The role of extended lymph node dissection in patients undergoing radical cystectomy

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ABSTRACT

Radical cystectomy (RC) with a pelvic lymph node dissection (LND) is the gold standard for the treatment of muscle invasive bladder cancer (MIBC) as well as for some high-risk non-muscle invasive bladder cancers. The therapeutic advantage of LND, in terms of cancer-specific survival (CSS), still divides opinion and, certainly, the question of the extent of LND at the time of cystectomy is still debated. In this article, we have reviewed the evidence supporting the practice of extending LND in order to help clinicians determine what is appropriate in their practice. There still remains a lack of prospective randomized studies addressing whether extended LND provides a survival benefit in patients undergoing RC for BC. However, there is large body of evidence that suggests there is a positive impact on the oncological outcomes in these patients without an apparent cost of unacceptable adverse events.

Keywords: Bladder cancer; lymph node dissection; radical cystectomy.

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Introduction

Radical cystectomy (RC) with a pelvic lymph node dissection (LND) is the gold standard of treatment for muscle invasive bladder cancer (MIBC) as well as for some high-risk non-muscle invasive bladder cancers. Lymph node (LN) involvement, along with worsening pathological tumor stage and grade, is a reliable predictor for poor cancer-specific survival. This was demonstrated with an autopsy study assessing LN involvement and pattern of spread.[1] The authors identified that 47% of those with LN metastases also had concomitant distant metastases. Furthermore, around 25% of patients are demonstrated to have LNs with metastatic deposits at the time of RC.[2] As such, the benefit of determining the pathological LN status for accurate staging and prognosis is clear.

The therapeutic advantage of LND, in terms of cancer-specific survival (CSS), still divides opinion. There are multiple publications to support superior oncological outcomes in patients undergoing any degree of pelvic lymphadenectomy compared with those who have had none at all.[3-10] The therapeutic advantage in LN-positive patients was first demonstrated by Skinner in 1982.[11] He reported on the long-term survival of patients with node metastases undergoing lymphadenectomy, as part of their radical cystectomy. These patients did not receive systemic therapy and their 5-year overall survival was 36%; clearly better than the historically dismal outcomes in node-positive patients who did not receive an LND. This long-term survival has been confirmed and reproduced in contemporary studies.[10]

However, the question of the extent of LND that is optimal for cancer control is still debated. The European Association of Urologists' (EAU) guidelines comment on the different extents of LND described and state that no firm conclusions can be drawn based on the evidence available.[12] There is a distinct lack of prospective trials addressing this issue, thus, making interpretation of best practice challenging. It is worth noting that a positive lymph node from the common iliac region is required for a patient to be classified as having N3 disease when using the TNM staging system.[13]

There is now an increasing body of evidence to support the practice of extending LND. In this

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article, we will continue to review this evidence to help clinicians determine what is appropriate in their practice.

Pelvic lymph node dissection anatomical boundaries

Reviewing the current literature comparing differing types of LND is made difficult by the lack of standardised nomenclature for LND. There is extreme heterogeneity in definitions of an LND's anatomical boundaries, thus, reducing the reliability and generalizability of outcomes across studies. For this review, we will be using the definitions of extent of LND as per the EAU working group unless stated differently (Figure 1).[12]

As well as defining the anatomical boundaries of an LND, it is also imperative to perform a thorough and meticulous dissection. For this reason, some authors have preferred to use the pathological lymph-node count as a surrogate marker for the quality of dissection. Shariat et al.[14] proposed, using a beta-binomial probability model, that in order to accurately stage patients, 6 nodes were needed in Ta/Tis, 9 were required for T1 disease and 25 for T2 disease. This was associated with a predicted overall 90% accuracy rate for staging. It is logical to extrapolate from this that the more extended the LND, the more LNs that will be removed. There is certainly evidence to support this.[10,15] However, it should be highlighted that this study was looking specifically at the effect on LN count in the context of staging and did not set out to assess the potential therapeutic effect of LN count. This approach is limited by confounding factors, such as the natural numbers of lymph nodes differing between patients, inter-surgeon heterogeneity, and also the techniques, for lymph node sampling and counting used by different pathologists. Stein et al.[16] 2007 study evaluated the difference in count when LN samples were sent in packets vs en bloc. They concluded that LN count increased significantly when samples were sent in packets ($p<0.001$). Studies have shown that there is great heterogeneity between LN yields, even when comparing equivalent dissection templates. Davies et al. analysed patients post-mortem and identified discrepancies in LN count.[17] They found a mean LN count of 18.3 from a standard dissection template with a range of 8-28; whereas, in super-extended LND, the average LN count was 28.5 but with a range of 10-53. European urology guidelines suggest that removal of at least 10 LNs is likely to be sufficient to give an accurate nodal status as well as to be beneficial to overall survival (OS).[12]

Main Points:

- There is clear evidence to support lymph node dissection at the time of radical cystectomy.
- Despite a lack of prospective randomized studies, there is a large body of evidence that suggests there is a positive impact on oncological outcomes in patients undergoing extended lymph node dissections compared with those that do not.
- There is a role for further research to identify subgroups that may benefit most from more extensive lymph node dissection.
- We await the outcome from the second of 2 RCTs evaluating the impact of different lymph node dissection templates on survival.

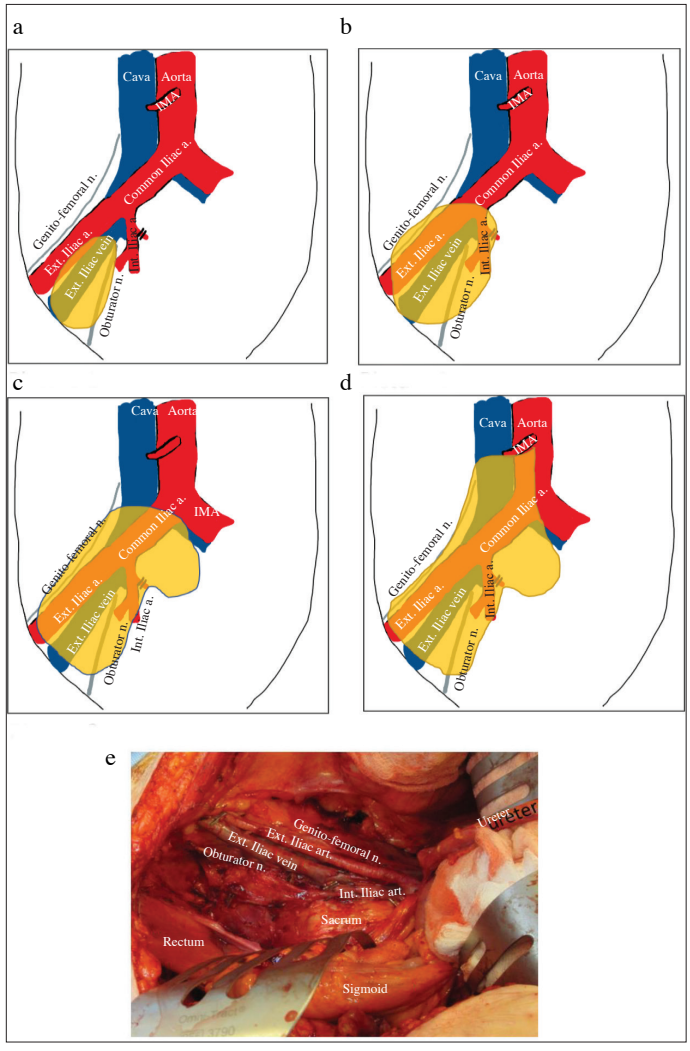

Figure 1. a-e. (a) Limited LND - Confined to the obturator fossa - external iliac vein superiorly, obturator nerve inferiorly and pelvic side wall laterally. (b) Standard LND – Extends up to the common iliac artery bifurcation as the superior extent. Includes obturator fossa distally, internal iliac artery inferiorly, and laterally the genitofemoral nerve. (c) Extended LND – As above, plus dissection up to the aortic bifurcation (commonly including presacral nodes). (d) Superextended LND – As above, with the inferior mesenteric artery (IMA) defining the superior border. (e) Example of extended LND with common iliac portion not visualised (*Figures – original drawings by author*)

Importantly, Dorin et al.[18] found 41% of patients with positive nodes had LNs outside the standard template boundary. It seems clear that individuals with known or suspected pathological nodes should undergo more extensive LND. Identifying these patients can be problematic. Pre-operative imaging is often unreliable. Sensitivity of CT to identify positive nodes is 52.6%.[19] Although there are evolving imaging modalities that improve on these sensitivity rates, namely Positron emission tomography-computed tomography (PET CT). A recent review assessed the utility of pre-operative PET CT in identifying pathological lymph nodes in patients undergoing RC.[20] The advantage of PET CT was its impressive sensitivity (92-100%) in ruling out pathological nodes that were identified as suspicious on CT, however, its ability to see positive nodes that were not seen on standard CT was less impressive.[20] Therefore, there may well be an important role for PET CT in individual cases. Frozen sections can be performed to determine node status intraoperatively. Frozen section has high sensitivity, specificity, and negative/positive predictive value and adds little morbidity to the procedure.[21] Conversely, they are time consuming to perform and as such one would need to debate the disadvantages (covered later) of simply performing an extended LND.

Oncological effect of the size of lymph node dissection: Retrospective studies

When discussing the therapeutic role of lymphadenectomy in patients undergoing radical cystectomy for bladder cancer, it must first be established if performing any form of LND is beneficial compared with none at all. Bruins et al.[10] systematically reviewed the literature looking at the impact of lymphadenectomy on oncological outcomes. Here, they found seven studies comparing LND with no LND at all.[3-9] All studies reported at least one benefit related to oncological outcome in patients who had undergone some degree of LND. Four of the seven studies identified a significant improvement in OS at 5 years where any form of LND had been carried out compared with none at all.[4-7] There were significant improvements seen in CSS in one of the remaining studies.[9] There is, therefore, convincing data that support a therapeutic benefit in patients receiving a lymphadenectomy at time of radical cystectomy for treatment of bladder cancer.

To address the question of whether the extent of LND effects outcome, there have been a number of studies that have compared different dissection templates with regard to recurrence and survival.[10] To maximize any potential difference in results, Holmer et al.[22] compared the two extremes of LND. They compared the outcomes of 170 patients who had radical cystectomy and LND. Sixty-nine patients had a limited LND and the remaining 101 patients underwent an extended LND. The median number of nodes removed were 8 and 37, respectively. In an adjusted multi-variant analysis, a benefit in disease-specific survival was seen in patients who underwent an extended LND. Furthermore, a subgroup analysis of patients with non-organ-confined disease, conferred a significantly longer time before recurrence in those who had had an extended LND. In another retrospective study of 469 patients, comparing limited LND with extended LND, Jensen et al.[23] failed to demonstrate any significant reduction in risk of recurrence in patients undergoing an extended LND. However, they too noted a benefit for node-negative patients with non-organ confined disease who received an extended LND. This is presumably due to micro-metastatic nodal disease that is missed by the standard pathological technique of simply halving the lymph node. For these patients, the 5-year overall survival was statistically improved from 62% to 76% (p=0.008). There was also improved prognosis in node-positive patients who underwent an extended LND compared with those who had had a limited dissection. Here, 5-year CSS was 29% vs 8%, respectively (p=0.002).[23]

These studies, although important, are now becoming historic as the majority of urological surgeons are convinced by the merits of LND and have moved away from a limited LND in favor of a standard LND as a minimum dissection template. The data comparing standard LND with extended/super-extended LND are, therefore, becoming more relevant. Dhar et al.[24] reviewed 658 patients who underwent RC for bladder cancer (for muscle invasive disease) between 1987 and 2000 across two separate sites. 336 consecutive patients underwent a standard LND, which included dissection up to the bifurcation of the common iliac vessels and 322 patients had an extended LND. In those undergoing a standard LND, 7% were identified as node positive, whereas 35% of patients in the extended LND group where found to have positive nodes. These groups were not randomized and, therefore, subject to selection bias; however, overall 5-year recurrence-free survival (RFS) was superior in the extended LND group regardless of T-stage or node status. The benefit appeared more apparent in higher T-stages, regardless of node status (5-yr RFS in pT3N0 = 23% in the standard LND group vs 57% in the extended LND group). A number of other studies have also demonstrated an oncological benefit to patients undergoing extended LND compared with those receiving a standard LND.[25-28] However, not all study outcomes have been consistent in these findings. Abd-El-Latif et al.[29,30] failed to demonstrate any improvement in post-cystectomy survival or RFS related to the extent of LND in both negative and positive lymph node patients across two separate studies.

There have been two systematic reviews to date, assessing LND dissection boundaries and their effect on survival outcomes.[10,15] Bruins et al.[10] conducted the more extensive of the two reviews, including 23 studies reporting on 19,793 patients, that compared anatomical extent of LND and its effect on oncological outcomes. Although the group concluded that the evidence

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base was not strong enough to make firm recommendations, they agreed there was fairly consistent reporting of the oncological benefit in extended LND groups. Bi et al.[15] analyzed 6 studies but still came to the same overall conclusion of benefit in extended LND groups. They also performed a subgroup analysis, which conferred a further advantage of extended LND in patients with T3/4 disease but not for patients with ≤pT2 disease. Both reviews state that analysis and conclusions were limited by the lack of high-level evidence amongst the studies. Despite the lack of randomized prospective studies eligible for analysis in these review articles, there still remains a large body of evidence that suggests the same superiority for extended LND over lesser dissections. They both also concluded that complication rates did not appear to be significantly affected by the extent of dissection.

Oncological effect of the size of lymph node dissection – Prospective randomized control trials

Until recently there has been a distinct lack of prospective studies. There have now been two, well designed trials. The first being the LEA (Eingeschränkte vs Ausgedehnte Lymphadenektomie - LEA) trial, which was published in 2018 and the second being the SWOG-S1011 trial (Clinicaltrials.gov identifier: NCT01224665) that has recruited but is still awaiting full follow-up prior to publication.[31] The LEA study was a phase III, prospectively randomized study comparing survival results in 401 patients undergoing standard LND (obturator and internal and external nodes) vs super-extended LND (standard + deep obturator, common iliac, presacral, precaval, inter-aortocaval, and para-aortic nodes up to IMA).[31] Primary endpoint of the study was RFS at 5 years, with secondary endpoints of CSS and OS. The trial was designed to show an absolute improvement of 15% in 5-year RFS; however, (super)extended LND failed to show superiority over non-extended LND (5-yr RFS 65% vs 59%; p=0.36). In retrospect, a 15% improvement in RFS may have been optimistic and, had they powered it for a 5% difference (as is accepted as beneficial with respect to overall survival for neo-adjuvant chemotherapy), they may have seen statistical significance. It should also be highlighted that patients who had received neo-adjuvant chemotherapy were not included in this trial, and approximately 15% of patients from each group received adjuvant chemotherapy. They also included patients with G3pT1 disease, which may have diluted any significant advantage seen for super-extended LND in those with MIBC. Previous studies have demonstrated a node-positive rate of 2-10% in patients with G3pT1 disease; therefore, inclusion of 14% of patients with this pathological staging may have significantly affected the results.[18,32-34] Interestingly, 56% of the total patients had ≤pT2 disease. A standard template LND will remove any positive nodes in these patients in over 95% of cases.[33] Another explanation as to why the primary endpoint was not reached was the high quality of their standard LND. The LN yield in both the standard and extended LND groups was exceptionally high (median 19 LNs vs 31 LNs). Higher LN yield, and certainly counts over 16, are associated with improved survival outcomes, and this may have affected the results in both groups.[32]

The SWOG-S1011 trial randomized 658 patients to standard vs extended LND. For this trial, photos of the dissection were collected to ensure quality of LND. Again, this trial was ambitiously powered to demonstrate a 10% improvement in 3-yr RFS with the extended LND compared with the standard LND. This trial has finished recruiting and the results are eagerly awaited although this author suspects that, due to the quality of the standard LND decreed for the trial, we will likely see a trend toward benefit but not one of statistical significance.

If we expect to see the largest benefit between the extremes of dissection (i.e., no LND vs extended LND), then it would be logical to presume that the benefit of a super-extended LND vs an extended LND is likely to be far more subtle, with numbers needed to demonstrate significance too large to be practical. However, there have been two multi-institutional studies, involving 1462 patients in total, comparing these two dissection templates.[35,36] As might be predicted, neither study was able to demonstrate a statistically significant difference in survival outcomes between the two groups.

Overall there is a significant body of evidence that appears to support the practice of extended LND over standard or limited LND in patients undergoing RC for BC. This evidence remains, primarily, based on retrospective comparative studies that, by design, are at risk of bias and confounding factors.

Differing LNDs and complication rates

In general, there does not appear to be a significant correlation between the extent of the LND and complication rates. The most common complication attributed to LND is the development of a lymphocele. Whilst Poulsen et al.[26] found very similar rates of lymphocele formation between standard and extended LND groups (1.5% vs 1.6%, respectively), Gschwend et al.[31] noted a significant increase in the rate requiring intervention in the extended LND group at 90 days. A number of other studies also found little difference in the complication rates between LND groups, however, it should be highlighted that the German group's study remains the only randomized prospective trial to date.[28,32,37,38] Perhaps, unsurprisingly, there is evidence to suggest that operating times are longer with super-extended LND compared with limited LND (median time: 330 vs 277 min; p<0.01).[38] Countering this, Jensen et al.[23] reported no significant difference in length of operation time between these same two cohorts. Brossner et al.[38] also found no significant difference in transfusion, lymphocele formation rate and in 30-day mortality and morbidity between super-

extended and limited LND groups. There remains a lack of long-term data in terms of adverse effects and complications comparing these groups. However, when personalizing care for a patient, it should be noted that patients with BC often have significant co-morbidities, posing a high anesthetic risk, and any additional time spent under anesthetic may increase morbidity. Although not statistically significant in most studies, the rates of patients with lymphoceles requiring intervention have been proven to be marginally higher in some studies.[31] One could argue that, given the recovery from RC and the overall prognosis of MIBC, any increase in risk of complication in this cohort of patients is unacceptable unless a proven survival advantage is apparent. Ideally, the extent of the LND should be tailored to provide maximal oncological control and optimal staging, while preventing peri-operative complications and long-term morbidity.

In conclusion, there still remains a lack of prospective randomized studies addressing whether extended LND provides a survival benefit in patients undergoing RC for BC. However, there is large body of evidence that suggests there is a positive impact on the oncological outcomes in these patients without an apparent cost of unacceptable adverse events. We await the outcome from SWOG (S1011), the second of 2 RCTs evaluating the impact of different LND templates on survival, which may take us a step further in determining the optimal extent of LND in patients undergoing RC for BC. There may be a role in individualizing extent of LND in patients based on pre-operative pathological stage and LN status. Dhar et al.[24] demonstrated an RFS advantage in patients with pT3/4 disease, regardless of node status, in those undergoing extended LND compared with limited LND. Holmer et al.[22] also found patients with non-organ-confined disease had a longer time before recurrence in receiving an extended LND. Future research identifying subgroups that benefit most from more extensive LND would be valid and would likely change clinical practice.

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