (0.49–1.51)	0.61
Asian	0.75 (0.46–1.21)	0.2	0.96 (0.57–1.6)	0.86	0.5 (0.18–1.38)	0.18
Hispanic	0.78 (0.54–1.13)	0.2	0.73 (0.45–1.2)	0.22	0.94 (0.53–1.68)	0.83
PSA (ng/ml)	1.00 (0.99–1.01)	0.07	1.01 (1–1.01)	0.03	1 (0.99–1.01)	0.88
Clinical T stage (cT1 as ref)						
cT2	0.95 (0.73–1.23)	0.6	1.01 (0.71–1.43)	0.96	0.94 (0.63–1.4)	0.76
cT3	0.87 (0.65–1.17)	0.4	1.15 (0.79–1.67)	0.46	0.57 (0.34–0.95)	0.03
cT4	1.71 (1.15–2.53)	0.008	2.35 (1.47–3.77)	<0.001	0.83 (0.38–1.83)	0.65
cTx	0.70 (0.22–2.24)	0.5	1.12 (0.33–3.83)	0.86	0 (0–0)	<0.001
Biopsy Gleason Grade Group (GGG 1 as ref)						
GGG 2	1.22 (0.65–2.28)	0.5	1.89 (0.61–5.82)	0.27	0.93 (0.42–2.07)	0.87
GGG 3	1.32 (0.72–2.42)	0.4	2.41 (0.82–7.06)	0.11	0.87 (0.39–1.95)	0.73
GGG 4	1.28 (0.72–2.28)	0.4	2.75 (0.97–7.83)	0.06	0.63 (0.3–1.33)	0.23
GGG 5	1.87 (1.08–3.26)	0.026	4.16 (1.49–11.6)	0.01	0.77 (0.38–1.55)	0.46
Unknown GGG	2.07 (1.08–3.97)	0.029	5.54 (1.85–16.6)	<0.001	0.58 (0.21–1.62)	0.3

Abbreviations: CI, confidence interval; CSM, cancer-specific mortality; EBRT, external beam radiotherapy; GGG, Gleason Grade Group; HR, hazard ratio; OCM, other cause mortality; OM, overall mortality; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy.

CSM and OCM on the National Cancer Database (NCDB).¹² Unlike NCDB, the SEER database allows the assessment of CSM and OCM as separate endpoints. Moreover, the availability of CSM and OCM allows the strictest methodological assessment of CSM after adjustment for potential bias originating from OCM, as well as of OCM after adjustment for potential bias originating from CSM.

To ensure maximal comparability with Seisen et al.⁴ methodology, we relied on two different adjustment techniques for population difference: PSM and IPTW, which was specifically used by Seisen et al. Our findings agree with those of Sarkar et al. with respect to multivariable HR that indicated lower CSM and OM, that was of comparable magnitude to our findings. However, the analysis of Sarkar et al. was undermined by an insufficient sample size that yielded insignificant *p* values. Conversely, our findings, which are based on a much larger sample size, yielded protective HRs with highly significant *p* values favoring lower OM, CSM, and OCM in cN1 RP patients relative to their RT counterparts.

Several limitations of our study need to be mentioned. First, since SEER is an observational database, data are

retrospective. However, this also applies to other institutional studies, which previously addressed RP versus RT in cN1 patients.^{4,5} This limitation should be considered in the context of currently unavailable RCTs comparing RP versus RT in the cN1 PCa population. Second, the SEER database does not include information regarding comorbidities, which could affect treatment assignment. However, we relied on adjustment for OCM, which represents a well-established proxy of significant comorbidities.^{13–15} Unfortunately, only the SEER-Medicare database allows the concomitant use of comorbidities and OCM. However, it only holds a fraction (approximately 30%) of the SEER database population used in the current analyses.¹⁶ In consequence, SEER-Medicare-derived observations may be more precise, but less robust. Additionally, the absence of earlier cancer-control outcomes, such as biochemical recurrence, progression-free survival, or metastatic progression may also be criticized. However, these endpoints are clearly not as definitive and not as established as the ultimate endpoint of CSM. Moreover, it is important to emphasize that even the strictest and most detailed adjustment methods (PSM, IPTW, competing-risks regression [CRR], etc.) cannot fully

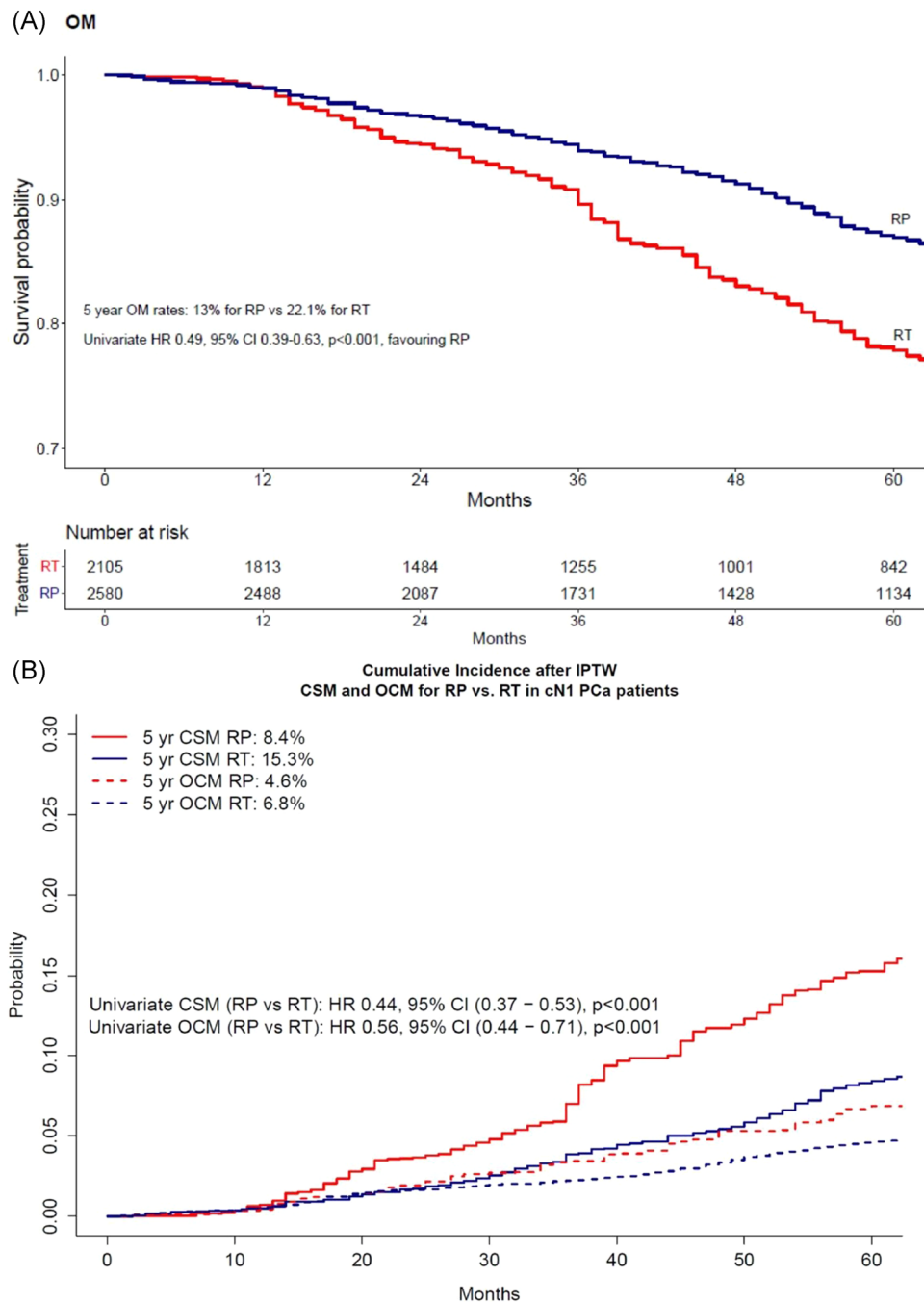


FIGURE 4 (A) Kaplan Meier and (B) cumulative incidence plots depicting (A) overall mortality (OM), and (B) cancer-specific mortality (CSM), and other cause mortality (OCM) after the inverse probability of treatment weighting (IPTW) in RP versus RT in clinical node-positive prostate cancer patients. CI, confidence interval; HR, hazard ratio; RP, radical prostatectomy; RT, radiotherapy [Color figure can be viewed at wileyonlinelibrary.com]

account for potential residual differences between RT and RP-treated patients.¹⁷

Finally, the absence of central pathology review, the lack of information on the treatment decision-making process, the type and duration of androgen deprivation, type and dosage of radiation therapy, and subsequent treatment after RP or RT may represent additional limitations.

5 | CONCLUSIONS

After adjustment for baseline PCa clinical characteristics, at competing risk regression analyses, RP was associated with both lower CSM and lower OCM, when compared to RT. In consequence, the potential benefit of RP in cN1 patients should be considered in treatment planning.

TABLE 4 Regression models testing for the differences in OM, CSM, and OCM in between RP versus EBRT, within the Surveillance, Epidemiology and End Results (2004–2016) database in 4685 nonmetastatic clinical node-positive PCa patients

	Cox regression		Competing risks regression			
	OM HR (95% CI)	p value	CSM HR (95% CI)	p value	OCM HR (95% CI)	p value
Treatment (RT as ref)	0.55 (0.45–0.66)	<0.001	0.49 (0.34–0.70)	<0.001	0.54 (0.36–0.79)	<0.001
Race (Caucasian as ref)						
African American	0.83 (0.62–1.12)	0.9	0.78 (0.59–1.03)	0.09	0.83 (0.6–1.17)	0.3
Asian	0.88 (0.53–1.46)	0.2	0.81 (0.53–1.26)	0.4	0.5 (0.25–1.03)	0.06
Hispanic	0.84 (0.59–1.21)	0.9	0.79 (0.58–1.08)	0.1	0.8 (0.54–1.18)	0.3
Propensity score	–	–	0.80 (0.46–1.40)	0.4	1.04 (0.58–1.89)	0.9

Note: We relied on Cox regression models after inverse probability of treatment weighting (IPTW) for OM. In the analyses on CMS and OCM, as a proxy of Fine and Gray's competing risks regression after IPTW, we relied on the use of the propensity score as a covariate of the regression model.

Abbreviations: CI, confidence interval; CSM, cancer-specific mortality; EBRT, external beam radiotherapy; HR, hazard ratio; OCM, other cause mortality; OM, overall mortality; RP, radical prostatectomy; RT, radiotherapy.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interests.

AUTHOR CONTRIBUTIONS

Protocol/project development, data collection or management, data analysis, and manuscript writing/editing: Francesco Chierigo; protocol/project development, data collection or management, data analysis, and manuscript writing/editing: Marco Borghesi; protocol/project development and manuscript writing/editing: Christoph Würnschimmel, Rocco Simone Flammia, Benedikt Horlemann, Gabriele Sorce, and Pierre I. Karakiewicz; data collection or management, and data analysis: Zhe Tian; manuscript writing/editing: Fred Saad, Markus Graefen, Michele Gallucci, Alberto Briganti, Francesco Montorsi, Felix K.H. Chun, Shahrokh F. Shariat, Guglielmo Mantica, Nazareno Suardi, and Carlo Terrone.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from SEER. Restrictions apply to the availability of these data, which were used under license for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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