Lymphadenectomy for Muscle-Invasive Bladder Cancer and Upper Tract Urothelial Cell Carcinoma

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KEYWORDS

• Cystectomy • Lymph node dissection • Transitional cell carcinoma • Urinary bladder neoplasms

KEY POINTS

- No randomized studies have been published to date examining lymph node dissection in either bladder cancer or upper tract urothelial carcinoma.
- It is estimated that one-quarter of patients undergoing radical surgery for bladder cancer or upper tract urothelial carcinoma harbor lymph node metastases.
- An extended pelvic lymph node dissection template is recommended for patients undergoing radical cystectomy to optimize prognostic and therapeutic benefit.
- Lymphadenectomy recommendations for patients with upper tract urothelial carcinoma are less clear but a complete dissection according to one of the two well-known templates seems to be required to maximize outcomes.

INTRODUCTION

Urothelial cell carcinoma is the ninth most common malignancy of which more than 95% arise in the bladder.[1] Although 15% to 25% of bladder cancers (BC) are invasive at the time of diagnosis, upper tract urothelial carcinomas (UTUC) are markedly more aggressive with approximately 60% of cancers demonstrating invasive characteristics at the time of presentation.[2] Therefore, radical surgery is widely recommended as the optimal management option in patients who do not have distant disease and can tolerate the stressors of surgery.[3–5] Although the role of surgery does not ignite much debate, there remains ongoing conjecture regarding the independent utility of lymphadenectomy for BC and UTUC. Several unanswered questions remain in this domain focused on the indications and patient selection for pelvic lymph node dissection (PLND), extent of dissection, its impact on outcome, and potential risks.

INDICATION AND PATIENT SELECTION

Considering the limitations of the available imaging modalities, accurate staging remains the primary benefit of performing a lymphadenectomy. Conventional modalities commonly used as part of the diagnostic work-up to stage BC or UTUC, such as computed tomography (CT) and MRI, are limited by their poor sensitivity, which is reported to range between 48% and 87%.[5] This is because CT and MRI rely on lymph node (LN) enlargement to discern the possibility of nodal metastases. The guidelines suggest that pelvic nodes

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greater than 8 mm and abdominal nodes greater than 10 mm in the short-axis maximal diameter should be considered to be abnormally enlarged.[6,7] However, normal-sized nodes can harbor metastatic disease and LNs can also be enlarged as a result of benign processes. It was thus hypothesized that functional imaging techniques, such as PET, could address these shortcomings but it too has demonstrated limited utility.[8,9] Therefore, relying on imaging to inform nodal status would result in a significant proportion of patients being understaged and thus not receiving optimal management in a timely manner.[10–12]

Bladder Cancer

The burden of nodal disease in patients with BC is considerable and has prognostic implications. An early autopsy study of 98 patients found nodal disease in a quarter of the cohort.[13] A second autopsy study reported that LN disease may be the only site of metastases in up to 40% of patients.[14] These figures have been supported by modern-day cohorts that have reported the incidence of nodal involvement to be approximately 25%.[15,16] There is a correlation between tumor stage and LN involvement with the rates of nodal metastases for pTa, pTis, pT1, pT2, pT3, and pT4 patients undergoing extended PLND (ePLND) being 0%, 2%, 4%, 14%, 35%, and 52%, respectively.[15] LN disease has been associated with poor survival outcomes. The 10-year cancer-specific survival rates between N0 and N+ disease is 66.9% versus 28.8%, respectively.[17]

There are no published randomized trials that compare radical cystectomy (RC) patients with or without concomitant lymphadenectomy. Therefore, current guidelines that suggest a benefit in performing nodal dissection rely on observational data to support their recommendations. Although not addressing the question of RC plus PLND versus RC alone, the preliminary results of a randomized trial comparing standard PLND with superextended PLND (sePLND) observed a trend for improved outcomes using the latter template but this was not statistically significant.[18] Details of this trial are outlined further later but it raises important questions regarding the value of lymphadenectomy. Reanalysis of the Southwest Oncology Group (SWOG 8710, INT-0080) randomized trial on neoadjuvant chemotherapy in muscle-invasive BC (MIBC) found that the extent of nodal dissection and the number of nodes removed significantly influenced survival outcomes on multivariable analysis, which included receiving neoadjuvant chemotherapy as a covariate.[19] In contrast, an Italian cohort study reported by Brunocilla and colleagues[20] demonstrated no benefit in cancer-specific survival when performing a limited PLND compared with omitting it all together. However, there was a survival benefit in this group when an extended dissection was performed. In a propensity matched study of patients who underwent RC alone or in conjunction with PLND, the all-cause survival rate (36% vs 45%; $P<.001$) and cancer-specific survival rate (54% vs 65%; $P<.001$) was greater in the latter group.[16] Subgroup analysis based on age and Charleson comorbidity index demonstrated that the relationship between lymph node dissection (LND) and improved survival outcomes only remained significant for patients younger than 75 years or who had a comorbidity index score of 0. An analysis of the Surveillance, Epidemiology and End Results (SEER) database demonstrated that not performing lymphadenectomy significant increased overall mortality rates across all stages of BC but only lowered cancer-specific mortality in less than or equal to pT2 disease.[17] This study also showed that PLND is omitted in a quarter of all patients undergoing RC, especially those with lower stage disease when they too would benefit from lymphadenectomy. Therefore, given the available data, bilateral LND should be considered in all patients undergoing RC for MIBC as recommended by guidelines.[3–5] However, the evidence supporting this is less than ideal. Although not studied in BC, there is high-level evidence in some cancers that LND may not provide any benefit despite lower-level evidence, and intuition, suggesting it would. In fact, two recent randomized trials in patients with breast cancer and melanoma with sentinel node metastases (ie, positive sentinel node biopsy) randomized to completion LND versus no further node dissection found no overall survival benefit in performing nodal dissection.[21,22] However, the latter report did suggest that LND improved regional disease control (disease-free survival: 68% vs 63%; $P = .05$) and provided valuable prognostic information because nonsentinel nodal metastases acted as a significant predictor of melanoma recurrence,[22] although this did not translate into a cancer-specific survival benefit at median follow-up of 43 months. In the breast cancer study, axillary node clearance did not impact disease control in patients with breast cancer compared with sentinel node dissection only (hazard ratio [HR], 08.85; 95% confidence interval [CI], 0.62–1.17; $P = .32$).[21] This type of data emphasizes the need for randomized trials to examine these questions, rather than relying on low-level evidence and/or expert opinion. It should be noted that there