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Current controversies on the role of lymphadenectomy for bladder cancer

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Abstract

Significant evidence exists regarding the diagnostic and therapeutic roles of pelvic lymph node dissection at the time of radical cystectomy for patients with bladder cancer. Despite this, lymphadenectomy for bladder cancer is still underutilized and even where performed, controversies exist in regard to what defines an adequate dissection and whether or not the indications for lymphadenectomy have changed now that we are firmly entrenched in the neoadjuvant chemotherapy era. A comprehensive literature review was performed to touch on these important issues and highlight future directions and current trials that will soon provide more clarity for surgeons and patients dealing with bladder cancer.

Keywords: Urothelial carcinoma; Lymphadenectomy; Cystectomy; Bladder cancer

Introduction

Pelvic lymphadenectomy (PLND) has long been a standard component in the management of muscle-invasive bladder cancer. In 1950, Leadbetter and Cooper proposed a role for en bloc regional lymphadenectomy (LND) at the time of total cystectomy. The impetus for their publication was an unacceptably high death rate after cystectomy, which they attributed to recurrence or metastases from cancer left behind in unrecognized pelvic lymphatics [1]. Shortly after Leadbetters report, Kerr and Colby published a series of 10 patients with bladder cancer who underwent total cystectomy, ureterosigmoidostomy, and PLND. Positive lymph nodes were found in 40% of the patients despite having grossly organ-confined disease. Acceptable operative morbidity and recurrence rates set the stage for regional LND as an adjunct to radical cystectomy (RC) in the treatment of bladder cancer [2]. Contemporary series now indicate that positive lymph nodes are found in a quarter of all patients undergoing RC and PLND [3–8]. Even in the presence of nodal metastases, long-term survival has been demonstrated with cystectomy and node dissection alone [3,5,7,9]. The merits of LND in serving both a diagnostic and therapeutic role, regardless of nodal status, are now well documented [4,6,10]. Despite this, LND for bladder cancer is underutilized in the United States and even when performed, 39% of patients still do not receive an adequate lymph node dissection [11]. Current controversies exist in regard to what defines an adequate LND and whether or not the indications for LND have changed now that we are firmly entrenched in the neoadjuvant chemotherapy era [12]. A comprehensive literature review was performed using PubMed to identify well referenced studies published in English that address such controversies. In this review we will touch on these important issues and highlight future directions and current trials that will soon provide more clarity for surgeons and patients dealing with bladder cancer.

What is an adequate lymph node dissection? The role of node count, density and anatomic templates

When Leadbetter proposed LND as a curative measure for bladder cancer, he noted that pelvic metastases from bladder cancer paralleled that of cancer from the cervix. The primary drainage was thus to the internal, external, and common iliac nodes as well as lateral and sacral promontory nodes [1]. Today, universal consensus regarding the boundary for an adequate PLND does not exist and there is

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significant variation among individual surgeons. In fact, a post hoc analysis of patients enrolled into SWOG 4B951, a cooperative group trial that aimed to identify the importance of p53 overexpression in patients undergoing RC and PLND for bladder cancer, showed significant variation in LND quality despite strict inclusion criteria [13]. In this trial, a standard template was requested by the protocol to be initiated at or above the aortic bifurcation including the common, external, and internal iliac nodes as well as the presacral and obturator lymph nodes. An extended dissection above the bifurcation of the common iliacs occured in 47% of patients and only 33% had dissection of the presacral nodes. The significant variation despite explicit entry criteria highlights the disagreement in what is considered an adequate node dissection.

In order to address variability in technique, a minimum number of lymph nodes excised has been suggested as a measure of LND adequacy. In 2000, Leissner et al. [4] performed a retrospective review of 447 patients who had undergone RC and PLND for invasive bladder cancer. Their standardized dissection included removal of the obturator, internal, external, common iliac, and presacral nodes as well as the nodes lateral to the aortic bifurcation. They found a mean of 14.6 nodes removed per patient with a significantly different number found per surgeon. The odds of finding a nodal metastasis was higher when greater than 16 nodes were removed and 80% of all node positive patients were found if 20 nodes were removed. Five-year overall survival (OS) was significantly higher when 16 or more nodes were removed compared to 15 or less (65% vs. 51%, $P < 0.013$). If 16 or more nodes were removed the 5-year tumor-free survival increased from 63% to 85% for organ-confined tumors, 40% to 55% for pT3 tumors, and from 25% to 53% in patients with at most 5 nodal metastases. The authors suggested that a minimum of 20 nodes should be removed during PLND as this would capture 80% of all node positive patients, thus improving staging and removing micrometastatic disease. In 2002, Herr et al. [6] studied 322 patients who underwent RC and PLND, 90% of whom had a cranial limit at the distal common iliac artery, including the presacral nodes. They found nodal metastases in 20% of the cohort with a local recurrence rate of 20% for node positive patients compared to 15% for those who were node negative. Among the node negative patients, survival was best for patients who had 9 or more nodes removed and in node positive patients, survival was best when more than 14 nodes were removed. They concluded that at least 9 nodes should be retrieved at the time of PLND as this would be easily achieved by most urologists and examined by most pathologists. A population based sample from the Surveillance, Epidemiology and End Results program (SEER) by Konety et al. [14] similarly found a correlation between node counts and survival . They included 1,923 patients who underwent RC for bladder cancer from 1988 to 1996. A maximum survival benefit was found when 10 to 14 nodes were removed (hazard ratio [HR] = 0.38, $P < 0.0001$). For patients with metastases, survival increased as the number of nodes examined increased even when controlling for chemotherapy. The number of positive lymph nodes did not correlate with survival, however, the positive-to-total number of nodes examined did correlate with survival. This correlation was in a negative manner such that having a ratio of positive to total nodes examined less than 50% was the strongest predictor of increased survival for patients with metastases ($r = -0.23$, $P < 0.0001$).

The concept of "density" or ratio of positive-to-total lymph nodes has been suggested as a more accurate measure of disease burden in patients with nodal involvement, especially as it controls for instances where fewer nodes are examined. The finding by Konety et al. was consistent with an earlier report from Lerner et al. [3] in 2003 where 591 patients undergoing RC and PLND were reviewed . The incidence of positive nodes was 22% for the entire cohort and increased with increasing pathologic stage (13% for pT1 and 45% for pT4). They found that having 25% or less positive nodes was associated with improved recurrence and survival rates. Stein et al. and Herr et al. both proposed a 20% cut off for lymph node density in separate studies [15,16]. Stein et al. showed that a density of 20% or less was associated with 43% 10-year recurrence-free survival compared to 17% with a lymph node density greater than 20%. On multivariate analysis of various predictors of survival and local recurrence, Herr et al. found the strongest predictors to be a lymph node density of 20% or less vs. greater than 20%. A later SEER review by Wright et al. [17] of 1,260 patients with at least 1 positive lymph node found a median density of 22% and suggested a lower density threshold for predicting survival with each higher quartile above a referent group of 0.1% to 12.5% showing worse survival. Just like Stein et al. and Herr et al., Wright et al. also found that the total number of positive and total lymph nodes removed still predicted OS. Removal of more than 10 lymph nodes was associated with increased OS (HR = 0.52, $P < 00.1$).

In 2003 a randomized intergroup trial, SWOG 8710 showed the benefits of neoadjuvant chemotherapy in improving the survival of patients with muscle-invasive bladder cancer [18]. Herr et al. [19] followed this study with an analysis of surgical factors from 268 patients enrolled in the trial to determine if these factors could similarly influence outcomes independent of chemotherapy usage. The 5-year OS and local recurrence rates were 54% and 15%, respectively. The original trial did not mandate specific limits for the PLND. A standard LND was done in 54% of patients, limited in 37% and 9% of the patients did not receive a lymph node dissection. The median number of nodes removed was 0 for no dissection, 7 for limited (range: 0–16), and 15 for a standard node dissection (range: 1–54). Nodal involvement was present in 21% of all patients. The 5-year OS was significantly lower and local recurrence rates higher in patients with positive nodes (60% vs. 22% and 12% vs. 29%, respectively). The 5-year

OS after RC and no node dissection was 33%, 46% after a limited dissection, and 60% with a standard dissection ($P = 0.01$). Local recurrence rates were 50%, 22%, and 5% with no, limited or standard dissection, respectively ($P < 0.0001$). A multivariate model controlling for chemotherapy, age, stage, and nodal status showed that negative margins and having more than 10 nodes removed predicted longer survival but the PLND variable (none, limited, or standard) was not a significant predictor. Given this lack of significance and the variation in the number of nodes removed per template, the authors suggested that node counts are a more accurate measure of the extent of lymph node dissection and that a minimum number should be agreed on as a proxy of quality of surgery.

The premise that node counts rather than anatomic templates should be the target measure for quality in PLND is challenging as the aforementioned studies were retrospective and with inconsistent templates. As noted in the study by Leissner et al., [4] despite a standardized PLND template performed by experienced surgeons at a single institution, there was significant variation in the number of lymph nodes removed by each surgeon ($P < 0.01$). The method of pathologic analysis of lymph node samples also effects the reported number of nodes retrieved. Bochner et al. [20] showed a significantly different number of nodes retrieved by the same surgeon performing the same surgery if the specimens were sent en bloc vs. as separate packets. In an analysis of lymph node count and cause of death in 735 patients with bladder cancer, Froehner et al. showed that though there was a clear association between lymph node count and 10-year OS (59% for>20 nodes removed and 32% for<10 nodes, $P = 0.0056$), there was no association between lymph node count and bladder cancer specific mortality ($P = 0.40–0.93$) [21]. They found that the differences in overall mortality were due to competing causes, suggesting a significant bias when stratifying outcomes by lymph node count. The degree to which an extended dissection template affects outcomes remained unanswered.

The use of extended dissection templates in regard to total node counts has been addressed in separate studies. Dorin et al. [8] reviewed 646 patients from 2 institutions where standardized RC and extended PLND, starting at the inferior mesenteric artery (IMA), was performed . There was a significant difference in the median number of lymph nodes retrieved at each institution (72 vs. 40, $P < 0.001$) but not in the incidence of patients with positive nodes found (11% vs. 12% for organ-confined disease, $P = 0.63$ and 45% vs. 44% for extravesical primary tumors, $P = 0.94$). The 5-year recurrence free and OS estimates for node positive patients did not vary despite the difference in node counts (36% vs. 33%, $P = 0.19$ and 53% vs. 41%, $P = 0.32$, respectively). This was mainly attributable to the definition of a distinct lymph node at each institution. Fransen et al. [22] found similar results when they reviewed 274 patients who underwent RC and PLND at 2 different hospitals with 2 separate pathology departments, but by the same 4 surgeons. The cranial extent of their dissection was at the crossing of the ureter over the common iliac arteries. Median lymph node count at hospital A was 20 and at B was 16 ($P = 0.003$). There was again significant variation amongst individual surgeons but neither the hospital nor the surgeon influenced OS, cancer specific survival, or recurrence rates. The summative conclusion from both studies was that lymph node count in and of itself does not affect long-term outcomes so long as surgeons adhere to a standardized template.

The value of an extended template PLND relative to a limited one was shown by Poulsen et al. [10]. They performed a retrospective review of outcomes from 1 surgeon when a limited dissection was done with a cranial limit at the bifurcation of the common iliac arteries vs. an extended dissection beginning at the bifurcation of the aorta and including the presacral nodes. There was a significant improvement in 5-year recurrence free survival for patients without nodal metastases with an extended compared to a limited dissection (90% vs. 71%) as well as 5-year risk of pelvic recurrence for patients with tumors confined to the bladder wall (2% vs. 7%). Dhar et al. [23] more recently performed a multicenter review of 336 patients who received a limited PLND and 322 with an extended PLND. They found significant understaging in the limited group as positive nodes were found in 13% of patients with a limited PLND and in 26% who had an extended PLND. The 5-year recurrence free survival was significantly improved for patients with an extended PLND, including those with pT3pN0–2 disease (49% vs. 19% for limited, $P < 0.0001$).

Defining the optimal limits of lymphadenectomy

Though it may seem intuitive that a more extended template will identify more patients with nodal involvement and clear more deposits of microscopic disease, the optimal limits of an extended dissection continue to be debated. Mapping studies have been done to address this issue. Roth et al. [24] performed a trial using single-photon emission computed tomography plus intraoperative gamma probe to map the primary landing sites of bladder cancer in 60 patients who underwent RC and extended PLND. They found that 92% of all lymph nodes were caudal to where the ureter crosses the common iliac arteries. A limited dissection covering the ventral portions of the external iliacs and obturator fossa only removed 50% of the primary lymphatic landing sites and extending dissection cephalad to the crossing of the ureter identified the remaining 8%. Given the roughly 25% rate of nodal involvement in clinically node negative patients and the 35% long-term survival rate of pathologically node positive patients, they surmised that extending dissection from the crossing of the ureter to the IMA was not justified as it only benefits 1 in 100 patients. Zehnder et al. [25] tested the benefits of a “super extended” vs. an extended PLND by evaluating 554 patients at a center with LND up to the IMA and presacral

Table 1
Outcomes among different lymphadenectomy templates

Author	Year	Template	Outcomes
Poulsen et al. [10]	1998	Limited dissection: proximal limit at bifurcation of common iliac vessels, distally to circumflex iliac vein and cloquet, posteriorly to bilateral internal iliac vessels and including bilateral obturator fossae Extended dissection: same dissection with proximal limit at bifurcation of aorta and including presacral nodes	Median of 25 nodes removed with an extended and 14 with a limited dissection, $P<0.0015$-y RFS (extended vs. limited) • 62% vs. 56%, $P = 0.33$ • 85% vs. 64% for pT3a or less, $P<0.02$OS (extended vs. limited) • pN0 - 78% vs. 70%, $P = 0.17$ • pT3a or less, pN0 - 90% vs. 71%, $P<0.02$ • pT3b or greater - 38% vs. 67%, $P = 0.46$
Herr et al. [19]	2004	No dissection Limited dissection: nodes medial to bilateral external iliac veins and bilateral obturator nodes Standard dissection: limited dissection plus bilateral distal common iliac and hypogastric nodes	Median of 0, 7, and 15 nodes removed with no, limited, or standard dissection, respectively 5-year OS • 44% vs. 61% for<10 vs. ≥10 nodes removed, $P = 0.007$ • 33% vs. 46% vs. 60% for no, limited, or standard dissection, $P = 0.01$Local recurrence • 25% vs. 6% for<10 vs. ≥10 nodes removed, $P<0.001$ • 50% vs. 22% vs. 5% for no, limited, or standard dissection, $P<0.0001$
Dhar et al. [23]	2008	Limited dissection: bounded by pelvic sidewall between genitofemoral and obturator nerves, bifurcation of the iliac vessels to the circumflex iliac vein. Extended dissection: cephalad dissection to the crossing of the ureters with the common iliac arteries and removal of all tissue along the lateral and medial portions of the internal iliac vessels	Median of 22 nodes removed with an extended vs. 12 with a limited dissection RFS (extended vs. limited) • pT2pN0 - 77% vs. 67%, $P = 0.12$ • pT2pN0–2 - 71% vs. 63%, $P = 0.22$ • pT3pN0 - 57% vs. 23%, $P<0.0001$ • pT3pN0–2 - 49% vs. 19%, $P<0.0001$ OS (extended vs limited) • pT2pN0 - 66% vs. 68%, $P = 0.12$ • pT2pN0–2 - 64% vs. 63%, $P = 0.10$ • pT3pN0 - 46% vs. 26%, $P = 0.0021$ • pT3pN0–2 - 42% vs. 22%, $P = 0.0002$
Zehnder et al. [25]	2011	Extended dissection: proximal border at the mid-upper third of the common iliac vessels. Including the presacral region medial to the internal iliac vessels but leaving intact the tissue containing the hypogastric nerves located medial to the retracted ureters and inferior to the aortic bifurcation. The obturator fossa with full exposure of the intrapelvic course of the obturator nerve (Marcille's triangle) and the internal iliac vessels posteriorly, and the tissue medial to these vessels. Superextended dissection: same lateral, distal, and posterior borders but proximally to the IMA takeoff and complete dissection of the presacral space from the bifurcation of the aorta into the sacral fossa.	Median of 38 nodes removed with a superextend and 22 with an extended template, $P<0.00015$-y RFS (superextended vs extended) • pT2pN0–2 - 57% vs. 67%, $P = 0.55$ • pT3pN0–2 - 32% vs. 34%, $P = 0.44$ Median OS (superextended vs. (extended) - 5 y vs. 5.8 y, $P = 0.45$ Overall recurrence rate - Superextended = 38% - Extended = 38%

Table 2
Current trials investigating the extent of lymphadenectomy for bladder cancer

Trial	LEA (AUO AB 25/02, NCT01215071)	SWOG S1011 (NCT01224665)
Start date	February 2006	August 2011
Completion date	August 2015	August 2022 (expected)
Enrollment	401	620 (estimated)
Design	Multicenter randomized open label clinical trial	Multicenter randomized open label clinical trial
Arms	Limited lymphadenectomy • Bilateral external iliac, obturator, and internal iliac lymph nodes Extended lymphadenectomy • Limited plus bilateral deep obturator, paracaval, interaortocaval, paraortic up to the inferior mesenteric artery	Standard lymphadenectomy • Bilateral external iliac internal iliac, obturator, and perivesical lymph nodes Extended lymphadenectomy • Standard plus bilateral common iliac, presacral, triangle of Marcille, and optionally paraortic and paracaval nodes
Stratification variables	None defined	Zubrod performance status, prior neoadjuvant chemotherapy, clinical stage (T2 vs. T3 vs. T4a)
Primary outcome	5-y RFS	DFS up to 6 y from registration
Secondary outcomes	• 5-y CSS • 5-y OS • Type and location of tumor progression (locoregional and distant metastases) • Effect of histopathological stage on (influence of extended lymphadenectomy on detection of lymph node metastasis)	• OS up to 6 y from registration • Perioperative, 90-d, and up to 6 y from registration morbidity and mortality • Operative time • Whether or not nerve sparing was performed • Length of hospital stay • Histology (pure urothelial vs. mixed) • Lymph node count and density • Adjuvant chemotherapy received • Local and retroperitoneal soft tissue recurrence • Blood and tumor specimens also collected periodically for translational studies
Inclusion criteria	• 18 y of age or older • Histologically proven cT1G3−T4a, NX urothelial carcinoma • Written consent • Patient compliance and geographic proximity to allow adequate follow up	• 18 y of age or older • Histologically proven T2−T4a urothelial carcinoma • Predominant urothelial carcinoma • Zubrod performance status 0−2 • ALT, AST, and alkaline phosphatase less than or equal to upper limit of normal • No other primary malignancy except adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer or stage I/II disease in complete remission for the past 5 y
Exclusion criteria	• Histologic or imaging proven organ metastases • Enlarged lymph nodes (>1 cm) above aortic bifurcation in conjunction with pelvic lymph node metastases • cT4b tumors • Prior neoadjuvant chemotherapy • Prior pelvic lymphadenectomy • Prior pelvic radiation therapy • Medical risk factors that require a shorter surgery • Palliative cystectomy • Evidence of another tumor restricting life expectancy	• CIS only, cT1, or cT4b urothelial carcinoma • Laparoscopic surgery • Pure squamous cell carcinoma or adenocarcinoma • Visceral or nodal metastases proximal to the common iliac bifurcation on preoperative imaging or via intraoperative identification • Prior partial cystectomy for invasive bladder cancer • Prior pelvic radiation therapy • Prior pelvic surgery that would obviate a complete extended lymphadenectomy
Locations	Germany	US, Canada

space including dissection over the sacral promontory vs. 405 at a separate institution that performed an extended PLND that started at the mid-upper third of the common iliac arteries, including the presacral region medial to the internal ilac arteries, while leaving the tissues containing the hypogastric nerves and inferior to the aortic bifurcation intact. The 5-year recurrence free survival was similar at both institutions regardless of nodal status (57% vs. 67%, $P = 0.55$ for pT2pN0−2 and 32% vs. 34%, $P = 0.44$ for pT3pN0−2). Recurrence rate was 38% at both institutions. Outcomes from studies comparing more than 1 dissection template are shown in Table 1.

Although the literature does not distinctly favor one definition for an adequate lymph node dissection, it does show support for a thorough LND over a minimum nodal yield in improving OS and recurrence rates. It is therefore our

practice to routinely perform a dissection to the IMA as the cephalad limit of dissection outside of clinical trials.

The role of lymphadenectomy in the neoadjuvant chemotherapy era

The improved OS in patients who undergo PLND has been attributed to 2 major factors: improved staging and removal of micrometastatic disease. Improved staging allows for the identification of node positive patients who will benefit from adjuvant chemotherapy [26], whereas removal of microscopic disease deposits improves OS in pathologically node negative patients [4]. Even in the absence of adjuvant chemotherapy, PLND alone has shown a benefit in node positive patients. Zehnder et al. [9] reviewed 521 patients with positive nodes, 48% were unfit for or never received adjuvant chemotherapy. Furthermore, 26% of these patients were free from recurrence at 10 years, suggesting the curative potential of node dissection alone. There has been a paradigm shift since SWOG 8710 with the gold standard management of muscle invasive bladder cancer now being neoadjuvant cisplatinum based chemotherapy (NAC) followed by RC and PLND [18]. The benefit shown with PLND has been derived largely from studies where patients had not received NAC. In a recent analysis of the National Cancer Database, Landenberg et al. [27] set out to answer the question of whether NAC plays a similar role as LND in eliminating micrometastatic disease. They identified 16,505 patients who underwent RC for localized bladder cancer (anyTN0M0) from 2004 to 2012. An adequate lymph node dissection, defined by the authors as 10 or more nodes removed, was performed in 52% of patients. Among the patients who did not receive NAC, adequate LND was associated with a significant OS benefit for all stages. This persisted when modifying the definition of adequate LND to 15 or more nodes removed. However, among patients who did receive NAC, adequate PLND (using either 10 or 15 nodes as the cut off) did not provide a statistically significant survival benefit. Though limited by study design, the results are provocative in bringing question to the role of PLND in clinically node negative patients after NAC.

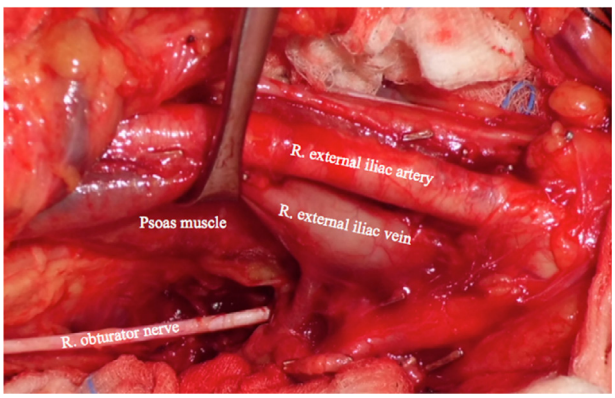

Fig. 1. Standard lymphadenectomy template per SWOG S1011 criteria. Figure shows dissection of the external and internal iliac nodes as well as nodes in the obturator fossa on the right side. (colour version of the figure is available online.)

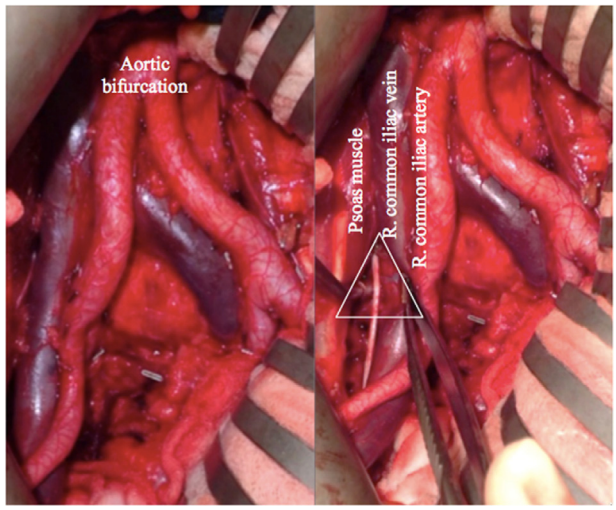

Fig. 2. Extended lymphadenectomy template per SWOG S1011 criteria. Figure shows cephalad dissection to the para-aortic and bilateral common iliac nodes as well as triangle of Marcille (outlined). (colour version of the figure is available online.)

The role of PLND in node positive patients who received preoperative chemotherapy was recently addressed in 2 studies. Zargar-Shostari et al. [28] performed a multi-institutional review of 304 patients with cN1-N3 bladder cancer who received chemotherapy followed by RC and PLND. Complete pathological nodal response to pN0 was achieved in 48% of patients and conferred a significant survival advantage compared to those with pN1−3 disease (median 71 vs. 13 mo, $P < 0.001$). On multivariate analysis, OS was associated with cisplatin therapy, pN0, negative surgical margins, and PLND with at least 15 nodes removed. Necchi et al. [29] reviewed data from 34 centers, including patients with node positive (pelvic or retroperitoneal) bladder cancer who received platinum based chemotherapy followed by RC and LND or observation only. There was a significant improvement in OS with surgery compared to no surgery (HR = 0.60, $P < 0.001$) but this difference was not significant with a matched analysis controlling for differences between the groups (HR = 0.91, $P = 0.628$). The interaction between surgery and extent of lymph node involvement showed a nonsignificant numerical improvement in 36 month OS for those with pelvic nodes (51.7% vs. 41%) but not with retroperitoneal nodes (HR = 0.75 and 1.12, respectively, $P = 0.182$). They concluded that postchemotherapy LND should not be performed in patients with metastases beyond the pelvic boundaries and that larger studies would need to be done to address those with pelvic nodal involvement.

There are important differences in the patients included in the studies by Zargar-Shostari and Necchi compared with those in Landenburg's paper. The former 2 included

patients with clinically node positive disease, whereas the latter only those with potential micrometastatic disease (i.e., cN0). Accordingly, the studies by Zargar-Shostari and Necchi do not necessarily provide information on the role of PLND after neoadjuvant chemotherapy. As more patients undergo RC and PLND with prior exposure to platinum based chemotherapy, the role of PLND as it pertains to node negative and node positive patients will be better elucidated. We are certainly in need of higher level evidence.

Future trials

The benefits of PLND for bladder cancer are all shown in retrospective series thus far. Inherant bias certainly exists when comparing historical cohorts, especially as improved outcomes have the potential to be due to a stage migration rather than a true therapeutic effect of more extensive PLND. This is an example of the Will Rogers phenomenon and occurs as node positive patients are appropriately identified and compared to those who are truly node negative [30]. Two randomized controlled trials have now been completed, with hopes to eliminate such bias and answer the questions that remain regarding extent and role of LND in the future (Table 2).

The German trial, (LEA AUO AB 25/02, NCT01215071) was a multi-institutional randomized controlled trial comparing a limited (bilateral obturator, internal and external iliac lymph nodes) to an extended (in addition bilateral deep obturator fossa, presacral, paracaval, interaortocaval, and para-aortic nodes up to the IMA) node dissection. The primary outcome was progression free survival and secondary outcomes included location of recurrence, disease specific survival, influence of adjuvant chemotherapy, complications, and effect on histopathological stage. Patients with cT2−T4aNX disease were included, but patients receiving neoadjuvant chemotherapy were excluded from this study. Data collection is complete with preliminary results showing a trend toward improved progression free survival (62% limited vs. 69.3% extended, HR = 0.80, $P = 0.28$) and cancer specific survival (66.2% limited vs. 77.5% extended HR = 0.70, $P = 0.13$) [31].

The similarly designed trial, SWOG S1011 (NCT01224665) was a multi-institutional randomized controlled trial comparing a standard dissection (bilateral external and internal iliac, obturator, and perivesical nodes) to an extended dissection (in addition bilateral common iliacs, presacral, and triangle of Marcille, and optionally para-aortic and paracaval nodes) (Figs. 1 and 2). The primary outcome of this study is disease-free survival with secondary outcomes of OS and morbidity. Eligibility criteria included patients with cT2−4aN0−1 disease and stratifying factors included receipt of NAC, clinical stage, and performance status. Enrollment is complete with results pending. The results of both trials will add significantly to a growing field of literature regarding PLND for bladder cancer.

Conclusion

Significant evidence exists regarding the diagnostic and therapeutic roles of PLND at the time of RC for patients with bladder cancer. Despite the various definitions of an adequate lymph node dissection, a meticulous template based dissection should be the standard of care. The final results of LEA (AB25/02) and SWOG S1011 are eagerly awaited to help settle the controversy regarding the appropriate extent of PLND. The results of SWOG S1011 will also help to answer growing questions as to the role of PLND in the setting of prior chemotherapy exposure.

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