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*WJGO* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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## Lateral pelvic lymph nodes for rectal cancer: A review of diagnosis and management

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**Shimpei Ogawa, Michio Itabashi, Yuji Inoue, Takeshi Ohki, Yoshiko Bamba, Kurodo Koshino, Ryosuke Nakagawa, Kimitaka Tani, Hisako Aihara, Hiroka Kondo, Shigeki Yamaguchi, Masakazu Yamamoto,** Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo 162-8666, Japan

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### Abstract

The current status and future prospects for diagnosis and treatment of lateral pelvic lymph node (LPLN) metastasis of rectal cancer are described in this review. Magnetic resonance imaging (MRI) is recommended for the diagnosis of LPLN metastasis. A LPLN-positive status on MRI is a strong risk factor for metastasis, and evaluation by MRI is important for deciding treatment strategy. LPLN dissection (LPLD) has an advantage of reducing recurrence in the lateral pelvis but also has a disadvantage of complications; therefore, LPLD may not be appropriate for cases that are less likely to have LPLN metastasis. Radiation therapy (RT) and chemoradiation therapy (CRT) have limited effects in cases with suspected LPLN metastasis, but a combination of preoperative CRT and LPLD may improve the treatment outcome. Thus, RT and CRT plus selective LPLD may be a rational strategy to omit unnecessary LPLD and produce a favorable treatment outcome.

**Key Words:** Diagnosis; Treatment; Rectal cancer; Lateral pelvic lymph node metastasis; Lateral pelvic lymph node dissection; Radiotherapy

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**Core Tip:** Diagnosis of lateral pelvic lymph node (LPLN) metastasis of rectal cancer is mainly made using magnetic resonance imaging (MRI). LPLN-positive status on MRI is a strong risk factor for metastasis, and evaluation by MRI is important for deciding treatment strategy. LPLN dissection (LPLD) reduces recurrence in the lateral pelvis but also has complications and may not be appropriate for cases predicted to not have

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## INTRODUCTION

Colorectal cancer (CRC) is the third most frequently diagnosed cancer worldwide, with an estimated 1.9 million new cases reported annually[1]. Moreover, CRC accounts for 9.4% of all cancer deaths, and about one-third of CRC cases are represented by rectal cancer. Lymph node (LN) metastasis is a risk factor for local recurrence and a poor prognostic factor in rectal cancer, and the treatment strategy is important. Rectal lymph flows upward, laterally and downward, and LN metastasis mainly advances along the mesorectal nodal chain along the inferior mesenteric artery nodes[2-5]. Lower rectal cancer on the anal side from the peritoneal reflection also advances to LNs of the extramesorectal lateral pelvis. The frequency of lateral pelvic lymph node (LPLN) metastasis of lower rectal cancer is 11.3%-22.4%, and the outcome of cases with LPLN metastasis is poor[6-13]. Regarding treatment outcomes, the survival rates of cases with internal iliac LN metastasis and more distant LPLN metastasis are comparable to those of the tumor-node-metastasis (TNM) classifications N2a and N2b, respectively[10].

In lower rectal cancer, local recurrence occurs as frequently as liver metastasis and lung metastasis, and reportedly in 4%-10% of rectal cancer cases treated with total mesorectal excision (TME) alone[14,15]. Of local recurrence cases, recurrence in the lateral pelvis is accompanied by serious complications, the possibility of salvage is low, and many patients do not survive, making this a significant clinical problem[16]. Moreover,  $\geq 40\%$  of LPLN metastasis cases with local recurrence do not have distant metastasis, which indicates the importance of local control[17]. Therefore, LPLN metastasis is closely linked to the treatment outcome of lower rectal cancer and control of LPLN metastasis may be key to improvement of outcomes. In this review, the current status and future prospects of diagnosis and treatment of LPLN metastasis of rectal cancer are discussed.

## DIAGNOSIS OF LN METASTASIS OF RECTAL CANCER

LN metastasis of rectal cancer can be evaluated by endoscopic ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and [ $^{18}\text{F}$ ]fluorodeoxyglucose-positron emission tomography (FDG-PET)[18]. Of these imaging modalities, MRI has superior contrast resolution of soft tissue and is an excellent method with multiplanar imaging capacity that is useful for the N staging of rectal cancer[19]. In the European Society for Medical Oncology (ESMO) guidelines, endorectal ultrasound is the recommendation for invasion depth evaluation in T1 cases, whereas MRI is recommended for evaluation of T2 or deeper invasion and LN metastasis because it can evaluate a wide range inside and outside the mesorectum[18,20].

### Diagnosis of LPLN metastasis by MRI

Diagnosis of LN metastasis of rectal cancer has been widely investigated in the perirectal lymph nodes (PRLNs), whereas fewer studies have investigated LPLNs[21]. The cut-off for LPLN size varies from 4 mm to 12 mm. Similar to those for PRLNs, various morphological criteria have also been described, including irregular border, mixed signal intensity, speculated appearance, indistinct border, and mottled heterogeneous appearance[22-34]. In a comparison of area under the curve-based diagnoses using 5-mm and 10-mm cut-offs for the short axis, we found values of 0.7418 on the

right and 0.7593 on the left at 5-mm, and of 0.6326 on the right and 0.6559 on the left at 10-mm[35]. The 5-mm values were significantly higher and indicated excellent diagnostic ability using a 5-mm short axis cut-off (Table 1).

### **Diagnosis of LPLN metastasis based on size criteria**

Results supporting the validity of size-based LPLN diagnosis have been reported. Ueno *et al*[11] divided the lateral region of excised specimens into six areas and compared the size of metastasis-positive and -negative LNs in each area, yielding the observation that the size of metastasis-positive LNs was significantly larger in all areas. Akasu *et al*[27] reported a relationship between LN size on MRI and histological metastasis for PRLNs and LPLNs. In PRLNs, the overlap of metastasis-positive and -negative LNs was large, as reported by Brown *et al*[36], but the overlap was small for LPLNs and very small or non-existent LNs that were visualized on imaging in most metastasis-negative cases; thus, the size criterion was concluded to work well.

### **LPLN-positive status on MRI as a risk factor for LPLN metastasis**

Female sex, lower rectum involvement, histopathological grade other than well or moderately differentiated adenocarcinoma, lymphatic invasion, venous invasion, wall depth of invasion  $\geq$  pT3, and PRLN metastasis have been reported as risk factors of LPLN metastasis of rectal cancer[6-10,37-39]. LPLN-positive status on imaging has also been identified as a risk factor. Fujita *et al*[9] defined cases with LPLNs of  $\geq$  5 mm on CT as LPLN-positive, and found the LPLN-positive status to be an independent risk factor for LPLN metastasis, with an odds ratio (OR) of 28.00, which was higher than that of other risk factors. We also found LPLN-positive status on MRI to be an independent risk factor, together with age ( $<$  64 years), histopathological grade (G3 + G4), M1, and pPRLN(+) status, with ORs for right and left LPLNs of 10.73 and 24.53, respectively[40]. These values were higher than those for the other risk factors, showing the importance of a LPLN-positive status on MRI.

### **Current diagnosis of LPLN metastasis**

Size-based diagnosis of LN metastasis of rectal cancer by MRI is simple and has only small inter-observer differences compared with those in morphology-based diagnosis, suggesting that size-based diagnosis is the most reliable, clinically[27]. Kim *et al*[17] also stated that LN size is the most reliable parameter for diagnosis of LN metastasis by MRI and that 5 mm is the most common criterion. In a meta-analysis of preoperative evaluation of rectal cancer by MRI, diagnosis of LN metastasis was evaluated as poor based on the diagnostic odds ratio (*i.e.*, "DOA") compared with those of the circumferential resection margin (CRM) and T category[21]. The diagnostic ability of LPLN by MRI had a pooled sensitivity, specificity, and DOA of 0.72, 0.80, and 10.2, respectively, in a meta-analysis[41], showing the need for further studies to improve this performance.

### **New diagnostic method for LN metastasis of rectal cancer**

Diffusion-weighted MRI, Gadofosveset-enhanced MRI, and LN-specific contrast medium ultrasmall superparamagnetic iron oxide contrast agent (*i.e.* 'USPIO')-enhanced MRI have been examined for improvement of diagnosis of LN metastasis of rectal cancer[42-48]. Using differences in enhancement patterns of Gadofosveset-enhanced MRI, the favorable results of negative predictive values of  $>$  95% per lesion and  $>$  85% per patient have been reported[42]. Regarding USPIO-enhanced MRI, USPIO is not approved for clinical use in Japan and its routine use in medical practice is not approved in Western countries, although favorable results (sensitivity of 93%, specificity of 96%) have been reported[43-45]. FDG-PET in combination with CT and MRI has been examined in post-CRT cases, with the cut-off for each method being determined from a receiver operating characteristic curve. Diagnosis using combined cut-offs of 12 mm on CT and MRI and SUVmax of 1.6 on FDG-PET give accuracy of 92.9%, sensitivity of 88.2%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 84.6%[46].

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## **TREATMENT STRATEGIES FOR RECTAL CANCER LPLN METASTASIS IN GUIDELINES**

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Treatment strategies for LPLN metastasis of rectal cancer differ between Eastern countries, especially Japan, and Western countries. In Japan, LPLN metastasis, which

**Table 1 Studies of magnetic resonance imaging diagnosis and criteria for lateral pelvic lymph node metastasis**

Ref.	Patients	Accuracy	Sensitivity	Specificity	PPV	NPV	Criteria
Kim <i>et al</i> [22], 1999	8				12.5%		> 1.2 cm
Kim <i>et al</i> [23], 2000	14				29%		> 10 mm
Arii <i>et al</i> [24], 2006	53	83%	56%	97%	91%	81%	> 7 mm Round shape
Matsuoka <i>et al</i> [25], 2007	51	78%	67%	83%			≥ 5 mm (short-axis) Ovoid shape
Min <i>et al</i> [26], 2009	66				86.4%		> 1.0 cm, > 0.5 cm (short-axis) Spiculated or indistinct borders, mottled heterogenic pattern
Akasu <i>et al</i> [27], 2009	104	87%	87%	87%	52%	97%	≥ 4 mm (short-axis)
Lim <i>et al</i> [28], 2013	67				39.0%		≥ 5 mm (short-axis) Spiculated or indistinct border, mottled heterogenic pattern
Akiyoshi <i>et al</i> [29], 2015	77		68%	85%			≥ 8 mm (short-axis)
Ishibe <i>et al</i> [30], 2016	84	88.1%	43.8%	98.5%	87.5%	88.1	≥ 10 mm (short-axis)
Lee <i>et al</i> [33], 2019	37		85.7%	84.0%	12.5%	99.5%	≥ 7 mm (short-axis)
Ogawa <i>et al</i> [35], 2016	268 (right)	77.6%	68.6%	79.7%	44.3%	91.5%	≥ 5 mm (short-axis)
	280 (left)	79.3%	70.8%	81.0%	43.6%	93.1%	

NPV: Negative predictive value; PPV: Positive predictive value.

is defined as progression beyond the mesorectum, is considered controllable by surgical LPLN dissection (LPLD), and TME + LPLD is the standard surgical procedure for advanced lower rectal cancer[49-51]. LPLNs are handled as regional LNs and the Japanese treatment guidelines for CRC recommend prophylactic dissection for T3 or deeper lower rectal cancer, even in cases without suspected LPLN metastasis[51]. In contrast, in Western countries, LPLN metastasis is handled as a systemic disease because distant metastasis is common and the outcome is poor[52,53].

In the American Joint Committee on Cancer (*i.e.*, "AJCC") Cancer Staging Manual, for the lateral pelvic regions, LNs in the internal iliac region, but not those in the obturator, external iliac and common iliac regions, are classified as regional LNs, and metastasis to the lateral pelvic regions, except of the internal iliac region, is handled as distant metastasis[54]. In Western countries, a combination of TME with radiation therapy (RT) and chemoradiation therapy (CRT) is the standard treatment for advanced lower rectal cancer because preoperative RT and CRT exhibit a partial local control effect. The combination of preoperative RT or CRT has been reported to reduce local recurrence to ≤ 10%[55].

The National Comprehensive Cancer Network (*i.e.*, "NCCN") guidelines recommend TME after CRT with concomitant fluorouracil for cStage II-III rectal cancer [56]. Induction chemotherapy before CRT is also recommended as a standard treatment. There is no specific description for LPLD, but extended dissection of LNs located outside the resection region, to which LPLNs correspond, is indicated for resectable LNs with suspected metastasis, whereas prophylactic dissection is not particularly recommended for LNs without suspected metastasis.

In the ESMO guidelines, the recurrence risk is classified into "early", "intermediate", "bad", and "advanced" based on the distance of the tumor from the anal verge, the T stage and N stage, while use of TME alone, preoperative RT, and preoperative CRT is recommended depending on the risk[18]. There is no description concerning prophylactic LPLD, and when LPLN metastasis is suspected, the case is classified as "advanced", with preoperative CRT followed by surgery (TME and more extensive surgery if indicated by tumor overgrowth) or preoperative short-course preoperative RT (5 × 5 Gy) plus the folinic acid + fluorouracil + oxaliplatin (*i.e.*, "FOLFOX") regimen and a delay of surgery are described as treatment methods. The ESMO guidelines also do not particularly recommend prophylactic dissection for LPLNs without suspected metastasis, similar to the NCCN guidelines, and LPLD is

not routinely performed in Western countries.

### **LPLD and CRT for cLPLN(-) cases**

Many studies on the treatment outcomes of LPLD have been reported, mainly from Japan[7,13,57,58]. Kanemitsu *et al*[13] determined the 5-year overall survival (OS) rates in LPLN metastasis(+) cases treated with LPLD at two high-volume centers in Japan as 53.1% and 45.2%, respectively, compared to those in LPLN metastasis(-) cases, which were 81.7% and 81.0%, respectively. The local recurrence risk ratio of unilateral to bilateral LPLD cases was 2.0, indicating the necessity of bilateral dissection. In a comparison of cases treated with and without LPLD in a matched cohort study, the 5-year OS rates were 68.9% and 62.0%, respectively, with a significantly higher OS in cases treated with LPLD[58].

The results of the JCOG0212 randomized controlled trial have provided insights into the outcomes of prophylactic LPLD in cLPLN(-) cases without suspected metastasis[57]. This trial examined TME alone (designated as the ME group) compared to TME + LPLD (designated as the LPLD group) as standard treatment. The primary endpoint of 5-year relapse-free survival (RFS) was 73.4% in the LPLD group and 73.3% in the ME group, which did not demonstrate non-inferiority of TME alone; moreover, the Kaplan-Meier curve for RFS was consistent, showing no superiority of LPLD. The secondary endpoint of 5-year OS was 92.6% in the LPLD group and 90.2% in the ME group, again showing no significant difference. The 5-year local recurrence-free rates were 87.7% in the LPLD group and 82.4% in the ME group, with no significant difference, but the local recurrence rate was significantly lower in the LPLD group [26 cases (7.4%) vs 44 cases (12.6%),  $P = 0.024$ ]. Local recurrence was in the lateral pelvis in 4 and 23 cases in the respective groups. Thus, recurrence in the lateral pelvis occurred in fewer cases in the LPLD group, indicating that LPLD is effective for reduction of recurrence in this region.

One reason for non-performance of LPLD in Western countries is that superiority of the treatment effect of LPLD compared to RT and CRT has not been demonstrated [52]. Kusters *et al*[59] adjusted patient background factors and compared treatment outcomes in a Japanese group (designated as the "NCCH" group) treated with TME + LPLD and groups treated with TME alone and RT + TME in a Dutch trial. The 5-year local recurrence rate was 6.9% in the Japanese NCCH group, 5.8% in the Dutch RT + TME group, and 12.1% in the Dutch TME-alone group. Thus, this rate was lower with TME + LPLD and TME + RT than with TME alone, and both LPLD and RT indicated a partial local control effect compared with TME alone. There was no difference between the effects of TME + LPLD and TME + RT.

Nagawa *et al*[60] performed 50-Gy preoperative RT in 45 patients with lower rectal cancer without LPLN enlargement in cases treated with TME alone and TME + LPLD. There was no difference in the OS and local recurrence rates between the two groups, and accordingly it was concluded that LPLD is unnecessary for lower rectal cancer without LPLN enlargement before treatment if preoperative RT is performed. In addition, Watanabe *et al*[61] also found no difference in the survival rate between RT-treated non-LPLD cases and LPLD-treated non-RT cases. In these studies, even though LPLD was added before treatment, if LPLN metastasis was not suspected before treatment, the oncological effect was small and the tumor could be controlled by preoperative RT. This suggests that a favorable outcome may be acquired even with TME alone if preoperative RT is performed.

The other reason for not performing LPLD in Western countries is the complications associated with LPLD[52]. Intraoperative complications of a long operative time and large-volume blood loss, and postoperative complications such as urinary and sexual dysfunction have been reported in LPLD-treated cases. Similarly, in the JCOG0212 study, the operative time was significantly longer and blood-volume loss was larger in the LPLD group, and the incidence of grade 3 or more severe complications was 22% in the LPLD group but only 16% in the ME group treated without LPLD[62]. In a recent meta-analysis, only Gao *et al*[63] reported a significantly lower 5-year local recurrence rate after LPLD than that in cases without LPLD treatment. In most reports, there was no difference in OS, DFS, or local recurrence (Tables 2 and 3)[63-69]. Postoperative urinary and sexual dysfunction was common, the operative time was long, and blood-volume loss was large in LPLD cases, but there are also serious complications of RT and CRT. These include dysuria, dyschezia, sexual dysfunction and secondary cancer as late complications and perineal wound complication of abdominoperineal resection and an influence on defecation function in cases treated with sphincter-preserving surgery[70-72].

Table 2 Variables in treatment of lateral pelvic lymph node dissection in recent meta-analyses and systematic reviews

Ref.	Study (RCT)	Treatment	Patients	CRT or RT	OS	DFS	TR	LR	LLR
Gao <i>et al</i> [63], 2020	12 (6)	TME + LPLD	1952	359	5-yr HR 0.93, 95%CI: 0.71-1.22, <i>P</i> = 0.62	5-yr HR 0.99, 95%CI: 0.74-1.34, <i>P</i> = 0.96	5-yr RR 0.98, 95%CI: 0.81-1.18, <i>P</i> = 0.83	5-yr RR 0.71, 95%CI: 0.56-0.89, <i>P</i> = 0.003	5-yr RR 0.49, 95%CI: 0.18-1.28, <i>P</i> = 0.14
		TME	2506	1009					
Wang <i>et al</i> [64], 2020	16 (4)	TME + LPLD	2984		HR 1.11, 95%CI: 0.77-1.61, <i>P</i> = 0.57	HR 1.05, 95%CI: 0.85-1.30, <i>P</i> = 0.64		OR 0.93, 95%CI: 0.56-1.54, <i>P</i> = 0.78	
		TME	3397						
Ma <i>et al</i> [65], 2020	26 (5)	TME + LPLD	3171	417	5-yr HR 1.14, 95%CI: 0.85-1.54	5-yr HR 1.07, 95%CI: 0.89-1.28, <i>P</i> = 0.496	OR 1.00, 95%CI: 0.80-1.24	OR 0.90, 95%CI: 0.76-1.06, <i>P</i> = 0.208	
		TME	3694	1102					
Emile <i>et al</i> [66], 2020	29 (5)	TME + LPLD	4194	551	HR 1.056, 95%CI: 0.98-1.13, <i>P</i> = 0.13	HR 1.02, 95%CI: 0.97-1.07, <i>P</i> = 0.37		HR 0.96, 95%CI: 0.75-1.25, <i>P</i> = 0.79	
		TME	6452	1467					
Hajibandeh <i>et al</i> [67], 2020	18 (2)	TME + LPLD	2762	321	5-yr OR 1.01, 95%CI: 0.78-1.30, <i>P</i> = 0.94	5-yr OR 1.07, 95%CI: 0.86-1.32, <i>P</i> = 0.54			
		TME	3371	735			OR 0.97, 95%CI: 0.72-1.29, <i>P</i> = 0.82	OR 1.01, 95%CI: 0.72-1.42, <i>P</i> = 0.97	
Law <i>et al</i> [68], 2020	6 (0)	CRT + TME + LPLD	268	268		5-yr OR 0.70, 95%CI: 0.20-2.39, <i>P</i> = 0.57		5-yr OR 0.42, 95%CI: 0.14-1.24, <i>P</i> = 0.12	
		CRT + TME	1210	1210					
Yang <i>et al</i> [69], 2020	8 (1)	CRT + TME + LPLD	435	435					
		CRT + TME	1461	1461	HR 0.78, 95%CI: 0.32-1.88, <i>P</i> = 0.58	HR 0.94, 95%CI: 0.62-1.43, <i>P</i> = 0.77		OR 0.82, 95%CI: 0.27-2.46, <i>P</i> = 0.72	OR 2.99, 95%CI: 1.20-7.44, <i>P</i> = 0.02

CI: Confidence interval; CRT: Chemoradiation therapy; DFS: Disease-free survival; HR: Hazard ratio; LLR: Local lateral recurrence; LPLD: Lateral pelvic lymph node dissection; LR: Local recurrence; OR: Odds ratio; OS: Overall survival; RCT: Randomized controlled trial; RR: Risk ratio; RT: Radiation therapy; TME: Total mesorectal excision; TR: Total recurrence.

### LPLD and CRT for cLPLN(+) cases

Difficulty with control of LPLN metastasis by RT or CRT alone has been reported. In cLPLN(+) cases with suspected LPLN metastasis, Kim *et al*[17] found local recurrence in 29 (7.9%) of 366 cases treated with TME alone without LPLD after preoperative CRT. Recurrence in the lateral pelvis was found in 24 (82.7%) of these cases and the local recurrence rates according to pretreatment LPLN size were 2.3%, 12.5% and 68.8% in cases with sizes < 5 mm, 5-10 mm and > 10 mm, showing that this rate was high in cases with LPLN enlargement. In 66 cases with LPLNs with a short axis of > 5 mm on MRI after CRT, Oh *et al*[73] found metastasis in LPLD in 22 (33.3%). Recurrence in the lateral pelvis reportedly occurs in 30%-60% of cases with post-treatment LPLNs of size ≥ 10 mm[74,75]. These reports show that control of LPLN metastasis by RT and CRT is difficult in cases with LPLN enlargement that is suspected to be due to metastasis. In contrast, LPLD has been found to be effective for CRT cases with LPLN enlargement and suspected metastasis[39,76-78].

In 127 CRT-treated cases, Akiyoshi *et al*[76] performed TME alone in 89 cases without suspected LPLN metastasis before treatment (the TME group) and TME + LPLD in 38 suspected cases (LPLD group). LPLN metastasis was found in 25 (65.8%) cases in the LPLD group, but local recurrence was noted in only 7 (7.9%) cases in the TME group and 1 (2.6%) case in the LPLD group. Lateral pelvic recurrence was found in only 3 cases (3.4%) in the TME group and none in the LPLD group. The 3-year RFS was 74.6% in the TME group and 83.8% in the LPLD group, with no significant

**Table 3 Variables in complications of lateral pelvic lymph node dissection in recent meta-analyses and systematic reviews**

Ref.	Study (RCT)	Treatment	Patients	CRT or RT	Operation time	Blood loss	Complications	Urinary dysfunction	Sexual dysfunction
Gao <i>et al</i> [63], 2020	12 (6)	TME + LPLD	1952	359	WMD 97.03 min, 95%CI: 75.35-118.72, $P < 0.001$	WMD 303.20 mL, 95%CI: 156.82-449.58, $P < 0.001$	RR 1.35, 95%CI: 1.05-1.74, $P = 0.02$	Pooled RR 1.44, 95%CI: 0.63-3.28, $P = 0.38$	Pooled RR 1.41, 95%CI: 0.87-2.31, $P = 0.17$
		TME	2506	1009					
Wang <i>et al</i> [64], 2020	16 (4)	TME + LPLD	2984				OR 1.48, 95%CI: 1.07-2.03, $P = 0.02$	OR 1.60, 95%CI: 0.66-3.87, $P = 0.3$	
		TME	3397						
Ma <i>et al</i> [65], 2020	26 (5)	TME + LPLD	417	417	WMD 92.50 min, 95%CI: 75.63-109.37	WMD 283.89 mL, 95%CI: 183.00-384.79	OR 1.30, 95%CI: 1.04-1.63	OR 2.14, 95%CI: 1.21-3.79, $P = 0.009$	OR 4.19, 95%CI: 1.55-11.33, $P = 0.005$
		TME	1102	1102					
Emile <i>et al</i> [66], 2020	29 (5)	TME + LPLD	4194	551	360 min (median), range 310-540, $P = 0.02$	582 mL (median), $P = 0.4$	OR 1.48, 95%CI: 1.18-1.87, $P < 0.001$	OR 2.1, 95%CI: 1.21-3.67, $P = 0.008$	OR 1.62, 95%CI: 0.94-2.79, $P = 0.08$
		TME	6452	1467	294.7 min (median) range 206-480	337 mL (median)			
Hajibandeh <i>et al</i> [67], 2020	18 (2)	TME + LPLD	2762	321	MD 116.02, 95%CI: 89.20-142.83, $P < 0.00001$		OS 1.59, 95%CI: 1.14-2.24, $P = 0.007$	OR 6.66, 95%CI: 3.31-13.39, $P < 0.00001$	OR 9.67, 95%CI: 2.38-39.26, $P = 0.002$
		TME	3371	735					
Yang <i>et al</i> [69], 2020	8 (1)	CRT + TME + LPLD	435	435					
		CRT + TME	1461	1461	MD -138.63 min, 95%CI: -219.66--57.60, $P < 0.01$	MD -226.24 mL, 95%CI: -505.76-53.27, $P = 0.11$		OR 0.20, 95%CI: 0.08-0.48, $P < 0.01$	

CI: Confidence interval; CRT: Chemoradiation therapy; LPLD: Lateral pelvic lymph node dissection; MD: Mean difference; OR: Odds ratio; RCT: Randomized controlled trial; RR: Risk ratio; RT: Radiation therapy; TME: Total mesorectal excision; WMD: Weighted mean difference.

difference. The 3-year RFS was 77.4% and the 3-year local recurrence rate was 5.8% in the entire cohort, showing favorable results.

Akiyoshi *et al*[77] also found LPLN metastasis in 57 (26.9%) of 212 cases with LPLN enlargement and LPLD treatment, in a study of 613 cases. Recurrence in the lateral pelvis occurred in 20 (76.9%) of 26 cases with local recurrence (5 with unilateral dissection, 15 without LPLD) and the 3-year DFS was 70% in LPLN metastasis(+) cases, which was significantly poorer than that of 88% in ypN0 cases but significantly favorable compared with that of 48% in ypN2 LPLN metastasis(-) cases. The 3-year cumulative local recurrence rate in LPLN metastasis(+) cases was 3.6%, which was significantly lower than that of 17% in ypN2 LPLN metastasis(-) cases and not significantly different from that of 8.0% in ypN1 LPLN metastasis(-) cases.

Ogura *et al*[78] found LPLN enlargement in 327 patients who underwent laparoscopic surgery. Metastasis was present in 26 (24.3%) of 107 cases treated with TME + LPLD. The operative time was significantly longer and blood-volume loss was larger in LPLD compared to non-LPLD cases but there was no significant difference in the incidence of major complications. The 3-year RFS rates were 84.7% and 82.0% in the LPLD and non-LPLD groups, respectively, and the local recurrence rate was 3.2% in the LPLD group and 5.2% in the TME group, with no significant differences between.

A recent meta-analysis similarly found no difference in OS between TME + CRT and TME + CRT + LPLD (Table 2)[68,69]. Yang *et al*[69] found no difference in overall local recurrence in cases with suspected LPLN metastasis but the incidence of local recurrence in the lateral pelvic region was significantly lower in the TME + CRT + LPLD group than in the TME + CRT group.

### Treatment strategy for LPLN in rectal cancer cases

The main advantage of LPLD is its ability to reduce the rate of lateral pelvic recurrence, but disadvantages such as a longer operative time as well as increased blood-volume loss and complications suggest that LPLD is not likely to be needed for cases that are unlikely to have LPLN metastasis, provided that the diagnosis is accurate. We have suggested possible omission of LPLD in PRLN metastasis-negative cases with a long LPLN axis of  $\leq 5$  mm on MRI[79]. A sub-analysis by stage in the JCOG0212 study showed improvement of RFS in clinical stage III in the LPLD group, based on which LPLD is recommended for stage III cases and can be omitted for stage II cases without improvement[80].

The JCOG0212 study also demonstrated a reduction effect of LPLD on recurrence in the lateral pelvis but not on local recurrence in the central region and anastomotic part of the pelvis[57]. A high local recurrence rate has been found in cases with a short CRM on MRI, and there is evidence to suggest that RT and CRT aimed at shrinking the tumor and securing the CRM may be effective in these cases[81,82]. In Japan, TME + LPLD is the standard treatment for advanced lower rectal cancer, but the latest guidelines recommend preoperative CRT for rectal cancer with a high local recurrence risk, although the recommendation is not strong[51]. Cases in which a sufficient CRM cannot be secured may correspond to this high-risk rectal cancer and preoperative CRT may be considered for these cases.

RT and CRT have not been performed in many previous studies on LPLN and it is thought that the outcome is poor and the local recurrence rate is high in LPLN metastasis cases[7,10,13,83]. No prospective comparative study on LPLD following RT and CRT has been performed in cases with suspected LPLN metastasis. As described above, preoperative RT and CRT cannot reduce LPLN metastasis and their effects are limited, but for cases with suspected LPLN metastasis, a combination of preoperative CRT and LPLD may improve outcomes[76,78,84-91]. Thus, preoperative RT and CRT + selective LPLD may be a rational strategy for omitting unnecessary LPLD while acquiring a favorable treatment outcome.

## CONCLUSION

In Western countries, LPLN metastasis is handled as a systemic disease, due to concerns about the treatment effect and the many complications of LPLD. However, the efficacies of RT boost (strengthening) and a combination of CRT and LPLD for LPLN metastasis have recently been reported in Western countries[85,92-95]. The accuracy of diagnostic imaging largely depends on the diagnostic equipment and may be increased by modification of this equipment and development of contrast media. This suggests that the significance of prophylactic LPLD will further decrease for LPLNs that are less likely to be metastasized. RT and CRT are rational methods that can omit unnecessary LPLD while giving a favorable treatment outcome. Current multidisciplinary treatment of rectal cancer, in addition to RT and CRT, which are local treatments, is progressing toward a strategy of use of systemic chemotherapy aimed at controlling distant metastasis and improving survival. Both multidisciplinary treatment and LPLD are established and further improvement of treatment outcomes can be expected by utilizing the advantages of these methods with optimum indications.

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