

## Urological Oncology

# Pattern of Lymph Node Metastasis Correlates with Tumor Location in Bladder Cancer

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**Purpose:** Resection of a large number of lymph nodes (LNs) increases survival in patients with LN-positive disease; however, morbidity also increases. Here, we investigated the correlation between tumor location and LN metastasis in bladder cancer.

**Materials and Methods:** Thirty-six patients with pathological N1 or higher bladder cancer, who underwent radical cystectomy with extended lymphadenectomy, were reviewed retrospectively. The tumor location was classified as right, left, front, posterior, or whole bladder. The LN metastasis pattern was classified as right, left, or bilateral. The correlation between tumor location and LN metastasis was determined by chi-square test. Survival rates were compared by Kaplan-Meier analysis.

**Results:** The numbers of patients with a tumor on the right (group 1), left (group 2), posterior (group 3), or whole (group 4) bladder were 16 (44.4%), 16 (44.4%), 2 (5.6%), and 2 (5.6%), respectively. In group 1, 14 patients (87.5%) had right-sided ipsilateral LNs, and 2 patients (12.5%) had left-sided contralateral LNs. In group 2, 4 patients (25%) had right-sided contralateral LNs, and 12 patients (75%) had left-sided ipsilateral LNs. In group 3, both patients (100%) had right-sided posterior LNs. In group 4, both patients (100%) had positive LNs on both sides. Tumor location and LN metastasis were significantly correlated ( $p < 0.05$ ). Moreover, the survival rate was significantly higher in patients with no LN metastasis than in patients with ipsilateral or contralateral LN-positive bladder cancer.

**Conclusions:** The location of the bladder tumor and direction of metastatic spread were significantly correlated. Mandatory bilateral lymphadenectomy during radical cystectomy should be questioned.

**Key Words:** Lymph node excision; Neoplasm metastasis; Urinary bladder neoplasms

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## INTRODUCTION

The pathological stage of primary bladder tumor and the presence of lymph node (LN) metastasis are the most important determinants of survival in patients with bladder cancer undergoing radical cystectomy (RC). A properly performed lymphadenectomy helps detect occult nodal metastases in 25% of the patients undergoing RC [1].

Currently, extended radical lymphadenectomy is strongly recommended for all patients undergoing RC for the treatment of bladder cancer, because of more accurate staging and improved postoperative survival [2]. Moreover, re-

cent reports have shown that the resection of a large number of LNs is associated with a survival advantage among patients with LN-positive disease. However, morbidity increases if large numbers of LNs are resected [3].

Most bladder cancer patients who are required to undergo RC are evaluated before the procedure by cystoscopy and computed tomography. Establishing a correlation between tumor location and the direction of LN metastatic spread is useful knowledge for surgeons performing RC with lymphadenectomy. The aim of this study was to determine the number and location of the tumors in the bladder and to determine the correlation between these factors and LN

**TABLE 1.** Demographic characteristics of the patients

Characteristic	Value
No. of patients	36
Age (yr)	66 (48-79)
Gender	
Male	30 (80)
Female	6 (20)
Pathologic T stage	
pT1	3 (8.3)
pT2	15 (41.7)
pT3	11 (30.6)
pT4	7 (19.4)
Pathologic N stage	
pN1	28 (77.8)
pN2	8 (22.2)
Pathology	
Grade 1	2 (5.5)
Grade 2	22 (61.1)
Grade 3	12 (33.4)
Mean dissected LNs	10.4 (4-29)
Mean positive LNs	1.8 (1-11)

Values are presented as mean (range) or number (%). LNs, lymph nodes.

metastasis.

## MATERIALS AND METHODS

### 1. Data collection

We retrospectively reviewed the records of patients who underwent surgery for bladder cancer (pathological N1 or higher) at Ilsan Hospital (Department of Urology, National Health Insurance Corporation Ilsan Hospital, Goyang, Korea) between 1 January 2000 and 31 August 2010. To ensure consistency, the same investigator reviewed all of the charts to extract data on demographics, admission and operation, and pathological conditions.

### 2. Patients

A total of 78 cases of patients who had undergone RC with extended lymphadenectomy were identified from the database. We excluded 42 patients without LN metastasis or any other organ metastasis (M1).

### 3. Study definitions

The location of the cancer within the bladder was classified as right or left (defined by a vertical line between the ureteral orifices), front or posterior (defined by a horizontal cross line between the ureteral orifices), or whole (defined as the presence of an invading mass in more than two zones) bladder. Additionally, the LN metastasis pattern was classified as right, left, or bilateral in reference to the aorta.

### 4. Statistical analyses

Statistical analyses were performed by using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Continuous variables

**TABLE 2.** Tumor location and direction of metastatic spread in patients with LN-positive disease

Tumor location	LN positive direction		
	Right	Left	Bilateral
Right	14 (87.5)	2 (12.5)	0
Left	4 (25)	12 (75)	0
Anterior	0	0	0
Posterior	2 (100)	0	0
Whole bladder	0	0	2 (100)

Values are presented as mean (range) or number (%). LN, lymph node.

were expressed as medians (ranges) and were compared by using an independent t-test. Correlations between the location of the bladder tumor and the site of LN metastasis were determined by using the chi-square test. A p value < 0.05 was considered significant. Survival was compared by using the log-rank test and Kaplan-Meier analysis.

## RESULTS

The patients included 30 men and 6 women with an average age of 66 years (range, 48 to 79 years). There were 3 (8.3%), 15 (41.7%), 11 (30.6%), and 7 (19.4%) pathologic pT1, pT2, pT3, and pT4 cases, respectively. The mean number of resected LNs was 10.4 (range, 4 to 29), and the mean number of pathologically positive LNs was 1.8 (range, 1 to 11). As shown in Table 1, we observed 28 and 8 patients with pathologic pN1 and pN2, respectively. We observed 16 patients (44.4%) with bladder cancer on the right side (group 1), 16 patients (44.4%) with bladder cancer on the left side (group 2), 2 patients (5.6%) with posterior bladder cancer (group 3), and 2 patients (5.6%) with whole bladder cancer (group 4). In group 1, 14 patients (87.5%) had right-sided ipsilateral positive LNs, and 2 patients (12.5%) had left-sided contralateral positive LNs (12.5%). In group 2, 4 patients (25%) had right-sided contralateral positive LNs, and 12 patients (75%) had left-sided ipsilateral positive LNs. In group 3, two patients (100%) had right-sided posterior positive LNs. In group 4, two patients (100%) had positive LNs on both sides (Table 2). We found a significant correlation between the location of the tumor and the site of LN metastasis (chi-square test,  $p < 0.001$ ).

Ipsilateral metastasis was found in 26 cases, contralateral metastasis in 6 cases, and no LN metastasis in 42 cases. Kaplan-Meier survival analysis showed that the 5 year median survival rate of patients with ipsilateral metastasis was 37%, with contralateral metastasis was 18%, and without LN metastasis was 61% ( $p < 0.001$ ) (Fig. 1). Hence, the presence of ipsilateral or contralateral metastasis predicts poor survival in patients with bladder cancer.

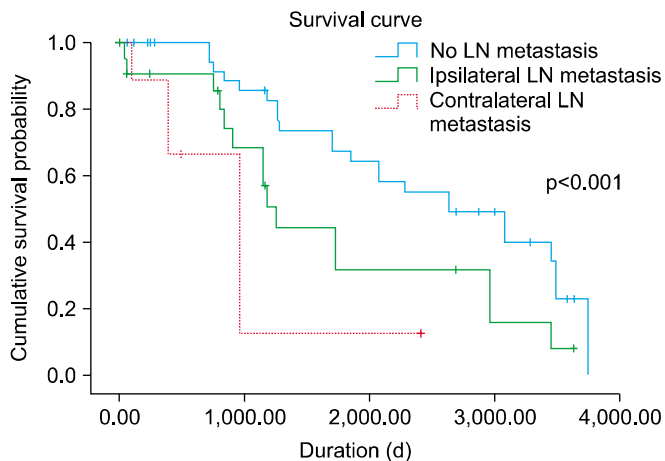


FIG. 1. Kaplan-Meier analysis of survival rates.

## DISCUSSION

Most bladder cancer patients experience lymphatic metastasis in the course of disease progression. Nonetheless, many studies have shown that patients with LN-positive disease can achieve long-term survival by extended radical lymphadenectomies despite initial poor prognosis. Those same studies have shown that a positive LN status is found in 23% of all bladder cancer patients. Furthermore, data from those analyses highlight that patients with LN-positive disease have a mean 5 year recurrence-free survival rate of 30% (range, 20.9 to 35%) [1].

The relationship between the location of the primary tumor and the direction of metastatic spread has not been fully investigated. Interestingly, however, a recent study has suggested a close correlation between the histologic characteristics of the primary tumor and the metastatic pattern [4]. To the best of our knowledge, this was the first study to analyze the correlation between tumor location in the bladder and pattern of LN metastasis relative to survival rates. Our data indicated a 5 year recurrence-free survival rate of 31%. The 5 year survival rate of the ipsilateral LN-positive group was 37%, whereas that of the contralateral LN-positive group was 18%. This result indicates that patients with contralateral LN metastasis might have a poorer prognosis than those with ipsilateral LN metastasis.

Of the 32 patients with a lateralized bladder tumor, 6 (19%) had LNs in the contralateral side. This finding is in contrast with the findings of others. These data suggest that bilateral nodal dissection in patients with invasive bladder cancer does not necessarily occur. In fact, invasive bladder cancer usually spreads around the circumference of the bladder in a large percentage of cases. On the other hand, Wishnow et al. [5] analyzed patients in whom the primary bladder tumor was localized clearly to one side of the bladder, and they observed unsuspected metastasis only in patients with ipsilateral LN cancer. On the basis of these findings, we advocate a restricted pelvic lymphadenec-

tomy for patients in whom gross examination shows no evidence of nodal metastasis during RC [6].

In our study, we found a significant correlation between the location of the bladder tumor and LN positivity. However, we are reluctant to not infer that there is no evidence of nodal metastasis on the contralateral side in patients with bladder cancer [3]. In fact, our data indicate that lymphadenectomies must be performed bilaterally, even if the primary cancer is limited to the right or left hemisphere of the bladder wall, because even contralateral nodal metastases may eventually occur. The risk of contralateral metastases is only slightly lower than that of ipsilateral metastases. In agreement with our claim, previous retrospective studies have shown a survival benefit for patients undergoing bilateral extended radical lymphadenectomies [6-8].

Notwithstanding the possible advantages, all of the participating urological surgeons unanimously agreed that an extended radical lymphadenectomy takes up to 60 minutes longer than does a lymphadenectomy that cranially ends at the level of the iliac arteries and is associated with increased morbidity [3]. Therefore, knowledge of the exact location of the tumor would be useful for surgeons performing RCs and lymphadenectomies.

Although the group with LN metastasis on the contralateral side had a poorer prognosis than did those with LN metastasis on the ipsilateral side, tumor grade was also a valid prognostic factor. When the latter is taken into account, the distance of the LN from the tumor itself may not be an independent prognostic factor.

The current study had some limitations: the surgeon may have been biased toward the presence of ipsilateral LN metastases, the sample population was small, a single operator was not used, and a single chemotherapy protocol was not performed.

## CONCLUSIONS

The site of LN metastasis was significantly correlated with the location of the bladder tumor. Moreover, survival was significantly affected in patients with ipsilateral and contralateral LN-positive bladder cancer.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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