

Preoperative chemoradiation and extended pelvic lymphadenectomy for rectal cancer: Two distinct principles

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the presence of metastatic lateral lymph nodes (LLNs), EPL performed by experienced surgeons definitely contributes to decrease local recurrence. On the other hand, a randomized controlled trial in Japan that compared EPL with conventional TME following preoperative RT revealed that EPL is associated with a higher frequency of sexual and urinary dysfunction without oncological benefits in the presence of preoperative RT. On this point, preoperative CRT followed by conventional TME without EPL would be a better therapeutic approach in patients without evident metastatic LLNs. For future treatment, it would be desirable to have a narrower indication for EPL using full advantage of recent improvement in image diagnosis. Although objective comparison of these two principles between Japan and the West is difficult due to differences in patient groups, further studies would lead to the next great step towards future improvement in treating lower rectal cancer.

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Abstract

Extended pelvic lymphadenectomy (EPL) with total mesorectal excision (TME) has been reported to provide oncological benefit in lower rectal cancer in Japan. In Western countries EPL is not widely accepted because of frequent morbidity but instead preoperative chemoradiation (CRT) followed by TME has been established as a standard treatment for decreasing local recurrence. Recently, several studies have focused on the comparison between these two distinct therapeutic approaches in Western countries and Japan. A study comparing Dutch trial data and Japanese data revealed that EPL and RT are almost equivalent in decreasing local recurrence in lower rectal cancer as compared with TME alone. Considering that almost 45% survival can be achieved by EPL even in

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HISTORICAL BACKGROUND OF SURGICAL APPROACH FOR LOWER RECTAL CANCER IN JAPAN AND WESTERN COUNTRIES

Lateral lymph node (LLN) metastasis is among the strongest causes of local recurrence as well as poor survival in locally advanced lower rectal cancer^[1,2]. Since the late 1970s, Japanese surgeons have carried out extended pelvic lymphadenectomy (EPL) with total mesorectal excision (TME) for lower rectal cancer. Retrospective studies from Japan indicate that EPL decreased local recurrence as well as prolonged survival^[3-5]. During the past 25 years, Japanese surgeons have made remarkable progress in the management of lower rectal cancer with EPL, including imaging modalities for diagnosis of LLN metastasis and nerve-sparing surgical techniques for decreasing sexual and urinary dysfunction^[5-8]. Based on these improved techniques, EPL is still recommended as a standard approach for locally advanced lower rectal cancer in the Japanese Society for Cancer of the Colon, Rectum's guidelines.

In Western countries the literature has been against EPL for rectal cancer^[9-12]. Studies criticized EPL for a low rate of LLN metastasis, poor survival in those with positive LLN, frequent morbidity after surgery and increased operation time as well as blood loss. Instead, Western surgeons have developed preoperative chemoradiation (CRT) as a standard therapeutic approach for locally advanced lower rectal cancer through several randomized controlled trials (RCTs)^[13-15].

Recently, several studies have focused on comparing CRT as the Western standard and EPL as the Japanese standard^[16-20]. Although there are several issues to be discussed in each study, objective comparison of these two standards seems a great step towards future improvement in the treatment of lower rectal cancer.

This review highlights the recent studies on EPL and CRT as two distinct principles for lower rectal cancer.

EPL AS A STANDARD TREATMENT FOR LOWER RECTAL CANCER: EVIDENCE FROM JAPAN

In 1982, Hojo *et al*^[21] in the National Cancer Center reported the outcomes of 160 patients who underwent wide anatomical resection with radical lymphadenectomy (extended surgery) for lower rectal cancer. The authors reported decreased local recurrence of 6.5% for Dukes B and 25% for Dukes C in those undergoing extended surgery as compared with 25% for Dukes B and 45% for Dukes C in conventional surgery. A report from the same group further indicated improved 5-year-survival of 83.2% for Dukes B and 52.5% for Dukes C in those undergoing extended surgery as compared with 63.7% for Dukes B and 30.8% for Dukes C in conventional surgery^[3]. However, Moriya *et al*^[22] also reported that extended surgery is highly associated with longer duration of operation, more blood loss and higher

Table 1 Answers to criticism of extended pelvic lymphadenectomy

Low rate of lateral lymph node metastasis
15.6% for Rb ^a , 12.2% for Rb T3, 25.1% for Rb T4 ^[1]
Poor survival for lateral lymph node positive cases even after dissection
5-year survival of 45.8% in lateral lymph node positive cases ^[1]
Increased Morbidity
Yes, but decreased by autonomic nerve-preservation ^[5,6]
Longer operative time and blood loss
Yes

^aRb: Lower rectal cancer below peritoneal reflection.

frequency of urinary dysfunction and sexual dysfunction. In 1995, Sugihara *et al*^[5] and Moriya *et al*^[6] reported that autonomic nerve-preserving surgery could reduce urinary and sexual dysfunction without deteriorating oncological outcomes. In this report, patients undergoing preservation of both hypogastric and pelvic nerves achieved 98% excellent or good urinary function, 68% ejaculation and 90% erection. Since this report, EPL with autonomic-nerve preservation has become a standard treatment for locally advanced lower rectal cancer in Japan. Studies from several referral institutions have revealed that the proportion of positive LLN was around 15%, varying from 10.6% to 25.5% in locally advanced lower rectal cancer below peritoneal reflection and the 5-year survival of those undergoing EPL in the presence of metastatic LLNs was around 45%, varying from 37.3% to 49.3%^[1,2,4,5,23-26]. It has been reported that the number of positive LLNs is among the most important predictive factors for survival after EPL. The number of positive LLNs was an independent risk factor for poor survival in patients with metastatic LLNs along with positive mesenteric lymph nodes, female gender, higher age and positive circumferential resection margin^[2,26]. Shirouzu *et al*^[25] also reported that 5-year survival reached over 60% if the involved LLNs were less than three, while the survival decreased to 16.7% with three or more positive LLNs. Risk factors for LLN metastases have been also investigated. Sugihara *et al*^[1] performed multivariate analysis using multi-institutional registry data in Japan and revealed that a short distance from the anal verge to the tumor was independently associated with positive LLNs along with poor histological grade, large tumor size, deeper depth of invasion and female gender. Ueno *et al*^[2] also reported that positive mesenteric lymph node correlated with positive LLNs. Based on the evidence during the past 25 years (Table 1), the present guideline by the Japanese Society for Cancer of the Colon and Rectum clearly states that EPL is indicated for lower rectal cancer with T3 or deeper invasion and the lower edge of the tumor located below the peritoneal reflection.

PREOPERATIVE CRT AS A STANDARD TREATMENT FOR LOWER RECTAL CANCER: EVIDENCE FROM THE WEST

The Dutch Colorectal Cancer Group reported the results

of RCT that randomly assigned 1861 patients with resectable rectal cancer either to preoperative radiation (RT) followed by TME or to TME alone^[13]. The rate of local recurrence at two years was 2.4% in the preoperative RT group and 8.2% in the TME-only group ($P < 0.001$). The German Rectal Cancer Study Group randomly assigned 823 T3/T4 or node-positive rectal cancer to either preoperative CRT followed by TME or TME followed by postoperative CRT^[15]. The overall 5-year survival rates were 76% and 74% for preoperative and postoperative CRT respectively ($P = 0.80$). However, the incidence of local recurrence at five years was 6% in the preoperative CRT and 13% in the postoperative CRT ($P = 0.006$). Grade 3/4 acute toxic effects occurred in 27% of the preoperative CRT group as compared with 40% of the postoperative CRT group ($P = 0.001$), and the rates of long-term toxic effects were 14% and 24% respectively ($P = 0.01$). Importantly, this study further suggested a statistically significant increase in sphincter preservation in preoperative CRT group compared with postoperative CRT group by subanalysis of the 194 patients that required an abdominoperineal excision before randomization as determined by the surgeon ($P = 0.004$). Based on this study, preoperative CRT therapy has become the standard treatment for patients with clinically staged T3/T4 or N1 disease in Western countries^[27]. It has been reported that complete pathologic response rates of 10% to 25% may be achieved with preoperative CRT and benefits of neoadjuvant CRT include tumor regression, downstaging and improvement in respectability and a higher rate of sphincter preservation and local control^[15,28-35]. On the other hand, preoperative CRT is also associated with increased morbidity compared with surgery alone, including increased surgical complications, chronic bowel dysfunction, anorectal sphincter dysfunction (if the sphincter was surgically preserved), and sexual dysfunction^[36-42].

There still remains several unsolved issues regarding preoperative RT and CRT. First, there have been few studies comparing conventional long-course fractionated CRT and short-course RT. Although the Polish trial demonstrated no differences in the oncological outcomes between the two groups, quality control of the study did not seem appropriate as local recurrence in the CRT group exceeded 14%^[39]. Second, there have been no studies that revealed oncological benefit of additional chemotherapy in short-course RT regimen, although its efficacy has been established in conventional long-course fractionated regimen^[14].

COMPARISON BETWEEN EPL AND CRT

There have been two important studies from Japan that investigated oncological and surgical outcomes of EPL and CRT for rectal cancer. Nagawa *et al.*^[19] conducted the first RCT that randomly assigned 45 patients who received neoadjuvant RT for rectal cancer to either TME alone or TME with autonomic nerve-preserving EPL. This trial

showed no difference in survival or local recurrence but more urinary and sexual dysfunction in those undergoing EPL (65% *vs* 27%, $P = 0.02$ and 92% *vs* 45%, $P = 0.02$, respectively). Although this trial included too small a number of cases, these results strongly suggest that EPL does not provide oncological benefit but rather increases autonomic-nerve dysfunctions on condition that patients have received preoperative RT for lower rectal cancer. Another study by Watanabe *et al.*^[20] retrospectively compared outcomes of preoperative RT without EPL and EPL without RT. This study showed no significant difference in survival or local recurrence between the two groups. The authors concluded that preoperative RT can be an alternative therapy in place of EPL for patients with lower rectal cancer. Although there are limitations including the small number of cases, these two studies are important in that they were conducted by the Japanese surgeons who are experienced with EPL for lower rectal cancer. Both studies suggested that EPL would be unnecessary with preoperative RT.

Recently, several studies have been published that compared oncological outcomes of EPL in Japan with that of CRT outside of Japan. Kim *et al.*^[17] compared the outcomes of 309 patients in Korea who received conventional TME plus postoperative CRT and 176 patients in Japan who underwent EPL without CRT for stage II/III lower rectal cancer. There were no significant differences in overall or disease-free survival. However, local recurrence in stage III lower rectal cancer occurred 2.2 times more frequently in the EPL group than the CRT group (16.7% *vs* 7.5%, $P = 0.044$). Accordingly, the authors concluded that adjuvant CRT is needed after EPL to reduce local recurrence. Although this study is important in shedding light on the international comparison between EPL and CRT, there are major issues to be discussed as pointed out by Watanabe *et al.*^[43], including different proportions of patients receiving adjuvant chemotherapy between the two groups and selection bias due to the different definition of lower rectal cancer between Korea and Japan.

Kusters *et al.*^[18] conducted a comparison between 324 patients undergoing EPL plus TME at National Cancer Center in Japan, 379 patients undergoing preoperative RT plus TME in the Dutch trial and 376 patients undergoing TME alone in the same trial. Rates of local recurrence were 6.9%, 5.8% and 12.1% for the Japanese, Dutch RT+TME and Dutch TME groups respectively. Notably, recurrence in the lateral pelvis was 2.2%, 0.8% and 2.7% in the Japanese, Dutch RT+TME and Dutch TME groups respectively, while presacral recurrence was 0.6%, 3.7% and 3.2% in each group. Based on these results, the authors concluded that both EPL and preoperative RT result in good local control as compared with TME alone. Furthermore, they speculated that preoperative RT can sterilize micrometastases in the lateral pelvis while extended surgery results in less presacral recurrence. In this study, tumor height from the anal verge was matched between the groups and the majority of the three groups did not receive adjuvant chemotherapy. However, it is still

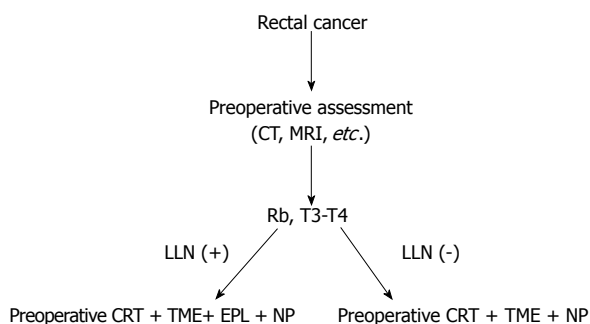


Figure 1 Proposal of rectal cancer management. Rb: Lower rectal cancer below peritoneal reflection; LLN: Lateral lymph node; CRT: Chemoradiation; TME: Total mesorectal excision; EPL: Extended pelvic lymphadenectomy; NP: Nerve preservation.

difficult to compare the Japanese patients with the Dutch patients and there could be potential bias including non-randomization and upstaging. Nevertheless, this study provides useful information on the therapeutic approaches to prevent local recurrence from the two representative referral centers in Japan and Europe.

Most recently, a meta-analysis of 20 studies was published that compared the perioperative outcomes, survival and recurrence between 2577 patients undergoing EPL and 2925 patients undergoing conventional surgery without EPL^[16]. The EPL group showed longer operating time and greater intra-operative blood loss than the non-EPL group. However, there was no difference in 5-year survival, 5-year disease-free survival and local or distant recurrence. Notably, in patients with Dukes C cancer, the EPL group had better survival as well as local recurrence than the non-EPL group, while there was no significant difference in patients with Dukes B. Regarding urinary function, data from three studies including 139 patients showed higher prevalence of urinary dysfunction in the EPL group. Individual studies showed higher frequency of male sexual dysfunction in the EPL group and therefore this outcome was not meta-analyzed. The authors concluded that EPL does not seem to provide oncological benefit but seems to be associated with increased urinary and sexual dysfunctions. This paper includes several issues to be discussed. First, most studies involved in this meta-analysis are retrospective, non-randomized trials. Second, seven out of the twenty studies included upper rectal cancer although LLN metastasis do not occur in the tumors at this level^[1] and furthermore, most studies did not include tumor height from the anal verge as matching criteria. Third, there was no information regarding the addition of adjuvant chemotherapy in each group. Fourth, there was only one study that all patients in each group underwent CRT and six studies had some patients who underwent CRT. Accordingly, there could be bias regarding the tumor height and proportion of those receiving adjuvant chemotherapy or CRT between the groups. Nevertheless, this study is the first meta-analysis that assessed the value of EPL. Although the authors' conclusion was unfavorable for EPL, an important implication of this study was that EPL provided better survival and local recurrence than non-EPL

in Dukes C cancers. Considering the incidence of metastatic LLNs in advanced lower rectal cancer is no more than 15%^[1,2,4,5,23-26], it is not surprising that statistical difference was not observed in this analysis as the majority of the patients undergoing EPL did not actually need EPL. Recently, Yano *et al*^[8] reported that LLNs metastasis can be diagnosed with high accuracy (sensitivity 95%, specificity 94%) in marked contrast to mesorectal node metastasis. It would be more practical to apply EPL to a narrower indication, i.e. patients with positive LLNs diagnosed by preoperative image or intraoperative findings and those carrying high risk for LLN metastasis such as Dukes C lower rectal cancer (Figure 1).

CONCLUSION

There still exists a great controversy regarding the oncological benefit of EPL. However, as suggested by Kusters *et al*^[18], EPL performed by experienced surgeons provides better local control than TME alone. Furthermore, almost 45% survival is achieved by EPL in the presence of metastatic LLNs even without RT or CRT^[1,2,4,5,23-26]. In the light of these findings, EPL definitely contributes to decrease local recurrence in lower rectal cancer. On the other hand, it is true that EPL is associated with high frequency of sexual and urinary dysfunction^[16,19]. On this point, preoperative CRT without EPL would be a better alternative to reduce local recurrence in patients without evident metastatic LLNs^[19,20]. For future treatment, it would be desirable to have a narrower indication for EPL using full advantage of recent improvement in image diagnosis. In patients with evident metastatic LLNs, preoperative CRT plus EPL plus perioperative chemotherapy would be the next promising challenge. Further objective comparison of the two principles between Japan and the West would lead to the next great step towards future improvement in treating lower rectal cancer.

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