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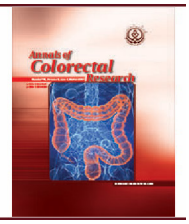

Lateral Pelvic Lymph Node Dissection for Low Locally Advanced Rectal Cancer: A Review

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Abstract

Lateral pelvic lymph node dissection (LPLND) for advanced low rectal cancer has generated much discussion in the literature in the last few years. Whilst it is still being debated as to whether it constitutes a locoregional disease amenable to surgery or whether it features distant metastases requiring neoadjuvant therapy, what is clear is that patients with enlarged LPLNs have higher rate of recurrence. In this review, we analyzed the current evidence and recommendations for LPLN dissection. In the case of advanced low rectal cancer (stage II-III) below the peritoneal reflection, the decision to perform LPLND depends on (1) size of the node on MRI (>5 mm) prior to neoadjuvant chemoradiotherapy and (2) non-responsive node after CRT (LPLN >5 mm before and after CRT). LPLN does prolong the operating time and cause greater blood loss, but is not associated with any greater morbidity. Preservation of the neurovascular structures, including the obturator nerves, hypogastric nerves, and the inferior vesical arteries, is essential. We also described the key steps in performing LPLND.

Keywords: Lateral pelvic lymph node, Low rectal cancer, Neoadjuvant therapy

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Introduction

History of Lateral Pelvic Lymph Node Dissection

The history of lateral pelvic lymph node dissection (LPLND) commenced with the discovery by Gerota in 1895 of the lateral and upward lymphatic flow from the rectum by injection of dye, which was followed by Poirier's description of the three lymphatics that travels along the lateral pelvic sidewall up to the common iliac bifurcation. In 1925, Villemin showed that these lateral pelvic lymphatics drain from the lower rectum. Soon after, in 1927, Senba from Japan found by injection of dye into fetal cadavers that these lateral pelvic lymphatics were around the internal iliac arteries and also inside the obturator space (1).

To understand the lymphatic drainage of the rectum, it is useful to use the three space model described by Takahashi (1). The pelvis is described as consisting of three concentric spaces (Figure 1).

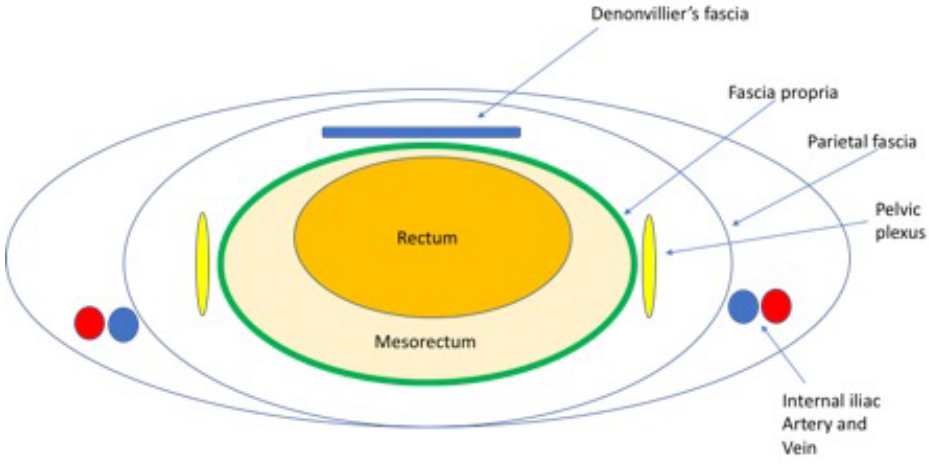

Figure 1: Three concentric circular model of the pelvis.

The inner space is the space surrounded by fascia propria, which is bound anteriorly by the Denonvillier's fascia in front of the rectum. Immediately lateral to this space is the pelvic plexus. This is the mesorectum, comprising the plane for the dissection in total mesorectal excision (TME).

The intermediate space is bounded by the parietal fascia. Immediately lateral to this space is the internal iliac arteries and its branches.

The outer space is the space outside the internal iliac arteries.

There are two lymphatic flows of the rectum. The first lymphatic flow follows the superior rectal artery to its origin, the inferior mesenteric artery (IMA). It lies within the inner space. Takahashi calls this as the 'upward lymphatic flow', comprising the target of high IMA ligation.

The second lymphatic flow arises mainly from the lower rectum below the peritoneal reflection. These lymphatics penetrate the intermediate and outer space through the lateral ligament and ascend along the internal iliac arteries. These are called the 'lateral lymphatics', and the lymph nodes (LNs) along the way are called lateral pelvic lymph nodes (LPLNs). They drain into the obturator, internal iliac, external iliac, and common iliac group of LNs (2).

The common iliac LN is located along the common iliac artery/vein, while the external iliac LN is located along the external iliac artery/vein. Obturator nodes lie lateral to the parietal pelvic fascia, around the obturator neurovascular bundle.

The internal iliac group includes the lateral sacral nodes (in proximity to the lateral sacral arteries), presacral nodes (anterior to the sacrum and posterior to the mesorectal fascia), anterior internal iliac nodes (located at the origin of the proximal branches of the anterior division of the internal iliac arteries), and hypogastric nodes (the most cephalic of the internal iliac nodes).

How Often Are Lateral Lymph Nodes Involved in Low Rectal Cancer

It is thought that removal of the LPLNs eliminates nodes that are suspiciously enlarged or even of normal size but with possible micrometastases, thus reducing the development of locoregional recurrences.

The incidence of LPLN involvement in low rectal cancer varies from 10 to 25% (3), with 7% of patients harboring occult micrometastases in LNs that are negative by conventional histopathology (4). Moreover, the presence of metastases in the LPLNs in the absence of positive nodes along the IMA has been documented in up to 15% of patients (5). Logically, it is found that the closer the low rectal tumor is to the anus, the higher the risk of lateral node involvement (above peritoneal reflection: 8.2; below peritoneal reflection: 14.9%), and, the higher the T-staging, the greater the risk of metastases to the LPLNs (T2: 7.1%, T3: 17.9%, T4: 31.6%) (5, 6).

Aim of Review

The aim of this review article is to provide a summary of the current evidence in the literature on: (1) Japanese vs. non-Japanese approaches; (2) whether neo-adjuvant chemoradiotherapy (CRT) and TME is adequate without LPLND; (3) the indications for LPLND in the group of patients who had neoadjuvant chemoradiotherapy and are to undergo TME; (4) the role of prophylactic LPLND of non-enlarged nodes; (5) survival impact of LPLND; and (6) the risks associated with the operation itself.

Results

Japanese Approach Versus the Non-Japanese Approach Neoadjuvant CRT or Not?

Since 1982, the TME dissection has been regarded as the gold standard for rectal cancer treatment (7). Whilst in the Western countries, neoadjuvant chemoradiotherapy for low rectal T3/4 cancer is the standard, in Japan, patients traditionally undergo TME with LPLND without neoadjuvant CRT. The reasoning for this difference in approach is from the Japanese perspective that lateral pelvic node metastases is a localized regional disease rather than

distant metastasis, and thus LPLND is performed along with TME. In a Japanese nationwide registry involving 5789 patients who underwent LPLND, there was no significant difference in overall and cancer-specific survival between (1) AJCC TNM stage N2a (4-6 LN met) versus internal LPLN (LN along internal iliac artery only), (2) AJCC TNM N2b (≥7 LN met) versus external LPLN (involving LN along other than internal iliac artery). More importantly, the overall survival and cancer-specific survival in the patients with external LPLN metastases were significantly better than in patients with distant metastases, with a five-year overall survival of 29 vs. 24% (P=0.024) and a cancer-specific survival of 34 vs. 27% (P=0.011) (8). Japanese studies have found that the therapeutic value of LPLND is greater than the therapeutic value of lymphadenectomy around the superior rectal artery and inferior mesenteric artery, with greater 'therapeutic value index for survival benefit' (5).

In comparison, in Western countries (and South Korea), neoadjuvant CRT and TME is standard for locally advanced rectal cancers. Thus, Japanese studies do not apply entirely to patients in Western countries (and South Korea) who undergo neoadjuvant CRT. In Western countries, metastases to LPLNs, apart from the internal iliac artery, has been regarded as distant metastases requiring adjuvant CRT (9). LPLND is not routine practice as it had been thought that neoadjuvant CRT and TME would be enough. What is clear from recent studies, however, is that neoadjuvant CRT and TME alone do not suffice, and LPLND is required in some situations, as will be explained below.

In a comparison of the Japanese and the Western/Korean approach, the literature suggests they are equally effective. A study compared the treatment approach in the Netherlands (data from Dutch TME trial) where 379 patients were given neoadjuvant radiotherapy and TME dissection (along with a further 376 patients who were given TME only) with the Japanese National Cancer Center Hospital's 324 patients who were given TME with LPLND. Five-year local recurrence was 6.9% in the Japanese group, and 5.8% in the Dutch TME+RT group, lacking a difference of statistical significance (95% comparative hazard ratio: 0.6-1.8). However, the criticism of this paper is that there were significant differences in the patient characteristics, including age, type of resection, as well as percent who had adjuvant chemotherapy or radiotherapy (10).

When Neoadjuvant CRT Is Given, is TME Enough?

A recent study published in January this year is a multinational retrospective cohort study based on a pooled analysis of patients from 7 countries, with 12 hospitals involved (11). The study looked at patients with cT3/T4, low rectal cancer, <8 cm from the anal verge, with no distant metastases. Patients underwent curative resections. There were 1216 patients recruited for the study, of which 703 patients (57.8%) had abnormal LNs detected on MRI scan prior to treatment, and 968 patients received neoadjuvant CRT. LPLND was performed in 142 patients (11.7%), and the median follow-up was 56.5 months. A total of 108 patients developed local recurrence, with 59 patients (54%) developing local recurrence in the lateral compartment. Five-year general local recurrence rate was 10%, while the five-year lateral compartment recurrence was 5.5%. The size of the LN on MRI has been shown to be an important predictor of local recurrence. Size of the lateral nodes in both short and long axis was significantly associated with five-year lateral local recurrence. The long axis of >7 mm was associated with significantly greater risk, and short axis of more than 5 mm was associated with significantly greater risk of lateral local recurrence. The long axis of >7 mm was associated with 12.6% five-year lateral local recurrence, and this increased to 13.9% when LN was >8 mm, to 17.8% at above 9 mm, and to 20.6% at above 10 mm. This occurred in the patient cohort, of which 80% (968 of 1216) received neoadjuvant CRT, with the rates appearing to be unacceptably high. The short axis of >5 mm was associated with 15.9% lateral local recurrence, >7 mm with 19.5% risk, and >10 mm with 35.6% five-year lateral local recurrence. On multivariate analysis, the location of the enlarged LN was important with internal iliac LNs being associated with more than double the risk to that of the obturator LN (HR 1.2 vs. 2.9, P=0.007). The size of pre-CRT MRI short axis of the LPLN had a significant impact on recurrence rates and survival. When the short-axis diameter of the LPLN was >7 mm, patients who underwent LPLND as compared to patient who didn't had significantly better outcomes, including lower five-year lateral local recurrence (5.7 vs. 19.5%, P=0.042), lower five-year local recurrence (5.7 vs. 25.6%, P=0.005), lower five-year distant recurrence (13.5 vs. 30.8%, P=0.028), and improved five-year cancer-specific survival (94.1 vs. 79.4%, P=0.032).

A 2014 retrospective Korean study by Kim et al. looked at 443 patients with stage 2-3 rectal cancer up to 15 cm from the anal verge (12). All patients had neoadjuvant CRT followed by TME dissection, and only 18 patients had LPLND. Median follow-up was 52 months. One hundred and seven patients developed a recurrence (23.2%), while locoregional recurrence occurred in 53 patients (11.9%), 12.2% had distant metastases, and 79% had both locoregional and distant metastases. Amongst the 53 pts who had a locoregional recurrence, lateral pelvic recurrence occurred in 20 patients (37.7%), central recurrence in 25 patients (47.2%) and both lateral/central in 8 patients (15.1%). The median time for lateral pelvic recurrence was 30 months. This result shows that CRT+TME is not enough, and patients are exposed to a high risk of locoregional recurrence. Interestingly, this paper found that the size of the LPLN was not a significant risk predictor of LPLN recurrence (<10 vs. >10 mm, P=0.085). However, this may be because they had set the criterion too high (>10 mm), and, as will be

discussed in the subsequent section, a size of >7 mm or even 5 mm is a more appropriate criterion for the at-risk LPLN. This paper found that the number of abnormal LPLNs (more than 2 vs. less than 2) was significantly associated with recurrence (RR=0.29, P=0.01).

Another Korean study from 2015 examined 900 patients with locally advanced (Stage II-III) low rectal cancer who had neoadjuvant CRT and TME (13). The study looked at recurrences in LPLNs and examined the risk factors. Locoregional recurrence occurred in 65 pts (7.2%), among which 42 pts (64.6%) had LPLN recurrence. The paper showed that the size of the LPLN is important. Compared to LNs with a short axis on MRI of <5 mm, when the LN was 5-10 mm or >10 mm, there was a higher risk of locoregional recurrence, lateral pelvic wall recurrence, and poorer overall survival. LPLN recurrence-free five-year survival was: 98.2% for <5 mm, 91.7% for 5-10 mm, and 40.1%. for >10 mm. Locoregional recurrence-free five-year survival was: <5 mm: 95.5%; 5-10 mm: 87.6%; and >10 mm: 40.1%. Relapse-free five-year survival was: <5 mm: 76.8%; 5-10 mm: 72.5% and >10 mm: 30.3%. Overall 5 year survival was: <5 mm: 86.3%, 5-10 mm: 83% and >10 mm: 57.5%. Therefore the study concluded that a short axis of >10 mm represents the high-risk group of locoregional recurrence and CRT/TME is not enough.

Another Korean study was conducted in 2008 on 366 patients with low locally advanced rectal cancer who underwent CRT and TME (14). It was found that 29 pts (7.9%) had a locoregional recurrence, of which 6 (20.7%) had a central pelvic recurrence and 24 (82.7%) had a lateral pelvic recurrence. The size of the LPLN and the ypN stage were important in predicting LPLN recurrence. Of the 250 ypN0 pts, lateral pelvic recurrence for each size of LPLN was: (1) <5 mm: 1.4%; (2) 5-10 mm: 2.9%; and (3) >10 mm: 50%. Of the 116 ypN+ pts, lateral pelvic recurrence developed in: (1) <5 mm: 4.3%; (2) 5-10 mm: 35.7%; and (3) >10 mm: 87.5%.

These three Korean studies, in which largely no LPLNDs were performed and had only CRT and TME, showed increased LPLN recurrence rates in patients.

A European study based on the United Kingdom and the Netherlands was published in 2017; it included 127 patients with locally advanced low rectal cancer (up to 8 cm from the anorectal junction) (15). The patients underwent CRT and TME. Notably, 14 pts (18.7%) developed local recurrence, nice of which were in the lateral compartment, giving rise to a five-year lateral local recurrence rate of 11.8%. Long axis measurement did not influence the lateral local recurrence rates (P=0.6); however, patients with a short axis LN >10 mm had a significantly higher lateral local recurrence rate (33.3 vs. 10.1% four-year rate, P=0.03) than in pts with a short-axis <10 mm. The paper concluded that CRT and TME dissection is not enough in patients with enlarged lymph nodes.

In both the European and Korean studies, more than half of the locoregional recurrences were limited to the lateral compartment, and even in patients with recurrent diseases, half did not have distant metastases. This suggested that the disease is a localized disease.

The question then arises, if CRT and TME are inadequate, then which subgroup of patients should undergo LPLND?

Indications for LPLND in Patients Receiving Neo-Adjuvant CRT and TME Dissection

Indication 1: Size of Lymph Node

The size of the lateral LN before treatment has been reported to be the main factor for predicting lateral pelvic recurrences and metastasis to lymph nodes.

As discussed above, Ogura (11) found that when the short-axis diameter of the LPLN was >7 mm, LPLND significantly reduced five-year lateral pelvic recurrence, lateral recurrence, and distant recurrence, and improved the five-year cancer-specific survival. A study by Kim concluded that LPLN short-axis >10 mm represents a high-risk group of locoregional recurrence, with much lower five-year relapse-free and overall survival (13). Similarly, the study by Kuster found the short axis of >10 mm resulted in a significantly greater lateral local recurrence (33.3 vs. 10.1%, P=0.03) (15).

A study by the Japanese Society for Cancer of the Colon and Rectum compared the 5 vs. 10 mm short-axis cut off on the preoperative MRI in terms of accuracy, sensitivity, and specificity (16). The study found that 5 mm was superior, with higher sensitivity (72.6 vs. 19.5%) and accuracy (63.7 vs. 57.7%), but lower specificity (54.7 vs. 96.4%).

An interesting finding of a study by the Japanese Society for Cancer of the Colon and Rectum was that the MRI based measurement of LPLN of more than 5 mm (short axis) was more predictive of LPLN metastases than the histopathological grade, lymphatic invasion, perirectal LN metastases, and distant metastases (17).

A smaller study in which all patients had CRT found LPLN (short axis) criteria of 7 mm was important in predicting five-year recurrence-free survival. When >7 mm, having LPLND improved survival more than when pts did not undergo LPLND (85.7 vs. 56.8%, P=0.0038) (18).

Indication 2: Responsiveness of LN Size to CRT

After the administration of neoadjuvant CRT, the change in the size of the LPLN has been debated as a factor to decide whether LPLND should be performed simultaneous to TME.

In a 2015 study, Akiyoshi had 77 patients with low locally advanced rectal cancer with LPLN >7 mm on the long axis undergo CRT. After the CRT, all patients underwent MRI, and LPLND was performed (19). Interestingly, in the comparison, short-axis diameter was used instead of the long axis (enough though long axis was used for criteria for LPLND). Before

CRT, LPLNs with a short-axis diameter of >8 mm had higher metastasis than LN <8 mm (75 vs. 20%, P<0.0001). After CRT, LPLNs with a short-axis diameter of >5 mm also had higher metastasis than in LN <5 mm (also 75 vs. 20%, P<0.0001). Whilst LPLN metastasis was associated with a worse three-year relapse-free survival than lack of LPLN metastasis, neither the MRI findings of >8 mm before CRT nor the response of LPLNs to CRT were associated with relapse-free survival. Also, amongst the patients who had responsive LPLNs (post-CRT MRI <5 mm), 10 patients were found to have metastasis in the LPLN. Moreover, the paper also showed a reduction in the volume of LPLNs after CRT by more than 60% (vs. <60%) was not associated with having less LPLN metastases. Therefore, the paper concludes that responsiveness of LPLNs after CRT is not as accurate as the pre-CRT MRI scan size measurements of the LPLNs.

A study by Kim et al. retrospectively analyzed 580 pts with advanced low rectal cancer who underwent CRT and then went on to have TME with LPLND (20). After the CRT, the patients were classified into three groups.

"No suspected LPLN" group: Pre-CRT <5 mm; Post-CRT<5 mm

"Responsive LPLN" group: Pre-CRT>5 mm, Post-CRT<5 mm

"Persistent LPLN" group: Pre-CRT>5 mm, Post-CRT>5 mm.

On univariate analysis, the "no suspected LPLN" group had better survival than "responsive LPLN" group, which, in turn, had better survival than the "persistent LPLN" group. The following results were reported in the various groups:

1) Five-year LPN recurrence-free survival: "no suspected LPLN" group: 98.6%; "responsive LPLN" group: 93.4%; and "persistent LPLN" group: 74.1%, P<0.001.

2) Five-year locoregional recurrence-free survival: "no suspected LPLN" group: 97%; "responsive LPLN" group: 89.4%; and "persistent LPLN" group: 71.7%, P<0.001.

3) Five-year relapse-free survival: "no suspected LPLN" group: 81.7%; "responsive LPLN" group: 76.6%; and "persistent LPLN" group: 56.9%, P<0.001.

4) Five-year overall survival: "no suspected LPLN" group: 89.1%; "responsive LPLN" group: 85.7%; and "persistent LPLN" group: 74.9%, P=0.006.

On multivariate analysis, the "no suspected LPLN" group had better LPLN recurrence-free survival and locoregional recurrence-free survival compared to the "responsive LPLN" and "persistent LPLN" groups. Furthermore, the "responsive LPLN" group had better LPN recurrence-free survival and locoregional recurrence-free survival compared with the "persistent LPLN" group.

A retrospective, multi-center (three Korean hospitals), cohort study analyzed 66 patients who had locally advanced low rectal cancer (below the peritoneal reflection) with radiologically suspected lateral LN (>5 mm) (21). All 66 patients were given CRT, before another MRI was performed. Then, the patients underwent TME with LPLND. Upon comparing the pre- and post-CRT MRIs, the patients were classified as "persistent" if the LPLN was still >5 mm, or "responsive" if the LPLN became less than 5 mm. Of the 66 patients, 36 were 'persistent', while 30 were 'responsive'. Of the 36 'persistent' patients, 23 had pathological evidence of metastasis (61%), whereas none of the 30 'responsive' patients had pathological evidence of metastasis (0%, P<0.001). The local recurrence (after a median follow-up of 39.3 months) was 20% in the 'responsive' group and 47.2% in the 'persistent' group (P=0.012). The 'responsive' group had significantly better five-year overall survival (77.1 vs. 44.6%, P=0.034) as well as five-year disease-free survival (72.5 vs. 33.7%, P=0.011) than the 'persistent' group. The authors, therefore, concluded that responsiveness of LPLNs to CRT should be part of the basis for performing LPLND.

Role of Removing LPLNs when Not Clinically Enlarged: the Question of Prophylactic LPLND

The randomized controlled trial by the Japanese Clinical Oncology Group (JCOG 0212), which happens to be the only randomized controlled trial involving LPLND, examined the role of prophylactic LPLND (22). Patients with low locally advanced rectal cancer (stage II-III, below the peritoneal fold), with no enlarged LPLNs (short axis <10 mm), and lack of CRT were recruited into the study. During the operation, after TME and following macroscopic confirmation of R0 resection and the confirmation that there was no abnormally enlarged lateral LN, pts were randomized to LPLND vs. no LPLND groups. A total of 701 pts were randomized intra-operatively, with 351 undergoing LPLND and 350 not having LPLND. Postoperatively, stage III patients were given adjuvant chemotherapy comprised of 5-Fluorouracil and leucovorin. However, patients were not given radiotherapy. The study showed no difference between the LPLND and no LPLND groups with regard to five-year relapse-free survival (73.4 vs. 73.3%), five-year overall survival (92.6 vs. 90.2%), and five-year local recurrence-free survival (87.7 vs. 82.4%). What is interesting is that despite having no effect on survival, the number of patients with local recurrence was significantly different between the no LPLND and LPLND groups, with the former having about double the local recurrence (13 vs. 7%, P=0.024). As this was a study to test the non-inferiority of not performing LPLND (i.e., TME only), the study concluded that "non-inferiority of TME alone to TME with LPLND was not confirmed in the intention to treat analysis", as the TME alone group (who did not get LPLND) had significantly

higher local recurrences. In other words, TME alone is inferior to TME with LPLND in reducing local recurrence, but LPLND has no impact on survival. Thus, at least in the Japanese population, LPLND can be used to reduce local recurrence in the absence of neoadjuvant CRT in patients with non-enlarged LPLNs.

A sublevel analysis of JCOG0212 published in 2019 examined the 351 patients who had LPLND for the risk factors for LPLN having tumor metastasis (23). Of the 351 patients, 328 patients were analyzed, of which 24 patients (7.3%) had pathologically confirmed tumor metastasis in the LPLN. On multivariate analysis, a tumor located below the peritoneal reflection (as compared to above the peritoneal reflection) was significantly associated with having LPLN metastasis (OR: 8.95, P=0.03). The size of the LPLN was also important, with LPLN >5 mm having four times the risk of harboring metastasis (P=0.003). Histological grade 3 was significantly associated with having LPLN metastasis (OR: 11.52, P=0.011).

The Risk Involved in Performing LPLND

Lateral pelvic lymph node dissection is technically challenging and associated with risks. Therefore, it is not routinely performed in Western countries. The perioperative risk and functional risk is examined here. Firstly, the perioperative risk must be differentiated between those who had and those who had not received neoadjuvant CRT.

A study by Lee et al. compared the perioperative risk in patients who underwent TME plus LPLND (37 patients) versus TME alone (15 patients) after neoadjuvant CRT (18). The group that underwent LPLND had significantly longer operating times (562 vs. 436 min, P=0.015), significantly greater blood loss (560 vs. 135 ml, P=0.05), but no significant difference in blood transfusion (40.5 vs. 33.3%, P=0.62) or postoperative complication rates (37.8 vs. 42.9%, P=0.74).

The JCOG0212 study compared the postoperative clinical outcomes of TME plus LPLND (351 patients) versus TME only (350 patients) among patients who did not undergo neoadjuvant CRT (24). The LPLND was performed by laparotomy. Patients who had LPLND had significantly longer operating times (360 vs. 254 min, P<0.0001) and greater blood loss (576 vs. 337 ml, P<0.0001). However, there was no significant difference in rates of grade 3/4 complications, anastomotic leaks, urine retention, postoperative infections, surgical site infection, pelvic abscess, and bowel obstructions.

The functional outcome after LPLND has been a major concern; LPLND involves danger to the nerves in the pelvic sidewall, with sexual and voiding function disturbances having been described. Previously, LPLND in Japan included an extended, systematic lymphadenectomy, which also involved dissection of the para-aortic and paracaval lymphatic tissues extending from the left renal vein to the aortic bifurcation along the adventitial layers of the IVC and aorta (25). This obviously resulted in very high rates of sexual impotence and urinary incontinence. A review by Kim et al. found that the extended, systematic lymphadenectomy resulted in greater urinary voiding failure (39.4 vs. 8.8%) and sexual impotence (76 vs. 37.5%) as compared to conventional LPLND (26). The JCOG0212 trial concluded that LPLND does not increase the risk of erectile or sexual dysfunction. However, the sexual dysfunction rates were very high (TME+LPLND: 79%, TME only: 68%, P=0.37) (27). During the operation, the identification and preservation of the neurovascular structures are essential, particularly the preservation of the hypogastric nerves, sacral plexus, and the obturator nerves. The vesical arteries, as branches of the internal iliac arteries, are preserved to maintain blood flow to the bladder. Sometimes, to ensure en bloc resection of the LPLN (and it also makes the operation easier), the vesical arteries are removed. A study found that the resection of vesical arteries increased the risk of urinary dysfunction. Bilateral inferior vesical artery removal increased the risk of urinary dysfunction to 77.8%, whilst preserving an inferior vesical artery resulted in urinary dysfunction in 12.7% (P<0.01). Thus, the author suggested preserving at least one inferior vesical artery (28).

Impact of Lateral Pelvic Lymph Node Dissection on Survival

The Impact on Survival of LPLND is Still under Debate

If no LPLND is performed, the survival depends on the preoperative short-axis size of the LPLN. A study by Kim et al. examined 900 patients with locally advanced low rectal tumor who did not have LPLND and showed that if the LPLN short axis was more than 10 mm, the survival fell dramatically (13). Of the 900 patients, 657 had neoadjuvant CRT and 243 had adjuvant CRT. Five-year lateral pelvic node recurrence survival was 98.2% if the short-axis diameter (SAD) of the LPLN was <5 mm, 91.7% if between 5-10 mm, and 40.1% if >10 mm (P<0.001 for both differences). The locoregional recurrence-free survival was 95.5% if the SAD was less than 5 mm, 87.6% if between 5-10 mmm, and 40.1% if more than 10 mm (P<0.001 for both differences). Five-year relapse-free survival was 76.8% if the SAD was less than 5 mm, 72.5% if between 5-10 mm, and 30.3% if more than 10 mm (P=0.223 and P<0.001, respectively). Five-year overall survival was 86.3% if the SAD was less than 5 mm, 83% if between 5-10 mm, and 57.5% if greater than 10 mm (P=0.219 and P<0.001, respectively).

In the JCOG0212, 351 patients who had TME and LPLND were compared against 350 patients who underwent isolated TME as a randomized controlled trial. None of these patients received neoadjuvant

CRT. There was no significant difference in five-year relapse-free survival (74.1 vs. 74.5%), overall survival (92.6 vs. 90.2%), and local recurrence-free survival (87.7 vs. 82.4%). However, the five-year local recurrence-free survival calculation included patients with recurrence or those who died. When only rates of local recurrence were calculated, they were significantly lower in the TME+LPLND group (7%; n=26) versus the isolated TME group (13%; n=44; P=0.024) (22). Regarding the interpretation of other survivals, one must take into consideration that one of the inclusion criteria for JCOG0212 was that that short-axis diameter of the LPLN must be less than 10 mm on preoperative MRI/CT scan. Thus, when one considers the results of Kim et al. (13), where the five-year survival dropped significantly with LPLNs larger than 10 mm in diameter, then the JCOG0212 must be considered as a randomized controlled trial comparing the five-year survival in the "low risk" group. In other words, the absence of significance may be from selectively looking at the group with LPLN <10 mm (false negative). If the inclusion criteria of JCOG0212 included patients with LPLN more than 10 mm, or better still if it examined only the high-risk group (LPLN >10 mm), the effect of TME +LPLND vs. isolated TME on the five-year survival would be significantly different.

Understandably, the size of the LPLN alone does not determine survival. In an enlarged LPLN, the presence of metastases obviously influences survival. Akiyoshi et al. examined patients with low rectal cancer who underwent neoadjuvant CRT and TME dissection. Of the initial 279 patients, 77 patients who had enlarged LPLNs (defined as long-axis >7 mm) underwent LPLND. Three-year survival was significantly worse if metastases were present in the enlarged lymph node as compared with no metastases (75.1 vs. 94.8%, P=0.0363). The short-axis diameter (greater than 8 mm) and reduction in the size of the short-axis diameter after neoadjuvant CRT did not impact the three-year survival (19). However, this study had a small cohort.

In the study by Ogura et al. (lateral node study symposium), the effect of LPLND was assessed depending on whether LPLN was visible on MRI scan and whether it measured more or less than 7 mm on the short axis. This study, however, must be interpreted with the view that 79.9% had preoperative radiotherapy treatment and that an R0 status was reached in 93.9% of patients. With regards to five-year lateral local recurrence, LPLND had no impact when performed if no LPLNs were visible or less than 7 mm in the short axis on MRI scan. However, if the short axis was more than 7 mm, the rate was significantly lower in the TME+LPLND group (5.7 vs. 19.5%, P=0.042). For five-year local recurrence, LPLND had no effect if the LPLN was not visible or was less than 7 mm on short-axis. However, if the short-axis was more than 7 mm, TME+LPLND offered a significantly lower five-year local recurrence rate (5.7 vs. 25.6%, P=0.005). Similarly, five-year distant recurrence rates were significantly lower if TME+LPLND was performed only if the short-axis was more than 7 mm (13.5 vs. 30.8%, P=0.028). The five-year cancer-specific survival was also significantly higher with TME+LPLND if the short axis was more than 7 mm (94.1 vs. 79.4%, P=0.032) (11).

The location of the LPLN metastases is also important in terms of survival. The study by Akiyoshi et al. looked at five-year survival in 8933 patients in a Japanese nationwide database of patients with low rectal cancer (8). It is interesting to note that the presence of LPLN metastases conferred worse overall survival and worse cancer-specific survival as compared to metastases within the 'mesorectum' (along the inferior mesenteric artery). The five-year overall survival was 55% if 'mesorectal' LN was positive compared with 45% if the internal iliac LPLN was positive. Similarly, five-year cancer-specific survival was lower if the internal LPLN was involved (49 vs. 61%). As discussed above, there are six regions of LPLNs (internal iliac, external iliac, common iliac, obturator, common iliac, aortic bifurcation, and median sacral). Involvement of LPLNs in a region other than the internal iliac LPLN was found to have worse prognosis than internal iliac LPLN metastases, with lower five-year overall survival (29 vs. 45%) and cancer-specific survival rates (34 vs. 49%) (8).

Conclusion

In the case of advanced low rectal cancer (stage II-III) below the peritoneal reflection, the decision to perform LPLND depends on (1) the size of the LPLN on MRI (>5 mm) prior to neoadjuvant CRT and (2) the non-responsiveness of the LPLN after CRT (LPLN >5 mm before and after CRT). With regard to the role of prophylactic LPLND, the only randomized controlled trial which set the criteria as >10 mm found that LPLND reduced locoregional recurrence but conferred no benefit in terms of survival. However, a sublevel analysis of the JCOG 0212 found that if the LPLN was >5 mm, there was a four-times greater risk of LPLN involvement. Therefore, in conclusion, the criterion of 5 mm appears to be the most appropriate. Although LPLND prolongs the operating time and gives rise to greater blood loss, it is not associated with greater morbidity. The neurovascular structures including the obturator nerves, hypogastric nerves, and the inferior vesical arteries must be identified and preserved.

Appendix: Performing the Lateral Pelvic Lymph Node Dissection

Performing LPLND is technically very demanding. Firstly, there are the complicated neurovascular structures in the deep narrow pelvic sidewall (Figure 2). Secondly, the sentinel LN of the low rectum lies in

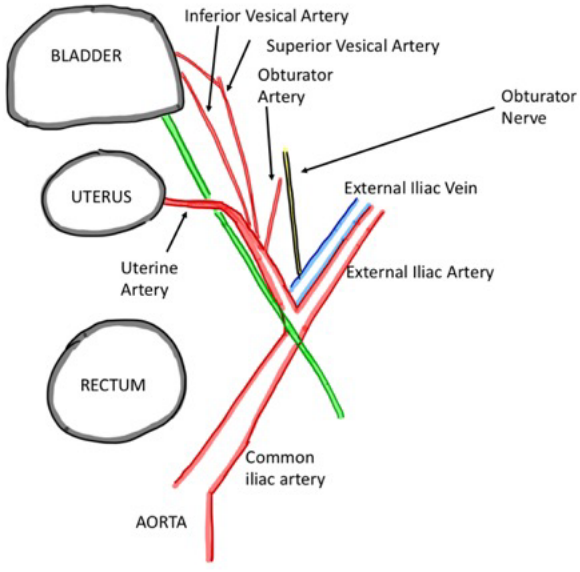

Figure 2: Anatomy of the lateral pelvic side wall

the deepest area of dissection, that is near Alcock's canal, adjacent to the internal pudendal artery.

The key to performing LPLND is understanding the pyramidal shape of the anatomic area of dissection (lateral, medial, inferior, and anterior borders), and breaking down the steps into several simple procedures by using specific anatomic landmarks.

The Japanese Society for Cancer of Colon and Rectum describes six areas of pelvic lymphatic drainage. The six groups are the common iliac, external iliac, internal iliac, obturator, median sacral, and aortic bifurcation groups. In LPLND, the commonly removed groups are the internal iliac and obturator groups of nodes.

First, it is important to understand the pyramidal planes of the dissection (Figure 3): laterally are the external iliac veins and the obturator internus; medially is the ureterohypogastric fascia containing the ureter and the hypogastric nerve; posteriorly are the internal iliac artery and its branches; and distally are the pelvic floor with Alcock's canal.

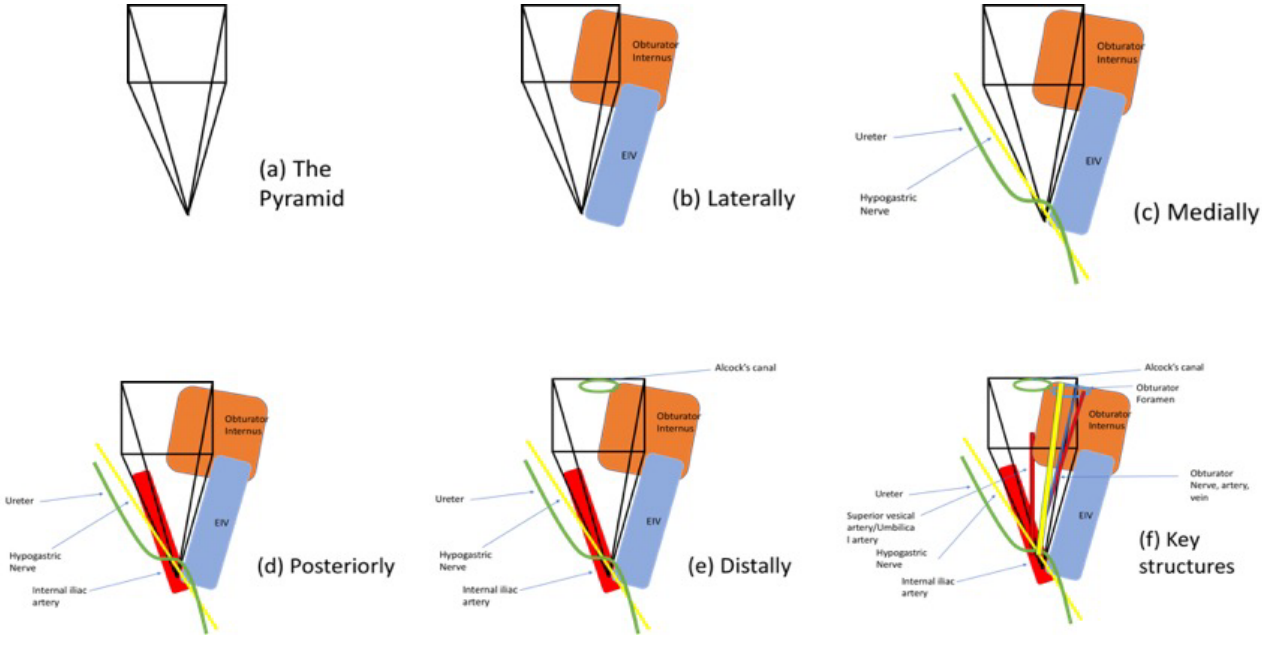

Figure 3: Pyramidal planes of the lateral pelvic side wall

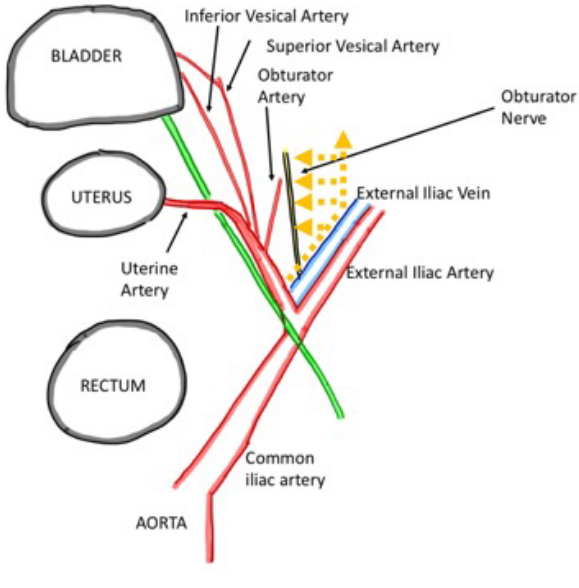

Figure 4: Lateral wall dissection

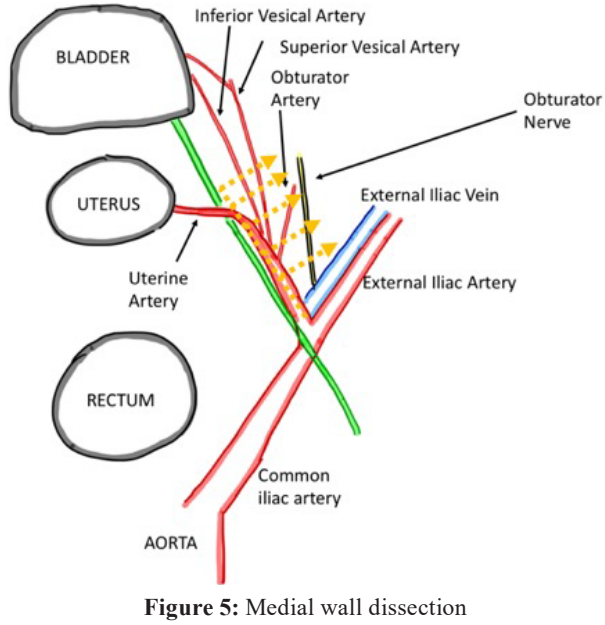

Figure 5: Medial wall dissection

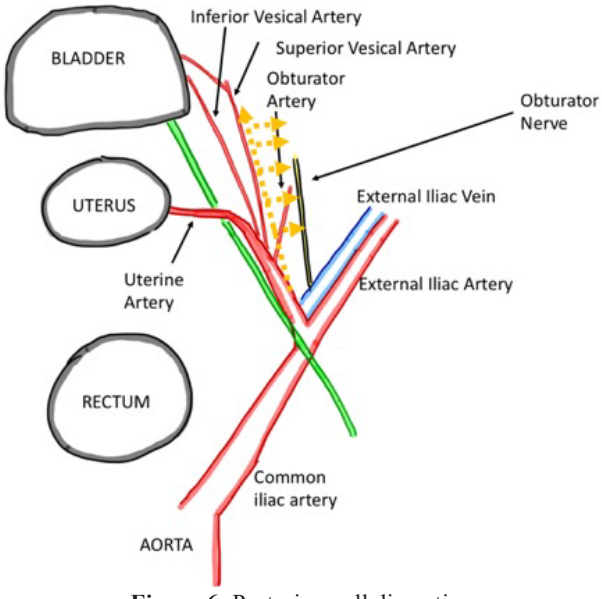

Figure 6: Posterior wall dissection

The key in lateral dissection is following the external iliac vein and identifying the obturator nerve and vessels. Start dissection from the inferior part of the external iliac vein. During dissection, inferiorly identify the obturator nerve and vessels. Skeletalize the obturator nerve and vessels and the surgeon will encounter the obturator internus and the obturator foramen (Figure 4).

The key to medial dissection is the ureter. Find the ureter and dissect the ureterohypogastric fascia, which contains the ureter and hypogastric nerve (Figure 5).

The key to posterior dissection is recognizing that the posterior border of the pyramid includes the branches of the internal iliac artery. Follow down from the CIA bifurcation to find the umbilical artery/superior vesical artery. Follow down the umbilical/superior vesical artery and dissect around it (Figure 6).

Distally, dissect down towards the levator ani and obturator internus. The distal extent of dissection is when the inferior vesical artery becomes visible. Dissect around Alcock's canal and remove nodes around the internal pudendal artery.

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