



The evolving role of lymphadenectomy for bladder cancer: why, when, and how

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Abstract: Radical cystectomy (RC) represents a standard treatment for non-metastatic muscle-invasive and select high-risk non-muscle invasive bladder cancer. Lymphadenectomy performed at time of RC identifies nodal metastases in up to 25% of patients despite normal imaging. There has been an increasing utilization of pelvic lymph node dissection (PLND) with RC since 1950, and in fact lymph node dissection is now recommended in contemporary National Comprehensive Cancer Network (NCCN) guidelines. Benefits of removing of nodal disease include improved staging, guidance for adjuvant treatment, and potentially improved oncologic outcomes. Advantages of dissection have been suggested among both node-negative and node-positive patients. Numerous studies have attempted to define the optimal dissection characteristics of lymphadenectomy with regard to nodal yield and anatomic boundaries of dissection. The ideal extent of lymphadenectomy remains uncertain due to the retrospective and non-randomized nature of the majority of existing reports, which are thereby limited by significant confounding and selection bias. Two randomized controlled trials have investigated this issue, one of which LEA AUO AB 25/02 recently reported its outcomes, demonstrating no significant improvement in 5-year outcomes with an extended dissection. Meanwhile, the Southwest Oncology Group 1011 trial has completed enrollment and data are maturing. While current data preclude definitive recommendations, herein we review the why, when, and how to perform a PLND for bladder cancer.

Keywords: Bladder cancer; radical cystectomy (RC); lymph node dissection; lymphadenectomy

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Introduction

There were an estimated 549,393 newly diagnosed cases of bladder cancer and 199,922 bladder cancer deaths worldwide in 2018 (1). Approximately 30% of patients with bladder cancer present with muscle-invasive disease (2). Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is a standard treatment for patients with muscle-invasive bladder cancer as well as for patients with non-muscle invasive bladder cancer that is endoscopically unresectable or unresponsive to intravesical therapy (3-6).

Despite normal preoperative imaging, 8% and 25% of patients undergoing RC for non-muscle invasive and muscle-invasive bladder cancer, respectively, have been reported to have pathologically involved lymph nodes at the time of PLND (7,8). Indeed, current National Comprehensive Cancer Network (NCCN) guidelines advocate that a lymph node dissection be performed with RC (3). This recommendation is based on existing observational data suggesting improved risk stratification and oncologic outcomes for patients who undergo PLND versus those who do not (9). At the same time, data remain

mixed and therefore consensus undefined on the optimal extent of PLND (10).

History of lymphadenectomy for bladder cancer

The concept of lymph node dissection for malignancy is rooted in 1886, when Halstead reported a survival benefit for patients with breast cancer who underwent regional lymphadenectomy at time of mastectomy (11). *En bloc* regional lymphadenectomy for bladder cancer was reported by Leadbetter in 1950, who postulated that the relatively high death rate from “palliative” cystectomy alone was due to unrecognized malignancy in pelvic lymphatic tissue (12). Several subsequent early series noted that the additional dissection with PLND minimally changed the morbidity profile of cystectomy (13,14). Interestingly, over the next decades, survival dramatically improved in node-positive patients, from <1% to 36% (13,15). The utilization of PLND has in fact continued to rise; for example, an analysis of the Surveillance, Epidemiology, and End Results (SEER) database by Cole *et al.* revealed that PLND increased from 26% in 1998 to 61% in 2010 (16).

Rationale for PLND

PLND with RC may confer several benefits. First, PLND provides the most accurate staging and prognostic information which in turn facilitates risk stratification and patient counseling. Second, PLND identifies patients with involved nodes who may be candidates for adjuvant therapies (17-20). Moreover, removing involved nodes may itself improve oncologic control.

With regard to staging, the American Joint Committee on Cancer (AJCC) TNM staging system classifies bladder cancer nodal stage as follows: N1—a single lymph node metastasis in the true pelvis (peri-vesical, obturator, internal and external iliac, or sacral lymph nodes); N2—multiple lymph node metastases in the true pelvis; N3—common iliac lymph node metastases (21,22). Of note, M1a designates lymph node metastases proximal to the common iliac vessels, which would correspond to nodes dissected by Level 3 or super-extended templates (see below), although some major centers argue these should still be considered regional nodes (23,24). The prognostic utility of this system has been confirmed in various studies (25).

Determining lymph node involvement also enhances our ability to establish prognosis. An increasing number of overall positive nodes has been associated with poorer

survival, with a wide range of prognostic thresholds suggested (18,26). Lymph node density, or ratio of positive lymph nodes, is the proportion of positive nodes to overall nodes removed. This measure somewhat accounts for extent of dissection and rigor of pathologic examination (27). Some series reported decreased survival with a lymph node density >20%, with 5-year overall survival (OS) dropping from 64% to 8% (27,28). Finally, the presence of extracapsular nodal extension (ECE) has been demonstrated to be associated with decreased cancer specific survival in institutional series and meta-analysis (29-31). Accurate identification of node-positive disease may also guide the administration of adjuvant therapy, which in turn may further improve survival. Indeed, guidelines recommend that patients who did not receive neoadjuvant chemotherapy and are found to have node-positive disease at cystectomy undergo adjuvant chemotherapy or enroll in clinical trials (3).

Perhaps the topic of greatest controversy with regard to the potential benefits of PLND is the ability of PLND to independently improve oncologic control. Notably, a survival benefit has been demonstrated with an increasing number of nodes removed as well as larger dissection templates in various series to date (9,17-20,32). The benefits from PLND have been observed in both pathologically node-negative and node-positive patients (18). In node-negative patients, the survival benefits conferred by PLND may be due to both elimination of micro-metastatic disease and by accurate prognostic staging, also known as the Will Rogers phenomenon (33). That is, node-negative group with a PLND would have decreased “contamination” with node-positive patients, and the node-positive group would include patients with a lower burden of metastatic disease. In node-positive patients, removal of involved nodes may also serve to debulk disease and improve the efficacy of adjuvant therapy, and be curative in select patients for whom all metastatic disease is resected. Since the majority of these observations are made in non-randomized series, confounding by patient factors and quality of operation that is associated with increasing node yield must be acknowledged.

When to perform a PLND?

The NCCN guidelines state to perform a bilateral PLND at time of RC, and to include at least the common iliac, internal iliac, external iliac, and obturator nodes (3). Contemporary clinical staging and prognostic criteria do not currently allow for selective or risk-adapted PLND.

Indeed, recent assessment of 1,016 patients attempted to predict nodal metastases based on preoperative pathologic and radiologic factors but showed that none were predictive of nodal involvement (34). Current radiographic staging predominantly includes computed tomography (CT) and magnetic resonance imaging (MRI), with positron emission tomography (PET)/CT scans utilized selectively as well. However, these modalities all have been found to have poor sensitivity for detecting lymph node metastases (35–39). Moreover, positive lymph nodes are identified in approximately 8% of those with non-muscle invasive bladder cancer and 25–30% of those with muscle-invasive bladder cancer without evidence of nodal metastases on CT scan, suggesting that even patients undergoing RC for non-muscle invasive disease, as well as patients with what is assessed as a “negative” staging evaluation, merit PLND (7,8,30). A study assessing 276 patients with preoperative CT reported accuracy in predicting lymph node metastases of 54%, with an 8.3% rate of over-staging and 29% rate of under-staging (35). MRI is limited by poor standardization of techniques and interpretation (36). With regard to PET/CT, Kibel *et al.* evaluated [18F] fluorodeoxyglucose (FDG)-PET/CT in 42 cT2–3 patients with negative conventional CT and bone scan, finding that FDG-PET/CT demonstrated a sensitivity of 70%, specificity of 94%, and positive predictive value of 78% (37). Another study recently found that altering the maximum standardized uptake value (SUV_{max}) of FDG-PET/CT resulted in varying sensitivity/specificity profiles, with sensitivity/specificity of 79%/66% for SUV_{max} >2, and sensitivity/specificity of 61%/84% for SUV_{max} >4 (38). The diagnostic efficacy of [11C] choline PET/CT was assessed in 44 patients who underwent RC in a German center, showing that accuracy with PET/CT was only 64% when compared to 61% for conventional CT (39).

Importantly, PLND should also be performed in conjunction with consolidative RC for patients receiving neoadjuvant chemotherapy. In fact, Herr *et al.* demonstrated that 92% of patients with regionally metastatic or unresectable bladder cancer who experienced major response to induction chemotherapy but did not undergo consolidative surgery died within 3 years. Moreover, Zargar-Shoshtari and colleagues assessed 304 patients with clinically node-positive disease who underwent neoadjuvant chemotherapy and showed that ypN0 was achieved in 48% (40). Of note, we recommend nodal biopsy in patients with clinical lymphadenopathy, in order to confirm histology and potentially guide treatment. Indeed, Moschini *et al.* evaluated 196 patients with clinical lymphadenopathy who underwent RC without neoadjuvant

chemotherapy and found an 18% sensitivity for pathologic nodal involvement (41).

With regard to PLND during minimally-invasive approaches to RC, the same oncologic principles should be adhered to as in open surgery. Utilization of robotic RC has increased considerably, with a recent National Cancer Data Base analysis showing increase in frequency from 26% in 2010 to 39% in 2013 (42). Desai and colleagues have demonstrated feasibility of robotic PLND dissection to the aortic bifurcation and even the inferior mesenteric artery (IMA) (43). Abaza *et al.* performed a retrospective comparison of 120 open and 35 robotic cystectomies with extended PLND including pre-sacral lymphadenectomy and observed similar lymph node yield (37 versus 38; P=0.68) and pathologic node-positive rate (30% versus 34%; P=0.73) between groups (44). Likewise, two randomized controlled trials of minimally-invasive versus open RC, CORAL and RAZOR, found no difference in lymph node yield between approaches (45,46). This observation was confirmed in a systematic review, which reported an average lymph node yield of 19 nodes and node-positive rate of 22% for robotic RC, with no significant difference in lymph node yield compared to the open approach (47).

Importantly, as with all steps in management of bladder cancer, competing comorbidities should be incorporated into the decision for and extent of PLND. For example, previous vascular stenting or renal transplantation may limit the ability to safely complete an extended dissection. A SEER-Medicare analysis by Novara *et al.* assessed 3,314 patients with RC alone versus RC and PLND, stratified survival by age and comorbidity subsets, and found that there was no difference in survival for patients older than 75 and with a Charlson-Comorbidity Index of 1 or greater based on performance of PLND (48). An example of this principle was demonstrated by Froehner *et al.*, who showed that in 735 patients who underwent RC, those with fewer lymph nodes removed had decreased OS but similar cancer-specific survival, suggesting that there were increased competing risks in patients with a limited number of lymph nodes removed (49).

Anatomy of lymphatic drainage and mapping studies

Colston and Leadbetter first identified isolated pelvic lymph node metastases in cadaveric studies which suggested a lymphatic spread of bladder cancer (50). Lymphatic

drainage was subsequently evaluated in numerous surgical and lymphoscintigraphy mapping studies as reviewed herein. Abol-Enein and colleagues performed a single-center surgical mapping study of 200 patients with routine dissection up to the origin of the IMA and demonstrated that lymph nodes were positive in 24% of cases, and of those positive cases, were bilateral in 39% (51). Furthermore, the investigators noted that removing only nodes in the pelvis, defined as internal iliac, external iliac, and obturator regions, would capture just 66% of the positive nodes, while additional dissection to the level of the aortic bifurcation to include common iliac and presacral nodes would clear 79% of positive nodes (51). Importantly, there were no cases of “skip” metastases, with positive nodes proximal to the common iliac arteries without concomitant involvement of obturator/internal iliac nodes. Leissner *et al.* qualified these findings in a multi-center study assessing 290 cystectomies with dissection to the level of the IMA and pathologic examination of 12 clearly-defined anatomic locations (52). This study showed that 6.6% of patients had positive lymph nodes identified proximal to the aortic bifurcation, and of these, no patients had lymph node metastases exclusively above the aortic bifurcation (52). However, in another 6.9% of patients, positive lymph nodes were found exclusively between the common iliac bifurcation and the aortic bifurcation (52). Notably, the location of a single positive lymph node was most commonly in the obturator packet (52). Meanwhile, Vazina *et al.*, in 43 patients with node-positive disease, found that all patients with disease proximal to the common iliac artery (16%) also had at least one positive node in the obturator or internal iliac artery locations (53). Furthermore, as study by Tarin *et al.* found that 6% of node-positive patients had “skip” lesions above the common iliac bifurcation, corroborating Leissner *et al.*'s results but not Abol-Enein *et al.*'s or Vazina *et al.*'s (23). These mapping studies are limited by inconsistent definitions of anatomic boundaries as well as unknown rates of incomplete resection.

Lymphoscintigraphy has been utilized to help identify nodal landing sites. A study by Roth *et al.* in 2010 utilized single-photon emission CT (SPECT) with six bladder injections of technetium Tc 99m (54). On subsequent extended PLND to the proximal level of uretero-iliac junction, 24 primary lymphatic landing sites per bladder and highly variable lymphatic patterns between patients were noted. The investigators concluded that dissection limited to the ventral external iliac artery and obturator packet would miss 48% of radiotracer positive nodes, while

only 8% of radiotracer-positive lymph nodes were found proximal to the uretero-iliac junction (54). The authors also identified bilateral lymphatic spread in 15% of patients following unilateral bladder injections of radiotracer in a later study (55). Collectively, from these mapping studies, several tenets emerge: (I) lymph node involvement is frequently bilateral; (II) there is a small but consistent proportion of lymph nodes involved above of the true pelvis, and (III) while isolated common iliac nodes may be found in approximately 6% of patients, “skip” metastases above the aortic bifurcation without involvement of pelvic lymph nodes appear to be quite rare.

PLND template nomenclature

As reported in previous systematic reviews, no standard definitions exist for the extent of PLND at the time of RC (9,56). A variety of classifications have been reported: Level I, II, and III; as well as limited, standard, extended, and super-extended. The level classification was coined by Leissner and colleagues in 2004 (52). In this system, Level I nodes include obturator, deep obturator, internal and external iliac lymphatics, with proximal extent to the common iliac bifurcation. Level II includes lymphatics lateral to the common iliac arteries, pre-sacral nodes, and extends proximally to the aortic bifurcation. Level III nodes include paracaval, interaortocaval, and para-aortic lymphatics to the root of the IMA. From reported series, the boundaries of standard PLND dissection have typically extended from the genitofemoral nerve laterally to the bladder wall medially, distally to the node of Cloquet or superficial circumflex vein, and proximally to the bifurcation of the common iliac artery (26,57). Descriptions of extended PLND templates have been quite heterogeneous, with a proximal boundary extending to the uretero-iliac junction, aortic bifurcation, or various length cutoffs of the common iliac artery, and with variable inclusion of presacral nodes (9,26). Meanwhile, super-extended templates have fairly consistently included resection of lymphatics up to the root of the IMA (58,59). Given such variability, an expert panel from the European Association of Urology (EAU) Working Group on Muscle-Invasive Bladder Cancer defined the boundaries of dissection for a systematic review by Bruins *et al.* in 2014 (9). These templates are defined as follows: limited node dissection is that confined to the obturator and/or peri-vesical fossa only; standard template extends proximally to the common iliac arteries; extended template extends proximally to the crossing of the common iliac

vessels with the ureters or to the aortic bifurcation, with or without the presacral LNs; super-extended template continues to the IMA.

Lymph node count versus PLND template

Various metrics have been described and reported to assess the adequacy of PLND. The two most common are lymph node count, which may in turn be used to calculate parameters such as lymph node density, as well as PLND template. With regard to lymph node count, the total number of nodes removed during PLND has been used as a surrogate for the quality of lymphadenectomy. An increasing number of nodes removed has moreover been associated with improved survival outcomes. Various specific node yield cutoffs have been put forth to represent an adequate PLND. In an early study by Herr *et al.*, dichotomization of node-negative patients with >8 versus <8 nodes and node-positive patients with >11 or <11 nodes was associated with survival differences (18). In a subsequent series, Herr identified >14 nodes to be an optimal cutoff, with 5-year OS rates of 33%, 44%, 73%, and 79% for patients with 0–5, 6–10, 11–14, and >14 nodes removed, respectively (60). Furthermore, in a re-analysis of SWOG 8710 data controlling for age, pathologic stage, node status, margins, and neoadjuvant chemotherapy administration, removal of < 10 nodes was associated with a significantly increased post-cystectomy mortality (HR 2.0; 95% CI, 1.4–2.8; P=0.0001) (61). Meanwhile, Leissner and colleagues reported that the ideal threshold node count was 16 (17). Likewise, May *et al.* assessed an exclusively node-negative cohort and demonstrated that patients with >16 lymph nodes dissected had a 5-year cancer-specific survival of 83% versus 72% for those with <16 lymph nodes removed (62). Using SEER data in 1,923 RC patients, Konety *et al.* demonstrated that increasing node yield generally yielded progressive improvement in survival for all stage subsets, but particularly for stage III node-positive patients (19). Whether these collective data in fact reflect a benefit to more extended dissection eliminating micro-metastatic disease versus simply improved staging (i.e., the “Will Rogers phenomenon”) cannot be definitively established (33).

In addition, it is important to acknowledge that the use of a lymph node count is subject to a number of variables other than the extent of dissection. One problem is that there is simply large variability in the number of nodes present in different patients, as shown in an autopsy study that demonstrated a node yield ranging from 8 to 56 for

standard template PLND in 30 cadavers (63). Furthermore, the surgeons who perform more thorough PLND may be more experienced and offer a higher quality RC operation than those generally performing limited dissections. Additionally, the institutions that these surgeons operate in may have superior process of care, which has been shown to improve outcomes (64). The reported node yield is also in the control of the pathologist assessing the lymphadenectomy specimen (65,66). The pathologist protocol for examining lymphadenectomy specimens was shown to dramatically influence reported node yield in a study by Fang *et al.* (65). After institution of a policy to re-review specimens with less than 16 nodes by a more experienced pathologist, the reported median node yields jumped from 15 to 20. Similarly, Bochner *et al.* showed that submission of nodes from extended PLND *en bloc* yielded significantly lower reported node yield compared to submission of nodes in discrete anatomic packets (23 versus 36 nodes, respectively).

An alternative approach to assessing the extent of PLND is by reporting the template of dissection performed. With this approach, a beneficial effect of PLND has also been noted in observational studies (67,68). Abdollah *et al.* utilized the SEER database to compare 11,183 patients who underwent RC with PLND versus without PLND between 1988 to 2006 (67). Patients with PLND had improved 10-year cancer-specific survival and OS compared to those without PLND among all pathologic tumor stages. Several series have compared extended or super-extended to limited PLND templates (69–71) (Table 1). Holmer *et al.* found that in 170 patients there was significant improvement in disease specific survival after age, sex, tumor stage, lymph node status, and adjuvant chemotherapy were controlled for in multivariate analysis (HR 0.47; 95% CI, 0.25–0.88; P=0.018) (70). Jensen and colleagues studied 429 patients who underwent extended or limited PLND and found significant improvements in recurrence free survival (RFS) for the extended PLND group for both pathologic node-negative and node-positive subsets (69). Dhar *et al.* compared 336 RC patients that underwent limited PLND at Cleveland Clinic and 322 patients that underwent extended PLND at University of Bern (71). Extended PLND conferred significant benefit in 5-year RFS across multiple subsets including pT2N0 (77% versus 67%), pT3N0 (57% versus 23%), pT2Nany (71% versus 63%), pT3Nany (49% versus 19%), pTanyN1 (35% versus 7%) (71). Several observational studies have further confirmed improved oncologic outcomes in patients undergoing extended or

Table 1 Select major comparative series of extended pelvic lymph node dissection versus other templates

Author, year	Trial design	Proximal limit of extended template	Number of patients	Median Follow-up, months	Median number LN removed	pN+ (%)	5-year RFS (%)	5-year OS (%)
Comparator: limited template								
Gschwend, 2018 (72)	RCT	IMA (super-extended)	198 vs. 203	43	31 vs. 19, P<0.0001	22 vs. 28	64.6 vs. 59.2; P=0.36	58.9 vs. 49.7; P=0.12
Dhar, 2008 (71)	Retrospective, two institutions	Uretero-iliac junction	322 vs. 336	51 vs. 36, P<0.001	22 vs. 12	26 vs. 13	pT2: 71 vs. 63; P=0.22 pT3: 49 vs. 19; P<0.001	pT2: 61 vs. 64; P=0.10 pT3: 42 vs. 22; P<0.001
Comparator: standard template								
SWOG1011, pending (73)	RCT	Aortic bifurcation	Estimated 310 vs. 310	-	-	-	-	-
Abol-Enein, 2011 (57)	Retrospective, single institution	Distal inch common iliac	200 vs. 200	50.2	49 vs. 16, P<0.001	24 vs. 24	67 vs. 55	NR
Comparator: super-extended template								
Møller, 2016 (74)	Retrospective, single institution	Aortic bifurcation	316 vs. 262	38 vs. 93; P<0.01	NR	NR	No difference; P=0.88	Super-extended superior; P=0.0001
Zehnder, 2011 (58)	Retrospective, two institutions	Uretero-iliac junction	405 vs. 554	118 vs. 130; P=0.06	22 vs. 38; P<0.001	28 vs. 35	pT2: 67 vs. 57; P=0.55 pT3: 34 vs. 32; P=0.44	pN0: 60 vs. 59 pN+: 38 vs. 34

All results for extended PLND vs. comparator. LN, lymph node; RFS, recurrence free survival; OS, overall survival; NR, not reported.

super-extended versus standard PLND (57,75-77). Abol-Enein and colleagues assessed outcomes of 400 patients who underwent super-extended versus standard PLND at the discretion of two surgeons at a single institution (57). This report demonstrated a significant improvement in 5-year disease-specific survival in patients with extended versus standard PLND (48% versus 28%). While there have been mixed results in other analyses of these templates, these results are from smaller series or incomplete publications (9). Super-extended versus extended PLND templates have likewise been compared (58,74). Zehnder *et al.* evaluated 554 University of Southern California patients who underwent super-extended PLND and 405 University of Bern patients who underwent extended PLND between 1985 to 2005 with no neoadjuvant chemotherapy, negative margins, and pT2/3 disease (58). Extended PLND included a proximal extent to the mid-upper third of the common iliac artery and super-extended PLND included all nodes up to the IMA. Super-extended dissection yielded a higher nodal yield (38 versus 22) and higher rate of lymph nodes metastases (35% versus 28%) (58). Nevertheless, there was almost identical 5-year distant disease-free survival for super-extended versus extended groups (65% versus 66%) regardless of stratification by tumor stage or node positivity (58). Møller *et al.* also compared super-extended versus extended PLND in 578 patients and found similar recurrence-free survival between groups (74).

In summary, the aforementioned existing observational data seems to suggest that performing a PLND is associated with improved outcomes compared to not performing a PLND, while an increasing extent of PLND, assessed either by lymph node yield or extent of template, is likely to be of benefit, but may reach a threshold above which further dissection does not incrementally enhance disease control. However, there are major limitations to these data that preclude clear recommendations regarding extent of PLND template, which has been noted by several systematic reviews on this topic (9,56). The majority of studies that compare extended or super-extended PLND to smaller templates have significant selection bias and confounding as templates were often not designated prospectively, left to surgeon preference, and amended intra-operatively. Furthermore, these studies were non-randomized and were evaluated in a retrospective fashion.

Clinical trials assessing PLND template

Two recent randomized controlled trials have evaluated the

association of extent of PLND with oncologic outcomes. The LEA trial, conducted by the Association of Urogenital Oncology of the German Cancer Society in 16 German centers from 2006 to 2010, compared extended versus limited PLND (72). Patients with T1G3–T4a bladder cancer who did not receive neoadjuvant chemotherapy were included. A total of 401 patients were randomized 1:1 to either extended or limited PLND, with limited PLND including obturator, internal, and external iliac nodes and extended PLND additionally including deep obturator, common iliac, presacral, paracaval, interaortocaval, and para-aortal nodes up to the IMA. Notably, the template referred to by the trial as an extended template is considered super-extended by other definitions. The study demonstrated a significantly higher nodal yield (31 versus 19, $P < 0.001$) and numerically higher rate of lymph node metastases (28% versus 22%; $P = 0.12$) in the extended versus limited PLND group. However, compared to a limited PLND, extended PLND was not associated with statistically significant improved 5-year recurrence-free survival (65% versus 59%; $P = 0.36$), cancer-specific survival (76% versus 65%; $P = 0.10$), or OS (59% versus 50%; $P = 0.12$). There was no difference in 90-day complication rates between groups, although extended PLND resulted in a higher rate of lymphoceles requiring intervention (8.6% versus 3.4%; $P = 0.04$). Importantly, the study was powered to detect a 15% difference in recurrence-free survival and therefore may have been underpowered to detect a true but smaller difference between groups. Furthermore, the inclusion of clinical T1G3 tumors and the finding that only one patient had pathologic N3 disease indicate a relatively low risk of the overall cohort. Thus, while the study was reported negative, it may have additionally been underpowered by its low risk population to detect a benefit from extended PLND.

S-1011 was a randomized trial run by SWOG that also compared standard versus extended PLND (73). A total of 620 patients were accrued between 2011 and 2017. The standard PLND template included peri-vesical, obturator, internal and external iliac lymph nodes up to the common iliac bifurcation. The extended template additionally included common iliac nodes to the bifurcation of the aorta as well as pre-sacral nodes. The study was powered to demonstrate 10% improvement in 3-year disease-free survival, and these data are estimated to mature by 2022. Important differences from the completed LEA trial include allowance for neoadjuvant chemotherapy, which is a stratification factor. Additionally, only patients with at least

clinical stage T2 disease were included. Finally, there is a less extensive proximal limit of dissection in the extended PLND group in this trial.

Complications from PLND

Relatively minimal additional morbidity secondary to the performance of PLND has been reported. While hemorrhage and nerve injury are unique side effects that can occur as lymphatics are skeletonized off the iliac vessels and obturator nerve, these are reported quite infrequently in the literature (9). One potential sequela of PLND is pelvic lymphocele formation. Lymphoceles represent a potential source of infection, and may compress iliac venous drainage, increasing the risk of lower extremity thrombosis. Lymphocele risk is likely related to the extent of dissection, as lymphoceles requiring drainage occurred at a higher rate in the extended PLND arm of the LEA trial (72). Other overall complications appear similar across increasing extent of dissection (78). Nevertheless, several comparative series have noted an approximately extra 60 min of operative time for extended versus limited PLND for both open and robotic approaches (77-79). This factor may be considered when deciding the extent of PLND in a patient with significant medical comorbidities for whom additional time under anesthesia would be of potential concern.

Future developments

The variability of initial lymphatic spread demonstrated in classic anatomic mapping studies require the detection of tracers throughout the pelvis, rather than limited to a single group of nodes as in breast cancer (52). The use of radiotracer and fluorescent markers to guide sentinel node dissections for bladder cancer have not yet shown reproducible and reliable outcomes. The use of radiotracers has had mixed results. A small series by Rosenblatt *et al.* reported a detection rate of 92% using peritumoral injection with Technetium tracers (80). However, another series by Aljabery *et al.* used peritumoral Nanacoll injections and demonstrated a sensitivity of only 67% (81). Meanwhile, a study by Polom *et al.* included both technetium radiocolloid (RadCol) and indocyanine green (ICG) cystoscopic peritumoral injections in 47 patients prior to RC (82). Pre-operative SPECT/CT and intra-operative gamma ray detection probes were used to assess RadCol while the robotic near-infrared fluorescent (NIRF) camera system

was used to assess ICG. The ICG method was found to reveal more nodes than RadCol; nevertheless, only 17% of patients with ICG fluorescence were truly metastatic. Patel *et al.* also assessed the feasibility of ICG and observed that in patients with ICG nodal fluorescence there was only 47% specificity (83).

Of note, as systemic therapy options for bladder cancer continue to expand, the role and timing of RC with PLND will require continued study. For example, the novel checkpoint inhibitor agents theoretically require an appropriate local tumor microenvironment and/or lymphatic milieu to allow tumor antigen-specific priming of cytotoxic T cells, and as such may benefit from preservation of both primary tumor and pelvic lymph nodes (84). To this end, there are a number of clinical trials investigating the utility of neoadjuvant checkpoint inhibition prior to RC (85). Early reports of these trials show promising rates of complete pathologic response, although longer-term follow-up for survival outcomes will be needed (86).

Conclusions

PLND during RC affords accurate pathologic stage, provides information on prognosis, facilitates timely consideration of adjuvant therapy, and potentially may confer oncologic benefit. Admittedly, the current evidence is mixed regarding whether an increasing extent of PLND results in improved survival. While the majority of studies to date on this topic have a low-quality of evidence, forthcoming prospective clinical trial data will offer opportunities to inform future lymphadenectomy guidelines for bladder cancer.

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