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Predictors of Lymph node involvement in bladder cancer treated with radical cystectomy

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Abstract

Objective: To identify the clinical variables associated with prevalence of lymph node metastasis in patients with bladder cancer treated by radical cystectomy and lymphadenectomy for primary bladder cancer.

Methods: Review of records of Ninety-five patients who underwent radical cystectomy and pelvic lymph node (LN) dissection during the period of 1995-2008 from a prospectively maintained database. Eighteen patients were excluded due to lack of data on the nodal status, leaving 77 evaluable patients. Associations between LN metastasis and age, gender, duration of disease, number of transurethral resection (TUR) prior to cystectomy, pathological grade and tumour stage was analyzed. Data was analyzed using the SPSS software, version 15. Statistical tests applied were independent sample t test or the Mann Whitney U test, the chi-square test and the Fischer exact test.

Results: The median age of the patients was 58 years in lymph node negative group and 63 years in lymph node positive group. There were 87% males and 13% females. LN metastasis was detected in 19 (25%) patients. Mean duration of disease in LN negative patients was 537±997 days compared to 509±708 days in LN positive patients. Mean number of TUR were same in both the groups, pathological grade was not found significantly different in both groups, where as primary tumour stage was found to be significantly ($p<0.05$) higher in LN positive patients.

Conclusions: Higher primary tumour stage at radical cystectomy is associated with higher prevalence of lymph node metastasis (JPMA 59:516; 2009).

Introduction

Pelvic lymph node dissection (PLND) has a role in the treatment of several genitourinary cancers. The pathological stage and grade of the bladder tumour and the presence of lymph node metastasis are the most important determinants of survival in patients with bladder cancer undergoing radical cystectomy.^{1,2} There has been a continuous search for reliable methods for preoperative assessment of lymph node status. Lymphangiography with fine needle aspiration has been evaluated in several studies, but it is not reliable due to a high false-negative rate.³ Preoperative imaging studies like computed tomography (CT) was investigated to determine its capacity to detect lymph node metastases in bladder cancer and the results have been largely disappointing with a high (21%) false-negative rate observed.⁴ In addition, results with positron emission tomography (PET) are not very promising either.⁵

Despite an early and aggressive approach towards high-grade invasive bladder cancer,⁶ nearly 25% of patients demonstrate pathologic evidence of lymph node metastases at the time of cystectomy.⁷ Radical cystectomy is considered the standard of care in the management of high grade and muscle invasive bladder cancer. Bilateral pelvic lymphadenectomy is now considered as an essential part of

the radical cystectomy for bladder cancer. There is little debate regarding the benefits of a lymph node dissection. The combination provides excellent local control and long term survival for most patients with $>pT2$ cancer.⁸ It is not only important for accurate staging but may also have a therapeutic benefit in terms of reducing loco regional recurrence. The limited lymph node dissection is generally described as an extirpation of the lymphatic tissue in the obturator fossa.⁹ Another method of dissection is standard dissection¹⁰ includes the area stretching laterally as far as the genito-femoral nerve, medially to the base of bladder and posteriorly to the bifurcation of common iliac vessels. Operative technique referred to as an extended nodal dissection^{11,12} has the cranial boundary of lymphadenectomy extended to the aortic bifurcation or even up to the inferior mesenteric artery (IMA).

Lymph node involvement is associated with increased risk of local recurrence and disease progression with survival rates varying from 20% to 40% in patients with and without lymph node metastasis respectively.^{13,14} The practice of lymphadenectomy is not standardized. Data from one centre showed that the number of nodes retrieved per patient could vary from 0-53.¹⁵ Recent evidence suggests that both the number of nodes removed⁸ and method of submission of nodal specimen¹⁶

affect the patient outcome.

Invasive bladder tumours tend to invade progressively from their superficial origin in the mucosa to the lamina propria and sequentially into the muscularis propria, perivesical fat, and contiguous pelvic organs, with an increasing incidence of lymph node involvement at each site. A surgically positive lymph node in invasive bladder cancer generally implies distant micro-metastasis; thus, preoperative identification of lymph node status is important. Various anti-oncoproteins were evaluated for their accuracy in predicting lymph node metastasis.¹⁷ The current work evaluates the practice of nodal dissection and the variables affecting nodal metastasis during radical cystectomy.

Methods

Between 1995 and 2008, 95 patients underwent radical cystectomy for primary bladder cancer. The hospital is in the private sector and not a referral centre for oncological surgery. It has three trained oncological urologists and all types of urinary diversions including orthotopic bladder replacements are performed. Tumour staging was performed using TNM (T, tumor stage i.e. T0-T4; N, nodal stage N0-N2; M, metastases i.e. Mx M1-2) staging system. Grading was done according to the classification of the World Health Organization (WHO) published in 1973 (WHO 1973) includes urothelial papilloma and three grades of papillary carcinoma (grade 1, or G1; grade 2, or G2; and grade 3, or G3).¹⁸ In case of pathological evidence prefix of small p is added (e.g. pT2).

Eighteen patients (19%) patients had lack of data on nodal status and were excluded. Patients were stratified according to the presence or absence of lymph node (LN) metastasis at the time of radical cystectomy. The prevalence of lymph node metastasis was correlated with age, gender, number of transurethral resections (TURBTs), duration of disease (from diagnosis to Radical cystectomy), tumour grade, stage of the tumour at radical cystectomy and type of lymphadenectomy. Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, and Chicago, Ill, USA). Continuous variables were compared between the groups using the independent sample t test or the Mann Whitney U test. The chi-square test and the Fischer exact test were used to compare categorical and dichotomous variables. A P value less than 0.05 was considered significant.

Results

Of the 95 patients, 18 were excluded due to lack of information on the pathological evaluation of the lymph nodes (Figure). There was significant male dominance in the series (male 87%, female 13%). Median age of the

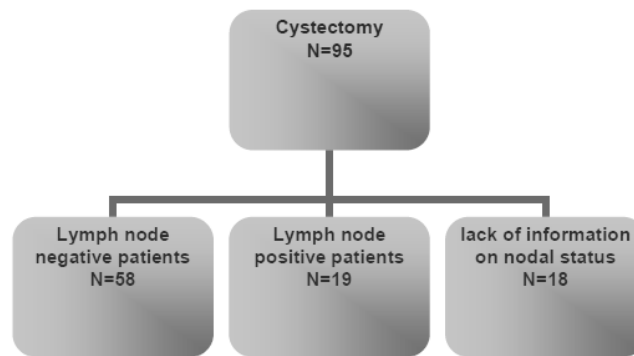


Figure: Patient's distribution according to the lymph node status.

patients was 58 years in lymph node negative group and 63 years in lymph node positive group which was not significant statistically. Out of 77 evaluable patients', pathologically nodal positive were 19 (25%) (Table-1).

Table 1: Difference in the nodal positivity in relation to gender, tumor stage, grade and type of lymphadenectomy.

		Lymph Node status			
		Negative (n = 58)		Positive (n = 19)	
		n	%	n	%
Gender					
(p-value=0.701)	Male	51	87.9%	16	84.2%
	Female	7	12.1%	3	15.8%
Primary Tumour Stage					
(p-value<0.05)	T0	7	12.1%	0	.0%
	T1	3	5.2%	0	.0%
	T2	31	53.4%	8	42.1%
	T3	9	15.5%	6	31.6%
	T4	8	13.8%	5	26.3%
TCC Grade					
(p-value=0.538)	G1	1	1.7%	0	.0%
	G2	14	24.1%	3	15.8%
	G3	43	74.1%	16	84.2%
Type of lymphadenectomy					
(p-value=0.434)	Standard (n=34)	24	41.4%	10	52.6%
	En bloc (n=43)	34	58.6%	9	47.4%

Mean duration of disease in LN negative patients was 537±997 days compared to 509±708 days in LN positive patients, mean number of transurethral resections were 1.43±0.5 in node negative, and 1.42±0.6 in node positive group (Table-2). The association of the grade of tumour at radical cystectomy showed that out of 18 patients with G1-2 lesion only 3 (16.6%) had lymph node metastasis, of the 59 patients with G3 lesion, 10 (27%) had lymph node metastasis, though lymph node positivity increases as the grade increases but the difference is not statically significant (p 0.538). Most of the patients had pT2 (51%) disease. None of the 10 patients with pT0-1 had positive nodes. Eight (20.5%) of 39 patients with pT2 disease had positive nodes, however, 11 (39.2%) out of 28

Table 2: Impact of number of TUR, mean duration of disease and age on the lymph node positive status.

Lymph Node positivity	N	Mean	Std. Deviation	Std. Error Mean
No	58	57.60	12.781	1.678
Yes	19	62.89	12.160	2.790
No	58	537.38	996.899	130.899
Yes	19	509.63	707.721	162.362
No	58	1.43	1.078	.142
Yes	19	1.42	.961	.221

patients had positive nodes in stage pT3-4 disease ($p < 0.05$). lymph node positivity was higher in patient who underwent standard lymphadenectomy as compare to en block dissection 29% vs. 21% (p -value=0.434).

Discussion

Lymph node (LN) metastasis is seen in 14 to 28% of patients who undergo pelvic lymphadenectomy during radical cystectomy for bladder cancer.^{6,7} LN metastasis is associated with an increased risk of local recurrence, regional disease progression and overall poorer outcome. Extended and standard lymphadenectomy is not only important in accurate disease staging but also provides direct survival benefit. The importance of nodal dissection with therapeutic intent is increasingly realized. Recent evidence has shown that node positive disease is a significant and independent prognostic factor. Imaging studies are not reliable in predicting nodal involvement prior to surgery, therefore other predictors could help in designing management plan. Duration of disease, number of TUR, age of the patient, stage and grade at cystectomy as predictors of nodal disease were analyzed. In the small cohort studied, primary tumour stage was found to have statistically significant association with nodal disease.

The absolute boundaries of lymphadenectomy remain a subject of controversy. Abol Enien and colleagues¹¹ noted that in extended lymphadenectomy there is 37% bilateral and 60% unilateral node positive disease. Dissection of only internal iliac nodes will miss 85% positive nodes, whereas dissection of internal, external iliac and Obturator nodes will identify 2/3rd of the nodes whereas dissection up the aortic bifurcation locates 4/5th of the nodes. A recent study has shown that compared to en bloc resection, standard lymphadenectomy increases the nodal yield and node positive disease.¹⁸

The guidelines published in March 2008 for the treatment of muscle invasive bladder cancer by The European Association of Urology recommends lymphadenectomy as an integral part of radical cystectomy but the extent of lymphadenectomy is not established yet.^{9,13,19} This consists of removing the tissue in the

Obturator fossa in patients undergoing surgery with a curative intent. Several authors have noted an improved 5-year survival with extensive pelvic lymph node dissection in patients with node positive bladder cancer.^{1,19,20} Herr and colleagues⁸ examined whether the number of nodes removed would affect outcomes after radical cystectomy. These investigators found that a minimum of nine nodes needed to be examined to accurately assess nodal status. They also found that survival improved in both node positive and node-negative patients as the number of nodes removed increased. The same investigators evaluated the impact of submitting nodes en bloc or as separate packages and suggested that submitting nodes as separate packages not only is easier but also optimizes the evaluation and number of the lymph nodes retrieved. Some studies indicate that lymphadenectomy, in combination with radical cystectomy — can cure a small fraction of node-positive patients.¹⁴

Conclusion

The current work indicates that although grade of tumour and mean age of the patient at radical cystectomy have a positive association with node positive disease, it is not statistically significant, due perhaps to the small number of patients. Among analyzed variables, only primary tumour stage was found significantly different in lymph node positive and lymph node negative group.

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