

# Survival outcomes for metastatic prostate cancer patients treated with radical prostatectomy or radiation therapy — A SEER based study

**Kun Jin**

urology

**Shi Qiu**

urology

**Shiyu Zhang**

urology

**Xiaonan Zheng**

urology

**Xiang Tu**

urology

**Xinyang Liao**

urology

**Jiakun Li**

urology

**Chunyang Li**

Center of biomedical big data

**Lu Yang**

urology

**Qiang Wei** (✉ [weiqiang933@126.com](mailto:weiqiang933@126.com))

Urology

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## Research article

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# Abstract

Background Patients appeared as metastatic prostate cancer (mPCa) have a very low 5-year-survival rate. How to choose proper treatment of mPCa remained **controversial**.

Method Within the Surveillance, Epidemiology, and End Results (SEER) database (2004-2015), we performed analyses of cancer specific mortality (CSM) and overall mortality (OM) in the comparisons of local treatment (LT) vs no local treatment (NLT) and radical prostatectomy (RP) vs radiation therapy (RT). To balance the characteristics between two treatment groups, propensity score matching were performed. Considering the selection bias, we additionally used an instrument variate (IVA) to calculate the unmeasured confounders.

Result Our study selected mPCa patients with average age more than 60 yr, high level of PSA, and tend to present as high GS. Multivariate regression showed that patients received LT had the lower risks of OM and CSM after adjustment of covariates (HR=0.39, 95% CI 0.35-0.44 and HR=0.39, 95% CI 0.34-0.45). In the IV-adjusted model, LT showed more survival benefits compared with NLT, with hazard ratios of 0.57 (95% CI 0.50-0.65) and cancer specific hazard ratios of 0.59 (95% CI 0.51-0.68), respectively. For those received LT, adjusted multivariate regression indicated that RP is superior to RT, (HR=0.60 [95% CI 0.43-0.83] for OM and HR=0.61 [95% CI 0.42-0.91] for CSM). The IV-adjusted model also showed that RP presented with potentially better survival outcome compared with RT, although the effect was not statistically significant (HR=0.63 [95% CI 0.26-1.54] for OM and HR=0.47 [95% CI 0.16-1.35] for CSM).

Conclusion Among patients with metastatic prostate cancer, local treatment might bring better survival benefits in decreasing cancer-specific mortality and all-cause mortality compared with non-local treatment. For those received LT, radical prostatectomy showed better survival outcomes than radiation therapy.

## Background

As the third most common malignancy, prostate cancer (PCa) was ranked as the sixth leading cause of cancer death in males in the USA with an estimated 160,000 new cases diagnosed in 2017 [1,2]. Patients who present with metastatic prostate cancer (mPCa) at diagnosis have a very low 5-year-survival rate of only 28% [3]. According to European Association of Urology (EAU) guidelines, androgen deprivation therapy (ADT) with or without chemotherapy is the recommended hormone therapy for mPCa [4]. However, the effectiveness of other therapies and combination therapies is not clear.

Recently, several studies reported that patients with mPCa might obtain benefits from local treatment (LT) consisting of radical prostatectomy (RP) and radiation therapy (RT). The proposed mechanism is that excision of the tumor changes the surrounding microenvironment, suppresses the secretion of lethal factors, and thus slows tumor progression [5]. In one SEER-based study that involved 8185 participants with mPCa, those who received surgical and brachytherapy exhibited higher 5-year overall survival rates and cancer-specific survival rates compared with those who received androgen deprivation therapy (ADT)

alone [6]. These data were confirmed by results from another research study based on the National Cancer Data Base. The results indicated that patients with mPCa obtained benefits from LT in terms of overall mortality (OM) [7]. However, some studies have reported opposite findings. Once the tumor grows beyond the prostate capsule, removal of the PCa does not improve the survival outcomes, but rather, merely alleviates local symptoms and promotes psychological comfort [8-11]. The way by which appropriate therapies are selected for mPCa remains controversial.

Based on this, we aimed to test the impact of LT on survival outcomes and to further explore the superior therapy by comparing RP and RT.

## Methods

### Participants

Within the Surveillance, Epidemiology, and End Results (SEER) databases (2004-2015), our analysis screened patients with adenocarcinoma of the prostate (International Classification of diseases-O-3 code: C61.9) diagnosed as primary mPCa (M1a, M1b, and M1c, respectively) according to the American Joint Committee on Cancer Staging Manual [12,13]. Inclusion and exclusion criteria are shown in detail in the flowchart (Figure 1). Overall, 19,612 patients with mPCa were identified and stratified based on treatment: NLT vs LT. Patients in the LT group were divided into two subgroups: RT vs RP. The total available covariates are listed in Table 1.

### Outcomes

Our main outcomes included CSM caused by PCa and OM caused by any reason reported in the SEER database. Survival time was calculated from the first diagnosis to death or the last follow-up.

### Statistical analysis

Differences in continuous variables were evaluated using a 2-tailed t test, whereas differences in categorical variables were compared using a 2-tailed  $\chi^2$  test (or Fisher exact test). Cox proportional hazards regression models were performed to assess CSM and OM between treatment groups after adjusting covariates. When other causes of death were considered, Fine-Gray competing risks regressions were also performed. Effect estimates were presented as cause-specific hazard ratios (HRs) for Cox models or sub-distribution hazard ratios for Fine-Gray models, with 95% CIs [14]. Propensity scores were estimated with logistic regression, with treatment (NLT and LT) as the outcome, and marital status, race, age, clinical TNM stage, Gleason score (GS), and prostate-specific antigen (PSA) level as pretreatment, prognostic covariates. The matched baseline characteristics between two groups were regarded as balanced when  $P > 0.05$ . Cumulative incidence survival curves were obtained by the Kaplan-Meier method.

Considering the selection bias, we also used an instrumental variable analysis (IVA) to calculate the unmeasured confounders. The yearly regional utilization rate as an IVA was selected in the two-stage residual inclusion analysis [15,16]. This IVA was previously used in the literature [17-20] and was calculated for each of the four American regions as follows: (See Formula 1 in the Supplementary Files)

Tests for the IV mainly included two parts. First, the F-statistic was calculated to confirm its correlation with the therapy option. Additionally, the residual was also calculated, which defined as the observed minus the predicted probability of receiving LT. The second IVA assumption was verified in that without the use of IVA, the correlation between exposure and outcome cannot be formally tested. Afterwards, another multivariate Cox proportional hazard model including all covariates and residual was presented.

Subgroup analyses were performed in the LT group. The same statistical methods were performed to compare RT and RP. Specifically, for this second comparison, the instrument was the yearly regional utilization rate of RP vs RT calculated as follows: (see Formula 2 in the Supplementary Files)

Several sensitivity analyses were performed to validate the robustness of the results: (1) Analysis of the CSM and OM after adjusting propensity scores; (2) Inverse probability of treatment weighting (IPTW) and standardized mortality ratio weighting (SMRW) calculated with the propensity score to estimate the relationship between treatment types and outcomes among the entire cohort; (3) Analyses of CSM and OM stratified by propensity scores.

All analyses were performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Inc., Boston, MA). A P value<0.05 was considered statistically significant.

## Results

Patient and treatment characteristics are presented in Table 1. Patients who received LT were significantly younger than those who received NLT, had lower PSA levels, and were more likely to have a lower GS. The TNM stages and the marital status of the two groups differed from each other (all P<0.001). However, race did not appear to be different between the two groups (P=0.25). In the LT subgroups, all the distributions of covariates, except race, showed significant differences in the comparison of RT and RP.

### NLT vs LT

Multivariate regression showed that patients who received LT had lower OM and CSM after adjustment of marital status, age, race, TNM stages, PSA, and GS [HR 0.39, 95% CI 0.35-0.44 and HR=0.39, 95% CI 0.34-0.45]. In the competing risk regression analysis, the results indicated that those who received LT presented better outcomes than those who received NLT (sub-distribution HR=0.49, 95% CI 0.43-0.57). The baseline characteristics after propensity score matching are shown in Table 3. Similar results were obtained in the multivariate regression after matching: LT was superior to NLT in reducing the risks of low

OM and CSM (HR=0.50, 95% CI 0.41-0.60 and HR=0.51, 95% CI 0.44-0.60). After the propensity score was adjusted, patients were less likely to die when treated with LT (OM: HR=0.57 95% CI 0.50-0.65 and CSM: HR=0.57 95% CI 0.49-0.66). In the IV-adjusted model, LT was associated with significantly longer OS and cancer-specific survival compared with NLT, with a hazard ratio of 0.57 (95% CI 0.50-0.65) and a cancer-specific HR of 0.59 (95% CI 0.51-0.68) ( $P < 0.001$  for both). Our subgroup analysis showed a comparable benefit with LT for patients with younger age, GS=6, T2 stage, and lower PSA levels. No significant interaction was observed between the effect of LT and M stage for CSM and OM ( $P$  value of interaction, 0.19 and 0.32, respectively, for CSM and OM).

## RT vs RP

Adjusted multivariate regression indicated that RP is superior to RT, with an HR of 0.60 (95% CI 0.43-0.83) and a cancer-specific HR of 0.61 (95% CI 0.42-0.91). The same results were obtained in the competing risk analysis (sub-distribution HR=0.36, 95% CI 0.27-0.49). In the propensity score matching model, the effect of RP was still significant in decreasing mortality rates (OM: HR=0.45 95% CI 0.32-0.65 and CSM: HR=0.49 95% CI 0.92-0.73). In propensity score-adjusted models, RP was associated with significantly higher survival rates than RT (OM HR of 0.59 [95% CI 0.44-0.81] and CSM HR of 0.61 [95% CI 0.43-0.87]). In the IV-adjusted model, RP was associated with potentially better survival outcomes compared with RT, although the effect was not statistically significant (HR=0.63 [95% CI 0.26-1.54] for OM [ $P=0.31$ ] and HR=0.47 [95% CI 0.16-1.35] for CSM [ $P=0.16$ ]). In the subgroup analysis, we did observe a larger degree of association between RP and survival outcomes in those with lower PSA levels and GS=6. Additionally, no significant interaction was observed between the effect of RP and M stage for CSM and OM ( $P$  value for interaction, 0.82 and 0.77, respectively, for CMS and OM).

## Discussion

In this study of patients with mPCa, LT was associated with lower rates of prostate cancer-specific mortality and overall mortality compared with NLT, especially in those with T2 stage and a lower GS and PSA level. For those who received LT, RP led to a lower risk of death compared with RT, particularly in those with a lower GS.

One retrospective study of the SEER database (2004-2010) compared RP, brachytherapy (BT), and NLT and showed that LT conferred a survival advantage compared with NLT [21]. However, no significant differences were found in the CSM between RP and BT. Another similar study identified patients undergoing treatment by RP, intensity modulated radiation therapy, conformal radiation therapy, or NLT and indicated that LT was associated with a survival benefit in patients with mPCa [22]. Nevertheless, the effects of RP and RT were not directly compared. This deficiency was compensated by one retrospective study, [23] which demonstrated the advantage of RP in decreasing mortality. Recently, a randomized controlled trial focusing on the treatment effect of radiation therapy concluded that RT plus ADT showed no benefit compared with ADT alone in terms of overall survival, but patients with low metastasis burden

obtained survival benefits from RT plus ADT [24]. In contrast, several studies have reported opposite findings. A prospective study that involved 432 individuals revealed no differences in survival rates when ADT plus RT was compared with ADT alone [25]. Although the baseline characteristics were balanced in the two treatment groups, the small sample size might have been the reason for the insignificance. Two retrospective studies using predictive models showed that not all patients could benefit from LT, especially those with more risk factors [26,27].

In our study, LT definitely improved survival outcomes. However, in the IPTW model, patients who received LT were more likely to die, which suggests that LT was not suitable for everyone. We speculated that some individuals in poor condition died soon after LT, and thus the effect of LT seemed unstable after weighting. However, most people with mPCa could benefit from LT, which was verified by the results from the SMRW model. Compared with other studies with similar results, we also performed various sensitivity analyses to assess the true effect of different treatments. The instrumental variable analysis helped to quantify the unmeasured confounders, which made the effect more significant.

Our study has several limitations. First, and most significantly, was its retrospective nature. Even after adjustment for propensity scores, significant biases remained in regard to treatment selection and follow-up duration. The long follow-up duration in patients who received LT led to increased mortality, but the superiority of LT was not changed. Second, information about ADT was lacking, which affected the oncological outcome. Third, for those who were more likely to have a higher mortality after receiving LT, the means to identify them were not determined in our study. Additional relevant studies are required. Fourth, mPCa patients with lower PSA levels might have the neuroendocrine subtype, which presented with a worse survival outcome. However, this was not analyzed in detail due to the small sample size. Additionally, treatments may be different with constant evolution. Particularly, the radiation dose of RT and the surgical procedures of RP, including robot-assisted, laparoscopic, and open surgery would be considered under-treatment by current standards.

## **Conclusion**

Among patients with metastatic prostate cancer, local treatment might provide better survival benefits in decreasing cancer-specific mortality and all-cause mortality compared with non-local treatment. For those who received LT, radical prostatectomy was associated with better survival outcomes than radiation therapy.

## **Declarations**

### **Competing interests**

The authors have no conflicts of interest to declare. Registries in the USA which update and publish the data were responsible for the ethical review and informed consent.

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### **Authors' contributions**

All authors contributed to the planning and design of the study. The contributions were presented as follows:

K J: Data collection; Data analysis

S Q: Data collection; Data analysis

SY Z: Analytical feedback

XN Z: Analytical feedback

X T: Manuscript writing

XY L: Manuscript writing

JK L: Chart making

CY L: Analytical feedback and checking

L Y: Manuscript modification

Q W: Project Development; Manuscript modification

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## Tables

Table 1 – Descriptive characteristics of 19 612 patients diagnosed with metastatic prostate cancer and 755 locally treated patients between 2004 and 2015 from the Surveillance Epidemiology and End Results database.

Characteristics	Local treatment			Overall	No local treatment	P value <sup>b</sup>
	Radiation therapy	Radical prostatectomy	P value <sup>a</sup>			
<b>NO. of patients</b>	320	435		755	18857	
<b>Age, yr mean (SD)</b>	67.73 (9.95)	62.76 (8.03)	<0.001	64.87 (9.22)	71.47 (11.01)	<0.001
<b>Race, n (%)</b>			0.318			0.25
White	242 (75.63)	342 (78.62)		584 (77.35)	14107 (74.81)	
Black	57 (17.81)	59 (13.56)		116 (15.36)	3440 (18.24)	
Other	20 (6.25)	30 (6.90)		50 (6.62)	1179 (6.25)	
Unknown	1 (0.31)	4 (0.92)		5 (0.66)	131 (0.70)	
<b>Marital status, n (%)</b>			0.026			<0.001
Married	207 (64.69)	325 (74.71)		532 (70.46)	10521 (55.79)	
Single	42 (13.13)	38 (8.74)		80 (10.60)	3011 (15.97)	
Divorced/Widowed	49 (15.31)	52 (11.95)		101 (13.38)	3925 (20.82)	
Unknown	22 (6.88)	20 (4.60)		42 (5.56)	1400 (7.42)	
<b>PSA level (ng/ml), mean (SD)</b>	42.10 (38.69)	19.37 (23.72)	<0.001	28.89 (32.84)	67.78 (36.60)	<0.001
<b>T stage, n (%)</b>			<0.001			<0.001
T1	119 (37.19)	11 (2.53)		130 (17.22)	4760 (25.24)	
T2	87 (27.19)	153 (35.17)		240 (31.79%)	5839 (30.97)	
T3	34 (10.63)	199 (45.75)		233 (30.86)	1679 (8.90)	
T4	26 (8.13)	64 (14.71)		90 (11.92)	2326 (12.34)	
Unknown	54 (16.88)	8 (1.84)		62 (8.21)	4253 (22.55)	
<b>N stage, n (%)</b>			<0.001			<0.001
N0	210 (65.62)	252 (57.93)		462 (61.19)	9682 (51.34)	
N1	41 (12.81)	162 (37.24)		203 (26.89)	4307 (22.84)	
Unknown	69 (21.56)	21 (4.83)		90 (11.92)	4868 (25.82)	
<b>M stage, n (%)</b>			0.02			<0.001
M1a	30 (9.38)	58 (13.33)		88 (11.66)	1207 (6.40)	
M1b	217 (67.81)	309 (71.03)		526 (69.67)	13704 (72.67)	
M1c	73 (22.81)	68 (15.63)		141 (18.68)	3946 (20.93)	
<b>Gleason Score, n (%)</b>			0.005			<0.001
≤ 6	30 (9.378)	27 (6.21)		57 (7.55)	845 (4.48)	
= 7	42 (13.13)	58 (13.33)		100 (13.25)	1421 (7.54)	
≥ 8	83 (25.94)	76 (17.47)		159 (21.06)	4578 (24.28)	
Unknown	165 (51.56)	274 (62.99)		439 (58.15)	12013 (63.71)	

SD = standard difference; PSA = prostate-specific antigen;

<sup>a</sup> Comparing RT versus RP

<sup>b</sup> Comparing NLT versus LT

Table 2 – Descriptive characteristics of 1 334 locally treated versus no locally treated patients and 336 patients received RP versus RT after propensity score matching (ratio 1:1) between 2004 and 2015 from the Surveillance Epidemiology and End Results database.

	NLT	LT	P value <sup>a</sup>	RT	RP	P value <sup>b</sup>
<b>NO. of patients</b>	667	667		168	168	
<b>Age, yr mean (SD)</b>	64.01 (10.20)	64.40 (9.01)	0.46	65.57 (9.26)	65.43 (7.72)	0.88
<b>Race, n (%)</b>			0.24			0.25
White	507 (76)	514 (77.1)		121 (72)	129 (76.8)	
Black	122 (18.3)	101 (15.1)		33 (19.6)	21 (12.5)	
Other	34 (5.1)	47 (7)		13 (7.7)	15 (8.9)	
Unknown	4 (0.6)	5 (0.7)		1 (0.6)	3 (1.8)	
<b>Marital status, n (%)</b>			0.01			0.40
Married	446 (66.9)	476 (71.4)		115 (68.5)	113 (67.3)	
Single	115 (17.2)	72 (10.8)		24 (14.3)	17 (10.1)	
Divorced/Widowed	79 (11.8)	84 (12.6)		19 (11.3)	28 (16.7)	
Unknown	27 (4)	35 (5.2)		10 (6)	10 (6)	
<b>PSA level (ng/ml), mean (SD)</b>	29.79 (32.00)	29.02 (32.89)	0.66	31.13 (34.04)	27.91 (31.18)	0.37
<b>T stage, n (%)</b>			<0.001			< 0.001
T1	173 (25.9)	119 (17.8)		50 (29.8)	10 (6)	
T2	216 (32.4)	212 (31.8)		55 (32.7)	70 (41.7)	
T3	83 (12.4)	218 (32.7)		17 (10.1)	74 (44)	
T4	93 (13.9)	77 (11.5)		18 (10.7)	14 (8.3)	
Unknown	102 (15.3)	41 (6.1)		28 (16.7)	0 (0)	
<b>N stage, n (%)</b>			0.09			< 0.001
N0	407 (61)	413 (61.9)		115 (68.5)	99 (58.9)	
N1	163 (24.4)	182 (27.3)		18 (10.7)	56 (33.3)	
Unknown	97 (14.5)	72 (10.8)		35 (20.8)	13 (7.7)	
<b>M stage, n (%)</b>			0.53			0.98
M1a	75 (11.2)	80 (12)		18 (10.7)	19 (11.3)	
M1b	487 (73)	469 (70.3)		122 (72.6)	121 (72)	
M1c	105 (15.7)	118 (17.7)		28 (16.7)	28 (16.7)	
<b>Gleason Score, n (%)</b>			0.26			0.02
≤ 6	53 (7.9)	50 (7.5)		18 (10.7)	11 (6.5)	
= 7	74 (11.1)	87 (13)		14 (8.3)	32 (19)	
≥ 8	174 (26.1)	146 (21.9)		41 (24.4)	32 (19)	
Unknown	366 (54.9)	384 (57.6)		95 (56.5)	93 (55.4)	

SD = standard difference; PSA = prostate-specific antigen; NLT = no local treatment; LT = local treatment; RP = radical prostatectomy; RT = radiation therapy

a Comparing NLT versus LT

b Comparing RT versus RP

Table 3 - Multivariate cox regression analyses for OS and CSM in the total cohort and matched population

Outcome	Treatment	Non-adjusted model	Adjusted model	PSM model	IVA-adjusted model
<b>OM</b>	NLT	Ref.	Ref.	Ref.	Ref.
	LT	0.39 (0.35, 0.44)	0.57 (0.50, 0.65)	0.51 (0.44, 0.60)	0.57 (0.50, 0.65)
	RT	Ref.	Ref.	Ref.	Ref.
	RP	0.47 (0.37, 0.59)	0.60 (0.43, 0.83)	0.45 (0.32, 0.65)	0.63 (0.26, 1.54)
<b>CSM</b>	NLT	Ref.	Ref.	Ref.	Ref.
	LT	0.39 (0.34, 0.45)	0.58 (0.50, 0.68)	0.50 (0.41, 0.60)	0.59 (0.51, 0.69)
	RT	Ref.	Ref.	Ref.	Ref.
	RP	0.43 (0.32, 0.56)	0.61 (0.42, 0.91)	0.49 (0.32, 0.73)	0.47 (0.16, 1.34)

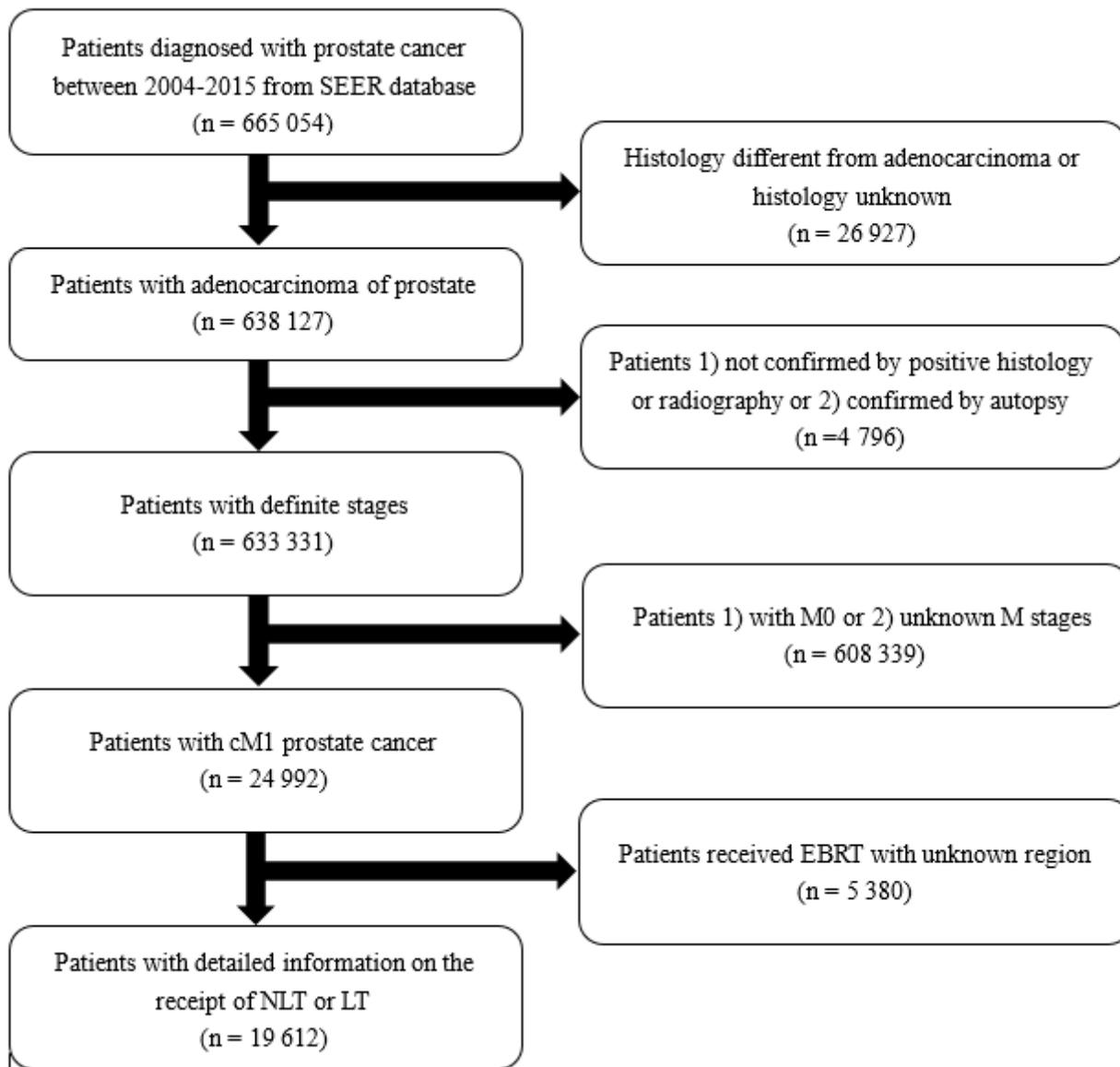
OM = overall mortality, CSM = cancer specific mortality, NLT = no local treatment; LT = local treatment; RP = radical prostatectomy; RT = radiation therapy, PSM = propensity score matching, IVA = instrument variable

Adjusted model: adjusted for race, age, marital status, TNM stages, Gleason score (GS) and prostate specific antigen (PSA)

Propensity score matching (PSM) model: matched according to race, age, marital status, TNM stages, GS and PSA

Instrument variate (IVA) adjusted model: adjusted for race, age, marital status, TNM stages, GS and PSA and residual

## Figures



**Figure 1**

Flowchart describing the selection of patients treated with local treatment or non-local treatment in the Surveillance, Epidemiology, and End Results database, 2004-2015 EBRT = external beam radiation therapy; NLT = non-local treatment; LT = local treatment

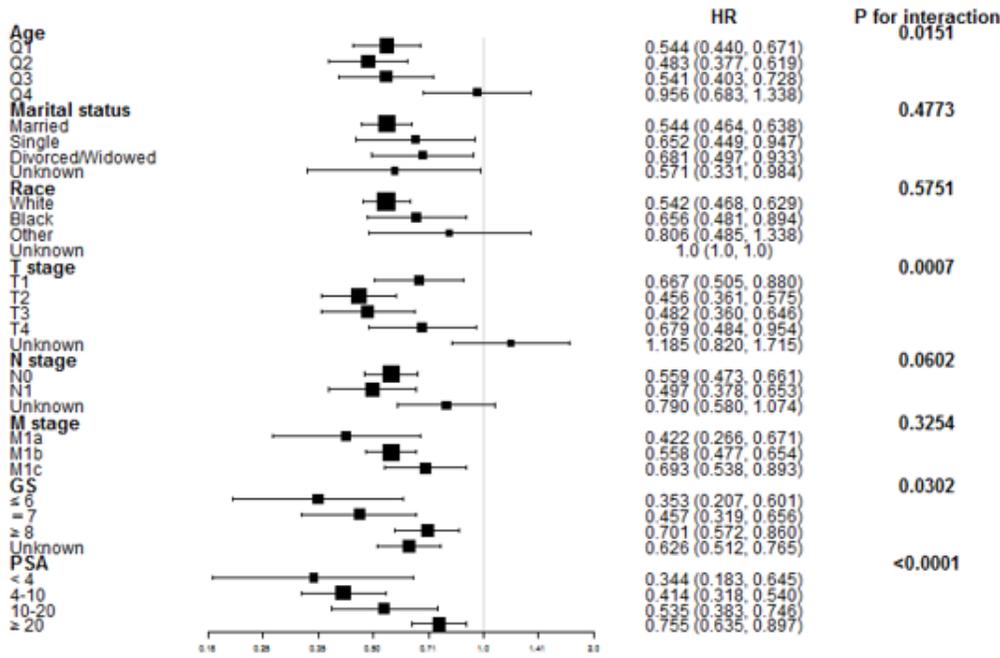


Figure 2a. Subgroup analysis of OM in the comparison of NLT and LT

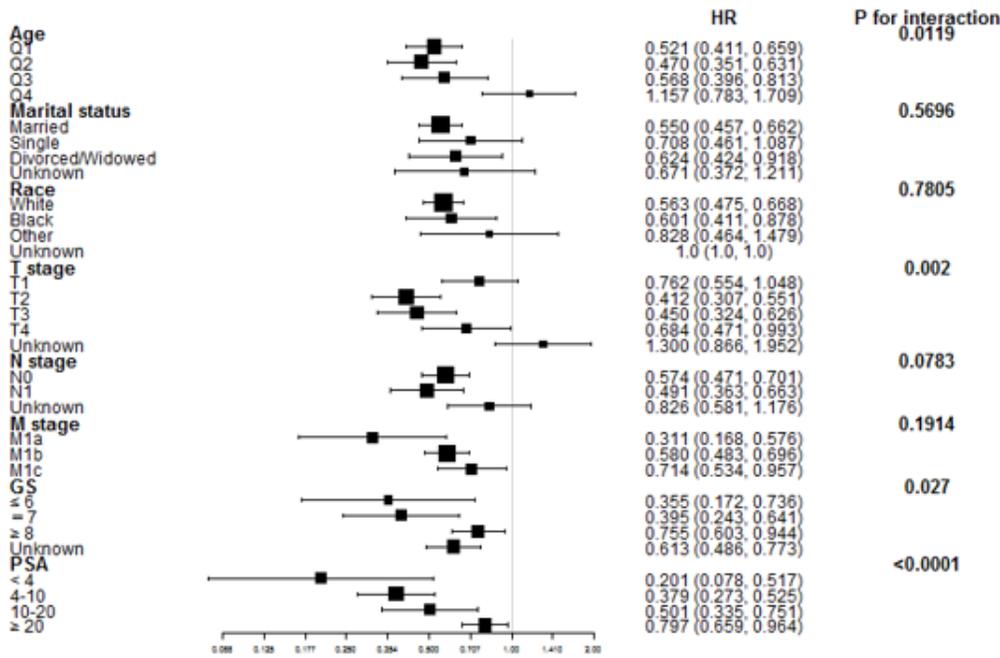


Figure 2b. Subgroup analysis of CSM in the comparison of NLT and LT

## Figure 2

Subgroup analyses of OM and CSM (NLT vs LT and RT vs RP)

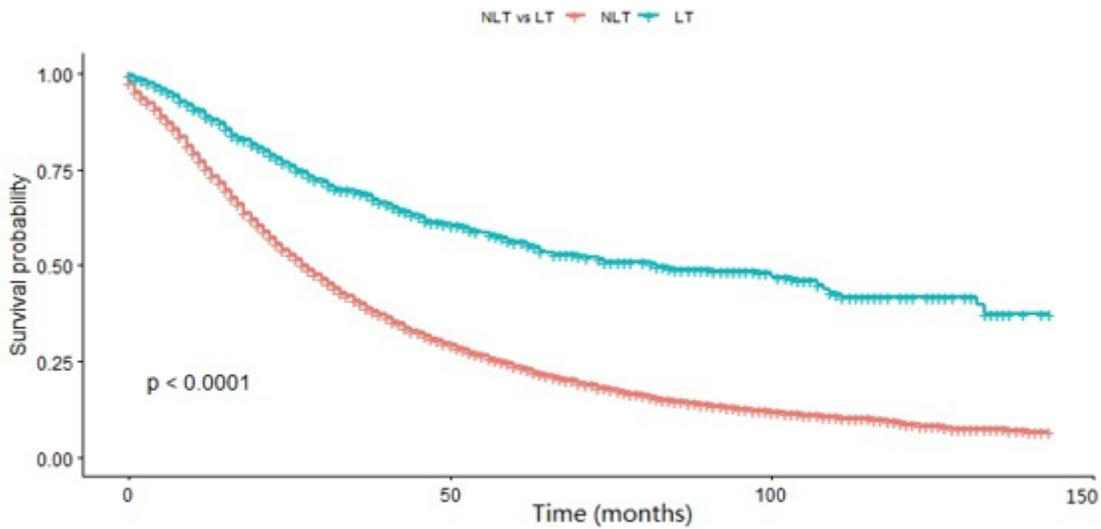


Figure 3a. Kaplan-Meier survival curve of OS in the comparison of NLT and LT

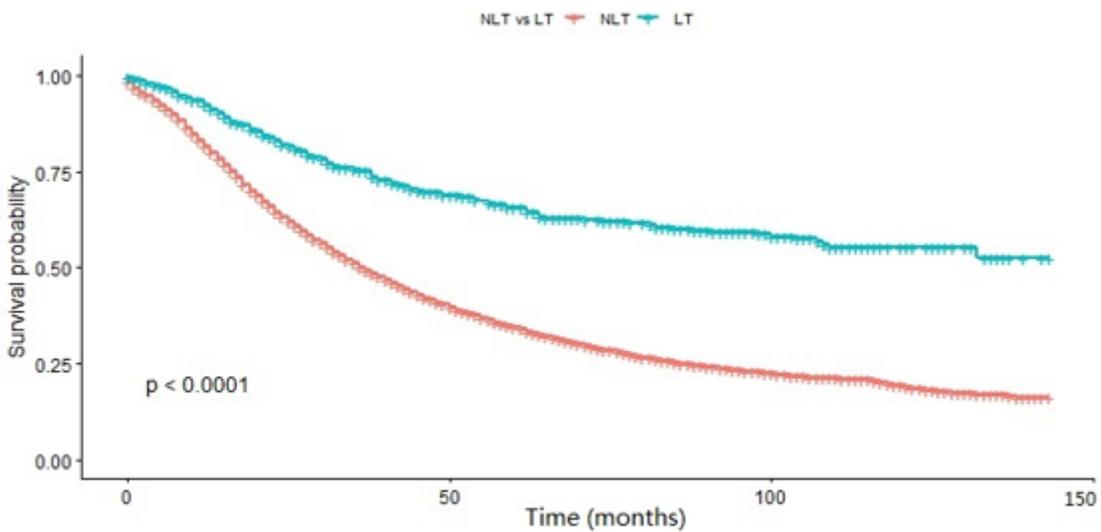


Figure 3b. Kaplan-Meier survival curve of CSS in the comparison of NLT and LT

### Figure 3

Kaplan-Meier survival curve of OS and CSS (NLT vs LT and RT vs RP)

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Formula1.jpg](#)

- [Formula2.jpg](#)
- [supplement.pdf](#)