



Lateral lymph node dissection in clinical stage 2–3 mid and lower rectal cancer: is there a clinical benefit?

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We have read with great interest the paper recently published by Fujita *et al.* (1) on *Annals of Surgery* reporting the 5-year oncologic results of a multicenter, randomized controlled, noninferiority trial comparing mesorectal excision with or without lateral lymph node dissection (LLND) for lower rectal cancer. The aim of this large randomized controlled trial is to shed additional light on this controversial topic bringing new level 1 of evidence data to the surgical community. The Japanese JCOG0212 trial (1) was designed to shed more light with a high level of evidence on the possible benefits of LLND in terms of long-term survival and recurrence rates. A total of 701 stage 2–3 mid-lower rectal cancer patients without enlarged lateral lymph node were enrolled: 351 patients were randomized to mesorectal excision with LLND and 350 patients to mesorectal excision alone. Primary endpoint was relapse-free survival, with a noninferiority margin for the hazard ratio of 1.34. Secondary endpoints were overall survival and local recurrence-free survival. With a median follow-up of 72.2 months, the 5-year relapse-free survival was 73.4% after LLND and 73.3% after mesorectal excision alone, the 5-year overall survival rates were 92.6% and 90.2%, and the 5-year local recurrence-free survival rates were 87.7% and 82.4%, respectively. Since the upper limit of the three 95% confidence intervals were above the noninferiority margin of 1.34, the noninferiority of mesorectal excision alone to LLND was not demonstrated. The local recurrence rate was significantly lower after LLND (7% *vs.* 13%, $P=0.024$), mainly due to significantly fewer recurrences in the lateral pelvis (1.1% *vs.* 6.6%, $P<0.05$). The results of this study

show better oncologic outcomes after LLND than after mesorectal excision alone. However, the interpretation of these results needs some caution for several reasons. First, the differences observed in terms of overall survival are less than 3% and it should be questioned if this difference is clinically relevant. Second, LLND led to lower local recurrence rates compared to mesorectal excision alone; however, LLND did not prevent the occurrence of lateral recurrence. Third, all patients included in this study did not receive neoadjuvant chemoradiation therapy.

Tumor involvement of lateral lymph nodes is reported in up to 20% of patients with locally advanced lower rectal cancer (2-5) and may represent a cause of poor survival in those patients who undergo total mesorectal excision (TME) alone.

During the last 20 years, several approaches have been developed to lower the local recurrence in rectal cancer patients. While TME with LLND is considered the standard procedure for the surgical treatment of extraperitoneal rectal cancer in Japan even in the absence of enlarged lateral lymph nodes (6), neoadjuvant chemoradiation therapy followed by TME is the standard of care in the Western countries (7,8). Several reasons may explain the adoption of such different strategies in the Western and Eastern countries. First, lateral lymph node metastases are considered distant metastases in Europe or North America and regional lymph node metastases in Asia (9). Second, the role of LLND has been challenged in the Western countries by the very low local recurrence rates obtained with the use of radiochemotherapy (that usually

includes the lateral pelvic lymph nodes in the radiation target volume) followed by TME (10). Third, the current evidence available from the literature is controversial and does not support LLND in rectal cancer patients without clinically suspected preoperative lateral lymph node metastases (11). Lastly, the incidence of lateral lymph node metastases might differ between Asia and Western countries. Kim *et al.* (12) published in 2008 the results of a retrospective analysis of 366 Korean patients who had undergone neoadjuvant chemoradiation therapy followed by TME for rectal cancer. Local recurrence occurred in 29 (7.9%) patients: 6 (20.7%) patients had central pelvic recurrence, while 24 (82.7%) lateral pelvic recurrence. One patient had simultaneous central and lateral pelvic recurrence. The size of the lateral lymph nodes was independently associated with lateral pelvic recurrence. In particular, among the 250 ypN0 patients, lateral pelvic recurrence developed in 1.4%, 2.9%, and 50% of patients with lateral lymph node sizes of <5, 5–9.9, and ≥ 10 mm, respectively. Among the 116 ypN+ patients, lateral pelvic recurrence occurred in 4.3%, 35.7%, and 87.5% of patients with lateral lymph node sizes of <5, 5–9.9, and ≥ 10 mm, respectively. On the contrary, Syk *et al.* (13) found that the lateral lymph node metastases are not a major cause of local recurrence after TME. They reviewed 880 rectal cancer patients undergoing curative TME in Sweden (528 of them after neoadjuvant short-course radiotherapy) and tumor recurrence originated in lateral lymph nodes only in 2 (0.2%) patients.

Only a few prospective studies comparing TME with or without neoadjuvant radiation therapy and TME with LLND have been published. A meta-analysis of 20 studies (of them, only 1 was a randomized controlled trial and 3 prospective non-randomized studies) including 5,502 patients found that LLND does not seem to significantly improve overall 5-year survival, 5-year disease-free survival, local recurrence and distant metastases rates, while operative time is longer and intraoperative blood losses are greater. Urinary and sexual dysfunctions appear to be increased after LLND (14). For instance, Nagawa *et al.* (15) reported the functional outcomes at 1 year after mesorectal excision with or without LLND, showing that LLND was burdened by a significantly higher rate of both urinary and sexual dysfunctions than the mesorectal excision alone. Similarly, Kyo *et al.* (16) reported significant impairment of sexual function, mainly ejaculation, in 15 patients undergoing mesorectal excision with LLND compared to 22 patients who received mesorectal resection alone.

A few years later, the poor short-term outcomes reported by Georgiou *et al.* (14) were confirmed by the results of the Japanese large prospective multicenter, randomized, non-inferiority JCOG0212 trial (17). A total of 701 patients with a stage 2 or 3 mid and lower rectal cancer with no lateral lymph node enlargement were enrolled in the study: 351 were randomly assigned to mesorectal excision with LLND and 350 to mesorectal excision alone. Mesorectal excision with LLND took significantly longer than mesorectal excision alone, and intraoperative blood losses were significantly higher. A slightly higher incidence of postoperative grade 3–4 complications according to Clavien-Dindo classification was observed in the group of patients treated with LLND (22% *vs.* 16%), with no significant differences in terms of anastomotic leakage between the two groups (6% *vs.* 5%, $P=0.46$).

One of the major reasons that have prevented the adoption of LLND in Western stage 2 and stage 3 rectal cancer patients is the evidence coming also from Asia that the use of neoadjuvant chemoradiation therapy achieves the same oncologic outcomes of LLND with less adverse outcomes. For instance, Kusters *et al.* (18) reviewed the pattern of local recurrence in 1,134 patients with rectal cancer. A total of 755 patients were selected from the database of the Dutch TME-trial: 379 underwent TME alone while 376 patients were treated with short-course neoadjuvant radiotherapy followed by TME. This group of patients was compared with a group of 324 patients who were selected from the database of the National Cancer Center Hospital in Tokyo and underwent rectal resection with LLND. The lateral recurrence rate was 0.8% among the patients who had neoadjuvant radiotherapy followed by TME. Higher recurrence rates in the lateral pelvis were observed among patients who underwent TME alone (2.7%) or rectal resection with LLND (2.2%), showing that neoadjuvant radiation therapy might play a major role in reducing the risk of local recurrence in the lateral lymph nodes. No significant differences in local recurrence rates and survival after neoadjuvant long-course radiotherapy followed by mesorectal excision with or without LLND were also found by Nagawa *et al.* (15) in their randomized controlled trial. The authors concluded that LLND does not add oncologic benefits in patients with locally advanced lower rectal cancer who receive neoadjuvant radiotherapy. These results are consistent with the findings reported by Watanabe *et al.* (19), who included 115 locally advanced rectal cancer patients in a retrospective comparative study: neoadjuvant radiotherapy was delivered in 78 patients

and mesorectal excision with LLND was performed in 75 patients. While a significantly higher 5-year disease-free survival rate was observed in patients who received preoperative radiotherapy (74.6% *vs.* 45.9%, $P=0.006$), survival rates did not significantly differ between those patients who had preoperative radiotherapy followed by mesorectal resection with or without LLND. Finally, a recent study from the United States has further challenged the role of LLND even in patients with enlarged lateral lymph nodes who receive neoadjuvant treatment. Dharmarajan *et al.* (20) compared 30 patients with enlarged lateral lymph nodes with 23 patients without suspected lateral lymph node metastases. All patients underwent neoadjuvant radiotherapy followed by TME. Local recurrence, overall and disease-free survival rates were similar regardless of the presence of enlarged lateral nodes.

In conclusion, the 5-year oncologic results of the JCOG0212 study bring new knowledge on the impact of LLND on the survival of patients with stage 2–3 rectal cancer without evidence of enlarged lateral lymph nodes with level 1 of evidence. However, large randomized controlled trials including neoadjuvant chemoradiation therapy in the study protocol are needed to give more definitive answers on the real oncologic benefits of LLND.

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