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Current perspectives on the management of lateral pelvic lymph nodes in rectal cancer

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Abstract

Significant controversies exist with regards to the optimal management of lateral pelvic lymph nodes metastases (mLLN) in patients with low rectal cancer. The differing views held by Japanese and Western clinicians on the management of mLLN have been well documented. However, the adequacy of pelvic lymph node dissection (PLND) or neoadjuvant chemoradiation (NACRT) alone in addition to total mesorectal excision (TME) have recently come into question, due to the relatively high incidence of lateral local recurrences following PLND and TME, or NACRT and TME alone. Recently, a more selective approach to PLND has been suggested, involving a combination of neoadjuvant therapy, followed by PLND only to patients in whom the oncological benefit is likely to outweigh the risk of potential adverse events. A number of studies have attempted to retrospectively identify certain nodal characteristics on preoperative imaging, such as nodal size, appearance, and size reduction following neoadjuvant therapy. However, no consensus has been reached regarding the optimal criteria for a selective approach to PLND, partly due to the heterogeneity and retrospective nature of most of these studies. This review aims to provide an overview of recent evidence with regards to the diagnostic challenges, considerations for, and outcomes of the current management strategies for mLLN in rectal cancer patients.

Key Words: Pelvic lymph node dissection; Lateral pelvic lymph nodes; Diagnostic criteria; Short axis diameter; Radiotherapy; Rectal cancer

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Core Tip: The optimal management strategy for lateral pelvic lymph node metastases (mLLN) requires a multimodal approach, involving chemoradiation and pelvic lymph node dissection (PLND), in order to achieve adequate local control in patients with locally advanced low rectal cancer. This selective approach requires careful selection of patients who would benefit most from PLND, using pre-treatment nodal short axis measurements as a surrogate for mLLN risk.

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INTRODUCTION

Total mesorectal excision (TME) and the circumferential resection margin have been widely accepted as crucial elements in the surgical treatment of rectal cancer. However, the management of pelvic side wall disease remains controversial, and historically divergent between countries in the West and those in the far East. While the former predominantly recommend the use of radiotherapy (with or without chemotherapy), pelvic lymph node dissection (PLND) is preferred in the latter. This has been reflected in guidelines published by their respective societies[1-3].

Results from the Dutch TME trial[4] (10-year local recurrence (LR) rates of 5% in the irradiated group *vs* 11% in the non-irradiated group, $P < 0.0001$) and the Swedish Rectal Cancer Trial[5] (LR rate of 9% in the irradiated group *vs* 26% in the non-irradiated group, $P < 0.001$) supported the use of neoadjuvant radiotherapy. These rates were comparable to patients who underwent PLND in some Japanese studies. In contrast, early results of PLND in the West[6,7] were discouraging due to high perioperative morbidity and limited reported oncological benefit[8], resulting in its slow uptake.

In Japan, however, lower local failure rates (Dukes B cases 8.4% *vs* 26.1%, $P < 0.01$, Dukes C cases 24.5% *vs* 44.3%, $P < 0.01$) and improved 5-year survival (Dukes B cases 83.2% *vs* 63.7%, $P < 0.05$; Dukes C cases 52.5% *vs* 30.8%, $P < 0.05$) were reported when extended lymphadenectomy was performed[9]. In addition, PLND was only associated with a slight prolongation of operating time (additional 60 min), a modest increase in operative blood loss (additional 150 mL), and no increase in operative mortality[9].

This article aims to elucidate the factors contributing to the contrasting recommendations in the management of lateral pelvic lymph nodes (LLN), and to provide a more contemporary approach to this conundrum. Literature search was performed electronically using PubMed (MEDLINE) and the *Reference Citation Analysis* (<https://www.referencecitation-analysis.com>) was applied. The search terms were as follows: pelvic lymph node dissection or PLND, lateral lymph node metastasis, and rectal cancer in combination with Boolean operators AND and OR. All studies in English were extracted for review by the authors.

THE SIGNIFICANCE OF THE LATERAL PELVIC LYMPH NODES

The difference in lymphatic drainage of the lower rectum from the upper rectum has been well documented, with Gerota [10] describing how tumours in the mid and lower rectum appear to exhibit lateral lymphatic drainage into the iliac nodes in addition to upward drainage through mesorectal nodes[11,12].

The risk of developing lateral lymph node metastases (mLLN) in rectal cancer has been shown to vary with several factors. Distance from the anal verge has been reported to be inversely related to the risk of mLLN, with rates of up to 33.3% observed in tumours 3.9cm from the anal verge[13]. Locally advanced pT3 and pT4 tumours tend to also be associated with higher rates of mLLN[13]. In particular, it has been demonstrated that mLLN were mostly located in the group of nodes along the internal iliac artery (IIA), being the first draining basin from the lateral rectal ligaments[14-16].

Traditional TNM staging for rectal cancer classifies malignant deposits in the external iliac and obturator nodes as distant metastases[17]. On the other hand, the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (3rd edition)[18], includes lymph nodes along the IIA, obturator, external iliac, common iliac (CIA), and median sacral arteries within its definition of regional lymph nodes, in the context of lower rectal cancers. This was based on survival data from the Japanese Nationwide Multi-Institutional Study on Lateral Pelvic Lymph Node Metastasis in Low Rectal Cancer[19]. Patients with metastasis to the above, so-called external lateral pelvic nodes, demonstrated more favourable overall survival and cancer-specific survival if they underwent PLND, than in patients with stage IV disease who underwent R0 resection (overall survival 29% *vs* 24%, $P = 0.0240$, cancer-specific survival 37% *vs* 27%, $P = 0.0117$). In addition, Ogura *et al*[20] determined that LLN enlargement did not appear to influence distant recurrence rate, suggesting that mLLN likely represent locoregional disease.

DIAGNOSTIC DILEMMAS – DIAGNOSTIC CRITERIA, MISDIAGNOSIS AND MISSED DIAGNOSES

However, epidemiological studies on mLLN suffer from the heterogeneous methods used in evaluating nodal disease, with incidence rates being reported to range between 8.8% and 34%[13,21]. Studies that do not involve PLND would base their diagnosis on imaging, whereas analyses involving patients who had undergone PLND would report based on pathological confirmation. Most studies that evaluate recurrences in the pelvic side wall do so by means of imaging parameters.

The main challenge in preoperative radiological assessment of LLN lies in not missing occult metastases within the nodes (missed diagnoses), while minimising cases of misdiagnoses. Most imaging modalities have been evaluated for their diagnostic accuracy in detecting suspicious lateral pelvic nodes. Ultrasonography was suggested as a potential imaging modality for this purpose, but failed to adequately examine obturator nodes[22], and has largely been surpassed by other imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). Even then, the sensitivity of CT and MRI in detecting mLLN varies greatly between studies[23,24]. More recently, the accuracy of F-fluorodeoxyglucose positron-emission tomography (¹⁸F-FDG PET) as a diagnostic adjunct in addition to CT or MRI has also been evaluated, although many guidelines do not include ¹⁸F-FDG PET scanning as part of the initial staging for rectal cancer patients[2,25]. A study by Ishihara *et al*[26] evaluated the accuracy of ¹⁸F-FDG PET scanning in identifying suspicious LLN post neoadjuvant chemotherapy, using a calculated maximum standard uptake value (SUV max) of 1.6, and reported an accuracy, sensitivity, and specificity of 85.7%, 76.5%, and 100% respectively. Metastatic LLN were found to have a significantly higher SUV max when compared to LLN without metastatic deposits (mean \pm standard deviation 2.2 ± 1.3 vs 1.2 ± 0.3 , $P < 0.01$). A similar study by Yukimoto *et al*[27] subsequently reported similar values (accuracy 92.3%, sensitivity 82.4%, specificity 93.4%) with a slightly lower SUVmax cutoff value of 1.5. These studies were mainly limited due to their small cohort size, and the utility of ¹⁸F-FDG PET scanning in rectal cancer in most units has been mainly limited to the evaluation of equivocal findings on contrast-enhanced CT, or in patients with a strong contraindication to intravenous contrast[3]. As a result, the European Society for Medical Oncology and the American Society of Colon and Rectal Surgeons still recommend the use of pelvic MRI for locoregional staging[2,25].

Apart from the type of imaging modality, there also exists a lack of consensus in what imaging features constitute a suspicious LLN, or mLLN. Table 1 summarises the various criteria used. Most studies retrospectively identify short (SAD), or long axis diameter (LAD) measurements and nodal features that correlate with pathological nodal metastases and/or oncological outcome. The multi-national Society of Abdominal Radiology – Rectal & Anal Cancer Disease-Focused Panel recently published a consensus statement[28] to promote consistent terminology and reporting standards amongst abdominal radiologists. The consensus statement recommended internal iliac and obturator nodes with SAD > 7 mm be reported as suspicious[28]. The MERCURY[29] study reviewed the preoperative MRI images of patients with biopsy-proven rectal adenocarcinoma within 15cm from the anal verge who underwent TME without PLND. The nodes were considered suspicious based on the presence of mixed signal intensity and/or an irregular nodal capsule border.

Further contributing to the heterogeneity is the inconsistent use of pre- or post-neoadjuvant imaging, or a combination of both sets of imaging (reflecting the response to neoadjuvant treatment). Akiyoshi *et al*[30] showed that the incidence of occult mLLN was as high as 20% even in patients with a post-neoadjuvant nodal size of 5 mm or less, supporting the recommendation of basing further treatment selection on pre-neoadjuvant imaging.

With regards to post-neoadjuvant nodal size, Cribb *et al*[31] found that a SAD of 5 mm on post-treatment MRI was associated with a worse 3-year local recurrence-free survival [hazard ratio (HR) 8.35, $P = 0.001$]. Malakorn *et al*[32] concluded that a post-neoadjuvant nodal size of 5 mm was 100% sensitive for identifying patients with mLLN and as such recommend using a post-neoadjuvant LLN size cutoff of 5 mm for PLND. The high reported sensitivity of a post-treatment nodal SAD of 5 mm is promising and has been recommended as suitable criteria for PLND[32,33]. In addition, the Lateral Node Study Consortium demonstrated that PLND can be safely omitted in patients with LLN measuring 4mm or less on restaging MRI due to the negligible risk of lateral local recurrence at 3 years in this subgroup of patients[14].

Akiyoshi *et al*[30] analysed patients with cT3/4 rectal cancers who underwent either bilateral (15.6%) or unilateral (84.4%) PLND, based on a nodal LAD cutoff of 7 mm on pre-neoadjuvant CT or MRI. Pathological mLLN were found in 40.3% of patients, and persistent LLN on restaging was associated with a higher rate of metastatic deposits when compared with LLN that responded to neoadjuvant chemoradiotherapy (CRT) (75% vs 20%, $P < 0.0001$)[30].

In publications reporting pathological results, incidence rates can also be confounded by potential missed diagnoses. The identification of micrometastatic disease or isolated tumour cells may sometimes pose a diagnostic challenge. Miyake *et al*[34] compared the sensitivity of one-step nucleic acid amplification assay results to conventional histological diagnosis, and identified a number of additional histologically-negative nodes with metastatic disease. Limitations in commonly utilised histological processing methods may have resulted in a small proportion of missed diagnoses of mLLN, with failure to pathologically upstage such patients resulting in adverse prognostic implications.

THE ADEQUACY OF PLND OR/AND CHEMORADIATION

While the efficacy of neoadjuvant CRT in reducing LR rates have been well documented[4,5], lateral pelvic recurrences have nonetheless been reported in cases where PLND was omitted after CRT[35]. Kim *et al*[36] reported a 64.6% lateral local recurrence (LLR) rate, out of a 7.2% LR rate following pre or post-operative chemoradiotherapy, after a median follow-up period of 65 mo. Kusters *et al*[37] similarly reported a 64.3% LLR rate and 18.7% LR rate. Both studies concluded that LLN measuring 10 mm were associated with an increased risk of recurrence and poorer overall survival, and that CRT alone in these patients did not confer adequate local control.

Table 1 Summary of diagnostic criteria for suspicious lateral pelvic lymph nodes

Study	Imaging modality	Nodal size	Nodal features
Schaap <i>et al</i> [53], 2021	MRI	Pre-treatment: SAD 7 mm	-
Amano <i>et al</i> [23], 2020	MRI; CT; PET-CT	(MRI or CT) SAD > 6 mm; (PET/CT) increased FDG uptake	-
Kim <i>et al</i> [54], 2020	MRI	Pre-treatment: SAD 7 mm; Post-treatment: SAD 4 mm	-
Lee <i>et al</i> [55], 2019	CT or MRI	Pre-treatment: SAD 8 mm	-
Sapci <i>et al</i> [56], 2019	MRI	Size > 5 mm	And either heterogeneity or border irregularity
Schaap <i>et al</i> [57], 2018	MRI	SAD 10 mm	-
Kim <i>et al</i> [58], 2018	MRI	Pre-treatment: SAD 5 mm	Signal intensity homo/heterogenous; Margins irregular or well defined; DWI signal intensity high or low; Size reduction rate
Akiyoshi <i>et al</i> [30], 2015	MRI	Pre-treatment: SAD 8 mm	-
Kobayashi <i>et al</i> [59], 2015	CT	LAD > 9 mm; SAD > 6 mm	-
Ogawa <i>et al</i> [60], 2015	MRI	SAD 10 mm or 5 mm (institution-dependent)	Enlarged LPLN on palpation; Enlarged perirectal node or LPLN 5 mm
Ogawa <i>et al</i> [61], 2014	MRI	LAD 5 mm; LAD < 5 mm	-
Shihab <i>et al</i> [29], 2011	MRI	No size criteria	Mixed signal intensity or irregular nodal capsule border
Matsuoka <i>et al</i> [62], 2007	MRI	LAD 10 mm; SAD 5 mm	Ovoid shape; heterogeneity

CT: Computed tomography; MRI: Magnetic resonance imaging; LAD: Long axis diameter; SAD: Short axis diameter; LPLN: Lateral pelvic lymph node.

On the other hand, the Japanese JCOG0212[38-40] randomised controlled trial illustrated the impact of bilateral prophylactic PLND alone, without the use of CRT, even though adjuvant chemotherapy was prescribed to pathological stage III patients. Only patients without clinically suspicious LLN nodes (SAD 10 mm on CT/MRI) were enrolled. The study reported that the addition of PLND resulted in a statistically significant reduction in LR rates (7.4% *vs* 12.6%, $P = 0.024$), and a higher local recurrence-free survival of 85.3%, compared to 80.3% with TME alone. The authors therefore concluded that the trial failed to demonstrate the noninferiority of TME alone, even though the significant reduction in LR may have resulted from the SAD cutoff of 10mm being insufficiently sensitive in predicting for mLLN. Nonetheless, the 7% incidence of occult mLLN in this trial suggests that a significant proportion of patients were subjected to the morbidity of PLND without deriving any oncological benefit.

Other studies evaluated the impact of combining the two treatment modalities. Kim *et al*[35] retrospectively analysed 366 patients with cT3/4 tumours within 8 cm from the anal verge who received CRT prior to TME without PLND. They reported a LR rate of 7.9% after a median follow-up duration of 40.1 mo, with 82.7% of these being LLR. Conversely, the addition of PLND to TME significantly reduced LR rates despite prior CRT (CRT+TME 19.5% *vs* CRT+TME+PLND 5.7%, $P = 0.042$)[20].

A three-armed multinational study by Kusters *et al*[41] compared patients with rectal cancer from the Netherlands and Japan who underwent either: (1) TME alone; (2) TME with (neo)adjuvant radiation; or (3) TME with PLND. Similar overall LR rates were reported between groups (2) and (3) (RT+TME 5.8% *vs* 6.9% PLND+TME, HR 1.0 (0.6-1.8). Only group (1) had a higher 5-year LR rate of 12.1%.

Recently, a multicentre retrospective study by Ogura *et al*[14] found that nodes along the internal iliac artery were less responsive to chemoradiation, and concluded that IIA nodes measuring 7 mm or more on pre-treatment MRI were predictors of lateral local recurrence. The study reported 5-year LLR rates of 52.3% following neoadjuvant chemoradiotherapy and TME surgery but without PLND[14]. When PLND was performed, the 5-year LLR risk was significantly reduced to 8.7% ($P = 0.007$)[14].

SELECTIVE PLND POST NEOADJUVANT RADIOTHERAPY

The optimal management of mLLN appears to therefore be shifting towards a selective multimodal approach, with selective PLND post neoadjuvant therapy appearing to offer higher rates of local control in several studies. Numerous variables have been proposed as potential indications for PLND due to their reported sensitivities in identifying occult mLLN, and their prognostic implications. In addition to the aforementioned studies, Akiyoshi *et al*[42] reviewed patients with stage II-III low rectal cancer who underwent preoperative CRT prior to surgery. PLND was performed in patients with suspicious LLN on pre-neoadjuvant CT or MRI, using SAD criteria of ≥ 7 mm[42]. Patients with clinically enlarged LLN underwent PLND irrespective of findings on post-treatment restaging[42]. The study observed that no LLR occurred in patients who underwent PLND, while 3.4% of patients who only underwent TME post chemoradiation developed LLR [42]. A similar study by Ishihara *et al*[43] reported similar findings. PLND was again performed based on the presence of suspicious pre-neoadjuvant nodes, irrespective of their response to neoadjuvant treatment[43]. The study reported LLR rates of 0% and 0.9% in patients who underwent TME with PLND and TME only respectively[43], suggesting that the selective addition of PLND is key in achieving local control in the lateral pelvis. Therefore, suspicious internal iliac or obturator nodes with pre-treatment SAD of ≥ 7 mm, or the presence of nodes displaying heterogeneity and/or irregular borders, should form indications for PLND.

TECHNICAL CHALLENGES OF PLND

In the treatment of rectal cancer, PLND typically involves removal of nodes in the internal iliac and obturator compartments[44]. The JCOG0212 trial concluded that the addition of PLND was associated with a significantly longer operative time (median 360 min *vs* 254 min, $P < 0.0001$) when compared to TME alone, and was associated with more intraoperative blood loss (576 mL *vs* 337 mL, $P < 0.0001$)[45]. No statistically significant differences were reported with regards to the incidence of anastomotic leakage ($P = 0.46$), urinary retention ($P = 0.18$), wound infection ($P = 0.81$), pelvic abscess ($P = 0.29$), or bowel obstruction ($P = 1.00$)[45]. A meta-analysis of extended lymphadenectomy *vs* conventional surgery for rectal cancer found similar results, with no significant differences in perioperative mortality ($P = 0.63$) or morbidity ($P = 0.13$)[46].

In a bid to promote the safe implementation of PLND, Ngu *et al*[47] conceptualised the use of origami to convert the pelvic side wall from a 2-dimensional region into a 3-dimensional compartment made up of two triangular pyramids. The authors sought to simplify PLND into a procedure involving three planes, three boundaries, and three steps. The three planes consisted of: (1) The ureterohypogastric nerve fascia (UHNF); (2) the vesicohypogastric fascia; and (3) the external iliac muscular plane. Following medialisation of the UHNF, the proximal boundary is marked by two key landmarks: superficially where the ureter crosses the CIA and, at a deeper plane, the bifurcation of the common iliac vein, where the obturator nerve enters the pelvic sidewall compartment. The distal boundary is delineated superficially by the vas deferens or round ligament, and, at a deeper level, the obturator foramen. The third (deep) boundary is marked by the terminal branches of the internal iliac vessels. The three steps of PLND involve: (1) The separation of these three planes, (2) followed by the delineation of the three boundaries, and (3) finally the dissection of the internal iliac vessels, with en bloc removal of the lympho-fatty tissue.

Tang *et al*[48] compared the short-term outcomes of laparoscopic PLND against open PLND, and concluded that laparoscopic PLND was associated with a shorter operative time (255 min *vs* 300 min, $P = 0.001$), less intraoperative blood loss (50 mL *vs* 300 mL, $P < 0.001$), lower incidence of postoperative complications (32% *vs* 15%, $P = 0.005$), shorter postoperative hospital stay (8 *vs* 14 d, $P < 0.001$), and excision of more lateral pelvic nodes (9 *vs* 7 nodes, $P = 0.025$) when compared to open PLND. Oncological outcomes were similar, with no differences reported in 3-year overall survival ($P = 0.581$) and disease-free survival ($P = 0.745$) rates[48]. Aside from the aforementioned postoperative complications, this study also reported other surgical complications such as chylous ascites and lower limb neuropathy, as well as systemic complications such as renal failure, pneumonia, and arrhythmias[48].

Utilization of the robotic platform in PLND has recently been shown to result in lower blood loss (25 mL *vs* 637 mL, $P < 0.0001$) and less postoperative complications including wound infection, anastomotic leakage, urinary retention, and small bowel obstruction when compared to open PLND, but operative times were longer (455 min *vs* 410 min, $P < 0.007$) [49]. Robotic PLND was also associated with superior 5-year local relapse-free survival rates compared to open PLND (98.6% *vs* 90.9%, $P = 0.029$), with similar overall survival (robotic 95.4% *vs* open 87.8%, $P = 0.106$) and relapse-free survival rates (robotic 79.1% *vs* open 69.9%, $P = 0.157$)[50]. Although PLND is a technically demanding procedure with significant risk of associated morbidity, robotic or laparoscopic assistance may be useful adjuncts, associated with lower postoperative morbidity rates when performed by experienced surgeons.

Although not traditionally a recordable perioperative morbidity, the potential of missed nodes during PLND may result in poorer oncological outcomes. A novel strategy to potentially mitigate the risk of intraoperatively missed nodes during PLND is the utilisation of indocyanine green (ICG) during laparoscopic PLND[51,52]. Ohya *et al*[52] conducted a retrospective study of patients who underwent PLND for tumours cT3 and above with clinically suspicious lateral pelvic nodes on pre-op imaging. The study demonstrated an increased lymph node yield (ICG 14 *vs* no ICG 9, $P < 0.001$), without a substantial difference in post-operative complications ($P = 0.57$), aside from a longer operative time (ICG 426 min *vs* no-ICG 369 min, $P < 0.001$). ICG use was also associated with a significant reduction in intraoperative blood loss (13 mL *vs* 100 mL, $P = 0.001$). The authors recently published their long-term follow-up data, and the higher lymph node yield with ICG translated into a reduction in 3-year cumulative LR rates (ICG 0% *vs* no-ICG 9.3%, $P = 0.048$), although no statistically significant difference was reported in relapse-free survival and overall survival rates[51].

CONCLUSION

The difficulty in reaching a global consensus with regards to the optimal management of LLN in rectal cancer stems from the heterogeneity of available data, mainly consisting of retrospective cohort studies using various parameters to define what constitutes a clinically suspicious LLN, or mLLN. Contemporary data appears to suggest that the optimal strategy may lie somewhere between the traditional views held by Western countries and the far East. Several conclusions can be drawn from the existing data: Firstly, pelvic lymph node dissection in rectal cancer has to be offered selectively. The JCOG0212[38-40] study demonstrated that in the absence of radiologically suspicious nodes, the majority of patients would not benefit from PLND, hence justifying a more selective, non-prophylactic approach to PLND. Secondly, the optimal management strategy for mLLN in patients with rectal cancer requires a multimodal approach, involving a combination of neoadjuvant chemoradiation and selective PLND. Thirdly, until more robust data is made available, a prudent choice would be to use a SAD of 7 mm, or the presence of suspicious features, as criteria for selective PLND. This assessment should be made based on pre-neoadjuvant MRI.

FOOTNOTES

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