Japanese Evidences on Nerve-Preserving Lateral Pelvic Lymph Node Dissection for Rectal Cancer

Major Historical Milestones and Clinical Impact: The Past, Present and Future

Yukihide Kanemitsu, MD¹ Dai Shida, MD, PhD¹ Shunsuke Tsukamoto, MD, PhD¹
Konosuke Moritani, MD, PhD¹ Ryohei Sakamoto, MD¹

¹ Department of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan

Address for correspondence Yukihide Kanemitsu, MD, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan (e-mail: ykanemit@ncc.go.jp).

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Abstract

In Japan, the standard treatment for advanced low rectal cancer has been total mesorectal excision (TME) + lateral pelvic lymph node dissection (LLND). On the other hand, in the West, preoperative chemoradiotherapy (CRT) + TME has been established as the standard. Japanese surgeons developed nerve-preserving LLND that could reduce complications associated with extended dissection. The Japan Clinical Oncology Group (JCOG)0212 trial investigated on the outcomes of so-called prophylactic LLND in patients without evident lateral lymph node metastasis in preoperative diagnostic imaging. Data from the JCOG0212 trial demonstrated scientific validity of the theory and practice of the Japanese approach. Data from the JCOG0212 trial supported the validity and safety of the Japanese approach, that is, TME + LLND for low rectal cancer without routine use of preoperative CRT. For future direction, modern approach for rectal cancer should involve both of the Eastern and Western strategies by combining LLND and CRT.

Keywords

- rectal cancer
- lateral lymph node dissection
- total mesorectal excision

The principle of surgical therapy for rectal cancer is to remove the primary lesion together with regional lymph nodes that are susceptible to metastasis, that is, en-bloc dissection of lymph nodes in the central direction and along the intestinal axis. In cases of advanced low rectal cancer, additional lateral lymph node dissection (LLND) is performed in some Eastern countries. Advanced low rectal cancer has traditionally been associated with poor prognosis due to its high local recurrence rates compared with other cancers of the large intestine. To improve treatment outcomes, various therapeutic methods have been employed. In Japan, metastasis to lymph nodes in the periphery of the internal iliac artery from the middle rectal artery has been considered the major cause of local recurrence. Thus, a unique surgery-based approach has been established in Japan, in which clearance of lymph nodes in the lateral area supplied by the internal iliac artery branches is recommended

for achieving local control. Although this surgical procedure became more sophisticated with the introduction of the systematic anatomy of the fascia, it faced limitations due to spatial constraints of the narrow pelvic cavity enclosed by the hip bones, and conflicting constraints of attempting to achieve “lymph node dissection” and “nerve preservation” in a compatible manner. Indeed, this procedure represents the “ultimate complexity” among cancer surgeries. After autonomic nerve-preserving LLND has been developed in Japan, 5-year survival rates of 30 to 50% have been reported in patients with lateral lymph node metastasis. This procedure is the current standard operative procedure in Japan. With regard to its oncological benefit, long-awaited results from a randomized controlled trial of total mesorectal excision (TME) versus TME + LLND (Japan Clinical Oncology Group [JCOG] 0212)¹ came finally available. In this article, we will introduce the

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Fig. 1 History of surgical therapy and preoperative treatment for rectal cancer between the West and Japan. CRT, chemoradiotherapy; LLND, lateral lymph node dissection; TME, total mesorectal excision.

history of LLND and discuss the JCOG0212 trial based on the results of the primary analysis,¹ together with the safety data previously reported.²

History of Surgical Therapy and Preoperative Treatment for Rectal Cancer (→ Fig. 1)

Dissection System

The history of lymph node dissection in rectal cancer surgery begins with the theoretical studies of lymphatic flow by Gerota in 1985³ and Cunéo in 1902,⁴ followed by Miles' practical approach in 1908.⁵ This operative procedure was groundbreaking in that excision of the rectum was performed with the primary goal of achieving lymph node dissection in three directions—toward the oral, anal, and lateral sides of the lesion. Miles' procedure left a solid footprint in the history of rectal cancer surgery in the sense that his approach was based on the rectal lymphatic flow, leading to the development of TME in 1982.⁶

However, in low rectal cancer, TME alone cannot feasibly cure patients with lateral lymph node metastasis. The concept of rectal lymphatic flow was reconfirmed by Senba⁷ and Villemain et al⁸ who followed the achievements of Gerota³ and Cunéo.⁴ Subsequently, Kuru⁹ and Kajitani et al¹⁰ conducted clinical studies on LLND. Based on these studies, LLND has come to be performed widely at major hospitals in Japan since the 1970s. LLND is now accepted as the standard treatment for advanced low rectal cancer in Japan, as local recurrence rates of LLND are clearly better than those

reported in the West before the introduction of TME. The JCOG0212 study,¹ a randomized controlled trial of TME versus TME + LLND, was conducted with the aim of scientifically verifying the significance of LLND.

Meanwhile, in the West, Bacon¹¹ and Stearns et al¹² advocated for the use of so-called aortopelvic lymphadenectomy, in which some lateral lymph nodes were dissected. However, the effectiveness of this procedure was not supported as lateral lymph node metastases were already considered a systematic disease. Thus, although this procedure was performed in some facilities (e.g., St. Mark's Hospital, University of Chicago, Memorial Sloan-Kettering Cancer Center), it never gained popularity in Western countries.

Functional Preservation System

Later, in 1977, the "Japanese Classification of Colorectal Carcinoma"¹³ was published in Japan, and offered a unified language with which guidelines on surgical treatment were developed. This led to the further spread of LLND to many institutions. The National Cancer Center of Japan reported the largest study in the world regarding extended dissection. The widespread use of this procedure was promoted by Koyama,¹⁴ Hojo et al,¹⁵ and Moriya et al,¹⁶ among others. Their results were clearly better (local recurrence rate of < 10%) than those reported in the West at that time. While LLND has become accepted as the standard treatment for advanced low rectal cancer, extended dissection was still associated with a high incidence of postoperative dysfunction. In an attempt to address this issue, a new technique "the autonomic nerve

Fig. 2 Nerve-preserving surgery with bilateral lateral lymph node dissection.

preservation procedure”¹⁷ was developed as a unique procedure in Japan (► **Fig. 2**).

Standard Operative Procedures in Japan

In short, LLND is indicated for patients with T3 to 4 rectal cancer extending below peritoneal reflection. The “JSCCR Guidelines for the Treatment of Colorectal Cancer for Physicians” describe the criteria for indication of LLND as follows: “patients with tumors of which the lower margin is located on the anal side of the peritoneal reflection, and infiltration with penetration through the muscularis propria.”¹⁸

At the time of diagnosis, 10 to 25% of such patients have synchronous lateral lymph node metastasis.¹⁹ It has been estimated that LLND could reduce the risk of intrapelvic recurrence by 50% and improve 5-year survival by 8 to 9%.²⁰

Although preoperative chemoradiotherapy is used to control local recurrence in the West, surgery without preoperative chemoradiotherapy is widely performed in Japan even in patients with advanced rectal cancer, based on the concept that TME + LLND can control local recurrence caused by lateral lymph node metastasis. Some Japanese institutions have reported the use of preoperative chemoradiotherapy in combination with surgery for rectal cancer.²¹ However, such Japanese studies were limited by a

small number of patients and a retrospective design. It remains controversial in Japan whether neoadjuvant radiotherapy adds oncological benefits in patients who undergo TME + LLND.

The JCOG0212 Study (► **Fig. 3**)

Surgical Therapies and Patients

In this multicenter randomized trial, patients with clinical stage II/III rectal adenocarcinoma with lower tumor margin below the peritoneal reflection (rectal examination, computed tomography/magnetic resonance imaging [CT/MRI], endoscopy), no lateral lymph node enlargement (shorter diameter <10 mm on CT/MRI), no invasion to other organs, PS 0–1, and no history of chemotherapy were included. Two surgical therapies, TME alone versus TME + autonomic nerve-preserving LLND, were directly compared. In autonomic nerve-preserving LLND, the area encompassing the distal internal iliac lymph nodes (263D) on both sides, proximal internal iliac lymph node (263P), common iliac lymph node (273), and obturator lymph node (283) is dissected (► **Fig. 4**). The questionnaire survey conducted by the Colorectal Cancer Study Group of JCOG included a question about the extent of LLND for the patient group. Most respondents (48%) answered that they “dissect bilateral 263D, 263P, 283, and 273 lymph nodes.”

Fig. 3 CONSORT diagram of JCOG0212. LLND, lateral lymph node dissection; ME, mesorectal excision.

Fig. 4 The lateral pelvic area: (#280) aortic bifurcation area, (#273) common iliac area, (#263P) internal iliac areas proximal and (#263D) distal to superior vesical artery, (#283) obturator area, and (#293) external iliac area.

End Points

Relapse-free survival (RFS) was set as the primary end point in this trial, with death and recurrence as events. Secondary end points were overall survival (OS), local recurrence-free survival (LRFS), incidence of adverse events, operative time, blood loss, incidence of sexual dysfunction, and incidence of urinary dysfunction. Since 5-year OS achieved by radical resection of local, liver, and lung metastases are 31,²² 38,²³

and 41%,²⁴ respectively, radical resection of these metastases was attempted in this trial if patients developed recurrence. The overall incidence of adverse events was assessed according to National Cancer Institute–Common Toxicity Criteria (NCI-CTC version 2.0) and JCOG criteria for intraoperative/postoperative complications. The validated international index of erectile function²⁵ was used for sexual dysfunction, and the amount of residual urine at

the time of first postoperative discharge (i.e., an indicator of whether self-catheterization is needed) was used for urinary dysfunction.

Clinical Hypothesis

TME has a lower incidence of adverse events compared with autonomic nerve-preserving LLND, with potential clinical usefulness (i.e., it is easy to perform). Therefore, the main hypothesis of this trial was that “if RFS of the test treatment (TME alone) is comparable (non-inferior) to that of the Japanese standard treatment (TME + LLND), then TME would be considered more useful.” In other words, the aim of this trial was to verify the noninferiority of TME to the Japanese standard treatment TME + LLND.

Short-Term and Functional Outcomes

Patient enrollment began in June 2003 and ended in August 2010, when the 701st patient was enrolled. As of June 12, 2011, intention-to-treat analysis had been performed to evaluate early postoperative complications, and the results were presented at ASCO 2011. The main findings were as follows: (1) the rate of pathologically confirmed lateral lymph node metastasis in the TME + LLND group was 7.4%; (2) operative time was significantly longer (360 vs. 254 minutes; $p < 0.0001$), and blood loss was significantly higher (576 vs. 337 mL; $p < 0.0001$) in the TME + LLND group. (3) The incidence of grade $\frac{3}{4}$ postoperative complications was 21.7% in the TME + LLND group and 16.0% in the TME alone group ($p = 0.07$). (4) Among all postoperative grade $\frac{3}{4}$ complications, wound dehiscence was the most frequent (6 vs. 5%), with one patient died of sepsis after having dehiscence in the TME + LLND group.²

Postoperative sexual and urinary dysfunctions were investigated. No significant differences were observed in sexual disorder (79 vs. 68%) and early (59 vs. 58%) and late (7 vs. 5%) postoperative urinary dysfunction.^{26,27} Although the incidence of urinary dysfunction was high in early postoperative period, considerable improvement was observed in late period, suggesting that autonomic nerve preservation was appropriately performed.²⁷

Long-Term Outcomes

As for the primary end point, 5-year RFS was 73.4% in the TME + LLND group and 73.3% in the TME alone group (hazard ratio [HR]: 1.07, 90.9% confidence interval [CI]: 0.84–1.36). The upper limit of the HR exceeded the preset noninferiority margin of 1.34, and hence, noninferiority of TME alone to TME + LLND was not demonstrated ($p = 0.055$). Both groups had good 5-year OS (TME + LLND group, 92.6%; TME alone group, 90.2%; HR: 1.25, 95% CI: 0.85–1.84). Five-year LRFS was 87.7% in the TME + LLND group and 82.4% in the TME alone group (HR: 1.37, 95% CI: 0.98–1.93). Although there were no statistical differences in LRFS, number of patients who had local recurrence was statistically lower in the TME + LLND group compared with the TME alone group (7.4 vs. 12.6%, $p = 0.024$) (→Table 1).¹ Notably, there were significantly fewer lateral pelvic local recurrences in the TME + LLND group.

Table 1 Patterns of local recurrence

Sites	ME + LLND (n = 351)	ME (n = 350)	p-Value
Anastomosis	7	2	
Anastomosis and central pelvis	0	1	
Central pelvis	11	12	
Central and lateral pelvis	3	2	
Lateral pelvis	4	23	
Definite residual tumor	1	4	
Total	26 (7.4%)	44 (12.9%)	0.024

Abbreviations: LLND, lateral lymph node dissection; ME, mesorectal excision.

Interpretation of the Findings

In summary, noninferiority of TME alone to TME + LLND was not demonstrated in terms of RFS (the primary end point), and further, TME alone was inferior to TME + LLND in terms of local recurrence. The findings of the JCOG0212 study implicated oncological benefit of LLND in terms of reducing lateral pelvic local recurrence. Occult lateral lymph node metastasis should be treated as a potentially curable regional disease rather than incurable stage IV disease as observed in 7.4% of the TME + LLND group. This trial had considerable impact on the future standard treatment for low rectal cancer in Japan. As the study did not support noninferiority of TME alone, the study concluded that TME + LLND should be the standard option for patients with clinical stage II/II low rectal cancer in the settings without preoperative chemoradiotherapy.

Limitation of the JCOG0212 Study

It should be noted that the JCOG0212 study was not a superiority study. Hence, it is difficult to conclude whether TME + LLND is truly superior to TME alone. Further, the results of the JCOG0212 study cannot be translated to the higher risk group who were excluded from the trial. As LLND did not reduce central pelvic local recurrences, TME + LLND without chemoradiation might be suboptimal for rectal cancer with higher risks, for example, bulky tumors with deep penetration or threatened circumferential margin.

Future Direction

Multidisciplinary management that appropriately combines preoperative treatment and radical surgery is important to improve outcomes in rectal cancer. A recent multi-institutional retrospective study showed that adding LLND to TME after chemoradiation was associated with lower 5-year lateral local recurrence (5.7 vs. 19.5%) in patients with enlarged lateral lymph nodes ≥ 7 mm on pretreatment MRI.²⁸ This study implicates that entrusting radiotherapy to sterilize lateral

nodal disease is likely an unrealistic expectation. Multidisciplinary treatment including LLND would be necessary for cases with enlarged lateral lymph nodes.

Overtreatment is commonly seen in both Japan and Western countries. Indication of LLND should be determined by balancing the expected therapeutic effect, surgical risk, and postoperative dysfunction. In the West, many rectal cancers that would be cured by surgery alone are treated with chemoradiation, leading to postoperative dysfunction and unnecessary rise of the cost. Treatment of rectal cancer needs to be individualized, optimizing all modalities by the tumor condition, oncological benefit, and functional outcomes.

Conflict of Interest

None.

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