Journal of Gastrointestinal & Digestive System

Kundagulwar et al., J Gastrointest Dig Syst 2016, 6:5
DOI: 10.4172/2161-069X.1000473

Research Article OMICS International

Is there a Role of Lateral Pelvic Lymph Node Dissection in the Current Era of Neoadjuvant Chemoradiotherapy for Rectal Cancer?

Girish K Kundagulwar, Vishwas D Pai and Avanish P Saklani*

Department of Surgical Oncology, Tata Memorial Centre, Mumbai, Maharashtra, India

***Corresponding author:** Dr. Avanish P Saklani, Associate Professor, Colorectal and Robotic Surgery, Department of Surgical Oncology, Tata Memorial Centre, Ernest Borges Road, Mumbai, Maharashtra, India, Tel:+91-9969506719; E-mail: asaklani@hotmail.com

Received date: September 9, 2016; **Accepted date:** September 23, 2016; **Publication date:** September 29, 2016

Abstract

Colorectal cancer is the third most common cancer in men. Total mesorectal excision remains the gold standard treatment for rectal cancer with chemoradiotherapy preceding the surgery in all locally advanced rectal malignancies. Lateral pelvic lymph node dissection (LPLND), although a part of standard surgery for rectal cancers treatment in Japan has not been adopted by surgeons in the rest of the world. There is a long-standing controversy on whether lateral pelvic node metastasis represents localized or metastatic disease. Current standard in Japan is to consider lateral pelvic nodes as regional disease and, hence, perform prophylactic LPLND in low rectal cancers of stage T3 or more or with involved mesorectal nodes. In contrast, standard therapy in west is to consider lateral pelvic nodes as systemic disease and, hence, to either ignore them or treat obvious nodes with chemoradiotherapy. In Japan, neoadjuvant chemoradiotherapy (NACTRT) is less commonly used for locally advanced rectal cancers in contrast to the practice in the west. The role of LPLND in patients receiving NACTRT remains to be established. The aim of this article is to review the evidence for the role of LPLND in the current era of NACTRT.

Keywords: Lateral pelvic lymph node dissection; Rectal cancer; Metastatic deposits in nodes; Neoadjuvant chemoradiotherapy

Introduction

Colorectal cancer is the third most common cancer in men [1]. Total mesorectal excision (TME) remains the gold standard treatment for rectal cancer with chemoradiotherapy (CRT) preceding the surgery in all locally advanced rectal malignancies. With the incorporation of neoadjuvant therapy and standardization of surgery, the prognosis has improved with a 5-year overall survival in excess of 60% [2,3]. Lateral pelvic lymph node dissection (LPLND), although a part of standard surgery for rectal cancers in Japan has not been adopted by surgeons in the rest of the world. There is a long-standing controversy on whether lateral pelvic node metastasis represents localized or metastatic disease. Current standard in Japan is to consider lateral pelvic nodes as regional disease and, hence, perform prophylactic LPLND in low rectal cancers (Rb according to Japanese classification) of stage T3 or more or with involved mesorectal nodes [4]. In contrast, standard therapy in the west is to consider lateral pelvic nodes as systemic disease and, hence, to either ignore them or treat obvious nodes with CRT. In Japan, neoadjuvant chemoradiotherapy (NACTRT) is less commonly used for locally advanced rectal cancers in contrast to the practice in the west. The role of LPLND in patients receiving NACTRT remains to be established. The aim of this article is to review the evidence for the role of LPLND in the current era of NACTRT.

Lymphatic Drainage of Rectum

Lymphatic drainage of the rectum below the peritoneal reflection follows two different pathways. Superiorly, the lymphatics follow superior rectal artery and drain to the lymph nodes along the inferior mesenteric artery and paraaortic nodes. Inferiorly, the lymphatics follow middle and lower rectal artery and drain to the obturator, internal iliac, external iliac and common iliac lymph nodes [5]. The former group is dissected as a part of standard TME worldwide, whereas it is the latter group that forms the area of controversy.

Common iliac group includes those nodes that are located along the common iliac artery and vein, caudal to the aortic bifurcation and cranial to the bifurcation of the common iliac vessels being bound by lower lumbar and upper sacral vertebral bodies posteromedially and by psoas muscle anterolaterally. External iliac group includes the nodes located along the external iliac artery and vein, caudal to the bifurcation of the common iliac vessels and cranial to the inguinal ligament. Although the subject of some debate, obturator nodes are generally considered to be a part of the medial external iliac node group and includes the lymphatic tissue lying lateral to the parietal pelvic fascia, around the obturator nerve and vessels. Internal iliac group includes lateral sacral nodes (in proximity to lateral sacral arteries), presacral nodes (anterior to sacrum and posterior to the mesorectal fascia), anterior internal iliac nodes (nodes located at the origin of the proximal branches of anterior division of internal iliac arteries), and hypogastric nodes (the most cephalic of the internal iliac nodes).

Incidence of Lateral Pelvic Lymph Node Involvement

The incidence of lateral nodal involvement in patients with lower rectal cancer has been reported as 8.6% to 27% [6,7]. The incidence of lateral nodal involvement in patients with lower rectal cancer in the east and the west may be similar but the management of LPLN completely differs. In the west, NACTRT is more commonly used, which is also seen in India, whereas, in Japan, patients are subjected to upfront surgery [8]. 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 [9]. Involvement of the lateral pelvic nodal in the absence of

mesenteric nodes has been documented in up to 15% patients [10]. As the distance from the anal verge decreases, the incidence of lateral pelvic nodes increases, with the reported incidence of lateral nodal involvement for tumors located below peritoneal reflection of 14.9% compared with 8.2% for those located above the peritoneal reflection [11]. Among the tumors situated below the peritoneal reflection, the incidence of lateral pelvic nodes for those situated within 2 cm from anal verge is as high as 42% [9]. 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%-7.1%, 17.9%, and 31.6%, respectively [10]. Lateral pelvic nodes are rarely involved in pT1 tumors or in high-grade dysplasia although development of recurrence in lateral pelvic nodes has occasionally been reported even in pT1 tumors [12].

Prognostic Value of Lateral Pelvic Lymph Nodes

Presence of lateral pelvic nodes has a poor prognostic factor with a 5-year survival rate among those with involved lateral pelvic nodes being 42% in contrast to 70.7% in those with uninvolved nodes [13]. However a Japanese Nationwide Multi-Institutional Study on LPLN metastasis in low rectal cancer with 11,567 patients has shown that prognosis in the presence of lateral pelvic nodes is similar to N2a /N2b mesorectal nodes but definitely better than distant metastasis [4]. In addition, patients who have involved lateral pelvic nodes in the absence of mesorectal nodes do better than those who have mesorectal nodes also involved.

Local recurrence rates of 30% or greater was seen in pre-TME era [14] which reduced to about 5% after TME became the standard surgical approach for rectal cancer. Local recurrences were higher in men and in patients with low rectal cancer [15] which was further reduced by addition of NACTRT or radiotherapy alone. One of the arguments in favour of LPLND is its role in reducing lateral recurrence. A Korean study demonstrated that lateral pelvic lymph nodes are the major cause of local recurrence and poor overall survival in low rectal cancers [16]. On the contrary, a Swedish study did show 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 [17]. A review by Nielsen et al. (2011) found that, although the introduction of TME made an improvement in complete resection, recurrences at the pelvic side wall are still common probably related to the lateral pelvic lymph nodes [18]. Similarly, a large study from Japan found that, although the rate of local recurrence was similar between the groups with or without LPLND, lateral pelvic lymph node involvement was an independent predictor of local recurrence [19]. Kusters et al. in their retrospective study of 351 patients found that, even after bilateral LPLND, lateral recurrence developed in 14% of patients who showed enlarged lateral pelvic nodes. On the contrary, in those patients without enlarged lateral pelvic nodes who did not undergo LPLND, only 0.8% developed lateral recurrence. Thus, lateral site recurrence may be reduced but cannot be eliminated by LPLND. This was a single-institution retrospective study, and patients did not receive preoperative radiation therapy [20]. Akiyoshi et al. in a prospective series of 127 patients of which 38 patients showed lateral pelvic nodes seen on multiple detector computed tomography (CT) or magnetic resonance imaging (MRI) and persisted post NACTRT, found that local recurrence was 3.4% in the TME-only group and 0% in LPLND group, thus supporting LPLND in patients who show enlarged lateral pelvic nodes post NACTRT [21]. However, they also found that relatively lower incidence of lateral pelvic nodal recurrence in the TME group favours omitting LPLND based on the findings of pre-treatment imaging if treated with NACTRT.

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 include ultrasound, CT pelvis, positron emission tomography-CT and MRI. Among these imaging modalities, high-resolution MRI is considered as highly accurate in detecting lateral pelvic nodes with 67% sensitivity, 75% specificity, and 73% overall accuracy. LN that is oval shaped with transverse axis diameter of 5 mm or larger showed 67% sensitivity, 83% specificity, and 78% overall accuracy [22]. In addition to the size, nodal margins and internal nodal characteristics may add more reliability as indicators of malignancy [23].

Impact of Radiotherapy on Lateral Pelvic Lymph Nodes

It is speculated that preoperative radiotherapy has a cytotoxic effect not only on the primary tumour but also on the lateral pelvic lymph nodes. Evidence suggesting favourable results of NACTRT is derived from subgroup analysis of two large trials. In a 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, MERCURY trial did show that, among the patients who revealed radiologically involved lateral pelvic nodes, prognosis was better in those who received radiotherapy [11]. A recent study also showed that, in patients receiving NACTRT, the presence of lateral pelvic nodes does not affect survival.

On the contrary, Kim et al. (2008) have shown that lateral pelvic node metastasis represent major causes of locoregional recurrence among patients who receive NACTRT followed by TME without LPLND [16]. In a retrospective study, Akiyoshi et al. [21] showed that the LPLN did not regress completely after CRT, with 66% showed positive LN metastasis on LPLND. In addition, similar to surgery, radiotherapy also results in long-term morbidity in the form of sexual dysfunction, impaired continence, and small bowel obstruction [24,25]. So, whether radiotherapy can completely replace LPLND with significantly lower adverse effects is not clear.

Lateral Pelvic Lymph Node Dissection

Sauer and Bacon were the first to publish the results of LPLND in 1951 [26]. 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. It is hypothesized that LPLND removes those nodes that contain micrometastasis and, hence, decreases the development of locoregional recurrence. Matsumoto et al. did show that incidence of micrometastasis in clinico-radiologically negative lateral pelvic nodes, which are detected by RT-PCR, was 15.5% [27]. Similarly, preliminary results of Japanese randomized trial did show that subclinical involvement of lateral pelvic nodes is seen in up to 7% of patients with locally advanced low rectal cancers [28]. However, clinical significance of such nodes in terms of the development of local recurrence and the impact of CRT on sterilizing them remains to be established.

Longer operating time, greater blood loss, functional impairment, and significant postoperative morbidity are the main constrains in the routine application of LPLND [29]. 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 [30,31]. The concept of LPLND with autonomous nerve preservation seems attractive in terms of lower incidence of urinary and sexual dysfunction [32]. Laparoscopic and robotic LPLND with the aid of greater magnification seems to be associated with encouraging short-term results in the short series reported although long-term results are still awaited [33,34].

Therapeutic LPLND

Georgiou et al. [29] did a meta-analysis comparing extended lymph node dissection versus conventional rectal cancer surgery in which they included 5502 patients from one randomized, three prospective nonrandomized, and 14 retrospective case-control studies. They 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 stay, and sexual and urinary dysfunctions were significantly higher with extended lymph node dissection. Hence, they concluded that extended lymphadenectomy does not confer a significant oncological advantage but increased complications. However, this was based on retrospective studies performed over a long period of time with significant heterogeneity between the groups.

Kobayashi et al. [19] studied 1272 patients of low rectal cancer in which LPLND was done in 784 patients. The oncological outcomes were compared between those who had undergone LPLND with those who had not undergone LPLND and found that the two groups were comparable in terms of rates of local recurrence and five-year overall survival. However, it was found that involvement of lateral pelvic nodes was an independent poor prognostic factor and indicator of local recurrence.

Watanabe et al. [35] retrospectively reviewed 115 patients of rectal cancer treated at their center. Whole cohort of patients was divided into four groups based on the use of NACRT and LPLND. They found that there was a significant 5-year survival advantage with the use of preoperative CRT. However, there was no significant difference in overall survival or local recurrence between the patients who had neoadjuvant radiotherapy with conventional surgery compared with those who had conventional surgery with LPLND without NACRT. Similar results were also seen when the results of rectal cancer treatment followed in the Netherlands and Japan were compared.

Akiyoshi et al. [21] studied the role of LPLND in 127 patients of locally advanced low rectal carcinoma. In this study, LPLND was offered selectively 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. On multivariate analysis, pathological nodal stage was the only independent prognostic factor predicting relapse-free survival. So, the authors advocated the application of LPLND in those patients of low rectal cancer who showed enlarged lateral pelvic nodes on imaging before NACTRT. In this study, they observed that, in all of the patients with enlarged nodes on pre-NACTRT MRI revealed residual nodes after NACTRT.

Prophylactic LPLND

Evidence for prophylactic LPLND is even sparser. Nagawa et al. [36] conducted a randomized-controlled trial comparing LPLND with no LPLND among 51 patients with low rectal cancer. They 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. But, this study is too small to draw any meaningful conclusion.

Japanese Clinical Oncology Group (JCOG) has started a phase 3 randomized-controlled clinical trial comparing TME alone and TME LPLND for stage II/III rectal cancer with extra mesorectal nodes less than 1 cm in size on MRI to determine the role of prophylactic LPLND [28]. The final results of this study may better define the role of prophylactic LPLND. However, those patients receiving neoadjuvant or adjuvant CRT are excluded. Hence, the value of radiotherapy, which might be an alternative to LPLND, will not be assessed.

Conclusion

Presence of lateral pelvic nodes implies nonmetastatic nodal disease but confers poor prognosis and, hence, is associated with increased local recurrence and decreased survival. MRI is the best imaging modality for identifying lateral pelvic nodes. An oval shape and a transverse axis diameter of 5 mm or more increase the specificity of such an imaging modality. In cases without enlarged lateral pelvic nodes before NACTRT, current evidence is against the use of LPLND. However, the role of prophylactic LPLND is being evaluated in a Japanese study. For those with enlarged lateral pelvic nodes before NACTRT, total mesorectal excision alone may be sufficient. However, for those in whom residual nodes persist after NACTRT, there is a need for a well-conducted randomized trial to establish the best approach. Possible trial design for such a trial will be to randomize the patients with residual lateral pelvic nodes after NACTRT into an LPLND group and observation group. However, such a trial would require very large number of patients and may not be feasible in near future.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, et al. (2015) Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108.
2. Martin ST, Heneghan HM, Winter DC (2012) Systematic review of outcomes after intersphincteric resection for low rectal cancer. Br J Surg 99: 60312.
3. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, et al. (2004) Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer. N Engl J Med 17: 1731-1740.
4. Akiyoshi T, Watanabe T, Miyata S, Kotake K, Muto T, et al. (2012) Results of a Japanese nationwide multi-institutional study on lateral pelvic lymph node metastasis in low rectal cancer: is it regional or distant disease? Ann Surg 255: 1129-1134.
5. Bell S, Sasaki J, Sinclair G, Chapuis PH, Bokey EL (2009) Understanding the anatomy of lymphatic drainage and the use of blue-dye mapping to determine the extent of lymphadenectomy in rectal cancer surgery: unresolved issues. Colorectal Dis 11: 443-449.
6. Ueno H, Mochizuki H, Hashiguchi Y, Hase K (2001) Prognostic determinants of patients with lateral nodal involvement by rectal cancer. Ann Surg 234: 190-197.
7. Moriya Y, Hojo K, Sawada T, Koyama Y (1989) Significance of lateral node dissection for advanced rectal carcinoma at or below the peritoneal reflection. Dis Colon Rectum 32: 307-315.

8. Yano H, Moran BJ (2008) The incidence of lateral pelvic side-wall nodal involvement in low rectal cancer may be similar in Japan and the West. Br J Surg 95: 33-49.
9. Ueno M, Oya M, Azekura K, Yamaguchi T, Muto T (2005) Incidence and prognostic significance of lateral lymph node metastasis in patients with advanced low rectal cancer. Br J Surg 92: 756-763.
10. Ueno H, Mochizuki H, Hashiguchi Y, Ishiguro M, Miyoshi M, et al. (2007) Potential prognostic benefit of lateral pelvic node dissection for rectal cancer located below the peritoneal reflection. Ann Surg. 245: 80-87.
11. MERCURY Study Group, Shihab OC, Taylor F, Bees N, Blake H, et al. (2011) Relevance of magnetic resonance imaging-detected pelvic sidewall lymph node involvement in rectal cancer. Br J Surg 98: 1798-1804.
12. Sueda T, Noura S, Ohue M, Shingai T, Imada S, et al. (2013) Case of isolated lateral lymph node recurrence occurring after TME for T1 lower rectal cancer treated with lateral lymph node dissection: report of a case. Surg Today 43: 809-813.
13. Hida J, Yasutomi M, Fujimoto K, Maruyama T, Okuno K (1997) Does lateral lymph node dissection improve survival in rectal carcinoma? Examination of node metastases by the clearing method. J Am Coll Surg 184: 475-480.
14. Heald RJ, Ryall RD (1986) Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1: 1479-1482.
15. Van Lingen CP, Zeebregts CJ, Gerritsen JJ, Mulder HJ, Mastboom WJ, et al. (2003) Local recurrence of rectal cancer after total mesorectal excision without preoperative radiotherapy. Int J Gastrointest Cancer 34: 129-134.
16. Kim TH, Jeong SY, Choi DH, Kim DY, Jung KH, et al. (2008) Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. Ann SurgOncol 15: 729-737.
17. Syk E, Torkzad MR, Blomqvist L, Ljungqvist O, Glimelius B (2006) Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer. Br J Surg 93: 113-119.
18. Nielsen MB, Laurberg S, Holm T (2011) Current management of locally advanced recurrent rectal cancer. Colorectal Dis 13: 732-742.
19. Kobayashi H, Mochizuki H, Kato T, Mori T, Kameoka S, et al. (2009) Outcomes of surgery alone for lower rectal cancer with and without pelvic sidewall dissection. Dis Colon Rectum 52: 567-576.
20. Kusters M, van de Velde CJ, Beets-Tan RG, Akasu T, Fujita S, et al. (2009) Patterns of local recurrence in rectal cancer: a single-center experience. Ann Surg Oncol 16: 289-296.
21. Akiyoshi T, Ueno M, Matsueda K, Konishi T, Fujimoto Y, et al. (2014) Selective lateral pelvic lymph node dissection in patients with advanced low rectal cancer treated with preoperative chemoradiotherapy based on pretreatment imaging. Ann Surg Oncol 21: 189-196.
22. Matsuoka H, Nakamura A, Masaki T, Sugiyama M, Nitatori T, et al. (2007) Optimal diagnostic criteria for lateral pelvic lymph node metastasis in rectal carcinoma. Anticancer Res 27: 3529-3533.
23. Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, et al. (2003) Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology 227: 371-377.
24. Marijnen CA, van de Velde CJ, Putter H, van den Brink M, Maas CP, et al. (2005) Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 23: 1847-1858.
25. Peeters KC, van de Velde CJ, Leer JW, Martijn H, Junggeburt JM, et al. (2005) Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients-a Dutch colorectal cancer group study. J Clin Oncol 23: 6199-6206.
26. Sauer I, Bacon HE (1951) Influence of lateral spread of cancer of the rectum on radicability of operation and prognosis. Am J Surg 81: 111-120.
27. Matsumoto T, Ohue M, Sekimoto M, Yamamoto H, Ikeda M, et al. (2005) Feasibility of autonomic nerve-preserving surgery for advanced rectal cancer based on analysis of micrometastases. Br J Surg 92: 1444-1448.
28. Fujita S, Akasu T, Mizusawa J, Saito N, Kinugasa Y, et al. (2012) Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): results from a multicentre, randomised controlled, non-inferiority trial. Lancet Oncol 13: 616-621.
29. Georgiou P, Tan E, Gouvas N, Antoniou A, Brown G, et al. (2009) Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis. Lancet Oncol 10: 1053-1062.
30. Akasu T, Sugihara K, Moriya Y (2009) Male urinary and sexual functions after mesorectal excision alone or in combination with extended lateral pelvic lymph node dissection for rectal cancer. Ann SurgOncol 16: 2779-2886.
31. Wu XJ, Huang MJ, He XS, Zhou XY, Zou YF, et al. (2009) Systematic review on safety and efficacy of lateral node dissection in rectal cancer. Chinese j gastroint surg 12: 229-235.
32. Kyo K, Sameshima S, Takahashi M, Furugori T, Sawada T. Impact of autonomic nerve preservation and lateral node dissection on male urogenital function after total mesorectal excision for lower rectal cancer. World J Surg 30: 1014-1019.
33. Liang JT (2011) Technical feasibility of laparoscopic lateral pelvic lymph node dissection for patients with low rectal cancer after concurrent chemoradiation therapy. Ann Surg Oncol 18: 153-159.
34. Bae SU, Saklani AP, Hur H, Min BS, Baik SH, et al. (2014) Robotic and laparoscopic pelvic lymph node dissection for rectal cancer: short-term outcomes of 21 consecutive series. Ann Surg Treat Res 86: 76-82.
35. Watanabe T, Tsurita G, Muto T, Sawada T, Sunouchi K, et al. (2002) Extended lymphadenectomy and preoperative radiotherapy for lower rectal cancers. Surgery 132: 27-33.
36. Nagawa H, Muto T, Sunouchi K, Higuchi Y, Tsurita G, et al. (2001) Randomized, controlled trial of lateral node dissection vs nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. Dis Colon Rectum 44: 1274-1280.