The Role of Pelvic Lymph Node Dissection During Radical Cystectomy for Bladder Cancer

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Abstract. Background: Radical cystectomy is the standard treatment for patients with invasive bladder cancer. Many aspects regarding the role of concomitant pelvic lymph node dissection (PLND), its extension and the oncological impact are still under discussion. Materials and Methods: A detailed literature review is presented to assess the impact of pelvic lymph node dissection during radical cystectomy in terms of staging and therapeutic procedure. Analysis of evidence: The study presented the role of imaging in the assessment of lymph node status, the anatomical account of bladder lymphatic drainage and the techniques for dissection. The evidence from the literature examined showed that pathological stage of the bladder, the extent of PLND in both node-negative and -positive disease, the lymph node density and the extracapsular involvement of metastatic lymph nodes are significant independent prognostic factors for disease-free survival. Conclusion: Radical cystectomy with bilateral pelvic iliac lymphadenectomy is a standard treatment for high-grade, invasive bladder cancer, providing the best survival outcomes and the lowest local recurrence rates. Even if the precise extent of lymph node dissection is still not standardized, many studies support a more extended lymphadenectomy to obtain better cancer-specific survival rates without significantly increasing the morbidity or mortality of the surgery. The concept of lymph node density may become a useful prognostic variable in high-risk node-positive patients.

Carcinoma of the bladder represents the fourth most frequent cancer in men and the eighth most frequent malignancy in women in the U.S.A. (1). Its incidence increases with age, peaking between the sixth and seventh decade of life, and is three times more frequent in men than in women. Risk factors for bladder cancer can be divided into three groups: the most frequent is lifestyle environmental exposure (aromatic amines, cigarette smoking, nitrates and nitrates and acrolein), followed by genetic and molecular abnormalities, and chemical and/or chronic inflammation (indwelling catheters, Schistosoma haematobium infestation and pelvic radiotherapy).

At the initial diagnosis of bladder cancer, approximately two thirds of the cases present as non-invasive tumours (stages Ta, T1 or tumours in situ [Tis, CIS]), but as many as 50-70% of the superficial tumours will recur and about 15% will progress to invasive disease (2). Moreover, approximately 20-30% of patients with stage T1-T4 N0 M0 bladder cancer who undergo radical cystectomy and pelvic lymph node dissection (PLND) are found to have lymph node disease (3, 4).

The standard treatment for bladder cancer invading the muscularis propria in male patients is radical cystoprostatectomy, while anterior pelvic exenteration (including the bladder, urethra, uterus and posterior vaginal wall with/without anterior vaginal wall) is the surgical treatment in female patients.

Lymph node involvement is the most important prognostic variable in determining patient outcome following radical cystectomy. Pelvic lymphadenectomy should, thus, be the standard approach in all cases of radical cystectomy, even if many aspects regarding the extension and oncological impact of PLND are still under debate.

Materials and Methods

A systematic literature review was undertaken. The electronic databases Pubmed/Medline, Cochrane and Embase were searched using the following key words: bladder cancer, transitional cell carcinoma, radical cystectomy, lymph node dissection and lymph node metastasis. From Medline/Pubmed, 554 references were obtained, 20 references were obtained from Cochrane and 661 references were obtained from Embase. Twenty-nine articles were selected based on abstract, content and study design. Randomised trials with higher levels of evidence were selected primarily.
Analysis of Evidence

**Imaging technique and lymph nodes status.** All current international guidelines recommend a pre-treatment assessment of lymph node status (dimension, morphological and vascular pattern) based on imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) with contrast enhancement. However, these tools have low accuracy, with an evident discrepancy between the morphological appearance of the nodes and their final pathological status. In fact, approximately 25% of patients who were staged as node-negative preoperatively proved to have lymph node involvement at final histopathology.

To overcome these deficiencies, several new techniques are currently being studied. One such technique is positron-emission tomography (PET), which permits the study of metabolic processes in vivo, such as membrane metabolism and proliferation rate. Information regarding metabolic activity may also support the recognition of lymph node metastases that are morphologically normal. The most common used radiotracers are $^{18}$F-fluorodeoxyglucose (FDG) and $^{11}$C-choline. Some studies have suggested that combined PET-CT may have a role in the detection of nodal and distant metastases, but these results should be confirmed by further studies. At the moment, the evidence suggests that currently utilised imaging techniques are not able to predict pelvic lymph node involvement, especially in cases of small metastases or micrometastases.

**Lymphatic drainage of the bladder, distribution of LN metastases and techniques of PLND.** A precise knowledge of the lymphatic drainage of the bladder is the first step in order to perform an appropriate lymphadenectomy during radical cystectomy. The primary contributions to the knowledge of bladder lymphatic drainage came from studies by Leadbetter and Cooper in 1950. The lymphatic drainage from the bladder is separated into six different areas: (i) the visceral lymphatic plexus into the bladder wall, developing in the submucosa and extending into the muscular layer of the organ; (ii) the intercalated lymph nodes (which are juxtapositional lymph nodes located in the perivesical fat), divided into anterior, lateral and posterior groups; (iii) pelvic collecting trunks, which are intermediate lymph nodes to the external iliac and hypogastric lymph nodes; (iv) regional pelvic lymph nodes, which include nodes around the external iliac, hypogastric and sacral vessels; (v) lymphatic trunks leading from the regional pelvic lymph nodes and (vi) common iliac lymph nodes, which are around the common iliac vessels. The last site of lymph node drainage is probably the secondary site of metastasis, in an intermediate position between the pelvic and the aortocaval lymph nodes.

Anatomical studies have revealed that the two most important sites of lymph node involvement are the external iliac and obturator lymph nodes. Smith and Whitmore reported that these sites of nodal metastases were involved in 74 and 65% of patients, respectively. They also demonstrated lymph node metastasis to the nodes around the common iliac vessels in 19% of patients. The need to extend lymph node dissection to a higher level remains controversial. The distribution of lymph node metastases was recently evaluated in a multicentre study in which an extended lymphadenectomy was performed in all patients with bladder cancer. This study demonstrated that positive lymph nodes were found most commonly in the obturator fossa and near the iliac vessels. It is interesting to note that approximately 16% of lymph node metastases also included nodes above the aortic bifurcation, while 8% involved the presacral region. Among the patients with lymph node metastases located within the limits of a ‘standard’ dissection (below the bifurcation of the common iliac vessels), a considerable proportion had also nodal involvement at the level of the common iliac vessels and above the aortic bifurcation. The importance of an extended lymphadenectomy was also demonstrated by Bochner et al., who found that 33% of patients with microscopic nodal involvement had metastasis to the common iliac nodes. Vazina et al. evaluated 176 pTxN0-1 patients who underwent radical cystectomy and PLND. Of 43 lymph node–positive patients, metastases were found in the following anatomic sites: aortic bifurcation (4%), common iliac nodes (right side: 5.7%; left side: 8%), presacral nodes (5.1%), pelvic nodes (right side: 12%; left side: 14%), perivesical nodes (2.8%) and unspecified pelvic nodes (5.7%). In order to remove all potential sites for nodal metastases at the time of cystectomy, these studies support the need for a more extended bilateral lymphadenectomy with a higher extent of dissection that includes the common iliac lymph nodes, as well as removal of the presacral nodal lymph nodes.

Mills et al. described the ‘extended’ lymphadenectomy as a pelvic dissection that involves all nodal tissue around the common iliac bifurcation, including the internal iliac (and presacral), obturator fossa, external iliac and distal common iliac. The authors also recommended the removal of tissue over the common iliac bifurcation up to the point where the ureter crosses the iliac vessel. In contrast, Stein et al. defined an ‘extended’ lymphadenectomy as a pelvic dissection that involves all lymph nodes around the aortic bifurcation and common iliac vessels (proximally), the circumflex iliac vein and lymph node of Cloquet (distally), the genitofemoral nerve (laterally), the hypogastric vessels (posteriorly) including the obturator fossa, the presciatic nodes bilaterally and the presacral lymph nodes.

However, a recent study questioned whether extended lymphadenectomy would increase the morbidity in patients undergoing radical cystectomy. A total of 46 patients undergoing an extended pelvic lymph node dissection were compared to 46 patients undergoing a standard PLND.
Although the extended lymphadenectomy increased the operative duration by approximately 63 minutes, there was no statistically significant difference in perioperative mortality, early complications or the need for blood transfusions between the two groups. The authors concluded that despite an increase in the surgical procedure time, extended lymph node dissection did not cause significant adverse effects during the postoperative period.

**Prognostic factors in patients with lymph node involvement following radical treatment for bladder cancer.** The prognosis for patients with lymph node metastasis undergoing radical cystectomy still remains poor; however optimum local control at the time of the initial treatment can be offered by radical cystectomy and extended PLND.

The presence of lymph node involvement after radical cystectomy is related to an increased risk of tumour recurrence and progression (4, 15, 16). Nevertheless, more than 30% of patients demonstrate long-term survival following radical cystectomy (4).

Pathological stage and tumour burden are now established prognostic factors of lymph node involvement (4, 17, 18). The final pathological stage remains one of the most important prognostic indicators for patients with node-positive disease following radical cystectomy (4, 16, 18). In a multivariate analysis, Vieweg et al. found that the extent of the primary bladder tumour remains an independent risk factor in patients with lymph node-positive tumours (16). The five-year survival probability in patients with organ-confined node-positive tumours was 46-58% compared to 22-30% in patients with extravesical, lymph node-positive disease (16, 18).

Another important factor in patients with bladder cancer following radical cystectomy is represented by the tumour burden (number of positive lymph nodes or number of lymph nodes involved with tumour) (4, 8, 17-19). In the largest series of 244 lymph node-positive patients with a median follow-up period of 10 years, Bochner et al. showed that tumour burden is a strong prognostic factor regarding survival (20). Similarly, Konety et al. found that survival was significantly improved for patients with node-positive disease if the patients had four or fewer positive lymph nodes, compared to those with more than four positive lymph nodes (37 versus 13%, respectively) (21). Obviously, survival and recurrence are inversely related to an increasing tumour burden; furthermore, in this node-positive group of patients, if more than 11 lymph nodes were removed, improved survival with better local pelvic control of the tumour was observed.

After a PLND, the number of lymph nodes removed is an important prognostic factor in bladder cancer. An important body of evidence suggests that a minimum number of lymph nodes should be removed and pathologically evaluated during radical cystectomy to identify patients with node metastasis (18, 19). The SEER database showed that only a minority of patients in a population-based analysis have more than four nodes removed with cystectomy (21, 22). The anatomical extent of node dissection was an important variable. However, several other factors such as the surgeon’s skills, and comorbidities may influence the number of nodes removed (22, 23). Poulsen et al. demonstrated that including the lymph nodes from the bifurcation of the common iliac vessels up to the level of the aortic bifurcation in the node dissection increased the median number of lymph nodes removed from 14 to 25, with a notable impact on survival in both node-negative and node-positive patients and with a reduced local recurrence rate (15). With 16 or more lymph nodes removed, Leissner et al. showed an improvement in five-year recurrence-free survival: from 63 to 85% in organ-confined tumours, from 40 to 55% in pT3 tumours and from 25 to 53% in patients with at most five lymph node metastases (17).

Nevertheless, the Will Rogers phenomenon should be taken into account when analysing prognosis results in such series (24). When large numbers of lymph nodes are removed, the likelihood of leaving behind undiscovered positive nodes is reduced and this results in a better prognosis for patients with an extended PLND when compared with patients undergoing a limited PLND who may still have undiscovered positive nodes.

Several other studies have confirmed that the absolute number of positive nodes is the most important factor for patient outcome and survival. Five, six and eight positive lymph nodes have been described as a ‘cut-off’ value (4, 18, 25). Subgroup analyses for all these studies have shown significantly better outcomes for patients with smaller absolute numbers of involved lymph nodes. Subsequently, the notion of lymph node density (LND), defined as the ratio of the number of positive nodes to the total number of nodes removed, arises from the combination of these two independent variables as prognostic factors (1-3). It has been demonstrated that LND has an independent prognostic significance in addition to the number of positive nodes, pathological tumour stage and adjuvant chemotherapy (4, 26). In a study by Stein et al., patients with lymph node density ≤20% had a 43% chance of ten-year recurrence-free survival compared with only 17% when LND was ≥20% (4). LND ≥20% also predicted decreased disease-specific survival in the series reported by Kassouf et al.: the five-year disease-free survival rate was 54.6% for patients with LND ≤20% versus 15.3% for patients with LND >20% (27).

The influence of the extracapsular extension of the lymph node metastasis (perforation of the capsule by tumour tissue with extranodal growth) on the recurrence-free survival after radical cystectomy has recently been suggested. A study by Fleischmann et al. evaluated 101 patients who underwent radical cystectomy and extended PLND with curative intent and who were diagnosed postoperatively with lymph node-
positive disease (28). The authors demonstrated that patients with extracapsular extension had a higher risk of relapse as shown by the results of recurrence-free survival (12 months versus 60 months) and overall survival (16 months versus 60 months) compared with patients with intranodal metastases. In the multivariate analysis, extracapsular extension of lymph node metastases was the strongest negative predictor for recurrence-free survival (28). The use of LND in clinical trials with adjuvant therapy should be encouraged to assess the real impact of the extent of lymphadenectomy in the choice of treatment and to reduce the surgical bias. The incorporation of LND into the TNM system should also be considered.

The oncological impact of the extent of PLND during radical cystectomy for bladder cancer. Retrospective studies suggest that limited PLND (external iliac vessels plus obturator fossa) is associated with suboptimal stages and poorer outcome for patients with node-positive and node-negative disease. Extended PLND may allow more accurate staging and removal of undetected micrometastases. This could improve the survival of patients with histopathological lymph node-positive and -negative disease.

In a study by Dhar et al., patients staged preoperatively as N0 M0 without adjuvant therapy were compared (29); 336 patients had limited PLND and 332 had extended PLND. The five-year recurrence-free survival rate of patients with lymph node-positive disease was 7% for limited dissection and 35% for extended PLND. The five-year recurrence-free survival rate for pT2 pN0 cases was 67% for limited PLND and 77% for extended PLND, while the respective rates for pT3 pN0 were 23% and 57% (p<0.001). The five-year recurrence-free survival rate for pT2 pN0–2 was 63% for limited PLND and 71% for extended PLND; for pT3pN0–2 cases the respective rates were 19% and 49% (p<0.001).

As noted above, extending the limits of the node dissection with an increased number of lymph nodes retrieved improves the survival for both lymph node-negative and node-positive patients, with a reduction in terms of local recurrence (15). In an analysis of over 20,000 patients with bladder cancer included in the SEER cancer registry, with 1,923 patients submitted to radical cystectomy, the strongest survival factor was the removal of 10-14 lymph nodes at the time of surgery (after controlling for age, tumour stage, histology, chemotherapy and radiation therapy) (21). The risk of death was also significantly higher in patients with fewer than four lymph nodes removed at cystectomy.

An extended PLND may have beneficial effects on tumour treatment but the associated risks should be considered. The risk for elderly patients, and especially for patients with comorbidities, needs to be taken into account in all therapeutic decisions. A study by Broessner et al. demonstrated that an extended lymph node dissection appears not to increase the complication rate during or after surgery despite a prolonged operation time (60 minutes longer for the extended PLND group compared with the limited PLND group) (14). Poulsen et al. reported no significant impact of the extent of lymph node dissection regarding mortality or lymphocele formation (15). The results of a multicentre prospective trial confirmed the longer operation time (approximately 60 minutes) for an extended approach, whereas none of the participating centres observed any significant adverse side-effects related to the extended PLND (9). Large prospective multicentre trials are needed to validate the influence of more extended PLND on disease-specific survival.

Conclusion

Radical cystectomy with bilateral pelvic iliac lymphadenectomy is a standard treatment for high-grade, invasive bladder cancer, providing the best survival outcomes and the lowest local recurrence rates and low rates of surgical complications. The limits of the lymph node dissection required are still under debate. The literature evidence suggests that the template for PLND should include at least the regions of the external and internal iliac vessels together with the obturator fossa and should encompass the distal part and the bifurcation of the common iliac vessels on both sides. There is a growing body of evidence to support a more extended lymphadenectomy at the time of cystectomy in all patients who are appropriate surgical candidates; it appears that extended dissection may provide a survival advantage in both node-positive and node-negative patients without significantly increasing the morbidity or mortality of the surgery.

The extent of lymph node dissection and the concept of LND are still not standardised but may improve stratification of lymph node-positive patients following radical cystectomy and may become a useful prognostic variable in high-risk node-positive patients, even in terms of staging.

References


