Role of lymphadenectomy for invasive bladder cancer

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Abstract

Radical cystectomy with lymph node dissection remains the standard of care in the treatment of muscle-invasive and refractory non-invasive bladder cancer. Over the past decade, the extent of lymphadenectomy has varied to include dissection up to the common iliac vessels and aortic bifurcation proximally (may also extend up to the level of the inferior mesenteric artery), the genitofemoral nerve laterally, the circumflex iliac vein and lymph node of Cloquet distally, and the hypogastric vessels posteriorly (obturator fossa, presciatic nodes bilaterally and the presacral lymph nodes over the sacral promontory). Evidence supports the role of lymphadenectomy as both a therapeutic and prognostic variable in patients with invasive bladder cancer. We review the literature regarding the role and extent of lymphadenectomy, as well as its impact on patient outcomes.

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Introduction

In Canada, bladder cancer is the fourth most common cancer in men and the 12th most common in women. It accounts for 6700 new cases and 1780 deaths per year.[1] Most patients will present with non-muscle-invasive bladder cancer (NMIBC) and 20% to 30% will present with muscle-invasive disease.[2] Radical cystectomy with lymphadenectomy remains the standard of care in the treatment of muscle-invasive and refractory non-invasive bladder cancer. It offers good long-term overall survival (OS) (59% to 60%, 5-year OS) and disease-specific survival (DSS) rates (55% to 65%, 5-year DSS) as well as excellent 5-year pelvic-control rates of 80% to 90%.[3-6] It also offers precise pathological staging of tumours, allowing for the application of adjuvant chemotherapy when needed. Furthermore, with improvements in surgical technique and postoperative care, complications and perioperative mortality rates are as low as 17% and 2%, respectively.[3-8]

Even in the era of a more aggressive approach towards high-grade NMIBC,[9] pathologic specimens from contemporary radical cystectomy series reveal lymph node metastasis in up to 26% of resected tumours.[2] There is also a strong correlation between lymph node involvement and the depth of invasion of the primary organ. The rate of lymph node metastasis increases from 5% in non-muscle-invasive bladder tumours (pT0, pTa, pTis, pT1) to 18% in superficial muscle-invasive tumours (pT2a), 27% in deep muscle-invasive tumours and 45% in extravesical tumours (pT3-4).[3] Autopsy specimens provide further support to the elevated incidence of lymph node metastasis with 30% to 40% of patients having lymph nodes as the only site of metastasis.[2] A 5-year OS up to 31% can be achieved in higher-risk groups with lymph node metastasis treated with surgical extirpation.[3] As such, lymphadenectomy is a crucial part of any bladder surgery, since up to one-quarter of clinically organ-confined tumours will have evidence of lymph node metastasis at the time of surgery, making it both an important therapeutic and prognostic tool in the treatment of bladder cancer.

Lymph node mapping

Initially introduced in the treatment of breast cancer by mastectomy in 1886,[10] lymph node dissection's (LND) role has broadened over the past decades and is now a mainstay in the approach to patients with muscle-invasive bladder cancer undergoing radical cystectomy. The lymphatic drainage of the bladder is quite extensive and consists of the visceral lymphatic plexus in the bladder muscle wall, the intercalated lymph nodes in the perivesical fat, the pelvic collecting trunks, the regional pelvic nodes (external iliac, hypogastric and sacral) and the lymphatic trunks, which abut on the common iliac nodes.[2]

Though metastasis is found most commonly in the regional pelvic nodes, mapping studies have shown involvement of nodes at or above the aortic bifurcation and at the presacral region in 9% to 19% and 5% to 8% of cases, respectively.[11-13] Additionally, in patients with lymph node metastasis within the standard dissection limits, 57% and 31% of nodes at the level of the common iliac vessels and above the aortic bifurcation respectively were found to be positive.[12] Consequentially, a standard LND would have failed to address 74% of the positive nodes and 7% of these patients' pathologies would have been falsely reported as negative.[12] Also of interest is that one-third of patients who had metastasis to the common iliac nodes showed positive nodes in

the presacral area.[13] Furthermore, when the bladder cancer was restricted to one side, contralateral nodal metastasis was noted in up to 41% of cases[14] and bilateral nodal spread was observed in 39% of lymph node-positive tumours.[15] In spite of supporting evidence for an extended bilateral lymph node dissection, controversy remains regarding its surgical limits. An extended LND encompasses the aortic bifurcation and common iliac vessels proximally (may also go up to the level of the inferior mesenteric artery), the genitofemoral nerve laterally, the circumflex iliac vein and lymph node of Cloquet distally, and the hypogastric vessels posteriorly (obturator fossa, presciatic nodes bilaterally and the presacral lymph nodes over the sacral promontory). A standard dissection, however, is usually limited superiorly by the common iliac bifurcation.[16]

Tumour burden

Tumour burden is defined as the number of positive lymph nodes. As one would predict, the larger the tumour burden, the worse the outcome. Herr and colleagues showed that in patients with positive nodes undergoing radical cystectomy, survival was significantly better when ≤4 positive nodes were present compared with >4 positive nodes (37% vs. 13%).[17] They also went on to show that when >11 nodes were resected, patients showed better survival and less recurrence. These findings were confirmed by another larger study with longer follow-up that showed survival was significantly better in patients with ≤8 metastatic nodes than in those with >8 metastatic nodes (40% vs. 10% 10-year recurrence-free survival [RFS]).[18] Improved OS was shown in a study by Steven and Poulsen when 5 or fewer positive nodes were detected (50% vs. 13%, $p < 0.002$).[19] Furthermore, the number of involved nodes was associated with improved RFS on univariate analysis ($p = 0.04$) in the study by Kassouf and colleagues but lost statistical significance on multivariate analysis.[20] The study from the Mansoura group, on the other hand, showed statistical significance on both univariate and multivariate analyses when stratifying positive nodes (1 vs. 2–5 vs. 5).[21] This was also the case in a population-based study from the Surveillance, Epidemiology and End Results (SEER) database (1 vs. 2 vs. 3 vs. >3 positive nodes).[22]

Number of lymph nodes resected

When pelvic recurrence occurs following radical cystectomy, patients usually have very poor prognosis even when offered adjuvant therapy and, as such, it is crucial to have adequate local control. In one study examining 130 patients who underwent limited bilateral pelvic LND and who later developed pelvic recurrence, the median time to recurrence was 7.3 months, with 98.5% of those patients dying of disease (median survival of 4.9 months).[23] Skinner was among the first to advocate radical cystectomy with wider resection of perivesical soft tissue and extended LND in an effort to decrease local recurrence of disease and improve cure rates for invasive bladder cancer. A combined effort between the Cleveland Clinic and the University of Bern compared 2 groups of patients who underwent radical cystectomy with either limited LND or extended LND; an extended LND was associated with improved survival in patients with organ-confined, non-organ-confined, and/or node-positive tumours. The 5-year RFS was 77% for pT2N0, 57% for pT3N0 and 35% for node-positive tumours in the extended LND group versus 67%, 23% and 7% respectively in the limited LND group ($p < 0.0001$).[23] Another study supported the role of an extended dissection in organ-confined node-negative patients with 90% 5-year RFS compared to only 71% when a standard LND was performed.[24] These findings were also confirmed in another cohort of 447 patients with and without nodal involvement undergoing radical cystectomy.[25]

When extended dissection was performed instead of standard dissection, the mean number of nodes collected increased from 14 to 25 and from 8.5 to 36.5 in 2 separate studies.[24,26] Recent studies have used the number of nodes resected as a surrogate for extent of dissection and surgical quality. When more than 16 nodes were resected the 5-year RFS jumped from 63% to 85% for organ-confined tumours and from 25% to 53% in patients with at most 1 to 5 positive lymph nodes. A review of the SEER database showed that the factor with the highest impact on survival of patients undergoing radical cystectomy regardless of nodal status and accounting for all traditional prognostic variables was a dissection of at least 10 to 14 nodes.[27] Furthermore, in the widely quoted Southwest Oncology Group (SWOG) Intergroup trial evaluating the role of neoadjuvant chemotherapy, Herr and colleagues examined surgical factors as surrogates for outcome.[28] The number of nodes removed (>10) in both node-negative and node-positive patients was associated with prolonged survival and remained an independent prognostic factor even after adjusting for the use of neoadjuvant chemotherapy, surgical margin status, pT stage and nodal status. Subsequently, Bochner and colleagues tried to establish a minimum number of resected nodes beyond which no effect on survival would be observed.[29] No such threshold could be determined, since the probability of survival continued to increase as the number of nodes resected increased.

In addition to extent of dissection, node counts are also affected by pathological factors and differences in surgeries, surgeons and institutions. From a pathology perspective, the manner in which specimens are submitted has an effect on yield. This was demonstrated in a prospective study by Bochner and colleagues which showed that submission of nodes in 6 separate lymph node packets versus

en bloc increases the number of nodes collected by 3-fold.[30] Variability of patient's pelvic anatomy is also another factor, with Weingaertner and colleagues demonstrating large interindividual differences with a range of 8 to 56 removed lymph nodes per patient in the pelvic region (mean: 22.7 ± 10.2).[31] As such, although number of nodes has been increasingly used as a surrogate for surgical quality, other factors may influence this variable; thus, it is rather important to ensure a standardized template of dissection is adopted that extends up to at least the aortic bifurcation. Furthermore, in addition to a therapeutic benefit with an extended LND compared to a limited/standard LND, it is evident that an extended LND offers more accurate staging, increasing detection of micrometastasis and allowing adjuvant chemotherapy to be offered early when tumour burden is lowest.

Morbidity and mortality

An extended LND, on average, prolongs operative time by 60 minutes and does not appear to be associated with increased morbidity or mortality compared to the standard approach. In large series, early complication and perioperative mortality rates of 28% and 3% respectively have been reported.[3] When comparing patients with positive lymph nodes and those with no lymph node involvement, there was no statistical difference in complications regardless of extravesical involvement (27% for early complication; 1% for perioperative mortality).[18] In a study comparing 2 well-matched cohorts in terms of comorbidities of 46 patients each, no differences were observed in early complication, perioperative mortality and blood transfusion requirement rates between those who underwent extended LND up to the level of the inferior mesenteric artery and those who underwent standard dissection.[32] These results were confirmed in a retrospective study comparing extended LND (up to the aortic bifurcation) to a more limited LND; similar mortality rates were observed in the 2 groups with lymphocele formation rates in 1.6% and 1.5% respectively.[24] A prospective, multicentre study comparing similar groups also confirmed these findings, showing higher postoperative lymphatic drainage in the extended LND group without, however, affecting the time to removal of the drains.[12] As such, extended LND is a safe option in experienced hands and may actually help decrease the rate of positive surgical margins because of wider LND boundaries and also benefits patients secondary to a more complete resection of undetected micrometastases.[33] It is important to note that extended LND is not recommended in patients who have received high doses of pelvic irradiation (>60Gy), since the procedure may increase the likelihood of vascular complications.[34]

Lymph node density

To account for both tumour burden and extent of lymphadenectomy as prognostic factors, Herr looked at the ratio of positive nodes to total number of nodes resected. Initially terming it "ratio-based" lymph node staging, Herr showed that in a cohort of 162 patients with nodal metastasis, the 5-year OS decreased from 64% when the ratio was ≤20% down to 8% when it was >20%.[35] This was later termed lymph node density by the University of Southern California group, which similarly showed worsening 10-year RFS from 43% when the lymph node density was ≤20% to merely 17% when it was >20%.[18] These findings were further validated by Kassouf and colleagues and showed that lymph node density remains prognostic even in patients who received adjuvant chemotherapy.[20] A pooled analysis of MD Anderson and Memorial Sloan-Kettering Cancer Centers showed that lymph node density is superior to TNM nodal status in predicting disease-specific survival after radical cystectomy for bladder cancer. For lymph node density to be powerful, a minimum number of nodes resected needs to be identified; one study showed that at least 9 nodes need to be removed.[36] This strategy has shown promise as a staging and prognostic tool and may be useful to better stratify patients when entering them in clinical trials designed to study the role of adjuvant therapy. Most of the data support the incorporation of lymph node density into the staging system (Table 1). The predictive power of lymph node density can potentially be enhanced by accounting for other variables such as the presence of extracapsular extension, volume of micrometastasis and anatomic location of positive nodes.

Conclusion

Radical cystectomy with bilateral pelvic lymphadenectomy remains the standard of care for muscle-invasive bladder cancer. An extended lymphadenectomy is recommended for patients without contraindications, such as serious comorbidities and prior high-dose pelvic irradiation since it offers survival benefit to patients with both node-positive and node-negative disease without increasing morbidity or perioperative mortality. There continues to be debate as to how high an extended LND should be performed, with evidence pointing towards reaching proximally to the level of the inferior mesenteric artery. Pathologic stage, tumour burden and extent of lymphadenectomy are well established risk factors; however, lymph node density appears to be the most promising prognostic tool for node-positive tumours.

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Table 1. Extent of lymphadenectomy studies

Studies	No. patients	Extent of LND	Median number of nodes resected	Cut-off number of nodes resected	Cut-off LND (%)	5-year OS	5-year RFS	5-year DSS
Stein et al.[18]	244	Above aortic bifurcation	30 (1–96)		≤ 20 > 20	43% 8% $p < 0.001$	44% 17% $p < 0.001$	N/A
				≥ 15 nodes < 15 nodes		N/A	36% 25% $p = 0.21$	N/A
Konety et al.[27]	361	Extended	N/A		≤ 50 > 50	N/A	N/A	HR = 1.55 $p = 0.27$
				10–14 nodes		N/A	N/A	HR = 0.38 $p < 0.0001$
Herr[35]	162	Distal common iliac	13 (2–32)		≤ 20 > 20	N/A	N/A	64% 8% $p = 0.002$
				≥ 13 nodes < 13 nodes		N/A	N/A	NSS
Kassouf et al.[20]	108	Below aortic bifurcation	12 (1–58)		≤ 25 > 25	37% 19% $p = 0.02$	38% 11% $p = 0.02$	N/A
				> 12 nodes ≤ 12 nodes		N/A	NSS	N/A
Kassouf et al.[36]	248	Below aortic bifurcation	12 (2–58)		≤ 20 > 20	N/A	N/A	55% 15% $p < 0.001$
				> 12 nodes ≤ 12 nodes		N/A	N/A	HR = 0.41 $p < 0.01$*
Fleischmann et al.[37]	101	Common iliac artery	22 (10–43)		< 20 ≥ 20	40% 15% $p = 0.002$*	41% 15% $p = 0.003$*	N/A
				≥ 5 nodes < 5 nodes		N/A $p = 0.0002$†	N/A $p = 0.0005$†	N/A
Wright et al.[22]	1260	Extended	9 (1–75)		≤ 12.5 > 12.5	HR = 1.31 $p < 0.001$	N/A	HR = 1.24 $p < 0.001$
				≥ 10 nodes < 10 nodes		HR = 0.52 $p < 0.001$	N/A	HR = 0.53 $p < 0.001$
Steven et al.[19]	64	Above aortic bifurcation	27 (11–49)		≤ 20 > 20	47% 25% $p < 0.05$	40% 15% $p < 0.01$	N/A
				N/A		N/A	N/A	N/A
Abdel-Latif et al.[21]	110	Distal common iliac	Mean 17.9 ± 6.7		≤ 20 > 20	N/A	39% 16% $p < 0.001$†	N/A
				Continuous		N/A	NSS	N/A
Lerner et al.[38]	132	Above aortic bifurcation	31 (3–96)		≤ 25 > 25	NSS	NSS	N/A
				N/A		N/A	N/A	N/A
Leissner et al.[25]	302	Variable	14.7 (1–46)		N/A	N/A	N/A	N/A
				≥ 16 nodes < 16 nodes		N/A	65% 51% $p < 0.016$	65% 51% $p < 0.013$
Herr et al.[28]	268	Variable	10 (0–54)		N/A	N/A	N/A	N/A
				≥ 10 nodes < 10 nodes		61% 44% $p = 0.0007$	25% 6% $p < 0.0001$	N/A
Herr et al.[17]	322	Variable	8 (0–44) for pN0		N/A	N/A	N/A	N/A
				≥ 8 nodes < 8 nodes		pN0 $p = 0.0000$	N/A	N/A
			11 (1–25) for pN+		N/A	N/A	N/A	N/A
				≥ 11 nodes < 11 nodes		pN+ $p = 0.004$	N/A	N/A
Koppie et al.[29]	1042	Variable	9 (0–53)		N/A	N/A	N/A	N/A
				Continuous		HR = 0.97 $p < 0.0005$	N/A	N/A
Poulsen et al.[24]	117				N/A	N/A		N/A
		Extended Limited	25 (9–67) 14 (5–30)	Extended Limited			≤ pT3a 85% 64% $p < 0.02$	N/A
Dhar et al.[23]	336, Cleveland Clinic; 322, University of Bern	Extended Limited	22 (10–43) 12 (2–31)	Extended Limited	N/A	pN+ 34% 7% $p < 0.0001$	pN+ 35% 7% $p < 0.0001$	N/A
				Extended Limited	N/A	pT3N0 46% 26% $p = 0.002$[1]	pT3N0 57% 23% $p < 0.0001$	N/A

DSS = disease-specific survival; LND = lymph node density; N/A = not available; NSS = not statistically significant; OS = overall survival; RFS = recurrence-free survival; HR = hazard ratio;
* = Univariate analysis, not statistically significant on multivariate analysis; † = mean 3-year survival.

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