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The Impact of Lymph Node Dissection on Survival in Intermediate- and High-Risk Prostate Cancer: A Population-Based, Propensity-Matched Study

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1. Abstract

1.1. Objective: Aimed to evaluate the therapeutic effect of pelvic lymph node dissection (PLND) on survival and determine the predictors of lymph node involvement (LNI) in patients with intermediate- or high-risk prostate cancer (PCa) treated with Radical Prostatectomy (RP).

1.1. Methods: 75,583 patients undergoing RP with or without PLND between 2010 and 2016 were extracted from the Surveillance Epidemiology and End Results database. We performed 1:1 propensity score matching due to potential differences according to the 2 cohorts. Cox regression models (CRMs) were used to test the effect of PLND on overall mortality (OM) and cancer-specific mortality (CSM). Logistic regression analysis was used to investigate the predictors of LNI.

1.3. Results: The propensity-score-matched cohort includes 52,314 patients with or without PLND. Kaplan Meier analysis confirmed that patients receiving PLND had a poorer prognosis than those without PLND (P<0.05). But the multivariable CRMs after adjustment showed that PLND was not an independent predictor for OM and CSM (P>0.05). According to multivariable CRMs, patients with locally advanced PCa in whom PLND was performed had higher OM (HR 1.67, CI 1.36-2.06) and CSM (HR 2.26, CI 1.16-3.12) risks compared to patients without PLND (p < 0.001). Compared to patients with intermediate-risk PCa, there was a higher risk of LNI in patients with locally advanced PCa (OR 16.82, 95% CI 5.05-56.06, P<0.001).

1.4. Conclusions: In the intermediate- or high-risk localised PCa, there was no significant difference in survival outcome in patients with or without PLND. Locally advanced PCa was significantly associated with LNI but can't benefit from PLND.

2. Introduction

Prostate cancer (PCa) is a serious disease that is harmful to men's health worldwide, ranking first in cancer incidence and second in cancer mortality for males in the United States [1]. To present, radical prostatectomy (RP) remains the main treatment option for D'Amico intermediate- and high-risk PCa according to European Association of Urology (EAU) guidelines [2-4]. Besides, the guidelines recommend pelvic lymph node dissection (PLND) in patients with a risk of nodal metastases over 5% [5,6]. Moreover, PLND refers specifically to extended PLND (ePLND) [7]. However, the curative effect of PLND is controversial. It is widely believed that PLND provides important staging and prognosis information that is unmatched by any other currently available procedure [8]. Moreover, several reports demonstrated a potential therapeutic effect of PLND in select patient with presence of lymph node involvement (LNI) [9,10]. Conversely a recent systematic review has shown that operating PLND during RP can't improve oncological outcomes, including survival [8]. Besides, the disadvantages of PLND are obvious, which refer to longer surgery time and more importantly, greater morbidity, such as formation of lymphoceles, thromboembolic, or neurovascular events [11,12]. In intermediate-risk PCa, the estimated risk of having positive lymph

nodes (LNs) is between 3.7-20.1%, and the risk for positive LNs in high-risk localisted PCa is 15-40% [13]. In locally advanced PCa, a PLND is considered the standard procedure during RP, but clinical nodal involvement (cN^+) was not a significant predictor of cancer-specific survival (CSS) [14]. Besides, there is no report about the effect of PLND on survival in locally advanced PCa patients. According to a latest article [15] of American Urological Association (AUA), it analyzed 9,742 patients from 4 centers and demonstrated that there was no significant difference in CSS, biochemical recurrence (BCR) and LNs metastasis in patients with or without PLND at RP. In the absence of prospective, randomized trials and studies on the role of PLND in contemporary patients, we sought to elucidate its potential curative value of PLND by retrospective analysis. Specifically, we tried to analyze which clinical or pathological factors might be associated with LNI. Moreover, we compared the oncologic outcomes in patients between limited PLND (lPLND) and ePLND according to different risk stages.

3. Materials and Methods

3.1. Database

The data on PCa patients over seven years (2010–2016) were selected from SEER database. The SEER*Stat software program (version 8.3.7) was used to collect all data. Data on about 28% of the U.S. population is stored in the SEER database. The data of this work came from the following resources available in the public domain: SEER database. There was no direct information about characteristics of D'Amico intermediate or high risk PCa in the SEER database, but we got that information indirectly by filtering it according to EAU guideline [16]. All the AJCC TNM stage was clinical diagnoses. In our study, due to the defects of SEER database, ePLND refers to dissection of more than three lymph nodes, and lPLND means the dissection of one to three lymph node(s).

3.2. Patients Selection

97,924 patients who underwent RP between 2010 and 2016 were extracted in this study from SEER database. Only patients with D'Amico intermediate-risk stage and patients at high-risk stage were included in analysis. The information about age at diagnosis, sex, race, marital status, pathological grade, state of radiotherapy, state of chemotherapy, prostate-specific antigen (PSA), Gleason score (GS), derived AJCC TNM stage (7th edition, 2010-2016) and pathological LNI condition was available. We excluded patients with unknown race, marital status, grade, PSA, GS or LNI. Eventually, 75,583 patients were enrolled in the cohort study (Figure 1).

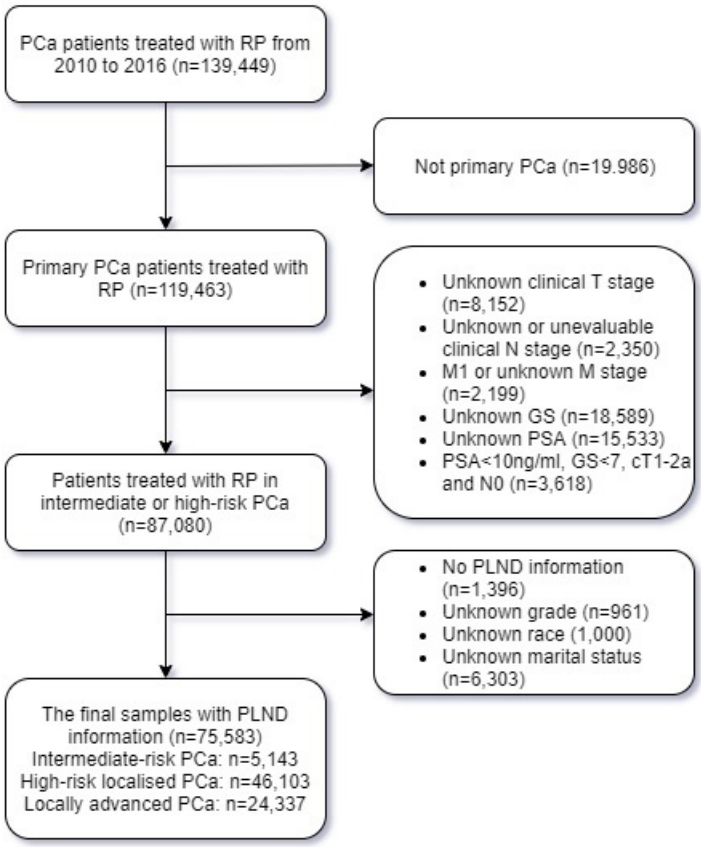

Figure 1: The flow chart describes the steps taken to identify 75,583 patients in the SEER database.

3.3. Statistical Analysis

We utilized SPSS v25.0 (SPSS Inc., Chicago, IL, USA) for all of the statistical analyses of the data. The $\chi 2$ test was used to compare clinical characteristics between patient groups. Logistic regression analysis was used to investigate the influences of different clinical and pathological factors on LNI. P values <0.05 were considered statistically significant. Variables with P<0.05 in univariate analysis were included in the final multivariate analysis model. The multivariate Cox regression analysis was used to determine the association with OM rate and CSM. In order to account for potential important differences between patients with vs without PLND performed during RP, we relied on 1:1 nearest neighbor propensity score matching (PSM) [17]. We used a caliper of 0.1 in order to achieve a standardized mean difference in all relevant variables. Therefore, propensity-score-matched cohort was balanced according to clinical and pathological characteristics. Kaplan-Meier analysis was done to graphically depict overall survival (OS) and cancer-specific survival (CSS) before and after PSM.

4. Results

4.1. General Characteristics

We identified 75,583 PCa patients with or without PLND during RP between 2010 and 2016. Most patients underwent PLND (48,792, 64.6%). Most patients included in our analysis were under 65 years old (No PLND: 18,141, 67.7%; PLND: 30,082, 62.7%), white (No PLND: 21,839, 81.5%; PLND: 38,878, 79.7%), married (No PLND: 21,704, 81.0%; PLND: 38,426, 78.8%),not receiving radiotherapy (No PLND: 25,854, 96.5%; PLND: 44,564, 91.3%), not receiving chemotherapy (No PLND: 26,770, 99.9%; PLND: 48645, 99.7%), PSA<10ng/ml (No PLND: 23,646, 88.3%; PLND: 36,263, 74.3%), GS 7 (No PLND: 16,907, 63.1%; PLND: 34,217, 70.1%), harboured clinical stage T2c (No PLND: 19,406, 72.4%; PLND: 26,273, 53.8%), cN0 (No PLND: 26,771, 99.9%; PLND: 45537, 93.3%) and at high-risk stage in localised PCa(-No PLND: 19,596, 73.1%; PLND: 26,507, 54.3%). Most patients without PLND had moderately differentiated tumor (12,668, 47.3%), while most patients with PLND had poorly differentiated tumor (28,657, 58.7%, Supplementary Table 1). The propensity-score-matched cohort consisted of 52,314 patients with or without PLND. Of those, 26,157 (50.0%) did not undergo PLND and 26,157 (50.0%) underwent PLND. No significant differences (Table 1) according to age, chemotherapy, PSA, GS, clinical T stage, N stage and D'Amico disease stage (all p > 0.05) in patients with and without PLND (Supplementary Table 1).

Table 1: Multivariable Cox regression models predicting overall mortality and cancer-specific mortality in 52,314 propensity-score-matched patients with D'Amico intermediate- or high-risk prostate cancer

Variables	OM	P value	CSM	P value
	HR (95% CI)		HR (95% CI)	
Age		<0.001		0.001
<65	1.00 (Ref.)		1.00 (Ref.)	
≥65	2.137 (1.86-2.46)	<0.001	1.65 (1.22-2.23)	0.001
Race		<0.001		/
White	1.00 (Ref.)			
Black*	1.44 (1.21-1.72)	<0.001		
Other**	0.85 (0.61-1.18)	0.324		
Marital status		<0.001		0.013
Married	1.00 (Ref.)		1.00 (Ref.)	
Non-married***	1.93 (1.66-2.24)	<0.001	1.54 (1.10-2.17)	0.013
Grade		0.317		0.630
Well, I	1.00 (Ref.)			
Moderately, II	0.81 (0.51-1.28)	0.364	1.76 (0.24-13.15)	0.580
Poorly, III	0.96 (0.58-1.57)	0.859	1.30 (0.17-10.17)	0.801
Undifferentiated, IV	-	0.890	-	0.864
Radiotherapy		0.947		0.351
Yes	1.00 (Ref.)		1.00 (Ref.)	
No/Unknown	0.99 (0.74-1.32)	0.947	0.82 (0.54-1.25)	0.351
Chemotherapy		0.087		0.011
Yes	1.00 (Ref.)		1.00 (Ref.)	
No/Unknown	0.42 (0.16-1.13)	0.087	0.27 (0.10-0.74)	0.011
PSA		<0.001		<0.001
<10ng/ml	1.00 (Ref.)		1.00 (Ref.)	

10-20ng/ml	1.40 (1.16-1.67)	<0.001	1.54 (1.06-2.23)	0.023
>20ng/ml	1.64 (1.21-2.22)	0.002	2.95 (1.84-4.73)	<0.001
Gleason score		<0.001		<0.001
≤6	1.00 (Ref.)		1.00 (Ref.)	
7	0.99 (0.79-1.23)	0.910	1.38 (0.75-2.55)	0.308
8-10	1.88(1.39-2.53)	<0.001	10.08 (4.96-20.47)	<0.001
T		0.896		0.837
cT1-2a	1.00 (Ref.)		1.00 (Ref.)	
cT2b	0.94 (0.55-1.62)	0.833	0.39 (0.05-3.07)	0.370
cT2c	1.09 (0.61-1.95)	0.780	0.94 (0.33-2.72)	0.914
cT3-4	2.16 (0.26-17.86)	0.576	-	0.829
N		0.200		0.048
N0	1.00 (Ref.)		1.00 (Ref.)	
N1	1.49 (0.81-2.75)	0.200	2.10 (1.01-4.38)	0.048
Disease stage		0.795		0.963
Intermediate-risk	1.00 (Ref.)		1.00 (Ref.)	
High-risk****	0.86 (0.46-1.61)	0.645	0.88 (0.24-3.23)	0.841
Locally advanced	0.52 (0.06-4.39)	0.549	-	0.846
PLND		0.667		0.075
No	1.00 (Ref.)		1.00 (Ref.)	
Yes	1.03 (0.90-1.19)	0.667	0.75 (0.55-1.03)	0.075

*Black or African American.

**Includes American Indian/Alaska Native, Asian, and Asian/Pacific Islander.

*** Includes widowed, never married, divorced, separated, unmarried, and domestic partner.

****Specifically refers to the high-risk stage of localised prostate cancer in the table.

Abbreviations: PLND, pelvic lymph node dissection; PSA, prostate-specific antigen; OM, overall mortality; CSM, cancer-specific mortality; HR, hazard ratio; CI, confidence interval; Ref, reference.

Supplementary Table 1: General characteristics of 75,583 patients with D'Amico intermediate- or high-risk prostate cancer and general characteristics of 52,314 patients with D'Amico intermediate- and high-risk prostate cancer after the propensity score matching.

Variables	All patients			Propensity-matched patients		
	No PLND	PLND	P value	No PLND	PLND	P value
	No. (%)	No. (%)		No. (%)	No. (%)	
Total	26791 (35.4)	48792 (64.6)		26157(50.0)	26157(50.0)	
Age			<0.001			0.076
<65	18141 (67.7)	30082 (62.7)		17635 (67.4)	17847 (68.2)	
≥65	8650 (32.3)	18710 (38.3)		8522 (32.6)	8310 (31.8)	
Race			<0.001			<0.001
White	21839 (81.5)	38878 (79.7)		21347 (81.6)	20957 (80.1)	
Black*	3681 (13.7)	6860 (14.1)		3542 (13.5)	3654 (14.0)	
Other**	1271 (4.7)	3054 (6.3)		1268 (4.8)	1546 (5.9)	
Marital status			<0.001			<0.001
Married	21704 (81.0)	38426 (78.8)		21147 (80.8)	21253 (81.3)	
Non-married***	5087 (19.0)	10366 (21.2)		5010 (19.2)	4904 (18.7)	
Grade			<0.001			<0.001
Well, I	2012 (7.5)	1285 (2.6)		1872 (7.2)	1225 (4.7)	
Moderately, II	12668 (47.3)	18800 (38.5)		12193 (46.6)	11130 (42.6)	
Poorly, III	12093 (45.1)	28657 (58.7)		12074 (46.2)	13785 (52.7)	
Undifferentiated, IV	18 (0.1)	50 (0.1)		18 (0.1)	17 (0.1)	
Radiotherapy			<0.001			0.003
Yes	937 (3.5)	4228 (8.7)		934 (3.6)	1565 (6.0)	
No/Unknown	25854 (96.5)	44564 (91.3)		25223 (96.4)	24592 (94.0)	

Chemotherapy			0.001			0.879
Yes	21 (0.1)	147 (0.3)		21 (0.1)	44 (0.2)	
No/Unknown	26770 (99.9)	48645 (99.7)		26136 (99.9)	26113 (99.8)	
PSA			<0.001			0.879
<10ng/ml	23646 (88.3)	36263 (74.3)		23016 (88.0)	20768 (79.4)	
10-20ng/ml	2598 (9.7)	8822 (18.1)		2594 (9.9)	4094 (15.7)	
>20ng/ml	547 (2.0)	3707 (7.6)		547 (2.1)	1295 (5.0)	
Gleason score			<0.001			0.823
≤6	8526 (31.8)	5908 (12.1)		7896 (30.2)	5554 (21.2)	
7	16907 (63.1)	34217 (70.1)		16903 (64.6)	17709 (67.7)	
8-10	1358 (5.1)	8667 (17.8)		1358 (5.2)	2894 (11.1)	
T			<0.001			0.711
cT1-2a	1656 (6.2)	2843 (5.8)		1655 (6.3)	2040 (7.8)	
cT2b	541 (2.0)	996 (2.0)		503 (1.9)	599 (2.3)	
cT2c	19406 (72.4)	26273 (53.8)		18826 (72.0)	15590 (59.6)	
cT3-4	5188 (19.4)	18680 (38.3)		5173 (19.8)	7928 (30.3)	
N			<0.001			1.000
N0	26771 (99.9)	45537 (93.3)		26137 (99.9)	25826 (98.7)	
N1	20 (0.1)	3255 (6.7)		20 (0.1)	331 (1.3)	
Disease stage			<0.001			0.582
Intermediate-risk	2004 (7.5)	3139 (6.4)		1965 (7.5)	2318 (8.9)	
High-risk****	19596 (73.1)	26507 (54.3)		19016 (72.7)	15862 (60.6)	
Locally advanced	5191 (19.4)	19146 (39.2)		5176 (19.8)	7977 (30.5)	

*Black or African American.

**Includes American Indian/Alaska Native, Asian, and Asian/Pacific Islander.

*** Includes widowed, never married, divorced, separated, unmarried, and domestic partner.

****Specifically refers to the high-risk stage of localised prostate cancer in the table.

Abbreviations: PLND, pelvic lymph node dissection; PSA, prostate-specific antigen.

5. Pelvic Lymph Node Dissection Effects

5.1. The Impact of PLND on the General Population After 1:1 PSM, Kaplan Meier analysis confirmed that the patients who received PLND had a poorer prognosis than those patients without PLND (P=0.010 in OS, P=0.038 in CSS, Figure 2). Similar outcomes can be obtained in the cohort before adjustment (P<0.001 in OS & CSS, Figure 2). Bedsides, in the Kaplan-Meier analysis of the cases before PSM, we found that patients without PLND at RP had a better survival outcome when compared to patients who underwent ePLND or lPLND (All P<0.001, Both OS and CSS, Figure 2). But there was no significant difference between patients with ePLND and lPLND (All P>0.05, Both OS and CSS). However, in multivariable Cox regression models after adjustment for clinical and pathological characteristics, PLND was not an independent predict factor for OS and CSS (OM: HR 1.03, 95% CI 0.90-1.19, P=0.667; CSM: HR 0.75, 95% CI 0.55-1.03, P=0.075. Table 1).

5.2. The impact of PLND on D'Amico intermediate- and high-risk PCa: After stratifying the disease stages, the K-M analysis demonstrated that there was no statistically significant effect of PLND on survival outcomes in patients with intermediate-risk (I-R) or high-risk (H-R) localised PCa (P=0.109 in I-R PCa and P=0.152 in H-R PCa, OS; P=0.488 in I-R PCa and P=0.466 in H-R PCa, CSS. Figure 3). However, in locally advanced PCa, the patients with PLND at RP had a poorer survival outcome than patients without PLND (All P<0.001, Both OS and CSS. Figure 3). When compared to patients without PLND at RP, the multivariable Cox regression models showed that PLND was an independent risk factor of locally advanced PCa (OS: HR 1.67, 95% CI 1.36-2.06, P<0.001; CSS: HR 2.26, 95% CI 1.63-3.12, P<0.001. Table 2). When No PLND, ePLND, and lPLND were compared in pairs, the K-M analysis determined that patients without PLND had a better survival prognosis than patients with ePLND or lPLND (P(NvsE)<0.001, P(NvsL)<0.001, Both OS and CSS. Figure 3), and that there was no significant difference between patients treated with expanded and limited lymph node dissection (P=0.262 in OS and P=0.692 in CSS). The multivariable Cox regression models showed the same results in locally advanced PCa when compared to patients without PLND (All P<0.001, Both OM and CSM. Table 3 and Figure 1).

Table 2: Multivariable Cox regression models predicting overall mortality and cancer-specific mortality in 75,583 patients with D'Amico intermediate- or high-risk prostate cancer stratified by lymph node dissection

Variables	No PLND	PLND for OM	PLND for CSM
	HR (95%CI)	HR (95%CI)	HR (95%CI)
Age			
<65	1.00 (Ref.)	1.74 (1.48-2.05) #	3.60 (2.54-5.11) #
≥65	1.00 (Ref.)	1.22 (1,04-1.43) ‡	1.94 (1.38-2.74) #
Race			
White	1.00 (Ref.)	1.62 (1.42-1.84) #	3.04 (2.30-4.02) #
Black*	1.00 (Ref.)	1.14 (0.87-1.58)	1.86 (1.06-3.29) ‡
Other**	1.00 (Ref.)	1.55 (0.90-2.65)	2.32 (0.78-6.80)
Marital status			
Married	1.00 (Ref.)	1.58 (1.38-1.82) #	2.72 (2.05-3.61) #
Non-married***	1.00 (Ref.)	1.31 (1.07-1.61) ‡	2.83 (1.74-4.59) #
Grade			
Well, I	1.00 (Ref.)	0.43 (0.16-1.17)	-
Moderately, II	1.00 (Ref.)	1.21 (0.96-1.52)	1.08 (0.56-2.11)
Poorly, III	1.00 (Ref.)	1.55 (1.32-1.74) #	2.63 (1.99-3.47) #
Undifferentiated, IV	-	-	-
Radiotherapy			
Yes	1.00 (Ref.)	2.02 (1.28-3.19) ‡	3.12 (1.58-6.18) ‡
No/Unknown	1.00 (Ref.)	1.41 (1.28-1.59) #	2.29 (1.75-2.98) #
Chemotherapy			
Yes	-	-	-
No/Unknown	1.00 (Ref.)	1.50 (1.34-1.68) #	2.70 (2.11-3.45) #
PSA			
<10ng/ml	1.00 (Ref.)	1.38 (1.21-1.58) #	2.24 (1.67-3.01) #
10-20ng/ml	1.00 (Ref.)	1.28 (0.97-1.69)	2.49 (1.40-4.46) ‡
>20ng/ml	1.00 (Ref.)	1.20 (0.71-2.03)	1.53 (0.70-3.34)
Gleason score			
≤6	1.00 (Ref.)	0.99 (0.76-1.31)	0.86 (0.36-2.05)
7	1.00 (Ref.)	1.19 (1.02-1.39) ‡	1.47 (0.99-2.18)
8-10	1.00 (Ref.)	1.47 (1.08-2.00) ‡	1.36 (0.94-1.97)
T			
cT1-2a	1.00 (Ref.)	1.10 (0.68-1.79)	1.16 (0.40-3.97)
cT2b	1.00 (Ref.)	1.61 (0.69-3.90)	1.89 (0.20-18.28)
cT2c	1.00 (Ref.)	1.15 (0.99-1.34)	1.31 (0.85-2.02)
cT3-4	1.00 (Ref.)	1.68 (1.36-2.07) #	2.26 (1.63-3.13) #
N			
N0	1.00 (Ref.)	1.35 (1.20-1.52) #	1.97 (1.52-2.54) #
N1	-	-	-
Disease stage**			
Intermediate-risk	1.00 (Ref.)	1.49 (0.91-2.42)	1.88 (036-9.64)
High-risk****	1.00 (Ref.)	1.12 (0.96-1.31)	1.18 (0.77-1.80)
Locally advanced	1.00 (Ref.)	1.67 (1.36-2.06) #	2.26 (1.63-3.12) #

*Black or African American.

**Includes American Indian/Alaska Native, Asian, and Asian/Pacific Islander.

*** Includes widowed, never married, divorced, separated, unmarried, and domestic partner.

****Specifically refers to the high-risk stage of localised prostate cancer in the table.

‡ P<0.05. # P<0.001.

Abbreviations: PLND, pelvic lymph node dissection; PSA, prostate-specific antigen; OM, overall mortality; CSM, cancer-specific mortality; HR, hazard ratio; CI, confidence interval; Ref, reference.

Table 3: Multivariable Cox regression models predicting cancer-specific mortality in 75,583 patients with D'Amico intermediate- or high-risk prostate cancer stratified by lymph node dissection.

Variables	No PLND	Limited PLND	Extended PLND
	HR (95%CI)	HR (95%CI)	HR (95%CI)
Total	1.00 (Ref.)	2.34 (1.73-3.16)#	2.98 (2.31-3.83)#
Age			
<65	1.00 (Ref.)	2.96 (1.94-4.51)#	3.93 (2.74-5.64)#
≥65	1.00 (Ref.)	1.73 (1.12-2.67)‡	2.04 (1.43-2.91)#
Race			
White	1.00 (Ref.)	2.56 (1.82-3.61)	3.27 (2.45-4.37)
Black*	1.00 (Ref.)	1.76 (0.87-3.55)	1.92 (1.05-3.50)
Other**	1.00 (Ref.)	1.32 (0.30-5.91)	2.76 (0.90-8.41)
Marital status			
Married	1.00 (Ref.)	2.34 (1.73-3.16)#	2.98 (2.31-3.83)#
Non-married***	1.00 (Ref.)	3.40 (1.96-5.91)#	2.57 (1.54-4.27)#
Grade			
Well, I	1.00 (Ref.)	-	-
Moderately, II	1.00 (Ref.)	1.48 (0.69-3.18)	1.24 (0.63-2.44)
Poorly, III	1.00 (Ref.)	2.28 (1.63-3.19)#	2.79 (2.09-3.71)#
Undifferentiated, IV	-	-	-
Radiotherapy			
Yes	1.00 (Ref.)	2.64 (1.23-5.63)‡	3.35 (1.67-6.70)‡
No/Unknown	1.00 (Ref.)	1.95 (1.39-2.73)#	2.45 (1.86-3.23)#
Chemotherapy			
Yes	-	-	-
No/Unknown	1.00 (Ref.)	2.32 (1.71-3.13)#	2.88 (2.24-3.72)#
PSA			
<10ng/ml	1.00 (Ref.)	1.83 (1.25-2.68)‡	2.46 (1.81-3.34)#
10-20ng/ml	1.00 (Ref.)	2.27 (1.16-4.44)‡	2.59 (1.43-4.69)‡
>20ng/ml	1.00 (Ref.)	1.62 (0.68-3.88)	1.50 (0.68-3.32)
Gleason score			
≤6	1.00 (Ref.)	1.35 (0.49-3.74)	0.54 (0.15-1.86)
7	1.00 (Ref.)	1.04 (0.59-1.81)	1.67 (1.11-2.52)‡
8-10	1.00 (Ref.)	1.40 (0.91-2.14)	1.34 (0.92-1.96)
T			
cT1-2a	1.00 (Ref.)	0.99 (0.18-5.41)	1.24 (0.34-4.64)
cT2b	1.00 (Ref.)	-	2.76 (0.28-26.63)
cT2c	1.00 (Ref.)	1.31 (0.74-2.32)	1.31 (0.81-2.11)
cT3-4	1.00 (Ref.)	2.17 (1.48-3.33)#	2.30 (1.65-3.21)#
N			
N0	1.00 (Ref.)	1.90 (1.38-2.62)#	2.00 (1.53-2.63)#
N1	-	-	-
Disease stage			
Intermediate-risk	1.00 (Ref.)	2.21 (0.31-15.69)	1.69 (0.28-10.15)
High-risk****	1.00 (Ref.)	1.13 (0.64-2.01)	1.20 (0.76-1.92)
Locally advanced	1.00 (Ref.)	2.16 (1.48-3.17)#	2.91 (1.64-3.20)#

*Black or African American.

**Includes American Indian/Alaska Native, Asian, and Asian/Pacific Islander.

*** Includes widowed, never married, divorced, separated, unmarried, and domestic partner.

****Specifically refers to the high-risk stage of localised prostate cancer in the table.

‡ P<0.05. # P<0.001.

Abbreviations: PLND, pelvic lymph node dissection; PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval; Ref, reference.

Supplementary Table 2: Univariable Cox regression models predicting overall mortality and cancer-specific mortality in 52,314 propensity-score-matched patients with D'Amico intermediate- or high-risk prostate cancer.

Variables	OM	P value	CSM	P value
	HR (95% CI)		HR (95% CI)	
Age		<0.001		<0.001
<65	1.00 (Ref.)		1.00 (Ref.)	
≥65	2.30 (2.01-2.63)	<0.001	2.50 (1.86-3.36)	<0.001
Race		<0.001		0.095
White	1.00 (Ref.)		1.00 (Ref.)	
Black*	1.53 (1.28-1.82)	<0.001	1.51 (1.03-2.21)	0.034
Other**	0.97 (0.70-1.35)	0.866	1.26 (0.66-2.39)	0.488
Marital status		<0.001		0.002
Married	1.00 (Ref.)		1.00 (Ref.)	
Non-married***	2.08 (1.80-2.41)	<0.001	1.70 (1.22-2.37)	0.002
Grade		<0.001		<0.001
Well, I	1.00 (Ref.)			
Moderately, II	0.86 (0.55-1.36)	0.528	2.50 (0.34-18.26)	0.368
Poorly, III	1.27 (0.81-1.99)	0.294	5.91 (0.82-42.41)	0.077
Undifferentiated, IV	-	0.898	-	0.962
Radiotherapy		0.001		<0.001
Yes	1.00 (Ref.)		1.00 (Ref.)	
No/Unknown	0.61 (0.46-0.80)	0.001	0.21 (0.14-0.31)	<0.001
Chemotherapy		0.008		<0.001
Yes	1.00 (Ref.)		1.00 (Ref.)	
No/Unknown	0.27 (0.10-0.71)	0.008	0.06 (0.02-0.15)	<0.001
PSA		<0.001		<0.001
<10ng/ml	1.00 (Ref.)		1.00 (Ref.)	
10-20ng/ml	1.79 (1.50-2.13)	<0.001	2.73 (1.91-3.90)	<0.001
>20ng/ml	2.50 (1.86-3.34)	<0.001	7.20 (5.63-11.20)	<0.001
Gleason score		<0.001		<0.001
≤6	1.00 (Ref.)		1.00 (Ref.)	
7	1.20 (1.02-1.42)	0.029	1.57 (0.95-2.60)	0.077
8-10	3.12 (2.52-3.87)	<0.001	18.34 (11.30-29.78)	<0.001
T		<0.001		<0.001
cT1-2a	1.00 (Ref.)		1.00 (Ref.)	
cT2b	0.90 (0.53-1.54)	0.699	0.35 (0.05-2.78)	0.322
cT2c	0.86 (0.66-1.12)	0.257	0.68 (0.34-1.37)	0.276
cT3-4	1.40 (1.06-1.85)	0.020	3.79 (1.92-7.47)	<0.001
N		0.001		<0.001
N0	1.00 (Ref.)		1.00 (Ref.)	
N1	2.70 (1.53-4.77)	0.001	8.90 (4.38-18.10)	<0.001
Disease stage		<0.001		<0.001
Intermediate-risk	1.00 (Ref.)		1.00 (Ref.)	
High-risk****	0.96 (0.74-1.25)	0.770	1.27 (0.55-2.94)	0.574
Locally advanced	1.55 (1.18-2.03)	0.002	6.70 (2.95-15.25)	<0.001
PLND		0.010		0.039
No	1.00 (Ref.)		1.00 (Ref.)	
Yes	1.19 (1.04-1.37)	0.010	1.37 (1.02-1.84)	0.039

*Black or African American.

**Includes American Indian/Alaska Native, Asian, and Asian/Pacific Islander.

*** Includes widowed, never married, divorced, separated, unmarried, and domestic partner.

****Specifically refers to the high-risk stage of localised prostate cancer in the table.

Abbreviations: PLND, pelvic lymph node dissection; PSA, prostate-specific antigen; OM, overall mortality; CSM, cancer-specific mortality; HR, hazard ratio; CI, confidence interval; Ref, reference.

Supplementary Table 3: Multivariable Cox regression models predicting overall mortality in 75,583 patients with D'Amico intermediate- or high-risk prostate cancer stratified by lymph node dissection.

Variables	No PLND	Limited PLND	Extended PLND
	HR (95%CI)	HR (95%CI)	HR (95%CI)
Total	1.00 (Ref.)	1.55 (1.34-1.79)#	1.50 (1.32-1.69)#
Age			
<65	1.00 (Ref.)	1.87 (1.52-2.29)	1.68 (1.41-2.01)#
≥65	1.00 (Ref.)	1.21 (0.98-1.49)	1.22 (1.03-1.45)‡
Race			
White	1.00 (Ref.)	1.69 (1.43-2.00)#	1.58 (1.37-1.82)#
Black*	1.00 (Ref.)	1.08 (0.76-1.53)	1.16 (0.88-1.55)
Other**	1.00 (Ref.)	1.41 (0.70-2.83)	1.61 (0.91-2.84)
Marital status			
Married	1.00 (Ref.)	1.58 (1.33-1.89)#	1.58 (1.36-1.84)#
Non-married***	1.00 (Ref.)	1.44 (1.11-1.86)‡	1.25 (1.01-1.56)‡
Grade			
Well, I	1.00 (Ref.)	0.38 (0.09-1.65)	0.48 (0.14-1.63)
Moderately, II	1.00 (Ref.)	1.23 (0.90-1.67)	1.20 (0.92-1.55)
Poorly, III	1.00 (Ref.)	1.61 (1.35-1.91)#	1.47 (1.27-1.71)#
Undifferentiated, IV	1.00 (Ref.)	-	-
Radiotherapy			
Yes	1.00 (Ref.)	1.95 (1.16-3.27)‡	2.05 (1.28-3.28)‡
No/Unknown	1.00 (Ref.)	1.46 (1.25-1.70)#	1.38 (1.21-1.57)#
Chemotherapy			
Yes	1.00 (Ref.)	-	-
No/Unknown	1.00 (Ref.)	1.54 (1.33-1.79)#	1.48 (1.31-1.68)#
PSA			
<10ng/ml	1.00 (Ref.)	1.49 (1.26-1.77)#	1.33 (1.15-1.53)#
10-20ng/ml	1.00 (Ref.)	1.25 (0.89-1.77)	1.29 (0.96-1.73)
>20ng/ml	1.00 (Ref.)	1.15 (0.63-2.11)	1.22 (0.72-2.08)
Gleason score			
≤6	1.00 (Ref.)	0.97 (0.66-1.42)	1.02 (0.74-1.41)
7	1.00 (Ref.)	1.30 (1.07-1.59)‡	1.14 (0.97-1.35)‡
8-10	1.00 (Ref.)	1.61 (1.14-2.27)‡	1.42 (1.04-1.94)‡
T			
cT1-2a	1.00 (Ref.)	1.36 (0.74-2.47)	0.97 (0.56-1.68)
cT2b	1.00 (Ref.)	1.74 (0.59-5.19)	1.55 (0.60-4.01)
cT2c	1.00 (Ref.)	1.22 (0.99-1.50)	1.11 (0.94-1.32)
cT3-4	1.00 (Ref.)	1.80 (1.40-2.31)#	1.64 (1.32-2.03)#
N			
N0	1.00 (Ref.)	1.45 (1.25-1.69)#	1.30 (1.14-1.48)#
N1	1.00 (Ref.)	-	-
Disease stage			
Intermediate-risk	1.00 (Ref.)	1.88 (1.05-3.38)‡	1.29 (0.75-2.22)
High-risk****	1.00 (Ref.)	1.18 (0.96-1.44)	1.09 (0.92-1.29)
Locally advanced	1.00 (Ref.)	1.81 (1.41-2.32)#	1.62 (1.31-2.02)#

*Black or African American.

**Includes American Indian/Alaska Native, Asian, and Asian/Pacific Islander.

*** Includes widowed, never married, divorced, separated, unmarried, and domestic partner.

****Specifically refers to the high-risk stage of localised prostate cancer in the table.

‡ P<0.05. # P<0.001.

Abbreviations: PLND, pelvic lymph node dissection; PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval; Ref, reference.

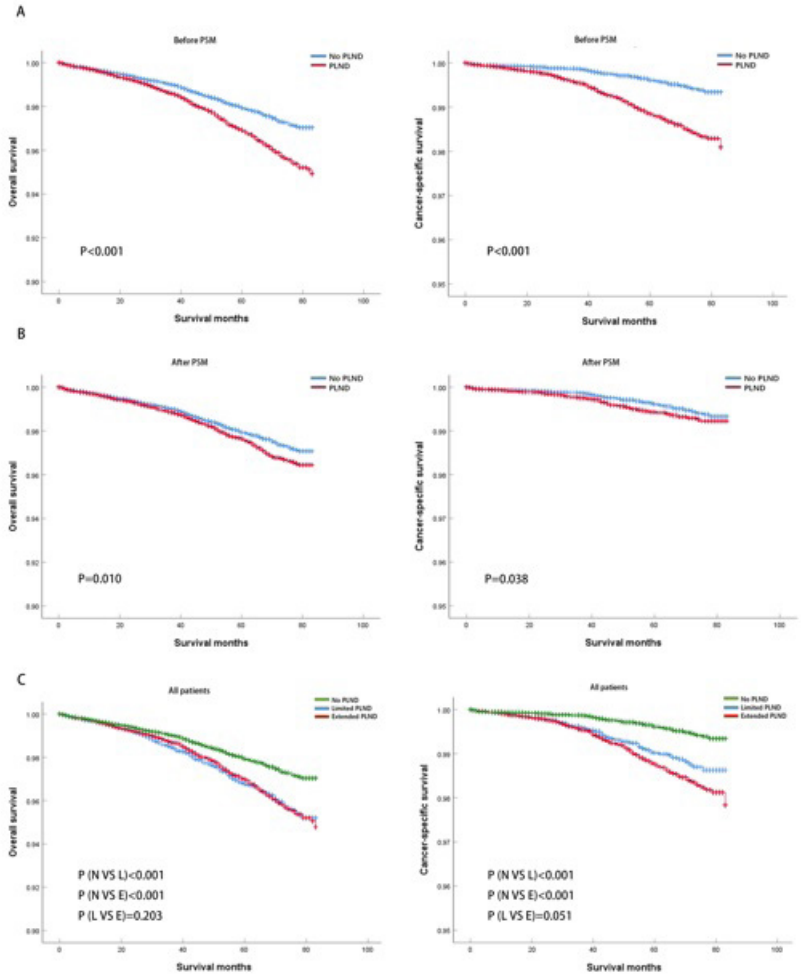

Figure 2: Kaplan–Meier plot: A). Overall survival and cancer-specific survival of 75,583 patients with D'Amico intermediate- or high-risk prostate cancer according to the status of PLND (PLND vs. No PLND); B). Overall survival and cancer-specific survival of 52,314 patients with D'Amico intermediate- or high-risk prostate cancer according to the status of PLND (PLND vs. No PLND); C). Overall survival and cancer-specific survival of 75,583 patients with D'Amico intermediate- or high-risk prostate cancer according to the status of PLND (No PLND vs. ePLND, No PLND vs. lPLND, ePLND vs. lPLND).

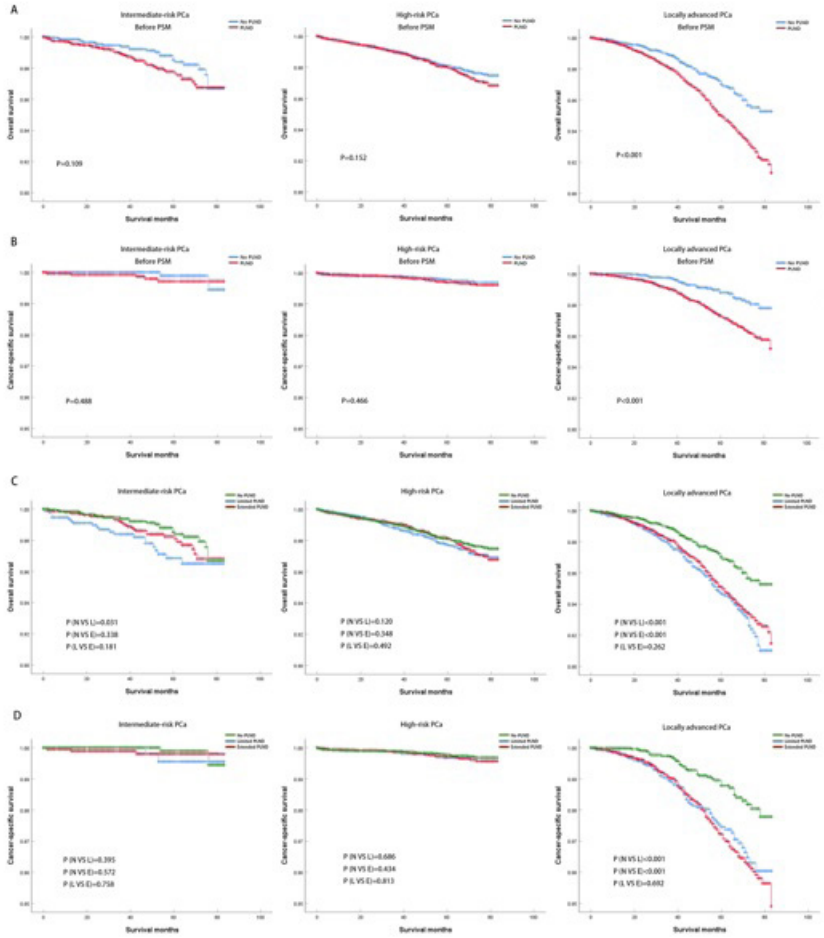

Figure 3: Kaplan–Meier plot: A and B). Overall survival and cancer-specific survival of 75,583 patients according to the status of PLND (PLND vs. No PLND) in different disease stages; C and D). Overall survival and cancer-specific survival of 75,583 patients according to the status of PLND (No PLND vs. ePLND, No PLND vs. lPLND, ePLND vs. lPLND) in different disease stages.

5.3. Predictor for Lymph Node Involvement

As shown in supplementary table 4, 45,128 (98.9%) patients without LNI underwent PLND at RP and only 3,664 (12.2%) patients with pathologically positive LNs underwent PLND. Besides, the sensitivity and specificity of clinical lymphatic diagnosis were 10.9% and 99.9%, respectively. Multivariable logistic regression analysis demonstrated that pathological grade, PSA, GS, clinical T stage and disease stage were all independent predictors of LNI (Table 4). Compared with patients who had PSA <10ng/ml, there was a higher risk of LNI in patients with PSA 10-20ng/ml (odds radio [OR] 1.40, 95% CI 1.15-1.69, P=0.001) and PSA >20ng/ml (OR 2.04, 95% CI 1.45-2.85, P<0.001, Table 4). Compared with patients with GS ≤6, patients with GS=7(OR 1.91, 95% CI 1.57-2.31, P<0.001). and GS 8-10 (OR 3.18, 95% CI 2.33-4.34, P<0.001) had a higher risk of LNI. Compared with patients with intermediate-risk PCa, there was a higher risk of LNI in patients with locally advanced PCa (OR 16.82, 95% CI 5.05-56.06, P<0.001, Table 4).

Supplementary Table 4: Baseline demographic and tumor characteristics of patients between with and without pathological lymph node involvement.

Variables	Lymph node involvement		P value
	Yes	No	
	No. (%)	No. (%)	
Total	29939 (39.6)	45644 (60.4)	
Age			<0.001
<65	19994 (66.8)	28229 (61.8)	
≥65	9945 (33.2)	17415 (38.2)	
Race‡			<0.001
White	34375 (81.4)	36342 (79.6)	

Black*	4115 (13.7)	6426 (14.1)	
Other**	1449 (4.8)	2876 (6.3)	
Marital status			<0.001
Married	24022 (80.2)	36108 (79.1)	
Non-married***	5917 (19.8)	9536 (20.9)	
Grade			<0.001
Well, I	2007 (6.7)	1290 (2.8)	
Moderately, II	13210 (44.1)	18258 (40.0)	
Poorly, III	14700 (49.1)	26050 (57.1)	
Undifferentiated, IV	22 (0.1)	46 (0.1)	
Radiotherapy			<0.001
Yes	1859 (6.2)	3306 (7.2)	
No/Unknown	28080 (93.8)	42338 (92.8)	
Chemotherapy			0.004
Yes	85 (0.3)	83 (0.2)	
No/Unknown	29854 (99.7)	45561 (99.8)	
PSA			<0.001
<10ng/ml	25082 (83.8)	34827 (76.3)	
10-20ng/ml	3545 (11.8)	7875 (17.3)	
>20ng/ml	1312 (4.4)	2942 (6.4)	
Gleason score			<0.001
≤6	8536 (28.5)	5898 (12.9)	
7	18348 (61.3)	32776 (71.8)	
8-10	3055 (10.2)	6970 (15.3)	
T			<0.001
cT1-2a	1713 (5.7)	2786 (6.1)	
cT2b	580 (1.9)	957 (2.1)	
cT2c	19741 (65.9)	25938 (56.8)	
cT3-4	7905 (26.4)	15963 (35.0)	
N			<0.001
N0	26678 (89.1)	45630 (99.9)	
N1	3261 (10.9)	14 (0.1)	
Disease stage			<0.001
Intermediate-risk	2033 (6.8)	3110 (6.8)	
High-risk****	19539 (65.3)	26564 (58.2)	
Locally advanced	8367 (27.9)	15970 (35.0)	
PLND			<0.001
No	26275 (87.8)	516 (1.1)	
Yes	3664 (12.2)	45128 (98.9)	

*Black or African American.

**Includes American Indian/Alaska Native, Asian, and Asian/Pacific Islander.

*** Includes widowed, never married, divorced, separated, unmarried, and domestic partner.

****Specifically refers to the high-risk stage of localised prostate cancer in the table.

Abbreviations: PLND, pelvic lymph node dissection; PSA, prostate-specific antigen.

6. Discussion

There is no deny that PLND plays an important role in PCa staging, but its potential curative value is controversial, and prospective trials of PLND are still missing. In view of the current research status, this paper had made some achievements, but also found some problems in it. PLND is recommended as a standard surgical procedure at RP in patients with a risk of nodal metastases over 5%. Several studies showed a better CSS in patients treated with more ePLND at RP [18]. Other studies showed that PLND has no effect on patients' survival outcomes in intermediate-risk PCa. This conclusion is consistent with the results shown in our study only after balancing variables according to PLND and No PLND. One recent study showed that ePLND and lymph node yield were found no statistical link to BCR in patients with intermediate-risk PCa. However, some scholars reported that higher lymph node yield was associated with biochemical free recurrence survival mainly because of identification of an increased number of positive LNs [19]. In fact, due to the heterogeneity of intermediate-risk PCa, more work needs to be done to further characterize patients within this group and identify the minority of patients with a more favorable prognosis for which expectant treatments would be effective. High-risk PCa actually includes any patient with a PSA >20, Gleason score 8 or higher, clinical T2c, or a locally advanced cancer (≥T3). In this context, we would like to call it high-risk PCa and locally advanced PCa, respectively. The EAU guidelines recommend that all patients with high-risk PCa should receive PLND when RP is planned. In high-risk stage of localised PCa, our data suggested that PLND or No PLND had no effect on OS and CSS in patients at RP. This is the first report about the survival outcomes of high-risk stage of localised PCa that we know of so far. Surgical treatment has been traditionally discouraged in locally advanced PCa. But increasing recent evidence in literature push urologists to operate for RP in cT3 PCa patients assessing no LNI is shown [20]. In terms of whether performing PLND at RP in patients with locally advanced PCa, this is even less reported. In the present study, patients treated with PLND at RP had a worse survival outcome than patients without PLND. This may be due to the fact that patients in the advanced stage are inherently inoperable, especially when combined with PLND. Furthermore, it may be due to surgical complications associated with lymph node dissection. But at the same time, locally advanced PCa had a high risk of lymph node invasion. Therefore, in these specific cases, individual based management must be discussed with the patients and tailored as part of a multiplex therapy. Due to the difference in recommendations within this patient category, urologists would be the center of decision making rather than following clear cut guidelines. According to the relationship between the number of nodes removed and oncologic outcomes, a recent study reported that a large number of PLND was associated with a significant improvement in time to BCR [21,22]. Unfortunately, our findings suggested that there was no significant difference between ePLND and lPLND. This may be due to limitations of SEER database, that we have to narrow the definition of ePLND and lPLND. Moreover, we assessed the impact of PLND on different populations according to age, sex, race, marital status, pathological grade, state of radiotherapy, state of chemotherapy, PSA, GS, T stage and N stage (Table 3). We found that in the majority of the population, patients with different subtypes did not benefit significantly from PLND compared to patients without PLND, and they had a worse OS and CSS. Although PLND has been reported to be useful for survival biochemical recurrence-free survival, its effect on actual survival of patients remains to be determined. Finally, we investigated the predictive function of different clinical and pathologic characteristics for LNI, and found that the sensitivity and specificity of clinical lymphatic diagnosis were 10.9% and 99.9%, respectively. This result indicated the inadequacy of current clinical work, leading us to have to stage PCa by lymphatic biopsy or PLND. In addition, the phenomenon that PSA >20ng/ml and GS 8-10 were significantly associated with LNI was consistent with clinical experience. We should be highly alert to the possibility of lymphatic invasion in in this group of patients. At present, PLND at RP is performed blind, without knowledge of the presence of metastases. The conventional PLND template only covers 50-60% of the entire pelvic lymph node backflow, and the tumor cells in positive pelvic lymph nodes may be in hibernation and not lethal. Second, sometimes the initial metastatic lymph nodes are outside the pelvic cavity, such as sigmoid colon, mesentery, para-aortic lymph nodes, subclavian lymph nodes, and even the lung [22]. Therefore, whether to perform PLND at RP should take all the information of the patients into consideration and combine with the patients' will. This article also has some inevitable limitations. First, our results came from retrospective observational data. Therefore, our findings required prospective randomized validation. However, to our knowledge, no such trials are currently being recruited or conducted. Moreover, since the SEER database lacks post-operative follow-up information such as the time of BCR, it is difficult to fully assess the efficacy of PLND with a single indicator in intermediate- and high-risk PCa. Nevertheless, OS and CSS are also one of the best indicators to evaluate the prognosis of PCa patients. Finally, the determination of tumor's characteristics largely depends on the clinician's expertise, and the reasons for performing or not performing PLND are not clear. The possibility of these differences may further confuse our results.

7. Conclusions

In intermediate- or high-risk localised PCa, there was no significant difference in survival outcome in patients with or without PLND at RP. Although locally advanced PCa has a higher risk of lymph node involvement, patients treated with PLND has a higher overall mortality and cancer-specific mortality risks compared to patients without PLND. Thus, for patients with locally advanced

PCa, if radical prostatectomy is necessary, PLND is worthy of serious discussion or even been avoided.

8. List of Abbreviations: PLND: Pelvic Lymph Node Dissection**;** PCa: Prostate Cancer**;** RP: Radical Prostatectomy

CRMs: Cox Regression Models; OM: Overall Mortality; CMS: Cancer-Specific Mortality; EAU: European Association of Urology; EPLND: Extended PLND; lPLND: Limited PLND; LNI: Lymph Node Involvement; BCR: Biochemical Recurrence; GS: Gleason Score; PSA: Prostate-Specific Antigen; PSM: Propensity Score Matching

OS: Overall Survival; CSS: Cancer-Specific Survival

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