



Lateral Pelvic Lymph Node Dissection—Are we ready to bridge the gap between the West and the East?

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Comment on: Fujita S, Mizusawa J, Kanemitsu Y, *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. *Ann Surg* 2017;266:201-7.

Received: 12 October 2017; Accepted: 30 October 2017; Published: 06 November 2017.

doi: 10.21037/ales.2017.10.04

View this article at: <http://dx.doi.org/10.21037/ales.2017.10.04>

Fujita *et al.* need to be commended for conducting a very large, long duration randomized controlled trial (RCT) which is an admirable attempt to further refine the treatment of low rectal cancer. However, there being a major philosophical difference in the treatment of rectal cancer between the West and Japan, the study needs to be carefully scrutinized for adoption into practice in the rest of the world. Lateral pelvic node metastasis is considered a localized disease in Japan but a systemic disease in the west. Lateral pelvic lymph node dissection (LPLND) without preoperative chemoradiation is a standard part of treatment for T3/T4 low rectal cancer in Japan, but in the west lateral pelvic lymph node (LPLN) metastasis is managed by neoadjuvant chemoradiation (NACTRT) (1). An intermediate group pursues selective LPLND for enlarged LPLN persisting after NACTRT balancing morbidity of LPLN dissection and preventing local recurrence (2,3).

This study started in 2003 and completed accrual in 2010 and it is crucial to note that revolutionary changes occurred in the management of rectal cancer during these years—adoption of NACTRT and routine use of magnetic resonance imaging (MRI) scans in predicting positive margins, nodal status and subsequently survival. Neither of these was applied in the design of the study which is an inherent drawback of such long drawn studies wherein the scientific advances that occur during the study period cannot be assessed in the analysis.

Local recurrences were more common laterally in the post total mesorectal excision (TME) era in low rectal cancers. Neilsen *et al.* showed in his review article that even after improvement in complete resection by introduction of TME, recurrences at the pelvic side wall are still common probably

related to the LPLNs (4).

The role of LPLND in the era of NACTRT is controversial. Akiyoshi *et al.* found that LPLN metastasis was present in 66% of the patients who underwent selective LPLND after NACTRT with enlarged lateral pelvic nodes on pre-treatment imaging. He also showed that there were no local recurrences in the LPLND group thus supporting therapeutic LPLND (2). This is further supported by the observation from Kim *et al.* that lateral pelvic recurrence was the major cause of locoregional recurrence among patients who receive NACTRT followed by TME without LPLND (5). Contrary to this, Watanabe *et al.* showed that in his paper, 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 NACTRT (6).

Also a meta-analysis of 5,502 patients assessed the addition of LPLND to standard TME surgery. Although limited by heterogeneity of studies, this showed no significant improvement in overall survival, local and distant recurrence rates. However, there was more significant blood loss and increased sexual and urinary complications (7). Similarly, Fujita *et al.* in their earlier analysis of postoperative complications in the same trial showed that there was more blood loss (significant), anastomotic leakage rate (not significant) and grade 3–4 complications (not significant) (8).

Kim *et al.* in his paper have divided patients with enlarged LPLN on pretreatment MRI into three groups. Those who had good response to NACTRT underwent either TME alone (Group A) or TME + LPLND (Group B) and those

who had persistently enlarged LPLN's underwent TME + LPLND (Group C). Local recurrence rates were 22.6%, 0%, 17.4% respectively. This study suggests that LPLND cannot be omitted even with good response to NACTRT (9).

Prophylactic LPLND is routinely performed as an adjunct to TME in locally advanced low rectal cancers in Japan. Fujita *et al.* in this well conducted RCT, have compared mesorectal excision with or without prophylactic lateral lymph node dissection for clinical stage II/III lower rectal cancer to show non-inferiority of TME to TME + LPLND (10). The primary endpoint was relapse free survival, and non-inferiority margin for hazard ratio was set at 1.34. They included stage II/III low rectal cancer (lower margin below peritoneal reflection) without enlarged lateral pelvic nodes [short axis diameter less than 10 mm on computed tomography (CT) or MRI]. Neoadjuvant treatment was not given and adjuvant chemotherapy was given to stage III patients.

They randomized 351 patients to TME + LPLND arm and 350 patients to TME alone arm. The 5-year relapse free survival and overall survival were equal in both groups which failed to show non inferiority of TME, supporting TME + LPLND as the standard of treatment. Because of low actual number of events, the actual statistical power is lower than expected. Local recurrence rates were 7% versus 13% in TME + LPLND and TME groups.

It is well known that CT scan is a poor indicator of nodal positivity and even small nodes in the mesorectum tend to have metastases. Akiyoshi in his data showed that 33% of patients had LPLN metastasis if short axis diameter in MRI was 6–7 mm and 53% had metastasis if short axis diameter was 8–9 mm (11). This might explain the higher local recurrence rates in the TME alone group which possibly had metastatic small (10 mm or less) LPLN. So standardized high-resolution MRI technique with reporting by trained radiologists taking into consideration both size and other nodal characteristics would be a better predictor of nodal involvement (12). It is a proven fact that neoadjuvant radiation (NART) reduces the local recurrence rate by approximately 6% (13). Similarly in this study, the local recurrence rate fell by 5% with the addition of LPLND to TME which is the same benefit obtained by NACTRT. Also, this paper shows LPLND is effective in preventing lateral pelvic recurrences but not central or anastomotic recurrences whereas NACTRT would be effective in decreasing all pelvic recurrences.

Not being able to specify the circumferential resection margin (CRM) status is a significant drawback of this study,

as CRM involvement is a very important confounding factor in determining local recurrence. It is very likely that patients with lateral pelvic nodes may have had nodes threatening/infiltrating the CRM and these patients would be obviously faring worse. Even the authors admit that patients with threatened CRM would be receiving NACTRT in the present day and this approach would automatically bring down local recurrence rates.

While the relapse free survival and overall survival were not different in the two groups, lateral pelvic recurrences were common where LPLND was not performed. Keeping this in mind, Prophylactic LPLND in Japan will be followed given their high local recurrence rates. However, the enthusiasm by which this was performed may decline in those who realize the drawback of selection criteria of nodal size (less than 10 mm) and the actual difference in local recurrence would be small if a small nodal size cut-off and other nodal characteristics were taken into account. As NACTRT is the norm in most countries other than Japan, this study is unlikely to influence the practice in the rest of the world.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Laparoscopic and Endoscopic Surgery*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/ales.2017.10.04>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/ales.2017.10.04

Cite this article as: Mahendra BK, Vallam KC, Saklani A. Lateral Pelvic Lymph Node Dissection—Are we ready to bridge the gap between the West and the East? *Ann Laparosc Endosc Surg* 2017;2:158.