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TOPIC PAPER

The role of lymph node density in bladder cancer prognostication

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Abstract Pelvic lymph node metastases from bladder cancer occur in about 25% of patients undergoing radical cystectomy. While the majority of patients with lymph node metastases will develop progressive disease, some patients do exhibit long-term survival with and without adjuvant chemotherapy. The concept of lymph node density has been proposed as a means to stratify patient prognosis since it takes into account two important factors—the number of positive nodes (tumor burden) and the total number of nodes removed/examined (extent of dissection). Due to the lack of agreement on the extent of lymphadenectomy, lymph node density facilitates standardization of lymph node staging, thus allowing for adjuvant therapies and clinical trials to be more uniformly applied. Whether lymph node density provides improved prognostication over the standard nodal staging or absolute number of positive lymph nodes remains controversial. We review the literature regarding the role of lymph node density in the prognostic stratification of node-positive bladder cancer.

Keywords Lymph nodes · Cystectomy · Bladder neoplasms · Lymphadenectomy

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Introduction

Pelvic lymph node involvement with urothelial cancer occurs in approximately 25% of patients undergoing radical cystectomy [1]. Despite an aggressive multimodal treatment approach, approximately 70% of the patients with pathologic lymph node metastases will develop a recurrence within 5 years of surgery with the majority eventually dying from metastatic progression [2–4]. Although nodal involvement portends a relatively poor prognosis, some patients do exhibit long-term survival following surgery with or without systemic chemotherapy [5–7]. Several prognostic factors have been previously reported for node-positive patients, including the number of nodes involved [8, 9], the number of lymph nodes removed at cystectomy [10–12], the pathologic stage of the primary tumor [13], the presence of lymphovascular invasion in the primary tumor [14], the presence of extranodal extension [15, 16], and lymph node density [17, 18].

The concept of lymph node density for bladder cancer, that is the number of lymph nodes containing metastatic deposits divided by the total number of nodes removed and examined, was first described in 2003 in two separate and independent reports by Herr at Memorial Sloan-Kettering [18] and Stein and colleagues at the University of Southern California [17]. This novel approach to stratifying patients with node-positive disease was an attempt to allow for standardization of lymph node staging, thereby providing a means by which adjuvant therapies and clinical trials could be more uniformly applied. It takes into account two important prognostic factors—the lymph node tumor burden (number of nodes involved) as well as the meticulousness of the node dissection (number of nodes removed). The potential usefulness of lymph node density to stratify node-positive patients, therefore, should not be surprising.

Herein, we review the literature on lymph node density as it relates to clinical outcomes following radical cystectomy for bladder cancer.

Studies on lymph node density

Ten retrospective studies were identified that reported on a total of 2,790 patients. Some of the studies represented updates of previously reported series and therefore the total number of unique patients reported on was approximately 2,027. Eight of the studies represented single- or double-institutional surgical series and two were based on the Surveillance, Epidemiology, and End Results (SEER) population registry. The data is summarized in Table 1.

The reported cephalad extent of the lymphadenectomy varied between studies as well as within some of the same studies that reported on outcomes from different surgeons. The cephalad border ranged from the distal common iliac region to the distal aorta (2 cm above the aortic bifurcation or level of the inferior mesenteric artery). Population-based studies did not report anatomic boundaries due to the nature of the pooled data.

Median follow-up for the series, when reported, ranged from 1.8 years to 15.5 years covering a treatment time period from 1971 to 2005. The median number of nodes removed/examined ranged from 9 to 31, while the median number of positive nodes was 2–3. Various cut-off values have been reported in the literature with regard to lymph node density. The most commonly utilized lymph node density cut-point was 20%.

While all of the studies showed a statistically significant difference between survival outcomes for patients with lymph node densities below the cut-off point compared to those with ratios above the predetermined value on univariate analysis, all but one of the studies also confirmed the independent prognostic significance of lymph node density on multivariate analysis. The study by Fleischmann and colleagues [15] noted that extracapsular extension of the lymph node metastasis was the strongest predictor of survival. The other studies did not examine this particular variable in a multivariate statistical model.

Is lymph node density superior to TNM nodal staging for prognostication?

The standard Tumor-Node-Metastasis (TNM) classification for lymph node involvement is based on the number and size of nodal metastases. Accurate assessment of nodal tumor volume (number of positive nodes), however, is intimately dependent on the surgeon's ability to remove the affected nodal tissue. Current staging schemes do not account for this factor and therefore may underestimate the extent of regional nodal involvement. By definition, lymph node density simultaneously reflects both tumor burden in the numerator and the extent of lymphadenectomy/pathologic examination in the denominator. Several studies have directly compared standard TNM nodal staging with lymph node density in predicting clinical outcomes.

Herr [18] initially reported the outcomes of 162 patients with node-positive disease at a median of 7.5 years of follow-up. The 1997 TNM staging system (pN1-1 positive lymph node ≤2 cm, pN2 multiple nodes ≤5 cm each, and pN3 positive nodes >5 cm) was compared to the number of positive nodes (≤4 vs. >4) and lymph node density (<20 vs. >20%). In a multivariate analysis, lymph node density better discriminated disease-specific survival ($P = 0.002$) than did either the conventional staging (pN status) ($P = 0.21$) or the absolute number of positive lymph nodes ($P = 0.6$).

Similarly Kassouf et al. [19] in analyzing the combined experiences from the MD Anderson Cancer Center and Memorial Sloan-Kettering Cancer Center, compared nodal status (based on the 2002 TNM staging system) and lymph node density in a multivariate model. Only lymph node density greater than 20% predicted decreased disease-specific survival (HR 2.75, $P < 0.01$). In addition, this study demonstrated that lymph node density remained a superior predictor of disease-specific survival even after accounting for the use of adjuvant chemotherapy, which is often employed in the multimodal treatment of node-positive patients.

In the report from Fleischmann and colleagues from the University of Bern, the 2002 TNM nodal status did not provide statistically significant stratification between pN1 and pN2 disease on univariate analysis, whereas lymph node density (<20 vs. ≥20%) was a significant predictor of recurrence-free and overall survival ($P = 0.0034$ and $P = 0.002$, respectively) [15]. However, as mentioned previously, when considering primary tumor stage, number of positive lymph nodes, lymph node density, and extracapsular nodal extension, only extracapsular extension retained statistical significance on multivariate analysis (HR 2.11, $P = 0.019$).

Is lymph node density superior to the number of positive lymph nodes for prognostication?

Several studies have demonstrated worse survival outcomes with greater numbers of cancer containing nodes. It makes intuitive sense, therefore, that a greater number of positive nodes implies greater tumor burden and a worse survival. Does a patient with four positive lymph nodes detected from a limited dissection of six total lymph nodes have a similar outcome to a patient with four positive nodes found after an extended template dissection yielding 40

Table 1 Studies on lymph node density

Reference/ institution	No. of patients	Time period	Cephalad extent of lymphadenectomy	Median follow-up (years)	Median no. LN's (range)	Median no. Pos. nodes (range)	Cut-off (%)	5-year RFS	5-year DSS	5-year OS
Stein JP et al./ USC [17]	244	1971–1999	2 cm above aortic bifurcation	10.1	30 (1–96)	2 (1–63)	<20	44%	NS	43%
							>20	17%	NS	8%
								$P < 0.001$		$P < 0.001$
Herr HW/ MSKCC [18]	162	1979–1999	Distal common iliac	7.5	13 (2–32)	3 (1–14)	<20	NS	64%	NS
							>20	NS	8%	NS
									$P = 0.002$	
Kassouf W et al./ MDACC [23]	108	1993–2003	≤Aortic bifurcation	2.1	12 (1–58)	2 (1–10)	<25	38.10%	NS	37.30%
							>25	10.60%	NS	18.70%
								$P = 0.02$		$P = 0.02$
Kassouf W et al./ MSKCC + MDACC [19]	248	1979–1999 1993–2003	<Aortic bifurcation	2	12 (2–58)	2 (1–14)	<20	NS	54.60%	NS
							>20	NS	15.30%	NS
									$P < 0.001$	
Fleischmann A et al./Bern [15]	101	1985–2000	Common iliac artery	1.75	22 (10–43)	2 (1–24)	<20	41%	NS	40%
							>20	15%	NS	15%
								$P = 0.003$*		$P = 0.002$*
Konety BR et al./ SEER [11]	361	1988–1996	Variable	5.3	NS	NS	1–25	NS	HR 1.00	NS
							26–50	NS	HR 0.89	NS
							51–75	NS	HR 1.55	NS
							76–100	NS	HR 1.72	NS
									$P < 0.0001$	
Wright JL et al./ SEER [25]	1260	1988–2002	Variable	NS	9 (1–75)	2 (1–38)	<12.5	NS	HR 1.00	HR 1.00
							12.6–25	NS	HR 1.24	HR 1.31
							25.1–50	NS	HR 1.62	HR 1.54
							>50	NS	HR 2.47	HR 2.40
									$P < 0.001$	$P < 0.001$
Steven K et al./ Copenhagen [22]	64	1993–2005	1–2 cm above aortic bifurcation	2.5	27 (11–49)	NS	<20	~40%	NS	47%
							>20	~15%	NS	25%
								$P < 0.01$		$P < 0.05$
Abdel–Latif M et al./ Mansoura [24]	110	1997–1999	Distal common iliac	3.4	Mean 17.9 ± 6.7	Mean 4.1 ±5.4	<10	56.2%[a]	NS	NS
							10–20	38.9%[a]	NS	NS
							>20	16.4%[a]	NS	NS
								$P < 0.001$		
Lerner SP et al./ USC [8]	132	1971–1989	2 cm above aortic bifurcation	15.5	31 (3–96)	2.5 (1–63)	<25	NS	NS	NS
							>25	NS	NS	NS
								$P = 0.014$		$P = 0.024$

[a] Mean 3-year survival reported

* Univariate analysis; multivariate $P = 0.43$

lymph nodes? While some studies have argued the advantages of extended lymphadenectomy, this remains a controversial issue in the absence of a prospective randomized trial [20–22]. Regardless, several studies have compared the absolute number of positive nodes to lymph node density in predicting disease-specific survival.

Stein et al. [17] reported the largest single-institution series of node-positive patients treated with cystectomy and extended lymphadenectomy. In this series, recurrence-free survival at 10 years for patients with up to eight positive nodes was significantly higher than in those with nine or more positive nodes (40 vs 10%, $P < 0.001$). Lymph node density of 20% or less also predicted a better 10-year recurrence-free survival (43%) compared to those with a density of >20% (17%) ($P < 0.001$ on univariate analysis). On multivariate analysis, the number of lymph nodes involved

(>8 vs. ≤8) (HR 1.91, $P = 0.008$) performed better than lymph node density (>20 vs. ≤20%) (HR 1.65, $P = 0.02$) for predicting recurrence-free survival, though both factors remained statistically significant.

Steven and Poulsen [22] also demonstrated improved overall survival in patients with five or less involved nodes (50 vs. 13%, $P < 0.002$) and in those with a lymph node density <20% (47 vs. 25%, $P < 0.05$). The results of the multivariate analysis unfortunately were not reported in their study. Kassouf et al. [23] also reported that the number of positive nodes was significantly associated with recurrence-free survival on univariate analysis ($P = 0.04$), but lost statistical significance when considered in a multivariable model ($P = 0.055$). In contradistinction, lymph node density (>25 vs. <25%) remained significantly associated with overall and recurrence-free survival (HR 1.88, $P = 0.02$ and HR 1.91, $P = 0.01$, respectively). Interestingly the report from the Mansoura group demonstrated just the opposite finding [24]. While both number of positive nodes (1 vs. 2–5 vs. >5) and lymph node density (<10 vs. 10–20 vs. >20%) showed statistical significance on univariate analyses, only the number of positive nodes remained significant on multivariate modeling.

The two population-based studies analyzing the SEER dataset also offer slightly different conclusions regarding the significance of the number of positive nodes and lymph node density. In Konety et al.'s [11] analysis of all stage IV bladder cancer patients, the number of positive nodes did not significantly correlate with survival, while the lymph node density did show some predictive ability especially at a cut-off of 50%. In contrast, Wright et al. [25] examined 1,260 patients with node-positive disease and found highly statistically significant correlation between the number of positive nodes (1 vs. 2 vs. 3 vs. >3) and lymph node density (divided into quartiles) and disease-specific and overall survival. Some of the differences in conclusions from the two studies may be explained by differences in inclusion criteria utilized.

Unresolved issues with lymph node density

Although lymph node density is an attractive alternative to lymph node staging, several issues have yet to be resolved. Thus far, all studies of lymph node density have been retrospective in nature with cut-off points based on statistical calculation. As with all retrospective studies, selection bias exists and other unmeasured patient characteristics may confound the outcomes. Prospective validation in larger cohorts is therefore needed.

Standardization of the anatomic boundaries of an "appropriate" lymphadenectomy is also needed to ensure an adequate dissection, not only for staging purposes, but potentially for therapeutic benefit as well. Traditionally, a "standard" pelvic lymphadenectomy implies a dissection encompassing the nodal regions bounded by the bifurcation of the common iliac vessels proximally, the genitofemoral nerve laterally, the deep circumflex iliac vein and Cloquet's node distally, and the obturator-hypogastric fossa. An "extended" lymphadenectomy encompasses these same areas, but also includes the common iliac nodes, distal para-aortic/paracaval nodes (1–2 cm above the aortic bifurcation or to the level of the inferior mesenteric artery), as well as the presacral nodal group. Although the number of lymph nodes reported may provide some crude measure of the extent of dissection, it is far from perfect and the strength of the correlation is not known. Inter-individual anatomic variability and differences in surgeries, surgeons, pathologists, and institutions all affect node counts [26]. The borders of the lymphadenectomy and the meticulousness of the surgeon in clearing the nodal basins must somehow be incorporated into this concept if one is to better define the role of lymph node density in prognostication.

In addition to the surgical technique, the technical aspects of pathologic evaluation of the surgical specimen also need to be standardized. Variations in specimen handling, sectioning techniques, and use of ancillary methods (such as immunohistochemistry) contribute to the differences in reported node counts [27, 28].

Furthermore, the effects of neoadjuvant systemic chemotherapy and previous pelvic radiotherapy on the ability to remove and identify (count) nodal tissue needs to be evaluated. As more patients are undergoing neoadjuvant chemotherapy prior to cystectomy, should different criteria be used to judge the adequacy of the lymph node dissection? Can lymph node density be applied in this setting with similar results?

Conclusions

Radical cystectomy with an "appropriate" pelvic lymphadenectomy remains the standard treatment for high grade invasive bladder cancer. Several recent studies have suggested that improved outcomes may be achieved with an extended nodal dissection. Despite this mounting evidence, controversy still exists with regards to the optimal anatomic boundaries for the dissection and the absolute number of nodes that should be removed and pathologically investigated. Perhaps even more concerning is that up to 40% of patients who undergo cystectomy do not undergo any lymph node dissection, and more that 65% have fewer than six nodes removed [11]. Due to the variability in the extent of lymphadenectomy performed among different surgeons, the meticulousness of the pathologist in identifying and reporting nodal counts, and the innate anatomic variability among individual patients, the concept of lymph node density has been proposed as a means to facilitate standardization of lymph node staging and prognostic stratification.

In a previously reported review of the literature regarding lymph node density, Herr concluded that "the concept of lymph node density compared to, or in addition to, the absolute number of involved pelvic lymph nodes" provided prognostic advantages in node-positive patients after cystectomy [29]. This review further supports the utility of lymph node density in stratifying patients with nodal involvement who may otherwise exhibit a heterogeneous outcome. The underlying limiting variable in standard nodal staging schemes (pN status) or the absolute number of involved nodes is the lack of a standardized template for lymph node dissection [10, 30, 31]. This is further compounded by the fact that lymph node counts rely not only on the anatomic boundaries of the dissection, but also the manner in which the surgical specimen is submitted to the pathologist (en bloc vs. separate packets) [28, 32], the meticulousness of the surgeon in removing the nodes, and the pathologist in identifying and examining the nodes [27, 33, 34], and finally interindividual anatomic variability. This has been clearly evident in our own clinical practice, where we have noted a greater than fivefold increase in average node counts from 10 (range 1–44) to 55 (range 26–105) since adopting the extended template (up to the level of the inferior mesenteric artery) and routinely submitting individual lymph node packets to the pathologist [35].

Due to the wide variations in lymph node counts within and between institutions, as well as the lack of standardization of the extent of lymphadenectomy, the concept of lymph node density attempts to provide a means to account for some of the differences in surgical techniques and pathologic reporting when estimating prognosis and considering patients for adjuvant therapy or clinical trial enrollment. Based on this review of the literature, there is a growing body of evidence to support the use of lymph node density in the pathologic staging of node-positive bladder cancer.

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