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Impact of lymph node dissection in radical cystectomy for bladder cancer: How many vs how far?

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ABSTRACT

Purpose: To determine whether the extent or number of lymph nodes (LNs) is important in muscle-invasive bladder cancer and high-risk non-muscle-invasive bladder cancer patients' oncologic outcomes.
Methods: A total of 448 patients who underwent radical cystectomy with lymphadenectomy of standard, extended, and super-extended template were included. Exclusion criteria were neoadjuvant chemotherapy and limited lymphadenectomy. Disease-free survival (DFS) including local recurrence and distant metastasis, cancer-specific survival (CSS), and overall survival (OS) were estimated using the Kaplan-Meier method. Cox hazard regression was applied to analyze risk factors.
Results: Standard (n = 124), extended (n = 216), and super-extended group (n = 108) did not show significant differences in the estimated 5-year DFS, CSS and OS rates. On multivariate analysis, the number of removed LNs was a significant factor for distant metastasis-free (hazard ratio [HR] 0.981, p = 0.0222), CSS (HR 0.980, p = 0.0021) and OS (HR 0.984, p = 0.0032). However, the template was not significant in distant metastasis-free survival, CSS and OS. On Kaplan-Meier curve, the number of removed LN showed significant differences in DFS, CSS, and OS. In the subgroup of positive LNs, number of removed LNs was associated with favorable DFS (HR = 0.969, p = 0.0115), CSS (HR = 0.967, p = 0.0068) and OS (HR = 0.971, p = 0.0028).
Conclusion: The number of removed LNs was a more important factor for CSS and OS than the extent of lymphadenectomy. Meticulous and extended LN dissection can be helpful in controlling recurrence, and its survival benefit might be maximized in cases with positive LN. Meanwhile, the survival benefit of super-extended lymphadenectomy was limited for this patient population.

1. Introduction

Bladder cancer is the ninth most common malignancy worldwide, with an incidence of approximately 429,793 in 2012 [1]. Bilateral pelvic lymphadenectomy is currently the standard treatment modality in cases indicated for radical cystectomy [2]. Recent guidelines recommend extended lymphadenectomy, i.e., the removal of the bilateral common iliac, external iliac, internal iliac, and obturator lymph nodes (LNs) [2]. The incidence of regional LN metastasis during radical cystectomy for bladder cancer as defined according to the stage of primary tumor, number of LNs retrieved, and extent of lymphadenectomy is between 13% and 30% [3]. The use of computerized tomography or positron emission tomography for staging is limited by its low sensitivity to detect LN metastasis [4,5]. Because regional LN metastasis is associated with an increased risk of recurrence and disease-specific death, lymphadenectomy plays a crucial role in accurate staging and identifying patients who may benefit from adjuvant treatment [6]. Moreover, more extensive lymphadenectomy and higher number of removed LNs were associated with improved staging accuracy [7,8].

In the present study, we aimed to determine LN-associated factors for predicting oncologic outcomes. We compared the clinical outcomes among three lymphadenectomy templates in patients with muscle-invasive bladder cancer and high-risk non-muscle-invasive bladder cancer to determine whether the extent or volume of LN plays an important role in patient outcomes.

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2. Materials and methods

2.1. Patient selection

The study protocol was approved by the Institutional Review Board of the Asan Medical Center (2016–0103). The need for informed consent was waived owing to the retrospective nature of the study. Between January 2006 and August 2014, 502 patients underwent radical cystectomy with bilateral retroperitoneal/pelvic lymphadenectomy for bladder cancer at our institution. Fifty-four patients who had received neoadjuvant chemotherapy or underwent limited lymphadenectomy were excluded. The medical records of the 448 remaining patients were reviewed, and information on their demographic characteristics and perioperative variables was obtained. According to the extent of lymphadenectomy, 124 patients were designated in the standard group, 216 in the extended group, and 108 in the super-extended group.

2.2. Surgical treatment and pathologic evaluation

Urinary diversions, including ileal conduit diversions and orthotopic bladder substitutions, were performed after radical cystectomy and bilateral retroperitoneal/pelvic lymphadenectomy. The operations were performed by 3 surgeons that had average annual surgeon volume of 18.6 cases during 10 years. The extent of lymphadenectomy was determined according to the surgeon's discretion and according to current trend. The boundaries of standard lymphadenectomy include bifurcation of the common iliac vessels cranially, the genitofemoral nerve laterally, the circumflex iliac vein and Cloquet's node caudally, the obturator fossa with full exposure of the intrapelvic course of the obturator nerve (Marcille's triangle) and the internal iliac vessels posteriorly, and the bladder medially. In level 1, individual LN packets include the external iliac, obturator, and internal iliac nodes. The boundaries of extended lymphadenectomy extended up to the crossing of the ureters with common iliac arteries or bifurcation of the inferior vena cava/aorta. In level 2, additional LN packets include the common iliac and/or presacral. The boundaries of super-extended lymphadenectomy are extended up to the inferior mesenteric artery cranially. In level 3, additional LN packets include the paracaval, inter-aortocaval, and para-aortic nodes. All nodal tissue removed from each packet was submitted separately and identified visually and via manual palpation without fat-clearing solution. The cystectomy specimens were processed according to standard pathology procedures, and pathology slides were reviewed by our expert genitourinary pathologists. The cystectomy specimens were pathologically staged and graded according to the 2009 American Joint Committee on Cancer TNM staging and 1973 WHO grading systems. LNs were examined for the total number of LNs, the number of positive LNs, and the site of positive LNs. Skip metastasis was defined as LN metastasis at level 2 or 3 without level 1 [9].

2.3. Follow-up strategy

Following radical cystectomy, patients were generally followed up every 3 months during the first year, every 6 months during years 2–6, and annually thereafter. Follow-up consisted of history-taking; physical examination; blood laboratory investigations; and urine sedimentation, culture, and cytology. Follow-up imaging included chest X–ray, computerized tomography, and bone scan at 6 and 12 months and annually thereafter. Pelvic soft tissue or LN inferior to the aortic bifurcation was defined as local recurrence, and all other sites were classified as distant metastasis. Urothelial carcinoma that occurred in the upper urinary tract or urethra was not considered as recurrence. The median duration from the operation date to the last follow-up date was 41.6 months (interquartile range [IQR]: 11.3–68.9 months).

2.4. Statistical analysis

Clinicopathologic characteristics were compared among the three groups using the Chi-square test for categorical variables and the *t*-test or Mann Whitney *U* test for continuous variables. The Shapiro-Wilk test was used to check the assumption of normality. The baseline characteristics of the patients and tumors were described as means ± standard deviation with IQR or numbers with percentages. Disease-free survival (DFS) was calculated as the time from radical cystectomy to the first documented disease recurrence. Patients who were alive or who died were censored at the date of last follow-up or death. DFS, cancer specific survival (CSS), and overall survival (OS) were estimated using Kaplan-Meier methods with log-rank tests according to established cutoff number of removed LNs. Harrell's concordance index (*C* index) was used to evaluate the discrimination of the survival analysis [10]. A *C* index of 1.0 implies perfect predictive accuracy while a *C* index of 0.5 represents agreement due to chance. A Cox proportional hazards regression model was used to estimate the prognostic significance of each variable. All statistical analyses were performed using IBM SPSS Statistics Version 21 (IBM Corporation, Somers, NY, USA) and R version 3.4.3 (R Project for Statistical Computing; http://www.r-project.org/). The R package “maxstat” was used to determine the cut-off value that resulted in maximal separation of Kaplan-Meier curves when stratified by the variables of interest [11]. All statistical tests were 2-tailed, with $p < 0.05$ considered significant.

3. Results

The clinicopathological characteristics according to the templates are presented in Table 1. There were no differences in age, sex, clinical and pathologic T stage, clinical LN positive, histologic variants, lymphovascular invasion and soft tissue margin status (all, $p > 0.05$). Charlson comorbidity index of ≥2 was related to a larger ratio in the standard group than in the others (both, $p < 0.05$). As time went on, the ratio of standard template decreased in comparison to the extended template ($p = 0.003$), but the ratio of super-extended template increased in comparison to the standard ($p < 0.001$). The median number of LNs removed in the standard, extended, and super-extended group was 14, 25, and 41, respectively ($p < 0.001$). Overall, 18.5% of patients in the standard group, 30.1% in the extended group, and 26.9% in the super-extended group had LN metastasis. A total of 11.6% of patients in extended group had level 2, and only one case of skip metastasis was noted. Meanwhile, 25.0% of patients in the super-extended group had level 2 and 3, and 3 cases of skip metastasis were noted.

At the time of analysis, 168 (37.5%) patients had disease recurrence, 144 (32.1%) patients had died from bladder cancer, and 214 (57.8%) patients had died from other cause. In Fig. 1, the estimated 5-year DFS rates were 57.7%, 63.8%, and 58.0% for the standard, extended, and super-extended group, respectively ($p = 0.516$). Meanwhile, the estimated 5-year CSS rates were 67.6%, 66.7%, and 68.3% for the standard, extended, and super-extended group, respectively ($p = 0.979$). The estimated 5-year OS rates were 59.3%, 57.5%, and 55.5% for the standard, extended, and super-extended group, respectively ($p = 0.803$). On multivariate analysis (Table 2), template and number of removed LNs were not significant risk factors for local recurrence-free survival. However, the number of removed LNs (hazard ratio [HR] = 0.981, 95% confidence interval [CI]: 0.965–0.997, $p = 0.0222$) was a risk factor for distant metastasis-free survival. The number of removed LNs was associated with CSS (HR = 0.980, 95% CI: 0.967–0.993, $p = 0.0021$) and OS (HR = 0.984, 95% CI: 0.974–0.995, $p = 0.0032$). Contrastively, template was not a significant determinant of distant metastasis-free survival, CSS and OS.

On the Kaplan-Meier curve (Fig. 2), > 26 removed LNs showed better DFS compared to ≤26 removed LNs ($p = 0.0159$). In addition, > 26 removed LNs displayed superior CSS ($p = 0.0030$) and > 27

Table 1
Clinicopathological characteristics according to templates.

	Standard (N = 124)	Extended (N = 216)	Super-extended (N = 108)	P value	
				Extended vs Standard	Super-extended vs Standard
Age (years), Mean ± SD (median, IQR)	63.4 ± 10.4 (66.0, 56.0–71.0)	63.9 ± 9.5 (65.0, 56.0–71.5)	63.6 ± 9.9 (65.5, 59.0–70.5)	0.649	0.879
Male gender	103 (83.1%)	191 (88.4%)	89 (82.4%)	0.220	1.000
Charlson comorbidity index				**0.015**	**0.043**
0	82 (66.1%)	162 (75.0%)	77 (71.3%)		
1	21 (16.9%)	39 (18.1%)	24 (22.22%)		
≥2	21 (16.9%)	15 (6.9%)	7 (6.5%)		
Clinical T stage				0.865	0.168
≤2	72 (58.1%)	122 (56.5%)	52 (48.1%)		
≥3	52 (41.9%)	94 (43.5%)	56 (51.9%)		
Clinical LN positive	9 (7.3%)	27 (12.5%)	17 (15.7%)	0.192	0.070
Year of operation				**0.003**	**< 0.001**
2006–2008	62 (50.0%)	83 (38.4%)	7 (6.5%)		
2009–2011	46 (37.1%)	71 (32.9%)	68 (63.0%)		
2012–2014	16 (12.9%)	62 (28.7%)	33 (30.6%)		
Pathologic T stage				1.000	0.173
≤2	65 (52.4%)	114 (52.8%)	46 (42.6%)		
≥3	59 (47.6%)	102 (47.2%)	62 (57.4%)		
Pathology				**0.012**	0.237
UC	119 (96.0%)	216 (100.0%)	107 (99.1%)		
Adenocarcinoma	2 (1.6%)	0 (0.0%)	1 (0.9%)		
Squamous cell carcinoma	3 (2.4%)	0 (0.0%)	0 (0.0%)		
Histologic variants in UC	17 (14.3%)	39 (18.1%)	25 (23.4%)	0.375	0.091
High grade	97 (78.2%)	197 (91.2%)	99 (91.7%)	**0.001**	**0.008**
Lymphovascular invasion	47 (38.2%)	101 (46.8%)	54 (50.0%)	0.158	0.095
Removed LN, Mean ± SD (median, IQR)	14.5 ± 7.6 (14.0, 9.0–20.0)	25.3 ± 11.4 (25.0, 16.0–32.0)	42.5 ± 15.7 (41.0, 30.5–52.5)	**< 0.001**	**< 0.001**
Positive LN, Mean ± SD (median, IQR)	0.7 ± 2.2 (2.0, 1.0–4.5)	1.3 ± 3.0 (3.0, 2.0–6.0)	3.7 ± 11.1 (5.0, 2.0–20.0)	**0.029**	**0.006**
Anatomical level of positive LN					
Level 1	23 (18.5%)	64 (29.6%)	26 (24.1%)		
Level 2	0 (0.0%)	25 (11.6%)	13 (12.0%)		
Level 3	0 (0.0%)	0 (0.0%)	14 (13.0%)		
Soft tissue margin status	1 (0.8%)	3 (1.4%)	0 (0.0%)	1.000	1.000
Adjuvant chemotherapy	23 (18.9%)	65 (30.4%)	32 (29.6%)	**0.029**	0.079
Recurrence	49 (39.5%)	75 (34.7%)	44 (40.7%)	0.443	0.956
Local recurrence	14 (11.3%)	23 (10.6%)	6 (5.6%)		
Distant metastasis	32 (25.8%)	47 (21.8%)	34 (31.5%)		
Both	3 (2.4%)	5 (2.3%)	4 (3.7%)		
Cancer specific death	42 (33.9%)	67 (31.0%)	35 (32.4%)	0.673	0.923
Overall death	62 (50.0%)	98 (45.4%)	54 (50.0%)	0.477	1.000

IQR, interquartile range; SD, standard deviation; LN, lymph node; UC urothelial carcinoma.

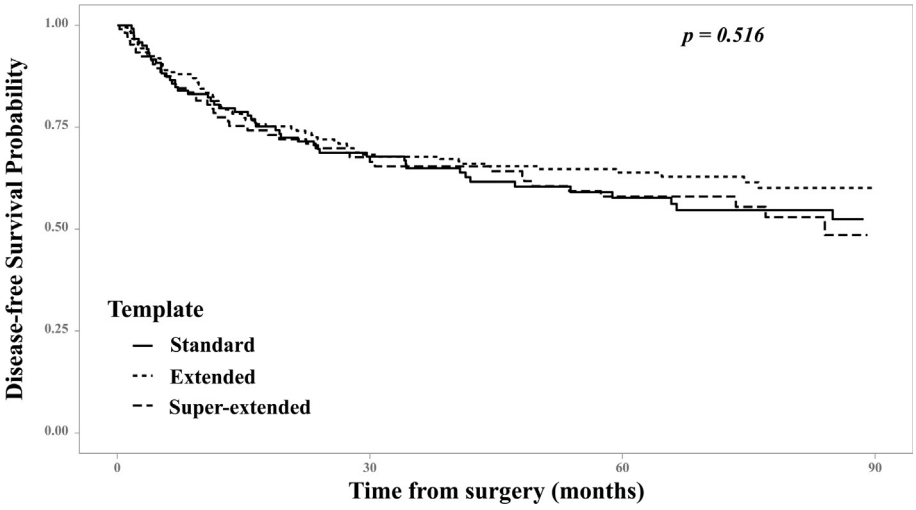


Fig. 1. Kaplan-Meier curves for survivals according to the template. (A) Disease-free survival (B) Cancer-specific survival. (C) Overall survival.

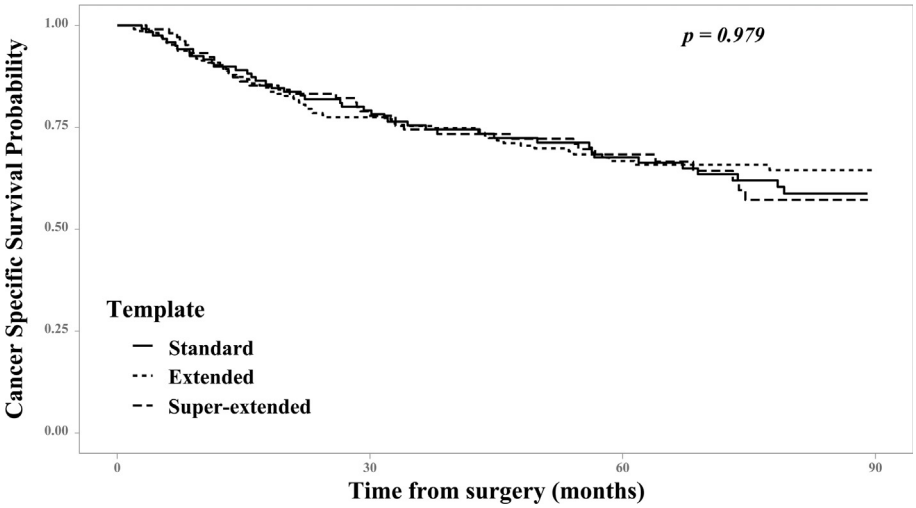


Fig. 1. (*continued*)

removed LNs showed better OS (p = 0.0087). The *C* indices for each cutoff value of removed LNs with pathologic TN stage were 0.7165 (> 26 for DFS), 0.7297 (> 26 for CSS), and 0.7240 (> 27 for OS).

In the subgroup of patients with positive LNs (Table 3), the number of removed LNs (HR = 0.969, 95% CI: 0.946–0.993, p = 0.0115) was associated with favorable DFS, while template (super-extended vs standard; HR = 4.083, 95% CI: 1.505–11.076, p = 0.0057) was associated with poor DFS. The number of removed LNs was associated with CSS (HR = 0.967, 95% CI: 0.944–0.991, p = 0.0068) and OS (HR = 0.971, 95% CI: 0.953–0.990, p = 0.0028). In the subgroup of patients with no positive LNs (Table 3), template and the number of removed LNs did not show significant impact on DFS, CSS, and OS.

4. Discussion

Since a possible curative role of pelvic lymphadenectomy was first reported in 1982 [12], the therapeutic value of lymphadenectomy in bladder cancer remains a topic of debate. Despite the large consensus supporting more extensive lymphadenectomy to achieve an accurate lymph node staging, the level of survival benefit from extensive lymphadenectomy and the optimal extent of lymphadenectomy remain controversial [13]. This lack of consensus is mainly due to a lack of prospective randomized studies. We hypothesized that super-extended lymphadenectomy may show better oncologic outcomes than standard lymphadenectomy because super-extended lymphadenectomy could cover a wide range of malignant area, thus covering LN metastasis. Contrary to our hypothesis, super-extended or extended lymphadenectomy did not make significant impact on local recurrence, distant metastasis, CSS, and OS compared to standard lymphadenectomy. We found that a high number of removed LNs could be associated with low HR for CSS and OS. We investigated local recurrence and distant metastasis among the total cases of recurrence and found that the significantly long DFS might have resulted from the decreased HR of distant metastasis in the multivariate analysis. The number of removed LNs was a significant risk factor for recurrence in the subgroup of patients with positive LN metastasis, but not in those with negative LN metastasis. This means that the removal of several LNs can help physicians to determine hidden positive LNs as well as to accurately diagnose patients, and consequentially may improve oncologic outcomes. Previous studies also showed that greater number of removed LNs was associated with more favorable outcomes [14].

There are several possible explanations for the oncological usefulness of removal of several LNs. First, accurate stage may induce the Will Rogers effect, that is, real N0 patients could show better oncologic outcomes than patients with hidden LN metastasis [15]. Second, meticulous removal of several LNs may have a therapeutic role by removing pathologically detectable and undetectable micrometastasis. Third, most patients with positive LNs receive adjuvant chemotherapy. In our subgroup of patients with positive LN metastasis, adjuvant chemotherapy significantly recued the risk for OS (HR = 0.683), which

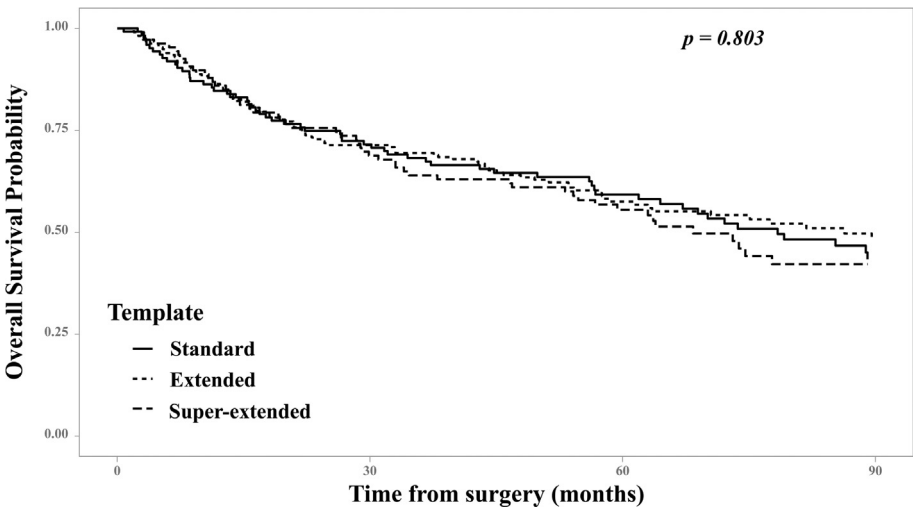


Fig. 1. (*continued*)

Table 2
Multivariate analyses using Cox proportional hazards models for predicting factors on survivals.

	Local recurrence-free survival		Distant metastasis-free survival		Cancer specific survival		Overall survival	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age (continuous)	1.004 (0.976–1.033)	0.7609	1.015 (0.997–1.034)	0.1020	1.021 (1.003–1.040)	**0.0201**	1.036 (1.020–1.051)	< **0.0001**
Comorbidity index (≥ 2 vs ≤ 1)	1.138 (0.459–2.819)	0.7803	0.725 (0.367–1.430)	0.3533	0.747 (0.404–1.383)	0.3537	1.139 (0.739–1.755)	0.5554
pT stage (≥ T3 vs ≤ T2)	2.486 (1.344–4.598)	**0.0037**	2.503 (1.609–3.894)	< **0.0001**	2.605 (1.721–3.944)	< **0.0001**	2.606 (1.862–3.647)	< **0.0001**
pN stage (N1 vs N0)	0.658 (0.206–2.102)	0.4804	1.515 (0.794–2.890)	0.2080	1.125 (0.577–2.193)	0.7291	1.763 (1.081–2.877)	**0.0232**
pN stage (N2 vs N0)	1.446 (0.510–4.101)	0.4876	2.662 (1.532–4.625)	**0.0005**	1.5720 (0.851–2.902)	0.1483	2.623 (1.701–4.046)	< **0.0001**
pN stage (N3 vs N0)	1.566 (0.495–4.953)	0.4454	3.036 (1.763–5.229)	**0.0001**	1.906 (1.002–3.624)	**0.0492**	2.370 (1.433–3.921)	**0.0008**
Template (Extended vs standard)	0.870 (0.418–1.814)	0.7109	0.806 (0.497–1.307)	0.3815	0.992 (0.629–1.564)	0.9725	1.009 (0.696–1.463)	0.9612
Template (Super-extended vs standard)	0.727 (0.234–2.263)	0.5825	1.735 (0.915–3.293)	0.0916	1.276 (0.674–2.417)	0.4538	1.368 (0.814–2.300)	0.2365
Number of removed LN (continuous)	0.973 (0.903–1.048)	0.4671	0.981 (0.965–0.997)	**0.0222**	0.980 (0.967–0.993)	**0.0021**	0.984 (0.974–0.995)	**0.0032**
Number of positive LN (continuous)	0.981 (0.914–1.053)	0.5940	1.018 (0.989–1.047)	0.2359	1.029 (1.007–1.051)	**0.0097**	1.023 (1.001–1.045)	**0.0386**
High grade (yes vs no)	0.562 (0.230–1.375)	0.2071	0.654 (0.337–1.266)	0.2071	0.880 (0.467–1.661)	0.6942	0.773 (0.480–1.245)	0.2892
Lymphovascular invasion (yes vs no)	1.005 (0.519–1.944)	0.9889	1.867 (1.200–2.905)	**0.0056**	1.866 (1.274–2.732)	**0.0013**	1.363 (0.997–1.881)	0.0599
Concomitant carcinoma in situ (yes vs no)	1.086 (0.608–1.942)	0.7801	1.319 (0.899–1.936)	0.1567	1.103 (0.770–1.580)	0.5920	0.941 (0.698–1.271)	0.6934
Adjuvant chemotherapy (yes vs no)	2.770 (1.560–4.917)	**0.0005**	1.458 (0.882–2.411)	0.1415	2.114 (1.462–3.057)	**0.0001**	1.209 (0.828–1.765)	0.3255

CI, confidence interval; HR, hazard ratio; LN, lymph node.

may result in better survival of patients in whom several LNs are removed. Fourth, patients who had more LNs in the same template may have a more robust immune system [16]. On the contrary, mortality differences associated with differing LN counts could be attributed to differences in competing mortality [17]. Healthier patients could have a higher probability of receiving a more extensive LN dissection.

Only few studies compared the outcomes between the number of removed LNs and extent of lymphadenectomy. Simone et al. [7] compared two prospective series composed of extended and standard templates. On their multivariate analysis, the template was a more important factor for DFS and CSS than the number of removed LNs. They concluded that extended lymphadenectomy should be carried out instead of the standard template. Brunocilla et al. [18] retrospectively evaluated 282 patients who either underwent no lymphadenectomy, extended lymphadenectomy, or super-extended lymphadenectomy. On their multivariate analysis, extended or super-extended lymphadenectomy and number of positive LNs were significant factors for CSS. They suggested that in terms of number of removed LNs and template of dissection, extended lymphadenectomy could be associated with better CSS. Both these studies suggest an extended template rather than the standard template in radical cystectomy. Although our results did not show significance in the Cox model, we do not oppose their findings. The greater number of removed LN in only the standard template was not associated with favorable survival [19]. The proper set-up of the extent of LN dissection is important to obtain proper number of removed LN [20]. Since the cutoff values that we calculated in the Kaplan-Meier curves were at least more than 26, extended lymphadenectomy is needed to reach the cutoff value. Our question is about the usefulness of super-extended lymphadenectomy. There were total 4 cases of skip LN metastasis, but there was only one case without level 2 LN metastasis or clinical LN metastasis. Zehnder et al. [21] reported that meticulous extended lymphadenectomy showed oncologic outcomes similar to super-extended lymphadenectomy. In addition, LN mapping researches displayed a few cases in level 3, and there was very few skip LN metastasis [22,23].

The present study has some limitations. First, our findings are subject to the inherent biases due to the nonrandomized nature of the study. A statistically significant difference was observed for the Charlson comorbidity index. Though, not statistically significant, there was a trend towards clinical positive LN in super-extended group ($p = 0.07$). Gschwend et al. [24] reported the result of the first randomized surgical phase-3 trial. Extended lymphadenectomy did not show significant improvement in DFS, CSS, and OS. In addition, SWOG S1011 trial will answer this question in approximately 2022 year. Second, different pathological compositions and high-grade tumor characteristics among the templates may lead to selection bias. However, non-urothelial carcinomas of bladder are rare, and lymphadenectomy is also recommended in non-urothelial carcinomas [2,25]. The reverse result of high-grade tumor in the DFS of the positive LN cohort (Table 3) was because most of the positive LN cohort had high-grade tumors. In addition, different surgeon volume by surgeon and different temporal trend by period could also cause selection bias. The proportion of positive LN was higher in patients who underwent more extensive lymphadenectomy, which might be related to the higher rate of clinical positive LN and higher detection rates. Third, treatment after radical cystectomy including adjuvant therapy was not controlled. Adjuvant therapy had a significant impact on survival; thus we adjusted the variables of template and removed LN by adjuvant therapy. The number of removed LN showed still significant results in positive LN cohort (Table 3). Our study has the advantage of being conducted in a single institutional cohort with standardized pathologic work-up to evaluate the impact of anatomically defined lymphadenectomy templates with regard to clinical outcome in patients undergoing radical cystectomy for bladder cancer.

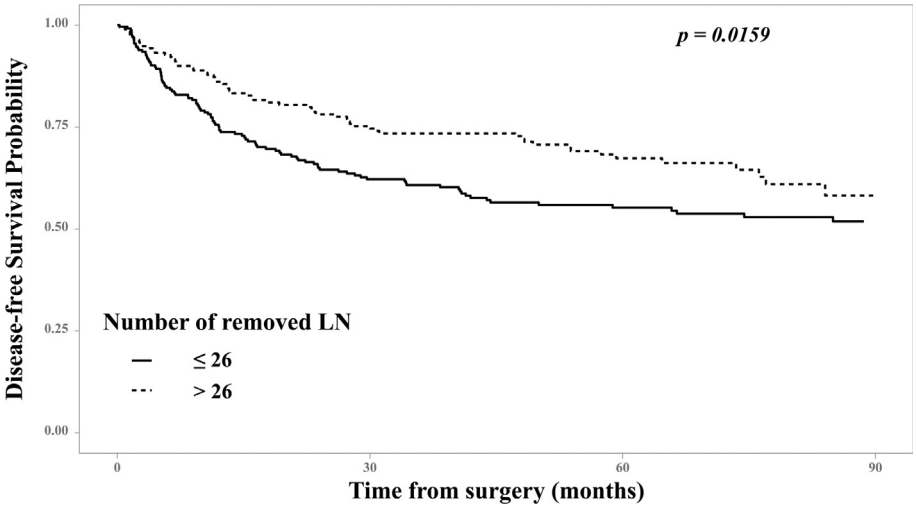
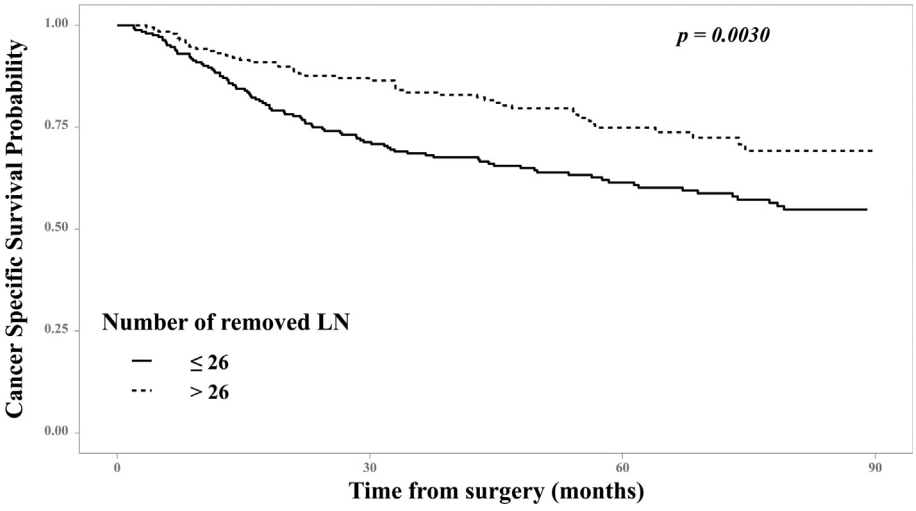


Fig. 2. Kaplan-Meier curves for survivals according to the number of lymph nodes removed. (A) Disease-free survival (B) Cancer-specific survival. (C) Overall survival.



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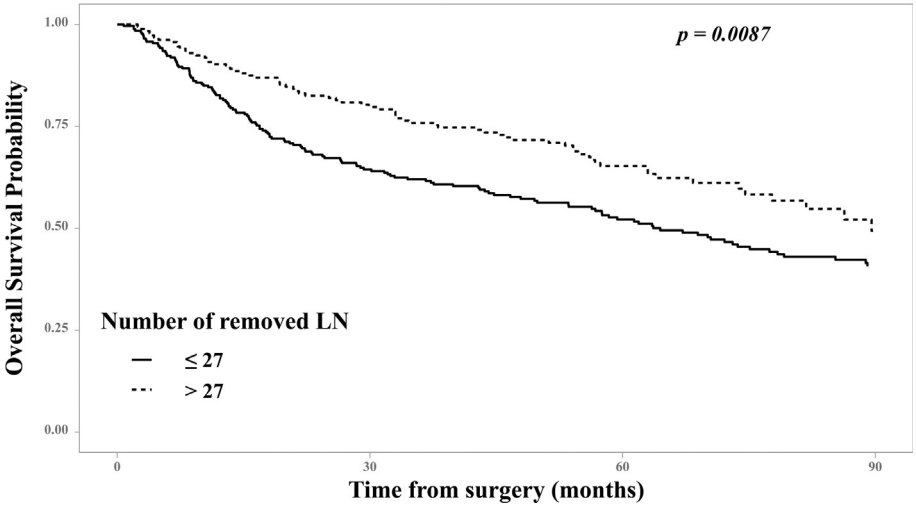

Fig. 2. (*continued*)

Table 3
Multivariate analyses using Cox proportional hazards models for predicting factors on disease-free, cancer specific and overall survival in patients who had positive lymph node and negative lymph node.

	Positive lymph node cohort						Negative lymph node cohort					
	Disease-free survival		Cancer specific survival		Overall survival		Disease-free survival		Cancer specific survival		Overall survival	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age (continuous)	1.011 (0.984–1.039)	0.4313	1.025 (0.995–1.055)	0.0990	1.024 (1.001–1.047)	**0.0451**	1.015 (0.994–1.037)	0.1657	1.020 (0.996–1.046)	0.1089	1.037 (1.016–1.059)	**0.0006**
Comorbidity index (≥2 vs ≤ 1)	0.603 (0.215–1.690)	0.3358	0.655 (0.222–1.929)	0.4425	1.047 (0.504–2.175)	0.9024	0.697 (0.335–1.454)	0.3363	0.714 (0.324–1.575)	0.4038	1.140 (0.641–2.027)	0.6558
pT stage (≥T3 vs ≤ T2)	3.226 (1.472–7.073)	**0.0034**	2.161 (1.016–4.595)	**0.0453**	1.645 (0.876–3.088)	0.1214	2.697 (1.753–4.150)	**< 0.0001**	2.983 (1.831–4.859)	**< 0.0001**	2.855 (1.919–4.248)	**< 0.0001**
pN stage (N2 vs N1)	2.658 (1.302–5.426)	**0.0073**	1.843 (0.822–4.131)	0.1377	1.778 (0.934–3.383)	0.0796	NA		NA		NA	
pN stage (N3 vs N1)	1.990 (1.000–3.958)	**0.0499**	1.434 (0.641–3.211)	0.3805	1.275 (0.664–2.452)	0.4656	NA		NA		NA	
Template (Extended vs standard)	1.623 (0.764–3.449)	0.2079	1.487 (0.671–3.294)	0.3287	1.175 (0.619–2.232	0.6214	0.640 (0.381–1.074)	0.0912	0.783 (0.443–1.384)	0.4001	0.898 (0.559–1.442)	0.6554
Template (Super-extended vs standard)	4.083 (1.505–11.076)	**0.0057**	2.532 (0.870–7.372)	0.0885	1.649 (0.679–4.005)	0.2689	0.730 (0.340–1.568)	0.4202	0.880 (0.382–2.029)	0.7640	1.298 (0.661–2.547)	0.4491
Number of removed LN (continuous)	0.969 (0.946–0.993)	**0.0115**	0.967 (0.944–0.991)	**0.0068**	0.971 (0.953–0.990)	**0.0028**	0.747 (0.427–1.308)	0.3075	0.987 (0.972–1.003)	0.1243	0.989 (0.975–1.002)	0.0915
Number of positive LN (continuous)	1.019 (0.987–1.051)	0.2471	1.034 (1.005–1.063)	**0.0197**	1.036 (1.013–1.059)	**0.0020**	NA		NA		NA	
High grade (yes vs no)	0.249 (0.092–0.672)	**0.0061**	0.441 (0.174–1.119)	0.0849	0.736 (0.298–1.817)	0.5064	1.115 (0.570–2.180)	0.7509	1.389 (0.611–3.160)	0.4334	0.872 (0.493–1.543)	0.6383
Lymphovascular invasion (yes vs no)	0.858 (0.382–1.925)	0.7099	1.335 (0.600–2.971)	0.4792	1.213 (0.642–2.292)	0.5510	1.699 (1.115–2.588)	**0.0137**	1.766 (1.104–2.827)	**0.0177**	1.431 (0.984–2.082)	0.0607
Concomitant carcinoma in situ (yes vs no)	1.331 (0.752–2.356)	0.3261	0.919 (0.802–1.683)	0.7850	0.773 (0.467–1.279)	0.3160	1.310 (0.864–1.988)	0.2040	1.296 (0.814–2.064)	0.2751	1.124 (0.765–1.653)	0.5509
Adjuvant chemotherapy (yes vs no)	0.683 (0.363–1.283)	0.2357	0.558 (0.306–1.016)	0.0564	0.605 (0.376–0.974)	**0.0386**	NA		NA		NA	

CI, confidence interval; HR, hazard ratio; LN, lymph node; NA, not analyzed.

5. Conclusion

In patients who underwent radical cystectomy with lymphadenectomy, the number of removed LN was a more important factor for CSS and OS than the extent of lymphadenectomy. Meticulous and massive LN dissection could be helpful in controlling recurrence, and its beneficial effect on survival might be maximized in cases with positive LN. The survival benefit of super-extended lymphadenectomy in these patients was limited, and large and comparative trials are needed.

Conflicts of interest

The authors declare no conflicts of interest.

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