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Chapter 5

Lymphadenectomy in Muscle Invasive Bladder Cancer

Mustafa Ozan Horsanali and Kutan Ozer

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67443

Abstract

Bladder cancer is the second most common genitourinary malignancy with urothelial cancer comprising nearly 90% of primary bladder tumors. Urothelial carcinoma of the urinary bladder is the fifth most common malignancy in the United States, with an estimated 76,960 new cases and 163,900 deaths in 2016. Radical cystectomy with lymph node dissection remains the standard treatment for patients with muscle-invasive urothelial carcinoma of the bladder, and also for nonmuscle-invasive disease, refractory to intravesical therapy. The current approaches to pelvic lymph node dissections are based on the removal of lymph nodes most commonly harboring metastatic disease, notably the external iliac, obturator, and hypogastric lymph nodes. The boundaries for a standard pelvic lymph node dissection generally include the bifurcation of the common iliac vessels superiorly and the genitofemoral nerve laterally. Extended pelvic lymph node includes the removal of lymph nodes between the bifurcation of the common iliac vessels and the level of the aortic bifurcation, sometimes including distal aortic and caval nodes up to the level of the inferior mesenteric artery, as well as presacral nodes. Extended and superextended dissection has been reported to be associated with superior survival outcome.

Keywords: bladder cancer, muscle-invasive, lymph node, cystectomy

1. Introduction

Bladder cancer is the second most common genitourinary malignancy with urothelial cell carcinomas comprising nearly 90% of primary bladder tumors. Urothelial carcinoma of the urinary bladder is the fifth most common malignancy in the United States, with an estimated 76,960 new cases and 163,900 deaths in 2016 [1]. Although up to 86% of patients present with superficial or localized tumors, 20–40% present with, or progress to develop, invasive disease that carries a significant increase in the likelihood of having occult metastases [2]. Standard treatment of muscle invasive bladder cancer and refractory to intravesical chemotherapy in

patients with nonmuscle invasive bladder is still radical cystectomy with lymph node dissection. Patients with muscle invasive bladder cancer have approximately 25% lymph node involvement during the radical cystectomy [3]; if lymph node involvement is observed, 10-year mortality rate can be up to 80% due to adjuvant chemotherapy [2, 3]. Although lymph node involvement portends a relatively poor prognosis, some patients exhibit long-term survival following surgery, with or without systemic chemotherapy [4]. The current approaches to pelvic lymph node dissections are based on the removal of lymph nodes most commonly harboring metastatic disease, notably the external iliac, obturator, and hypogastric lymph nodes. Standard pelvic lymph node dissection is described removing the lymph nodes including bifurcation of the common iliac vessels superiorly and the genitofemoral nerve laterally. And the limit of inferior and medial boundaries includes the obturator nerve, bladder, and internal iliac vessels medially and the endopelvic fascia, circumflex iliac veins, and Cloquet's node inferiorly [5–8] (**Figure 1**). For the standard pathological evaluation of lymph nodes to detect the presence of tumor cell after surgery, formalin fixation with hematoxylin and eosin (H&E) staining of 5-μm thick sections of each node is done. After these evaluations, nearly 25% of the patients are found to be involved with tumor in the lymph nodes during the cystectomy [9].

In the literature, the nomenclature of lymph node dissection has been variable and is defined differently by urologists. Dangle et al. divided lymph node dissection into four groups categorized as follows:

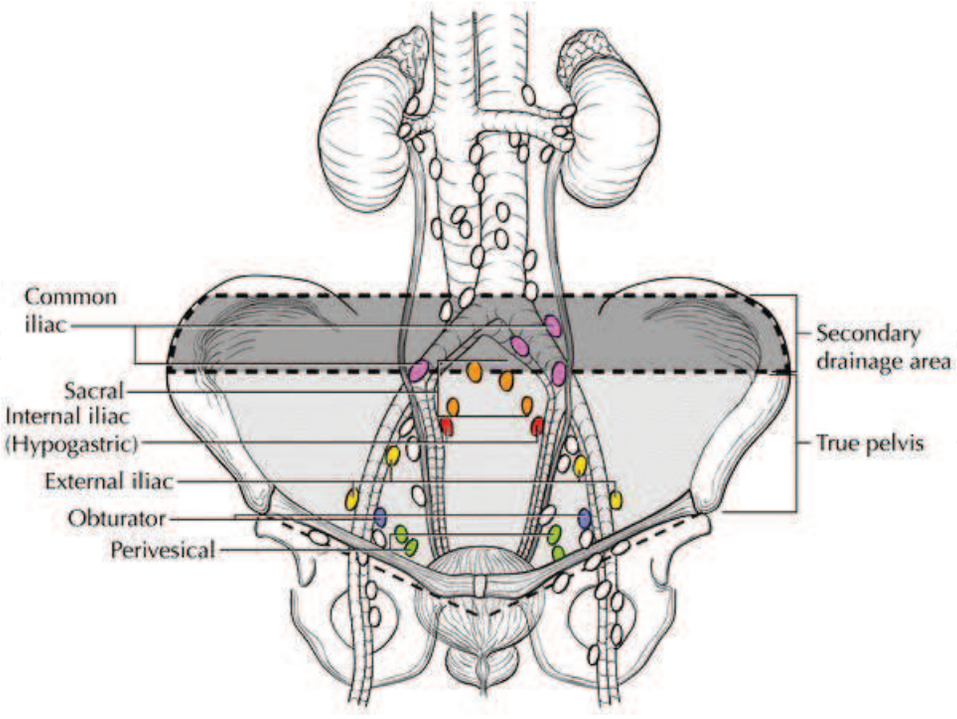

Figure 1. Regional lymph nodes of the urinary bladder. The true pelvis is the primary lymphatic drainage area for the urinary bladder. The secondary drainage area superior to the true pelvis includes the common iliac nodes and all nodes up to the level of the aortic bifurcation.

1. Limited lymphadenectomy (removal of the external iliac and obturator lymph nodes).
2. Standard lymphadenectomy (limited lymphadenectomy plus removal of the internal iliac lymph nodes).
3. Extended lymphadenectomy (standard lymphadenectomy plus removal of the common iliac and presacral lymph nodes).
4. Super-extended lymphadenectomy (extended lymphadenectomy plus removal of any additional lymph nodes above the aortic bifurcation) [10].

The boundaries of extended pelvic lymph node dissection generally include the removal of lymph nodes superior to the bifurcation of the common iliac vessels, to the level of the aortic bifurcation, sometimes including distal aortic and caval nodes up to the level of the inferior mesenteric artery and presacral nodes [11]. Extended and superextended dissection has been reported to be associated with superior survival outcome. The potential for meaningful bias, however, prohibits drawing definite conclusions [12–14].

2. Lymphatic drainage of bladder

The bladder is an extraperitoneal muscular urine reservoir that lies behind the pubic symphysis in the pelvis [15]. The lymphatic drainage of the bladder is into the obturator, external iliac, internal iliac (hypogastric), and common iliac lymph nodes. As with any region of the body, prior surgery may alter the lymphatic outflow of the region [16]. According to description of Leadbetter and Cooper in 1950, the lymphatic drainage of the bladder can be divided into six groups anatomically:

1. The visceral lymphatic plexus is located into the bladder wall, initiating inside the submucosa and extending into the muscular layer of bladder.
2. The intercalated lymph nodes that are located in the juxtavesical lymph nodes within the perivesical fat align into anterior, lateral, and posterior groups.
3. The pelvic collecting lymph nodes that drains medial side of the external iliac and hypogastric lymph nodes.
4. Regional pelvic lymph nodes that drains the external iliac, hypogastric, and presacral lymph node groups.
5. Lymphatic vessels that drains the regional pelvic lymph nodes.
6. Common iliac lymph nodes around the common iliac vessels [17].

The primary drainage of the bladder initiate from the external and internal iliac and obturator lymph nodes, secondary drainage continues from the common iliac lymph nodes, and tertiary drainage to the presacral nodes is from the trigone and posterior wall of the bladder [18]. Remarkably, a researcher from Mansoura supported the importance of the endopelvic that includes obturator and internal iliac lymph nodes as sentinels for lymphatic drainage of the bladder [19] (**Figure 1**).

3. The frequency of lymph node involvement in muscle invasive bladder cancer

Radical cystectomy with pelvic lymph node dissection remains the standard of care for patients with muscle-invasive urothelial cancer of the bladder and select patients with high-risk in nonmuscle-invasive bladder cancer. Approximately, 25% of patients with muscle-invasive bladder cancer have lymph node metastases at radical cystectomy, with 45% of patients with T3 or T4 disease, harboring nodal disease [19]. Steven and Poulsen [20] showed that 34% of their patients with lymph node-positive disease were positive in lymph nodes that are not usually included in standard lymphadenectomy. A study of autopsy including 1933 patients showed that the incidence of pelvic and retroperitoneal lymph node metastasis is 25% in 98 patients with bladder cancer [21]. Contemporary series supported that lymph node metastasis is observed in 18–24% of patients with bladder cancer [22, 23].

4. The importance of the number of positive lymph nodes

Lymph node positivity is a critical factor for disease-specific survival and a primary determinant of therapeutic course following surgery. Multi-institutional series of patients treated with radical cystectomy have shown that approximately 80% of patients with pathologic node positive disease experience disease recurrence, compared with 30% of patients with extravesical disease and pathologically negative lymph node [24–26]. Patients with regional lymph node metastasis at the time of cystectomy are at considerable risk for disease relapse and cumulative probability of survival for these patients' remains at 5–30% [27]. There is an increasing perception that extensive pelvic lymph node dissection is an important therapeutic measure associated with improvement in cancer-specific survival in both lymph node-negative and lymph node-positive patients [19, 28]. Honma et al. reported that patients with less than four positive nodes had a statistically significant survival advantage compared with four or more positive nodes, and the number of nodes removed has a significant impact on disease-specific survival in node-positive patients. The removal of 13 or more nodes had a survival benefit even in the node-positive patients [29]. If pelvic nodal involvement is proven, it should be considered a manifestation of a systemic disease. However, the independent value of pelvic lymph node dissection for survival in patients with bladder cancer remains controversial, although it has been demonstrated that pelvic lymph node dissection cures some node-positive patients [30].

Lymph node mapping studies show a significant percentage of metastases in lymph node-positive patients occurring above the common iliac bifurcation [11, 18]. Lymph node-positive patients with standard lymphadenectomy had significantly worse 5-year disease-free survival compared with lymph node-positive patients who underwent extended lymphadenectomy, and extended lymphadenectomy was an independent prognostic factor for disease-free survival [31]. Tarin et al. reported that number of positive lymph nodes was significantly associated with cancer-specific survival, whereas location of the positive node and lymph node density were not. A total of 25% of patients with pN3 disease were recurrence-free at 5 year,

http://dx.doi.org/10.5772/67443

which is not significantly different from patients with pN1 or pN2 disease [32]. Prior to the practice of pelvic lymph node dissection, series reported dismal 5-year survival rates of 4–7% in lymph node-positive patients [33–35]. Skinner reported a 36% improvement of 5-year survival in bladder cancer patients with limited nodal disease undergoing bilateral pelvic lymph node dissection at the time of cystectomy. Skinner concluded that a "meticulous" pelvic lymph node dissection could provide cure and control of pelvic disease in some patients with regional lymph node metastases without increasing the morbidity [36]. Knowledge of lymph node status is important because it influences patient counseling and, more importantly, clinical decision-making regarding follow-up scheduling and adjuvant chemotherapy [37].

The study of International Bladder Cancer Nomogram Consortium analyzed 9064 patients who underwent radical cystectomy and lymphadenectomy for bladder cancer and reported that 1550 patients treated with surgery alone have lymph node-positive disease. As the result of this study, the authors have developed an international bladder cancer nomogram. The aim of the nomogram is using information on patient age, sex, and time from diagnosis to surgery, pathologic tumor stage and grade, tumor histological subtype, and regional lymph node status to predict recurrence risk in patients with bladder cancer after surgery. Following this study, a lot of nomogram series were published that include either total number of lymph nodes removed, number of positive lymph nodes, or lymph node density, and finally, node parameters placed in the final nomogram model [38].

Although lymph node metastasis is related to a relatively poor prognosis, some patients prove long-term survival after surgery, with or without systemic chemotherapy. Because of the different prognostic factors, stratification of lymph node-positive patients is needed to obtain more individualized risk estimations. Although some studies have reported several prognostic factors for lymph node-positive patients, predictive factors for survival in lymph node-positive patients have not been controversial [39].

5. The importance of the size of lymph nodes (extra capsular invasion of tumor, tumor burden, and lymphovascular invasion)

The extent of nodal involvement, or tumor burden, has also been reported as an independent prognostic factor for survival in patients with bladder cancer [40]. Several recent studies have also shown the prognostic influence of the degree of lymph node positivity on survival rates [25, 41, 42]. The presence of tumor cells in the endothelium-lined space is defined as lymphovascular invasion. The prognostic value of lymphovascular invasion is controversial in bladder cancer [43, 44]. Some studies reported that lymphovascular invasion was present in 36% of all the specimens in patients presenting with higher chances of metastatic disease [3, 45]. Quek et al. found a statistical correlation between lymphovascular invasion and positive surgical margins, high pathological stages, older patients, and female gender. Ten-year survival was lower in patients with lymphovascular invasion than patients without lymphovascular invasion (43 vs. 18%) [3]. Similarly, Lotan concluded in his study that lymphovascular invasion was an independent predictor of recurrence and decreased disease-specific and overall survival in

lymph node-negative patients. Blood vessel invasion of tumor cells of 22 patients who had a 5-year survival of 29% [44]. In another study, 5-year survival is estimated in 56% of the 347 patients without lymphovascular invasion (p = 0.0011). Significantly higher 5-year survival was demonstrated for the 259 patients without lymphatic invasion compared to 110 with lymphatic invasion (61 vs. 39%, $p < 0.0000$). Prognosis was significantly worse in patients with perineural invasion compared with without perineural invasion (44 vs. 56%, $p = 0.0007$) [46].

6. The importance of number of removed lymph nodes

It is common knowledge that removing more nodes can improve survival. In an effort to reduce understaging and maximize survival, many studies have tried to establish a minimum number of lymph nodes needed to be taken at the time of radical cystectomy [40, 47, 48]. Several studies have indicated that the number of lymph nodes removed is a prognostic factor in bladder cancer patients [7, 46, 47]. Researchers have tried to identify the minimum necessary number of lymph nodes needed to be removed at radical cystectomy. However, the analysis of a large tertiary care center's database revealed that the probability of survival continues to rise as the number of lymph nodes removed increases and that no minimum number of lymph nodes can be determined [48]. Although several groups defined a minimum number of lymph nodes to be removed to confer a survival benefit [40, 49], Koppie et al. reported that the probability of survival rises as the number of lymph node removed increases [48]. Herr reported in his study that lymph node-negative patients have increased survival and correlated with the number of nodes removed, regardless of the stage of the tumor. As a result of this study, the authors advised a minimum of nine lymph nodes should be removed [42]. Stein et al. [41] demonstrated that patients with 15 or more nodes removed had better recurrence-free survival than did those with less than 15 nodes removed. Leissner reported in his study that adjuvant chemotherapy has positive effects on survival for lymph node-positive patients or with extravesical disease, if 16 nodes were removed. Moreover, when lymph node positivity is observed, survival increases, if the number of lymph node-positive was ≤5 [44]. Konety et al. [47] reported decreased risk of mortality when 10–14 lymph nodes were removed. The Southwest Oncology Group study 8710 showed that the survival advantage conferred by the removal of 10 or more nodes was found even in node-negative patients [50].

Fleischmann et al. performed only standard lymphadenectomy and removed a mean of 23 pelvic lymph nodes. But when patients were divided into quartiles by the number of nodes examined, researchers could not find any significant differences in recurrence-free and overall survival rates [51].

7. Factors that affect the number of removed lymph nodes in cystectomy

Different factors affect the actual number of lymph nodes removed and/or examined. A lot of studies about the number of lymphadenectomy is high, but all have the limitations of retrospective studies, and the boundaries of lymphadenectomy were variable and the mean numbers

http://dx.doi.org/10.5772/67443

of removed nodes were different. Because of the different surgeons and pathologists, the number of removed lymph nodes and evaluated number of lymph node and detected positive number of lymph nodes may vary [52]. In the surgical series, the number of retrieved lymph nodes can be influenced by many factors, including the extent of pelvic lymph node dissection, intraoperative decisions regarding the amount of tissue to remove within each region of the pelvic lymph node, surgeon's experience, and presentation of pathologic specimens [53].

8. What should be the limit in pelvic lymph node dissection?

There still exists no consensus about the optimal boundaries of lymph node dissection, the number of removed lymph nodes, and procedure's prognostic and therapeutic role for patients who underwent radical cystectomy for muscle-invasive bladder cancer, although the importance of lymph node status is proven for treatment of the bladder cancer [18, 49]. The histopathological results and the extent of lymph node removal have significance as prognostic criteria and thus as indicators for adjuvant therapy [8, 19, 28].

Nowadays, the European Association of Urology and the American Urological Association guidelines could not advise clear recommendations about the boundaries of lymphadenectomy and the number of removed lymph nodes [54]. The International Consultation on Urological Diseases 2012 guidelines recommend the removal of all lymphatic tissue around the common iliac, external iliac, internal iliac, and obturator group bilaterally because one-third of all positive nodes are located around the common iliac artery [55].

Poulsen et al. [6] observed that extending the pelvic lymph node dissection to the bifurcation of the aorta improved survival in patients with organ-confined (pT3a or less) disease.

Bi et al. reported a meta-analysis of six studies. They compared patients who underwent extended lymph node dissection with nonextended lamp node dissection. They reported that extended lymph node dissection have better recurrent-free survival than patients who underwent nonextended lymph node dissection. And also, in a subgroup analysis, they showed that patient who underwent extended lymph node dissection have better recurrent-free survival than nonextended patients in both patients with lymph node positive and negative [56].

Crozier reported that nonurothelial cancers are more advanced tumors than urothelial cancers at the time of diagnosis. According to their results, more aggressive surgical treatment must be performed for patients with nonurothelial muscle invasive cancer. Because of the potential survival benefits for these patients, they recommend standard extended lymphadenectomy in patients diagnosed with nonurothelial muscle invasive cancer [57].

At present, the limitation of exact boundaries of pelvic lymph node dissection remains controversial both in the literature and in the guidelines [58]. It is obvious that a pelvic lymph node dissection must be performed during cystectomy; however, in some studies, pelvic lymph node dissection was not performed in 8, 11, and 60% of patients [59–61]. On the other hand, in another recent SEER analysis performed between 1992 and 2003, 3603 cystectomies were analyzed. In this study, including the hospitals, cystectomies were divided into groups

according to the number of lymph nodes removed. The authors demonstrated that only 0–4 nodes were removed in 88.9% of patients in low-node count hospitals and 52.8% of cases in the high-node count hospitals; likewise, 10–14 nodes were removed in 7.2% in low-node count hospitals and 14.2% of patients in the medium- and high-node count hospitals [61].

9. Morbidity and mortality of pelvic lymph node dissection

Cystectomy is a one of major surgical procedure among urological operations with potential complications often related to the urinary diversion. However, a pelvic lymph node dissection does not have any effect on overall morbidity; it can increase operation time and sometimes facilitate the execution of the cystectomy. The different parameters may affect the morbidity related to pelvic lymph node dissection. Especially, in experienced hands, removing of pelvic lymph node did not increase operative morbidity and using the anatomical approach may decrease perioperative complications and perioperative mortality [62]. Moreover, increasing the number of nodes removed did not increase morbidity. Some complications related to lymphadenectomy, such as lymphoceles and lymphoedemas, were reported in 2% of patients with <16 lymph nodes removed and 1% with 16 nodes removed [63]. As a result, pelvic lymph node dissection is recommended if patients have no absolute contraindication and fit enough to undergo a radical cystectomy, regardless of age and comorbidities.

10. Conclusion

Presence of lymph node metastasis is associated with poor recurrence-free and overall survival. Cystectomy with pelvic lymph node dissection is crucial for appropriate staging, removal of micrometastatic disease, and identifying candidates for adjuvant chemotherapy in patients with muscle invasive bladder cancer. Although there is still no consensus about the limit of pelvic lymph node dissection, extended lymphadenectomy must performed in patients with high risk of metastasis because of the potential survival benefit of the lymphadenectomy.

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