World Journal of Urology (2018) 36:1399–1407
https://doi.org/10.1007/s00345-018-2310-y

ORIGINAL ARTICLE

Survival after radical prostatectomy or radiotherapy for locally advanced (cT3) prostate cancer

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Received: 27 February 2018 / Accepted: 24 April 2018 / Published online: 2 May 2018

Abstract

Purpose No prospective data examined the effect of radical prostatectomy (RP) vs. external beam radiotherapy (EBRT) in locally advanced prostate cancer (PCa). We aimed to compare survival outcomes of RP and EBRT in patients harboring cT3N0-1 PCa.

Methods Within the SEER database (2004–2014), we identified 5500 cT3N0-1 PCa patients. Cumulative incidence plots and competing-risks regression models (CRRs) tested cancer-specific mortality (CSM) and other cause of mortality (OCM) according to treatment type. The multivariable relationship between baseline prostate-specific antigen (PSA) values and 10-year CSM after either RP or EBRT was graphically depicted using the LOESS smoothing method. Sensitivity analyses were performed in cT3N0-only patients, after OCM propensity score matching, and through landmark analyses.

Results Ten-year CSM and OCM rates were significantly higher after EBRT (15.8 and 28.2%) than RP (8.1 and 10.4%) (all $p < 0.0001$). In multivariable CRRs, RP yielded lower CSM [hazard ratio (HR): 0.64] than EBRT. Significantly lower 10-year CSM rate was recorded after RP vs. EBRT through the entire range of baseline PSA values. The same results were recorded in cT3N0 subgroup, as well as after OCM propensity score matching. Finally, landmark analyses at 6, 12, 24, and 36 months rejected the effect of favorable survival bias after RP.

Conclusions CSM was significantly lower after RP than EBRT in cT3N0-1 PCa. A lower CSM was recorded throughout the entire range of baseline PSA and even in cT3N0 subgroup, as well as after OCM propensity score matching and landmark analyses.

Keywords Prostate cancer · Radical prostatectomy · External beam radiotherapy · Locally advanced disease · SEER program

Introduction

A small, nonetheless significant proportion of newly diagnosed non-metastatic prostate cancers (PCa) shows characteristics of locally advanced disease with or without clinical lymph node invasion [1]. Clear and concise treatment guidelines have not been defined for the management of PCa in

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00345-018-2310-y) contains supplementary material, which is available to authorized users.

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this patient population, and the choice of radical prostatectomy (RP) or external beam radiotherapy (EBRT) remains debatable.

Several advantages and disadvantages differentiate the two procedures. In general, RP is associated with more accurate staging of the disease, prostate-specific antigen (PSA) level reliability for prediction of recurrence, and fewer bowel/rectal problems than EBRT. However, RP requires hospitalization, and it is associated with general risk of surgery and higher risk of incontinence and impotence compared to EBRT [2]. On the other hand, patients treated with EBRT do not require hospitalization or surgery, and they usually present lower risk of urinary incontinence than RP patients. Such advantages are compensated by lack of post-treatment staging information, higher rate of bladder irritation, and higher rates of bowel/rectal problems than RP patients [2].

To date, international guidelines agreed that RP as part of a multimodal therapy or EBRT plus androgen deprivation therapy (ADT) can be recommended to all locally advanced PCa patients with life expectancy more than 10 years. However, whether the choice should prefer one or the other option is not yet defined due to the absence of level 1 evidence [3].

Only few and non-randomized studies examined oncological outcomes of RP and EBRT in patients harbouring cT3 PCa. Here, such uncontrolled retrospective case series demonstrated comparable cancer-specific mortality (CSM) rates after RP (10-year CSM lower 13%) [1, 4, 5] or EBRT with ADT (10-year CSM lower 14%) [6–8] in locally advanced PCa (cT3).

To address the uncertainty regarding the choice of RP vs. EBRT for cT3N0-1 PCa, especially in the absence of prospective randomized phase III trials, we examined CSM rates after either RP or EBRT, within the most contemporary Surveillance Epidemiology and End Results (SEER) database, spanning years 2004–2014.

Materials and methods

Study cohorts

The current study relied on the SEER database, which samples 26% of the United States and approximates the United States in terms of demographic composition, as well as of cancer incidence and mortality [9]. We relied on the SEER research data 1973–2014, where an extensive data quality review of SEER PSA values from 2004 to 2014 has been completed [10].

We focused on subjects diagnosed between 2004 and 2014 with histologically confirmed adenocarcinoma of the prostate [International Classification of Disease for Oncology (ICD-O-3) code 8140 of the prostate (site code C61.9)] [11]. We only considered men with locally advanced PCa (cT3N0-1, M0, PSA < 50 ng/ml) treated with RP (surgery site codes 50 or 70) [12] or EBRT (radiation code: beam radiation) [13], aged less than 79 years. According to the SEER records, clinical T stage was mainly assessed with digital rectal examination (DRE). Moreover, for the definition of the lymph node status, we relied on the SEER variables "CS Lymph Nodes" and "CS Lymph Nodes Eval" for either RP or EBRT patients [14]. Exclusion criteria consisted of unknown PSA, unknown biopsy Gleason score, unknown clinical N stage, and metastatic disease (M1), or combination of RP and EBRT. CSM was defined according to the SEER mortality code (code 28010). All other deaths were considered as other-cause mortality (OCM).

Statistics

Descriptive statistics focused on frequencies and proportions for categorical variables [year of diagnosis, race, marital status, biopsy Gleason grade group [15] (GGG), and clinical N stage]. Means, medians, and ranges were reported for continuously coded variables (age and PSA). The statistical significance of differences in medians and proportions was tested with the Kruskal–Wallis and Chi-square tests. All statistical tests were two sided with a level of significance set at $p < 0.05$.

Analyses consisted of seven steps. First, we evaluated the temporal local treatment trends: RP vs. EBRT. To quantify annual temporal trend differences, we relied on annual percentage change (APC) with the least-squares linear regression. Second, treatment type-specific CSM and OCM cumulative incidence rates were generated and differences were tested with the Gray test [16]. Third, univariable and multivariable (MVA) competing-risks regression (CRR) methodology was used to test the effect of treatment type (RP vs. EBRT) on CSM [17]. Covariates included age, race, marital status, year of diagnosis, PSA, GGG, and cN stage. The latter was established in all RP and EBRT patients according to pre-treatment imaging evaluation of the lymph node status. Fourth, the LOESS smoothing method was used to graphically explore the relationship between baseline PSA values and 10-year CSM rates, derived from CRR multivariable analysis and adjusted for all covariates [18]. Fifth, for the purpose of sensitivity analysis, MVA CRR, as well as LOESS analyses, was repeated in cT3N0 patients. Sixth, to account for OCM rate differences between RP and EBRT patients, we relied on 1:1 nearest neighbor (caliper 0.5; R package "*matchit*") propensity score matching defined according to individual OCM risk [14, 19]. Thus, defined OCM propensity score matching was applied to the entire study population, and MVA CRR models predicting CSM were refitted and the graphical depiction of treatment

type-specific 10-year CSM rates (LOESS methodology) was also generated. Last, landmark analyses were performed at 6, 12, 24, and 36 months after the time of diagnosis, to address the potential effect of immortal time bias, which may favorably affect patients treated with RP, relative to EBRT patients [20].

All statistical tests were two sided with a level of significance set at $p < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 3.3.0; http://www.r-project.org/).

Results

We identified 5500 men with locally advanced (cT3N0-1) PCa, diagnosed between 2004 and 2014. Median age was 65 years [interquartile range (IQR) 59–71]. Most were Caucasian (3996, 72.7%), married (3908, 71.1%), harbored Gleason score ≤ 7 (3093, 56.2%), and cN0 (3215, 58.5%). Median PSA value at diagnosis was 12.6 ng/ml (IQR 5.5–16.5). RP or EBRT was performed in 2507 (45.6%) and 2993 (54.4%) patients, respectively (Table 1).

Temporal trend analyses

During the study period, the proportion of EBRT patients decreased from 63.8 to 50.9% (APC − 2.38%, CI − 3.56 to − 1.10, $p = 0.003$) vs. an increase from 36.2 to 49.1% (APC + 3.00%, CI + 1.12 to + 1.19, $p = 0.007$) for RP (Fig. 1).

Cumulative incidence analyses

Overall, 10-year CSM rates were 15.8 for EBRT patients vs. 8.1% for RP patients ($p < 0.0001$). 10-year OCM rates were 28.2 for EBRT patients vs. 10.4% for RP patients ($p < 0.0001$) (Fig. 2). Similarly, 10-year CSM and 10-year OCM rates were recorded in cT3N0, respectively, 15.5 vs. 3.9% ($p < 0.0001$) and 27.8 vs. 5.9% ($p < 0.0001$).

Competing-risks analyses

In MVA CRR models, that were stratified according to treatment type, RP yielded lower CSM evidenced by hazard ratio (HR) of 0.62 [confidence interval (CI) 0.45–0.86] (Table 2). In cT3N0 patient subset, RP also yields lower CSM evidenced by HR of 0.45 (CI 0.25–0.81, Supplementary Table 1).

Graphical depiction of MVA adjusted CSM rate according to treatment type (LOESS)

Significantly lower 10-year CSM rates were recorded after RP vs. EBRT through the entire range of baseline PSA values (Fig. 3). The same results were recorded in cT3N0 patient subgroup.

Sensitivity analyses

For the purpose of propensity score adjustment for potential OCM differences, analyses predicting OCM for the entire study period were fitted (Supplementary Table 2). Based on the propensity score cohort of 933 RP and 933 EBRT patients, we refitted MVA CRR models that focused on CSM. Here, significantly lower 10-year CSM rates were recorded after RP vs. EBRT, through the entire range of baseline PSA values (Supplementary Fig. 1). To confirm the validity of our approach, virtually, the same 10-year OCM rates (16 vs. 15.9%, $p = 0.8$, Supplementary Fig. 2) were recorded and validated the correctness of OCM propensity score matching with a HR of 0.98 (CI 0.68–1.39), indicative of no meaningful OCM rate difference. Finally, we performed landmark analyses to reject the hypothesis of immortal time bias. Here, at 6, 12, 24, and 36 months after the diagnosis of PCa, the decrease in CSM recorded after RP remained unchanged relative to "naïve" analyses, where the potentially favorable survival bias toward individuals who benefited from RP was unaccounted for.

Discussion

To date, no randomized controlled phase III trial has compared RP with EBRT in locally advanced non-metastatic PCa. Only historical (1988–2004) [7] and relatively small-scale [6] retrospective studies compared RP with EBRT in cT3. In consequence, the choice of RP or EBRT in this setting of patients remains controversial.

To address this void, we relied on a large population-based dataset (the SEER database) to compare CSM in 5500 cT3 PCa patients according to treatment type: RP vs. EBRT. To control for differences in baseline patient characteristics, we restricted the analyses to patients aged 79 years or less and with baseline PSA values less than 50 ng/ml. We then repeated the analyses after OCM propensity score matching, as well as in cT3N0 patient subset, which represents the vast majority of the study population. Our study yielded several noteworthy findings.

First, despite significantly higher rate of EBRT at the beginning of the study period, RP rate increased and EBRT rate decreased over time. In consequence, the proportion of patients treated with RP vs. EBRT changed over time. Initially, EBRT was favored. However, within the five most recent study years, RP and EBRT rates were virtually the same. This finding validates the confidence in RP as increasingly selected treatment modality for cT3N0-1 PCa. Our findings also agree with a contemporary report by Hager

Table 1 Clinical and pathological characteristics of 5500 patients with locally advanced prostate cancer (cT3), M0

Variables	Overall, $n=5500$	Radical prostatectomy, $n=2507$	Radiotherapy, $n=2993$	p
Age at diagnosis				
Mean (STE)	64.8 (0.104)	61.9 (0.138)	67.2 (0.137)	<0.0001
Median	65	62	68	
Range	59–71	57–67	62–73	
PSA (ng/ml)				
Mean (STE)	12.6 (0.14)	9.8 (0.161)	15 (0.209)	<0.0001
Median	8.6	7.1	10.9	
Range	5.5–16.5	4.9–11.4	6.3–20.7	
Year of diagnosis				
2004	484 (8.8)	175 (7)	309 (10.3)	<0.0001
2005	450 (8.2)	159 (6.3)	291 (9.7)	
2006	573 (10.4)	252 (10.1)	321 (10.7)	
2007	559 (10.2)	259 (10.3)	300 (10)	
2008	546 (9.9)	264 (10.5)	282 (9.4)	
2009	470 (8.5)	231 (9.2)	239 (8)	
2010	529 (9.6)	231 (9.2)	298 (10)	
2011	508 (9.3)	258 (10.4)	250 (8.3)	
2012	428 (7.8)	214 (8.5)	214 (7.2)	
2013	462 (8.4)	218 (8.7)	244 (8.2)	
2014	491 (8.9)	246 (9.8)	245 (8.2)	
Race				
White	3996 (72.7)	1829 (73)	2167 (72.4)	0.045
African American	645 (11.7)	306 (12.2)	339 (11.4)	
Hispanic	471 (8.6)	220 (8.8)	251 (8.4)	
Other	349 (6.3)	141 (5.6)	208 (6.9)	
Unknown	39 (0.7)	11 (0.4)	28 (0.9)	
Marital status				
Married	3908 (71.1)	1854 (74)	2054 (68.6)	<0.0001
Unknown	277 (5)	117 (4.7)	160 (5.3)	
Unmarried	1315 (23.9)	536 (21.3)	779 (26.1)	
Gleason grade groups				
I	597 (10.9)	332 (13.2)	265 (8.9)	<0.0001
II	1411 (25.7)	829 (33.1)	582 (19.4)	
III	1085 (19.7)	546 (21.8)	539 (18)	
IV	1050 (19.0)	363 (14.5)	687 (23)	
V	1357 (24.7)	437 (17.4)	920 (30.7)	
Clinical N stage				
N0	3215 (58.5)	681 (27.1)	2534 (84.7)	<0.0001
N1	226 (4.1)	37 (1.5)	189 (6.3)	
NX	2059 (37.4)	1789 (71.4)	270 (9)	

et al. [21], where the investigators compared cT3-T4 PCa treatment rates in the United States.

Second, several consecutive analytic steps demonstrated lower CSM rates after RP was compared to EBRT. Specifically, 10-year CSM rate was 7.7% lower for RP vs. EBRT. Lower CSM was confirmed in MVA CRR analyses and was evidenced by a 38% HR reduction. Lower 10-year CSM rates were also graphically depicted across the entire range of baseline PSA values in LOESS smoothed plots that focused on RP vs. EBRT, after multivariable adjustment for all covariates. Moreover, lower CSM rates were also identified after RP vs. EBRT in the subset of cT3N0 PCa patients. Similarly, as in the entire population, also these subset analyses showed lower 10-year CSM rates across the entire range of PSA values, after adjustment for all covariates. The aforementioned subset analyses allowed the examination of

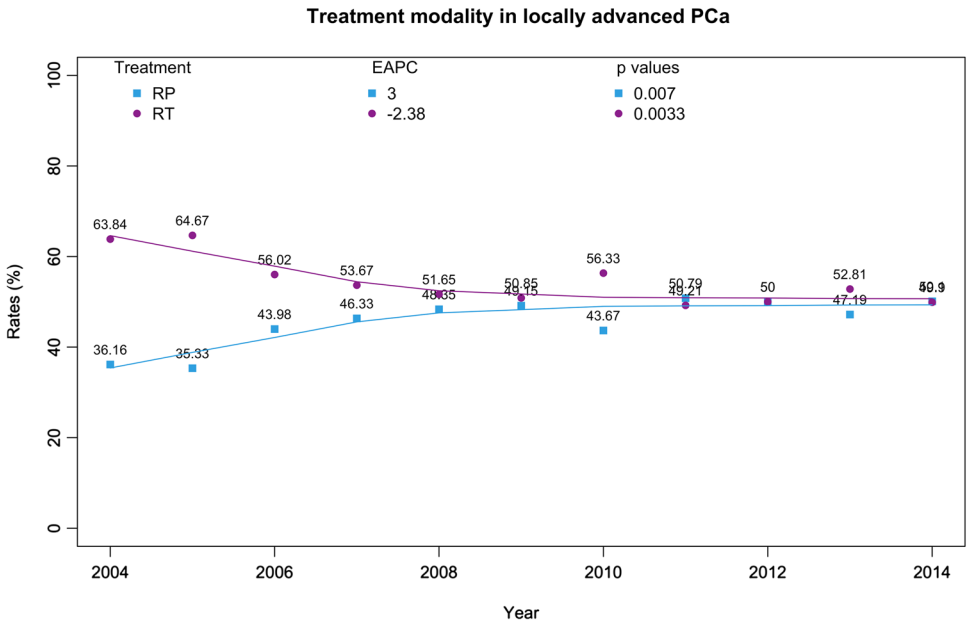

Fig. 1 Graphical representation of temporal trends for radical prostatectomy and external beam radiotherapy in locally advanced prostate cancer (cT3N0-1M0) spanning years 2004–2014

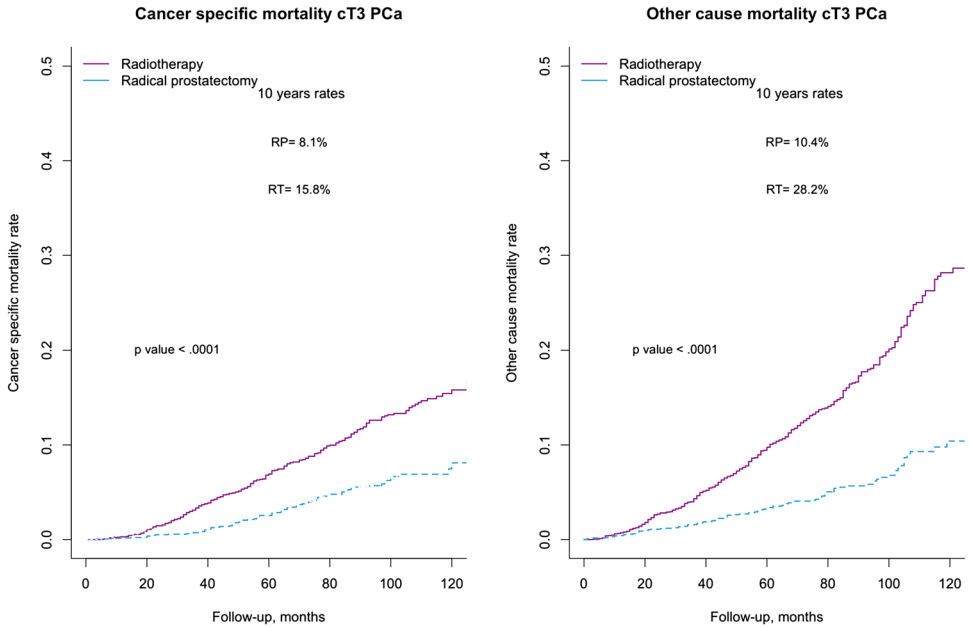

Fig. 2 Cumulative incidence plots depicting cancer-specific mortality rates and other-cause mortality rates in cT3N0-1 prostate cancer stratified according to treatment received: radical prostatectomy vs. external beam radiotherapy

CSM rates in a more homogeneous and selected patient subgroup population (cT3N0). Furthermore, lower CSM rates were also recorded after additional OCM propensity score matching, which focused on potential bias that could result from higher OCM rates in EBRT patients. The results of all CSM analyses clearly demonstrated lower CSM rates after RP, regardless of analytical approach or adjustment type or patient cohort that was examined. Last but not least, landmark analyses performed at 6, 12, 24, and 36 months after PCa diagnosis failed to show that patients selected for RP have benefited from a favorable survival bias.

The incremental complexity of hypothesis testing with multiple adjustment levels and subgroup analyses serve the purpose of rejecting the possibility that the null hypothesis of no differences was incorrectly rejected. In consequence, it appears justified to conclude that based on thorough, albeit retrospective analyses, a survival benefit might exist when RP was selected instead of EBRT. Nonetheless, lack of randomization and the retrospective nature of the current analyses reduce our findings to lesser evidence level (level III) than if our findings originated from a randomized controlled trial (level IB or II).

Table 2 Univariable and multivariable competing-risk models (CRRs) predicting cancer-specific mortality in 5500 patients with locally advanced (cT3, cN0-1) prostate cancer, according to clinical and pathological characteristics

Competing-risk regression models	HR cancer univariable	*p* values univariable	HR cancer multivariable	*p* values multivariable
PSA	1.03 (1.02–1.03)	< 0.0001	1.01 (1–1.02)	0.0043
Age at diagnosis	1.01 (1–1.03)	0.058		
Radiotherapy	1.00 (Ref.)	–	1.00 (Ref.)	–
Radical prostatectomy	0.44 (0.34–0.56)	< 0.0001	0.62 (0.45–0.86)	0.0039
GGG				
I	1.00 (Ref.)	–	1.00 (Ref.)	–
II	1.87 (0.91–3.87)	0.09	1.91 (0.92–3.94)	0.082
III	3.88 (1.92–7.82)	0.0002	3.65 (1.81–7.38)	0.0003
IV	5.24 (2.62–10.48)	< 0.0001	4.50 (2.24–9.02)	< 0.0001
V	10.74 (5.5–20.98)	< 0.0001	9.16 (4.66–17.97)	< 0.0001
Year of diagnosis				
2004	1.00 (Ref.)	–		
2005	0.71 (0.49–1.03)	0.075		
2006	0.75 (0.53–1.07)	0.11		
2007	0.92 (0.64–1.3)	0.62		
2008	0.85 (0.58–1.25)	0.42		
2009	0.64 (0.4–1.04)	0.072		
2010	0.62 (0.37–1.05)	0.075		
2011	0.54 (0.27–1.06)	0.072		
2012	0.92 (0.43–1.97)	0.83		
2013	0.99 (0.31–3.23)	0.99		
2014	1.74 (0.22–13.53)	0.6		
cN0	1.00 (Ref.)	–	1.00 (Ref.)	–
cN1	3.01 (2.03–4.47)	< 0.0001	1.91 (1.27–2.87)	0.0018
cNX	0.67 (0.52–0.85)	0.001	0.99 (0.73–1.34)	0.95
Race				
Caucasian	1.00 (Ref.)	–		
African American	0.98 (0.71–1.36)	0.91		
Hispanic	0.84 (0.55–1.28)	0.41		
Other	0.52 (0.28–0.95)	0.033		
Unknown	0 (0–0)	0		
Marital status				
Married	1.00 (Ref.)	–	1.00 (Ref.)	–
Unmarried	1.35 (1.07–1.72)	0.013	1.33 (1.04–1.69)	0.023
Unknown	0.93 (0.52–1.66)	0.81	0.93 (0.52–1.67)	0.82

HR hazard ratio, *CI* confidential interval, *GGG* Gleason grade group, *PSA* prostate specific antigen

Similar to our study, others have previously compared RP to EBRT in high-risk PCa. However, none focused specifically on cT3 PCa [7, 22–25]. For example, Boorjian et al. [7] relied on a historical cohort (1988–2005), that included a subset of 411 cT3 PCa patients, as well as 817 cT1-2 PCa, and they found no differences in CSM rates according to treatment type: RP vs. EBRT.

Recently, a retrospective single-institution study attempted to identify the best treatment approach in cT3-only PCa patients [6]. The investigators relied on 231 PCa treated with either RP or EBRT. Despite lower CSM rate (7%) after RP vs. EBRT (15%), Yamamoto et al. [6] did not identify a statistically significant difference because of the sample size limitation.

Our study does have some limitations that merit discussion. First, the SEER database does not include baseline performance status (Eastern Cooperative Oncology Group) and comorbidities. In that regard, we attempted to obviate this limitation by relying on CRR that accounts for OCM. In addition, we also relied on OCM propensity score matching

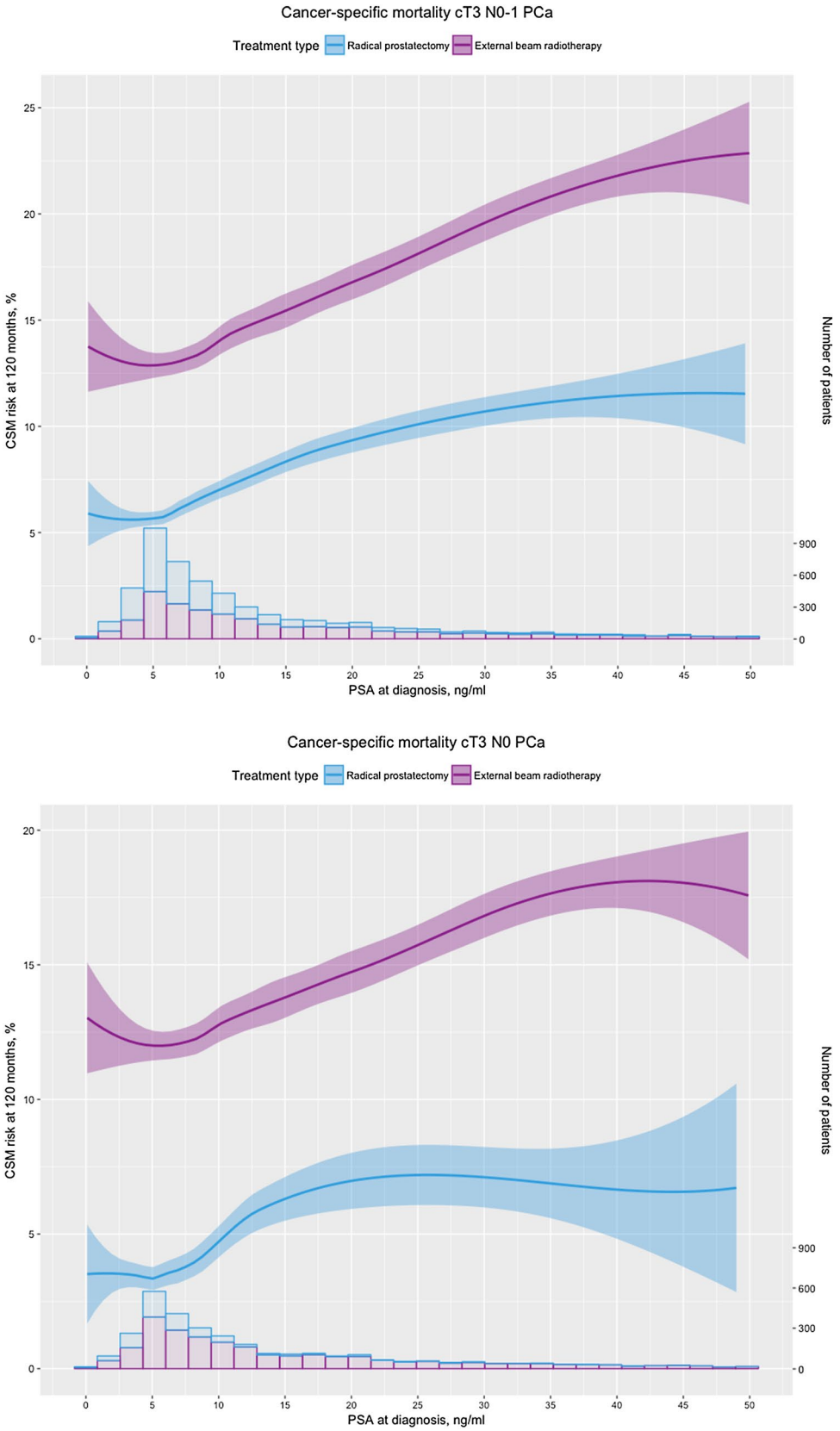

Fig. 3 Graphical depiction of multivariable adjusted cancer-specific mortality rate (LOESS) in 5500 cT3N0-1 PCa patients and in 3215 cT3N0 subgroup according to treatment received: radical prostatectomy vs. external beam radiotherapy

to maximally reduce the potential OCM rate differences between RP and EBRT patients. Second, according to the SEER records, clinical T stage and clinical lymph node stage were assessed using DRE and CT scan, respectively. However, both presented low accuracy and limited reliability [26]. On the other hand, magnetic resonance imaging or positron emission tomography (PET)/CT scan was neither diffused nor approved for these specific purposes during the study period. In consequence, DRE and CT scan represented the only albeit inaccurate staging methodologies that could be used between years 2004 and 2014. Third, ADT and chemotherapy data are not recorded in the SEER database. Such missing data might have affected the results of our study. Moreover, concomitant ADT during EBRT, as well as timing of ADT or adjuvant chemotherapy, also might have affected the results of our study. Fourth, it should be noted that clinical N status data were missing for a significant proportion (40%) of patients. Unfortunately, this limitation is shared with all SEER-based analyses that stratify patients treated with EBRT or RP according to clinical lymph node status. Fifth, lack of standardized preoperative imaging evaluation might have hampered the uniformity of our patient population by including also patients with metastatic disease (M1). However, such possibility was partially compensated by relying on an upper PSA threshold of 50 ng/ml, which might have excluded the vast majority of patients with metastatic PCa. Sixth, the SEER database also lacks of information about RT dose (Gy) and regiments, as well as data on relapse and follow-up treatments. In consequence, our analyses were not adjusted for such covariates. Seventh, changes in the Gleason-grading system according to the International Society of Urologic Pathology Conference 2005 could have influenced our findings. These changes may have resulted in reporting of higher Gleason score and more patients with high-risk characteristics within more recent study years. Last but not least, even with the most sophisticated statistics, our study is limited by its retrospective design. This said, prospective randomized data are neither available nor will be available due to the lack of ongoing trial on cT3 PCa. In consequence, our study represents the largest and most contemporary source of evidences that support RP instead of EBRT in cT3 PCa patients.

Conclusions

Taken together our study showed that CSM was significantly lower after RP than EBRT in cT3N0-1 PCa. A lower CSM was recorded throughout the entire range of baseline PSA values and in cT3N0 subgroup, as well as after OCM propensity score matching. Survival bias did not affect the observed lower CSM rate after RP vs. EBRT. Despite its design limitation, our findings qualify for being considered an important signal that should prompt the design of randomized controlled trial comparing RP to EBRT in cT3N0-1 PCa. Until such trial is completed and its results yield mature observations, similar analyses should be performed in other large-scale databases to corroborated or refute our findings. In the absence of contradictory findings, our study represents the largest and most contemporary source of evidence prompting the use of RP in cT3 patients. Although it would be tempting to generalize such practice to all cT3N0-1 PCa patients, we must restrict our interpretation to cT3N0 patients, since sample size limitations precluded us from performing valid comparisons in cT3N1 patient subgroup.

Author contribution MB: protocol/project development, data collection or management, data analysis, manuscript writing/editing. FP: data collection or management. MM: manuscript writing/editing. ZT: data analysis. EZ: manuscript writing/editing. DT: data analysis. FM: protocol/project development. SFS: data collection or management. AB: protocol/project development. FS: manuscript writing/editing. PIK: manuscript writing/editing, protocol/project development.

Compliance with ethical standards

Conflict of interest This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors have stated that they have no conflict of interest.

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