

Is the Routine Dissection of Lateral Lymph Nodes Really Necessary After Mesorectal Excision for Clinical Stage II/III Lower Rectal Cancer?

To the Editor:

We read with interest the article of Fujita et al “Mesorectal Excision With or Without Lateral Lymph Node Dissection for Clinical Stage II/III Lower Rectal Cancer (JCOG0212). A Multicenter, Randomized Controlled, Noninferiority Trial” published in *Annals of Surgery*.¹

The guidelines of Japanese Society for Cancer of the Colon and Rectum (JSCCR) recommend lateral lymph node dissection (LLND) for clinical stage II/III low rectal cancer: “Lateral lymph node dissection is indicated, when the lower border of the tumor is located distal to the peritoneal reflection and the tumor has invaded beyond the muscularis propria.” Actually, according to JSCCR “the incidence of lateral lymph node metastasis was 20.1% among patients whose lower rectal tumor border was located distal to the peritoneal reflection and whose cancer invaded beyond the muscularis propria.” After performing LLND for this indication, it is expected that the risk of intrapelvic recurrence decreases by 50%, and 5-year survival improves by 8 to 9%.² In contrast, the Western practice does not warrant the LLND in the absence of clinically suspected lateral lymph node metastasis (LLNM), due to the few number of LLNM, the negligible survival impact of LLND over CRT, and high postoperative morbidity.³

The initial answer to this unresolved dilemma was reported in 2012, when the authors published the postoperative morbidity and mortality results of the same trial (JCOG0212).⁴ Currently, they reported the oncological results after a minimum follow-up of 5 years.¹ Fujita et al included only patients with T3–T4 lower rectal cancer, who due to the high frequency of positive LLNM (16.7% in T3 and 34% in T4) were included in the trial. This selection parameter reduced the bias of the Dutch trial, which included 30% of stage I rectal cancers and reported with local recurrences in 6% in the

CRT with TME and 12% in the TME group.⁵ Differently, the Fujita’s trial has a low risk of bias in all domains, except for the allocation procedure that was not masked to investigators or patients. In the 701 patients randomized the noninferiority of TME alone versus TME with LLND was not confirmed in the intent-to-treat analysis—the 5-year relapse-free survival in the TME with LLND and TME alone groups was 73.3% and 73.4%, respectively ($P = 0.0547$). The 5-year overall and local-recurrence-free survival in the TME with LLND versus TME alone groups were 92.6% versus 90.2%, and 87.7% versus 82.4%. TME with LLND had lower overall (7%) and lateral local recurrences (15%) compared with TME alone (13% and 54%).¹

LLND requires high expertise in rectal surgery with pelvic autonomic nerve preservation to obtain radical oncological treatment without urinary and sexual dysfunction. In the first paper, Fujita et al reported that the LLND, although performed in specialized centers, was associated with significantly longer operation time and greater blood loss than TME alone—median 360 minutes versus 254 minutes and 576 mL versus 337 mL.⁴ These results led some surgeons to a “limited LLND strategy” only for patients with suspicious LLNM based on the pretreatment imaging.

On the other hand, the systematic review and meta-analysis of Georgiou et al (20 studies, 5502 patients) reported that TME with LLND did not confer significantly better 5-year overall and disease-free survival in LLND compared with nonextended lymphadenectomy. The major limitation of this meta-analysis, however, was the inclusion of retrospective studies and patients with different Dukes’ stages (A–C).⁶

Probably, the major limitation of Fujita’s trial is the lack of neoadjuvant CRT which was explained as follows: “First, the effectiveness and safety of adjuvant or neoadjuvant chemoradiotherapy for rectal cancer had not been clearly shown when we designed the protocol of this study. Second, adjuvant radiotherapy is not commonly used in Japan because of the lower local recurrence rate and better prognosis for patients in Japan than for those in Europe and North America.”⁴

Notwithstanding, the role of neoadjuvant CRT in LLNM remains unclear with few reports published in the literature. In the study by Akiyoshi et al, 127 patients with stage II–III low rectal cancer who underwent neoadjuvant CRT and TME were reported. LLND was performed only in patients with suspected metastasis on CT or MRI. LLNM was confirmed by pathologists in 66% of the LLND group. Local recurrence developed in

3.4% only in the TME group. The 3-year relapse-free survival was insignificantly higher in the LLND group—84% versus 75%. The authors concluded that the LLNM “itself was not a poor prognostic indicator after preoperative CRT and LPLD, suggesting that LPLN metastasis is a regional disease that is amenable to curative resection.”⁷ In the study by Inoue et al none of the patients in the downsized LLN group developed recurrence versus 55% recurrence rate in persistent positive LLN.⁸ In the study by Nagasaki et al the addition of CRT to LLND was compared. The 5-year overall, relapse-free survival, and local recurrence rates were significantly lower in the CRT group—78%, 72%, and 3.5% versus 41%, 25%, and 39.6%, respectively. Fifty percent of the patients with LLND without neoadjuvant CRT developed LR in the lateral pelvic region. The authors concluded that “these poor long-term outcomes suggest that LLND without preoperative CRT is a suboptimal treatment for patients with LLNM”⁹ and the present results strongly support the use of preoperative CRT in patients with LALRC with suspected LLNM.⁹ All studies came to the same conclusion—CRT and LLND separately cannot cure the LLNM so they should be combined.

Fujita et al¹ included only patients with no clinical evidence of LLNM and lateral lymph nodes less than 10 mm in short-axis on CT/MRI were defined as negative. However, they found metastases in 7.4% of LLND, “suggesting that the diagnostic accuracy of clinical lateral pelvic lymph node metastasis might not have been sufficient.”¹ Differently, Yamaoka et al¹⁰ reported a cut-off value of 6.0 mm with a sensitivity of 79% and specificity of 83%.

Actually, Fujita et al demonstrated the effectiveness of TME with LLND, but new RCTs are needed to evaluate the role of neoadjuvant CRT in addition to LLND and to define more accurate indications for LLND, especially after neoadjuvant CRT.

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