Importance of Node Dissection in Relation to Neoadjuvant and Adjuvant Therapy

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Key Words

Bladder cancer, pelvic lymph node dissection, lymphadenectomy, chemotherapy

Abstract

Since the advent of effective chemotherapeutic regimens for treating transitional cell carcinoma, multimodal therapy has become part of the contemporary management of patients with muscle-invasive bladder cancer. However, radical cystectomy with pelvic lymphadenectomy remains the cornerstone of treatment for patients with localized and regionally advanced muscle-invasive disease. The effectiveness of chemotherapy models in bladder cancer can depend greatly on the quality of surgery. Unfortunately, without sufficient level I data, the boundaries of lymphadenectomy and the diagnostic and therapeutic ramifications of variations in the pelvic lymph node dissection remain undetermined. This article examines the role of pelvic lymph node dissection during perioperative chemotherapy and discusses the current challenges in establishing standards for lymphadenectomy in patients undergoing treatment for muscle-invasive bladder cancer. (*JNCCN* 2006;4:1019–1026)

Muscle-invasive transitional cell carcinoma (TCC) of the bladder is a potentially lethal epithelial malignancy characterized by the ability to invade, locally progress, and subsequently metastasize. Of the 63,000 annual new diagnoses of bladder cancer in the United States, 90% are of TCC histology, with roughly one fourth of patients presenting with muscle invasive disease.[1] Patients with muscle invasive TCC account for most of the 12,500 bladder cancer–related deaths each year,[1] because the depth of invasion is strongly associated with the development of regional lymph node (LN) involvement, distant disseminated disease, and death.[2,3]

Radical cystectomy with pelvic lymphadenectomy (RC/PLND) is currently the gold standard treatment for managing localized and regionally advanced invasive bladder cancer. Although RC/PLND cures most patients with organ-confined disease, the risk for recurrence after surgery significantly increases for tumors extending beyond the confines of the bladder or involving the regional pelvic LNs.[4–6] The incidence of node-positive bladder cancer in contemporary surgical series is relatively high, with approximately 25% of patients who undergo RC/PLND showing pathologic evidence of LN metastasis.[1,5–8] Autopsy studies and clinical observations have documented that the risk for nodal or distant metastatic disease directly correlates with the depth of invasion of the primary tumor within the bladder.[2,3,9] Regional LN involvement has been identified in 6% to 19% of patients with organ-confined, invasive bladder cancer and in 30% to 75% of patients with extravesical or locally advanced primary tumors.[5,10,11] The presence of LN involvement is a poor prognostic characteristic associated with a high risk for disease recurrence and reduced overall survival.[4–6,12] Data from a large consortium of centers of excellence (The International Bladder Cancer Nomogram Consortium) on more than 9000 patients treated with RC/PLND document that those with organ-confined, LN-negative tumors have a 5-year survival rate of approximately 80% compared with 30% for patients with involved regional LNs.[12]

Chemotherapy and Bladder Cancer

Because of the poor prognosis associated with disseminated TCC, a great deal of effort has gone into developing effective systemic treatments for advanced disease. TCC is a chemotherapy-sensitive neoplasm, with cisplatin emerging as the most effective systemic agent.[13] Although

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limited responses were initially observed with cisplatin as a single agent,[14] results from clinical trials incorporating cisplatin into a multiagent drug regimen showed improved response proportions. In the late 1980s, investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) reported that 69% (± 10%) of patients with metastatic bladder cancer treated with a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) experienced complete or partial responses.[15] Multiple randomized control trials then compared MVAC with single-agent cisplatin and other multiagent platinum-containing regimens,[16,17] showing its superiority, and established it as the standard for patients with metastatic bladder cancer. Unfortunately, MVAC is associated with considerable toxicities, including granulocytopenia, renal toxicity, and peripheral neuropathy.[15–17]

To lessen the morbidity associated with treatment, alternative regimens were evaluated, including the doublet of gemcitabine and cisplatin (GC). In a phase III randomized, multicenter trial, the combination of GC resulted in equivalent response and survival rates compared with MVAC in patients with metastatic TCC. However, patients treated with GC experienced significantly lower rates of granulocytopenia, neutropenic fever, and sepsis.[18] Based on the similar response rates and lower toxicity profile, GC has emerged as the preferred regimen for patients undergoing systemic chemotherapy for TCC.

Because of the significant risk for distant failure in patients undergoing cystectomy for locally advanced or regionally metastatic disease, strategies to incorporate effective systemic chemotherapy in the perioperative period have been completed. Multiple trials evaluating both neoadjuvant and adjuvant chemotherapy have documented a survival benefit in patients undergoing chemotherapy in conjunction with RC/PLND.[19–25] Regardless of the chemotherapeutic approach, RC/PLND continues to be the cornerstone of the overall treatment plan. This article focuses on the role of surgery, specifically PLND, in the multimodal management of high-risk bladder cancer and discusses the problems associated with establishing contemporary standards for PLND.

Role of Surgery in Muscle-Invasive Bladder Cancer

RC has long been considered the most effective local treatment for muscle-invasive bladder cancer, providing excellent rates of local control and long-term survival, particularly in patients with localized disease.[12] With significant reductions in treatment-related morbidity and mortality and the advent of orthotopic bladder substitution techniques, the popularity of RC has increased. Although wide excision of the bladder and the perivesical tissues is recognized as an essential component of the surgical management of invasive bladder cancer, mounting data also support a critical role for PLND in optimizing surgical outcomes.

The importance of controlling the regional lymphatics became apparent soon after the earliest cystectomy series reported unacceptably high local recurrence rates. The initial techniques used for surgical extirpation of the bladder made little attempt to completely excise the perivesical tissues or control the regional pelvic LNs. Poor local tumor control and dismal long-term survival observed in historical series led to the development of more radical surgical techniques, which were largely based on autopsy studies and clinical observations published from the 1930s through the 1950s.[2,3,9,26] Based on an understanding of the pathways of invasive bladder cancer progression and the relationship between the depth of invasion of the primary tumor and the development of regionally metastatic disease, procedures were adopted that incorporated a thorough PLND at bladder removal. Reports then emerged documenting the ability of RC and PLND to reduce the risk for local recurrence and improve overall survival.[3,26,27]

Over the next 30 years, RC/PLND became popular, and reported outcomes confirmed that the addition of a thorough PLND could be performed safely with improvements in outcomes.[28,29] Unlike the poor initial outcomes that patients with surgically treated, node-positive bladder cancer experienced, contemporary series show that approximately one third of all node-positive patients can be rendered disease-free when treated with RC and a thorough PLND.[5,6,29] Despite the consensus among urologic surgeons that a PLND should be performed at cystectomy, controversy remains as to the optimal extent of PLND required for the most favorable outcome. No clear guidelines exist regarding the boundaries of lymphadenectomy or the critical number of nodes that should be removed during RC/PLND to ensure adequate staging and provide maximum therapeutic benefit. Without a universally accepted standard,

significant variations in the quality of RC/PLND have been noted in most published series and data obtained from general clinical practices within the community.[30,31] However, increasing evidence suggests that these variations may have significant ramifications not only on patient outcomes but also on the actual or interpreted effectiveness of neoadjuvant and adjuvant chemotherapy regimens.

Pelvic Lymphadenectomy

Difficulties in Establishing Standards

Ideally, the standards for PLND should be based on data from prospective randomized clinical trials in the same way that standards for chemotherapy regimens were established. Because this prospective level 1 evidence does not exist, the question remains whether standards can be reasonably established from the available peer-reviewed data. Although retrospective data strongly support that staging, overall survival, and local control improve with PLND compared with RC alone,[3,26] conflicting opinions regarding the extent of dissection have made establishing a standardized template for PLND difficult. Multiple anatomic autopsy studies and historical and contemporary surgical mapping studies in patients undergoing RC/PLND have clearly documented the pattern of dissemination of disease to the regional LNs.[2,3,7,9,32] The primary landing zones for bladder cancer include the perivesical, external iliac, obturator, hypogastric, and presacral nodal regions (Figure 1). All primary landing sites subsequently drain into more proximal common iliac node chains and then the retroperitoneal nodes.

Currently, a PLND with a proximal margin of resection at the bifurcation of the common iliac vessels removes the external iliac, internal iliac, and hypogastric LNs. This dissection is often considered adequate for patients undergoing RC for bladder cancer. This template is based on data from small series showing that a limited dissection is adequate for identifying occult LN metastasis in patients with no evidence of gross pelvic adenopathy.[33,34] Subsequently, many surgeons have adopted this template for all routine RC procedures, and it is now recognized as the standard PLND. Others, however, have supported a more complete PLND that extends to the bifurcation of the aorta and vena cava, resulting in the removal of the common iliac, presacral, lower para-aortic, and vena caval LN regions, in addition to the more distal chains

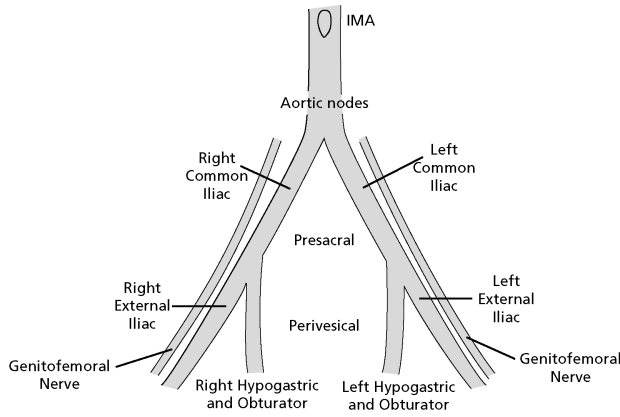

Figure 1 Primary and secondary bladder cancer landing sites.

noted earlier. Routine use of this extended PLND is supported by detailed surgical, autopsy mapping, and prognostic studies that have shown improved tumor control and survival were associated with more extensive PLNDs.[4,7,30,32,35,36]

Several studies have documented the inadequacies of the more limited template for effectively removing involved pelvic lymph nodes in patients with bladder cancer. The study by Vazina et al.[32] showed that 16% of patients undergoing RC for locally advanced bladder cancer (pT3 or pT4) had LN metastasis outside the boundaries of a limited LN dissection. Similarly, a prospective, multi-institutional study of 290 patients undergoing an extended mapping PLND to the level of the inferior mesenteric artery at RC showed that 25% of 81 node-positive patients had metastatic LNs outside the boundaries of the limited dissection, including 6.8% of patients with nodal involvement exclusively outside these limits (skipped nodes).[7]

In a recent prospective evaluation from MSKCC of 144 patients with grossly normal LNs, 35% of all positive nodes were found outside the standard template in nodes residing above the bifurcation of the common iliac vessels.[37] Additionally, in contrast to previously published findings from M. D. Anderson Cancer Center, microscopically positive LNs above the common iliac LNs were identified despite no evidence of gross nodal involvement. These findings suggest that intraoperative identification of gross adenopathy cannot be used as a reliable indicator for excluding removal of secondary drainage regions. Although some contemporary tumor mapping studies in patients with bladder cancer identified skipped nodes,[7,32] this does not seem to be a common event.

Staging

Accurate staging of the regional LNs is essential in patients with invasive bladder cancer. Accurate LN staging during perioperative chemotherapy provides precise pathologic data and properly identifies patients requiring adjuvant chemotherapy. Furthermore, the ability to accurately interpret the outcomes from adjuvant and neoadjuvant chemotherapy trials relies on a valid assessment of the node status of the various study groups within the trial. The strong impact of regional LN involvement on disease recurrence and survival makes this variable essential for understanding the nature of the study populations represented in such trials.

Because of the staging accuracy of current imaging modalities (some series report a sensitivity of approximately 10%)[38,39] and the paucity of data showing a true "sentinel node region,"[8] the surgical removal and pathologic examination of regional LNs remains the most precise and reliable method to identify metastasis and accurately stage bladder cancer. An optimal PLND provides a greater degree of confidence that the nodal status was correctly determined, minimizing the risk for understaging and subsequent undertreatment caused by insufficient sampling. Because of the lack of prospective trials, data establishing the optimal extent of dissection can only be based on anatomic studies of LN drainage from the bladder and tumor mapping studies that have documented patterns of LN metastases in patients with bladder cancer.

Based on these studies, all primary landing zones should be cleared during surgery, including the presacral nodes, because, although they are involved less frequently, they are a primary region. Given the reported median numbers of nodes from these landing zones, a median yield of approximately 12 to 15 nodes is expected. However, using a defined number of LNs to establish a standard for dissection is challenging and should be considered with caution. The literature clearly documents significant interinstitutional and intrainstitutional variability in LN yields reported from similar anatomic regions and extent of dissections. Reported LN yields may be influenced by several factors, including individual patient variability (age, comorbidity, and physiology), exposure to preoperative chemotherapy, anatomic divergence, surgeon variability, primary tumor pathologic stage, completeness and manner of pathologic evaluation (including the use of fat clearing solutions), and how nodes are submitted. In a prospective study that attempted to identify the factors associated with LN yield in 144 consecutive patients undergoing RC/PLND performed by 4 experienced surgeons at a tertiary referral center,[37] only the extent of dissection (limited vs. extended) was found to correlate with LN counts. Patient age, previous exposure to systemic or intravesical treatments, and body mass index were not associated with differences in reported LN counts (Table 1).

The authors recommend that a thorough and complete dissection of the primary landing zones be performed routinely to provide tissues for adequate staging of the lymph nodes. Therefore, a series of patients undergoing a complete dissection is expected to yield a median LN count of approximately 12 reported by the pathologist. If median counts are significantly lower, alterations in surgical or pathologic techniques should be considered. No defined minimal number of lymph nodes exists in which adequate pathologic staging can be confirmed. Although a median lymph node count of 12 would be a convenient number to establish a

Table 1 Factors Associated with Total Node Counts

		Coefficient	
	***P* Value**	**Estimate**	**95% CI**
Surgeon	.137	*	*
Pathologist	.216	*	*
Neoadjuvant chemotherapy (yes vs. no)	.912	0.3	-4.4–4.9
BCG within past 6 mo (yes vs. no)	.082	-3.4	-7.2–0.4
Age (y)	.155	-0.1	-0.022–0.03
Days from TUR to RC	.557	0	-0.01–0.0003
Type of dissection (extended vs. standard)	< .001	7.3	3.7–10.7

Source: Bochner BH, Cho D, Herr HW, et al. Prospectively packaged lymph node dissections with radical cystectomy: evaluation of node count variability and node mapping. J Urol 2004;172:1286–1290;with permission.

* Random effects.

Abbreviations: BCG, bacillus Calmette-Guérin; CI, confidence interval; RC, radical cystectomy; TUR, transurethral resection.

minimal standard, by definition, one half of all patients with complete template dissections of the primary landing zones would have LN counts below this number. Therefore, patients undergoing adequate surgical excision of the LN regions based on the primary landing zones could potentially be considered inadequately staged if a lower number of LNs were evaluated. Ongoing work is needed to standardize the pathologic evaluation of the submitted nodal tissues and better define a minimum number of LNs that must be identified and examined to provide a confident statement about the regional spread of disease.

Implications on Therapeutic Benefit

The therapeutic value of the PLND at RC has received considerable attention and is supported by a growing body of literature; however, its overall importance remains controversial. Although no randomized prospective studies have been performed to document the therapeutic benefits of extending the limits of the LN dissection, several retrospective, single-institutional reports suggest improved outcomes after a more extensive dissection.[4,6,36,40] Proponents of the therapeutic benefits of a more extended PLND cite evidence from mapping studies that indicate frequent involvement of nodes outside the standard PLND template. Studies have shown that such a limited dissection (obturator, hypogastric regions) may only remove 25% of involved LNs, leaving most tumor-bearing pelvic nodes unresected.[32] Additional supportive evidence of a therapeutic role of the PLND is provided by large clinical series that document a 30% long-term disease-free survival in all patients with LN metastases after RC/PLND, with an improved outcome (40%–50% 5-year disease-free survival) in LN-positive patients with only limited involvement.[5,6,11,29]

Several series have examined oncologic outcomes in relation to various LN parameters, including the number of LNs retrieved, the absolute number of positive LNs (used as surrogate for tumor burden), and the percentage of positive LNs to total number of LNs removed (LN density).[32,35,40–42] Despite the many published reports noting an association between improved outcomes and increased LN counts,[4,40,41] no consensus exists as to the number of nodes that should be removed to optimize outcomes after RC. Recent publications have recommended that as few as 4 and as many as 20 LNs should be removed to maximize therapeutic benefit.[11,30,40,43] Unfortunately, these recommendations have been based on various criteria, including common practice patterns, and single variable, retrospective analyses. All of these studies have failed to consider potential biases associated with patient selection for limited or more extended dissections, such as patient comorbidity and age at radical cystectomy, or the effects of subsequent treatment (i.e., chemotherapy).

Koppie et al.[44] recently performed a multivariable analysis on more than 1121 patients with bladder cancer treated by RC/PLND to determine if a threshold effect on survival could be detected for the extent of lymphadenectomy. Unlike previous studies, the analysis simultaneously considered various factors (e.g., age, comorbidity, perioperative chemotherapy, pathologic stage, surgeon, pathologist) that may effect the extent of lymphadenectomy, the reported LN yield, and survival. When correcting for all of these important covariables, LN yield continued to show an important positive association with survival (Table 2). A continuous positive association of increasing survival with LN yield was noted for up to 25 reported LNs with no threshold effect observed (Figure 2). Based on the limited number of patients with LN counts above 25, no conclusions could be made about the association beyond this number. In the authors' experience, as well as in the experience of others, an average LN yield of 25 nodes requires an extended PLND. Based on these data, the authors presently recommend the routine use of an extended PLND in addition to perioperative chemotherapy to optimize any potential therapeutic advantages unless obvious contraindications exist.

To overcome the shortcomings associated with overall LN counts, the concept of LN density has also garnered some recent interest. By incorporating 2

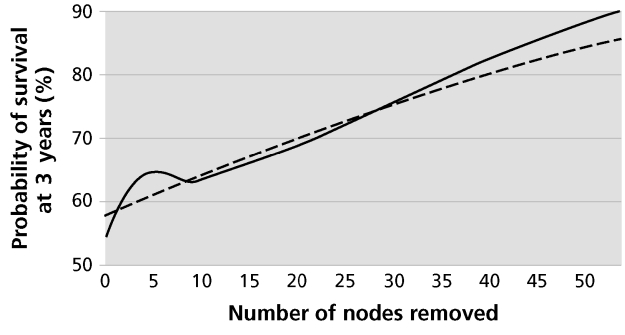

Figure 2 Survival probability based on the number of lymph nodes removed. Modified from Koppie T, Vickers A, Vora K, et al. Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? Cancer 2006; in press.

Table 2 Predicted Probability of Survival by Number of Nodes Removed*

Number of Nodes Removed	Survival Probability at 3 Years (%)		Survival Probability at 5 Years (%)		Survival Probability at 10 Years (%)	
	Nonlinear Model	Linear Model	Nonlinear Model	Linear Model	Nonlinear Model	Linear Model
0	53.6	57.5	38.0	41.8	20.6	23.3
4	65.0	60.7	49.6	45.0	29.4	25.8
8	65.6	63.8	50.3	48.3	30.0	28.4
12	66.3	66.8	51.1	51.6	30.7	31.2
16	68.4	69.6	53.4	54.9	32.7	34.1
20	71.0	72.4	56.5	58.2	35.5	37.1
24	73.9	74.9	60.0	61.3	38.9	40.2
32	80.0	79.5	68.0	67.4	47.3	46.7

Source: Koppie T, Vickers A, Vora K, et al. Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? Cancer 2006; in press; with permission.
*Data are adjusted for pathologic stage, age, and comorbidity.

reported prognostic indicators—the number of positive LNs (tumor burden) and the number of LNs removed (extent of lymphadenectomy)—LN density has been found to have some prognostic significance in several series.[11,41,42] Although this parameter is still of clinical interest, a study by Fleischmann et al.,[45] in which a large series of preoperatively staged N0M0 patients with invasive bladder cancer underwent an RC with a standardized "extended" PLND, refuted the importance of LN density. This study not only showed the large variability in nodal counts despite a standardized template for PLND, but also reported that the LN number and LN density were not significant predictors of recurrence-free survival in multivariate analysis (P = .43). Given the contradictory findings of the reported series, no consensus exists on the importance of LN density.

PLND in the Setting of Neoadjuvant Chemotherapy

Unlike adjuvant chemotherapy, pathologic staging is unknown before neoadjuvant chemotherapy is administered. Therefore, although the PLND does not play a role in staging in neoadjuvant chemotherapy, it can play an important therapeutic role in the use of neoadjuvant chemotherapy.

Randomized studies and meta-analyses show a small but significant advantage in survival for patients undergoing neoadjuvant chemotherapy.[19–21] In most studies, an overall survival advantage of 5% is noted. Furthermore, these studies show that neoadjuvant chemotherapy (including MVAC) can be given preoperatively without precluding surgery or increasing the complication rates associated with surgery. Like all perioperative chemotherapy trials involving surgery, the results from neoadjuvant chemotherapy trials are limited by significant variations in surgical technique. The variability in surgery (which includes differences in the "quality" of RC and the extent of dissection in the PLND) seems to have a significant influence on survival rates, even with the use of neoadjuvant chemotherapy.

Recently, an analysis of the Southwest Oncology Group 8710 neoadjuvant chemotherapy trial was performed to determine the impact of surgical variables on post-cystectomy outcomes of patients with bladder cancer who had undergone preoperative chemotherapy.[31] In this series, approximately half of the patients underwent a standard bilateral PLND, whereas 37% underwent a limited node sampling and approximately 10% underwent no PLND at all. This resulted in approximately 25% of the patients having nodal counts in 4 ranges: 0 to 4, 5 to 9, 10 to 15, and greater than 15 nodes. On univariate and multivariate analysis, the number of LNs removed (< 10 vs. ≥10) was found to be independently predictive of both post-cystectomy survival and local recurrences.[31] These data suggest that regardless of the effectiveness of neoadjuvant chemotherapy, PLND has a significant influence on outcomes, reinforcing the need to establish guidelines for surgical quality.

For patients with locally advanced disease (but no evidence of visceral or distant metastatic disease), chemotherapy can be given before cystectomy to downstage disease and provide an opportunity for

complete resection. Although most patients succumb to their disease, those who experience a complete response (downstage to pT0/T1) have significantly improved rates of survival.[19,46,47] However, most patients with locally advanced disease will only experience a partial response to chemotherapy. Therefore, complete resection of residual disease (consolidative surgery) after chemotherapy involves removal of not only the bladder but also the regional pelvic LNs, which have a high likelihood of being involved. This notion is supported by data showing that patients with locally advanced disease who experience a response to chemotherapy tend to relapse at the previous sites of involvement.[48] Several studies have examined the outcomes of postchemotherapy surgery in patients with locally advanced disease. These studies show that surgery to remove the primary tumor and all regionally involved LNs after chemotherapy can provide a combined complete response to treatment that is associated with a reasonable survival advantage in these patients.[49,50]

Conclusions

The PLND plays a crucial role in the multimodal approach to muscle-invasive bladder cancer. Increasing evidence suggests that extending the boundaries of lymphadenectomy provides more accurate patient staging and improves disease outcomes after RC/PLND. Despite the available data, no consensus on the LN numbers needed to optimize patient outcome has been achieved. Because of significant variability of LN counts from similar dissections, establishing an anatomic extent of dissection may be a more reliable parameter for establishing surgical standards. Currently, unlike with malignancies such as breast, colon, and stomach,[51–53] a minimum or critical number of excised LNs required to provide either optimal staging or therapeutic benefit remains controversial for patients undergoing treatment for muscle-invasive bladder cancer.

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