The Role of Lymphadenectomy in Radical Cystectomy

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Abstract
Detection of lymph node metastases in patients undergoing radical cystectomy and pelvic lymph node dissection (PLND) for bladder cancer indicates poor prognosis. For pretreatment assessment of lymph node status, computed tomography and magnetic resonance imaging are generally performed, both of which show a low sensitivity of approximately 30%. Newer imaging techniques are being developed; however, it will take time until they can be used in everyday clinical practice. Therefore, PLND remains the only reliable method for lymph node staging in the pelvis. The extent of PLND remains a matter of discussion, but a recent study mapping the lymphatic drainage from the bladder suggests that the template for an appropriate PLND at cystectomy should include the external iliac, obturator, and internal iliac region (lateral and medial to the internal iliac vessels) as well as the common iliac vessels up to the uretero-iliac junctions bilaterally. Additionally, the lymph nodes of the fossa of Marcille should be removed. Questions remain about whether it is worthwhile to resect the few draining lymph nodes between the uretero-iliac junctions and the inferior mesenteric artery with regard to both the increased risk of complications and the injury to the autonomic sympathetic nerves. In addition, PLND at the time of radical cystectomy not only is associated with more accurate staging but also allows removal of undetected micrometastases in patients with bladder cancer. Evidence is growing that extended PLND in patients with bladder cancer may confer a survival benefit for node-positive and node-negative patients without increasing morbidity.

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1. Introduction
Bladder cancer is one of the most common cancers worldwide [1], and 20–40% of all bladder cancers are or will become muscle invasive [2]. Standard preoperative imaging assessment of lymph node status includes computed tomography (CT) or magnetic resonance imaging (MRI) with contrast enhancement [3]. These techniques, which assess the nodal status simply by size, are unable to identify metastases in normal-size lymph nodes [4]. Therefore, discrepancies exist between clinical and pathologic staging [5]: Approximately one of four patients without clinical evidence of metastatic disease (cN0, cM0) based on CT or MRI are found to have lymph node metastases [6–12]. To overcome these shortcomings, several new imaging techniques are currently being evaluated. Positron emission tomography (PET)–CT has been reported to improve detection of nodal metastases [13]. The use of ultrasmall superparamagnetic iron oxide (USPIO), a lymph node–specific contrast agent, in combination with MRI is
another promising imaging technique with a reported high sensitivity and specificity for the diagnosis of lymph node metastases [14]. Although the initial reports appear encouraging, larger clinical trials are necessary to confirm these results. Nomograms designed to predict the risk of positive nodes are well designed but have inherent problems [15].

Surgical excision and histologic examination of the pelvic lymph nodes still provide the most accurate staging regarding pelvic lymph node status in patients undergoing radical cystectomy for invasive bladder cancer.

2. Influence of pelvic lymph node dissection on staging and survival

In addition to the pathologic stage, histologic lymph node status is the most important predictor of outcome in patients undergoing cystectomy for bladder cancer [9]. Lymph node metastases are associated with an increased risk of local recurrence and disease progression and a decreased chance of survival [16]. Prior to the practice of pelvic lymph node dissection (PLND), series reported dismal 5-yr survival rates of 4–7% in lymph node–positive patients [17–19]. In 1982, Skinner [6] reported a 36% improvement of 5-yr survival and disease progression and a decreased chance of metastases are associated with an increased risk of local recurrence (4–7%) in lymph node–positive patients [17–19]. In 1982, Skinner [6] reported a 36% improvement of 5-yr survival in bladder cancer patients with limited nodal disease undergoing bilateral PLND at the time of cystectomy. Skinner concluded that a “meticulous” PLND could provide cure and control of pelvic disease in some patients with regional lymph node metastases without increasing the morbidity. Since Skinner’s findings, more contemporary data originating from other centres, including the University of Southern California in Los Angeles, the Memorial Sloan-Kettering Cancer Centre in New York, and the University of Bern in Switzerland have confirmed that with extended PLND, approximately one-third of bladder cancer patients with lymph node metastases (31–35%) are alive after 5 yr [11,20–22]. Stein et al. [11] evaluated the long-term experience in the largest reported series of 1054 patients treated uniformly with radical cystectomy and PLND for invasive bladder cancer. They found 246 patients (23%) to have positive lymph nodes, and the 5- and 10-yr recurrence-free survival of these node-positive patients was 35% and 34%, respectively.

Findings from other bladder cancer studies have demonstrated unanimously that greater nodal burden results in a more adverse outcome. Besides demonstrating that long-term survival is possible in node-positive bladder cancer, Mills et al. also showed an influence of the number of afflicted nodes [23]. In a series of 83 of 452 patients preoperatively staged N0M0 with histologically confirmed node-positive disease, patients with fewer than five involved nodes had a statistically significant survival advantage over those with five or more involved nodes. Lerner et al. analysed 591 consecutive patients who underwent curative PLND with an en bloc radical cystectomy for bladder cancer [24]. They concluded that PLND at cystectomy can provide long-term progression-free survival in patients with pathologically proven nodal metastases, particularly for patients with localised primary tumours and fewer than six involved nodes. All of these data support a benefit of PLND in patients with limited lymph node metastases at the time of radical cystectomy.

In a large consecutive cystectomy series, Stein et al. analysed 244 node-positive patients [25]. They concluded that lymph node density may better stratify lymph node–positive cases because this concept collectively accounted for the total number of positive lymph nodes (tumour burden) and the total number of lymph nodes removed (extent of lymphadenectomy).

However, not only the number of positive nodes but also the extent of lymph node involvement seems to be important. Fleischmann et al. [16] evaluated 101 patients who were treated with radical cystectomy and standardised extended bilateral pelvic lymphadenectomy with curative intent and had postoperatively confirmed lymph node metastases. They found that extracapsular extension of lymph node metastases was associated with a very poor prognosis.

There may also be a benefit of extended PLND in patients with more extensive lymph node metastases. Herr and Donat [26] analysed the outcome of 84 patients with grossly node-positive (N2–3) bladder cancer after PLND and radical cystectomy. No adjuvant chemotherapy was given, so they were able to analyse the impact of surgery alone. During a follow-up of up to 10 yr, 20 patients (24%) survived; 64 (76%) died of disease. Although this retrospective study deals with a selection bias potentially influencing the outcome, they concluded that PLND may improve survival in some patients with grossly node-positive bladder cancer. However, based on more recent results, preoperative chemotherapy is preferable in these patients.

To summarise, the evidence from retrospective studies suggests that PLND provides a survival benefit in patients found to have positive lymph nodes at the time of radical cystectomy.

3. Advantages of extended pelvic lymph node dissection

The optimal extent of PLND is still debated. In a cohort from the Surveillance, Epidemiology and End Results registry, Wright et al. evaluated the long-term survival in bladder cancer patients who underwent cystectomy and PLND with removal of at least one lymph node and no distant metastases [27]. They found an increased number of lymph nodes removed to be associated with improved survival in lymph node–positive patients, and this finding supports performing a more extended lymphadenectomy at the time of cystectomy. Hollenbeck et al. [28] evaluated the outcome of bladder cancer patients after cystectomy and PLND in relation to the number of lymph nodes removed at different hospitals. They found that hospitals with high lymph node counts tend to have higher survival rates after cystectomy for bladder cancer. However, this effect was modest and, in large part, was explained by confounding patient and hospital factors.

Still, growing evidence indicates that extended PLND in patients with bladder cancer may confer a survival benefit not only for node-positive patients but also apparently for
node-negative patients. Poulsen et al. [29] demonstrated that an extended PLND is beneficial in patients with organ-confined, lymph node-negative disease. The 5-yr recurrence-free survival rate was 90% in patients with organ-confined and lymph node-negative disease in the extended PLND group versus 71% in the standard PLND group (p < 0.02). Moreover, extended PLND reduced the rate of pelvic and distant metastases. Leissner et al. [8] showed that extended PLND significantly improved the prognosis of patients with invasive bladder cancer in both node-negative and node-positive patients when a greater number of lymph nodes was resected. They set a cut-off of ≥16 lymph nodes to be removed in clinically lymph node-negative patients for a significant increase in 5-yr tumour-free survival from 63% to 85% in patients with tumour confined to the bladder wall (pTis, pT1, and pT2), from 40% to 55% in pT3 tumours, and from 25% to 53% in patients with at most five positive lymph nodes. They concluded that extended PLND presents a potentially curative procedure in patients with nodal metastases.

Herr et al. [7] analysed data of 322 patients with muscle-invasive bladder cancer who underwent radical cystectomy and bilateral PLND. They found a statistically significant survival benefit in node-positive patients with at least 11 lymph nodes examined (p = 0.004). Interestingly, patients with node-negative disease also had a significantly better survival rate if eight or more lymph nodes were identified by the pathologist in the surgical specimen (p < 0.001).

In a secondary analysis of a randomised cooperative group trial involving many centres and surgeons [30], twice as many patients survived longer if they had an extended (so-called standard) rather than a limited PLND. The results were independent of whether patients received neoadjuvant chemotherapy.

Dhar et al. [22] compared recurrence pattern and survival in two consecutive series of preoperatively staged NO/M0 patients treated with radical cystectomy and limited PLND (336 patients; Cleveland Clinic, OH, USA) and extended PLND (322 patients; University of Bern, Bern, Switzerland) without adjuvant therapy. They found significantly higher recurrence rates in pT3pN0pT1 patients with limited PLND with a median of 12 nodes resected (23% 5-yr recurrence-free survival) versus those undergoing more extended PLND with a median of 22 nodes resected (57% 5-yr recurrence-free survival; p < 0.0001). The 5-yr recurrence-free survival rates for pT3pN0–2 patients were 19% and 49%, respectively (p < 0.0001). Again, these data strongly support the benefit of extended bilateral PLND at cystectomy in node-positive and node-negative patients.

All of these promising results must be interpreted with caution. It is still not clear whether the benefit in survival is due to the potentially curative removal of pelvic lymph node metastases in node-positive patients and removal of histologically not detected micrometastases in lymph node-negative patients or due to the Will Rogers phenomenon [31]. A patient with fewer tumour-negative lymph nodes removed is more likely to still have undiscovered lymph nodes harbouring (micro)metastases than a patient with more negative lymph nodes removed. The node-negative patients with an extended PLND are more likely to be “real” node-negative patients, and the risk of harbouring occult metastases with a consecutive worse survival is lower than in patients with a smaller number of lymph nodes resected. However, stage migration from node negative to node positive is more likely in the extended PLND population with a very limited tumour burden only, leading to a better outcome in the node-positive population of the extended rather than the limited PLND population.

Overall, these retrospective data show that extended PLND is not only associated with a more accurate staging but allows removal of undetected micrometastases. This may improve survival in patients with both node-positive and node-negative bladder cancer. Limited PLND of the external iliac and obturator region bilaterally seems to be associated with less accurate staging and a poorer outcome. However, the retrospective nature of all of these analyses makes interpretation difficult. Prospective randomised trials such as the German randomised AUO-multicentre study AB 25/02 comparing limited versus extended PLND are urgently needed, provided that the PLND templates are exactly defined and the dissection is accurately performed in all centres.

4. Templates

The anatomic boundaries of PLND are hotly debated. In 1962, Whitmore and Marshall [32] described a standard template for bilateral PLND with the following limits: lateral, genitofemoral nerve; medial, bladder wall; distal, inguinal ligament; proximal, common iliac artery up to where the ureter crosses the vessel; and inferior, pelvic floor and hypogastric vessels on both the medial and the lateral side. However, urologists themselves have added to the confusion surrounding the definitions of PLND. Some authors call the standard PLND described by Whitmore and Marshall an extended PLND. Others set the proximal border of their extended PLND above the level of the aortic bifurcation [9] or as high as the inferior mesenteric artery [33,34], a so-called superextended PLND. Again, some others define a standard PLND as a dissection along the external iliac vessels and of the obturator fossa, which is in fact a limited PLND.

Lymph node mapping studies may help to define the pattern of lymphatic tumour spread [9,33,34]. Leissner et al. [34] examined the lymphadenectomy specimens in 290 patients who underwent radical cystectomy, and they extended PLND up to the inferior mesenteric artery. They divided the template into 12 different anatomic sites: paracaval, interaortocaval, para-aortic, right and left common, external and internal iliac as well as right and left obturator fossa. Sixteen percent of the lymph node metastases were found above the aortic bifurcation but only in patients with two or more lymph node metastases. Interestingly, none of the 29 single solitary positive lymph nodes was located cephalad to the aortic bifurcation. Vazina et al. [9] evaluated 176 patients undergoing radical cystectomy and PLND. Of those with T3 or T4, 16% had lymph node metastases along the common iliac
artery and at the level of or above the aortic bifurcation. However, positive lymph nodes above the aortic bifurcation were always combined with other positive nodes in the small pelvis. In a prospective mapping study of 200 patients, Abol-Enein’s group [33] again found no skipped lesions outside the small pelvis. They concluded that the endopelvic region (internal iliac and obturator groups of lymph nodes) is the sentinel region and that negative nodes in this endopelvic region indicate that a more proximal dissection is not necessary.

Still, pathoanatomic studies can only enumerate positive lymph nodes without precise node-to-node identification, and definition of the optimal template is difficult due to some overlap between the various areas of lymph node dissection. Furthermore, a lymph node at the bifurcation of the common iliac artery can be attributed to either the external iliac, internal iliac, obturator fossa, or even common iliac region depending on the surgeon’s interpretation. Because of this, striking differences exist.

A very recent study published by Studer’s group in Bern shed light on the debate [12]. To elucidate the pattern of lymphatic drainage from the bladder, they performed a three-dimensional fusion imaging mapping study by combining preoperative single-photon emission computed tomography (SPECT)/computed tomography (CT) data sets and confirmed by surgery were subsequently transferred into a template projection of the pelvis. LNs are color coded in relation to the vascular structures and ureters.

vessels (Fig. 2). However, all of these patients had simultaneous lymphatic drainage to the endopelvic region. Interestingly, 4% of the primary lymphatic landing sites were located in the fossa of Marcille. The authors concluded that because the lymph nodes in the fossa of Marcille were easily accessible (ie, do not harbour a higher risk of complications and injury to the autonomic nerves), they should be included in the template of PLND instead of lymph nodes cephalad to the uretero-iliac junction. Moreover, they found that 42% of the nodes identified as primary lymphatic landing sites along the internal iliac lymph nodes were on their medial aspect. This observation supports performing a meticulous dissection of the internal iliac vessels and their branches on both the lateral and the medial side.

In the same study, Roth et al. [12] could show that the number of nodes draining the bladder varies largely from patient to patient. They concluded that due to this individual variability, it may not be appropriate to judge the quality of PLND by comparing the number of nodes resected. Lymph node counts not only vary from patient to patient and depend on the extent of the PLND [35] but also on how the lymphadenectomy specimens are sent to the pathologist. Stein et al. [36] demonstrated that the total number of lymph nodes removed and analysed was significantly higher if sent in separate nodal packets compared with en bloc submission. In addition, lymph node counts vary depending on the pathologic workup. Therefore, instead of defining PLND by node counts, the template described by Whitmore and Marshall in 1962 should be taken as a standard for an adequate PLND.

To summarise, the definition of an adequate PLND should not be determined by the number of nodes removed but by the extent of dissection performed. Based on the literature, the template first described by Whitmore and
coworkers can be considered appropriate for PLND in bladder cancer. If the nodes removed from this template are negative, positive nodes are not to be expected above the aortic bifurcation. PLND should be performed on both sides, should include removal of the lymphatics in the fossa of Marcille, and special attention should be placed on removing the tissue medial and lateral to the internal iliac vessels.

5. Complications of pelvic lymph node dissection

Node-positive and node-negative patients may benefit from an extended PLND. But does the extended PLND increase morbidity, as implied by some? Poulsen et al. [29] found no impact of the extent of PLND on mortality and formation of lymphoceles. These results were confirmed by Brossner et al. [37], who compared a cohort of 46 patients undergoing extended PLND (proximal border, inferior mesenteric artery) with a matched group of 46 patients undergoing a standard (“limited”: external iliac vessels and obturator fossa) PLND. The operating time for the extended PLND group was 60 min longer, which has to be taken into account when operating on elderly patients with many comorbidities; however, they could not find a difference in perioperative mortality, a need for blood transfusion, or early complications. They concluded that extended PLND does not increase the complication rate of surgery. Leissner et al. [8] could not find more lymphoceles or lymphoedema in cystectomy patients with ≥16 lymph nodes resected (1.1%) compared with patients with <16 lymph nodes resected (2%). In a single-centre series of 200 patients, Abol-Enein et al. [33] reported a mortality of 1%, and 10 patients (5%) had prolonged lymphatic drainage when the proximal border of PLND was the inferior mesenteric artery. In a multicentre prospective trial [34], a longer operating time was seen for an extended approach, whereas none of the centres observed any side effects related to the extent of PLND. Although these data collectively suggest that an extended PLND can be performed without higher morbidity, a lymph node resection up to the inferior mesenteric artery increases the risk of complications and injury to the autonomic sympathetic nerves, threatening both continence and sexual function [38]. This has to be acknowledged because many patients undergoing radical cystectomy may be candidates for orthotopic bladder substitution.

To summarise, evidence suggests that although the operating time is prolonged, morbidity and mortality are not increased as a result of an extended PLND.

6. Conclusions

Growing retrospective evidence from many centres indicates that PLND improves survival in patients with both node-negative and node-positive bladder cancer. In fact, some patients may be cured by PLND, provided that the lymph nodes harbouring (micro)metastases are removed. Extended PLND is not only associated with a more accurate staging but may improve survival in patients with bladder cancer compared with a limited PLND. Data of several pathoanatomic studies and especially from a recent lymphatic bladder mapping study suggest that the template for an appropriate PLND at cystectomy should include the external iliac (including the fossa of Marcille), obturator and internal iliac region (lateral and medial to the internal iliac vessels), as well as the common iliac vessels at least up to the uretero-iliac junction bilaterally. Higher resection may be too demanding in both time and extent of surgical field, increasing the risk of complications and injury to the autonomic sympathetic nerves, threatening both sexual function and continence in patients who are candidates for orthotopic bladder substitution.

Conflicts of interest

The authors have nothing to disclose.

Funding support

None.

References


