Role of lymph node dissection in radical cystectomy

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Abstract. The number of lymph node dissections (LNDs) is an independent factor influencing the survival time of patients with bladder cancer (BCa) after radical resection (RC). The present study aimed to investigate the association between the number of LNDs and the survival of patients with BCa at different stages and who underwent RC in the United States of America and China. Records from 17,730 American patients with BCa and 158 Chinese patients with BCa were collected from the Surveillance, Epidemiology and End Results (SEER) and the Shanghai Tenth People's Hospital (China) databases, respectively. Kaplan-Meier curve and χ^2 test were used to determine the overall survival time (OS) of patients with BCa. Cox regression analysis was used to analyze the effects of LND number on OS. Overall, 13,421 (75.7%) patients were negative for lymph node metastasis (N0) and 4,309 (24.3%) were positive for lymph node metastasis (N+) among the 17,730 American patients with BCa. In the group of 158 Chinese patients, 125 (79.1%) were N0 and 33 (20.9%) were N+. In the American patients, the median number of dissected nodes was 11.0 [interquartile range (IQR)=3.0-21.0] for N0 patients and 14.0 (IQR=8.0-23.0) for N+ patients. The median number of LNDs was 5.0 (IQR=2.0-7.0) for Chinese N0 patients and 5.0 (IQR=1.5-10.5) for Chinese N+ patients. The number of LNDs may therefore be an independent factor associated with survival in patients who underwent RC. Furthermore, a higher number of LNDs was associated with longer OS in patients with BCa [American patients, ≥13 nodes vs. ≤5 nodes, hazard ratio (HR)=0.62, 95% confidence interval (CI)=0.59-0.65, P<0.001; Chinese patients, ≥5 nodes vs. ≤1 node, HR=0.27, 95% CI=0.12-0.62, P=0.002]. The number of LNDs in patients with BCa and N+ was higher compared with number of LNDs in patients with BCa and N0 who underwent RC. More extensive LND improved the OS in both the patients from USA and China. Increasing the number of LNDs may therefore be crucial when treating patients with BCa.

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Introduction

Bladder cancer (BCa) is one of the most common type of cancer of the urinary system (1). In USA, ~81,190 new cases of BCa were diagnosed in 2018, accounting for 4.7% of all new cancer cases, and ~17,240 BCa-associated mortality cases were reported, accounting for 2.8% of all mortality cases (2). According to the tumor invasion depth, BCa can be divided into non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC) (3). Furthermore, ~70% of BCa cases are NIMBCs, which are characterized by a high-recurrence rate (30-80%) (4,5). Surgery is the main treatment for patients with BCa. Transurethral resection of bladder tumors remains the most commonly used treatment for NMIBC (6), whereas radical cystectomy (RC) combined with pelvic lymph node dissection (LND) is currently the main procedure to treat MIBC (7,8).

Based on a statistical analysis of clinical data, it was reported that increasing the extent of pelvic lymph node clearance might improve the survival rate of patients with BCa following RC (9,10). Furthermore, a previous study demonstrated that extended LND improves the survival rate of patients with BCa (11). However, the optimal range of surgical resection and the number of LNDs remain unclear (12-14). The present study aimed therefore to evaluate the appropriate number of LNDs to be performed in patients with BCa.

Following a review of the literature, the majority of studies investigating the impact of LNDs on the survival rate and perioperative results of patients with BCa treated with RC were based on data from medical centers in developed countries (15-17). A multicenter prospective study on this issue has been previously conducted in Germany (18). To the best of our knowledge, there are only a few comparative studies of data obtained from two medical centers of different countries. The present study compared data on the degree of LND performed in patients with BCa who underwent RC treatment in our medical center with data from USA patients with BCa who underwent RC, which were collected from the Surveillance, Epidemiology and End Results (SEER) database.

Materials and methods

Data source and patients. Data from 17,859 patients with BCa who underwent RC and pelvic lymphadenectomy between January 2004 and December 2015 were collected from the SEER using the National Cancer Institute's SEER*Stat software version 8.3.5 (19). Bladder malignancies with the ICD-O-3 surgical method site code C670-C679 (seer.cancer.gov/manuals/2018/appendixc.html) were selected. BCa surgical treatment information was obtained from the RX summary variable (codes 50, 60-64, 70-74 and 80 were defined as RC). The SEER database provides information about patients with cancer, including demographic information, primary tumor location, cancer staging, treatment and survival time, from 18 registries, which covers ~28% of the American population (19).

The exclusion criteria were as follows: i) Patients with unknown number of lymph nodes; ii) patients with unknown survival time; iii) patients with unknown Tumor-Node-Metastasis (TNM) stage (20); and iv) patients aged under 18 years. A total of 17,730 patients with BCa were qualified and included in the present study.

A total of 158 patients with BCa diagnosed at the Shanghai Tenth People's Hospital between January 2016 and December 2018 were included in this study. Patients were followed up until December 2018. The study was approved by the Ethics Committee of Shanghai Tenth People's Hospital of Tongji University, and written informed consent was obtained from the patients or their next of kin if the patient did not have the ability to sign due to lack of consciousness or physical difficulties.

Study variables. Patient-level clinical information was extracted from the SEER and the Shanghai Tenth People's Hospital databases and included age at diagnosis, sex, ethnicity, marital status, tumor grade, histological type, SEER stage, TNM stage and number of lymph nodes removed. According to the status of lymph node metastasis, patients were divided into two groups: N0 and N-positive (N+). (N+) included the three stages N1, N2 and N3. The clinicopathological characteristics included age at diagnosis (<68, 68-78 and >78 years), sex (female and male), ethnicity (white, black and others) and marital status (married and unmarried). Tumor variables included SEER stages (localized, regional and distant), histological type (transitional cell carcinoma and other), T stage (Ta + Tis, T1, T2, T3 and T4) and M stage (M0 and M1; cancer.gov/publications/dictionaries/cancer-terms/def/overall-survival). Tumor grades I, II, III and IV represented well-differentiated, moderately differentiated, poorly differentiated and undifferentiated tumors, respectively.

Statistical analysis. χ^2 test was used to analyze the clinicopathological characteristics associated with N-stage. Kaplan-Meier curves and log-rank test were used to assess the overall survival (OS) time of patients with BCa. Univariate and multivariate Cox regression analyses were used to determine the clinicopathological characteristics associated with OS. Multivariable Cox regression was used to analyze the patients' median survival time (MST) following stratification by N-stage in the SEER and Shanghai Tenth People's Hospital Urology databases. The stratification boundary for optimal number of LNDs was determined using X-tile software version 3.6.1 (21). SPSS (version 20.0; IBM Corp.) was used for all the statistical analyses. P<0.05 was considered to indicate a statistically significant difference.

Results

Demographic and clinical characteristics of patients with BCa. A total of 17,730 and 158 patients with BCa were identified from the SEER database and Shanghai Tenth People's Hospital databases, respectively. For American N0 and N+ patients, the median number of dissected nodes was 11.0 [IQR (interquartile range)=3.0-21.0] and 14.0 (IQR=8.0-23.0), respectively. The median number of LNDs for Chinese N0 and N+ patients was 5.0 (IQR=2.0-7.0) and 5.0 (IQR=1.5-10.5), respectively. Table I presents the association between the clinicopathological characteristics and N-stage of patients with BCa from the two aforementioned databases following χ^2 test analysis. The age at diagnosis was stratified using X-tile software. The age of patients from the SEER and Shanghai Tenth People's Hospital database was divided into three groups as follows: <68, 68-78 and >78 years (Fig. S1). The majority of patients with BCa were men (75.0% American patients and 86.1% Chinese patients). The results from χ^2 test demonstrated a significant association between N-stage and numerous variables, including age at diagnosis (P<0.001), sex (P<0.001), ethnicity (P=0.020), marital status (P=0.002), SEER stage (P<0.001), tumor grade (P<0.001), histological type (P=0.009), T-stage (P<0.001) and M-stage (P<0.001), in patients from the SEER database. In Chinese patients, N-stage was associated with T-stage (P<0.001) and M-stage (P<0.001; Table I).

Effects of N-stage on the OS of patients who underwent RC. The effect of N-stage on the OS of patients who underwent RC from the two aforementioned databases was analyzed by Kaplan-Meier curves. The results demonstrated that the survival time of American patients from the SEER database was significantly different depending on the N-stage (P<0.001; Fig. 1A). In addition, a significant difference in the survival time of Chinese patients between the N-stage subgroups was demonstrated (P<0.001; Fig. 1B). These findings suggested that N-stage was significantly associated with OS, and that the survival time of patients decreased as N-stage increased.

Identification of risk factors for patients with BCa who underwent RC. Univariate and multivariate Cox regression were used to analyze the clinicopathological characteristics associated with the OS of patients with BCa who underwent RC. The results from univariate Cox regression analysis demonstrated that age at diagnosis (P<0.001), sex (P<0.001), ethnicity (P<0.001), marital status (P<0.001), SEER stage (P<0.001), histological type (P<0.001), tumor grade (P<0.001), T-stage (P<0.001; TI: P=0.824), N-stage (P<0.001), M-stage (P<0.001) and number of removed lymph nodes (P<0.001) were significantly associated with the OS of American patients from the SEER database (Table II). The results from univariate Cox regression analysis demonstrated that age at diagnosis (P<0.001; 68-78: P=0.041), N-stage (P<0.001), M-stage (P=0.003) and number of removed lymph nodes (≥8 nodes: P=0.009) were significantly associated with the OS of Chinese patients from the Shanghai

Table I. Clinicopathological characteristics of patients with bladder cancer stratified by N-stage in the SEER and Shanghai Tenth People's Hospital Urology databases.

A, SEER database

Characteristic	All patients, n (%)	N0 Number (%)	N+ Number (%)	P-value
Total	17,730	13,421 (75.7)	4,309 (24.3)	
Age at diagnosis, years				<0.001
<68	8,279 (46.7)	6,083 (73.5)	2,196 (26.5)	
68-78	6,567 (37.0)	5,119 (78.0)	1,448 (22.0)	
>78	2,884 (16.3)	2,219 (76.9)	665 (23.1)	
Sex				<0.001
Female	4,431 (25.0)	3,257 (73.5)	1,174 (26.5)	
Male	13,299 (75.0)	10,164 (76.4)	3,135 (23.6)	
Ethnicity				0.020
White	15,722 (88.7)	11,932 (75.9)	3,790 (24.1)	
Black	308 (6.3)	802 (72.3)	308 (27.7)	
Other	211 (5.1)	687 (76.5)	211 (23.5)	
Marital status				0.002
Yes	11,192 (63.1)	8,558 (76.5)	2,634 (23.5)	
No	6,538 (36.9)	4,863 (74.4)	1,675 (25.6)	
SEER stage				<0.001
Localized	2,432 (13.7)	2,432 (100.0)	0 (0.0)	
Regional	14,045 (79.2)	10,436 (74.3)	3,609 (25.7)	
Distant	1,253 (7.1)	553 (44.1)	700 (3.9)	
Grade				<0.001
I	183 (1.0)	167 (91.3)	16 (8.7)	
II	889 (5.0)	758 (85.3)	131 (14.7)	
III	5,090 (28.7)	3,751 (73.7)	1,339 (26.3)	
IV	10,545 (59.5)	7,896 (74.9)	2,649 (25.1)	
Unknown	1,023 (5.8)	849 (83.0)	174 (17.0)	
Histological type				0.009
Transitional cell carcinoma	16,014 (90.3)	12,166 (76.0)	3,848 (24.0)	
Others	1,716 (9.7)	1,255 (73.1)	461 (26.9)	
T-stage[a]				<0.001
Ta + Tis	495 (2.8)	494 (99.8)	1 (0.2)	
T1	2,067 (11.7)	1,974 (95.5)	93 (4.5)	
T2	6,617 (37.3)	5,799 (87.6)	818 (12.4)	
T3	5,452 (30.8)	3,481 (63.8)	1,971 (36.2)	
T4	3,099 (17.5)	1,673 (54.0)	1,426 (46.0)	
M-stage[a]				<0.001
M0	16,874 (95.2)	13,106 (77.7)	3,768 (22.3)	
M1	856 (4.8)	315 (36.8)	541 (63.2)	
Removed lymph nodes				0.810
Mean	15.1	14.3	17.6	
Median	11.0	11.0	14.0	
IQR	4.0-21.0	3.0-21.0	8.0-23.0	

Table I. Continued.

B, Shanghai Tenth People's Hospital Urology database

Characteristic	All patients, n (%)	N0 Number (%)	N+ Number (%)	P-value
Total	158	125 (79.1)	33 (20.9)	
Age at diagnosis, years				0.969
<68	91 (57.6)	72 (79.1)	19 (20.9)	
68-78	46 (29.1)	36 (78.3)	10 (21.7)	
>78	21 (13.3)	17 (81.0)	4 (19.0)	
Sex				0.819
Female	22 (13.9)	17 (77.3)	5 (22.7)	
Male	136 (86.1)	108 (79.4)	28 (20.6)	
T-stage[a]				<0.001
Ta + Tis	6 (4.8)	6 (100.0)	0 (0.0)	
T1	61 (38.6)	56 (91.8)	5 (8.2)	
T2	29 (18.4)	27 (93.1)	2 (6.9)	
T3	31 (19.6)	22 (71.0)	9 (29.0)	
T4	31 (19.6)	14 (45.2)	17 (54.8)	
M-stage[a]				<0.001
M0	150 (94.9)	123 (82.0)	27 (18.0)	
M1	8 (5.1)	2 (25.0)	6 (75.0)	
Removed lymph nodes				<0.001
Mean	5.2	4.9	6.3	
Median	5.0	5.0	5.0	
IQR	2.0-7.3	2.0-7.0	1.5-10.5	

[a]TNM staging (20). Grade I, well differentiated; grade II, moderately differentiated; grade III, poorly differentiated; and grade IV, undifferentiated. Percentages may not total 100 due to approximation of decimal values. IQR, interquartile range; SEER, Surveillance, Epidemiology and End Results; T, tumor; N, node; M, metastasis.

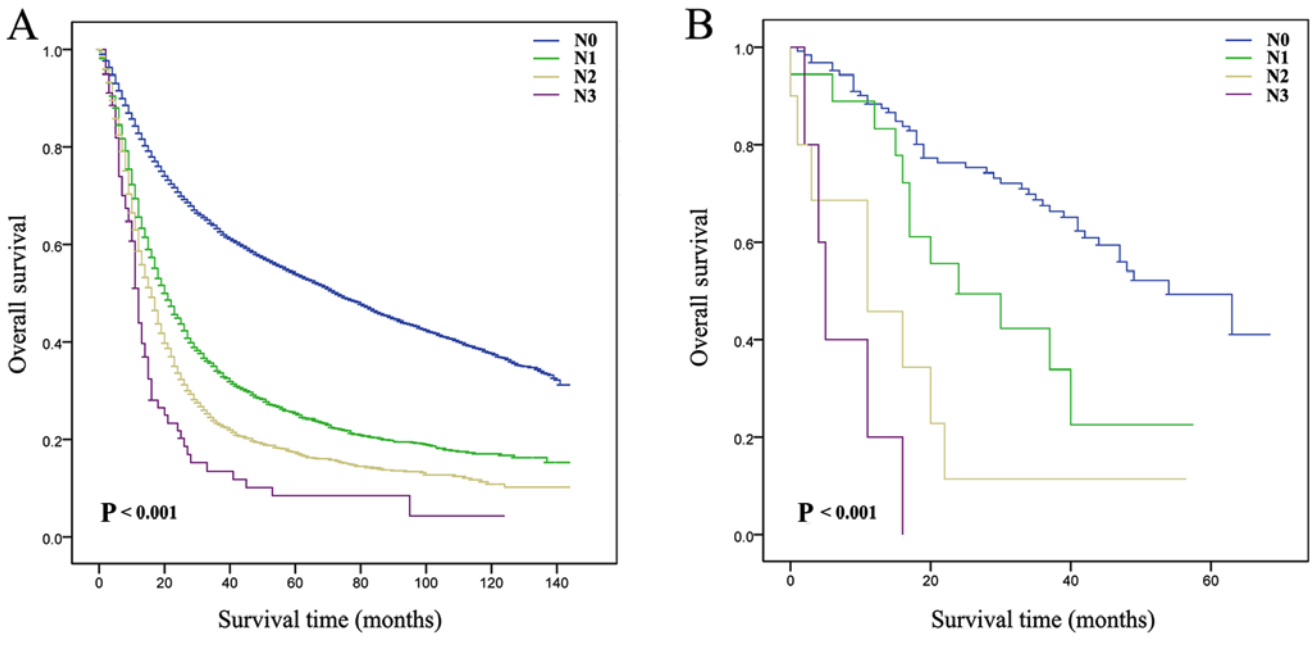

Figure 1. Kaplan-Meier survival curves according to N-stage (N0, N1, N2 and N3) in (A) American patients with BCa from the Surveillance, Epidemiology and End Results database and (B) Chinese patients with BCa from the Urology database of the Shanghai Tenth People's Hospital. BCa, bladder cancer; N, node.

Table II. Univariate and multivariate Cox regression analyses predicting the overall survival of patients with bladder cancer from the SEER database.

	Univariate Cox regression		Multivariate Cox regression	
Characteristic	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age at diagnosis, years				
<68	Reference		Reference	
68-78	1.37 (1.31-1.43)	<0.001	1.39 (1.33-1.46)	<0.001
>78	2.09 (1.98-2.21)	<0.001	1.98 (1.87-2.09)	<0.001
Sex				
Female	Reference		Reference	
Male	0.88 (0.84-0.92)	<0.001	-	0.198
Ethnicity				
White	Reference		Reference	
Black	1.33 (1.23-1.44)	<0.001	1.24 (1.15-1.35)	<0.001
Other	0.83 (0.750.92)	<0.001	0.81 (0.73-0.90)	<0.001
Marital status				
Yes	Reference		Reference	
No	1.26 (1.21-1.31)	<0.001	1.19 (1.14-1.25)	<0.001
SEER stage				
Localized	Reference		Reference	
Regional	2.11 (1.96-2.28)	<0.001	1.47 (1.14-1.90)	0.003
Distant	6.34 (5.77-6.98)	<0.001	2.72 (2.09-3.54)	<0.001
Grade				
I	Reference		Reference	
II	1.48 (1.16-1.89)	0.002	1.26 (0.99-1.67)	0.065
III	1.66 (1.32-2.09)	<0.001	1.38 (1.10-1.74)	0.006
IV	1.48 (1.18-1.86)	0.001	1.28 (1.01-1.61)	0.038
Unknown	1.28 (1.01-1.64)	0.046	1.24 (0.97-1.59)	0.084
Histological type				
Transitional cell carcinoma	Reference		Reference	
Others	1.37 (1.28-1.46)	<0.001	1.22 (1.14-1.31)	<0.001
T-stage[a]				
Ta + Tis	Reference		Reference	
T1	1.02 (0.86-1.21)	0.824	1.04 (0.87-1.25)	0.646
T2	1.30 (1.11-1.53)	0.001	0.90 (0.66-1.22)	0.488
T3	2.84 (2.43-3.34)	<0.001	1.65 (1.22-2.24)	0.001
T4	4.25 (3.62-4.99)	<0.001	2.11 (1.56-2.85)	<0.001
N-stage[a]				
N0	Reference		Reference	
N+	2.41 (2.30-2.51)	<0.001	1.85 (1.76-1.94)	<0.001
M-stage[a]				
M0	Reference		Reference	
M1	3.12 (2.88-3.38)	<0.001	-	0.113
Removed lymph nodes, no.				
≤5	Reference		Reference	
6-12	0.85 (0.80-0.90)	<0.001	0.72 (0.68-0.76)	<0.001
≥13	0.71 (0.68-0.75)	<0.001	0.62 (0.59-0.65)	<0.001

[a]TNM staging (20). Grade I, well differentiated; grade II, moderately differentiated; grade III, poorly differentiated; and grade IV, undifferentiated. CI, confidence interval; SEER, Surveillance, Epidemiology and End Results; T, tumor; N, node; M, metastasis.

Tenth People's Hospital Urology database (Table III). The results from multivariate Cox regression analysis demonstrated that only sex, T-stage and M-stage were not associated with the OS in both American and Chinese patients.

Table III. Univariate and multivariate Cox regression analyses predicting the overall survival of patients with bladder cancer from the Shanghai Tenth People's Hospital Urology database.

	Univariate Cox regression		Multivariate Cox regression	
Characteristic	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age at diagnosis, years				
<68	Reference		Reference	
68-78	1.74 (1.02-2.96)	0.041	1.25 (0.71-2.19)	0.435
>78	3.04 (1.66-5.56)	<0.001	3.60 (1.84-7.05)	<0.001
Sex				
Female	Reference		Reference	
Male	0.85 (0.46-1.58)	0.600	-	0.236
T-stage[a]				
Ta + Tis	Reference		Reference	
T1	1.56 (0.21-11.73)	0.669	1.05 (0.14-8.07)	0.966
T2	2.83 (0.37-21.93)	0.320	1.77 (0.22-14.12)	0.592
T3	4.11 (0.55-30.91)	0.170	2.96 (0.39-22.56)	0.296
T4	7.53 (1.02-55.56)	0.048	4.74 (0.60-37.22)	0.139
N-stage[a]				
N0	Reference		Reference	
N+	3.39 (2.06-5.57)	<0.001	2.40 (1.33-4.35)	0.004
M-stage[a]				
M0	Reference		Reference	
M1	3.33 (1.52-7.28)	0.003	-	0.591
Removed lymph nodes, no.				
≤1	Reference		Reference	
2-7	0.73 (0.44-1.22)	0.236	0.66 (0.39-1.13)	0.131
≥8	0.36 (0.17-0.77)	0.009	0.27 (0.12-0.62)	0.002

[a]TNM staging (20). CI, confidence interval; T, tumor; N, node; M, metastasis.

The number of LNDs was stratified using X-tile software (21). The number of LNDs in American patients from the SEER database was divided as follows: ≤5, 6-12 and ≥13 nodes (Fig. 2A). The number of LNDs in Chinese patients from the Shanghai Tenth People's Hospital database was divided as follows: ≤1, 2-7 and ≥8 nodes (Fig. 3A). The number of LNDs was also stratified according to patients with BCa patients with different N stages. American patients with BCa with N0-stage was classified as: ≤3, 4-10 and ≥11 nodes (Fig. 2B); the N+-stage patients as: ≤6, 7-17 and ≥18 nodes (Fig. 2C). Simultaneously, the same stratified analysis was performed on data from Chinese patients with BCa. Results were as follows: ≤1, 2-6 and ≥7 nodes for N0-stage (Fig. 3B); ≤3, 4-7 and ≥8 nodes for N+-stage (Fig. 3C).

The results from multivariate Cox regression analysis demonstrated that the number of LNDs [6-12 vs. ≤5 nodes, hazard ratio (HR) =0.72, 95% confidence interval (CI)=0.68-0.76; P<0.001; ≥13 vs. ≤5 nodes, HR=0.62, 95% CI=0.59-0.65, P<0.001] was significantly associated with the OS of American patients from the SEER database (Table II). The results from multivariate Cox regression analysis demonstrated that the number of LNDs (≥8 vs. ≤1 nodes, HR=0.27, 95% CI=0.12-0.62, P=0.002) was significantly associated with the OS of Chinese patients from the Shanghai Tenth People's Hospital Urology database (Table III). These findings suggested that higher number of LNDs was a protective factor for patients with BCa who underwent RC.

Effect of LND on the MST of patients with BCa according to N-stage. Patients from the two aforementioned databases were divided into two subgroups according to N-stage, namely N0 and N+. The difference between the number of LNDs and the prognosis of patients with BCa who underwent RC according to the N-stage subgroup was evaluated (Table IV). The number of LNDs in N0 and N+ patients was stratified using X-tile software. The results demonstrated that LND [N0:4-10 vs. ≤3 nodes, HR=0.72, 95% CI=0.68-0.77, P<0.001; ≥11 vs. ≤3 nodes, HR=0.58, 95% CI=0.54-0.61, P<0.001; N+:7-17 vs. ≤6 nodes, HR=0.75, 95% CI=0.68-0.82, P<0.001; ≥18≤6 nodes, HR=0.62, 95% CI=0.56-0.68, P<0.001] remained an independent prognostic factor for the MST of American patients with BCa at different N-stages (Table IV). Among N0 Chinese patients, those in the ≥7 nodes group had increased MST compared with that of patients in the ≤1 node group (43.0 vs. 30.5 months; P=0.226; failed to calculate HR and 95% CI because there was no difference in statistical analysis;

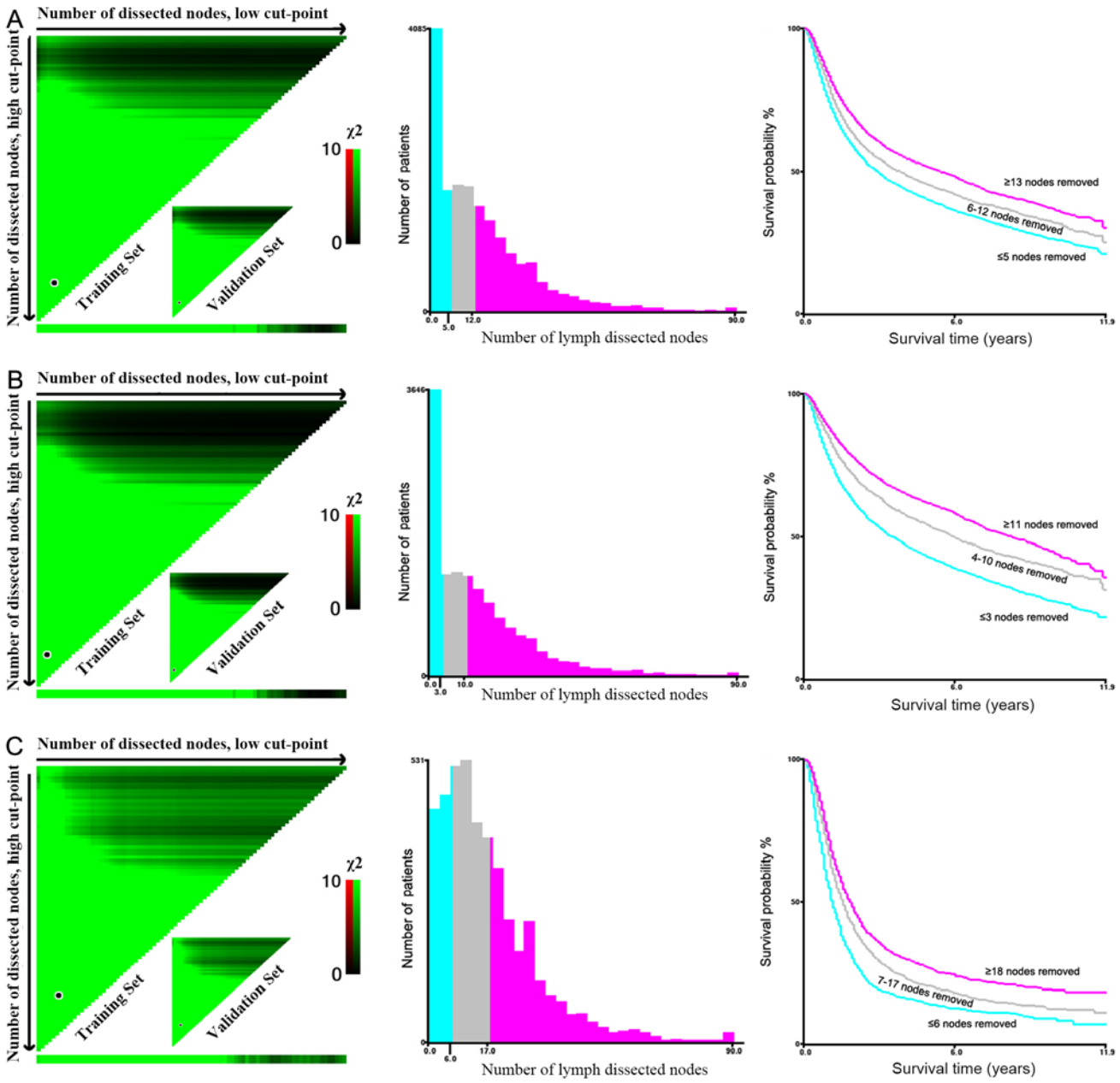

Figure 2. Estimation of the cut-off value for the number of lymph node dissection stratification determined by X-tile software (21). Increasing the number of LNDs will promote OS, regardless of N-stage. Pink represents patients who had ≥13 nodes removed, gray represents patients who had 6-12 nodes removed and blue represents patients who had ≤5 nodes removed. (A) All American patients, (B) American patients with N0 stage and (C) American patients with N+ stage. N, node.

Table IV). In addition, N+ Chinese patients in the ≥8 nodes group had a longer MST compared with that of patients in the ≤3 nodes group (23.5 vs. 10.5 months; HR=0.19, 95% CI=0.07-0.56; P=0.003; Table IV). Furthermore, regarding N0 American patients, those in the ≥11 nodes group had a longer MST compared with that of patients in the ≤3 nodes group (MST, 34.0 vs. 27.0 months; HR=0.58, 95% CI=0.54-0.61; P<0.001; Table IV). Among the American N+ patients, those in the ≥18 nodes group had a longer MST compared with that of patients in the ≤6 nodes group (MST, 17.0 vs. 12.0 months; HR=0.62, 95% CI=0.56-0.68; P<0.001; Table IV). For Chinese patients, only ≥8 nodes was significant for MST in N+-stage patients (HR=0.19, 95% CI=0.07-0.56, P=0.003; Table IV). In addition, the number of LNDs in each N-stage was generally higher in American patients (Table IV).

Discussion

The present study analyzed data from American and Chinese patients with BCa, and demonstrated that LND was an independent prognostic factor for OS. Furthermore, increased number of LNDs was associated with increased survival time. These results were similar to those from previous studies, which reported that extended LND can increase the survival time of patients with BCa who underwent RC, and reduce the recurrence rate (22,23). Numerous studies reported these results in American patients (24,25), although no comparison has been made to date with Chinese patients.

At present, it is usual to divide the LND during RC in patients with BCa into four grades according to the size of the clearing scope as follows: Limited LND, standard LND,

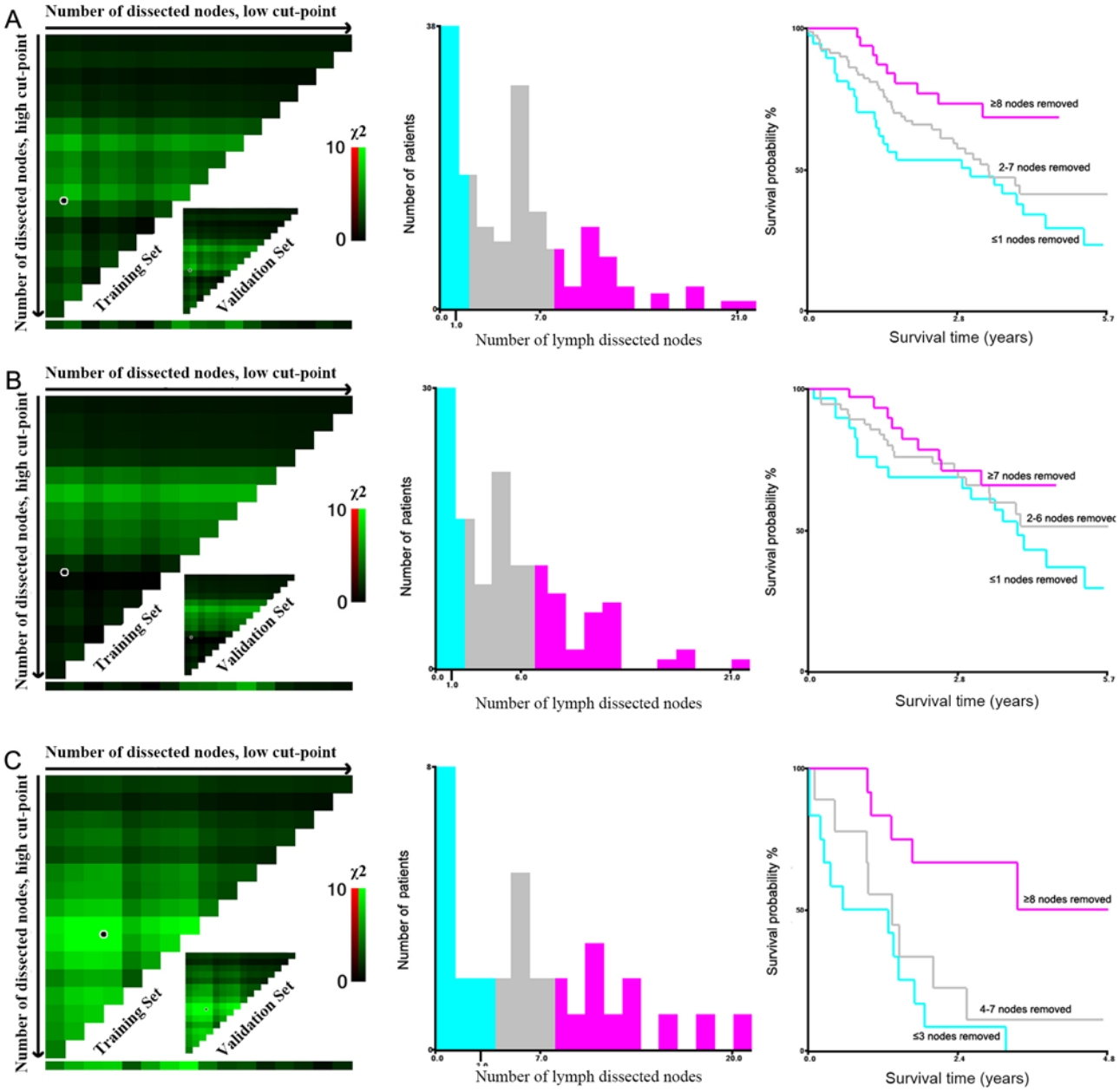

Figure 3. Estimation of the cut-off value for the number of lymph node dissection stratification determined by X-tile software (21). Pink represents patients who had ≥13 nodes removed, gray represents patients who had 6-12 nodes removed and blue represents patients who had ≤5 nodes removed. (A) All Chinese patients, (B) Chinese patients with N0 stage and (C) Chinese patients with N+ stage. N, node.

extended LND and super-extended LND (15). Previous studies reported that expanding the extent and number of LNDs has a crucial impact on the prognostic significance, not only for lymph node-positive patients but also for the postoperative prognosis of lymph node-negative patients (26,27). In addition, it was reported that LND might be an independent prognostic factor for the prognosis of patients with BCa, since extended LND can reduce micrometastasis (28). Dhar *et al* (29) demonstrated that patients with extended LND have a higher lymph node positivity rate (extended lymph node dissection (26%) vs. limited lymph node dissection (13%). Abol-Enein *et al* (30) demonstrated that the 5 year disease-free survival rate of patients undergoing extended LND in a non-randomized prospective cohort study was 66.6% (extended lymphadenectomy) vs. 54.7% (standard lymphadenectomy). In addition, extended LND can also reduce the probability of pelvic organ metastasis (27,31). Although numerous studies reported this result, some controversies exist. Gschwend *et al* (18) demonstrated in a prospective randomized trial that extended LND failed to present a significant advantage over limited LND regarding the recurrence-free survival, cancer-specific survival and OS of patients with BCa. Whether LND may be considered as an independent prognostic factor for BCa remains unclear.

The present study analyzed data from 17,730 American patients with BCa from the SEER database. For comparative analysis, the clinical information of 158 Chinese patients with BCa was collected from the center database of the Shanghai Tenth People's Hospital. One experienced senior surgeon performed operation on all Chinese patients in order to ensure reliable and convincing data, and to avoid unreliable data

Table IV. Multivariate Cox regression analyses for patients stratified by N-stage in the SEER and Shanghai Tenth People's Hospital Urology databases.

A, SEER database

Characteristic	MST, months	Hazard ratio (95% CI)	P-value
N0[a]			
Removed lymph nodes, no.			
≤3	27.0	Reference	
4-10	33.0	0.72 (0.68-0.77)	<0.001
≥11	34.0	0.58 (0.54-0.61)	<0.001
N+[a]			
Removed lymph nodes, no.			
≤6	12.0	Reference	
7-17	15.0	0.75 (0.68-0.82)	<0.001
≥18	17.0	0.62 (0.56-0.68)	<0.001

B, Shanghai Tenth People's Hospital Urology database

Characteristic	MST, months	Hazard ratio (95% CI)	P-value
N0[a]			
Removed lymph nodes, no.			
≤1	30.5	Reference	
2-6	34.0	-	0.919
≥7	43.0	-	0.226
N+[a]			
Removed lymph nodes, no.			
≤3	10.5	Reference	
4-7	16.0	0.59 (0.24-1.48)	0.262
≥8	23.5	0.19 (0.07-0.56)	0.003

[a]TNM staging (20). CI, confidence interval; MST, median survival time; SEER, Surveillance, Epidemiology and End Results; N, node.

deviations from different surgeons. The result from this study demonstrated that N-stage may be considered as a risk factor for the OS of both American and Chinese patients. In addition, the OS of N+ patients was significantly lower compared with that of N0 patients in the two populations. In addition, the survival time was significantly prolonged as the number of LNDs increased for different N-stage patients form the two different populations.

In the present study, the results from multivariate Cox regression analysis demonstrated that the number of LND was correlated with patient's OS time and directly proportional to the postoperative survival benefit. The increased number of LNDs reduced the likelihood of potential lymph node metastases. This increased the possibility of prolonged survival time after surgery. In addition, the median number of LNDs in American patients was significantly higher compared with that in Chinese patients (11.0 vs. 5.0 nodes). These findings suggested that the removal of a larger quantity of lymph nodes increased the patients' survival. These results were consistent with those from previous reports (32,33). Furthermore, it has been reported that extended LND can reduce the risk of recurrence and tumor burden (34). Extended LND can provide survival benefit in patients and facilitate the collection of other prognostic information, including tumor burden, lymph node density and lymph node extracapsular infiltration (9,10,17). The present study also demonstrated that the number of LNDs in Chinese patients was generally low compared with that in American patients. It could therefore be recommended that surgeons expand the range of LND in order to increase the number of LNDs during radical resection in patients with BCa. This may increase the patients' OS time and reduce the disease recurrence rate.

Stratified analysis demonstrated that, different LND groups could achieve better survival benefits compared to ≤3 groups (N0-stage) and ≤6 groups (N+stage) for American patients with different N-stage (P<0.001). For Chinese patients, only the ≥8 nodes group had a longer MST compared with the ≤6 groups in N+stage (P=0.003). The minimum number of LNDs according to data from the Shanghai Tenth People's Hospital database was only 1 node. The median LND for American patients was more than twice the median LND for Chinese patients. In addition, the median LND in Chinese patients was ≤6 nodes, which the number in SEER database analysis presented a worse prognosis

and a shorter OS time in American patients. These observations may be due to the lack of universal robot surgery in Shanghai Tenth People's Hospital and inaccurate postoperative pathological lymph node count. The lack of awareness by our institution (Department of Urology, Shanghai Tenth People's Hospital) about the prognostic value of LND may explain these results.

This study presented some limitations. Firstly, the SEER database is a retrospective dataset with limitations inherent to retrospective research, for example retrospective analysis is prone to selection and recall bias (35). Moreover, the data from the SEER database were collected by different cancer centers and, depending on the statistician, there may be selection bias. Secondly, data from Chinese patients were only collected from Shanghai Tenth People's Hospital and may therefore not be representative of all Chinese patients with BCa. Thirdly, information of only 158 Chinese patients was collected, which is a small sample size. Further multicenter prospective clinical trials are therefore required.

In conclusion, the present study demonstrated that the number of LNDs was an independent prognostic factor for the survival of patients with BCa. In addition, an increased number of LNDs had a protective effect on the OS of patients with BCa. Furthermore, the number of LNDs in Chinese patients was lower compared with that in American patients. The number of LNDs should therefore be increased when treating patients with BCa in China.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KW, HS, WM and BP were involved in the study conception and design. LY, WL and JX obtaining and performing relevant statistical analysis from two databases . KW, GW and DF were involved in data analysis and interpretation. KW and BP wrote the manuscript.

Ethics approval and consent to participate

The study protocol was approved by The Biomedical Ethics Committee of the Tenth People's Hospital in Shanghai. Written informed consent was obtained from the patients or their next of kin if the patient did not have the ability to sign due to lack of consciousness or physical difficulties. All authors read and approved the final manuscript.

Patient consent for publication

Written informed consent was obtained from each patient prior to publication.

Competing interests

The authors declare that they have no competing interests.

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