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Lymph Node–Positive Bladder Cancer Treated With Radical Cystectomy and Lymphadenectomy: Effect of the Level of Node Positivity

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Abstract

Background—The extent of lymphadenectomy needed to optimize oncologic outcomes after radical cystectomy (RC) for patients with regionally advanced bladder cancer (BCa) is unclear.

Objective—Evaluate the effect of the location of lymph node metastasis on recurrence-free survival (RFS) and cancer-specific survival (CSS) for patients undergoing RC with a mapping pelvic lymph node dissection (PLND).

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Design, setting, and participants—A study of 591 patients undergoing RC with mapping PLND was completed between 2000 and 2010. Median follow-up was 30 mo.

Intervention—RC with mapping PLND.

Measurements—We evaluated the impact of lymph node involvement by location on disease outcomes using the 2010 TNM staging system. Survival estimates were described using Kaplan-Meier methods. Gender, age, pathologic stage, histology, number of positive nodes, node density, use of perioperative chemotherapy, and grade were evaluated as predictors of RFS and CSS using multivariate Cox proportional hazard regression.

Results and limitations—Overall, 114 patients (19%) had lymph node involvement, and 42 patients (7%) had pN3 disease. On multivariate analysis, the number of positive lymph nodes (one or two or more) was significantly associated with increased risk of cancer-specific death (hazard ratio [HR]: 1.9 [95% confidence interval (CI), 1.04–3.46], $p = 0.036$; versus HR: 4.3 [95% CI, 2.25–8.34], $p < 0.0005$). Positive lymph node location was not an independent predictor of RFS or CSS. Five-year RFS for pN3 patients undergoing RC with PLND was 25% (95% CI, 22–54). This finding was not statistically different from our pN1 and pN2 patients (38% [95% CI, 22–54] and 35% [95% CI, 11–60], respectively). This study is limited by the lack of prospective randomization and a control group.

Conclusions—The outcome for patients with involved common iliac lymph nodes was similar to the outcome for patients with primary nodal basin disease. These data support inclusion of the common iliac lymph nodes (pN3) in the nodal staging system for BCa. Lymph node location was not an independent predictor of outcome, whereas the number of positive lymph nodes was an independent predictor of worse oncologic outcome (pN1, pN2). Further refinements of the TNM system to provide improved prognostication are warranted.

Keywords

Bladder cancer; Pelvic lymphadenectomy; TNM staging system

1. Introduction

Contemporary surgical series demonstrate that approximately one-third of regionally node-positive patients are rendered disease-free after radical cystectomy (RC) with pelvic lymph node dissection (PLND). While most clinicians agree that PLND is critical for accurate staging, the extent needed to optimize outcomes remains controversial [1–4]. The impact of PLND on survival for patients with common iliac node involvement remains to be established. The 2002 American Joint Committee on Cancer (AJCC) staging system defined positive nodes outside the true pelvis as metastatic disease, suggesting that outcomes for patients with common iliac nodal involvement were significantly worse than outcomes for patients with regional disease in the true pelvis only.

The 2010 changes to the AJCC TNM staging system for bladder cancer (BCa) reflect the accumulating evidence that a more extensive PLND during RC that includes removal of common iliac lymph nodes is associated with improved recurrence-free survival (RFS) [3,5–7]. Patients with a single positive regional lymph node are now considered to have pN1

disease; multiple positive regional lymph nodes are considered pN2, and positive lymph nodes at the common iliac vessels are pN3.

Our objective was to evaluate the effect of the location of regional pelvic nodal involvement on RFS and on cancer-specific survival (CSS) in patients who undergo RC with PLND.

2. Patients and methods

After institutional review board approval was obtained, prospective data were collected on 891 patients treated with RC at a single high-volume tertiary care cancer center between 2000 and 2010. Patients were staged preoperatively with radiographic imaging and physical examination after transurethral resection of the bladder tumor. Surgery was performed by one of two experienced surgeons (B.H.B., G.D.). A packeted submission technique for PLND was prospectively established at the beginning of the study period. Patients treated with salvage cystectomy ($n = 12$), patients who did not have a packeted lymph node submission ($n = 283$), and patients with M1 disease ($n = 5$) were excluded, leaving 591 patients eligible for analysis. The proximal limits of the PLND for this study extended to the level of the aortic bifurcation. The lateral limit of dissection was the genitofemoral nerve, and the inferior limit was the node of Cloquet. Lymph nodes were removed and packeted based on location within defined anatomic boundaries. The lymph node packets included the right and left common iliac, the presacral, the right and left external iliac, and the right and left hypogastric and obturator lymph nodes. The margins of resection are demonstrated in Figure 1.

2.1. Pathologic review

Specimens were evaluated according to our institution's standard protocol. Lymph nodes were processed by a standard method that included dissection from the adipose tissue under bright light. No fat-clearing solutions were used. All identified nodes were sectioned and pathologically evaluated.

2.2. Follow-up

During the follow-up period, patients were routinely evaluated for clinical and radiographic evidence of disease. All patients with lymph node involvement were referred to medical oncology for evaluation for chemotherapy. *Disease recurrence* was defined as any radiographic documentation of disease or pathologically proven failure. Cause of death was prospectively entered and verified by chart review and corroborated by the death certificate.

2.3. Statistical methods

We compared RFS and CSS for patients following RC/PLND, stratified by the 2010 AJCC nodal staging criteria. Patients were given a consensus pathologic stage based on the higher stage identified at the time of the transurethral resection or RC. RFS was calculated as the time from surgery to the earliest event of a recurrence, metastasis, or death from disease. Survival estimates were described using Kaplan-Meier methods. Gender, age, pathologic stage, histology, grade, number of positive lymph nodes, lymph node density, and perioperative chemotherapy were evaluated as predictors of RFS and CSS using multivariate

Cox proportional hazard regression. Surgical margin status was not a significant predictor of disease progression and thus was not included in the multivariate model.

3. Results

Overall, 591 patients treated with RC and PLND between 2000 and 2010 were included in our analysis. Patient characteristics are shown in Table 1. Lymph node involvement was identified in 114 patients (19%). Stratified by tumor stage <pT2, pT2, pT3, and pT4, lymph node involvement was identified in 20 patients (6%), 17 patients (19%), 68 patients (40%), and 12 patients (60%), respectively. Additionally, 6 of 312 patients with <pT2 disease (2%), 5 of 88 patients with pT2 disease (6%), 28 of 171 patients with pT3 disease (16%), and 3 of 20 patients with pT4 disease (15%) were found to have pN3 disease. Overall, 7% of our entire cohort had pN3 disease, including 13% of all patients with pT2 disease.

Median follow-up was 30 mo. During follow-up, 195 patients died (106 from BCa), and 156 patients were diagnosed with a recurrence. The 5-yr RFS and CSS for patients with node-negative disease were 69% (95% confidence interval [CI], 63–74) and 81% (95% CI, 75–85), respectively. The 5-yr RFS and CSS for node-positive disease were 33% (95% CI, 22–44) and 40% (95% CI, 28–52), respectively (Fig. 2). Stratified by nodal stage, the respective 5-yr RFS and CSS were 38% (95% CI, 22–54) and 45% (95% CI, 27–61) for pN1 disease, 35% (95% CI, 11–60) and 31% (95% CI, 8–59) for pN2 disease, and 25% (95% CI, 10–42) and 45% (95% CI, 23–59) for pN3 disease (Fig. 3).

Of the 42 patients who had pN3 disease, 24 patients (57%) also had two or more positive lymph nodes in the true pelvis, and 11 patients (26%) had one positive pelvic lymph node. Seven patients (17% of pN3 patients, 6% of the node positive group) had no positive lymph nodes within the true pelvis. All patients had clinically negative nodes either by imaging, by biopsy of suspicious nodes, or by palpation at the time of surgery.

After adjustment for age, gender, pathologic histology, stage, node density, perioperative chemotherapy, and grade, we found that the number of positive lymph nodes (none, one, or two or more) was significantly associated with cancer-specific death (reference, $p = 0.036$, and $p < 0.0005$) (Table 2). Lymph node density was not a significant predictor of recurrence ($p = 0.6$; 95% CI, 0.4–1.7) or CSS ($p = 0.8$; 95% CI, 0.5–2.4). We did not find evidence that RFS or CSS differed significantly between pN1, pN2, and pN3 ($p = 0.11$ and $p = 0.6$, respectively). In our multivariable analysis, location of the positive node (ie, the common iliac region) did not provide additional prognostic information over the total number of positive lymph nodes. These results did not differ when patients with <pT2 disease or patients who received neoadjuvant chemotherapy (Table 3) were excluded from the analysis.

4. Discussion

The goal of our study was to determine cancer-specific outcomes related to location of the positive node or nodes identified at RC. The belief that nodes outside the true pelvis represent advanced disease and would not likely be cured by surgery has led many urologists to underestimate the importance of performing a meticulous PLND that includes the common iliac nodes. Jensen et al first reported the outcomes of nodal involvement based

on the 2010 AJCC nodal staging system [4]. Our study supports their findings with a larger cohort of pN3-positive patients and demonstrates that a significant proportion of patients with lymph node involvement will harbor pN3 disease. Number of positive lymph nodes was significantly associated with CSS, whereas location of the positive node and lymph node density were not. We found that 25% of patients with pN3 disease were recurrence-free at 5 yr, which is not significantly different from patients with pN1 or pN2 disease. These data support the 2010 staging changes that include the common iliac nodes.

Currently, there are no published randomized trials that define the optimal boundaries for lymph node dissection during RC [3,7,8]. The absence of randomized trials is partly due to difficulty obtaining the numbers needed to power the study appropriately. If we hypothesize that the patients most likely to benefit from a PLND that removes the common iliac nodes are those with pN3 disease, then understanding the incidence and outcome of patients with pN3 disease is necessary to estimate the potential benefit of an extended PLND. In our series, 13% of patients with pT2 disease had pN3 disease. Given the observed 42% CSS at 3 yr, a potential benefit of approximately 5% improvement in disease-specific survival is a reasonable estimate (42% of 13%) that could be obtained with routine removal of the common iliac lymph nodes in patients with pT2 disease. This potential improvement in outcome is clinically relevant and would be comparable to that achieved with neoadjuvant systemic chemotherapy [9,10]. Based on our results, to design a trial with 80% power to identify a 5% difference in 3-yr CSS in patients undergoing extended PLND compared with standard PLND, the trial would need to accrue >2000 patients. These calculations could have important implications for current and future prospective trials. While the authors strongly believe that leaving involved common iliac lymph nodes would likely lead to greater recurrence risk compared with the complete removal of involved nodes, a properly powered randomized controlled study would be needed to clarify the extent of dissection that optimally supports improved survival.

In our series, we did not find that the location of positive lymph nodes significantly predicted outcome; however, we did find that patients with surgically removed positive common iliac lymph nodes had similar disease-specific outcomes compared with patients with disease limited to the true pelvis. Under the 2002 AJCC TNM staging system, pN3 patients were staged as pM1. Contemporary data demonstrate a 5-yr estimated CSS of approximately 20% for patients with pM1 disease [4]. The recent changes to the AJCC nodal staging system provide improved discrimination between patients with resectable pN3 disease and patients with pM1 lesions. The number of positive lymph nodes was prognostically important, supporting the pN1, pN2 designations. However, given that location of the positive node was not significantly associated with outcome, further optimization of the AJCC nodal staging system is needed.

Accurate pathologic staging during RC is paramount for the optimal treatment of patients with BCa. In our series, lymph node involvement was found in 19% of patients (114 of 591), which is consistent with other reported series [6,7,11]. In patients with lymph node involvement, 37% (42 of 114 patients) had common iliac involvement, which would have been missed if a limited template were used. Improving accuracy in staging creates the potential for a Will Rogers phenomenon because of stage migration [12]. Similar to other

published data [7], 6% of our node-positive patients had a positive lymph node in the common iliac region without any positive nodes identified within the true pelvis, suggesting that a subset of patients may have a sentinel node basin located outside the true pelvis. This idea is supported by multicenter mapping data [3] and a recent single-photon emission computed tomography/computed tomography lymphatic drainage study, in which a radionuclide tracer injected into the bladder wall was used to determine the location of the primary lymphatic drainage of the bladder [13]. The researchers demonstrated that 19% of the primary lymphatic drainage sites are located proximal to the bifurcation of the common iliac vessels. Unresected regionally metastatic disease is unlikely to remain biologically dormant and would presumably negatively affect oncologic outcomes.

There are important limitations to this study. First, these data do not represent a randomized study and do not compare outcomes with a control group; thus, the possible impact of patient selection cannot be evaluated. Potential downsides to the extended dissection include additional operative time and possible injury to autonomic nerves responsible for sexual function and the pelvic floor. A more limited dissection is performed at the discretion of the operative surgeon based on the patient's treatment history (prior PLND or pelvic irradiation) or the presence of severe vascular disease (ie, aneurysmal formation or severe atherosclerotic disease). Second, accuracy of lymph node positivity is dependent on multiple factors, including surgical and pathologic technique. Surgeon variability can affect the number of nodes removed and the designated location of identified lymph nodes. We aimed to minimize this limitation by reporting the outcomes of two experienced surgeons who used identical anatomic boundaries of dissection and routinely sent the nodes to pathology in discrete packets, which has been shown to improve lymph node identification [14,15]. Additionally, the number of lymph nodes left within a template remains unknown; however, meticulous dissection within a given template may be more important than overall lymph node counts [16]. The effect of neoadjuvant chemotherapy could also result in nodal downstaging in this cohort of patients; however, our separate outcomes analysis of previously untreated patients was identical to the overall group (Table 3). Third, median follow-up was limited to 30 mo, which reflects the contemporary nature of this cohort of patients. In a large multicenter series, Bochner et al reported that the median time to recurrence was 12 mo; and of patients who experienced recurrence, 86% did so within 3 yr [17]. Thus, the vast majority of BCa recurrences will be captured in this dataset. Notwithstanding these limitations, our study represents the largest series of prospectively collected data in a contemporary cohort of patients treated with RC and a mapping PLND.

5. Conclusions

BCa patients with positive common iliac lymph node metastasis removed at the time of RC have a similar outcome when compared with patients with nodal disease limited to the true pelvis. We did not find that the location of positive lymph nodes significantly predicted outcome; however, we did find that the number of positive lymph nodes was an independent predictor of worse oncologic outcome. Our data support the inclusion of common iliac nodes in staging for BCa; however, further refinements to provide improved prognostication are warranted.

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Take-home message

Bladder cancer patients with resected pN3 disease experience outcomes similar to those of patients with nodal disease limited to the true pelvis. Inclusion of the common iliac lymph nodes in the nodal staging system for bladder cancer improves prognostication; however, further refinements are warranted.

Fig. 1.

Location of lymph node packets and boundaries of dissection for extended pelvic lymphadenectomy, including the inferior mesenteric artery superiorly, the genitofemoral nerve laterally, and the node of Cloquet inferiorly.

Fig. 2. Kaplan-Meier curve for recurrence-free survival and cancer-specific survival, stratified by the absence of lymph node involvement (pN0) or the presence of lymph node involvement (pN+) at radical cystectomy ($p < 0.0005$).

Fig. 3.

Kaplan-Meier curve for recurrence-free survival and cancer-specific survival, stratified by N category at radical cystectomy. We did not observe a statistically significant difference between nodal groups pN1, pN2, or pN3 ($p = 0.6$ and $p = 0.2$, respectively).

Table 1

Summary of patient characteristics*

Characteristic	<i>n</i> = 591
Age at surgery, yr, median (IQR)	66 (59–73)
Male gender, no. (%)	473 (79)
High grade at cystectomy, no. (%)	483 (81)
Stage, no. (%)**	
pT0	102 (17)
pTa	28 (5)
pTis	98 (17)
pT1	84 (14)
pT2	88 (15)
pT3	171 (29)
pT4	20 (3)
Pure urothelial cell carcinoma, no. (%)	442 (75)
Positive surgical margin, no. (%)	16 (2.7)
Nodal stage (2010), no. (%)	
pN0	477 (80)
pN1	53 (9)
pN2	19 (3)
pN3	42 (7)
Received adjuvant chemotherapy, no. (%)	61 (10)
pN0	17 (3.6)
pN1	17 (32)
pN2	5 (26)
pN3	22 (55)
Received neoadjuvant chemotherapy, no. (%)	137 (23)
pN0	112 (23)
pN1	12 (23)
pN2	6 (32)
pN3	7 (17)

IQR = interquartile range.

* Consensus staging was used for the statistical analysis.

** Stage is reported as the pathologic stage at the time of radical cystectomy.

Table 2

Multivariable Cox proportional hazards regression models for the outcome of disease-specific survival or recurrence-free survival

	Cancer-specific survival		Recurrence-free survival	
	HR	95% CI	HR	95% CI
Positive nodes				
0	Ref	Ref	Ref	Ref
1	1.9	1.04–3.46	1.58	0.93–2.66
2	4.33	2.25–8.34	3.62	2.03–6.44
Positive node density >20%	1.09	0.50–2.38	0.816	0.40–1.65
Positive nodes in the common iliac	0.83	0.41–1.65	1.25	0.68–2.29
Age, yr	1.03	1.01–1.05	1.02	0.99–1.03
Male	1.07	0.66–1.74	0.936	0.64–1.38
Pure UCC	0.52	0.27–0.98	0.60	0.35–1.02
High grade	2.47	0.95–6.45	1.74	0.85–3.56
Pathologic T3+	3.12	1.98–4.93	2.94	2.02–4.29
Perioperative chemotherapy	1.34	0.84–2.13	0.85	0.576–1.25

HR = hazard ratio; CI = confidence interval; Ref = reference; UCC = urothelial cell carcinoma.

Multivariable Cox proportional hazards regression models for the outcome of disease-specific survival or recurrence-free survival after excluding patients who received neoadjuvant chemotherapy

Table 3

	Cancer-specific survival			Recurrence-free survival		
	HR	95% CI	p value	HR	95% CI	p value
Positive nodes						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	2.21	1.05–4.65	0.036	1.70	0.90–3.24	0.1
2	5.90	2.65–13.2	<0.0005	4.36	2.16–8.78	<0.0005
Positive node density >20%	1.08	0.38–3.04	0.9	0.87	0.36–2.14	0.8
Positive nodes in the common iliac	1.00	0.40–2.49	1	1.35	0.62–2.93	0.4
Age, yr	1.02	1.0–1.05	0.07	1.01	0.99–1.03	0.2
Male	0.70	0.40–1.25	0.2	0.70	0.45–1.09	0.11
Pure UCC	0.66	0.29–1.54	0.3	0.87	0.44–1.72	0.7
High grade	2.74	0.74–10.1	0.13	1.15	0.48–2.72	0.8
Pathologic T3+	3.19	1.84–5.53	<0.0005	3.27	2.09–5.13	<0.0005
Adjuvant chemotherapy	0.65	0.32–1.29	0.2	0.47	0.26–0.84	0.01

HR = hazard ratio; CI = confidence interval; Ref = reference; UCC = urothelial cell carcinoma.