Editorial Commentary

Robot-assisted laparoscopic surgery beyond total mesorectal excision for rectal cancer

Yukihide Kanemitsu

Department of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan

Correspondence to: Yukihide Kanemitsu, MD. 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Email: ykanemit@ncc.go.jp.

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Rectal surgery is the standard treatment for patients with non-metastatic rectal cancer. Expert surgery, which includes total mesorectal excision (TME) (1), is of crucial importance for mid-rectal and low rectal cancer patients in that it provides complete removal of the tumor-bearing rectum and its associated lymph nodes within the mesorectum and thus minimizes the risk of resection margin positivity and local recurrence. However, patients with advanced low rectal cancer occasionally develop metastases to the lateral pelvic lymph nodes like common iliac, internal iliac, external iliac, and obturator nodes, which are located outside the surgical field of TME (2,3). Additional treatment is therefore often required to reduce local recurrence.

The West and East differ in terms of the treatment that is combined with TME, particularly in Japan. Western surgeons rely on preoperative chemoradiotherapy (CRT) to sterilize remnant cancer cells, including those in lateral pelvic lymph nodes (LLNs). In contrast, Japanese surgeons rely on a surgical approach to prevent local recurrence, which includes lateral lymph node dissection (LLND) without CRT (4). A retrospective multicenter study in Japan has reported an 18.1% incidence of LLN metastasis in patients with T3 or T4 lower rectal cancer that is has developed at or below the peritoneal reflection (2). However, these data included those of all patients, irrespective of suspected lateral lymph node metastasis, making the evidence insufficient to be able to recommend LLND for patients with rectal cancer without clinically suspected LLN metastasis (5).

We previously conducted a randomized controlled trial to confirm the non-inferiority of TME alone to TME with LLND in terms of efficacy for stage II and III low rectal cancer patients without obvious LLN enlargement where CRT is not performed (JCOG0212, ClinicalTrials.gov; NCT00190541, UMIN-CTR; C000000034). The postoperative short-term outcomes have already shown that lateral dissection can be performed safely (6). In the primary analysis, not only the non-inferiority of TME alone to nerve-preserving LLND was not demonstrated in relapse-free survival (RFS) as the primary endpoint, but also the inferiority of TME alone to TME + LLND was demonstrated in the local recurrence rate as the secondary endpoint. The frequency of lateral recurrence was much lower in the LLND group (4 of 351 patients) than in the TME group (23 of 350 patients) (7). The main message from this trial was that failing to treat the lateral pelvic area will result in high rates of local recurrence (5-year recurrence rate of 17.6%).

Two different types of LLND indications must be taken into consideration: “prophylactic LLND” and “therapeutic LLND”, both of those are invariably performed together with standard TME. These procedures can be carried out regardless of nerve-sparing procedures. Prophylactic LLND is typically performed for locally advanced low rectal cancer without obviously enlarged lateral pelvic lymph nodes. However, therapeutic LLND is performed only when the lateral lymph nodes appear enlarged on preoperative imaging: for example, when the nodes are greater in diameter than 10 mm. The Japanese national guidelines indicate that prophylactic bilateral LLND should be performed in all locally advanced rectal cancers below the peritoneal reflection (4). Some researchers have suggested that dissection can be omitted in cases that do not show lateral metastasis provided the presence or absence of

lateral lymph node metastasis can be efficiently determined. However, the false negative rate for lateral metastasis was 7% in JCOG0212 (6). Lateral metastasis without mesorectal metastasis (skip metastasis) was observed in 5%, and the bilateral metastasis rate among lateral metastasis cases was 15% to 20% in our previous retrospective study (8), with many of these cases being difficult to identify by preoperative diagnostic imaging. The findings from JCOG0212 and our own case studies support the validity of TME + bilateral dissection, which is the standard procedure for advanced low rectal cancer in Japan, in which adjuvant radiotherapy for curatively resected rectal cancer is not routine.

Minimally-invasive surgical procedures, including laparoscopic surgery (LAP), have been suggested to improve the surgical management of patients with rectal cancer. LAP is widely accepted as the standard of care for colectomy in colon cancer patients (9). Conversely, preliminary results of studies assessing LAP for TME in patients with rectal cancer have raised various questions regarding the safety and effectiveness of this procedure (10). Recent studies have found that LAP for rectal cancer is both safer and associated with lower postoperative morbidity than with the conventional open surgical procedure (11,12); however, there are few reports on the long-term oncological outcomes of LAP in rectal cancer patients. LAP for rectal cancer achieves a good field of view in the pelvis, but due to concerns such as forceps interference and limited range of motion, the technical difficulty of LAP is particularly high in the deep pelvis, with a learning curve of 50-90 cases needed. Compared with open surgery, JCOG0404 (13) demonstrated differences in the frequency of postoperative complications and 5-year RFS rate between facilities with LAP. Moreover, two RCTs [the ALaCaRT trial (14) and the ACOSOG Z6051 trial (15)] did not find LAP to be non-inferior to open surgery with respect to the pathological completeness of rectal surgical specimens. Follow-up results of both trials also failed to demonstrate the non-inferiority of LAP for disease-free survival and local recurrence (14,16). There were no significant differences in locoregional recurrence, disease-free survival, or overall survival in the ALaCaRT trial of open versus LAP for rectal cancer; however, the 2-year findings for recurrence and survival are consistent with changes that increasingly favor of the open technique. Caution must be exercised when recommending laparoscopic procedures, though, and, from the ALaCaRT results alone, LAP cannot be considered a routine standard treatment for rectal cancer (14).

The robot-assisted laparoscopic technique using the da Vinci surgical system involves stable operation with free multi-joint forceps with motion scaling and a shake correction function under three-dimensional high-resolution imaging. Even in the deep pelvis, cuts can be made at an ideal angle based on the ideal cutting line, and thus delicate and accurate surgery along the anatomical structure can be performed smoothly. The learning curve is reportedly 15–30 cases (17), which is more achievable than that for conventional laparoscopic surgery. The da Vinci surgical system is currently in its fourth generation (Xi), and at the same time, a range of devices have been developed and continue to evolve, such as sealing devices, robot staplers, and operating tables with robot-compatible table motion functions. This new surgical system offers several advantages over conventional LAP that may ultimately overcome its drawbacks like use of straight and inflexible devices, unreliable intraoperative views, and surgeons having to adopt ergonomically uncomfortable postures. The technical advantages of robotic surgery may eventually help to achieve complete and thorough lymphadenectomies. LLND, however, remains technically demanding.

In *Surgical Endoscopy*, Yamaguchi *et al.* (18) compared the long-term survival outcomes after open LLND (OLLND) versus robot-assisted laparoscopic LLND (RALLND) for patients with locally advanced low rectal cancer. In this retrospective study, 87% of patients underwent prophylactic LLND and 23% underwent therapeutic LLND, with fewer than 8% of patients receiving neo CRT. Using exact matching, patients were stratified into RALLND (n=78) and OLLND (n=78) groups. No significant differences between the groups were seen in pathological stage or number of harvested lymph nodes. The rate of positive resection margin in the RALLND group tended to be lower than that of the OLLND group (P=0.059). The 5-year overall survival rates were 95.4% in the RALLND and 87.8% in the OLLND groups (P=0.106), the 5-year RFS rates were 79.1% and 69.9%, respectively (P=0.157), and the 5-year local RFS rates were 98.6% and 90.9%, respectively (P=0.029). Based on the more favorable outcomes with RALLND, the authors concluded that RALLND may be a useful modality for locally advanced low rectal cancer.

However, several inherent biases may limit the study's impact. While RALLND may indeed provide a survival benefit, several points need to be studied before reaching any conclusions. The matching technique used in the study is based on the matching of available and chosen data. For instance, a total of 155 (49.8%) patients were not 'matchable' (6% of RALLND and 65.8% of OLLND)

and were therefore excluded. Since the authors matched pairs based on cT, cN, and neo CRT, several factors that might influence survival were not matched for. Information regarding the actual year of treatment, tumor size, number of lateral lymph node metastases, and diameter of enlarged lateral lymph nodes was not available and thus was not controlled for. Moreover, histological type was not matchable due to the small number of poorly differentiated/mucinous carcinoma cases. Thus, those who received RALLD may have been intrinsically more suited to a minimally-invasive approach, or had less extensive disease overall.

LAP-LLND has been successful in many branches of surgery, with numerous reports available on its feasibility, safety, and short-term effectiveness in rectal cancer (19, 20). As mentioned by the authors, if robotic surgery offers better dexterity of movement, especially when working in confined spaces such as the pelvis, the benefits of RALLND need to be established after comparison with conventional LAP-LLND techniques other than OLLND. Since robotic surgery is expensive, cost data should also be reviewed to evaluate the financial impact of having a surgical robot in the hospital. The median BMI of patients in the study (18) was 22.7 kg/m^2. When comparing the feasibility of LLND between Japanese and Western patients, differences in BMI might have a major impact. Japanese patients are usually thinner than Western patients (21). Obesity renders LLND with nerve-sparing techniques particularly difficult to perform, which increases both the number of complications and morbidity. These could overshadow oncologic outcomes and worsen the results of LLND to a greater extent in Western patients than in Japanese patients. However, robots might be able to overcome the obesity-related limitations of LLND for rectal cancer.

Although the study by Yamaguchi *et al.* (18) is of major importance, given its focus on the assessment of long-term outcomes after RALLND, it also raises the broader question concerning the optimal surgical approach for the lateral compartment in the modern era of multimodal therapy. Further studies will be needed to better define the role of robot-assisted laparoscopic surgery in enhancing oncological outcomes in patients undergoing LLND for low rectal cancer.

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