

# Importance of the Number of Retrieved Lymph Nodes During Cystectomy

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**Purpose:** To evaluate the effect of the number of dissected lymph nodes (LNs) during radical cystectomy on survival outcomes.

**Materials and Methods:** Medical files of 211 patients who underwent cystectomy between 1996 and 2009 were retrospectively evaluated. Seventy-four patients were included in the study and divided into two groups regarding the median number of retrieved LNs (median number = 13); 36 patients in the 1<sup>st</sup> and 38 in the 2<sup>nd</sup> group. Radical cystectomy, urinary diversion, and pelvic LN dissection were done in all the patients. When necessary, adjuvant chemotherapy was applied. Kaplan-Meier survival analysis was performed to compare survival outcomes of the groups.

**Results:** Of 74 patients, 67 (90.5%) were men and 7 (9.5%) were women, with the mean age of 61.7 years (range, 39 to 83 years). Age distribution, pathologic stages, carcinoma in situ occurrence, adjuvant chemotherapy rates, LN involvement, and median follow-up period were similar in both groups. Mean dissected LNs number in the 1<sup>st</sup> and 2<sup>nd</sup> groups was 6.17 (range, 1 to 12) and 21.6 (range, 13 to 41), respectively. Five-year estimated overall survival rates were 24.5% and 60.5% ( $P = .002$ ) while five-year estimated disease-specific survival rates were 43.7% and 74.4% ( $P = .049$ ), respectively.

**Conclusion:** Although exact guidelines are not described, it seems that dissection of high number of LNs during radical cystectomy is crucial.

*Keywords: lymph nodes, lymph node excision, cystectomy, prognosis, transitional cell carcinoma*

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## INTRODUCTION

Radical cystectomy plays an important role in the treatment of muscle-invasive bladder cancer. The aim of radical cystectomy is complete eradication of local and regional disease with excision of the bladder, perivesical soft tissues, adjacent organs, and regional lymph nodes (LNs). Consequently, lymph node dissection (LND) is considered as one of the most important steps of surgery. Exact staging of primary tumor and LNs have paramount importance due to the fact that pathologic stage and LN status are the most significant

predictors for recurrence-free and overall survival.<sup>(1)</sup>

Debate on LND concerning the extent and curative value is still ongoing in literature.<sup>(2)</sup> Although the number of dissected LNs is an important factor in interpretation of accurate nodal status, different cut-off values have been described.<sup>(1,3,4)</sup> Therapeutic effect of LND is another question that has to be addressed. Various studies have indicated the therapeutic effect of LND and demonstrated the importance of careful lymphadenectomy.<sup>(5)</sup>

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In this study, our radical cystectomy series was retrospectively reviewed and the effect of the number of retrieved LNs on survival outcomes was discussed in the light of current literature.

## MATERIALS AND METHODS

Between 1996 and 2009, 211 radical cystectomy procedures with different indications were performed by a single attending surgeon (T.K.). Prior to surgery, a written informed consent was obtained from all the patients, and principals of Declaration of Helsinki were followed.

To analyze a homogeneous group, only those patients with no evidence of LN or distant organ metastasis pre-operatively, who underwent radical cystectomy, pelvic LND, and urinary diversion for curative intent with transitional cell carcinoma histology, and who did not receive any neoadjuvant chemotherapy were included in the study. According to cystectomy specimen pathology, patients with pT2 or pT3 disease with negative surgical margins and a minimum of one LN reported in pathologic examination were also included. Patients without adequate follow-up period or with peri-operative deaths (0 to 2 months after surgery) were excluded from the study.

Pathologic stages were determined using the 2002 TNM system and previous pathology reports were reappraised and transformed to 2002 TNM system. Standard radical cystectomy and pelvic LND were performed. En bloc LND that comprised the external iliac, hypogastric, and obturator LNs where the cranial limit was the iliac bifurcation was carried out.

The specimens were fixed immediately in formalin and interpreted by different pathologists; however, all pathologic evaluations were made in the same manner. The LNs were evaluated microscopically and the number of LNs retrieved and tumor containing nodes were noted. During LN evaluation, fat solvent was not applied. All specimens were stained by Hematoxylin and Eosin.

Following radical surgery, patients with LN involvement or pT3b disease received adjuvant chemotherapy. All patients were followed up

regularly after the surgery with comprehensive metabolic panel as well as computed tomography of the chest, abdomen, and pelvis every 6 months for 2 years and annually thereafter.

Demographic characteristics and survival outcomes were assessed for all the patients. Since the aim of this study was to evaluate the effect of the number of dissected LNs on survival outcomes, two groups were formed according to the median number of dissected LNs in all the patients (median dissected LN = 13). The 1<sup>st</sup> group consisted of 47 patients, who had 12 or less retrieved LNs, and the 2<sup>nd</sup> group included 45 patients, who had 13 or more retrieved LNs.

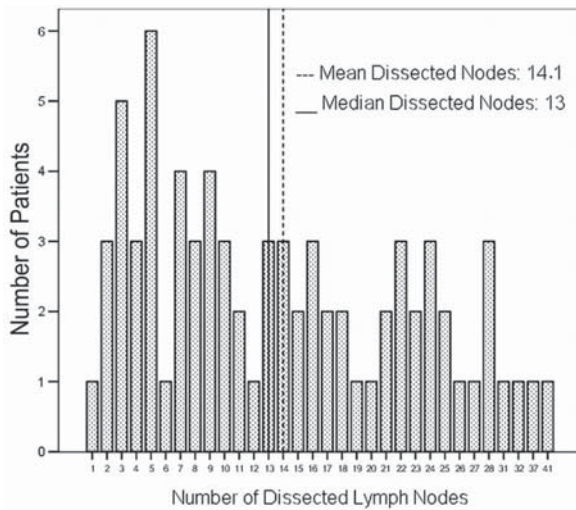
After data gathering, 92 patients were eligible for the study. However, 11 patients in the 1<sup>st</sup> and 7 patients in the 2<sup>nd</sup> groups were lost to the follow-up and were excluded from the study (statistically insignificant,  $P = .052$ ). Eventually, 74 patients, including 36 patients in the 1<sup>st</sup> and 38 patients in the 2<sup>nd</sup> group, met the criteria and remained for the data analysis.

Statistical analysis was performed with SPSS software (the Statistical Package for the Social Sciences, version 13.0, SPSS Inc., Chicago, Illinois, USA) using Chi-square or Fisher's Exact test and Mann-Whitney  $U$  test to compare non-parametric and parametric variables, respectively. The Kaplan-Meier method was used to calculate the estimated survival rates. The log-rank test  $P$  values were used to evaluate the significance of differences in univariate analyses.  $P$  values less than .05 were considered statistically significant.

## RESULTS

Of 74 patients, 67 (90.5%) were men and 7 (9.5%) were women, with the mean age of 61.7 years (range, 39 to 83 years). Thirty (40.5%) and 44 (59.5%) patients had pT2 and pT3 disease, respectively. Concomitant carcinoma in situ was diagnosed in cystectomy specimens of 27 (36.5%) patients. Mean and median dissected LNs were 14.4 (range, 1 to 41 nodes) and 13, respectively (Figure 1).

In total, 18 (24.3%) patients had transitional cell carcinoma involvement in the LNs. Mean and median number of involved LNs were 2.44 (range,



**Figure 1.** Distribution of retrieved lymph nodes in 74 patients individually.

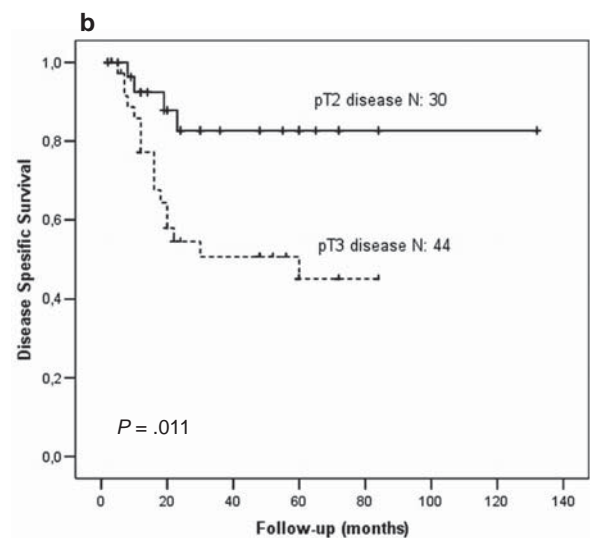
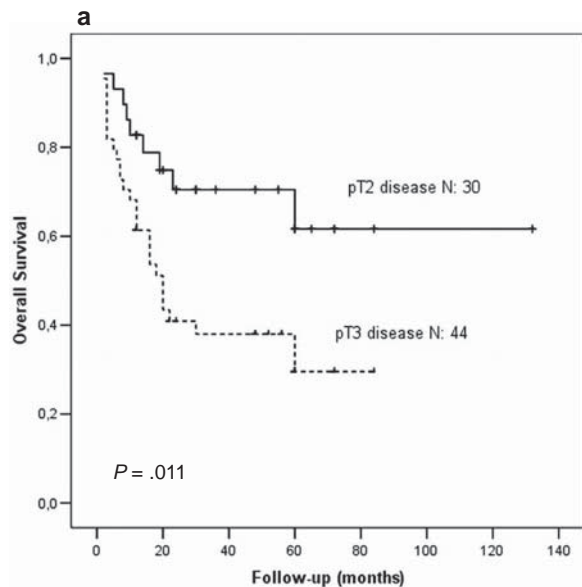
1 to 7) and 2, respectively. A total of 24 (32.4%) patients received adjuvant chemotherapy. Median follow-up period for all the patients was 20 months. Half of the patients (37) were alive at the time the study was planned. In univariate analyses, pT3 pathologic stage and LN involvement showed negative impact on overall and disease-specific survival (Figures 2 and 3).

Characteristics of the groups constituted according to the median number of dissected LNs are

Features of the groups constituted according to median number of dissected lymph nodes.

	Group 1	Group 2	P
N	36	38	
Gender			
Male	34	33	.43
Female	2	5	
Age, mean (range), y	62.2 (41 to 83)	61.3 (39 to 79)	.84
P Stage			
pT2	11	19	.089
pT3	25	19	
Carcinoma in situ (+)	12	15	.58
Mean dissected lymph nodes (range)	6.17 (1 to 12)	21.6 (13 to 41)	<.001
Patients with lymph node involvement	8	10	.79
Patients received adjuvant chemotherapy	13	11	.1
Median follow-up, months	16	22.5	.13

presented in Table. Five-year estimated overall survival rate in Kaplan-Meier survival analyses was 24.5% in the 1<sup>st</sup> and 60.5% in the 2<sup>nd</sup> group ( $P = .002$ ). Furthermore, statistical difference was found in five-year estimated disease-specific survival rates, which were 43.7% and 74.4% in the 1<sup>st</sup> and 2<sup>nd</sup> groups, respectively ( $P = .049$ ; Figure 4). Moreover, when node-positive patients in both groups were compared, a survival advantage was observed in the 2<sup>nd</sup> group. Estimated overall two-year survival rates



**Figure 2.** (a) Overall and (b) disease-specific survival of 74 patients stratified by pT stage.

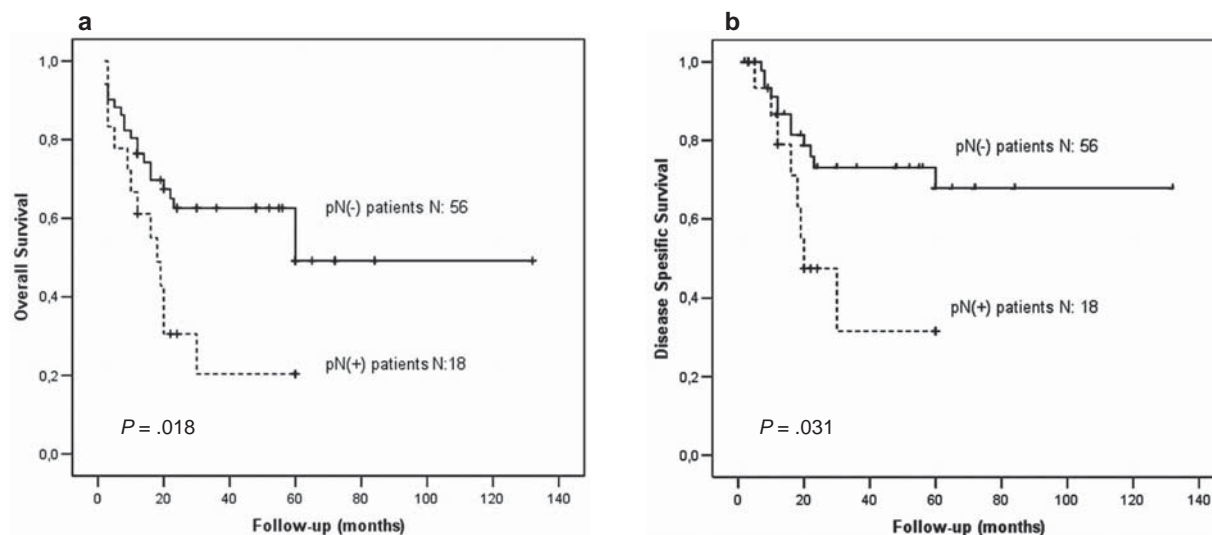


Figure 3. (a) Overall and (b) disease-specific survival of 74 patients stratified by nodal status.

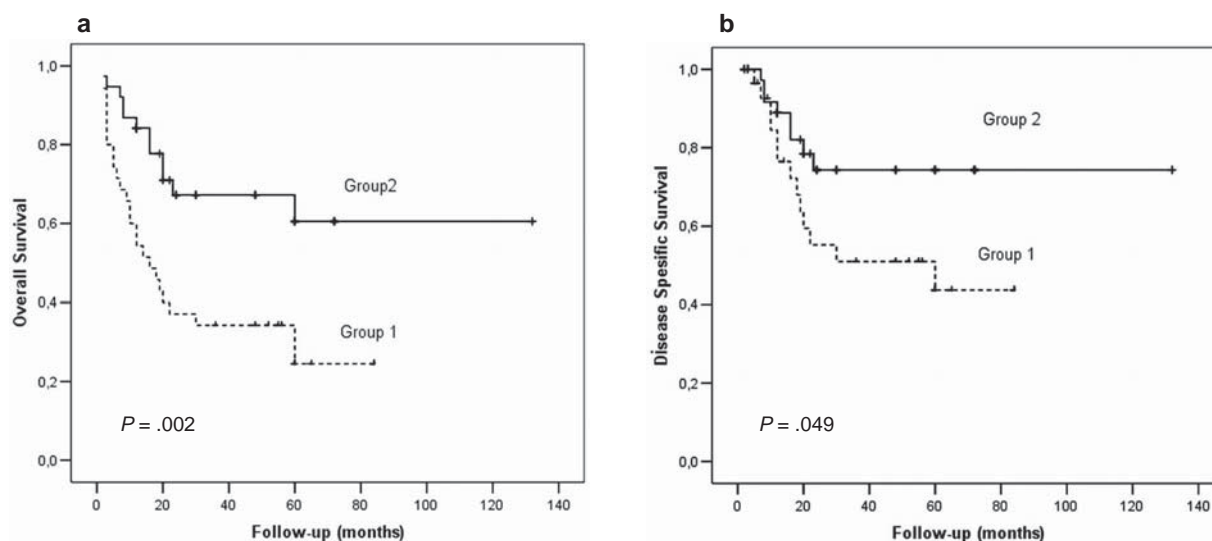


Figure 4. (a) Overall and (b) disease-specific survival of groups stratified by median number of retrieved lymph nodes.

in the 1<sup>st</sup> and 2<sup>nd</sup> groups were 12.5% and 45.7%, respectively ( $P = .016$ ). None of the patients in the 1<sup>st</sup> group with LN metastasis survived for five years. Estimated two-year disease-specific survival rate was 20.8% in the 1<sup>st</sup> and 63.5% in the 2<sup>nd</sup> group ( $P = .034$ ). Statistical analyses revealed that the 2<sup>nd</sup> group had a significant advantage in both overall and disease-specific survival rates as well as in node-positive patients.

## DISCUSSION

Bladder cancer is a challenging disease for the

urologists as the major curative treatment is radical surgery and urologists have the main responsibility in management. Therefore, every single determiner of survival has to be taken into consideration in surgical intervention. Different variables, such as pathologic stage, LN status, surgical margin status, and the number of dissected LNs, have been addressed in literature as factors that may affect survival outcomes.<sup>(6)</sup> Before grouping the patients, we also found a statistically significant survival advantage in patients with pT2 stage and negative LNs. Surgical margins were

not assessed since all the patients with positive surgical margins had already been excluded.

In this study, after grouping the patients according to the number of LNs, distribution of the patients in compliance with the pathologic stage and LN status was not different. Interestingly, although the number of retrieved LNs was significantly different in two groups, the number of node-positive patients was not different. Leissner and colleagues commented that extended LND increased nodal staging.<sup>(7)</sup> Herr<sup>(8)</sup> and Abdel-Latif and associates<sup>(9)</sup> also showed a correlation between the number of removed LNs and the number of patients detected with positive LNs. However, correlation coefficients were low in both studies and diagnostic power of LND is controversial according to our results, which did not reveal any statistical difference. The rates of patients with positive nodes were 22.2% in the 1<sup>st</sup> and 26.3% in the 2<sup>nd</sup> group ( $P = .79$ ). Based on our results, retrieval of more nodes during radical cystectomy does not provide any nodal staging advantage when the groups are compared according to LN-positive patient rates.

On the other hand, Skinner clearly showed the importance of pelvic LND three decades ago and commented that LND can make a difference in patients with metastatic disease.<sup>(10)</sup> Several authors from different centers have also figured the importance of extended pelvic LND.<sup>(7,11)</sup> In our study, we found a statistically significant difference between the two groups concerning overall and disease-specific survival rates. Similar results have been reported in literature. Honma and coworkers stated that removal of 13 or more LNs has an advantage in disease-specific survival in node-positive patients.<sup>(12)</sup> However, their patient group was not homogeneous as they had included patients in every pathologic stage into the study. Patients with pT0, pT1, or pT4 which might distort survival outcomes were excluded from our study. Additionally, an overall survival advantage between the groups was observed in our study.

Herr stated that the number of retrieved LNs depends on the extent of dissection and also showed a survival advantage with the increase in

the number of dissected LNs. Patients without any LN in pathologic specimen were included as pN0 in his study whereas they had to be defined as pNx.<sup>(4)</sup> In our study, however, all the patients without any reported LNs in pathologic evaluation were excluded.

Dhar and colleagues reported the results of two referral centers (Cleveland Clinic and University of Bern), where the median numbers of dissected LNs were 12 and 22, respectively. They showed a statistically significant difference in survival rates in favor of the University of Bern where the extended LND had been performed. Similar to our results when limited LND was performed, survival outcomes especially in node-positive patients were poorer.<sup>(3)</sup>

Different cut-off values for survival benefit from LND have been mentioned in the literature. Stein and coworkers showed that dissection of 15 or more LNs yields better recurrence-free survival.<sup>(5)</sup> Herr and associates indicated the removal of at least 11 nodes in order to improve survival outcomes in node-positive patients.<sup>(13)</sup> Defining different cut-off values in different studies is logically normal since when the median numbers of dissected LNs are different, so are the minimum number of LNs retrieved to observe the survival effect. Due to this fact, a cut-off value that would probably differ from other studies in the literature was not established in this study. Instead, patients were divided into two groups based on the median number of dissected LNs in order to evaluate the effect of the number of retrieved LNs on survival. Leissner and colleagues also employed a similar grouping in their study and suggested that 16 or more LNs should be recovered to identify the LN metastasis. This correlation was only limited to patients with pT3 or pT4 tumor. On the other hand, they reported an increased survival rate when 16 or more nodes are removed.<sup>(14)</sup> Our results are in parallel with all these observations recommending the dissection of more LNs during radical cystectomy.

Limitations of this study are the retrospective design without randomization and limited experience due to restrictive study inclusion criteria.

## CONCLUSION

Our results show a statistically significant survival advantage in patients with higher numbers of dissected LNs during radical cystectomy. We recommend that all urologists who perform radical cystectomy for the bladder cancer should attempt to dissect more LNs as current literature supports the retrieval of higher numbers of LNs, which improves survival rates.

## CONFLICT OF INTEREST

None declared.

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