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Review Article

# Standard or Extended-the Controversy of Extent of Lymphadenectomy during Radical Cystectomy Continues

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## Abstract

Radical cystectomy in patients with bladder cancer includes regional lymph node (LN) dissection. There is growing body of evidence suggesting that extended bilateral pelvic LN dissection may confer a survival benefit for surgically appropriate patients with bladder cancer. Accurate node status can only be ascertained by lymphadenectomy. Besides pathological tumor stage, lymph node status is the strongest prognostic factor. The pelvic lymphadenectomy (LND) during radical cystectomy for muscle invasive bladder cancer is now standard of care. However, the optimal extent of the LND remains dubitable. Some recent work from the mapping studies and retrospective analyses has shown that the extended LND up to the mid-upper third of the common iliac vessels appears to provide further prognostic and therapeutic benefit and therefore should be defined as standard LND. The extent of LND suggested is applicable to all form surgical extirpation of the urinary bladder i.e. open surgery, minimally invasive approach (laparoscopic and robot assisted). The role of LND is more controversial in non-muscle invasive cancer.

The concept of total lymph node count is now not considered a quality criterion because nodal yield is overly influenced by the individual patient's anatomy, surgical technique, template applied and pathological work-up. Lymph node density is thought to be a superior prognostic factor, but it is similarly influenced by the above-mentioned factors. Concerning molecular techniques to improve the sensitivity of postoperative nodal staging further research is necessary. There are few ongoing prospective randomized trials will potentially help to further define the optimal LND template.

**Keywords**: Urothelial cancer bladder; lymph node dissection; PLND; Anterior pelvic exenteration

## Introduction

Radical cystectomy (RC) with pelvic lymph node dissection is the mainstay in the surgical management of muscle invasive and high-risk non- muscle invasive bladder cancer [1,2]. It provides effective local and regional control along with most accurate staging of the disease. The pathological stage and nodal status are two very important criteria in prognosticating and determining progression free period following RC. As the pathological tumor grade and lymph node status can only best be assessed on pathological evaluation, cystectomy provides ideal staging modality [3]. About 20-40% of patients with bladder cancer have muscle invasive disease at presentation [4]. It spreads in a stepwise predictable manner to the pelvic lymph nodes. Depending upon the clinical stage of the disease, the overall incidence of lymph node metastasis varies from 10-40% [5]. It is about 5% in non-muscle invasive bladder cancer and can be as high as 27% in pT2 and up to 45% in extra-vesicle disease (pT3-pT4) [6,7]. Other significant factors in the development of lymph node metastasis include grade of the tumor and presence of lymph vascular invasion [8]. The SEER (surveillance, epidemiology and end result) data from 1992-2005 indicates that the quantity and quality of lymphadenectomy has improved over time and role of lymphadenectomy in the surgical treatment of bladder cancer is getting established [9]. However, its extent has been a topic of discussion [10]. Pelvic lymph node dissection (PLND) not only improves staging but also improves the survival. The long-term survival is seen in approximately 30% of patients treated with radical cystectomy and pelvic lymphadenectomy [11]. The therapeutic benefit is potentially both diagnostic by primarily improved staging and therapeutic by removal of micro-metastasis [12]. Imaging modalities like CT scans and MRI have historically failed to accurately identify the pelvic lymph node metastasis in 21% and 15% of patients respectively with muscle invasive bladder cancer [13]. PLND provides important pathological (staging) information which is essential to correctly identify the patients at high risk for developing disease progression and who could potentially benefit from adjuvant therapy and/or more aggressive surveillance regimen [14]. Despite the well-documented therapeutic benefit of PLND, there is no uniform consensus regarding the optimal boundaries of pelvic lymphadenectomy during radical cystectomy. By increasing the extent of lymphadenectomy, more lymph nodes will be removed and consequently chances of identifying the positive lymph node will be increased [15,16]. PLND which is not performed adequately will result in under estimation of true disease burden and need for potentially therapeutic adjuvant therapies [17]. The role of LND during radical cystectomy for NMI BC is controversial. In a recent retrospective review of data Lin and colleagues [18] failed to note impact of LND on recurrence free survival. The impact of lymphadenectomy in managing micro metastatic nodal disease in




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muscle invasive bladder cancer is dubitable. Karl and colleagues [19] looked at the impact of lymph node metastases and the extent of lymphadenectomy on the outcome of patients treated with radical cystectomy. They concluded that an extended pelvic lymph node dissection (encompassing the external iliac vessels, the obturator fossa, the lateral and medial aspects of the internal iliac vessels, and at least the distal half of the common iliac vessels together with its bifurcation) could be curative in patients with metastasis or micro metastasis to a few nodes. Therefore, the procedure may be offered to all patients undergoing radical cystectomy for invasive bladder cancer. Skinner in 1982, for the first time defined the curative role of a meticulous pelvic node dissection extending up to common iliac vessels [7]. It not only provides control of loco-regional disease by decreasing the overall tumor burden and allows the immune system and chemotherapeutic agents to attack a smaller number of cancer cells with potentially greater efficacy [20].

## Morbidity of Lymphadenectomy

In large radical cystectomy series, an early complication rate of 28% and mortality of 2.6-3% has been reported. Extending the boundaries of pelvic lymphadenectomy may prolong the operative time by 30-60 minute but it does not increase the morbidity and mortality considerably as compared to standard approach [21].

## The Concept of Sentinel Lymph Nodes

The mapping studies using pathological analysis and scintigraphic techniques have defined the lymphatic drainage pathways of bladder and hence that of bladder tumor [22,23]. The lymphatic channels drain through anterior, lateral and posterior intercalated lymph nodes located within the peri-vesical fat. The primary drainage is from external and internal iliac and obturator lymph nodes, secondary drainage is from common iliac sites and tertiary drainage is from the trig one, posterior bladder wall up to pre-sacral lymph nodes [8]. It is unusual for the skip lesions to occur patients with bladder cancer, suggesting that pelvic lymph nodes are the only primary lending sites and metastasis occurs in an orderly fashion [24,25]. The most common lymph nodes group is the obturator group, which is involved in 74%, external iliac nodes in 65%, peri-vesical in 16%, pre-sacral lymph nodes in 25%, just-regional common iliac lymph nodes in 70% of patients [26].

Sentinal lymph nodes are the initial sites of lymphatic drainage from the primary tumor [27]. A group from Mansoura introduced the concept of sentinel lymph node region. They advocated that the role of endo-pelvic (obturator and internal iliac lymph nodes) to be removed as they represent the areas involved in first step of nodal metastasis and skip lesions are very rare. The authors therefore recommend the endo-pelvic lymph nodes as the limit of pelvic lymph node dissection in cases of negative lymph nodes at frozen section at this level [28,29].

### The extent of PLND

There is considerable variability in the extent of lymph node dissection performed during radical cystectomy for bladder cancer. Various templates have been designed and modified for the performance of pelvic lymphadenectomy. In the published data, 4 types of PLND have been described; i) limited PLND, which is removal of lymph nodes of obturator region only, ii) Standard (conventional) PLND which involves removal of all lymph nodes from bifurcation of common iliac vessels proximally, Genitofemoral nerve laterally, obturator fossa posteriorly, medially up to bladder and up to deep circumflex iliac vein and lymph nodes of cloquet with hypo gastric group distally. There is some confusion in the literature about defining the limited and standard PLND and some authors refer to limited and standard PLND in the same fashion. iii) Extended PLND which includes standard PLND template along with extension up to level of aortic bifurcation including pre-sacral lymph nodes, iv) Super extended PLND which is more extensive PLND extending proximally up to level of inferior mesenteric artery [30]. The role of limited dissection (template) is only diagnostic and is performed in selected cohort of patients. The standard template drains whole of the primary lymphatic drainage and extended/ super extended template provides the most accurate staging by potentially complete removal of primary, secondary and tertiary lymph node drainage [31]. In order to define the appropriate extent/ template of PLND, Studer group used a multi-modality technique to define primary lymphatic landing sites of bladder. They injected technetium nano colloid under cystoscopic guidance followed by a pre-operative radioactive lymph node detection by SPECT/ CT and then verified the nodal uptake intra-operatively via a gamma probe. They found that only 5% of all primary lymphatic sites were removed in limited PLND as compared to extending the dissection up to uretero-ileal crossing which removed 90% of primary drainage [32]. This supports the belief that extending the template/ boundaries of PLND results in removal of more lymphatic drainage and therefore potentially more metastatic disease, which would not be included in the limited PLND.

### Parameters of Lymph node dissection

There is no accepted standard for the surgical limits of lymph node dissection and optimal number of lymph nodes to be removed because of marked variation in the quality of lymph node dissection. Many nodal factors are important in the prognosis of patients who are lymph node positive. These includes number of lymph node retrieved (Tumor burden), Lymph node density, presence and absence of extra-capsular extension, gross nodal involvement and extent of primary bladder tumor related to positive lymph nodes.

Historically, using the lymph node count during radical cystectomy and PLND has been a surrogate marker for procedural quality; however, it represents a crude measure and can't determine the extent of lymphadenectomy. Similarly, there is no consensus and controversies have remained regarding the optimal (minimum) number of lymph nodes to be retrieved during Radical cystectomy and PLND. Removing a larger number of pelvic lymph nodes during cystectomy is strongly correlated with improved overall survival both in lymph node negative and lymph node positive metastasis [34-38]. There is considerable variability with regard to median lymph nodal counts from Radical cystectomy series and it ranges between 9-30 [39]. An average 8-14 nodes are removed in standard PLND while extending it up to aortic bifurcation yields up to 25-45 lymph nodes [40,41]. There are many factors, which explain the variability in the yield of lymph nodes. These include pathological, surgical, clinical, anatomical and institutional factors.

### Pathological factors

The methods of pathological examination of harvested lymph

nodes affect the yield of lymph nodes. Routine microscopic analysis of nodal tissue might miss small foci of metastatic cancer. Epithelial tissue proteins such as Cytokeratin CK-19 and CK-20 and Uroplakin –II are observed on molecular analysis of nodal tissue in reportedly negative specimen on histo-pathological assessment [42].

Another factor is diligence of pathologist to locate lymph nodes in the available specimen. This includes the processing of tissue including degreasing vs. palpation, labeling of lymph nodes on the presence or absence of afferent and efferent lymphatic vessels or mere presence of lymphocytes surrounded by a capsule [43]. The clinical factors include surgeon's education and expertise and thoroughness to dissect any elected template (limited, extended or super-extended). Radical cystectomy done in an academic setting with high patient volumes has been reported to have higher nodal yield [44]. In addition to that, the inherent anatomical variability between patients can influence the number of lymph nodes removed [45].

### Separate vs. en bloc submission of lymph nodes

The retrieved lymph nodes should be submitted in separate nodal packets rather than en bloc to increase the number of examined lymph nodes and to achieve highest possible amount of information as each separate submitted packet will receive independent diagnosis and can also define the level of node positivity [46-48].

### Minimum (cut off) number of retrieved lymph nodes

A positive correlation between total number of removed lymph nodes and outcome of patients is well known, however, there is no consensus about what should be the minimum number of lymph nodes necessary to achieve a survival advantage [49,50]. A SEER data based study showed that removal of at least 10 lymph nodes is a strongest independent predictor of survival. Many published studies have used various cut off values such as 9, 5 and 16 lymph nodes and their impact on the patient outcome [5,52,53].

A study by southwest oncology group (SWOG) evaluating 1091 radical cystectomy/PLND patients who are treated at 4 high volume centers showed that 5 year overall survival improved from 44% to 61% in patients who had more than 10 lymph nodes removed [54].

In a review of 447 radical cystectomy patients, Leissner et al 5found improvement in recurrence frees survival. He found that if more than 16 lymph nodes were removed, the recurrence free survival increased from 63% to 85% in organ-confined tumors, 40-55% in pT3 tumors and 25-53% in patients with 1-5 positive lymph nodes.

### Extra-capsular extension of lymph node metastasis

Other features that define poor prognostic implications relevant to lymph nodes are lympho-vascular invasion and extra-capsular extension of tumor, which is defined as perforation of capsule of lymph node by tumor tissue with extra-nodal growth. Fleishman et al [55], analyzed in a cohort of 101 patients who underwent radical cystectomy with extended PLND for lymph node positive disease and found the effect of extra-capsular extension (found in 58 %) on the prognosis of patient. The recurrence free survival decreases from 60 months to 12 months in patients with extra-capsular extension compared with patients with intra-nodal disease. The multivariate analysis confirmed that extra-capsular extension of lymph node metastasis is the strongest negative predictor for recurrence free survival. There is an important question however, to answer; what is more important the number of lymph nodes or the dissection limits.

A more proximal dissection leads to increase number of lymph nodes retrieved and survival benefit and also removal of micro-metastatic lesions outside the standard template boundaries that would have not been resected and remained undiagnosed with prognostic implications.

### Extent of lymphadenectomy

There is a lack of unanimity about the optimal extent of PLND at radical cystectomy for bladder cancer. An ideal PLND must be able to completely clear the entire lymph node drainage of urinary bladder, must maintain strict anatomical boundaries of dissection and therefore it demands a high degree of technical expertise [56]. Extended PLND provide the accuracy of staging by increasing the probability of complete tumor burden removal and thus high likelihood of their correct prognosis [57]. It is also shown in recent investigations to provide improved survival outcomes. Extending the limits of PLND also defines the other important prognostic variables like number of positive lymph nodes, total number of lymph nodes removed, lymph node density and presence of metastasis at higher level i.e. above the iliac bifurcation [58-60].

In a recent report, Abol enein et al showed that 5-year recurrence free survival was better for patients undergoing extended template removal as compared to standard template (66.7% vs 54.7 %) [61].

### Benefits of extended pelvic lymph node dissection

Dissection of all the lymphatic tissue along the template of e PLND result in complete clearance of 80 % of all positive lymph nodes and by removing occult microscopic metastasis not visible on conventional histo-pathological analysis [62]. By increasing the number of lymph nodes removed and fewer positive margins, the local recurrence rate is decreased and cancer specific survival is also improved [63,64]. This is explained by "Will Roger phenomenon'" which states that routine removal of PLN among minimal nodal disease patients serves to enrich node positive patients (removing the tumor burden) and in node negative patients (removing the undetectable micro metastasis) will minimize the patients with node positive disease the therefore has a therapeutic benefit and enhanced patient survival in both these groups [65].

### Safety of extended pelvic lymph node dissection

Concerns have been raised regarding the potential for added morbidity associated with PLND. The template involves dissection of highly vascular bed around the great vessels and can potentially injure the autonomic nerves of hypo gastric nerve plexus in para-aortic, para-caval and pre-sacral lymph regions [66], and theoretical risk of impaired continence and sexual dysfunction. It is also technically more challenging, requiring excellent bowel mobilization and meticulous exposure to retro peritoneum up to the level of IMA. However, other than taking longer time to perform i.e. additional 30-60 min, the studies have shown no difference in lymphocele rates, transfusion requirement s and hospital stay [67,5,68].

### Lymph node density

Lymph node density is the ratio between positive lymph nodes and total number of removed lymph nodes. This concept was first described by stein et al in 2003 and it combines the two most reliable

predictors of outcome i.e. in the numerator the number of positive lymph nodes i.e. tumor burden with denominator i.e. total number of retrieved lymph nodes in a 1:1 ratio. This index is considered to be a good indicator of efficacy of PLND [69,70].

It defines, prognosticate and stratify the patients with node positive muscle invasive bladder cancer. This index however must be used in conjunction with total (standard) number of lymph nodes removed and standard level of PLND [71]. Herr found in a retrospective study that cases with a ratio of >20% of positive lymph nodes had significantly better survival than with a ratio of > 20% [72]. However, the prognostic significance of lymph node density is unclear in patients who have undergone adjuvant chemotherapy and it is yet to define as what additional measure to be taken in-patient with a lymph node density above 20% [73].

## Lymph node density and 2002 TNM staging system

The 2002 TNM staging for lymph node metastasis (N category) was based upon the absolute number and size of positive lymph nodes, which are dependent upon the removal of those lymph nodes, by the surgeon. This classification system thus has a limitation as it potentially under stages the disease if there is failure to remove a sufficient number of lymph nodes and a defined template [74].

A pooled analysis of 248 patients with node positive disease from MD Anderson and Memorial Sloan Kettering cancer centers showed that lymph node density is superior to TNM nodal status in predicting disease specific survival after radical cystectomy irrespective of adjuvant chemotherapy status. The authors confirmed non-correlation between TNM and lymph node density further suggesting increase predictive value of lymph node density in disease specific survival. In a retrospective study, Herr investigated lymph node density with a threshold value of 20%, number of positive lymph nodes with a threshold value of 4 and 2002 N stage with respect of their effect on cancer specific survival. On multivariate analysis, only lymph node density exhibited an independent effect [75].

## Modification of 2010 TNM classification

Under the 2002 American joint committee on cancer (AJCC) staging system, the positive lymph nodes outside the true pelvis (pN3) were staged as metastatic disease (M1), suggesting a significantly worse outcome for patients with common iliac lymph node involvement as compared to patient with disease limited to pelvis. This belief that nodes outside the true pelvis with advanced disease and no likely chance to be cured by surgery led many urologists to underestimate importance of performing meticulous PLND including the common iliac lymph nodes [76-78].

Recent changes in 2010 AJCC TNM staging system have provided improved discrimination between patients with respectable pN3 disease and patients with advanced M1 lesion. These changes were based on evidence that an extensive PLND is associated with improved recurrence free survival [79,80].

Patients with single positive regional lymph nodes are now pN1; multiple positive regional lymph nodes pN2 and positive lymph nodes at common iliac vessels are pN3.

## Studies supporting the extended pelvic lymph node dissection

Numerous studies have reported about the beneficial role of extended PLND over limited or standard one. Extended PLND not only provides most accurate staging but also has impact on the therapeutic outcome. In a study by Dhar et al [81] compared two consecutive series of patients treated with radical cystectomy and bilateral PLND at two institutions, (Cleveland clinic n=336) with limited PLND (University of Bern n=322) with extended pelvic lymph node dissection over a period of 14 years (1987-2000). They included only pT2 and pT3 stage patients and excluded NMIBC (pT1 and pTis) and pT4 to rule out the confounding effect of low/ high stage disease in-patient with N0M0 prior to surgery. None of the patients received any neo-adjuvant chemo or radiation therapy. The authors reported a 13% lymph node positive rate for patients with limited and 26% rate for those with extended pelvic lymph node dissection.

This 2-fold increase in lymph node positive disease in extended lymph node dissection suggests significant under staging in patients with limited PLND and they concluded that leaving the pN0 group with undetected positive lymph nodes with limited dissection contaminated the prognostic implications. Regarding the oncological outcome, they reported that 5-year recurrence free survival for lymph node positive disease was 7% in limited dissection group and 35% for extended PLND.

In lymph node negative group, the stage specific survival also improved with 5-year recurrence free survival for pT2 group was 67% in limited and 77% in extended PLND group. For pT3N0 group the rates were 23% and 57% respectively. The values for pT2N0-2 cases were 63 % for limited and 71% for extended PLND. For pT3N0-2, the cases were 19% and 49%.

Thus they concluded that limited PLND is associated with suboptimal staging, poorer outcome for patients with lymph node positive and lymph node negative disease and higher rate of local progression.

The first group to compare the prognostic significance of limited vs. extended PLND was Poulson et al [82] did a retrospective analysis of 194 patients undergoing radical cystectomy. The 5-year recurrence free survival was 85% vs. 64% in patients with lymph node involvement and 90% vs. 71% with lymph node negative disease. The results by Bochner et al [83] in a prospective trial were contrary to the above-mentioned reports. They evaluated 144 consecutive patients with 56 undergoing standard and 88 extended PLND. The median number of positive lymph nodes was significantly different between both groups (22.5 vs. 8) however; the lymph node density was 21% in both the groups.

The authors also found that patients with involvement of higher (para-aortic) lymph nodes had positive lymph nodes in lower packages and thus only extensive loco-regional metastatic disease involves the retroperitoneal areas that are associated with dismal prognosis anyhow.

A study involving the SEER linked database [84] from Jan 1992 tp Dec 2005 including 4472 patients found that nearly 70% of patients underwent pelvic lymph node dissection and only 571 patients (22.1%) had > 10 lymph nodes removed. They found that more extensive lymph node dissection (> 10 count) were common in patients with high volume disease, high volume surgeons and those

practicing in comprehensive cancer care centers.

Another SEER database study for TCC bladder [85] between 1988-2004, including 8072 patients undergoing radical cystectomy and pelvic lymph node dissection, 21% of patients did not have any lymph nodes in cystectomy specimen while 79% had 10 or more, 60% had 5 or more and 30% had 10 or more lymph node in the specimen. In a recent prospective non-randomized study Abol enein et al [86] compared 200 patients with extended lymphadenectomy with 200 patients undergoing standard lymphadenectomy at Mansoura. None of the patients received neo-adjuvant or any adjuvant therapy. The median follow up was 50.2 months. They found that extended template was associated with better 5-year recurrence free survival (66.7% as compared to 54.7%) in patients who underwent a standard template.

In patients with lymph node positive disease, patients with extended lymphadenectomy had much better 5-year disease free survival (48%) compared to patients with standard lymph node dissection 28.2%.

In univariate analysis, age at radical cystectomy, gender, grade and histology were not associated with disease free survival while in multivariate analysis, pT category, Lymph node involvement and extended lymphadenectomy were independently associated with disease free survival. May et al [87] in a large study compared the outcome of 447 lymph node positive patients who underwent radical cystectomy and bilateral pelvic lymph node dissection over a median follow up of 28 months.

They did the multi-variate cox regression analysis to test the effect of various pelvic lymph node dissection variables on cancer specific survival and found median number of lymph nodes to be twelve. 60.8% patients presented with stage N2 disease. The mean lymph node density was 29%. They found that lymph node density threshold value of 20% had significant effect on cancer specific survival both for limited PLND (<12 lymph nodes) and for extended PLND (> 12 lymph nodes).

Another study by Tarin et al [88] that was a prospective study without any randomization and without any control arm evaluated the effect of level of lymph node metastasis on recurrence free and cancer free survival in lymph node positive bladder cancer treated with radical cystectomy and lymphadenectomy.

Overall 591 patients were treated with radical cystectomy and bilateral PLND between 2000 and 2010 and 114 patients (19% had lymph node involvement). The analysis showed that number of positive lymph node (none, one or two or more) was significantly associated with cancer specific death, while lymph node density was not a significant predictor of recurrence of cancer specific survival.

Interestingly, they did not find on multivariate analysis that location of positive lymph nodes (i.e. common iliac region) did not provide any prognostic information over the total number of lymph nodes removed.

## Laparoscopic and Robotic Pelvic Lymphadenectomy

Robot assisted laparoscopic PLND is oncologically feasible and acceptable in patients with muscle invasive bladder cancer undergoing radical cystectomy and it allows more meticulous dissection at proximal location [89]. However, there are few questions that need to be answered in the future about the template. Extended vs. standard, separate vs. en bloc submission of lymph nodal packets and optimal number of lymph nodes to be removed.

Many reports have been published which concluded that robotic/laparoscopic radical cystectomy + PLND in bladder cancer patients to be oncologically well tolerated alternative to open procedure with a positive margin rate of 5-10% and median lymph node yield between 10-20 [90-93].

Pruthi et al [94] in a series of 100 consecutive patients who underwent robotic radical cystectomy at a single institution did both standard and extended PLND. The mean number of lymph nodes removed was 19 (8-40) and there were no reported positive surgical margins. The recurrence free survival was 85 % at a short mean follow up of 21 month.

In a recently published article comparing the quality of lymphadenectomy between robotic (n= 35) and open cystectomy (n=120) using and extended lymph node dissection, Abaza et al [95] found that mean number of lymph nodal count in open group was 36.9 compared to 375 in robotic group. The lymph nodes were processed in one or two packets for robotic cases and as 10 or more packets for open surgery cases.

The other parameters like node positivity, and soft tissue surgical margins, which reflect procedural quality, were similar in this study. The authors concluded that robotic extended lymphadenectomy quality is comparable to open group with respect to lymph node yield and node positivity and does not sacrifice the oncological efficacy for the sake of minimally invasive procedure.

In another prospective RCT comparing 20 open and 21 robotic cystectomies in a single institute, Nix et al reported a similar node yield with a mean of 18 nodes in open surgery and 19 nodes in robotic cases at a single institute [96].

## Limitations and controversies of studies

Despite of all existing literature, there is still controversy regarding the appropriate boundaries of PLND in bladder cancer due to absence of any published randomized controlled trials comparing the extended vs. standard PLND in cystectomy patients [97-99].

There are many limitations of these available literatures. The published studies are single center or multi center trials with different population groups and different outcome measures. There is a lack of uniformity in defining the cut off values of parameters like lymph node density, lymph node numbers, the universal definition of a template and its extent. Moreover, due to retrospective nature and lack of randomization and control arm, there are inherent selection biases.

Thus the available data regarding the required extend of lymphadenectomy and it possible therapeutic effects are conflicting and therefore the clear recommendation about the field and extent of lymphadenectomy are missing in European association of urology (EAU) guidelines [100]. RCTs are needed to confirm the benefit of extended over standard PLND and to define the patient cohort who will get greatest benefit from this procedure [101]. Fortunately, 2

randomized controlled trials addressing the extent of lymph node dissection for bladder cancer are under way and the results are forthcoming [102]. The first of them were initiated by the association of urological oncology of German cancer society is a multi-center trial. This study (LEA) is comparing the outcome of patients who underwent radical cystectomy with standard lymph node dissection (obturator fossa, external and internal iliac lymph nodes) and super-extended lymph node dissection (all lymphatic tissue from pelvic floor up to inferior mesenteric artery) is included. The recruitment phase has been closed and 457 patients have met the inclusion criteria. The Southwest oncology group (S1011) conducted the other trial. This trial started enrolling the patients in fall of 2011. It aims to compare an extended vs. standard nodal template in a randomized controlled trial and the target number of patients is 620. The standard template includes peri-vesical, internal iliac, obturator and external iliac lymph nodes up to the bifurcation of common iliac arteries. The extended template comprised of all lymph nodes in standard template and pre-sacral and common iliac lymph nodes up to the bifurcation of aorta. A 10-12% improvement in 3-year survival is expected.

There are many differences in between SWOG and German trial. This includes the upper boundary of extended lymph node dissection (Bifurcation of aorta vs. inferior mesenteric artery), the clinical stage of patients to be recruited (T2 or higher in SWOG trial vs. T1 or higher in German trial and inclusion (SWOG) or exclusion (German) of patients who have received neo-adjuvant chemotherapy.

## Conclusion

Several conclusions can be drawn from the available literature. First PLND is an essential component of radical cystectomy for muscle invasive bladder cancer. Bilateral PLND should always be done because the lymphatic cross over is a common phenomenon. Standard template ending at iliac bifurcation yields lesser number of lymph nodes and lymph node density and therefore is insufficient form oncological perspective. Patients who have lymph node involvement higher up (above the iliac bifurcation) should receive adjuvant chemotherapy to improve their outcome and an institutional based algorithm should be followed with extending the lymph node dissection up to the level of aortic bifurcation if endo-pelvic lymph nodes are found positive on frozen section analysis.

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