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Comparing effectiveness of radical prostatectomy versus external beam radiotherapy in patients with locally advanced prostate cancer
A population-based analysis

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Abstract

Currently, the standard management for locally advanced prostate cancer (PCa) is still controversial. In our study, we aimed to compare the survival outcomes of radical prostatectomy (RP) versus external beam radiotherapy (EBRT).

We conducted analyses with a large cohort of 38,544 patients from the Surveillance, Epidemiology, and End Results (SEER) database (2004–2016). Propensity score matching, Kaplan-Meier method, and Cox proportional hazard regression were used to reduce the influence of bias and compare the overall survival (OS) and cancer specific survival (CSS). Several different sensitivity analyses including inverse probability of treatment weighting and standardized mortality ratio weighting were used to verify the robustness of the results.

Totally, 33,388 men received RP and 5,156 men received EBRT with cT3-4N0M0 PCa were included in this study. According to the Kaplan-Meier curves, RP performed better in both OS and CSS compared with EBRT ($P < .0001$). In the adjusted multivariate Cox regression, RP also showed better OS and CSS benefits (OS: HR=0.50; 95% confidence interval [CI]: 0.46–0.54; $P < .0001$ and CSS: HR=0.43; 95% CI: 0.38–0.49; $P < .0001$). After propensity score matching, RP is still the management that can bring more survival benefits to patients. (OS: HR=0.46; 95% CI: 0.41–0.51; $P < .0001$ and CSS: HR=0.41; 95% CI: 0.34–0.48; $P < .0001$).

Our research demonstrated the significantly better survival benefits of RP over EBRT in patients with locally advanced PCa. The results of this study will provide more evidence to help clinicians choose appropriate treatment strategies.

Abbreviations: ADT = androgen deprivation therapy, BT = brachytherapy, CI = confidence interval, CSS = cancer-specific survival, EBRT = external beam radiotherapy, GS = Gleason score, HR = hazard ratio, OS = overall survival, PCa = prostate cancer, PSA = prostate specific antigen, RP = radical prostatectomy.

Keywords: external beam radiotherapy, prostate cancer, radical prostatectomy

1. Introduction

Prostate cancer (PCa) is 1 of the most common malignant tumors in the world, and there might be 174,650 new cases in the United States in 2019.[1]

The European Association of Urology pointed out that patients with locally advanced PCa (cT3-4 or cN+) had an increased risk of disease progression and cancer-specific death.[2] Owing to various factors, such as the American national guidelines advising against prostate specific antigen (PSA) screening, increasing implementation of active surveillance, and so on, the proportion of locally advanced PCa is growing in recent years.[3–5]

According to the guidelines, as first-line treatment options of locally advanced PCa, radical prostatectomy (RP) as part of multimodal therapy is recommended for highly selected patients, and external beam radiotherapy (EBRT) plus long-term andro-gen deprivation therapy (ADT) is considered to be applicable to larger population.[2,6] However, due to the absence of high-quality randomized trials to directly compare the 2 treatments, it is still controversial that which treatment can bring patients better survival benefits.

In fact, a few recent retrospective studies have yielded conflicting results with the guidelines, in which RP was significantly associated with better long-term overall survival (OS) or cancer-specific survival (CSS) than EBRT in various study populations.[7–11] However, these previous studies still have some
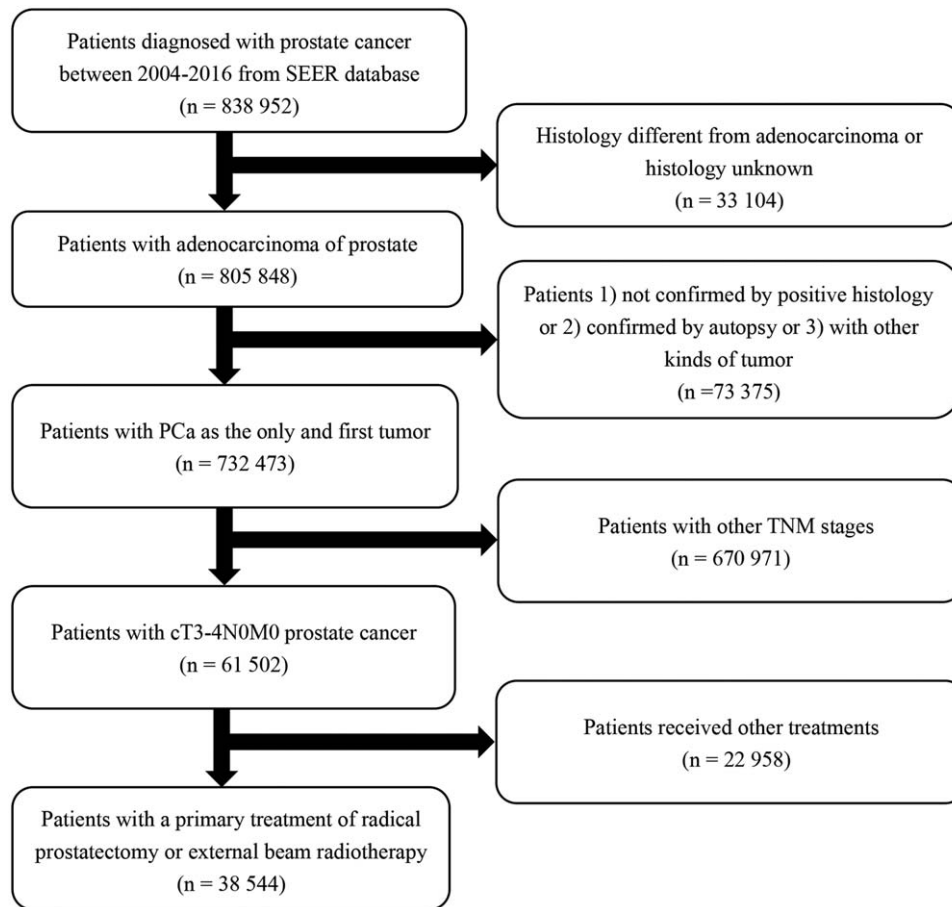
Figure 1. Flowchart describing the selection of patients in the surveillance, epidemiology, and end results database, 2004-2016.

weaknesses, such as too strict inclusion and exclusion criteria, relatively fewer cases and obsolete data from 10 years ago, and so on. We still need the latest data from a larger population to compare the 2 treatments.

To circumvent the defect in knowledge, in our study, we used a large population-based cohort to evaluate the long-term survival outcomes of locally advanced PCa patients after primary RP or EBRT.

2. Materials and methods

2.1. Ethics

This study used a general dataset from the Surveillance, Epidemiology, and End Results database built by a public health program, and therefore did not require institutional review board approval and the patients' data were atomized.

2.2. Population selection

The Surveillance, Epidemiology, and End Results (SEER) database is a population-based cancer registry covered over 25% population of the United States.[12] It releases cancer patient's general information annually. Due to the need for reviewing and proofreading, the current latest version includes data up to 2016.

From the SEER database, patients with a diagnosis of adenocarcinoma of the prostate (International Classification of diseases-O-3 code: C61.9) between 2004 and 2016 were selected. The TNM stage of PCa was defined according to the 7th edition of American Joint Committee on Cancer [AJCC] Cancer Staging Manual.[13] Our study excluded patients with clinically detectable nodal involvement (cN+) because of the small samples relatively. Detail inclusion and exclusion criteria were shown in Figure 1. All the included patients were divided into the RP cohort and the EBRT cohort by the primary treatment.

2.3. Data collection

For each patient, the following information was collected: age, year of diagnosis, marital status (including married, single, and divorced/widowed), follow up time from PCa diagnosis, race (including white, black, and other), region (including Pacific coast, east, southwest and other), clinical T stage (including T3 and T4), PSA, and Gleason score (GS) biopsy (categorized as ≤6, 7, 8, 9, and 10). We summarized these baseline characteristics and follow-up information in Table 1.

2.4. Outcome definition

The outcomes of the study were OS and CSS. OS was measured by deaths from any cause. CSS was measured by all deaths caused

Table 1

Descriptive characteristics of 38,544 patients undergoing radical prostatectomy or external beam radiotherapy as the primary treatment between 2004 and 2016 from the Surveillance Epidemiology and End Results database.

	RP (N = 33388)	EBRT (N = 5156)	P value
Age, yr mean (SD)	62.43 (6.98)	68.73 (8.60)	<.001
PSA level (ng/mL), mean (SD)	11.71 (16.36)	24.10 (26.22)	<.001
Year of Diagnosis, n (%)			<.001
2004	411 (7.97%)	1812 (5.43%)	
2005	412 (7.99%)	1763 (5.28%)	
2006	449 (8.71%)	2082 (6.24%)	
2007	428 (8.30%)	2576 (7.72%)	
2008	398 (7.72%)	2587 (7.75%)	
2009	321 (6.23%)	2448 (7.33%)	
2010	421 (8.17%)	2836 (8.49%)	
2011	345 (6.69%)	2939 (8.80%)	
2012	316 (6.13%)	2681 (8.03%)	
2013	334 (6.48%)	2560 (7.67%)	
2014	348 (6.75%)	2613 (7.83%)	
2015	429 (8.32%)	3051 (9.14%)	
Marital status, n (%)			<.001
Married	25206 (75.49%)	278 (64.95%)	
Single	3641 (10.91%)	50 (11.68%)	
Divorced/Widowed	2879 (8.62%)	72 (16.82%)	
Unknown	1662 (4.98%)	28 (6.54%)	
Race, n (%)			.004
White	27083 (81.12%)	4090 (79.33%)	
Black	4043 (12.11%)	661 (12.82%)	
Other	1952 (5.85%)	360 (6.98%)	
Unknown	310 (0.93%)	45 (0.87%)	
T stage, n (%)			<.001
T3	31208 (93.47%)	4646 (90.11%)	
T4	2180 (6.53%)	510 (9.89%)	
Gleason Score biopsy, n (%)			<.001
≤6	5242 (15.70%)	379 (7.35%)	
7	20235 (60.61%)	1792 (34.76%)	
8	4495 (13.46%)	1260 (24.44%)	
9	3255 (9.75%)	1508 (29.25%)	
10	161 (0.48%)	217 (4.21%)	

EBRT = external beam radiotherapy, PSA = prostate-specific antigen, RP = radical prostatectomy, SD = standard deviation.

Table 2

Descriptive characteristics of 4629 patients received radical prostatectomy versus 4629 patients received external beam radiotherapy after propensity score matching (ratio 1:1).

	RP (N = 4629)	EBRT (N = 4629)	P value
Age, yr mean (SD)	66.46 (7.53)	67.81 (8.27)	<.0001
PSA level (ng/mL), mean (SD)	21.30 (27.67)	21.25 (23.24)	.9198
Year of Diagnosis, mean (SD)	2010.95 (3.67)	2009.94 (3.91)	<.0001
Marital status, n (%)			<.0001
Married	3513 (75.9%)	3112 (67.2%)	
Single	453 (9.8%)	566 (12.2%)	
Divorced/Widowed	438 (9.5%)	670 (14.5%)	
Unknown	225 (4.9%)	281 (6.1%)	
Race, n (%)			.0271
White	3729 (80.6%)	3687 (79.7%)	
Black	511 (11%)	589 (12.7%)	
Other	352 (7.6%)	309 (6.7%)	
Unknown	37 (0.8%)	44 (1%)	
T stage, n (%)			.0114
T3	4144 (89.5%)	4217 (91.1%)	
T4	485 (10.5%)	412 (8.9%)	
Gleason Score biopsy, n (%)			<.0001
≤6	419 (9.1%)	378 (8.2%)	
7	1558 (33.7%)	1773 (38.3%)	
8	1170 (25.3%)	1154 (24.9%)	
9	1369 (29.6%)	1186 (25.6%)	
10	113 (2.4%)	138 (3%)	

SD = standard deviation, PSA = prostate-specific antigen, RP = radical prostatectomy, EBRT = external beam radiotherapy.

by PCa, complications of treatments, or unknown processes in patients with active PCa. Follow-up time was defined as the time between the first treatment and patient's death or last follow-up.

2.5. Propensity score matching

Propensity score matching was utilized to reduce selection bias and mimic randomized controlled trial. We performed propensity score matching in 1:1 ratio using nearest-neighbor matching with calliper width of 0.05, emerged similar patient characteristics between RP cohort (n = 333,88) and EBRT cohort (n = 5,156). Patient characteristics of the post-matched cohorts were shown in Table 2.

2.6. Statistical analysis

First, we analyzed the baseline characteristics of the 2 cohorts. Continuous variables were compared with the Wilcoxon rank sum test and presented as mean (standard deviation) or

(interquartile range). And categorical variables were compared with the 2-tailed $\chi2$ test (or Fisher exact test) and presented as the frequency with its proportion. Second, the Kaplan-Meier method and log-rank test were used to compare OS and CSS outcomes between the RP cohort and the EBRT cohort. To assess important prognostic factors besides treatments, in the entire cohort, we used a multivariable Cox regression analysis to study the impact of multiple variables on survival outcomes of patients, including treatments, age, T stage, PSA, GS, marital status, and race. Another multivariable Cox regression analysis was performed to test the association between 2 different treatments and survival outcomes in the crude models and adjusted-covariate models.

Third, the propensity score matching was carried out with the propensity scores estimated by logistic regression, calculated by the following factors: treatments as the outcome and age, clinical T stage, GS, PSA level as prognostic covariates. When $P > .05$, the baseline characteristics of the matched cohorts could be considered balanced.

After matching, we implemented a series of sensitivity analyses to assess the robustness of our findings. Like previous analyses in the primary cohort, Cox proportional hazards regressions were applied to the matched cohort to study the association between the 2 treatments and survival outcomes. Besides, by utilizing the propensity scores, inverse probability of treatment weighting and standardized mortality ratio weighting were performed to estimate the relationship between treatment types and outcomes among the whole pre-post cohorts. At the same time, we also stratified the entire pre-matched cohorts according to propensity scores, age, clinical T stage, PSA level, and GS biopsy to analyze the impact of different treatment methods on survival outcomes using the Cox model. Finally, we subdivided the EBRT group into
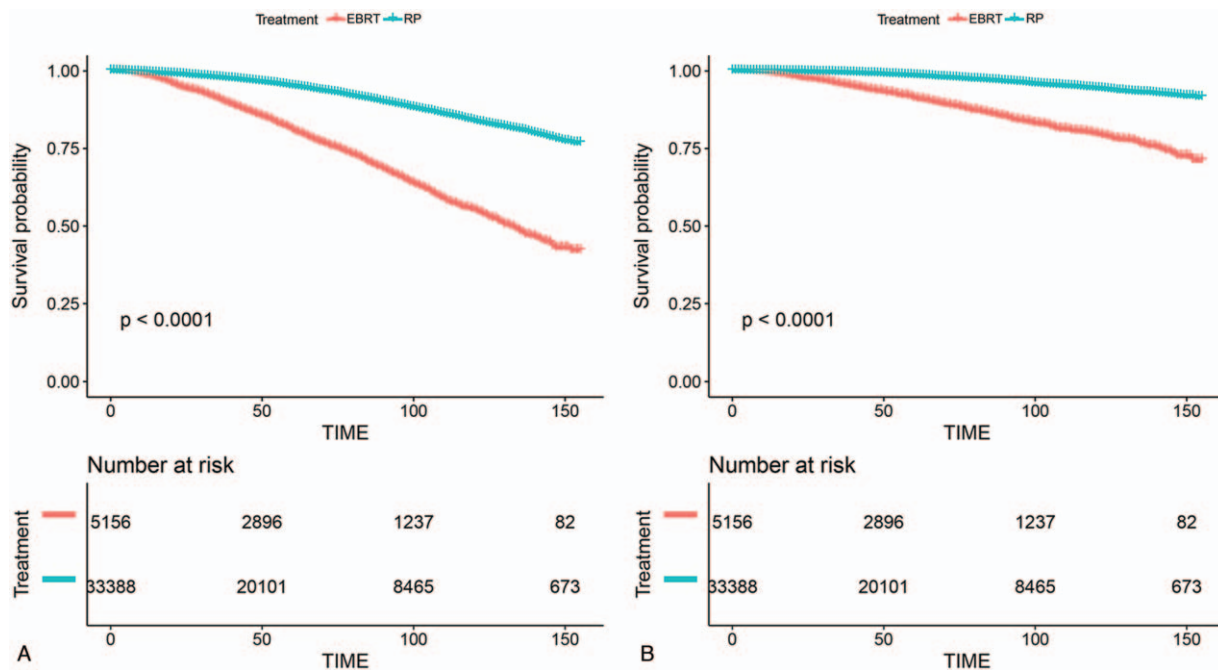
Figure 2. A, Kaplan-Meier survival curve of OS in the comparison of RP and EBRT. B, Kaplan-Meier survival curve of CSS in the comparison of RP and EBRT. CSS = cancer-specific survival, EBRT = external beam radiation, OS = overall survival, RP = radical prostatectomy.

the EBRT-ONLY group and EBRT+ Brachytherapy (BT) group, and then compared the survival results with RP using Cox proportional hazards regressions to assess whether BT's participation would affect our results.

The statistical software packages R (The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) were used in the above statistical analyses. A P-value ≤.05 was considered statistically significant.

3. Results

Finally, a total of 38,544 eligible patients were included in our study as the primary cohort. Of which, 33,388 patients received RP while 5156 patients received EBRT as the primary treatment, and then they were assigned to the RP cohort or EBRT cohort accordingly. The inclusion and exclusion criteria were presented in Figure 1 in detail.

Table 1 showed a summary of patients' baseline characteristics. Compared with patients in the EBRT cohort, patients in the RP cohort were more likely to have a younger average age, lower PSA level, and lower GS. At the same time, they had more possibilities to be married, white race, and with a clinical T stage in T3. Median follow-up time was 63 mo (interquartile range: 58–67) in RP cohort while 69 mo (interquartile range: 63–75) in EBRT cohort, respectively.

Overall, 30,777 patients in RP cohort and 3,783 patients in EBRT cohort died during the follow-up, of which 853 deaths in RP cohort and 555 deaths in EBRT cohort were related to PCa. The Kaplan-Meier curves we obtained showed that the patients received RP had significantly better survival outcomes than those received EBRT in both OS ($P<.0001$) and CSS ($P<.0001$) (Fig. 2). The findings were confirmed in following multivariable Cox regression analysis, in which RP was associated with better OS benefits (hazard ratio [HR]: 0.28;

95% confidence interval [CI]: 0.26–0.29; $P<.0001$) and CSS benefits (HR: 0.22; 95% CI: 0.20–0.25; $P<.0001$) compared with EBRT. In the entire cohort, the results of the multivariable Cox regression analysis demonstrated that besides treatments, age, clinical T stage, PSA level, GS biopsy and marital status were also independent prognostic factors for both OS and CSS. We found that older age, higher clinical T stage, PSA level and GS biopsy and single or divorced status were associated with worse prognosis of patients with locally advanced PCa. (Supplementary Table 1, Available at: http://links.lww.com/MD/E740) After adjusting covariates including age; clinical T stage; PSA level; GS biopsy, RP still showed a better ability to improve patient survival outcomes (OS: HR: 0.50; 95% CI: 0.46–0.54; $P<.0001$ and CSS: HR: 0.43; 95% CI: 0.38–0.49; $P<.0001$, respectively) (Table 3).

Following the propensity score matching, 4,629 patients received RP matched 4,629 patients received EBRT to emerge matched RP and EBRT cohorts. Through matching, the statistical difference in PSA level between the 2 groups was no longer significant ($P=.9198$), while other baseline characteristics remained unbalanced (Table 2 and Supplementary Table 2, Available at: http://links.lww.com/MD/E741). The Kaplan-Meier curves showed that for the matched cohort, both the OS and CSS, the survival outcomes of the RP group were better (Fig. 3).

In the matched cohorts, the results of multivariable Cox regression analysis demonstrated that RP as a primary treatment could bring greater survival benefits to patients in both OS (HR: 0.46; 95% CI: 0.41–0.51; $P<.0001$) and CSS (HR: 0.46; 95% CI: 0.39–0.55; $P<.0001$), compared with EBRT. And we adjusted the imbalanced covariates in the matched cohort, RP's advantage over EBRT in survival benefits had not changed. (OS: HR: 0.46; 95% CI: 0.41–0.51; $P<.0001$ and CSS: HR: 0.41; 95% CI: 0.34–0.48; $P<.0001$, respectively) (Table 3).

Multivariate cox regression analyses for OS and CSS in the primary cohort and post-matched cohort.

Outcome	Treatment	Non-adjusted model	Adjusted model	PSM model	PSM adjusted model
OS	RP	0.28 (0.26, 0.29) <0.0001	0.50 (0.46, 0.54) <0.0001	0.46 (0.41, 0.51) <0.0001	0.46 (0.41, 0.51) <0.0001
	EBRT	Ref.	Ref.	Ref.	Ref.
CSS	RP	0.22 (0.20, 0.25) <0.0001	0.43 (0.38, 0.49) <0.0001	0.41 (0.34, 0.48) <0.0001	0.41 (0.34, 0.48) <0.0001
	EBRT	Ref.	Ref.	Ref.	Ref.

CSS = cancer specific survival, EBRT = external beam radiotherapy, OS = overall survival, PSM = propensity score matching, RP = radical prostatectomy. Adjusted model: covariates including age, T stage, Gleason score (GS) and prostate specific antigen (PSA) level.
Propensity score matching (PSM) model: matched according to propensity score.
PSM adjusted model: adjusted model applied on post-matched cohort.

Subsequent sensitivity analyses further confirmed the robustness of our findings (Supplementary Table 3, Available at: http://links.lww.com/MD/E742). The inverse probability of treatment weighting-adjusted model and standardized mortality ratio weighting-adjusted model both showed that RP was significantly superior to EBRT in promoting patients' OS and CSS. In the entire pre-matched cohorts, propensity score adjusted model also reached the same outcome: in the aspect of improving the survival of patients, RP performed significantly better than EBRT. In the subgroup analyses, we used propensity scores, age, clinical T stage, PSA level, and GS biopsy to stratify the entire pre-matched cohorts into different subgroups. Except for the subgroup of patients with GS = 10 (CSS: HR: 0.63; 95% CI: 0.37–1.07; $P = .0868$), all subgroup analyses yielded the same results as the previous statistical analyses (Supplementary Table 4, Available at: http://links.lww.com/MD/E743). The interaction was not significant, which proved that the independent action was stable, that was, RP was better than EBRT. For those with GS = 10, although the difference between the CSS outcomes of RP and

EBRT was not significant, it could still be seen that RP tended to be the better 1 (HR: 0.63; 95% CI: 0.37–1.07; $P = .0868$).

After subdividing the EBRT group into the EBRT-ONLY group and the EBRT + BT group, we found that the addition of BT still did not make radiotherapy achieve better survival results than RP. Our Cox proportional hazards regressions revealed that the survival results of the EBRT + BT Group were better than those of the EBRT-ONLY group, however, the survival results of the RP group were still the best (OS: HR: 0.64; 95% CI: 0.54–0.75; $P < .0001$ and CSS: HR: 0.31; 95% CI: 0.24–0.39; $P < .0001$). (Supplementary Table 5, Available at: http://links.lww.com/MD/E744)

4. Discussion

For localized low and intermediate-risk PCa. RP and EBRT have no obvious difference in long-term oncologic and survival outcomes,[14] while their differences are mainly reflected in early complications.[15] However, for locally advanced PCa, it is still
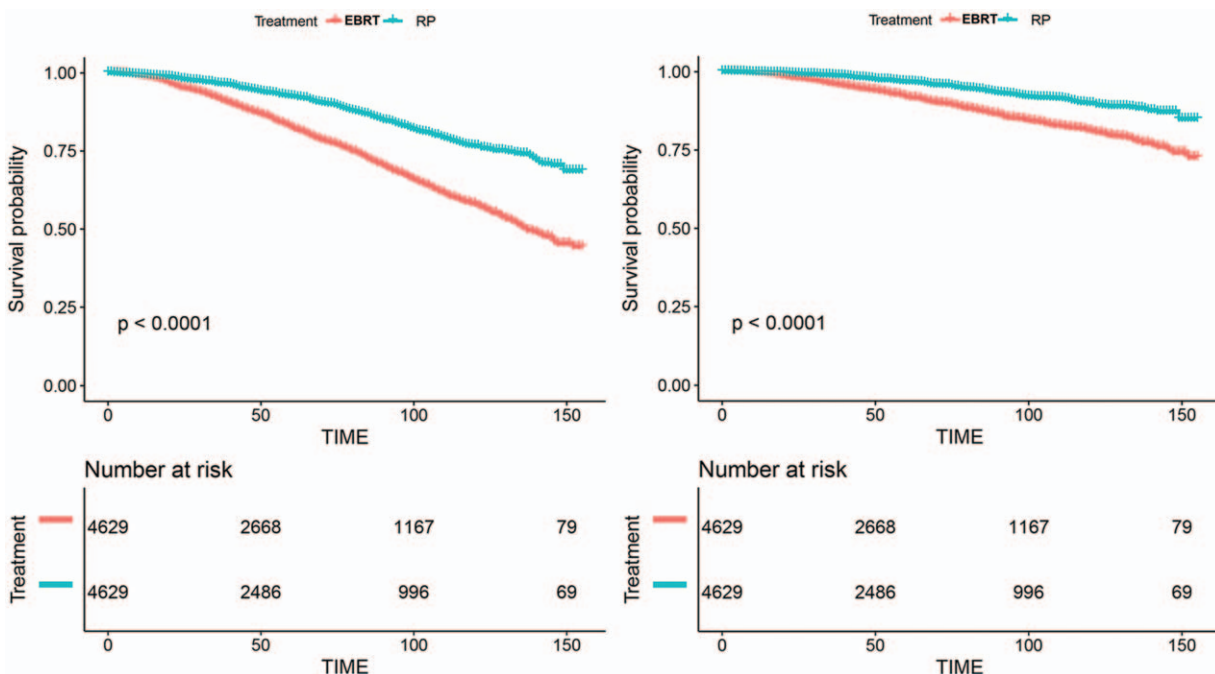
Figure 3. In the matched cohorts, A, Kaplan-Meier survival curve of OS in the comparison of RP and EBRT. B, Kaplan-Meier survival curve of CSS in the comparison of RP and EBRT. CSS = cancer-specific survival, EBRT = external beam radiation, OS = overall survival, RP = radical prostatectomy.

controversial that which kind of treatment is better as a primary treatment due to the absence of high-quality randomized controlled trials.

In order to address the void in the choice of treatment, we aimed to compare the survival outcomes including OS and CSS of RP versus EBRT in locally advanced PCa patients in a large population-based cohort. From the SEER database, we selected 38,544 cT3-4N0M0 locally advanced PCa patients and divided them into RP and EBRT cohorts according to the primary treatment. Besides basic statistical analysis, we carried out propensity score matching to reduce selection bias in our study to maximize the simulation of randomized trials.

A series of statistical analyses in our study demonstrated that RP performed significantly better in OS and CSS compared to EBRT. After adjusting for the covariates, the hazard of overall deaths and cancer-specific deaths in the RP cohort was still only almost half that of the EBRT cohort. In the post-matched cohorts after propensity score matching, we found that the difference of PSA level had been eliminated as much as possible, and the difference between other baseline characteristics had also been reduced. Based on the post-matched cohorts, the association of RP with much better overall survival and cancer-specific benefits was confirmed again. As a result, it could be seen that the difference in treatment was the main reason for the difference in survival outcomes. We divided the entire cohort into multiple subgroups based on covariates to validate in a more homogenous and specific population. In almost all subgroups, RP was significantly better than EBRT in OS and CSS, further confirming that our findings were widely true in various cT3-4N0M0 locally advanced PCa patients. At the same time, the sensitivity analyses helped us to reduce the bias from statistical methods themselves as much as possible. Through these statistical analyses, we thought that RP could indeed bring significantly greater OS and CSS benefits to patients, and this result does not change due to other various covariates.

Some retrospective studies had yielded results similar to ours.[7,9,10,16,17–20] For instance, A 9-year follow-up of 275 cT3-4 or N1 and M0 patients diagnosed in 2004 showed that patients received RP had significantly higher CSS than those received EBRT. However, this study didn't focus on the comparison of RP and EBRT, while the number of samples was small.[10] Earlier, a group of researchers followed patients diagnosed with localized PCa from 1992 to 1994 for a median follow-up time of 13.3 years. In their D'Amico high-risk group, the cancer-specific mortality of patients received radiotherapy was 2.3 times higher than those received surgery.[17] Another study with a cohort of 518 high-risk PCa patients (including locally advanced PCa partly) had been published.[9] The researchers reported that patients received EBRT had more possibility of dying of other causes except for cancer itself than those received RP within 5 years. But they did not find the statistical difference in CSS between the 2 treatment methods. The possible reason may be the high-risk group in this study did not fully comply with the locally advanced PCa's definition, the duration of follow-up is only 5 years, and the sample size was not large. In the end, only 10 patients developed cancer-specific deaths, and the difference was not observed. In fact, a prospective, multi-centre, open randomized phase III trial is recruiting patients, which mainly aimed at comparing (EBRT+ADT) with (RP + extended pelvic lymph-node dissection).[18] Our findings would also add confidence to this trial. Moreover, a recent retrospective study showed that the proportion of patients with cT3-4N0M0 PCa undergoing RP

increased significantly in the United States and Germany during the past decade,[19] and our findings provided evidence to support the trend.

There are still several limitations to our study. First, our research is constructed by retrospective data. Therefore, although we have used statistical methods like propensity score matching to improve the reliability of our conclusions, there still may be some undetected potential bias in the study. Second, some common baseline information such as Charlson Comorbidity Index and ECOG are not recorded in SEER database. However, in this study, statistical analyses including multiple subgroup analyses of various baseline factors showed that the treatments had a significant impact on the OS and CSS independently, so the missing baseline data such as ECOG and Charlson Comorbidity Index would not have an obvious impact on the findings. Third, due to the limitation of the database, we did not carry out the comparison of side effects. According to the results of a previous study, which mainly focused on patients with PCa of cT3N0M0, the possibilities of urinary and sexual toxicities were higher with primary RP, while EBRT was associated with higher possibilities of gastrointestinal injury.[16] Besides, also because of the limitation of the database, the outcomes including cancer progression and biochemical recurrence were not assessed in our study. Fourth, the usage of ADT wasn't registered in our study. But there were already a lot of studies and some guidelines that strongly recommend RT + ADT for high-risk PCa, while did not recommend common ADT after RP for patients with N0 high-risk PCa.[2,6,20,21] Therefore, the usage of ADT in patients was relatively standard, and the impact on the results will not be too great to change the findings.

5. Conclusion

To sum up, RP as the primary treatment was related to better OS and CSS compared to EBRT in cT3-4N0M0 locally advanced PCa patients.

Our research conclusion can be used as an important reference for cT3-4N0M0 locally advanced PCa patients' treatment choice before the higher level of evidence is put forward. At the same time, our findings can also provide confidence for future prospective studies.

Author contributions

X.Z., K.J., S.Q. contributed equally to this study. Q.W and L.Y. designed the study. X.Z., K.J., and S.Q. partly designed the study, performed the statistical analysis, and drafted the manuscript. D. J. and X.L. performed the statistical analysis. X.T., X.Zheng. and J.L. performed the data collection. All authors reviewed and final approval of the manuscript.

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