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AIM AND SCOPE

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INDEXING/ABSTRACTING

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EDITORS FOR THIS ISSUE

Observational Study

Prophylactic lateral pelvic lymph node dissection in stage IV low rectal cancer

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Abstract

AIM

To assess the clinical significance of prophylactic lateral pelvic lymph node dissection (LPLND) in stage IV low rectal cancer.

METHODS

We selected 71 consecutive stage IV low rectal cancer patients who underwent primary tumor resection, and enrolled 50 of these 71 patients without clinical LPLN metastasis. The patients had distant metastasis such as liver, lung, peritoneum, and paraaortic LN. Clinical LPLN metastasis was defined as LN with a maximum diameter

of 10 mm or more on preoperative pelvic computed tomography scan. All patients underwent primary tumor resection, 27 patients underwent total mesorectal excision (TME) with LPLND (LPLND group), and 23 patients underwent only TME (TME group). Bilateral LPLND was performed simultaneously with primary tumor resection in LPLND group. R0 resection of both primary and metastatic sites was achieved in 20 of 50 patients. We evaluated possible prognostic factors for 5-year overall survival (OS), and compared 5-year cumulative local recurrence between the LPLND and TME groups.

RESULTS
For OS, univariate analyses revealed no significant benefit in the LPLND compared with the TME group (28.7% *vs* 17.0%, *P* = 0.523); multivariate analysis revealed that R0 resection was an independent prognostic factor. Regarding cumulative local recurrence, the LPLND group showed no significant benefit compared with TME group (21.4% *vs* 14.8%, *P* = 0.833).

CONCLUSION
Prophylactic LPLND shows no oncological benefits in patients with Stage IV low rectal cancer without clinical LPLN metastasis.

Key words: Prophylactic lateral pelvic lymph node dissection; Stage IV; Low rectal cancer

Core tip: The clinical significance of prophylactic lateral pelvic lymph node dissection (LPLND) in stage IV low rectal cancer has not been proven. In this study, we showed two main findings concerning treatment strategy in these patients. First, prophylactic LPLND was not a significant prognostic factor for overall survival and did not contribute local control. Second, R0 resection was an independent prognostic factor for overall survival. These results suggest that prophylactic LPLND is not an important component of surgical treatment in stage IV low rectal cancer patients.

INTRODUCTION

In rectal cancer, lymphatic spread accords with the anatomical level of the tumor[1,2]. When the tumor is located above the peritoneal reflection, lymphatic cancer metastasis is predominantly associated with upward mesenteric spread along perirectal vessels originating from the inferior mesenteric artery. In contrast, when the tumor is located at or below the peritoneal reflection, lymphatic cancer metastasis can show upward mesenteric spread and lateral extramesenteric spread along the internal iliac vessels. Based on the rationale of lateral extramesenteric spread, lateral pelvic lymph node dissection (LPLND) is performed to eradicate LPLN metastasis in patients with rectal cancer located at or below the peritoneal reflection[3-9].

The management of LPLN associated with low rectal cancer differs considerably between Western countries and Japan. In Western countries, LPLN metastasis is generally considered as a metastatic disease, and preoperative chemoradiation and total mesorectal excision (TME) is the standard treatment[10]. In contrast, LPLN metastasis is regarded as a local disease in Japan, and TME with LPLND is performed for patients with locally advanced low rectal cancer[11]. Large-scale retrospective studies in Japan evaluated the survival outcome of patients with LPLN metastasis, and concluded that LPLN could be considered as regional lymph nodes in low rectal cancer[12].

LPLN metastasis was identified in approximately 20% of Japanese patients with T3 or T4 tumors who underwent LPLND[11,13]. Nevertheless, the clinical significance of LPLND has not been fully proven and a prospective study is needed to resolve whether LPLND has any survival benefit in patients with low rectal cancer. Accordingly, a randomized controlled trial was conducted to clarify the clinical significance of prophylactic LPLND for clinical stage II and III low rectal cancer (JCOG0212)[14]. However, to date, no studies have addressed the surgical outcome of TME with LPLND for stage IV low rectal cancer, and the clinical significance of LPLND for stage IV low rectal cancer is still unclear.

We retrospectively evaluated 50 consecutive stage IV low rectal cancer patients without clinical LPLN metastasis to assess the survival benefit of prophylactic LPLND in patients with stage IV low rectal cancer. We analyzed various prognostic factors including LPLND with respect to overall survival (OS), and evaluated cumulative local recurrence of patients with LPLND.

MATERIALS AND METHODS

Patients
We selected patients from our colorectal cancer databases with stage IV low rectal cancer according to the AJCC 7th edition[15], applied the following inclusion criteria: Adenocarcinoma confirmed on histological examination, preoperative pelvic computed tomography (CT) scan negative for clinical LPLN metastasis, and primary tumor resection undertaken at Niigata University Medical and Dental Hospital or Niigata Cancer Center Hospital between January 2000 and December 2015. We selected 71 consecutive stage IV low rectal cancer patients who underwent primary tumor resection, and enrolled 50 of these 71 patients without clinical LPLN
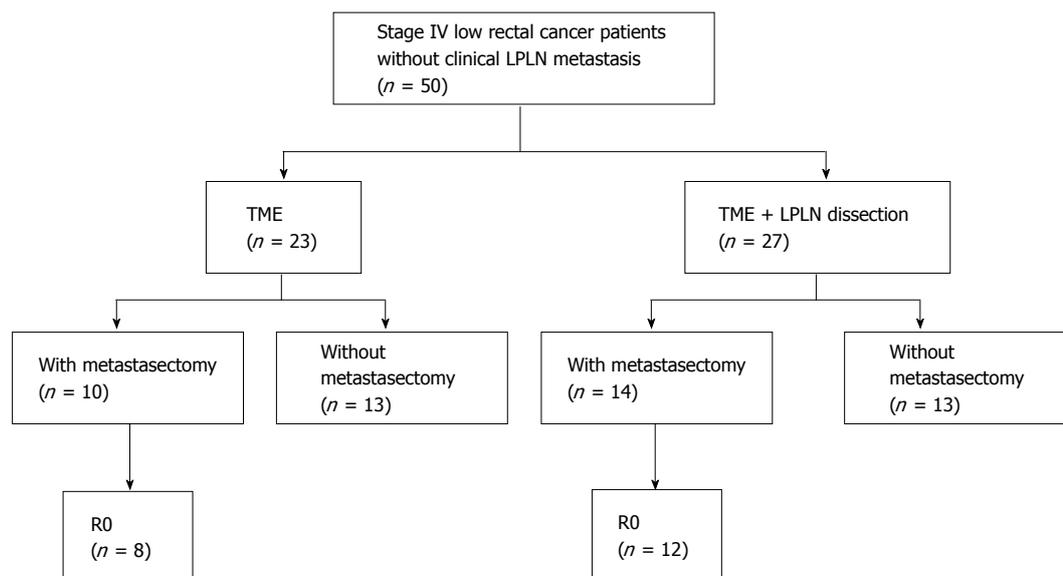
Figure 1 Flowchart of surgical treatment. TME: Total mesorectal excision; LPLN: Lateral pelvic lymph node.

metastasis (Figure 1, Table 1). All the patients had negative circumferential resection margin. Twenty of these 71 patients were excluded in the present study because they were diagnosed as positive for clinical LPLN metastasis by preoperative pelvic CT scan, and 1 patient was excluded because of loss of follow-up. Clinical LPLN metastasis was defined as LN with a maximum diameter of 10 mm or more on preoperative pelvic CT scan. In this study period, "therapeutic LPLND" was carried out for patients with clinical LPLN metastasis. For patients without clinical LPLN metastasis, whether "prophylactic LPLND" was performed or not was determined by preoperative conference. Neoadjuvant chemoradiotherapy (NACRT) was not administered at the participating institutions because it is uncertain whether this approach improves OS[16,17]. Distant metastasis was classified according to the JSCCR classification[18]. Liver metastases were classified into three categories (H1: 1-4 metastatic tumors all of maximum diameter 5 cm or less; H2: Those other than H1 or H3; H3: 5 or more metastatic tumors at least one of which has a maximum diameter of more than 5 cm). Lung metastases were classified into three categories (LM1: Metastasis limited to one lobe; LM2: Metastasis to more than one lobe in one side of lung; LM3: Metastasis to both sides of lungs). Peritoneal metastases were classified into three categories (P1: Metastasis localized to adjacent peritoneum; P2: Metastasis limited to distant peritoneum; P3: Diffuse metastasis to distant peritoneum). This retrospective study was performed in accordance with the Helsinki Declaration, and the Ethics Committee of the School of Medicine, Niigata University approved the study protocol (approval number: 2330), waiving patient consent.

Procedure of TME with LPLND and postoperative complications

Twenty-three patients underwent only TME ("TME group"), and 27 patients underwent TME with LPLND

("LPLND group"). Regarding LPLND, 26 procedures were performed as open surgery and 1 procedure was done as laparoscopic surgery. The LPLN were classified into five areas (distal internal iliac, proximal internal iliac, obturator, external iliac and common iliac) according to the JSCCR classification[18]. In the LPLND group, LPLND was carried out in accordance with previously reported methods[3,13,14]. Bilateral LPLND was performed simultaneously with primary tumor resection in LPLND group. Post-operative complications were monitored for 90 d after surgery and graded according to a standard classification[19]. Major complications were defined as grade ≥ 3.

Metastasectomy and residual tumor status

To achieve R0 resection of metastatic lesion, simultaneous or staged metastasectomy was planned according to the patients' condition. Essentially, simultaneous metastasectomy was performed when the patients had resectable intra-abdominal metastasis such as solitary liver metastasis which could be respected by partial hepatectomy, limited peritoneal dissemination, or paraaortic lymph nodes. Staged metastasectomy was planned when the patients had extra-abdominal metastasis such as lung metastasis, or liver metastasis which needed major hepatectomy such as right hepatic lobectomy. In this cohort, there were no patients who received conversion therapy such as hepatectomy for initially unresectable multiple liver metastasis. We classified the patients according to residual tumor status, *i.e.*, the patients who received R0 resection of both primary lesion and distant metastasis were classified as "R0", and the other patients in whom R0 resection could not be achieved were classified as "R2".

Prognostic factors

We evaluated possible prognostic factors including LPLND

for OS, and compared cumulative local recurrence rates between the TME and LPLND groups. To elucidate the factors influencing OS after surgery, 16 variables were tested in all 50 patients: Age (< 65 *vs* ≥ 65 years), sex, preoperative Carcinoembryonic antigen (CEA) level (< 20 ng/mL *vs* ≥ 20 ng/mL), tumor size (< 60 mm *vs* ≥ 60 mm), T category (T2, 3 *vs* T4), histopathological grading (G1, 2 *vs* G3), lymphatic invasion (absence *vs* presence), venous invasion (absence *vs* presence), lymph node metastasis (absence *vs* presence), LPLND (absence *vs* presence), number of metastatic organs (1 *vs* 2), metastatic organ (liver only *vs* others), Grade 3 complication of primary tumor resection (absence *vs* presence), residual tumor status (R0 *vs* R2), Preoperative chemotherapy (absence *vs* presence), and Postoperative chemotherapy (absence *vs* presence).

Statistical analysis
After the operation, the patients were followed-up by physical examination, laboratory testing, and imaging. CEA and carbohydrate antigen 19-9 were monitored periodically. Disease recurrence and tumor progression were determined mainly by chest-abdominal-pelvic CT scans. Colonoscopy was performed to detect local recurrence at the anastomotic site. The median follow-up period of all 50 patients was 23.6 mo (range: 1-130). Statistical analyses were performed with IBM SPSS Statistics 22 (IBM Japan Inc., Tokyo, Japan). The relationships between each of the clinicopathological variables and residual tumor status were analyzed using Fisher's exact test. Five-year OS and cumulative local recurrence rates were estimated using the Kaplan-Meier method. The log-rank test was used to assess for significant difference between the subgroups by univariate analysis. To investigate independent prognostic factors for OS, factors with a *P* value of less than 0.10 in univariate analyses were entered into multivariate analysis. The Cox proportional hazards regression model was used to identify factors that were independently associated with OS after surgery. *P* values less than 0.05 were considered statistically significant.

RESULTS

Procedure and postoperative complications of primary tumor resection
All patients received R0 resection of primary site with the operative procedure as follows: 31 patients received low anterior resection, 18 patients received abdominoperineal resection, 1 patient received pelvic exenteration. Dysuria was observed in 20 patients, and all of them were grade 1 or 2. Major complications (grade ≥ 3) were observed in 12 of 50 patients (24.0%); anastomotic leakage, surgical site infection, and anastomotic stenosis were observed in 4, 7, and 1 patients, respectively. Postoperative histopathological analysis revealed LPLN metastasis in 12 of 27 patients (44.4%) who received prophylactic LPLND, with a median number of 1 metastatic node per patient (range:

1-4). The sites of LPLN metastases were as follows: distal internal iliac nodes, proximal internal iliac nodes, obturator nodes, external iliac nodes, and common iliac nodes in 6, 5, 3, 1, and 1 patients, respectively.

Metastasectomy
Of the 50 patients, 24 received metastasectomy and 20 received R0 resection of both primary and metastatic sites (Figure 1). Sixteen patients simultaneously underwent primary tumor resection and metastasectomy. The details of the metastasectomy sites are as follows: Liver in 8 patients, limited peritoneal dissemination in 7 patients, and liver and paraaortic lymph node in 1 patient. Successful R0 resection was achieved in 14 of 16 patients; however, two patients who had liver and lung metastases underwent only hepatectomy because of progression of lung tumor after hepatectomy. In contrast, 8 patients underwent staged metastasectomy after primary tumor resection. The details of the metastasectomy sites are as follows: Liver in 4 patients, lung in 3 patient, liver and lung in 1 patient. R0 resection was achieved in 6 of these 8 patients; however, 1 patient who had liver and lung metastases underwent only hepatectomy because of progression of lung tumor after hepatectomy, and 1 patient who had lung metastasis underwent margin positive surgery. In contrast, 26 of 50 patients did not undergo metastasectomy because of tumor progression or development of new metastatic lesions after primary tumor resection.

Factors influencing OS after primary tumor resection
A comparison of clinicopathological characteristics between the LPLND and TME groups showed that there were no significant differences in 15 tested variables (Table 2). Five-year overall cumulative survival rates after primary tumor resection were 74.0% at 1 year, 43.7% at 3 years, and 23.4% at 5 years. Univariate analyses revealed that the LPLND group showed no significant benefit compared with TME group (28.7% *vs* 17.0%, *P* = 0.523) (Table 3 and Figure 2), and that age (≥ 65 years) and R0 resection were factors whose *P* values were less than 0.10 for OS. Multivariate analysis identified R0 resection as significant independent prognostic factor for OS (*P* < 0.001) (Table 3).

Efficacy of prophylactic LPLND for local control
Five of the 50 patients showed local recurrence. The details of local recurrence sites are as follows: Anastomotic site in 2 patients, and the other intrapelvic space in 3 patients. One patient who had LPLND showed local recurrence of the right LPLN area. Twenty-seven patients with LPLND showed no significantly improved 5-year cumulative local recurrence rate compared with the 23 patients without LPLND (21.4% *vs* 14.8%, *P* = 0.833) (Figure 3).

DISCUSSION
In the present study, we showed that prophylactic

Table 1 Clinicopathological characteristics of the 50 patients

Variable	
Age (yr)[1]	58.5 (31-78)
Sex	
Male:female	43:7
Preoperative CEA level (ng/mL)[1]	24.5 (1.6–6856.5)
Tumor size (mm)[1]	63.0 (22–130)
T category	
T2:T3:T4	2:31:17
Histopathological grading	
G1:G2:G3	1:35:14
Lymphatic invasion	
Absence:Presence	6:44
Venous invasion	
Absence:Presence	10:40
Lymph node metastasis	
Absence:Presence	9:41
Pathological LPLN metastasis	
Absence:Presence	15:12
No. of metastatic organs	
1:2:3	44:5:1
Metastatic organ	
Liver:Lung:Peritoneum:Paraaortic LN:Bone	28:16:10:1:2
Grade of liver metastasis[2]	
H1:H2:H3	14:5:9
Grade of lung metastasis[2]	
LM1:LM2:LM3	8:7:1
Grade of peritoneal metastasis[2]	
P1:P2:P3	8:1:1
Grade ≥ 3 Complication of primary tumor resection	
Absence:Presence	38:12
Residual tumor status	
R0:R2	20:30
Preoperative chemotherapy	
Absence:Presence	41:9
Postoperative chemotherapy	
Absence:Presence	7:43
Chemotherapy regimen	
5FU-LV and/or S-1 and/or capecitabine	25
FOLFOX and/or CapeOX and/or FOLFIRI	33
Bevacizumab	18
Cetuximab or panitumumab	4

[1]Data are expressed as median (range); [2]Distant metastasis was classified according to the Japanese Society for Cancer of the Colon and Rectum classification (See material and method). FOLFOX oxaliplatin, leucovorin, and 5FU, CapeOX oxaliplatin and capecitabine, FOLFIRI irinotecan, leucovorin, and 5FU. CEA: Carcinoembryonic antigen; LPLN: Lateral pelvic lymph node; LN: Lymph node; TME: Total mesorectal excision; 5FU: 5-Fluorouracil; LV: Leucovorin.

Table 2 Clinicopathological characteristics of patients in the lateral pelvic lymph node dissection and total mesorectal excision groups

Variable	TME group (n = 23)	LPLND group (n = 27)	P value
Age (yr)			
< 65	13	19	0.382
≥ 65	10	8	
Sex			
Male	20	23	0.999
Female	3	4	
Preoperative CEA level (ng/mL)			
< 20	10	11	0.999
≥ 20	13	16	
Tumor size (mm)			
< 60	7	8	0.999
≥ 60	16	19	
T category			
T2, 3	11	14	0.999
T4	12	13	
Histopathological grading			
G1, 2	19	17	0.206
G3	4	10	
Lymphatic invasion			
Absence	3	3	0.999
Presence	20	24	
Venous invasion			
Absence	7	3	0.155
Presence	16	24	
Lymph node metastasis			
Absence	7	2	0.062
Presence	16	25	
No. of metastatic organs			
1	21	23	0.647
2, 3	2	4	
Metastatic organ			
Liver only	12	13	0.999
Others	11	14	
Grade ≥ 3 complication of primary tumor resection			
Absence	17	21	0.999
Presence	6	6	
Residual tumor status			
R0	8	12	0.569
R2	15	15	
Preoperative chemotherapy			
Absence	18	23	0.715
Presence	5	4	
Postoperative chemotherapy			
Absence	4	3	0.689
Presence	19	24	

CEA: Carcinoembryonic antigen; LPLND: Lateral pelvic lymph node dissection; TME: Total mesorectal excision.

LPLND was not a significant prognostic factor for OS and did not contribute to local control. These results suggest that prophylactic LPLND is not an important component of surgical treatment in stage Ⅳ low rectal cancer.

It is possible that there are several acceptable treatment strategies in stage Ⅳ low rectal cancer patients without clinical LPLN metastasis. When the primary and metastatic sites are resectable, the patient can be treated with a staged or simultaneous resection to achieve R0 resection of both primary and metastatic sites. To achieve R0 resection of the primary site, the options are: (1) TME only; (2) TME with LPLND; (3) NAC followed by TME; and (4) NACRT followed by TME, *etc*. However, optimal treatment of patients with primary metastatic rectal cancer is controversial[20,21].

The NCCN guidelines state that NACRT is a standard treatment for stage Ⅱ/Ⅲ rectal cancer[10], however, it is also associated with increased toxicity (*e.g.*, radiation-induced injury, hematological toxicities). To date, the clinical significance of NACRT for stage Ⅳ low rectal cancer remains still unclear. van Dijk *et al*[20] reported that radical surgical treatment of all tumor sites carried out after short-course radiotherapy, and bevacizumab-

Table 3 Univariate and multivariate analyses of different prognostic factors for overall survival

| Variable	Modality	n	Univariate		Multivariate	
			5-yr OS (%)	*P* value	HR (95%CI)	*P* value
Age (yr)	< 65	32	27.9	0.095	1	
	≥ 65	18	14.8		1.5 (0.8–3.0)	0.197
Sex	Male	43	19.8	0.618		
	Female	7	42.9			
Preoperative CEA level (ng/mL)	< 20	21	23.7	0.671		
	≥ 20	29	22.9			
Tumor size (mm)	< 60	15	29.6	0.634		
	≥ 60	35	20.9			
T category	T2, 3	25	17.3	0.515		
	T4	25	32.5			
Histopathological grading	G1, 2	36	25	0.348		
	G3	14	21.4			
Lymphatic invasion	Absence	6	0	0.446		
	Presence	44	24.2			
Venous invasion	Absence	10	40	0.215		
	Presence	40	19.1			
Lymph node metastasis	Absence	9	0	0.904		
	Presence	41	27.5			
LPLND	Absence	23	17	0.523		
	Presence	27	28.7			
No. of metastatic organs	1	44	23.8	0.866		
	2	6	22.2			
Metastatic organ	Liver only	25	36	0.241		
	Others	25	10.6			
Grade ≥ 3 complication of primary tumor resection	Absence	38	28.8	0.398		
	Presence	12	9.5			
Residual tumor status	R0	20	59	< 0.001	1	
	R2	30	3.6		2.1 (1.4–3.0)	< 0.001
Preoperative chemotherapy	Absence	41	17.6	0.254		
	Presence	9	55.6			
Postoperative chemotherapy	Absence	7	38.1	0.397		
	Presence	43	24.3			

OS: Overall survival; CEA: Carcinoembryonic antigen; LPLND: Lateral pelvic lymph node dissection.
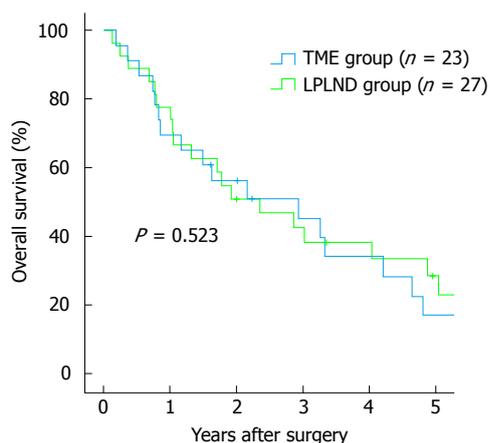
No. of patients at risk
TME group	23	16	12	8	6	3
LPLND group	27	21	13	10	8	5

Figure 2 Comparative overall survival rates of patients with total mesorectal excision and lateral pelvic lymph node dissection groups. TME: Total mesorectal excision; LPLND: Lateral pelvic lymph node dissection.
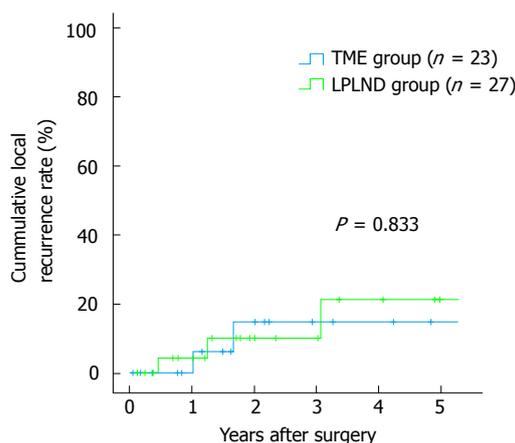
No. of patients at risk
TME group	23	16	10	6	5	3
LPLND group	27	20	11	9	6	4

Figure 3 Comparative cumulative local recurrence rates of patients with total mesorectal excision and lateral pelvic lymph node dissection groups. TME: Total mesorectal excision; LPLND: Lateral pelvic lymph node dissection.

capecitabine-oxaliplatin combination therapy is a feasible and potentially curative approach in primary metastasized rectal cancer. Conversely, Butte *et al*[21]

reported that selective exclusion of radiotherapy may be considered in rectal cancer patients who are diagnosed with simultaneous liver metastasis, because systemic

sites were overwhelmingly more common than pelvic recurrences after primary tumor resection. In stage Ⅳ patients, we surmised that subsequent metastasectomy and systemic chemotherapy are essential for cure; hence, a treatment strategy without NACRT could be a reasonable and acceptable approach to avoid the toxicity associated with NACRT.

To the best of our knowledge, this is the first report regarding the clinical significance of prophylactic LPLND in stage Ⅳ low rectal cancer patients without clinical LPLN metastasis. We demonstrated that prophylactic LPLND has no oncological benefits regarding OS and cumulative local recurrence in this setting. Previous studies reported that TME with LPLND is associated with significant morbidity, longer operative time, greater blood loss, and functional impairment, particularly impotence and bladder dysfunction[3,12-25]. To avoid the post-operative complications associated with LPLND and achieve early induction of postoperative chemotherapy, we think that prophylactic LPLND could be omitted for stage Ⅳ low rectal cancer patients without clinical LPLN metastasis.

We recognize several limitations in this study. First, this retrospective study included a small sample size. Second, we could not investigate how many patients, such as those who had multiple distant metastases, were excluded from the indications for primary tumor resection, because those patients were generally not referred to surgeons. Third, we could not investigate detailed parameters such as resectability criteria of distant metastases, comorbidity and response to chemotherapy. Fourth, it is possible that the LPLND group included patients with suspicious clinical LPLN metastasis of maximum diameter less than 10 mm, because histopathological LPLN metastases were observed in 12 of 27 patients (44.4%) patients in the LPLND group. Fifth, we included only patients without clinical LPLN metastasis. Hence, we could not assess the value of therapeutic LPLND for patients with clinical LPLN metastasis, and the clinical significance of LPLND for these patients is still unclear. In future, a multicenter prospective study is required to clarify the clinical significance of LPLND for stage Ⅳ low rectal cancer patients.

In conclusion, prophylactic LPLND shows no oncologic benefits in patients with stage Ⅳ low rectal cancer without clinical LPLN metastasis.

COMMENTS

Background
No studies have addressed the surgical outcome of total mesorectal excision with lateral pelvic lymph node dissection (LPLND) for stage Ⅳ low rectal cancer, and the clinical significance of LPLND for stage Ⅳ low rectal cancer is still unclear.

Research frontiers
There is little clinical information relating to LPLND for stage Ⅳ low rectal cancer.

Innovations and breakthroughs
This study is the first report regarding the clinical significance of prophylactic

LPLND in stage Ⅳ low rectal cancer patients without clinical LPLN metastasis.

Applications
Prophylactic LPLND shows no oncologic benefits in patients with stage Ⅳ low rectal cancer without clinical LPLN metastasis.

Peer-review
To assess the clinical significance of prophylactic lateral pelvic lymph node dissection is the first research in stage Ⅳ low rectal cancer. The article is well-designed and important for clinical practice.

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