Original Article

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Effects of Lymphovascular Invasion on Overall and Cancer-specific Survival after Radical Cystectomy in Patients with Bladder Cancer

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Abstract

Objective: We aimed to investigate the effects of lymphovascular invasion (LVI) on survival rate, as well as the relationship of this parameter with lymph node (LN) involvement and other prognostic factors, in patients undergoing radical cystectomy (RC) for bladder cancer.

Materials and Methods: Patients who underwent RC in our clinic for muscle invasive bladder cancer (MIBC) or high-risk non-muscle invasive bladder cancer (NMIBC) between 2006 and 2019 were retrospectively reviewed. Patients were divided into four groups: LVI (−) and LN (−) patients were in group 1, LVI (+) and LN (−) patients were in group 2, LVI (−) and LN (+) patients were in group 3, and LVI (+) and LN (+) patients were in group 4. All data were compared among the groups.

Results: A total of 177 patients with a mean age of 64.4 years and mean follow-up time of 30.2 months were evaluated in this study. The mean overall survival (OS) and cancer-specific survival (CSS) of the patients were 56.6±4.2 and 68.9±4.5 months, respectively. When factors affecting survival rates were analyzed, LN positivity was not a significant factor influencing the OS (p=0.570) and CSS (p=0.533) of the patients. However, LVI [p=0.002, hazard ratio (HR)=0.402] and surgical margin (SM) positivity (p=0.001, HR=0.321) were significant factors influencing OS. SM positivity (p=0.003, HR=0.314), LVI (p=0.011, HR=0.416), and adjuvant chemotherapy (ACT) (p=0.009, HR=0.460) were also found to be independent factors affecting CSS. ACT was higher in group 3 than in other groups, and overall and cancer-specific mortality rates were lower in group 1 than in other groups. OS and CSS in group 2 (15.3±2.9 and 21.2±4.6 months, respectively) and group 4 (21.5±7.2 and 24.5±8.1 months, respectively) were lower than those in other groups (p<0.001).

Conclusion: SM positivity and LVI are independent factors affecting OS and CSS. ACT, especially in group 3, could increase CSS. OS and CSS were lower in patients with LVI than in those without.

Keywords: Bladder cancer, lymphovascular invasion, lymph node involvement, overall survival, cancer-specific survival

Introduction

Bladder cancer is one of the most common malignancies of the urinary system, and its prevalence is high in developing countries (1). The annual mortality rate of this type of cancer is 1-5/100000 for males and 0.5-1.5/100000 for females (2). Approximately, 98% of all bladder cancers originate from the epithelial layer, and 80-90% of these carcinomas are urothelial in nature (3). At the time of diagnosis, approximately 75% of patients are found to have non-muscle invasive bladder cancer (NMIBC), while 25% have muscle invasive bladder cancer (MIBC) (4,5). Radical cystectomy (RC) with extended lymph node (LN) dissection and urinary diversion is the gold standard treatment for patients with MIBC (6). Besides this treatment, adjuvant chemotherapy (ACT) is required for patients with poor prognosis. Morbidity and mortality can be observed in approximately 50% of patients after RC (7). The prognostic criteria of bladder cancer include LN metastasis, surgical margin (SM) positivity, presence of carcinoma *in situ* (CIS), lymphovascular invasion (LVI), and ineligibility to receive ACT (8,9,10,11,12). LVI is defined as the presence of tumor cells in lymphatic vessels and the vascular wall, which could increase the frequency of LN metastasis. Intravasation of cancer cells to the circulation via LVI and the development of micrometastases is one of the most important processes for metastatic disease (13). Previous research showed that LVI is a poor prognostic marker for testicular cancer and penile cancer (14). LVI in RC specimens is also known to be an independent prognostic factor for LN involvement, recurrence, and survival in patients with MIBC (15). Earlier studies demonstrated that LVI has negative effects on survival, especially among LN (-) patients (16). Therefore, in the present study, we aimed to investigate the effects of LVI and

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LN involvement on the overall survival (OS) and cancer-specific survival (CSS) of patients groups divided according to LVI and LN status after RC; the relationships of LVI with other prognostic factors are also evaluated.

Materials and Methods

Patients who underwent RS for MIBC or high-risk NMIBC between 2006 and 2019 in our clinic were retrospectively evaluated. Patients who had complete data and followed up in our clinic were included in the study. Patients diagnosed with other types of bladder cancer except urothelial carcinoma, those who received neoadjuvant chemotherapy, and those who had missing follow-up data were excluded from the study. The patients' characteristics and preoperative, perioperative, and postoperative data were reviewed. Clinical (i.e., age, gender, and preoperative hydronephrosis), preoperative pathological (i.e., preoperative T-stage and grade and presence of CIS), postoperative pathology (i.e., RC T-stage, number of LNs removed, LN involvement, and LVI), and oncological (i.e., upstaging, ACT, overall mortality, OS, cancer-specific mortality, and CSS) data were evaluated. Patients were divided into four groups according to their LVI and LN status described their final RC pathology reports. LVI (–) and LN (–) patients were categorized into group 1, LVI (+) and LN (–) patients were categorized into group 2, LVI (–) and LN (+) patients were categorized into group 3, and LVI (+) and LN (+) patients were categorized into group 4. All data were compared among the groups.

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences version 22.0 (SPSS, Chicago, IL, USA). The Kruskal-Wallis and chi-squared tests were used for univariate analysis. For multivariate analysis, Cox regression analysis was used to investigate the factors affecting OS and CSS. Inter-group survival analysis was evaluated by Kaplan-Meier survival analysis. Statistical significance was accepted as $p<0.05$.

Results

A total of 177 patients with a mean age and follow-up time of 64.4±9.4 years (range, 32-83 years) and 30.2±31.1 months (range, 1-116 months) were evaluated in this study. The mean OS and CSS of the patients were 56.6±4.2 and 68.9±4.5 months, respectively. When factors affecting survival rates were analyzed, LN positivity was not a significant predictive factor for OS (p=0.570) and CSS (p=0.533). However, LVI [p=0.002, hazard ratio (HR)=0.402] and SM positivity (p=0.001, HR=0.321) were significant predictive factors for OS. SM positivity (p=0.003, HR=0.314), LVI (p=0.011, HR=0.416), and ACT (p=0.009, HR=0.460) were also found to be independent predictive factors for CSS.

When we analyzed the groups based on LN and LVI status, 121 patients were categorized into group 1, 15 were categorized into group 2, 24 were categorized into group 3, and 17 were categorized into group 4. The distribution of pathological and clinical features and comparative results of the groups are given in Table 1. The demographic and preoperative pathological data were statistically similar between the groups. However, T-stage in the RC final pathology, SM positivity, and upstaging were significantly lower in group 1 and higher in group 4 than in other groups. The numbers of dissected LNs were similar between the groups. The ACT rate was higher in group 3 than in other groups, and overall and cancer-specific mortality rates were generally lower in group 1 than in other groups. The OS and CSS of group 2 (15.3±2.9 and 21.2±4.6 months, respectively) and group 4 (21.5±7.2 and 24.5±8.1 months, respectively) were found to be lower compared with those of other groups ($p<0.001$). The OS and CSS plots are given in Figures 1 and 2.

Discussion

MIBC often leads to high mortality despite RC and additional adjuvant or neoadjuvant treatments. Several prognostic factors have been found to be related to this high level of mortality. Thus, in the present work, we aimed to focus on one of these prognostic factors.

LVI has been shown in previous studies to be a risk factor for LN metastasis, recurrence, and poor OS (13). In our study, when we examined the effect of LVI on OS and CSS, we found that it was an independent factor for poor prognosis (p=0.002, HR=0.402 and p=0.011, HR=0.416, respectively). OS and CSS times were found to be lower in group 2 (15.3 and 21.2 months, respectively) and group 4 (21.5 and 24.5 months, respectively) than in group 1 (66 and 77.8 months, respectively) and group 3 (43.9 and 54.8 months, respectively) ($p<0.001$). This finding reveals that LVI is an independent prognostic factor that is as equally effective as LN positivity for predicting survival. Previous research reported that LVI is an independent predictor for LN metastasis (17,18). An earlier meta-analysis also showed that LVI occurred in 64.4% of LN (+) patients and 36% of LN (-) patients (19,20). In the current study, LVI was found in 41.5% (group 4) of LN (+) patients (groups 3 and 4) and in 11% (group 2) of LN (-) patients (groups 1 and 2). LN positivity is generally acknowledged to have a negative effect on survival rates. However, in the present study, LN positivity did not have a statistically significant effect on OS and CSS (p=0.570 and p=0.533, respectively). When we examined the factors responsible for this finding, we found that the rate of patients receiving ACT in group 3 was as high as 54.2%. The rates of patients receiving ACT were not distributed similarly among the groups. Moreover, group 4 revealed the highest upstaging rates and RC T-stages. As an important limitation of this study, the low number of patients in the groups may have contributed to this finding.

Another prognostic factor affecting OS in our study was SM positivity (p=0.001, HR=0.321). The independent prognostic factors affecting CSS were SM positivity (p=0.003, HR=0.314) and ACT (p=0.009, HR=0.460). OS and CSS were higher in group 3 than in group 4. Although LVI positivity in group 4 may contribute to this finding, the higher rate of ACT in group 3 than in group 4 may also explain this result (54.2% vs 35.3%). When we planned this study according to our hypothesis, we aimed to investigate how LVI affects OS and CSS, especially among LN (-) patients. However, our findings appeared to be more important than our hypothesis (21). Similar to our hypothesis, Lotan et al. (22) showed the prognostic significance of LVI in LN (-) patients

Table 1. Distribution of pathological and clinical features in groups based on LVI and LN status						
		Group 1 LVI (–) and LN (–) (n=121)	**Group 2 LVI (+) and LN (–) (n=15)**	**Group 3 LVI (–) and LN (+) (n=24)**	**Group 4 LVI (+) and LN (+) (n=17)**	**p**
Age		64.2±9.7 (32-83)	66.3±9.1 (54-80)	64.9±8.3 (47-79)	63.5±9.3 (46-79)	0.903
Gender	Male	111 (91.7)	13 (86.7)	22 (91.7)	16 (94.1)	0.894
	Female	10 (8.3)	2 (13.3)	2 (8.3)	1 (5.9)	
Preoperative hydronephrosis		37 (30.6)	5 (33.3)	14 (58.3)	5 (29.4)	0.082
Preoperative T-stage	≤T1	15 (12.7)	2 (13.3)	1 (4.3)	0 (0)	0.06
	T2	101 (85.6)	11 (73.3)	22 (95.7)	17 (100)	
	T3	2 (1.7)	2 (13.3)	0 (0)	0 (0)	
Preoperative grade	G1	3 (2.5)	1 (6.7)	0 (0)	0 (0)	0.577
	G2	5 (4.2)	0 (0)	1 (4.3)	1 (5.9)	
	G3	110 (93.2)	14 (93.3)	22 (95.7)	16 (94.1)	
Presence of CIS		30 (24.8)	6 (40)	6 (25)	6 (35.3)	0.528
T-stage at the RC final pathology	≤T1	30 (25.4)	2 (13.3)	1 (4.2)	0 (0)	<0.001
	T2	63 (53.4)	5 (33.3)	10 (41.7)	0 (0)	
	T3	14 (11.9)	4 (26.7)	9 (37.5)	6 (35.3)	
	T4	11 (9.3)	4 (26.7)	4 (16.7)	11 (64.7)	
Number of dissected lymph nodes		12±5.7 (1-30)	11.7±4.1 (7-24)	13.4±6.2 (4-33)	14.1±4.2 (8-21)	0.333
Upstaging		31 (25.8)	9 (60)	9 (90)	17 (100)	<0.001
SM positivity		9 (7.4)	4 (26.7)	5 (20.8)	7 (41.2)	0.001
ACT		25 (20.7)	5 (33.3)	13 (54.2)	6 (35.3)	0.01
Overall mortality		46 (38)	12 (85.7)	14 (58.3)	9 (69.2)	0.001
Overall survival		66±4.9 (56.4-75.6)	15.3±2.9 (9.7-20.9)	43.9±10.6 (23.2-64.6)	21.5±7.2 (7.5-35.6)	<0.001
Cancer-specific mortality		31 (25.6)	8 (57.1)	11 (50)	8 (61.5)	0.003
Cancer-specific survival		77.8±5 (68-87.6)	21.2±4.6 (12.1-30.2)	54.8±12.2 (30.7-78.8)	24.5±8.1 (8.6-40.4)	<0.001
LVI: Lymphovascular invasion, LN: Lymph node, RC: Radical cystectomy, CIS: Carcinoma *in situ*, SM: Surgical margin, ACT: Adjuvant chemotherapy						

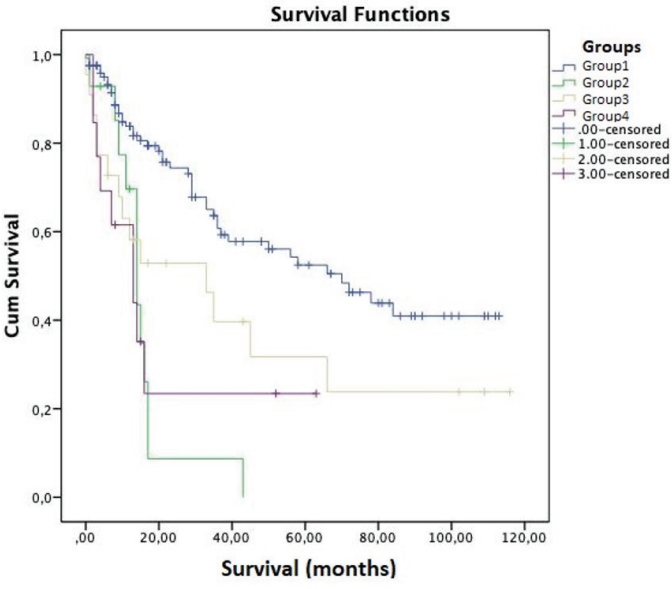

Figure 1. Overall survival curves of the groups based on LN and LVI status

LN: Lymph node, LVI: Lymphovascular invasion

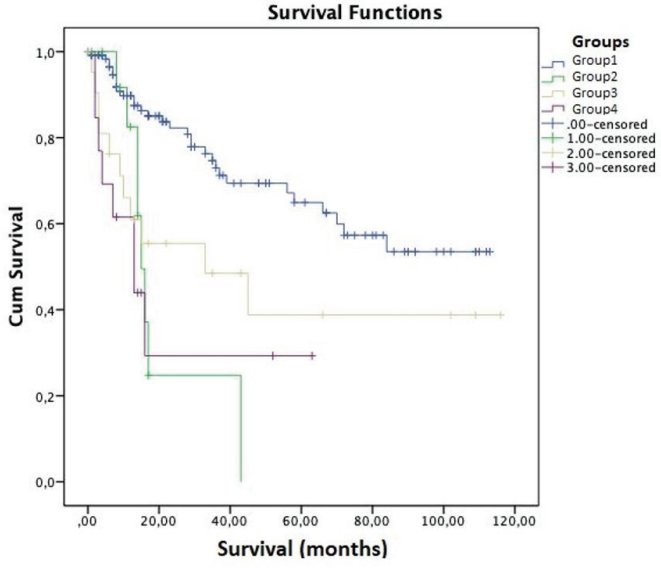

Figure 2. Cancer-specific survival curves of the groups based on LN and LVI status

LN: Lymph node, LVI: Lymphovascular invasion

only. Another study conducted by Lotan et al. (22) revealed that LVI is also an important risk factor for local recurrence, distant metastasis, and overall disease recurrence in LN (-) patients only. LVI was observed to have a negative effect on OS and CSS in LN (-) patients (16). When we evaluated the OS and CSS data of group 1 [LVI (-); 66 and 77.8 months, respectively] and group 2 (LVI (+); 15.3 and 21.2 months, respectively), survival was favored in LVI (-) patients, in accordance with the literature. These data reveal that the negative effect of LVI on survival is more important in LN (-) patients than in LN (+) ones. Therefore, these patients should be followed up regularly. Despite the limited number of patients included in this research, complete data and detailed examinations of the four groups reduced the possibility of bias. Thus, the oncological results determined in this work are similar to those reported in previous studies. This similarity and additional findings highlight the importance of our study.

Study Limitations

The small number of patients and the weak distribution among the groups are important limitations in our study.

Conclusion

LVI was observed to be an independent prognostic factor affecting OS and CSS. ACT, especially in group 3, improved CSS, but SM positivity had a negative effect on survival rates. Although LVI is an important factor for predicting survival, especially in LN (-) patients, large-series studies are needed to investigate the importance of LVI in LN (+) patients and clarify its relationship with LN positivity.

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Ethics

Ethics Committee Approval: This study is a retrospective cohort study.

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: G.C., S.Ç., İ.B., Design: G.C., S.Ç., E.Ş., Data Collection or Processing: A.Y., Analysis or Interpretation: S.Ç., İ.H.B., T.D., Literature Search: G.C., S.Ç., B.G., Writing: G.C., S.Ç., S.Y.

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