Anatomic Extent of Pelvic Lymphadenectomy in Bladder Cancer

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1. Introduction

Radical cystectomy with pelvic lymphadenectomy (PLA) represents the standard treatment for muscle-invasive bladder cancer. PLA is included as part of the surgical procedure to control locoregional disease and to potentially improve cancer-specific survival. Survival after radical cystectomy is usually predicted by the pathologic tumor stage, status of surgical margins, and the involvement of lymph nodes (LNs).

Although earlier studies have already demonstrated a prognostic benefit of extended PLA (EPLA) as compared to a limited lymphadenectomy, the anatomically adequate extent of LN dissection to obtain reliable staging results is still controversial.

2. Pelvic lymphadenectomy in bladder cancer

In a recent prospective randomized phase 3 trial on the clinical efficacy of neoadjuvant chemotherapy plus cystectomy [1], it was shown that surgical factors, including the extent of LN dissection and the individual surgeon’s experience, have a major impact on the therapeutic outcome and overall survival [2]. The data from this trial...
also indicate that chemotherapy was more likely to be beneficial if patients received a high-quality surgery by an experienced surgeon. It was concluded that it is extremely important to develop universally accepted standards for radical cystectomy and pelvic LN dissection (PLND) in patients with invasive bladder cancer to improve outcome [3].

3. **Anatomical extent of pelvic lymphadenectomy**

Although it has been shown that long-term survival is possible in patients with LN-positive bladder cancer, the anatomic extent of PLA associated with radical cystectomy still has to be defined. Some take the crossing of the ureters with the common iliac vessels as the most cranial limit for LN dissection [4], whereas others extend lymphadenectomy up to the aortic bifurcation. It is generally agreed that the more LNs removed, the higher the number of patients with positive LNs [5]. Furthermore, it has been demonstrated that survival after radical cystectomy is predicted by the pathologic stage of the primary bladder tumor and pelvic nodes. Leissner et al. [6] suggested that a significant survival benefit was maintained if >16 LNs are removed. Stein et al. [7] reported that survival in patients with positive LN disease was better if >15 pelvic LNs had been retrieved. On the other hand, Abdel-Latif and coworkers [8] and Herr [9] could not reproduce the relationship between survival and number of dissected LNs by using multivariate statistical analysis.

In this context, it has to be emphasized that the number of retrieved LNs can be influenced by many factors, such as extent of lymphadenectomy [4–6], presentation of the pathologic specimen [10], and pathohistologic work-up and techniques of analysis [11], thus raising questions about the clinical relevance of LN as a routine prognostic marker.

Despite these suboptimal clinical factors, a few studies have demonstrated a significant impact of the technique of PLND with regard to therapeutic outcome. Poulsen et al. [12] was one of the first groups to compare the prognostic significance of limited versus EPLA in a retrospective analysis of 194 patients undergoing radical cystectomy. Limited PLA (LPLA) began at the iliac bifurcation, including the LNs along the external and internal iliac artery and the obturator fossa. EPLA began at the aortic bifurcation and included the common, external, and internal iliac artery and the obturator fossa. The authors observed a substantial improvement of 5-yr recurrence-free survival in patients with tumors confined to the bladder wall (85% vs 64%, p < 0.02) and without LN involvement (90% vs 71%, p < 0.02). They found that 5-yr probabilities for locoregional (7% vs 2%) and systemic recurrences (21% vs 10%) were reduced substantially in patients with bladder cancer confined to the bladder wall in the EPLA group; however, this did not reach statistical significance.

In a retrospective analysis of 484 patients undergoing radical cystectomy and PLA, Leissner et al. [11] demonstrated that the total number of LNs retrieved had a significant impact on recurrence-free survival (p < 0.01). The 5-yr recurrence-free survival was 25% and 53% in patients with ≤14 and ≥15 LNs being removed, respectively.

Furthermore, the surgeon had a significant impact on the prognosis as it was shown the number of LNs dissected ranged between 10.6 and 25.7 and differed significantly between the 11 surgeons involved in the study.

These data are further corroborated by a recent paper on the standardization of radical cystectomy and PLA [3]. However, the authors did not demonstrate a significant overall and cancer-specific survival advantage for patients undergoing EPLA as compared to those undergoing LPLA only.

The authors further evaluated the concept of EPLA in a prospectively collected clinical trial comprising 290 patients [13]. The cranial limit of EPLA was the inferior mesenteric artery, the lateral border was the genitofemoral nerve, and the caudal limit was the pelvic floor. A mean number of 43.1 ± 16.1 LNs were removed with 27.9% of the patients demonstrating positive LNs. Although the researchers identified a preferred pattern of metastatic spread, they were not able to identify a well-defined sentinel LN or LN area.

These data are in contrast to the recently published prospective trial of Bochner et al. [14] on the evaluation of LN count and LN mapping. This single-center evaluation included 144 consecutive patients, with 56 and 88 patients undergoing standard and extended PLA, respectively. Standard PLA included the nodal regions of the external iliac, hypogastric, and obturator fossa with the iliac bifurcation representing the cranial limit of LN dissection. EPLA included the LNs at the aortic bifurcation ≤2 cm cranially to the bifurcation and the nodal regions of standard PLA. Although the median number of positive LNs differed significantly between both groups (22.5 vs 8), there was no difference with regard to the percentage of positive nodes, which was 21% in both groups. Interestingly, all patients with positive nodes above the aortic bifurcation also had positive nodes detected in the lower packages, indicating that only extensive locoregional metastatic disease might involve the retroperitoneal areas, which are associated with a dismal prognosis anyhow.

Including the LNs along the common iliac artery above the iliac bifurcation, however, appears to be of prognostic value and of clinical significance. In the study of Bochner et al. [14], four patients had unexpected micrometastatic LN disease at the common iliac region only. Reflecting the survival data of patients exhibiting micrometastatic LN disease at time of radical cystectomy, most of these patients are expected to have a relatively favorable outcome. Morbidity of PLA is not increased by including the common iliac region in routine PLND, so this area should be removed as standard part of staging lymphadenectomy.

Further evidence to include the common iliac region derives from the prospective multi-institutional study published recently by Leissner et al. [13] in which 81 (27.9%) patients demonstrated LN involvement and 35% of all positive LNs derived from above the iliac bifurcation. Furthermore, 20 patients (6.9%) were shown to harbor positive LNs above the bifurcation of the common iliac artery only. Although no data with regard to the prognostic
significance in terms of cancer-specific or progression-free survival are available, these data strongly support the idea of including the LNs of the common iliac region up to the aortic bifurcation in routine LN dissection technique for muscle-invasive bladder cancer.

In another study, Abol-Enein et al. [15] evaluated the locoregional distribution of positive pelvic LNs in 200 consecutive patients undergoing radical cystectomy. The authors also attempted to identify the probability of LN clearance with increasingly wide fields of node dissection. In their investigation, EPLA included the lymphatic tissue up to the inferior mesenteric artery, the common, external, and internal iliac regions. A mean number of 50.6 LNs were retrieved per patient with 48 (24%) patients exhibiting positive nodes. More than one-third of these patients (39.6%) demonstrated bilateral involvement; a single positive LN was identified in 22 (45.8%) patients. The authors demonstrated that close to 80% of all positive nodes could be cleared completely from the field of PLND including all lymphatic tissues along the common, external, and internal iliac regions. Metastases outside the true pelvis were only detected in multinoodal disease and these metastatic deposits were always associated with metastases at the obturator fossa and/or the internal iliac region. Therefore, the authors concluded that standard lymphadenectomy in bladder cancer should always include all lymphatic tissues in the true pelvis; LN dissection might be extended up to the inferior mesenteric artery if frozen section examination exhibits positive LNs in the sentinel region of the true pelvis.

Recently, Capitanio et al. [16] evaluated the likelihood of finding one or more positive LNs according to the number of LNs removed at radical cystectomy. In this study, 731 assessable patients underwent radical cystectomy and bilateral PLA at three different institutions. Receiver operating characteristic (ROC) curve coordinates were used to determine the probability of identifying one or more positive LNs according to the total number of removed LNs. LN metastases were found in 174 (23.8%). The mean number of LNs removed was 18.7 (median: 17, range: 1–80). The ROC coordinate-based plots of the number of removed LNs and the probability of finding one or more LN metastases indicated that removing 45 LNs yielded a 90% probability. Conversely, removing either 15 or 25 LNs indicated, respectively, a 50% and 75% probability of detecting one or more LN metastases. These data indicate that removing 25 LNs might represent the lowest threshold for the extent of lymphadenectomy at radical cystectomy.

Dhar and coworkers [17] evaluated the impact of LPLA and EPLA in a cohort of 336 and 322 patients, respectively, who were treated at two different institutions. The overall LN positive rate was 13% for patients with limited and 26% for those who had extended PLND (ePLND). The authors identified a significantly better recurrence-free survival for patients who underwent EPLA. These figures held true for both organ-confined and locally advanced disease. The 5-yr recurrence-free survival of patients with LN-positive disease was 7% for limited and 35% for ePLND. The 5-yr recurrence-free survival for pT2pN0 cases was 67% for limited and 77% for ePLND, and the respective percentages for pT3pN0 cases were 23% and 57% (p < 0.0001). The 5-yr recurrence-free survival for pT2pN0-2 cases was 63% for limited and 71% for ePLND, and for pT3pN0-2 cases the respective figures were 19% and 49% (p < 0.0001). These data confirm that ePLND allows for more accurate staging and improved survival of patients with non–organ-confined and LN-positive disease (Fig. 1).

In another single-institution analysis the clinical importance of dissecting all lymphatic tissue up to the aortic bifurcation became evident when the outcome was analyzed of 336 patients who underwent radical cystectomy and EPLA including the common and external iliac LNs, and the periaortic, presacral, and obturator fossae nodes [18]. The lymphatic tissue removed above and below the bifurcation of the common iliac vessels was submitted separately for histopathologic analysis. Overall, 64 patients (19%) had LN metastases, of which 22 (34.4%) had LN involvement above the bifurcation of the common iliac vessels outside the template of the standard LN dissection. The median number of retrieved LNs was 27 (range: 7–78) and in those with LN metastases was also 27 (range: 11–49). The latter included 8 (range: 0–17) above the bifurcation and 18 (range: 8–41) below the bifurcation of the common iliac vessels in the true pelvis. Lymph node involvement proved a significant adverse prognostic factor with a 5-yr probability of survival of 39% versus 76%. The overall 5-yr survival rate was similar in patients with LN involvement above the bifurcation of the common iliac vessels (37%)
compared with the entire population with LN metastasis (41%) and to those with lymphatic metastases in the true pelvis below the bifurcation of the common iliac vessels (42%). The survival rate was significantly higher in patients with five or fewer involved LNs (50% vs 13%, p < 0.002) and in those with a LN density (number of LNs involved vs total number of LNs removed) of < 20% (25% vs 47%, p < 0.05), but it did not relate to the total number of retrieved LNs.

These data underscore the contention that extended dissection not only provides the most accurate staging but also offers the patient the best chance of survival. Following radical cystectomy, patients can be stratified into risk groups according to tumor stage, LN involvement, number of metastatic nodes, and LN density. The results of Steven et al. [18] support the idea that the benchmark for radical cystectomy should include extensive PLND with anatomic boundaries including the common iliac and presacral nodes.

4. Summary of the anatomic extent of pelvic lymph node dissection in bladder cancer

As has been shown by the previous studies, the anatomic extent of PLND in patients undergoing radical cystectomy for muscle-invasive bladder cancer can be well defined. Standard lymphadenectomy should include all lymphatic tissues around the common iliac, intercommon iliac, and internal iliac groups, and the obturator group bilaterally, since up to one-third of all positive nodes are located around the common iliac artery. This technical variant will enable clearance of 80% of all positive nodes; if frozen section will demonstrate no positive LNs in the true pelvis, LN dissection does not need to be carried out further cranially. If, however, frozen section examination is not performed, or if it identifies positive nodes, the inferior mesenteric artery represents the cranial border of LN dissection.

5. Critical issues in anatomic pelvic lymphadenectomy for bladder cancer

Although the above-cited studies have apparently demonstrated the clinical importance of EPLND with regard to the most efficient retrieval of micrometastatic LNs, there are still some unresolved critical issues.

Pathohistologic examination of dissected LN specimens in these studies was done more thoroughly and extensively than in other studies concentrating on issues such as overall survival, cancer-specific survival, and regional versus distant failure. Therefore, some critical facts have to be considered for the general community if EPLA becomes common practice in all patients undergoing radical cystectomy. Lymphatic tissues dissected from different areas should be sent in separate, instead of en bloc, submissions for pathohistologic evaluation, since it has been demonstrated recently that the yield of LNs increases significantly, thereby increasing the frequency of micrometastatic deposits [10]. Intra-institutional standardization of PLA appears to be of utmost importance to generate reliable and reproducible results, since staging lymphadenectomy is extremely surgeon dependent, as has been demonstrated by Leissner et al. [11].

Last but not least, although the various types of EPLAs have been associated with an improved progression-free survival, none of the trials has demonstrated an advantage with regard to cancer-specific survival. Benefit in terms of progression-free survival might be due only to a stage migration associated with extensive LN dissection. The majority of patients found to harbor positive LNs will die due distant metastatic spread in the long run and only the few patients with one or two metastatic LNs might benefit from the extended variant of lymphadenectomy. In order to answer this question, the Association of Urological Oncology of the German Cancer Society has initiated a prospective randomized clinical phase 3 trial to evaluate the true clinical efficacy of EPLA.

In bladder cancer, the biologic aggressiveness of a particular cancer may have already been expressed at time of diagnosis and the impact of less or more extensive surgery in terms of recurrence and survival might be completely overestimated. For the future, it will be necessary to shed light on the important clinical questions of the biologic role of LN metastases in the likelihood of synchronous or metachronous distant metastases. It will be necessary to biologically evaluate the expression of various growth factors and mediators of systemic spread in patients with LN metastases and to correlate these findings with clinically important end points, such as cancer-specific survival, overall survival, and locoregional versus systemic recurrence.

Conflicts of interest

The author has nothing to disclose.

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References


