Does Lateral Lymph Node Matter in Rectal Cancer?

Mohammad Reza Keramati, MD FEBS FASCRS

Associate Professor of Colorectal Surgery

Division of Colorectal Surgery, Department of Surgery, Tehran University of Medical Sciences

Email: mr-keramati@tums.ac.ir
TME is currently the gold standard treatment of rectal cancer.

Lateral pelvic lymph node dissection has been suggested as an approach to decrease recurrence and improve survival.

In recent years, there have been debates regarding the clinical relevance of lateral pelvic lymph nodes (LPLN) for mid to low rectal cancers.
Lymphatic Drainage of the Rectum & Lateral Pelvic Lymph Nodes

Figure 1 – Lymphatic drainage of the rectum and lateral pelvic lymph nodes

1. Inferior mesenteric artery
2. Common iliac artery
3. External iliac artery
4. Obturator artery
5. Obturator nerve
6. Internal pudendal artery
7. Middle rectal artery
8. Inferior rectal artery

Extent of Lymphadenectomy (D1, D2, and D3)

LPLND was first described in 1950’s, however, because of its significant morbidity and postoperative functional disabilities, was abandoned.

Benefits of LPLND and routine LPLND for patients with rectal cancer were proposed later in Japan.

Surgeons include neoadjuvant pelvic radiation therapy for the management of extra-mesorectal disease in locally advanced rectal cancer.

The focus has been predominantly on the quality of the mesorectal excision with the aim of decreasing central recurrences in Western countries.

The emphasis has been on the completeness of lymphadenectomy in Eastern countries.

GUIDELINES
• The NCCN panel does not recommend extension of nodal dissection beyond the field of resection (eg, into the distribution of iliac lymph nodes) unless these nodes are clinically suspicious.
• LPLND is indicated when
  • the lower border of the tumor is located distal to the peritoneal reflection
  &
  • the tumor has invaded beyond the muscularis propria

CLINICAL TRIALS
Non-inferiority phase III trial
- on prophylactic LPLND for patients without radiological evidence of suspicious LPLN metastasis

Included patients:
- clinical stage II–III rectal cancer below the peritoneal reflection and no lateral lymph node enlargement.

Patients were randomized into: TME or TME+LPLND

Primary endpoint: Recurrence-Free Survival (RFS) using long-term follow-up data.

No. of patients: 701 (TME+LPLND=351, TME=350)

**Results:**

- **RFS:**
  - TME+LPLND=71.1% , TME= 70.7%
  - (hazard ratio=1.09, P =0.064)
- **Subgroup analysis:**
  - Improved RFS among patients with clinical stage III disease who underwent TME+LPLND

**Conclusion:**

- TME+LPLND is recommended for patients with clinical stage III disease.
- LPLND could be omitted in those with clinical stage II tumors.
• **Aim**: ad-hoc analysis was to evaluate the impact of LPLND on survival

• **No of patients**: 445
  - TME+LPLND = 215, TME = 230

• **Result**:
  - Main analysis: LPLND had **no impact** on
    - relapse-free survival
    - overall survival
  - Subset analysis: LPLND **improved** relapse-free survival in
    - female patients
    - patients with stage B/C or N3/4 disease
ad-hoc analysis of ACTS-RC Trial

Conclusion

• LPLND **does not improve** relapse-free survival and overall survival in patients with mid and low rectal cancer.

• LPLND have a **prognostic impact** on patients with highly invasive rectal cancer.
Meta-analysis & Systematic Reviews
Aim:
  - to compare outcomes of TME+LPLND and TME alone

No. of included studies: 29
No. of included patients: 10,646

Groups:
  - TME+LPLND = 39.4%
  - TME = 60.6%
Outcome of lateral pelvic lymph node dissection with total mesorectal excision in treatment of rectal cancer: A systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Country</th>
<th>Design</th>
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* Reported different outcomes of the same cohort of patients, thus were included in the total number of patients as a single study.
RESULTS

• Median operation time
  • TME+LPLND > TME (360 vs. 294.7 minutes, P = 0.02)

• Overall complications
  • TME+LPLND > TME (Odds ratio = 1.48, P < .001)

• Urinary dysfunction
  • TME+LPLND > TME (Odds ratio = 2.1, P = .008)

• Male sexual dysfunction
  • TME+LPLND = TME (Odds ratio = 1.62, P = 0.08)

• Anastomotic leakage
  • TME+LPLND = TME (Odds ratio =1.15 , P =0.59)

• Local recurrence
  • TME+LPLND = TME (hazard ratio = 0.96 , P =0.79)

• Distant metastasis
  • TME+LPLND = TME (hazard ratio =0.96 , P =0.72)

• Overall survival
  • TME+LPLND = TME (hazard ratio = 1.056, P = 0.13)

• Disease-free survival
  • TME+LPLND = TME (hazard ratio = 1.02, P =0.37)
They concluded:

• LPLND was not associated with a significant reduction of recurrence rates or improvement in survival as compared with TME alone.

• However, LPLND was associated with longer operation time and increased complication rate.
• No. of studies: 15
• Aim:
  • to compare the prognostic benefits of LPLND in patients with **locally advanced** rectal cancer.
• Outcomes:
  • 5-y overall survival
  • 5-y disease-free survival
  • local recurrence
  • distant recurrence
  • grade 3-4 postoperative complications
Table 1 – Characteristics of the 15 selected studies in the meta-analysis.

<table>
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<tr>
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<th>Year</th>
<th>Country</th>
<th>Type</th>
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CRT = preoperative chemoradiotherapy; LPLD = lateral pelvic lymph node dissection; LPLN = lateral pelvic lymph node; NR = not reported; RCT = randomized controlled trial.
• LPLND significantly increased grade 3-4 postoperative complications.

• There were no significant differences in
  • 5-y overall survival (hazard ratio = 0.90, P = 0.17)
  • 5-y disease-free survival (hazard ratio = 1.12, P = 0.73)
  • local recurrence (OR = 0.89, P = 0.68)
  • distant recurrence (OR = 0.85, P = 0.24)
Algorithm:

1. **Low risk** of LPLN disease (cT1/T2/early T3 with clinically negative LPLN on MRI)
   - \(\rightarrow\) TME alone

2. **Moderate risk** of LPLN disease (cT3+/T4 with clinically negative LPLN on MRI, potential microscopic disease)
   - \(\rightarrow\) neoadjuvant treatment + TME or TME+LPLND

3. **High risk** of LPLN disease (clinically abnormal LPLN on MRI, macroscopic disease)
   - \(\rightarrow\) neoadjuvant treatment + TME and LPLN dissection (particularly if the abnormal nodes do not respond to neoadjuvant treatment based on interval imaging)
Interpreting the literature

• Important challenge for interpreting the literature is the **heterogeneity of the patient groups in the studies**

  • high-risk vs. low-risk disease
  • intent of dissection
  • use of neoadjuvant radiotherapy
  • underlying clinical assessment of LPLN metastasis
• The role of LPLND versus neoadjuvant radiation therapy continues to be debated.

• Recommendations for future studies:
  • to evaluate therapeutic role of LPLND after neoadjuvant chemoradiation for patients with clinical LPLN
  • to decrease the risk of complications associated with LPLND.
Thank you for your attention.