
The Importance of Lymphovascular Invasion at Radical Cystectomy

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Abstract: Objectives: To investigate relationship between the lymphovascular invasion(LVI) and tumor characteristics and to evaluate effect on survival of LVI in patients who underwent radical cystectomy because of bladder cancer. Materials and Methods: Five hundred and six patients were enrolled the study between 1990 and 2013. Patients were divided into two groups in terms of lymphovascular invasion at final pathology after radical cystectomy. There were 108 patients with LVI(group1) and 244 patients without LVI(group2). Both groups were compared in terms of clinicopathologic features and survival. Results: There was no statically different for gender in both group($p=0,222$).Lymh node involvement, grade, and p T stage were higher significantly in group 1($p<0,05$). Positive lymph node number was 2.3 ± 3.1 in group 1 and 0.6 ± 2.1 in group 2($p<0.001$). Lymph node density was 24.3 ± 30.1 in group 1 and 5.6 ± 9.2 in group 2 ($p<0.001$).Estimated mean survival time was 27.2 ± 3.4 months in group 1 and 80.2 ± 8.1 months in group 2 ($p<0.001$). Conclusions: Lymphovascular invasion is an independent prognostic factor for disease specific survival and effects survival negatively in patients who underwent radical cystectomy for bladder cancer. Patients with lymphovascular invasion should be considered for close monitoring after cystectomy.

Keywords: Lymphovascular Invasion (LVI), Radical Cystectomy, Survival, Urethelial Carcinoma

1. Introduction

Bladder cancer is the ninth most common cancer diagnosis worldwide, with more than 330,000 new cases each year and more than 130,000 deaths per year, with an estimated male-female ratio of 3.8:1.0. At any point in time, 2.7 million people have a history of urinary bladder cancer [1].

At the initial diagnosis of bladder cancer, 70% of cases are diagnosed as non-muscle-invasive bladder cancer and approximately 30% as muscle invasive bladder cancer [2]. Approximately one-third of patients diagnosed with muscle invasive bladder cancer have undetected metastases at the time of treatment for the primary tumour [3], while 25% of patients who undergo radical cystectomy present with lymph node involvement at the time of surgery. Radical cystectomy with extended bilateral lymphadenectomy is the standard therapy in patients with muscle invasive disease or in some cases of high grade superficial cancer refractory to conservative treatment [4].

Traditionally, independent variables of disease specific survival are grading, pathological stage and presence of

lymph node involvement [5-7]. The prognostic value of lymphovascular invasion (LVI) has previously been investigated by others [8,9].

The aim of our study was to assess prognostic role of lymphovascular invasion at final pathology after radical cystectomy for bladder cancer.

2. Materials and Methods

Five hundred and six consecutive patients underwent radical cystectomy with bilateral pelvic lymphadenectomy and consequently a urinary diversion for a primary muscle-invasive and refractory superficial bladder tumor from June 1990 to July 2013. Datas of 352 patients of all were achieved and analyzed retrospectively. Patients were divided into two groups in terms of lymphovascular invasion at final pathology after radical cystectomy for bladder cancer.

There were 108 patients with lymphovascular invasion (group 1) and 244 patients without lymphovascular invasion

at cystectomy specimen (group 2). Both groups were compared in terms of clinicopathologic features and survival.

LVI is defined as the presence of neoplastic cells within an endothelium-lined space. Patients with a non-transitional cell carcinoma or submitted to a salvage procedure or neoadjuvant/adjuvant chemo-radiotherapy were excluded

Chi-squared tests were used to evaluate the association between categorical variables. Independent T tests were used to compare parametric values. The Kaplan-Meier method was used to calculate survival functions, *p*-value of less than 0.05 was considered statistically significant. The SPSS (Statistical Package for Social Science, Chicago, IL, USA) software was used for the statistical analysis.

3. Results

Of the 352 patients, 326 were males and 26 females. LVI was present in 108 pathological specimens (30%). The mean age was 60.80 ± 8.6 years in group 1 and 61.20 ± 9.2 years in group 2 ($p=0.803$). There was no statically different for gender in both groups ($p=0.222$). Lymph node involvement, grade, and p T stage were higher significantly in group 1 ($p<0.001$, $p<0.001$, $p<0.001$ respectively). Demographic

and histopathological features stratified according to LVI are listed in Table 1.

Table 1. Demographic and histopathological features of patients.

	LVI+ (n)	LVI- (n)	P value
Mean age	60.84 ± 8.6	61.2 ± 9.2	0.803 ^a
Male	96	230	0.222 ^b
Female	12	14	
Grade 1	2	14	
Grade 2	10	60	<0.001 ^b
Grade 3	96	170	
pT1	2	64	
pT2	16	10	<0.001 ^b
pT3	46	44	
pT4	4	18	
Lymph node involvement	78	38	<0.001 ^b

^aindependent student t test, ^bchi square test

Mean follow up time was 15.10 ± 12.7 months in group 1 and 34.7 ± 34.7 in group 2 ($p<0.001$). Positive lymph node number was 2.3 ± 3.1 in group 1 and 0.6 ± 2.1 in group 2 ($p<0.001$). Lymph node density was 24.3 ± 30.1 in group 1 and 5.6 ± 9.2 in group 2 ($p<0.001$) (Table2). Estimated mean survival time was 27.2 ± 3.4 months in group 1 and 80.2 ± 8.1 months in group 2 ($p<0.001$) (Figure 1).

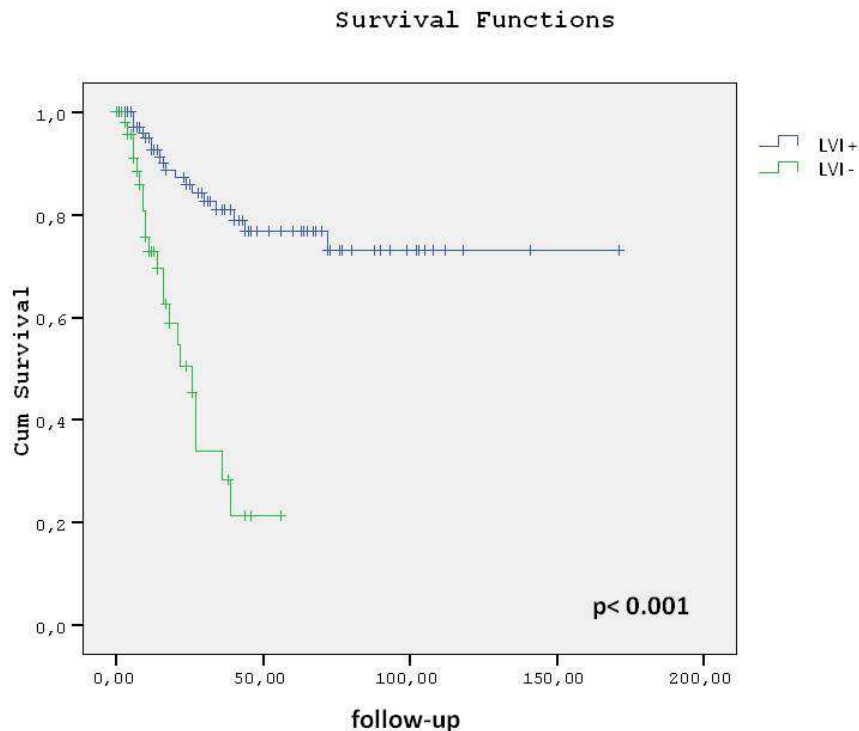


Figure 1. The effect on the survival of lymphovascular invasion (Kaplan-Meier)

In cox regression analyses; lymphovascular invasion ($p<0.005$), p T stage ($p<0.001$) and lymph node involvement ($p=0.02$) were independent significant prognostic for disease-specific survival.

Table 2. Association of lymphovascular invasion with lymph node status and follow-up time.

	LVI+	LVI-	p*
Mean follow-up time (months)	15.1 ± 12.7	34.7 ± 34.7	<0.001
Positive lymph node number	2.3 ± 3.1	0.6 ± 2.1	<0.001
Lymph node density	24.3 ± 30.1	5.6 ± 9.2	<0.001
Estimated mean survival time	27.2 ± 3.4	80.2 ± 8.1	<0.001

*Independent student t test

4. Discussion

LVI is the first step of metastatic spread in the natural history of cancer and corresponds to infiltration of the local vascular and lymphatic microcirculation by tumor cells. LVI can be detected on hematoxylin and eosin stained sections [10].

The predictive value and prevalence of lymphovascular invasion is strongly dependent on the type of cancer. In other words, LVI in one type of cancer may be much less important than LVI in another type of cancer.

Generally speaking, it is associated with lymph node metastases which themselves are predictive of a poorer prognosis [11-13]. In the context of (histologically) proven lymph node metastases, LVI may have less prognostic significance or no prognostic significance. In other studies, however, LVI was not a predictor of lymph node metastases [14] or survival [5,15]. In our study, lymph node involvement was significant higher in patients with LVI.

Stein et al. demonstrated that LVI was a significant and independent prognostic factor for cancer-specific survival, as well as pathological staging and presence of node metastasis. In the present study, we found similar results between the lymphovascular invasion and survival and prognostic factors [4]. Herrmann et al. reported that pathological tumour stage ($p < 0.0001$), lymph node status ($p = 0.004$) and LVI ($p = 0.001$) were independent prognostic factors associated with unfavourable overall survival in a cohort of 833 patients [16]. Canter et al. analysed data from 356 patients treated with radical cystectomy at the University of Pennsylvania and at univariate analysis found that the presence of LVI conferred a risk for decreased overall, cancer-specific and recurrence-free survival ($p < 0.0001$) [9]. Bassi et al. found that only tumor stage and nodal involvement were independent prognostic variables on multivariate analysis [5]. Lymphovascular invasion is also important for superficial bladder cancer especially high grade tumors [17,18].

In our multivariate analyse; lymphovascular invasion, pT stage and lymph node involvement were independent significant prognostic for disease-specific survival

Other parameters were association of lymphovascular invasion with positive lymph node number and lymph node density in our study. Positive lymph node number and lymph node density are significant prognostic factors for disease specific survival [19-21]. In our study, mean positive lymph node number and lymph node density were significantly higher for lymphovascular invasion. In the presence of lymphovascular invasion, lymph nodes should be examined carefully and considered for close monitoring after cystectomy

There are several limitations in this study including retrospective design, single-centre and small size of groups. Our results should be supported by prospective randomized studies.

5. Conclusion

Lymphovascular invasion is an independent prognostic

factor for disease specific survival and effects survival negatively in patients who underwent radical cystectomy for bladder cancer. Patients with lymphovascular invasion should be considered for close monitoring after cystectomy.

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