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Lateral Pelvic Lymph Node Dissection in Rectal Cancers. Does it have a Place in Era of Neoadjuvant Chemoradiation?

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Abstract

Globally Cancer of colorectal origin is the 4th most common. Prognosis of colorectal cancers has improved dramatically in last few decades with the advent of neoadjuvant chemoradiation and total mesorectal excision. However locoregional recurrence still remains a challenge and there is an ongoing debate regarding the role of Lateral Pelvic Lymph Node Dissection (LPLND) in rectal cancer surgery to lessen these recurrences. LPLND is a part of standard surgery for rectal cancers in Japan with stage T3 or more or with involved mesorectal nodes but has not been adopted by surgeons in the rest of the world. This difference in treatment approach is due to difference in ideology towards Lateral Pelvic Nodes (LPN) with Japanese considering LPN as regional disease whereas in the west LPN is considered as systemic disease. The aim of this article is to review the current evidence on LPLND and to better define its role especially post-neoadjuvant chemoradiation.

Introduction

Cancer of colorectal origin is the 4th most common with incidence of 6.1%. They account for 9.2% of all cancer related deaths making them the 2nd most common cause of cancer related death [1]. With the turn of the century the prognosis for rectal cancers have improved with a 5-year overall survival in excess of 60% Neoadjuvant Chemo Radiotherapy (CRT) and Total Mesorectal Excision (TME) have become the gold standard treatment for all locally advanced rectal malignancies [2].

However locoregional recurrence still remain a challenge and there is an ongoing debate regarding the role of Lateral Pelvic Lymph Node Dissection (LPLND) in rectal cancer surgery to lessen this recurrences. LPLND is a part of standard surgery for rectal cancers in Japan with stage T3 or more or with involved mesorectal nodes but has not been adopted by surgeons in the rest of the world. This difference in treatment approach is due to difference in ideology towards Lateral Pelvic Nodes (LPN) with Japanese considering LPN as regional disease whereas in the west LPN is considered as systemic disease. The aim of this article is to review the current evidence on LPLND and to better define its role especially post-neoadjuvant chemoradiation.

Surgical Anatomy

Lymph nodes draining the rectum below the peritoneal reflection (Rb) are found to follow two major pathways: (a) Along the superior rectal artery and the inferior mesenteric artery into the para-aortic nodes (b) Along the middle and inferior rectal artery into the obturator, internal iliac, external iliac and common iliac nodes [3]. The former group is dissected as a part of standard TME worldwide, whereas it is the latter group that forms the area of controversy.

Among these lateral regions, the internal pudendal artery region, the internal iliac artery and obturator region have the highest rate of nodal involvement, which is called as "Vulnerable field" in the lower rectal cancers (Figure 1).

Lateral pelvic lymph node metastasis in rectal cancer: Incidence and prognostic value

In rectal cancers, the incidence of lateral lymph node involvement has been reported as 10% to 25% [5-9] (Table I). According to the Japanese Society for Cancer of the Colon and Rectum data, the incidence of LLN involvement in tumors below the peritoneal reflection, with positive mesorectal nodes, is 27% [10].

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Incidence varies according to the tumor location, size of the tumor, pathological T stage, number of mesorectal nodes, and grades of differentiation and presence of lymphovascular emboli [5].

Increasing incidence of lateral pelvic nodes is seen as the distance of the tumor from the anal verge decreases with the reported incidence for tumors located below peritoneal reflection of 14.9% compared with 8.2% for those located above the peritoneal reflection [11]. The incidence of lateral nodal involvement is directly proportional to pathological T stage. Incidence of lateral nodes in pT2, pT3, and pT4 being 6.5% to 7.1%, 17.9%, and 31.6%, respectively [12].

Incidence of LLN involvement has not been proven to be dependent on geography. El-Khoury et al. after a detailed analysis concluded that the incidence is same in East and the West [13].

Lateral pelvic nodes are considered a poor prognostic factor associated with poor survival. In MERCURY study group 11.7% patients had MRI identified suspicious LPLN. Five year DFS was 42% and 70.7% respectively for patients with and without suspicious nodes. Among patients undergoing primary surgery the survival was significantly worse in patients with MRI suspected LLN than those without LLN, 5 year DFS 31% and 76.3% respectively. However, presence of suspicious nodes had no impact on survival among patients who received preoperative therapy [12].

With universal usage of neoadjuvant Chemo-Radiation (nCRT) and Total Mesorectal Excision (TME) local recurrence rates have decreased to 5% to 10%. However local recurrence majority of which can be attributed to LPNs still remain a major concern and a major factor for treatment failure in locally advanced rectal cancers. About half the local recurrences occur in the LLN basin without evidence of distant metastasis [14].

According to the Japanese Society for Cancer of Colon and Rectum (JSCCR), Lateral Lymph Node Dissection (LLND) is expected to decrease the intra-pelvic recurrence by 50% and improve the 5-year survival by 8% to 9%. On the contrary, a Swedish study reported that lateral pelvic lymph node metastases are not a major cause of local recurrence after TME alone with majority of recurrence seen at the anastomotic site [10].

A large Japanese Nationwide Multi-Institutional Study on LPLN metastasis in low rectal cancer with 11,567 patients has shown that with resection of metastatic iliac lymph nodes the outcomes are similar to patients undergoing TME with clinical stage TxN2aM0, and those undergoing resection of obturator and external iliac lymph nodes have survival better than that of liver metastasis [15].

Japanese guidelines therefore recommend that patients with stages II/III rectal cancer below the peritoneal reflection undergo regular TME + LPLND [16]. On the contrary, Western countries favor nCRT and TME for LLN metastases, holding that the rate of LLN metastases is relatively low, and LLN metastases other than internal iliac are equivalent to systemic metastases.

Lateral pelvic lymph node dissection

Sauer and Bacon were the first to publish the results of LPLND in 1951 [17]. It is hypothesized that LPLND removes those nodes that contain micrometastasis and, hence, decreases the development of locoregional recurrence. LPLND may be therapeutic in the presence of enlarged lateral pelvic nodes or may be prophylactic in the absence of any obviously enlarged lateral pelvic nodes.

However longer operating time, greater blood loss, functional impairment, and significant postoperative morbidity are the main constrains in the routine application of LPLND [18]. Damage to the hypogastric nerves and pelvic nerve plexus is the main pathology responsible for urinary dysfunction, which occurs in 42% to 73% of patients undergoing LPLND [19,20]. With the evolution of the concept of autonomic nerve preservation and recent advances in instruments and magnified imaging system in minimally invasive approach surgeon are able to perform LPND with lower complication rates.

The literature on a nerve-preserving lymphadenectomy demonstrates that autonomic nerve preservation offers advantages in maintaining urinary and sexual functions [19,21]. In the recent Japan Clinical Oncology Group 0212 trial, postoperative urinary dysfunction developed in 59% of patients who underwent LLLD, and sexual dysfunction occurred in 79% of such patients; these results were not significantly different from those for the TME-alone group [20].

LPND in therapeutic setting

Georgiou et al. [22] did a meta-analysis comparing extended lymph node dissection *vs.* conventional rectal cancer surgery in 5502 patients from one randomized, three prospective nonrandomized, and 14 retrospective case-control studies found that there was no significant benefit with extended lymph node dissection in terms of survival or recurrence.

Although intraoperative blood loss, duration of hospital stays, sexual and urinary dysfunctions were significantly higher with extended lymph node dissection. Authors concluded that extended lymphadenectomy does not confer a significant oncological advantage but increased complications [22]. However, the results need to be interpreted keeping in mind that results were based mainly on retrospective studies performed over a long period of time with significant heterogeneity between the groups.

Akiyoshi et al. [23] studied the role of LPLND in 127 patients of locally advanced low rectal carcinoma. In this study, LPLND was selectively done to those patients who had enlarged lateral pelvic nodes on imaging before NACTRT. For those in whom lateral pelvic nodes were not enlarged, only TME was performed after NACTRT. They found that three patients in the TME group developed local recurrence in lateral pelvic nodes in contrast to none in LPLND group, which was statistically significant. So, the authors advocated the application of LPLND in those patients of low rectal cancer who showed enlarged LPNs on imaging before NACTRT [23].

Recently, selective lateral Pelvic lymph Node Dissection (LPND) for suspected LPNs metastasis has been suggested in patients with rectal cancer who have undergone preoperative CRT.

In a Korean study by Kim et al. [24], On 377 patients who had received preoperative CRT for rectal cancer, 84 (22.3%) had suspicious LPNs on pretreatment MRI. Sixty one patients showed good response to CRT on post-treatment MRI (short-axis LPN diameter <5 mm). Among them, 31 patients underwent TME alone (group A), and 30 underwent TME plus LPND (group B). The remaining 23 patients had persistently suspicious LPNs on post-CRT MRI and underwent TME plus LPND (group C). Pathologic LPN metastasis was confirmed in five patients (16.7%) in group B and 15 (62.5%) in group C. Local recurrence developed in 7 (22.6%), 0 (0%), and 4 (17.4%) patients in groups A, B, and C, respectively. The 3-year disease free survival rates were 53.7%, 74.2%, and 46.9% in groups A, B, and C, respectively.

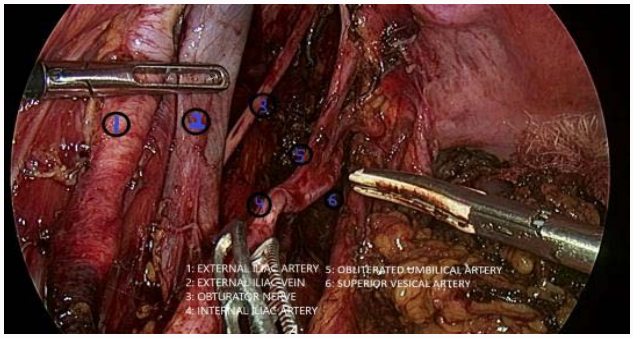

Figure 1: Surgical Anatomy.

The authors concluded that LPND cannot be omitted for patients with suspicious LPNs on pretreatment MRI even with good response to CRT. Findings from pretreatment MRI should be considered to determine whether LPND is indicated [24].

Contrasting to this in another Korean study on 580 patients suggests that patients with persistent lateral pelvic lymph nodes (>5 mm) post NACTRT are the one who benefit from LPLND while those with lateral pelvic nodes responsive to preoperative NACTRT may not benefit from LPLND. In this study patients were divided into three groups: group > (no suspicious lateral LNs), i.e., lateral LN <5 mm pre- and post-CRT; group II (responsive lateral LN), lateral pelvic node ≥ 5 mm pre-CRT, but <5 mm post-CRT; and group III (persistent lateral pelvic node), lateral pelvic node ≥ 5 mm pre- and post-CRT. Group III had significantly poorer lateral pelvic node recurrence-free survival than groups I and II [25].

The difference in results in Japanese and Korean studies can probably be attributed to the learning curve of technique as Koreans compared to Japanese have a lesser experience with lateral pelvic lymph node dissection. However they are now evolving there technique with use of ICG dye to ensure complete LLN clearance and future studies may show results similar to Japan.

A multicenter pooled cohort analysis on 1216 patients was done by Ogura et al. [26] to ascertain whether LLND results in fewer LLR after NACRT with TME in locally advanced rectal cancers and to ascertain size after multivariable analyses, LLNs with a short axis of at least 7 mm on pretreatment MRI resulted in a significantly higher risk of LLR (hazard ratio, 2.060; P=0.045) compared with LLNs of less than 7 mm. In patients with LLNs at least 7 mm, (C) RT plus TME plus LLND resulted in a 5-year LLR of 5.7%, which was significantly lower than that in patients who underwent (C) RT plus TME (5-year LLR, 19.5%; P=0.042) [26]. Although there was a significant difference in local recurrences no change in metastases or cancer specific survival was seen.

The same group recently reported their experience with restaging MRI on to identify subset of patients who can be better selected for LLND. Of the 1,216 patients in the original cohort 741 patients had undergone a restaging MRI and were included in this analysis. Authors reported that in patients with shrinkage of lateral nodes from a Short Axis (SA) node size of 7 mm or greater on primary MRI to an SA node size of 4 mm or less on restaging MRI, LLND can be avoided. This occurs in about 30% of cases. However, persistently enlarged nodes in the internal iliac compartment indicate an extremely high risk of LLR of 52.3% and LLND significantly lowers this to 8.7% [27].

Table 1: Lateral lymph node involvement report.

S No.	Study	Total cases	LPLN metastasis
1	Kinugasa et al. (2000)	944	206 (22%)
2	Takahashi et al. (2000)	764	66 (8.6%)
3	Fujito et al. (2003)	204	29 (11.9%)
4	Ueno et al. (2007)	244	41 (17%)
5	Min et al. (2009)	151	36 (23.8%)
6	Fujito et al. (2012)	784	117 (14.9%)

Prophylactic LPLND

A Randomized-Controlled Trial (RCT) by Nagawa et al. [28] comparing LPLND with no LPLND among 51 patients with low rectal cancer found that there was no difference between the two groups in terms of overall or disease-free survival. Although at 1-year after surgery LPLND was associated with significantly higher incidence of urinary and sexual dysfunctions [28]. But, the sample size is too small to draw any meaningful conclusion.

Similarly a recent RCT from Japan also failed to demonstrate the benefit of prophylactic Lateral Lymph Node Dissection (LLND) in rectal cancer. JCOG 212 aimed at confirming the non-inferiority of Mesorectal (ME) excision alone to ME with LLND in terms of efficacy, primary end point being relapse free survival. It enrolled 701 patients between June 2003 to August 2010 with clinical stage II/III rectal cancers with lower margin of tumor below the peritoneal reflection with no lateral pelvic lymph node enlargement on imaging (lymph node size <10 mm).

On follow-up there was no significant difference in 5 year relapse free and overall survival between the two groups. However the numbers of patients with local recurrence were significantly more in ME alone group 12.6% *vs.* 7.4% in ME+LLND (P 0.024). Authors concluded ME with LLND had a lower local recurrence, especially in the lateral pelvis, compared to ME alone. Secondary end points from the same study including the incidence of urinary and male sexual dysfunction were not found to be higher in the LLND group [29].

The caveats in this study were that only patients without LPN enlargement with a short-axis diameter of <10 mm were included, and all patients did not undergo preoperative Chemo Radiotherapy (CRT). The local recurrence rate in TME with prophylactic LPND group in this study was not superior to that reported in TME alone with preoperative CRT from western literature.

However the Japanese philosophy is that since prophylactic lymph node dissection decreases local recurrences, as seen in this study it is worth doing it but probably if the lymph node cut off size for labeling the nodes as N zero was kept at 7 mm then this difference in local recurrence would have also not been significant in this study. So at this point it is unlikely that prophylactic LPND will be recognized as a necessary procedure in patients with rectal cancer especially those treated with preoperative CRT.

Impact of radiotherapy on lateral pelvic lymph nodes

It is speculated that preoperative radiotherapy has a cytotoxic effect and leads to tumor down staging, and can also sterilize lymph nodes located in mesorectum and lateral pelvic side-wall. Subgroup analysis from two large trials suggests favourable results of NACTRT. In Dutch TME trial, it was observed that incidence of lateral recurrence in the group that received radiotherapy (0.8%) was significantly lower compared with that in the group that underwent TME alone

(2.7%), suggesting that radiotherapy might have been the main factor responsible in reducing this incidence. Similarly in MERCURY trial among the patients who revealed radiologically involved lateral pelvic nodes, prognosis was better in those who received radiotherapy [12].

On the contrary, in a retrospective study, Akiyoshi et al. showed that the LPLN did not regress completely after CRT, with two third of the patients having positive LN metastasis on LPLND [23]. Similarly Kim et al. noted that 83% of patients with locoregional recurrence had lateral pelvic recurrence even after preoperative CRT and a curative proctectomy [30]. Kusters et al. reported a 5-year lateral local recurrence rate of 11.8% in the Western population, and patients with lateral nodes with malignant features had a lateral local recurrence rate (20.9%) twice as high as those without malignant-looking nodes (10.3%) [31].

These findings suggest that preoperative chemoradiotherapy could not completely eradicate lateral pelvic lymph node metastasis, and that LLND should be considered if lateral pelvic lymph node metastasis is suspected even after chemoradiotherapy, given that LLND can macroscopically eradicate lateral pelvic lymph node metastasis and reduce lateral recurrence.

In addition, similar to surgery, radiotherapy also results in long-term morbidity in the form of sexual dysfunction, impaired continence, and small bowel obstruction. So, whether radiotherapy can completely replace LPLND with significantly lower adverse effects is not clear.

Detection of lateral pelvic lymph nodes

Detection of lateral pelvic lymph nodes is of paramount importance as treatment at present is tailored depending on the involvement of nodes. Various imaging modalities that have been used and MRI is generally considered the best, but diagnostic criteria for reliably detecting metastatic lymph nodes on MRI are still lacking. Lymph node size a widely accepted criterion has limited accuracy. The cutoff size of lateral nodes has been reported to vary from 5 mm to 8 mm [32,33]. The problem is even bigger for restaging MRI after preoperative CRT because there are no definitive criteria for differentiating between metastatic and irradiated lymph node change on post-CRT MRI.

Akiyoshi et al. reported that 85.7% of patients with metastatic LPNs after LPND had a short-axis diameter ≥ 8 mm before CRT [23]. A recent JSCCR report has identified a 5 mm cutoff on the short axis as being optimal for detecting metastatic nodes. The rate of lateral pelvic recurrence increases as the size of the lateral LN increase, and when the diameter of the largest lateral LN is in the range from 5 mm to 10 mm or more than 10 mm, the incidence of lateral spread is 20% or 36.7%, respectively. Based on MRI imaging, JSCCR studied the optimum cutoff for lateral lymph node size to identify metastatic nodes; it found that a 5 mm cutoff on the short-axis was superior to a 10 mm cutoff. It also reported that compared with other factors, including histopathological grade, perirectal nodes, and distant metastasis, an enlarged pelvic node status with a short axis ≥ 5 mm on MRI was the most important risk factor for metastasis [33].

Ogura et al. [26] performed a multicentre pooled analysis of patients with low, locally advanced rectal cancer from 12 hospitals in seven Eastern and Western countries. After multivariable analysis, LPLN with a short axis equal to or greater than 7 mm resulted in a significantly higher risk of lateral local recurrence (HR 2060; P=0.045) compared with LPLN of less than 7 mm [26]. The same group reported that nodes that are greater than 4 mm on restaging MRI needed to be addressed by surgery [27].

Using a larger cut-off value for LPNs can lead to small-sized metastatic LPNs go undetected and potential under treatment and smaller values cut off will render substantial number of patients to overtreatment. To counter this problem the MERCURY study group proposed morphologic criteria, such as signal heterogeneity and irregular border. However there is a lack of consensus among radiologists.

Recently role of PET scan for detection of pelvic lymph nodes has also been evaluated. Initial results are encouraging, with good accuracy and more nodes being detected on PET scan compared to conventional imaging [34].

Conclusion

A lateral pelvic node in low rectal cancer is not uncommon. It implies non-metastatic nodal disease associated with increased local recurrence and decreased survival. In the present era of NACRT with the available evidence it seems that in the absence of involved CRM and lateral pelvic LN standard TME alone is sufficient & prophylactic lateral lymph not dissection is not indicated. Although it may have a role in therapeutic settings in patients having lymph nodes more than 7 mm size on pre chemoradiation imaging and greater than 4 mm on restaging, which can help in decreasing the local recurrence rate. However at this point of time it is not clear whether this decrease in recurrence would translate in to better survival rates.

For patients presenting with clear CRM & lateral pelvic lymph nodes there is no head to head data comparing upfront surgery with lateral lymph node dissection *vs.* chemoradiation followed by surgery. Trials are needed in this setting for a definite answer but at this point of time these group of patients would be best treated by Neoadjuvant chemoradiation followed by surgery.

More research also needs to be done on improving restaging after nCRT, new technologies such as PET scan offer promise but results need to be substantiated in larger studies. Lastly proper training in LPLND is of utmost importance and there is a need for collaborating with Japanese centers to improve the surgical technique of lateral lymph node dissection in rectal cancers.

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