



# Long-Term Oncologic Outcomes after Radical Cystectomy for Bladder Cancer at a Single Institution

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The aim of this study was to evaluate our experience using radical cystectomy to treat patients with bladder cancer and to describe the associations between pathologic features and clinical outcomes. All 701 patients who underwent radical cystectomy for bladder cancer were evaluated. The patient population consisted of 623 men and 78 women. The overall 5 and 10 yr recurrence-free survival (RFS) rates were 61.8% and 57.7%, respectively, and the 5 and 10 yr cancer-specific survival (CSS) rates were 70.8% and 65.1%, respectively. Multivariate analysis showed that factors significantly predictive of RFS and CSS included extravesical extension ( $P = 0.001$ ), lymph node metastasis ( $P = 0.001$ ), and lymphovascular invasion ( $P < 0.001$  and  $P = 0.007$ ). The 5 and 10 yr RFS rates for patients with lymph node metastasis were 25.6% and 20.8%, respectively, and the 5 and 10 yr CSS rates were 38.6% and 30.9%, respectively. Adjuvant chemotherapy significantly improved RFS ( $P = 0.002$ ) and CSS ( $P = 0.001$ ) in patients with lymph node metastasis. Radical cystectomy provides good survival results in patients with invasive bladder cancer. Pathologic features significantly associated with prognosis include extravesical extension, node metastasis, and lymphovascular invasion. Adjuvant chemotherapy improves survival in patients with advanced stage disease.

**Keywords:** Urinary Bladder Neoplasms; Cystectomy; Prognosis

## INTRODUCTION

Bladder cancer is the seventh most common cancer in men, estimated to affect 4.5% of patients with primary malignancy in Korea (1). Although the annual incidence of bladder cancer is about 4-fold higher in men than in women, 5 yr overall survival rates are higher in men than in women (66% vs 60%) (2, 3).

About 25% of patients newly diagnosed with bladder cancer have muscle-invasive bladder cancer (MIBC) (4). Non-muscle-invasive bladder tumors are usually managed by transurethral resection, but their 1 yr recurrence rates vary from 15% to 70% (5), with 7% to 40% of these tumors progressing to MIBC within 5 yr (6). Patients with MIBC have a poorer prognosis than those with non-MIBC. Radical cystectomy with pelvic lymphadenectomy has been shown to be effective against MIBC (7-9). The pathologic stage of the primary tumor and regional lymph node status have been shown to be the most accurate predictors of disease recurrence after radical cystectomy (10-12).

Surgical approaches, including en bloc cystectomy, bilateral pelvic iliac lymph node dissection, and various forms of lower urinary tract reconstruction, have been developed to enhance survival in patients with MIBC. Improvements in medical, surgical, and anesthetic methods have reduced the morbidity and mortality associated with surgery. Radical cystectomy provides

an accurate evaluation of both the primary bladder tumor and the regional lymph nodes, allowing for adjuvant treatment strategies based on clear pathologic rather than clinical staging (11, 13). Moreover, radical cystectomy, coupled with improvements in continent urinary diversion, especially orthotopic lower urinary tract reconstruction to the native urethra, now provides both male and female patients with a more acceptable means for storing and eliminating urine, thus lessening the impact of cystectomy on their quality of life (14, 15). Although outcomes and prognosis after radical cystectomy for bladder cancer have been reported (10, 11), less is known about the outcomes of this method in Korean patients. We therefore evaluated our experience over the last 22 yr using radical cystectomy to treat patients with bladder cancer at our institute, as well as assessed the association between pathologic features and clinical outcomes.

## MATERIALS AND METHODS

### Study participants and design

The medical records of 711 consecutive patients with bladder cancer who underwent radical cystectomy between 1990 and 2011 were retrospectively reviewed. Indication for radical cystectomy was MIBC or invasion into the prostatic stroma, or recurrent Ta, T1, or carcinoma in situ refractory to transurethral

resection with or without intravesical chemotherapy or immunotherapy. Patients receiving neoadjuvant chemotherapy or radiotherapy were excluded. Finally, a total of 701 patients who received radical cystectomy for bladder cancer were included in this study. Patient demographic characteristics and clinical and pathologic status were evaluated. All patients underwent preoperative chest radiography, computerized tomography of the abdomen and pelvis, and bone scan for disease staging. No patient showed evidence of metastatic disease on physical examination or staging.

### Surgical procedures

Radical cystectomy and pelvic lymphadenectomy were performed by two senior surgeons. The extent of lymph node dissection was determined by each surgeon and ranged from standard lymphadenectomy, including the distal common iliac, external iliac, hypogastric, obturator, and perivesical lymph nodes, to extended lymphadenectomy, which included these lymph nodes as well as those at the level of the proximal common iliac artery, distal aorta, and vena cava. Nodal tissue removed from each anatomic location was submitted as a separate packet and identified visually and by manual palpation without the use of clearing solution. Urinary diversions, including ileal conduit diversions and orthotopic bladder substitutions (OBS), were performed after radical cystectomy and bilateral pelvic lymphadenectomy.

### Pathologic evaluation

All surgical specimens were processed according to standard pathological procedures. Tumors were graded according to the 2004 WHO grading system (16), and all tumors were pathologically restaged according to the 2010 American Joint Committee on Cancer tumor node metastasis (TNM) staging system (17). Positive soft tissue surgical margin status was defined as tumor at inked areas of soft tissue on cystectomy specimens; urethral or ureteral margin status was not considered positive in this analysis (18). Lymphovascular invasion was defined as the unequivocal presence of tumor cells in an endothelium-lined space but not in the underlying muscular walls (19).

### Adjuvant chemotherapy

Adjuvant chemotherapy at our institute is routinely recommended with full counseling for pathologic  $\geq$  T3 and/or node-positive patients, except for those who are medically intolerant or refuse this treatment. Chemotherapy was initiated within 3 months of surgery and consisted of three to six cycles of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC,  $n = 45$ ), or gemcitabine and cisplatin (GC,  $n = 116$ ). MVAC regimens were used from 1992 to 2000, whereas GC regimens were used from 2001 to 2011. GC and MVAC regimens have similar survival benefits, but the former has a better safety profile and is better tol-

erated by patients with advanced or metastatic bladder cancer (20).

### Follow-up

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. Imaging included chest radiography, computed tomography of the abdomen and pelvis, and bone scanning, all performed at 6 and 12 months postoperatively and annually thereafter. Recurrence was defined as local recurrence at or below the common iliac bifurcation, with distant metastasis documented by imaging and biopsy. A malignant tumor in the ureter or urethra was considered a second primary tumor, rather than a local or distant recurrence. The median follow-up duration was 64.3 months (range: 1-231.4 months).

### Statistical analysis

Quantitative data are expressed as mean  $\pm$  standard deviation. Recurrence-free survival (RFS) was calculated as the time from the start of radical cystectomy to the first documented clinical recurrence. Patients who died before any clinical recurrence were censored at death. Cancer-specific survival (CSS) was measured from the date of initiation of treatment to the date of death from bladder cancer. RFS and CSS curves were calculated by the Kaplan-Meier method and compared using the log-rank test. A Cox proportional hazards regression model was used to estimate the prognostic significance of each variable. All statistical tests were 2-tailed, with  $P < 0.05$  considered significant. Correlations between outcomes and variables are expressed as hazards ratio (HR) with 95% confidence intervals (CIs). Separate analyses were performed for patients with T3-4N0M0 or lymph node metastasis to evaluate the impact of advanced disease. All statistical analyses were performed using the Statistical Package for Social Sciences, version 18.0 (SPSS, Chicago, IL, USA).

### Ethics statement

This study was performed with the approval and oversight of the institutional review board of the Asan Medical Center (IRB No. 2013-0773), and the requirement for informed consent was waived due to the retrospective design of the study.

## RESULTS

### Patient characteristics

The clinicopathological characteristics of the 701 included patients are shown in Table 1. Of these, 623 (88.9%) were men and 78 (11.1%) were women. The mean age was 62.4 yr, and the median follow-up period was 64.3 months (range, 1-231.4 months).

**Table 1.** Patient characteristics and pathologic profiles

Variables	Number (%)
No. patients	701
Age (yr, mean $\pm$ SD)	62.4 $\pm$ 9.6
Sex, No (%)	
Male	623 (88.9)
Female	78 (11.1)
Smoking status, No (%)	
Never	346 (49.4)
Former	211 (30.1)
Current	144 (20.5)
Follow-up period, mean $\pm$ SD (days) from last TURBT	41.1 $\pm$ 99.1
Clinical Stage, No (%)	
$\leq$ T2	426 (60.8)
$\geq$ T3	275 (39.2)
Pathologic T-stage, No (%)	
T0	74 (10.5)
Tis	28 (4.0)
Ta	33 (4.7)
T1	107 (15.3)
T2	143 (20.4)
T3	221 (31.5)
T4	95 (13.6)
Pathological nodal status, No (%)	
N0	522 (74.5)
N1	62 (8.9)
N2	116 (16.5)
N3	1 (0.1)
Positive lymph nodes mean $\pm$ SD (median, range)	4.5 $\pm$ 5.5 (3, 1-37)
Lymph node removed mean $\pm$ SD (median, range)	19.7 $\pm$ 14.4 (16, 1-118)
Lymph node density (%) mean $\pm$ SD (median, range)	26.9 $\pm$ 24.5 (17.6, 2.6-100)
Grade, No (%)	
Low	100 (14.3)
High	601 (85.7)
Lymphovascular invasion, No (%)	
Yes	294 (41.9)
No	407 (58.1)
Carcinoma in situ, No (%)	
Yes	165 (23.5)
No	536 (76.5)
Soft tissue surgical margin status, No (%)	
Positive	23 (3.3)
Negative	678 (96.7)
Adjuvant chemotherapy, No (%)	
Yes	161 (23.0)
No	540 (77.0)
Urinary diversion, No (%)	
Orthotopic bladder substitutions	454 (64.8)
Ileal conduit	247 (35.2)
90 day mortality, No (%)	15 (2.1)

SD, standard deviation; TURBT, transurethral resection of bladder tumor.

Of the 701 patients, 454 (64.8%) underwent OBS and 247 (35.2%) underwent ileal conduit as urinary diversions. Pathological staging confirmed that 522 patients (74.5%) had node-negative disease and 179 (25.5%) had lymph node metastases. The median number of lymph nodes evaluated per patient was 16 (range, 1-118), the median number of positive lymph nodes was 3 (range, 1-37), and the median lymph node density was 17.6% (range, 2.6%-100%). A total of 375 (53.5%) patients had organ-confined primary tumors (pT2 or less), 294 (41.9%) had lymphovascular invasion (LVI), and 60 (3.3%) had positive soft tissue resection

margins. Postoperative adjuvant chemotherapy was administered to 161 patients (23.0%).

### RFS and CSS in the entire cohort

The overall 5 and 10 yr RFS rates in the entire patient cohort were 61.8% and 57.7%, respectively, and the 5 and 10 yr CSS rates were 70.8% and 65.1%, respectively. Kaplan-Meier analysis showed that RFS and CSS rates were lower in patients with high than low pathologic T-stage and high than low pathologic N-stage ( $P < 0.001$ ), and were lower in patients with than without LVI ( $P < 0.001$ ).

Multivariate analysis showed that factors significantly predictive of RFS and CSS included extravesical extension (RFS: HR, 1.94; 95% CI, 1.42-2.66,  $P = 0.001$ ; CSS: HR, 1.89; 95% CI, 1.33-2.69,  $P = 0.001$ ), pathologic N-stage (RFS: HR, 2.00; 95% CI, 1.32-3.03,  $P = 0.001$  for N1 and HR, 3.20; 95% CI, 2.29-4.47;  $P < 0.001$  for N2,3; CSS: HR, 1.82; 95% CI, 1.12-2.96,  $P = 0.017$  for N1 and HR, 4.01; 95% CI, 2.76-5.80,  $P < 0.001$ , for N2, 3) and LVI (RFS: HR, 1.85; 95% CI, 1.36-2.51,  $P < 0.001$ ; CSS: HR, 1.58; 95% CI, 1.21-2.34,  $P = 0.007$ ) (Tables 2 and 3).

### RFS and CSS in patients with T3-4N0M0 tumors or lymph node metastasis

Adjuvant chemotherapy did not improve RFS ( $P = 0.937$ ) and CSS ( $P = 0.913$ ) in the 174 patients with T3-4N0M0 tumors. The 5 and 10 yr RFS rates in patients with lymph node metastasis were 25.6% and 20.8%, respectively, and the 5 and 10 yr CSS rates were 38.6% and 30.9%, respectively (Fig. 1A and B). An 18% cut-off point for lymph node density (LND) showed statistically significant differences in RFS and CSS ( $P = 0.001$ , Fig. 1C and D). The number of positive lymph nodes, as a continuous variable, was a significant predictor of RFS (HR, 1.04; 95% CI, 1.01-1.07,  $P = 0.012$ ) and CSS (HR, 1.05; 95% CI 1.02-1.08,  $P = 0.003$ ). Adjuvant chemotherapy significantly improved RFS ( $P = 0.013$ , Fig. 1E) and CSS ( $P = 0.001$ , Fig. 1F) in the 178 patients with lymph node metastasis. Multivariate analysis showed that adjuvant chemotherapy was the only factor significantly predictive of RFS (HR, 0.52,  $P = 0.002$ ) and CSS (HR, 0.42,  $P = 0.001$ ) (Tables 4 and 5).

## DISCUSSION

Invasive bladder cancer is generally a lethal disease requiring aggressive therapy, with fewer than 15% of untreated patients surviving to 2 yr after diagnosis (21). The optimal goals of treatment for any invasive bladder cancer include long-term survival, prevention of pelvic recurrence or development of metastatic bladder cancer, and an excellent quality of life. Metastatic bladder cancer after local treatment failure is nearly uniformly fatal, with few durable complete responses to any form of systemic chemotherapy (10). In assessing a large series of patients with bladder cancer treated over a 22 yr period and followed up

**Table 2.** Univariate and multivariate analysis of factor influencing recurrence-free survival

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (continuous)	1.02 (1.01-1.03)	0.005	1.02 (1.01-1.04)	0.001
Sex (male)	1.31 (0.90-1.89)	0.159	1.32 (0.85-1.89)	0.160
Smoking history (yes)	0.73 (0.52-1.01)	0.058	0.97 (0.69-1.37)	0.882
Duration from last TURBT (continuous)	1.00 (0.99-1.00)	0.527	1.00 (0.99-1.00)	0.532
Pathologic T-stage ( $\geq$ T3)	3.54 (2.71-4.64)	0.001	1.94 (1.42-2.66)	0.001
Pathologic N-stage				
NO	1	-	1	-
N1	3.08 (2.09-4.52)	0.001	2.00 (1.32-3.03)	0.001
N2, 3	5.51 (4.15-7.31)	0.001	3.20 (2.29-4.48)	0.001
Grade (high)	1.53 (1.04-2.27)	0.033	0.89 (0.58-1.35)	0.584
Lymphovascular invasion (yes)	3.63 (2.79-4.73)	0.001	1.85 (1.36-2.51)	0.001
Carcinoma in situ (yes)	0.83 (0.61-1.14)	0.258	0.82 (0.58-1.15)	0.247
Soft tissue surgical margin (yes)	1.39 (0.91-2.15)	0.127	0.83 (0.52-1.33)	0.440

HR, hazard ratio; CI, confidence interval.

**Table 3.** Univariate and multivariate analysis of factor influencing cancer-specific survival

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (continuous)	1.02 (1.01-1.04)	0.003	1.03 (1.01-1.04)	0.001
Sex (male)	1.19 (0.78-1.83)	0.421	1.11 (0.73-1.73)	0.661
Smoking history (yes)	0.67 (0.46-0.97)	0.038	0.85 (0.57-1.25)	0.422
Duration from last TURBT (continuous)	1.00 (0.99-1.01)	0.868	1.00 (0.99-1.00)	0.954
Pathologic T-stage ( $\geq$ T3)	3.57 (2.65-4.81)	0.001	1.89 (1.33-2.69)	0.001
Pathologic N-stage				
NO	1	-	1	-
N1	2.61 (1.67-4.08)	0.001	1.82 (1.12-2.96)	0.017
N2, 3	6.24 (4.59-8.48)	0.001	4.01 (2.76-5.80)	0.001
Grade (high)	1.48 (0.97-2.27)	0.071	0.85 (0.54-1.34)	0.484
Lymphovascular invasion (yes)	3.26 (2.44-4.36)	0.001	1.58 (1.21-2.34)	0.007
Carcinoma in situ (yes)	0.69 (0.46-0.97)	0.037	0.64 (0.45-0.99)	0.027
Soft tissue surgical margin (yes)	1.27 (0.76-2.13)	0.351	0.92 (0.56-1.67)	0.755

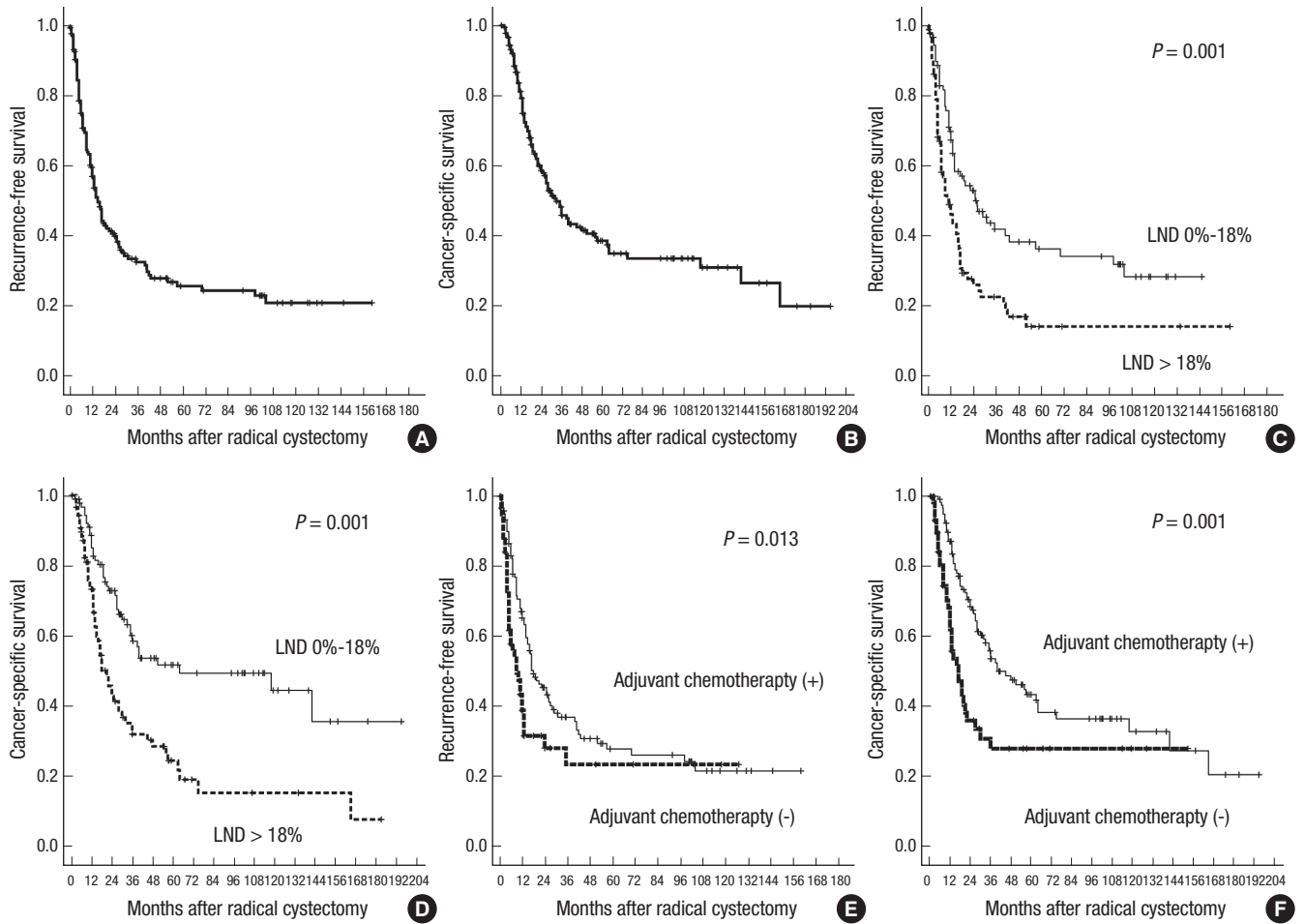
HR, hazard ratio; CI, confidence interval.

for a median of 64.3 months, we found that radical cystectomy with pelvic lymphadenectomy and urinary diversion can be performed safely, with excellent bladder tumor control and a low incidence of local pelvic recurrence. Furthermore, patients had an improved quality of life after cystectomy, as lower urinary tract options have evolved into an orthotopic form of diversion, allowing most of these patients (64.8%) to store urine and void per urethra, without needing stoma or catheterization. Current guidelines recommend OBS in patients without contraindications and without tumors in the urethra or at the level of urethral dissection (22). We previously reported that older age, female sex, low performance status, clinically node-positive disease, anemia, hypoalbuminemia, and azotemia are associated with non-OBS (23). The option of lower urinary tract reconstruction to the urethra has also been shown to decrease physician reluctance and increase patient acceptance of earlier cystectomy for bladder cancer, when the disease may be more curable (24).

This study found that pathologic stage is an important surviv-

al determinant in patients undergoing radical cystectomy for bladder cancer. In addition, certain pathologic subgroups stratify patients into different prognostic categories. The 385 patients (54.9%) with pathologically organ-confined bladder tumors had excellent survival outcomes, whereas the patients with extravesical invasion or lymph node metastasis had a poor prognosis. At the time of cystectomy, 25.5% of our patients had lymph node metastasis, with 5 and 10 yr RFS rates of 25.6% and 20.8%, respectively, and 5 and 10 yr CSS rates of 38.6% and 30.9%, respectively. Patients who did not receive adjuvant chemotherapy had an even poorer prognosis, and patients with extravesical tumor extension or lymph node-positive disease were at increased risk for recurrence and may therefore benefit from adjuvant treatment. In addition, neoadjuvant chemotherapy may be beneficial for patients with advanced stage disease (25).

LND, or the ratio of positive to total nodes removed, has been shown to be a better predictor of disease-specific survival (DSS) than TNM nodal status, suggesting that LND may be better for risk stratification of node-positive patients (26, 27). Using recei-



**Fig. 1.** Kaplan-Meier analysis of survival after radical cystectomy in 178 lymph node metastasis patients. (A) Recurrence-free survival and (B) cancer-specific survival. (C) Recurrence-free survival and (D) cancer-specific survival by lymph node density (LND) 18%. (E) Recurrence-free survival and (F) cancer-specific survival by adjuvant chemotherapy.

**Table 4.** Univariate and multivariate analysis of factor influencing recurrence-free survival in lymph node metastasis patients

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Pathologic T-stage ( $\geq$ T3)	1.16 (0.73-1.84)	0.052	1.37 (0.85-2.19)	0.196
Pathologic N-stage (N2-3)	1.79 (1.19-2.68)	0.005	1.30 (0.75-2.24)	0.342
No. positive lymph node (continuous variable)	1.04 (1.01-1.07)	0.012	1.02 (0.98-1.06)	0.374
Lymph node density (18%)	1.91 (1.32-2.77)	0.001	1.49 (0.89-2.49)	0.122
Adjuvant chemotherapy (yes)	0.62 (0.41-0.91)	0.016	0.52 (0.34-0.79)	0.002

HR, hazard ratio; CI, confidence interval.

**Table 5.** Univariate and multivariate analysis of factor influencing cancer-specific survival in lymph node metastasis patients

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Pathologic T-stage ( $\geq$ T3)	1.01 (0.62-1.64)	0.971	1.18 (0.72-1.94)	0.526
Pathologic N-stage (N2-3)	2.39 (1.50-3.82)	0.001	1.93 (1.07-3.47)	0.028
No. positive lymph node (continuous variable)	1.05 (1.02-1.08)	0.003	1.02 (0.98-1.06)	0.348
Lymph node density (18%)	2.27 (1.52-3.40)	0.001	1.43 (0.85-2.41)	0.178
Adjuvant chemotherapy (yes)	0.52 (0.34-0.78)	0.002	0.42 (0.27-0.65)	0.001

HR, hazard ratio; CI, confidence interval.



ver operating characteristic curve analysis, we found that the optimal LND cutoff value for predicting RFS and CSS was 18%, providing an optimal balance between sensitivity and specificity. Patients with LND > 18% had relatively high local recurrence and low survival rates.

This study had several limitations, including the retrospective nature of the analysis and the significant difference in some variables between arms. For example, factors such as renal function not captured in the clinicopathological variables may have contributed to the selection of patients for adjuvant chemotherapy. However, the clinical results obtained from this large group of patients over an extended period of time demonstrate that radical cystectomy provides good survival results, with excellent local recurrence rates, in patients with bladder cancer.

In conclusion, radical cystectomy provides good survival results in patients with bladder cancer. Pathologic features are significantly associated with prognosis, and adjuvant chemotherapy improves survival in patients with advanced stage disease. These results provide a standard to which other therapies for invasive bladder cancer can be compared.

## DISCLOSURE

The authors have no conflict of interest or financial disclosures.

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