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ORIGINAL RESEARCH

The Role of Lymph Node Density in Predicting Survival Post-Cystectomy in Patients with Bladder Cancer; A Single-Center Retrospective Analysis

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Abstract: **Background:** Lymph Node involvement in patients with bladder cancer directly affects their prognosis after cystectomy. With the advent of various extensions for lymphadenectomy during radical cystectomy, Lymph Node Density (LND) has been introduced as a stable measure to quantify the extent of LN involvement. This study evaluates the prognostic value of LND on the survival of these patients in our center. **Methods:** Our historical cohort reviewed the clinical records of 165 patients who underwent cystectomy at Modarres Hospital in Tehran, Iran during 2012-2018. The presence of positive LNs, the total number of positive LN, and LN density were evaluated for their effect on Overall survival (OS) and recurrence-free survival (RFS) at 3- and 5-years post-surgery. In addition, we assessed the impact of age, gender, type of diversion, P stage, lymphovascular invasion (LVI), location of involved LNs, ureteral involvement, positive surgical margin, and the presence of carcinoma in situ on patients' survival. **Results:** According to ROC curve analysis, an LND cut-off point of 10.82 was calculated to predict patients' survival (AUC:0.70, 95%CI: 0.496-0.691). An LND >10.82 significantly increased the risk of cancer-related death. Among all study variables, LND had the most prominent effect on OS (HR:2.49, 95% CI:1.3-4.4, P=0.002). For 3- and 5-year RFS, LVI had the highest impact (HR: 2.63, 95% CI: 1.3-5.1, P=0.005 and HR: 1.96, 95% CI: 1.2-3.0, P=0.002, respectively) **Conclusion:** Our analysis indicates that an LND >10.82 has the highest predictive potential for OS among the pathological features of patients undergoing cystectomy.

Keywords: Bladder cancer, Lymph-node density, Radical cystectomy, Overall survival

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1. Introduction

Bladder cancer imposes a significant burden on the healthcare system, with over 430,000 new cases diagnosed each year worldwide. Muscle-invasive bladder cancer is a particularly lethal form, with only 15% of affected individuals surviving beyond 2 years if left untreated (1). Radical cystectomy (RC) with Lymph Node (LN) dissection is the standard treatment for muscle-invasive bladder cancer and the presence of positive LNs has been mentioned as an adverse prognostic factor in these patients (2).

Attempts to provide better stratification of LN-positive patients have led to the introduction of LN density (LND) (the ratio of positive LNs to the number of total LNs removed) as a prognostic marker. LND was first introduced in two separate studies by Stein (3) and Herr (4) as a marker of worse prognosis in cystectomy patients. It has also been noted to have superior prognostic value than the AJCC (American Joint Committee on Cancer) TNM staging (5). However, despite these studies and also some controversies regarding N staging in standard TNM, LND has not been included as a standard prognostication tool (6). Additionally, while the presence of positive LNs after surgery is considered a prognostic tool and an indication for adjuvant treatments, no definitive cut-off value for LND has been established.

To report LND in patients with cystectomy with standard

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template lymph node dissection, and due to the lack of national studies in the Iranian population regarding LND, we designed this cohort to test the predictive potential of LND as a prognostic tool in cystectomy patients at our center.

2. Materials and Methods

2.1. Study Population

Patients with bladder cancer who underwent RC and lymphadenectomy with curative intent at Modarres Hospital between 2012 and 2018 were considered for this cohort. Our ethics committee approved the design under the code: IR.SBMU.MSP.REC.1399.736. Only cystectomies accompanied by lymph node dissection were included. Patients without LN dissection, inconclusive pathology reports, a history of neoadjuvant chemotherapy, or palliative cystectomies were excluded from the analysis. In the end, 165 patients were eligible for the final analysis. All lymph adenectomies followed the standard template, including the external iliac vein, the internal iliac artery with an extension over the common iliac artery distal to ureter crossing, and the obturator fossa.

All patients were staged using the 2017 AJCC TNM staging. Pathology reports before this were re-evaluated to meet the new staging definitions. Pathologic T stage, N stage (including location, total number of resected LNs, and the number of positive LNs), presence of Lympho-Vascular Invasion (LVI), ureteral involvement, presence of Carcinoma in Situ (CIS), and surgical margin were extracted from patients' records.

All patients had a routine follow-up plan with periodic laboratory evaluations, physical exams and imaging. Recurrences were defined as any enhancing lesion in radiologic evaluations. The cause of death was confirmed by death certificate. Results were calculated based on clinical recurrence and overall survival. Time of clinical recurrence or recurrence free survival was measured from the time of cystectomy until the emergence of the first verified clinical recurrence or until the time of the last follow-up visit without evidence of clinical recurrence.

3. Statistical Analysis

Mean and standard deviation were used for description of quantitative data while the qualitative data were described by prevalence and percentage. Chi-square, Fisher's exact, and t-tests were used to evaluate the relationship between clinical and pathological variables with disease outcomes. Kaplan Meyer analysis was used to evaluate recurrence-free survival and overall survival. Hazard ratios for variables affecting RFS and OS were measured using Cox regression. The Area Under the Curve (AUC) of the Receiver Operating Characteristics (ROC) curve was used to quantify the predictive accuracy of LND. A cut-off point was calculated to determine the predictability potential of LND in foretelling the study parameters. P<0.05 was considered statistically significant. SPSS version 22 software was used for all analyses.

4. Results

Out of 165 patients, 49 (30%) died of cancer. The mean age of deceased patients was older than that of surviving patients (67.98 vs. 63.92 years, P=0.03). Tumor burden significantly affected patient survival, as 75% of those without positive LNs were alive at the time of analysis (P=0.027).

According to ROC curve analysis, an LND cut-off point of 10.82 was calculated to predict patient survival (AUC:0.70, 95%CI: 0.496-0.691).

Seventy-six percent of patients with an LND lower than 10.82 were alive at the time of the study (P=0.004). The distribution of clinical and pathologic features of our study population is presented in Table 1.

Overall survival (OS), and 3- and 5-year Recurrence Free Survival (RFS) were 49.62%, 75.14%, and 71.40%, respectively. LVI (p<0.0001), the presence of positive LNs (P=0.014), and LND (P=0.015) had a statistically significant effect on 3-year RFS. Only LVI (P=0.011) had a positive effect on 5-year RFS (Table 2).

Figure 1 demonstrates the Kaplan-Meyer curve for survival analysis of patients with LVI, positive LNs, and LND. The 3- and 5-year RFS for patients with LVI was 70.06% and 66%, respectively. For patients without LVI, it was 84.45% and 76.42%, respectively. For patients with an LND of ≤10.82, the 3- and 5-year RFS was 82.75% and 70.74%, respectively, whereas for patients with an LND >10.82, it was 53.84% and 53.84%, respectively.

Survival analysis of our study population demonstrated that in patients without LVI, the 3-year RFS was 2.63 times higher than in patients with LVI (P=0.005). For 5-year RFS, this was 1.96 times higher (P=0.002). In patients with an LND >10.82, the risk of cancer-related death was 2.49 times higher than in patients with LND ≤10.82 (P=0.002).

5. Discussion

Given that the total number of positive LNs is directly influenced by the extent of LN dissection during cystectomy, and since there is no consensus on the appropriate extent of dissection for different clinical stages of bladder cancer, calculating LND as a measure to stratify LN involvement is pertinent.

The importance of LND and its effect on the survival analysis of patients with bladder cancer who underwent cystectomy with curative intent has been highlighted in multiple studies (5-19). Furthermore, it has been reported as superior to TNM

staging in predicting survival (5, 20), and its significance as a prognostic tool has also been noted in upper tract urothelial carcinoma (21).

Consistent with previous studies, our research demonstrated the role of lymph node involvement in the survival of these patients. Among all the variables we reviewed, only the extent of LN involvement had a significant effect on overall survival. The impact of lymph node involvement was also evident in 3- and 5-year RFS. The predictive accuracy of LN density has been evaluated in several studies and different cut-off values (ranging from 10 to 25) have been introduced. In the study by Herr et al., with a 7.5-year follow-up of patients after radical cystectomy, only an LND of 20% had a statistically significant effect on patients' recurrence and survival in multivariable analysis, while the presence of positive lymph nodes or pathological stage did not demonstrate a positive effect on recurrence or survival (4). After analyzing 248 cystectomy patients with LN metastasis (without a history of neo-adjuvant chemotherapy), researchers found that both the number of involved LNs and LND were predictive of patients' survival in univariate analysis. However, in multivariate analysis, only an LND > 20% was an independent factor (20). These results were also repeated in other studies, including those by Fleischmann and colleagues (15). Several studies have shown that an LND threshold of 20% had more predictive potential than the pathological stage in predicting survival (11, 14, 15, 19).

Other cut-off values in the literature are 15% (12), 18% (17), and 25% (13, 16), with the common conclusion that LND has a better prognostic value than the number of positive LNs in predicting survival. Our calculated cut-off value of 10.82% is close to studies by Weisner and co-workers (11%), and Jensen and colleagues (10%) (6, 7). In these studies, the extent of LN dissection extended up to inferior mesenteric artery, compared to other studies which included various extents of dissection. Additionally, the median number of removed LN in Weisner's study was 33, which was higher than other studies, partly explaining the lower threshold of LND cut-off value.

Compared with our study, despite the lower amount of removed LNs, we had a similar threshold to Weisner's study. This could be attributed to the higher number of pT3-pT4 stage patients in our cohort (82 vs 64). However, we reached the same conclusion that LND is an independent predictor of survival in LN-positive patients.

The limitations of our study include its retrospective nature, with its inherent flaws. Furthermore, the extension of lymph node dissection is not identical to other studies due to the lack of a standardized plan for LN dissection, which limits the generalizability of our data.

6. Conclusion

In a nutshell, we confirmed the prognostic relationship between LND and survival in cystectomy patients with involved pelvic LNs. Although there is no unified threshold for LND, it is apparent that with an increase in LND, the prognosis of patients worsens. Further studies to better characterize LN dissection plan according to cancer stage will further increase the applicability of LND in bladder cancer prognostication.

7. Appendix

7.1. Acknowledgment

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7.2. Conflict of Interest

None.

7.3. Funding and supports

None.

7.4. Authors contributions

None.

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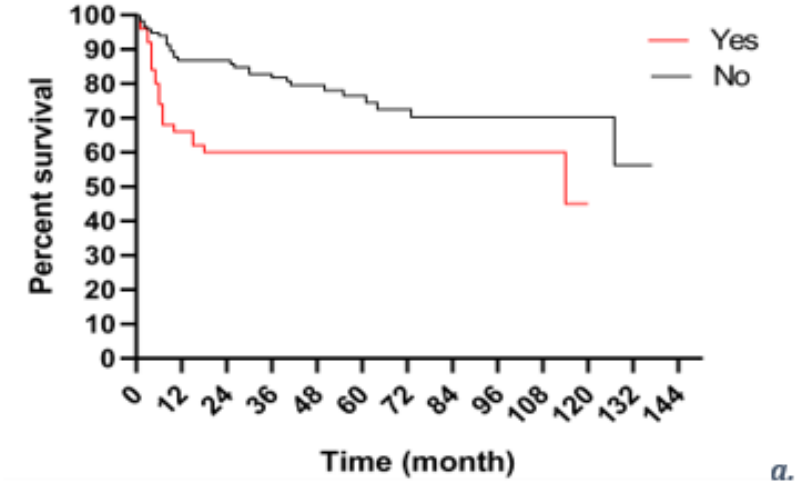
Table 1: Clinical and pathological characteristics of our study population

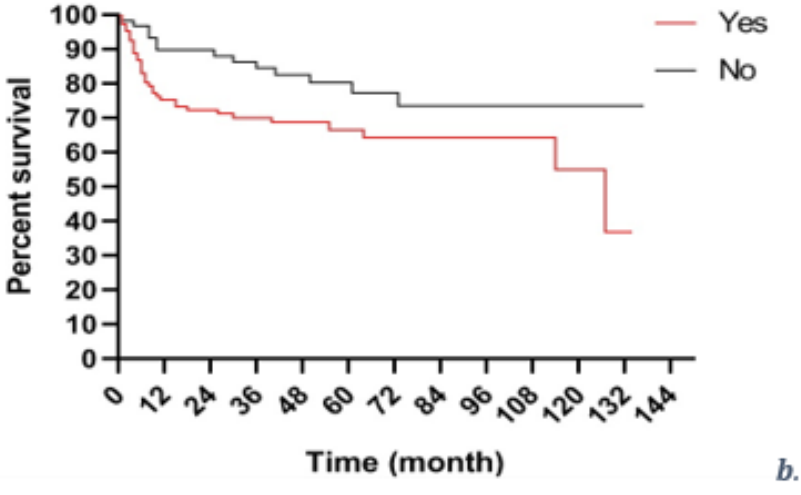
Variable	Sub Group	Frequency (%)		Mean ± SD		P- Value
		Alive (n=116)	Deceased (n=49)	Alive (n=116)	Deceased (n=49)	
Gender	Male	(90.5)105	(95.9)47	-	-	0.348
	Female	(9.5)11	(4.1)2	-	-	
Age (years)		-	-	63.92±10.72	67.98±11.32	0.03
Type of diversion	Ileal Conduit	(50.9)59	(61.2)30	-	-	0.214
	Orthotopic	(19.8)23	(22.4)11	-	-	
	Uretero-cutaneous	(29.3)34	(16.3)8	-	-	
Adjuvant Chemotherapy	Yes	13(11.2)	19(38.8)	-	-	<0.0001
	No	103(88.8)	30(61.2)	-	-	
P stage	Ta	(1.7)2	(2)1	-	-	0.066
	T1	(20.7)24	(10.2)5	-	-	
	T2a	(16.4)19	(16.3)8	-	-	
	T2b	(10.3)12	(4.1)2	-	-	
	T3a	(24.1)28	(36.7)18	-	-	
	T3b	(0.9)1	(8.2)4	-	-	
	T4a	(25.9)30	(22.4)11	-	-	
Lympho-vascular invasion	Yes	(60.3)70	(73.5)36	-	-	0.144
	No	(39.7)46	(26.5)13	-	-	
Mean number of removed LNs	-	-	-	11.52±10.01	12.06±10.13	0.751
Mean Number of Positive LNs	-	-	-	2.78 ± 1.01	3.11 ± 1.86	0.086
Presence of positive LNs	Positive	(25)29	(42.9)21	-	-	0.027
	Negative	(75)87	(57.1)28	-	-	
Lymph node density	≤10.82	(82.8)96	(61.2)30	-	-	0.003
	>10.82	20(17.2)	19(38.8)	-	-	
Positive lymph nodes' location	Iliac	(9.5)11	(12.2)6	-	-	0.117
	Obturator	(2.6)3	(8.2)4	-	-	
	Obturator and Iliac	(59.5)69	(65.3)32	-	-	
Ureteral involvement	Yes	(12.1)14	(12.2)6	-	-	1
	No	(87.9)102	(87.8)43	-	-	
Positive margin	Yes	(14.7)17	(8.2)4	-	-	0.314
	No	(85.3)99	(91.8)45	-	-	
Carcinoma in Situ	Yes	(22.4)26	(28.6)14	-	-	0.399
	No	(77.6)90	(71.4)35	-	-	

Table 2: Cox-regression analysis of effective risk factors in 3- and 5-year Recurrence Free Survival (RFS) and Overall Survival (OS)

Variable		Hazard Ratio	95% CI	P-value
3-years RFS	LVI	2.63	5.198- 1.329	0.005
	Positive LNs	1.29	3.306- 0.500	0.603
	LND	1.30	3.458- 0.490	0.598
5-years RFS	LVI	1.96	3.004- 1.284	0.002
OS	LND	2.49	4.444- 1.391	0.002

LVI: Lymph-Vascular Invasion, LN: Lymph Node, LND: Lymph Node Density, CI: Confidence Interval.





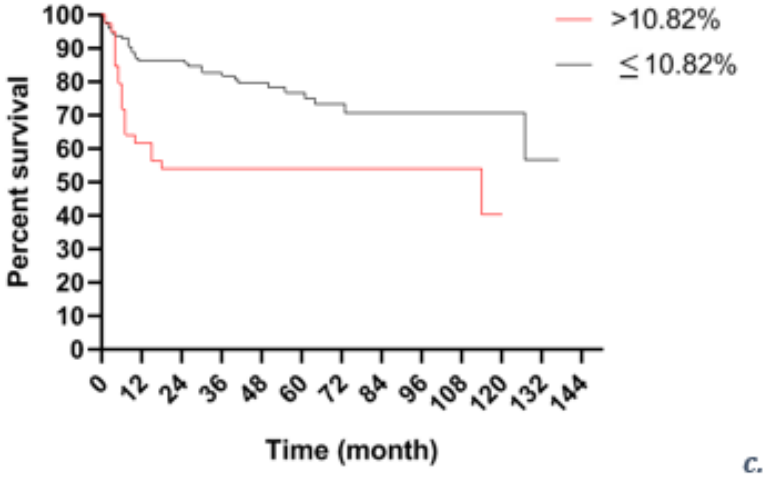


Figure 1: Kaplan-Meyer curve for survival analysis of patients with Lympho-vascular Invasion (LVI) (a), presence of positive Lymph Nodes (LN) (b) and Lymph Node density (LND) (c).