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REVIEW

Pelvic lymph node dissection in the context of radical cystectomy: a thorough insight into the connection between patient, surgeon, pathologist and treating institution

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Abstract: Pelvic lymph node dissection (PLND) in patients with bladder cancer varies widely in extent, technique employed, and pathological workup of specimens. The present paper provides an overview of the existing evidence regarding the effectiveness of PLND and elucidates the interactions between patient, surgeon, pathologist, and treating institution as well as their cumulative impact on the final postoperative lymph node (LN) staging. Bladder cancer patients undergoing radical cystectomy with extended PLND appear to have better oncologic outcomes compared to patients undergoing radical cystectomy and limited PLND. Attempts have been made to define and assess the quality of PLND according to the number of lymph nodes identified. However, lymph node counts depend on multiple factors such as patient characteristics, surgical template, pathological workup, and institutional policies; hence, meticulous PLND within a defined and uniformly applied extended template appears to be a better assurance of quality than absolute lymph node counts. Nevertheless, the prognosis of the patients can be partially predicted with findings from the histopathological evaluation of the PLND specimen, such as the number of positive lymph nodes, extracapsular extension, and size of the largest LN metastases. Therefore, particular prognostic parameters should be addressed within the pathological report to guide the urologist in terms of patient counseling.

Keywords: bladder cancer, outcome, pathological workup, postoperative staging

Introduction

In the early cystectomy era, the prognosis of patients with lymph node (LN) metastases was thought to be uniformly bleak. The value of meticulous LN dissection for patients undergoing radical cystectomy (RC) for muscle-invasive bladder cancer was first demonstrated in 1982 when Skinner[1] showed that cure is possible even in patients with LN metastases following RC and concomitant pelvic LN dissection (PLND). In that series, PLND provided better local control without adding substantially to morbidity. Additionally, postoperative histologic LN staging allowed identification of patients at risk who could be directed to adjuvant therapies. Despite this early description, no prospective randomized trials have yet been finalized to test this concept. Nevertheless, the necessity of PLND within the context of RC is generally accepted, and the majority of oncologic urologists perform at least some form of PLND. The present paper provides an overview of the existing evidence regarding the effectiveness of PLND and elucidates the interactions between patient, surgeon, pathologist, and treating institution, as well as their cumulative impact on the final postoperative LN staging.

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Bladder cancer surgery and natural course of the disease

Simple cystectomy without PLND was an early surgical approach to treating patients with muscle-invasive bladder cancer. However, its survival rates were frustrating.[2] Urologists later experimented with expanded dissection areas and found that extended dissections were feasible from both the technical and perioperative mortality standpoints.[3–8] However, the perioperative mortality could be considerable, as illustrated by a case series reported mid-20th century; although there were no intraoperative deaths, five of the 22 patients died within the first 2 postoperative weeks.[5]

In 1950, Leadbetter and Cooper[6] were the first to describe the surgical principles of RC before Marshall and Whitmore[9] substantiated the procedure 6 years later. Nowadays, RC represents a standard intervention with a 1%–2% rate of perioperative deaths in experienced centers.[10]

Of all patients diagnosed with bladder cancer, 20%– 40% initially present with muscle-invasive disease. For those undergoing RC with PLND, postoperative tumor stage and LN status are important predictors of outcome. The rate of LN metastasis is associated with the primary tumor stage, and increases from 5%–10% in non-muscle-invasive bladder tumors (pT0, pTa, pTis, pT1), to 18% in superficial muscle-invasive tumors (pT2a), to 27% in deep muscle-invasive tumors (pT2b), and to 45% in extravesical tumors (pT3-4). Accordingly, LN-negative pT0, pTa, and pT1 patients have the best outcomes, with recurrence-free rates at 5 years and 10 years of >90%.[11] The recurrence-free rates for patients with pT2 pN0-N2 tumors are around 75% and 70% at 5 years and 10 years, respectively. The rates decrease to 45%–50% at 5 years and 45% at 10 years for patients with pT3 pN0-N2 tumors.[12] Due to the various sites of local invasion, pT4 tumor patients represent a heterogeneous cohort with recurrence-free rates around 45% and 35% at 5 years and 10 years, respectively.[11,13,14] In general, progression following radical surgery is associated with a dismal prognosis and usually occurs within the first 2 years. Overall, survival following radical surgery alone remains modest at 43%–57%. It is the patient with an organ-confined primary tumor (<pT3) and limited LN involvement[15] that has the best chance for long-term cure. In contrast, patients with intraoperative grossly LN-positive disease have even a 25% chance of cure following radical surgery with extended PLND.[16]

Pelvic lymph node dissection – ongoing controversies

The main controversy regarding PLND is related to the optimal extent of PLND. The fact that the prognostic and therapeutic benefits of PLND are based on retrospective cohort studies[12,17–20] explains the lack of consensus in this matter. It is hoped that two ongoing prospective randomized trials (the SWOG trial S1011[21] and the German multicenter study LEA[22]) will soon be able to elucidate this important problem and provide the necessary information to define a "standard" oncologic template for PLND. The variety of PLND templates currently applied makes outcome comparisons difficult.

In addition to the template problem, numerous attempts have been made to define the proper extent of PLND based on the number of LNs identified, and to determine the prognostic value of LN density. These topics will be discussed with reference to the inherent connection between patient, surgeon, pathologist, and the treating institution.

Pelvic lymph node dissection – fundamental considerations

The physiology of lymphatic drainage of the urinary bladder is complex. Applying their technetium-based mapping study, Roth et al[23] identified not fewer than 24 primary lymphatic landing sites per urinary bladder. Of these, only 8%–10% were detected proximal to the mid-upper third of the common iliac vessels. Moreover, no radioactive solitary extra pelvic LNs (skip lesions) were identified. Focusing on the small pelvis, one-fourth of the primary lymphatic landing sites were located in the internal iliac region, with almost half (42%) of them lying medial to the internal iliac artery.[23] In terms of laterality, following strictly unilateral technetium injection, at least one primary lymphatic landing site was found on the ipsilateral side and 40% of patients had at least one additional primary lymphatic landing site on the contralateral side.[24] This underscores the necessity of bilateral PLND in all cystectomy patients.

Prior to the technetium-based analyses, conventional LN mapping studies provided important information regarding common sites of pelvic LN metastases.[25–27] However, these studies had considerable limitations, such as overlapping dissection areas and the substantial reliance of intraoperative labeling on the surgeon's discretion.

Fundamentally, any analysis of lymphatic tissue based on the tissue specimen removed involves an inherent bias; it remains unknown how much tissue/how many LNs were left behind. As a consequence, the reliable definition of an adequate PLND based on postoperative pathologic findings or number of LNs removed/identified is not feasible. A possible approach would be to develop an imaging technology that can identify lymphatic tissue left in situ after RC and PLND.

The patient

Physiologically, there exist considerable interindividual differences in terms of LN counts. Weingärtner et al[28] identified a mean of 22.7 ± 10.2 pelvic LNs per patient in their autopsy series (n = 30) with a wide range of eight to 56 LNs. In another recent cadaver study, the range of identified pelvic lymph nodes was high (19–53 LNs), even with evaluation by a single pathologist.[29] In our intra-institutional analysis including oncologic outcomes we found a similarly wide range of LNs per patient (eight to 55 LNs) without an impact on survival.[30,31] More recently, Mitra et al[32] demonstrated that patient characteristics such as age, body mass index, clinical tumor stage, type of tumor growth, multifocality, and surgical margins can substantially influence total nodal yields. Therefore, interindividual variation is an important factor affecting the number of identified LNs in the context of PLND.

The surgeon

Since the surgeon decides upon the performance, extent, and quality of a PLND, he/she may be a key factor for success. Nevertheless, in a Surveillance, Epidemiology, and End Results (SEER) program database analysis capturing approximately one-fourth of the US population, 40% of all patients (n = 1,923) undergoing RC between 1988 and 1998 did not have a PLND.[33] Hollenbeck et al[34] demonstrated in a similar more resent study (n = 3,603) that the majority of cystectomy patients had only a few pelvic LNs (≤4 LNs) removed at the time of RC, irrespective of hospital volumes. In contrast, the rate of patients with ≥10 LNs decreased from 35.3%, to 12.7%, to 0% when comparing hospitals with high, medium, and low LN counts, respectively. Furthermore, high-volume hospitals achieved a more even distribution of LN counts.

Without doubt, PLND is performed near to delicate anatomic structures and is time consuming. On the other hand, a meticulous PLND helps to identify pelvic structures, facilitates cystectomy, and offers better vascular control[35] without increasing perioperative morbidity.[27,36] It is difficult to estimate the impact of surgical education/experience, institutional philosophy, and possible economic considerations (reimbursement) on the extent and thoroughness of PLND. Nevertheless, these factors may explain, to some extent, the differences in practice among urologists.

A critical issue for the surgeon is whether to adopt a new surgical approach, eg, whether to switch from open to minimally invasive RC. While it has been shown that even a super-extended PLND is feasible and safe with robotic assistance,[37] PLND is often omitted in the initial phase of the procedural learning curve.[38] The performance of an extended PLND is significantly associated with institutional and individual surgeons' case number and surgical volume.[9] However, urothelial cancer does not allow any oncologic compromise and requires a thorough extended PLND, irrespective of surgical approach.

The pathologist

Because pathology findings are greatly impacted by the specific local tissue workup process, several factors have to be considered when comparing pathology reports on LN specimens from various institutions.[39] First, the submission of specimens in separate packets instead of en bloc significantly increases the number of reported LNs.[40] The use of smaller specimens might facilitate macroscopic identification of LNs by the pathologist and may also allow for better fixation and processing,[41] thus improving the detection of LNs. Second, the use of certain fixation and processing methods, eg, acetone or Carnoy's solution, results in resolution of fatty tissue and enhances the macroscopic visibility of LNs,[42] facilitating identification of LNs and potentially increasing nodal counts. Third, the more meticulous the pathologist's examination of the specimens, the greater the number of LNs identified. Moreover, the more accurate the pathologist's report on the embedding of nodes, the easier the counting of LNs under the microscope (Figure 1).[43] Fourth, and a rarely reported factor, the amount of tissue that is embedded for microscopic examination affects LN yield; embedding the entire specimen, for example, increases the number of nodes identified.[42] According to personal, unpublished data (2009),

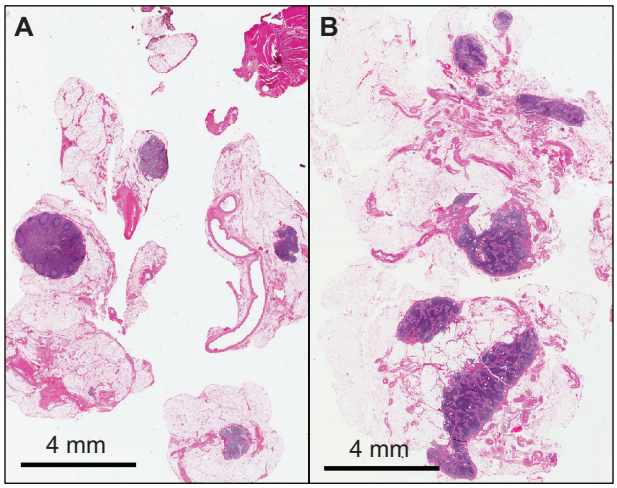

Figure 1 Images of two histopathological lymph node slides.
Notes: (**A**) Described macroscopically as containing four embedded lymph nodes, (**B**) and containing one sliced lymph node. This information made the lymph node counting both easier and more accurate.

approximately two additional nodes are found per packet in the remaining, not routinely embedded lymphadenectomy tissue. Fifth, although the histological criteria defining LNs are clearly established, the determination of a LN in a microscopic slide not only depends on the sectional plane through the LN, but also varies between pathological institutes and pathologists.[43] Parkash et al[43] evaluated LN counts on slide scans performed by ten pathologists, each pathologist receiving the same series of slides for review. They noted considerable interobserver and intra-observer variability, which was particularly dependent on the macroscopic description of the slide given by the study coordinator.

Finally, molecular staging techniques, such as reverse transcription real-time quantitative PCR (RT-qPCR), have been investigated to determine whether they can detect the presence of missed micrometastases in LNs during routine pathological workup. RT-qPCR has been applied in breast,[44] colon,[45] and urinary bladder cancers[46,47] to detect small changes in gene expression (eg, CK-19, CK10, or Uroplakin II) indicative of micrometastases or disseminated cancer cells. In line with findings on other neoplasias, the detection of micrometastases in bladder cancer is increased by RT-qPCR,[46,47] and is linked to unfavorable tumor characteristics[47] and even associated with adverse outcomes.[46] However, in bladder cancer, the true clinical impact of these molecular micrometastases remains largely unknown and external validation of these data is urgently needed. Therefore, these techniques are not routinely used.

Another evaluated molecular technique is keratin immunohistochemistry (keratin IHC). In breast cancer, keratin IHC appears to increase the detection of occult micrometastases, particularly in sentinel LNs.[48] However, the sentinel LN hypothesis is not a reliable concept in bladder cancer patients due to the high rate of false negative nodes.[49] Furthermore, it has been shown that keratin IHC does not detect additional micrometastases within a complete lymphadenectomy specimen.[50] As a consequence, investigation of keratin IHC is no longer being investigated.

In bladder cancer patients, neoadjuvant chemotherapy significantly improves survival,[51,52] which in future might shift the paradigm towards a routinely administered neoadjuvant chemotherapy.[53] The challenge for the pathologist will then be to define prognostic and predictive features in medically pretreated surgical specimens. The number of evaluated lymph nodes in lymphadenectomy specimens after neoadjuvant chemotherapy seems to be virtually the same compared to treatment naïve specimens.[54] However, as in rectal[55,56] and esophageal[57–59] cancers, tumor regression grades, which are thought to quantify the histopathological extent of tumor response to chemotherapy, have shown stronger prognostic impact in bladder cancers than the classification of malignant tumors (yTNM) stages.[54] Consequently, pathologists should start to report and urologists should become accustomed to these pathologic alterations in order to better interpret patient outcomes.

The treating institution

With increasing numbers of RCs performed using robotic assistance, interesting data are emerging regarding the impact of surgical experience on the performance of PLND. The International Robotic Cystectomy Consortium has demonstrated that the performance, extent, and thoroughness of robotic-assisted surgery are affected by both individual surgical volumes and institutional case volumes.[9]

Additionally, it is not solely the surgeon's personal experience and preference, but also the institutional philosophy that decide on the choice of template applied at RC. The surgical template impacts patient outcome, as demonstrated in two consecutive observational studies[12,17] evaluating three differing PLND templates from three cystectomy centers. Dhar et al[17] compared the oncologic outcomes of patients undergoing RC with limited PLND to that of patients undergoing RC with extended PLND. With an extended PLND up to the mid-upper third of the common iliac vessels instead of a limited PLND only, the rate of LN-positive patients doubled. This indicates the substantial under-staging of patients undergoing limited PLND. Furthermore, the application of extended PLND resulted in a significantly better 5-year recurrence-free survival, irrespective of the final pathologic LN status. The removal of all lymphatic tissue up to the inferior mesenteric artery does not confer an additional survival benefit, as shown with the subsequent template comparison.[12]

Fang et al[60] demonstrated the effect of a policy requiring identification of a minimum number of LNs. According to this policy, any lymphadenectomy specimen with fewer than 16 LNs was resubmitted to a senior pathologist for review. As a consequence, the median number of LNs identified per patient increased by five, and the rate of specimens with more than 16 LNs almost doubled from 43% to 70%.

Postoperative lymph node staging

Despite improved imaging technology, PLND remains the most accurate and reliable approach to staging LNs in bladder cancer patients. Different parameters have been

investigated in lymphadenectomy specimens in terms of their prognostic value, such as number of identified and positive LNs, LN density, the diameter of the largest metastasis, and the extracapsular extension of LN metastases.

Multicenter[61–63] and single institution studies[18,20] have shown that a higher number of identified LNs can be associated with better outcomes. However, as discussed above, the number of LNs varies substantially between institutions. This must be taken into account when numbers of identified LNs are evaluated in terms of a generally applicable prognostic tool. If, in single institution series, the outcomes of patients analyzed according to interquartile LN ranges is virtually identical, variations of LN counts might depend more on individual physiological variations and procedural (histological workup) differences and could reflect the uniformity of the lymphadenectomy performed in this cohort.[30] Thus, analysis of interquartile ranges of LN counts for survival might serve as an institutional quality control for lymphadenectomy. As such, total LN yield is a problematic measure of dissection extent or oncologic quality. This was demonstrated by Dorin et al,[64] who compared LN counts between two cystectomy centers, applying the same PLND template. Despite differing median LN counts (40 versus 72 LNs), neither the proportion of LN-positive patients nor the oncologic outcomes of the two cohorts were found to be different. The authors concluded that the applied PLND template is more important than total LN yield.

Different investigators have proposed LN density (ratio of positive and identified nodes) as a prognosticator of survival.[15,65,66] In various series,[15,65,66] LN density predicted survival in univariate analyses. In contrast, multivariable confirmation was only achieved in few studies.[15] LN density is not only a function of nodal tumor burden and extent or quality of lymphadenectomy, but also of the natural variation in the number of pelvic LNs and differences in pathological workup. Therefore, this concept is of questionable value. Similar to total LN yield, LN density depends substantially on institutional standards. Hence, categorical LN densities used to risk stratify patients for counseling regarding prognosis may be useful on an institutional level,[67] but any interinstitutional comparison will be difficult.

The size of the largest LN metastasis is a prognostic factor in different cancers[68–70] and, according to the 7th TNM classification, determines postoperative LN (pN) stages in head and neck, as well as in gynecological cancers.[71] In bladder cancer, however, the diameter of the largest LN metastasis is not an independent risk factor and therefore is not included in the current 7th TNM classification.

The prognostic relevance of extracapsular extension (ECE) in patients with LN metastases (Figure 2) has been evaluated in five single center cohorts[30,72–76] and one multicenter analysis[77] with divergent results. ECE was the strongest independent adverse risk factor in our own cohort.[30,75] Poor outcomes of patients with ECE was also noted in other series.[72–74,76] However, in the study of Frank et al,[72] ECE was found not to be an independent risk factor in patients after limited PLND, while the study of Jeong et al[73] reported a low frequency of ECE. Conversely, ECE was not a prognosticator in the MD Anderson cohort,[74] but the information on ECE was based on pathology records instead of a slide review. Similarly, Stephenson et al[76] could not detect a prognostic impact. Finally, ECE was identified as an independent unfavorable parameter for cancer recurrence and death in a recently published multicenter retrospective study.[77] Unfortunately, in that study, PLND was not uniformly performed and a central pathologic review of all slides was not performed. Taken together, the substantial differences between cohorts and methods existing between the aforementioned studies might have contributed to the conflicting results.

Lymphovascular invasion (LVI) is another prognostic factor in the assessment of bladder cancer. LVI is particularly investigated in cystectomy and transurethral resection specimens of primary tumors,[78,79] and only Fritsche et al[80] evaluated the prognostic impact of perinodal LVI in PLND specimens. Although the latter multicenter study lacks a

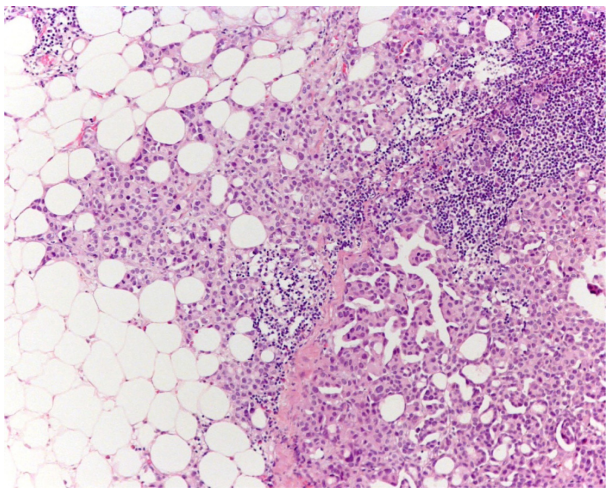

Figure 2 Extracapsular extension of lymph node metastases.
Notes: Lymph node metastasis of urothelial bladder cancer perforating the lymph node capsules and extending to the perinodal soft tissue.

complete pathological review, perinodal LVI was found to be an independent risk factor for early cancer-related death. Therefore, this parameter should be routinely reported in the final pathological report.

Conclusion

The optimal extent of PLND in bladder cancer is still under debate. Based on the present analysis of retrospective cohort studies, meticulous extended PLND to the mid-upper third of the common iliac vessels should be the standard of care for patients with high risk non-muscle-invasive and muscle-invasive bladder cancer. By reporting the number of LNs identified, we outline the lymphatic tissue that has been removed; however, the lymphatic tissue that has been left behind may be responsible for cancer recurrence and remains unquantified. Moreover, LN counts depend on multiple factors such as patient, surgeon, pathologist, and institution, and consequently are not the best markers of the quality of a PLND. Nevertheless, some histopathological parameters resulting from the pathological workup help to better predict patient outcomes.

Disclosure

The authors report no conflicts of interest in this work.

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