Neoadjuvant (chemo)radiotherapy and Lateral Node Dissection: Is It Mutually Exclusive?

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Abstract

The importance of total mesorectal excision (TME) has been the global standard of care in patients with rectal cancer. However, there is no universal strategy for lateral lymph nodes (LLN). The treatment of the lateral compartment remains controversial and has gone to the opposite directions between Eastern and Western countries in the past decades. In the East, mainly Japan, surgeons consider LLN metastases as regional disease and have performed TME with lateral lymph node dissection (LLND) without neoadjuvant (chemo)radiotherapy ([C]RT) in patients with clinical Stage II/III rectal cancer below the peritoneal reflection. In the West, neoadjuvant radiotherapy or has been the standard, and surgeons do not perform LLND assuming the (C)RT can sterilize most lateral lymph node metastasis (LLNM). Recent evidences show that lateral nodes are the major cause of local recurrence after (C)RT plus TME, and LLND reduces local recurrence particularly from the lateral compartment. Probably a combination of the two strategies, that is, neoadjuvant (C)RT plus LLND, would be needed to improve outcomes in patients with lateral nodal disease.

Keywords

- rectal cancer
- lateral lymph node
- lateral lymph node dissection
- radiotherapy
- chemoradiotherapy

The importance of total mesorectal excision (TME) has been globally recognized to improve the prognosis in patients with rectal cancer¹ and is the gold standard of care. However, there is no universal strategy for lateral lymph nodes (LLN). The treatment of the lateral compartment remains controversial and has gone to the opposite directions between Eastern and Western countries in the past decades.²

In the East, mainly Japan, surgeons consider LLN metastases as regional disease (► **Fig. 1**) and have routinely performed TME with “prophylactic” lateral lymph node dissection (LLND) without neoadjuvant (chemo)radiotherapy ([C]RT) (► **Figs. 2, 3**), even in the presence of suspicious lateral nodal involvement, in patients with clinical Stage II/III rectal cancer below the peritoneal reflection.³ This resulted in a relatively good local control, with a local recurrence rate around 10%. On the other hand, incidence of positive LLN metastasis is relatively low (10–25%). LLND is associated with disadvantages including longer operation time, increased blood loss, and a

higher risk of sexual and urinary dysfunction.⁴ Further, half of the local recurrences after LLND in patients with clinical/pathological positive LLN occurred in the lateral compartment.^{5,6} These findings suggest that prophylactic LLND without neoadjuvant treatment for all patients is overtreatment and not sufficient for local control although TME + LLND is still the standard in the Japanese national guidelines.³

In Western countries, preoperative radiotherapy or (C)RT with TME has been established as the standard treatment for clinical Stage II/III rectal cancer.^{7,8} Assuming the (C)RT can sterilize most LLN metastasis, Western colorectal surgeons do not routinely perform LLND. In fact, (C)RT + TME offers similar local control to TME + LLND with 5 to 10% 5-year local recurrence rate in patients with advanced rectal cancer.

Recent studies have demonstrated that majority of local recurrences after (C)RT + TME occur in the lateral compartment.^{9,10} This can be partly explained by decreased central recurrences by improved quality of the TME and neoadjuvant

Fig. 1 T2-weighted axial image of enlarged lateral lymph nodes between arrowheads in obturator region (A) and internal iliac region (B).

Fig. 2 Laparoscopic view after mobilization of lateral lymph node based on the anatomical landmarks.

(C)RT, but rather be explained by neglected lateral nodal disease. Importantly, half of the patients with lateral local recurrences (LLRs) have no distant recurrences at the time of diagnosis, suggesting LLN metastasis being a regional recurrent issue due to failed local control.⁹

This review highlights the recent evidences in lateral nodal disease in rectal cancer, focusing on the role of prophylactic LLND, neoadjuvant (C)RT, and the combined approach.

Prophylactic Lateral Lymph Node Dissection

In 2012, Akiyoshi et al analyzed 11,567 patients with low rectal cancer who underwent TME + prophylactic LLND

without neoadjuvant (C)RT using a Japanese nationwide multicenter database.¹¹ It was concluded that involved LLN should be considered as a regional disease as the cancer-specific survival (CSS) and overall survival (OS) of those patients were similar to mesorectal N2 disease and significantly better than Stage IV disease. The internal iliac LNs behaved like mesorectal N2a disease in terms of CSS and OS. These findings are supported by the American Joint Committee on Cancer definition, in which internal iliac LNs are classified as regional LNs in rectal cancer staging.

Georgiou et al conducted a meta-analysis in 2009 to assess the benefits of LLND compared with conventional surgery based on the results of 18 studies.⁴ It demonstrated no

Fig. 3 Laparoscopic view after right lateral lymph node dissection with en-bloc resection of internal iliac artery. TME, total mesorectal excision.

significant survival benefits of LLND in spite of increased urinary dysfunction, which supported the idea of many Western surgeons that LLND is not beneficial for rectal cancer. However, the results also showed that there were oncological survival benefits in the N+ subset. Another limitation was that only one randomized study was included and 14 studies (78%) analyzed were retrospective case-control studies.

Recently, the results of a Japanese multicenter randomized study,⁶ JCOG0212, were published. The aim was to identify noninferiority of TME alone to TME + LLND for patients with clinical Stage II/III rectal cancer below peritoneal reflection and without enlarged LLN on preoperative images as defined less than 10 mm in short axis (SA). The study compared 350 patients with TME alone to 351 with TME + LLND. It was concluded that LLND significantly decreased LLR, but failed to offer an advantage in the local recurrence-free survival. The 5-year local-recurrence-free survival were 87.7% (95% confidence interval [CI], 83.8–90.7%) in the TME + LLND arm and 82.4% (95% CI, 78.0–86.1%) in the TME alone arm. Although disease-free survival (DFS) and OS were completely equivalent, noninferiority of TME compared with TME + LLND was not statistically proven in this trial. LLND was associated with significantly longer operation time, larger amount of blood loss, and a slightly higher rate of grade 3 to 4 adverse events.

It was suggested by the authors that LLND would be effective for local control to some extent in patients with low rectal cancer. However, unfortunately the results of the study would not change clinical practice in the Western world for several reasons. First, none of the patients underwent neoadjuvant (C)RT. The local recurrence rate in the

TME + LLND arm (7.4%) was similar to the outcomes in the West, while performing LLND in obese Western patient would probably be much more difficult. Second, the rate of LLN metastasis (7%) was not very high, indicating that prophylactic LLND for patients with clinically negative LLN might be overtreatment. Third, patients with clinically positive LLN were excluded from this study, and the oncological benefits of “curative” LLND for positive nodes were unknown.

Neoadjuvant (chemo)radiotherapy

Based on several landmark studies, such as the Swedish Rectal Cancer Trial,¹² the Dutch TME trial,¹³ and the German Rectal Cancer Study Group trial,¹⁴ Western surgeons consider pre-operative (C)RT as a standard therapy for clinical Stage II/III rectal cancer. Recently more selective use of radiotherapy according to the risk for recurrence stratified by radiological assessment was introduced in daily practice to avoid unnecessary (C)RT.⁸ The European Society for Medical Oncology (ESMO) guidelines, for instance, recommend omission of radiotherapy for patients with cT3a/b rectal cancer (invasion up to 5 mm from muscularis propria) without a threatened circumferential resection margin, extramural vascular invasion or extramesorectal nodal involvement.⁸

In a study that compared a Japanese single center cohort treated with TME plus LLND without neoadjuvant therapy and a cohort in the Dutch TME trial, local recurrence rates were similar between the Japanese cohort and RT + TME cohort. The patterns of local recurrence demonstrated that RT + TME could reduce 5-year LLR compared to TME alone (0.8 vs. 2.7%).⁵

Prophylactic LLND versus (C)RT

There are no studies comparing prophylactic LLND versus (C)RT in a randomized fashion, but there is one small randomized study comparing (C)RT + TME versus (C)RT + TME + LLND. In 2001, Nagawa et al published a prospective randomized controlled trial that randomly assigned 45 patients with low rectal cancer without clinical involvement of LLN who underwent neoadjuvant RT into either TME alone or TME + prophylactic LLND. The study demonstrated no significant difference in OS, DFS and local recurrence rate between the two groups, but a higher rate of urinary and sexual dysfunction in the TME + LLND group ($p = 0.02$).¹⁵

Multiple retrospective studies have also been reported. Watanabe et al retrospectively analyzed 115 patients with clinical Stage II/III low rectal cancer and compared the DFS between RT + TME and TME + LLND. The study demonstrated no significant differences between the two groups (81.0% DFS in RT + TME vs. 72.2% in TME + LLND).¹⁶

In 2009, Kusters et al compared the oncological outcomes in matched cohorts of patients with low rectal cancers who underwent TME + LLND in Japan ($n = 324$) and RT + TME in the Netherlands ($n = 379$). Comparable 5-year LR rates were reported; 6.9% of TME + LLND and 5.8% of RT + TME, both of which were significantly better than 12% of TME alone.⁵

Although the current evidences are limited by small sample size and mostly retrospective design, these studies suggest that neoadjuvant (C)RT and prophylactic LLND both result in similar local recurrence rates for rectal cancer. It seems reasonable for the Western surgeons to treat the lateral compartment with (C)RT rather than technically demanding LLND.

Lateral Local Recurrence and Nodal Size

Several Korean studies demonstrated that neoadjuvant (C)RT + TME without LLND was not sufficient for local control in patients with enlarged LLN on baseline magnetic resonance imaging (MRI). Kim et al analyzed 366 cases of local recurrences in patients who underwent neoadjuvant CRT + TME without LLND for rectal cancer. The study showed that majority (82.7%) of local recurrences occurred in the lateral pelvic compartment (LLR).⁹ They also demonstrated linear increase in LLR with lateral nodal size.

A retrospective multicenter study,¹⁷ which involved 900 patients with rectal cancer who underwent (C)RT + TME, showed that enlarged LLN (≥ 10 mm in SA) led to a significantly worse 5-year lateral recurrence-free survival of 40.1% compared with 98.2% in SA < 5 mm and 91.7% in SA 5 to 10 mm ($p < 0.05$). Recently, two Western series showed similar results. Analyses of a cohort in England demonstrated similar results with a significantly higher rate of LLR of 33.4% in patients with LLN ≥ 10 mm in SA, compared with 10.1% in LLN < 10 mm at 4 years ($p = 0.03$).¹⁸ Secondary MRI features, such as internal heterogeneity and irregular border, were less predictive for LLR in this study. A Dutch cohort also confirmed that LLN ≥ 10 mm in SA resulted in a

significant higher 5-year rate of lateral and presacral local recurrence (37.0%) compared with 7.7% in LLN < 10 mm ($p = 0.041$).¹⁹ These findings suggest that (C)RT is not sufficient for local control of lateral nodal disease, thereby raising the question whether an “indicated” LLND would reduce such high local recurrence rates.

Combined Approach

Japanese centers reported a combined approach of (C)RT with an indicated LLND in lateral nodal disease.

In 2014, Akiyoshi et al analyzed 127 consecutive patients with clinical Stage II/III low rectal cancer.²⁰ LLND was performed selectively in 38 patients with LLN ≥ 7 mm in long-axis in pretreatment imaging, and patients without clinically positive LLN ($n = 89$) underwent only (C)RT + TME. There were three local recurrences (3.4%) in the (C)RT + TME group and no local recurrences in the (C)RT + TME + LLND group. Interestingly, majority (66%) of the latter group had pathological residual metastasis in lateral nodes after (C)RT, suggesting (C)RT did not eliminate cancer cells in lateral nodes.

In another Japanese study published in 2017 from the group of Ishihara et al,²¹ a total of 222 consecutive patients with rectal cancer who underwent preoperative (C)RT were studied. Thirty-one patients (14.0%) with LLN ≥ 8 mm in SA who underwent LLND had no local recurrences, in which 16 patients (52%) had pathologically positive lateral node metastasis. Of 191 patients who received CRT + TME, only two patients (0.9%) had LLR.

Response of Lateral Nodes to (C)RT

Literatures remain inconclusive on the question whether response of the lateral node to (C)RT changes clinical indication for LLND. Oh et al analyzed 66 patients who underwent CRT + TME + indicated LLND for patients with LLN > 5 mm in SA on pre-treatment MRI.²² Of the 36 patients with LLN persistently enlarged after (C)RT (> 5 mm in SA), 22 patients (61.1%) had pathologically positive lateral nodes. Of 30 patients with responsive shrunk nodes (< 5 mm), no pathological metastasis was identified. They concluded that LLND should be indicated for patients with persistently enlarged lateral nodes after (C)RT. In contrast, another Korean study by Kim et al investigated 377 patients who underwent CRT + TME for rectal cancer. Of 84 patients with suspicious LLN (> 5 mm in SA) on pretreatment MRI,²³ 61 (72.6%) had responsive nodes to (C)RT on posttreatment MRI (< 5 mm) including 31 treated with TME alone and 30 with TME + LLND. Patients with TME + LLND had significantly lower local recurrence at 3 years (23.1% in TME alone compared with 0% in TME + LLND). The authors concluded LLND cannot be omitted for patients with suspicious LLN on pretreatment MRI regardless of the response to (C)RT.

International Multicenter Study

In 2018, a retrospective international multicenter pooled analysis²⁴ was published including 12 centers from both

Table 1 Risk and benefit of prophylactic lateral lymph node dissection and neoadjuvant (chemo)radiotherapy

Prophylactic lateral lymph node dissection		Neoadjuvant (chemo)radiotherapy
None	Survival benefit	None
5-year local recurrence rate 10% Lower rate of lateral lymph node recurrence	Local control	5-year local recurrence rate 5–10%
Low rate of LLN metastasis 10–25%	Risk	Insufficient effect on swollen lateral lymph node
Longer operation time and larger blood loss		Late dysfunction (sexual/urinary/anal)
Sexual and urinary dysfunction		
Patients selection	Task	Patients selection

Abbreviation: LLN, lateral lymph node.

Eastern and Western countries to analyze the role of enlarged lateral nodes and to define guidelines on their management. A total of 1,216 clinical Stage II/III rectal cancer cases up to 8 cm from the anal verge were analyzed. All baseline MRIs were reviewed according to a standardized protocol with an MRI color atlas.

More than half of the patients ($n = 703$, 58%) had visible LLN on baseline MRI, of which 192 (16%) had a SA of ≥ 7 mm. LLN with a SA of ≥ 7 mm was associated with a significantly higher risk of LLR (hazard ratio; 2.060, $p = 0.045$). Notably, in patients with LLN ≥ 7 mm, LLND significantly reduced LLR (5.7% 5-year LLR in (C)RT + TME + LLND compared with 19.5% in (C)RT + TME, $p = 0.042$). It was concluded that LLR remains a significant problem after (C)RT + TME in LLN with a SA ≥ 7 mm on pretreatment MRI, and LLND results in reduced LLR.

The major limitations of this multicenter study were its retrospective nature and lack of information on the coverage of lateral compartments with irradiation. Nevertheless, this

study strongly impacted the Western surgeons as a “practice-changing study” because of its clear message that lateral nodal disease is the major cause of local recurrence after CRT, and LLND reduces the local recurrence even in the presence of lateral nodal involvement.

Conclusions

Quality of TME will likely improve with development of surgical techniques. Further reduction in central local recurrences will be expected in future. LLR will become an increasing issue unless adequately treated. In patients with positive lateral nodes, neoadjuvant (C)RT and LLND is not mutually exclusive (►Table 1). The combination of the two approaches would be needed (►Fig. 4). A prospective trial with standardized radiotherapy and surgery in an international setting will clarify the role of combining these two approaches, which will convert clinical practices of the East and the West.

Fig. 4 Risk-adapted strategy for patients with cT3/4 low rectal cancer. LLND, lateral lymph node dissection; MRI, magnetic resonance imaging; TME, total mesorectal excision.

Conflict of Interest

None.

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