






ORIGINAL ARTICLE

Efficacy of lateral lymph node dissection for local control of rectal cancer: A multicenter study

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Abstract

Background: This study aimed to evaluate the efficacy of lateral lymph node dissection (LLND) for rectal cancer by comparing the local control in patients with and without pathological lateral lymph node metastasis (LLNM).

Methods: We included 189 patients with rectal cancer who underwent total mesorectal excision and LLND at 13 institutions between 2017 and 2019. Patients with and without pathological LLNM were defined as the pLLNM (+) and (-) groups, respectively. Propensity score-matching helped to balance the basic characteristics of both groups. The incidences of local recurrence (LR) and lateral lymph node recurrence (LLNR) were compared between the groups.

Results: In the entire cohort, 39 of the 189 patients had pathological LLNM. The 3-year LR and LLNR rates were 18.3% and 4.0% ($p=0.01$) and 7.7% and 3.3% ($p=0.22$) in the pLLNM (+) and (-) groups, respectively. After propensity score matching, the data from 62 patients were analyzed. No significant differences in LR or LLNR were observed between both groups. The 3-year LR and LLNR rates were 16.4% and 9.8% ($p=0.46$) and 9.7% and 9.8% ($p=0.99$) in the pLLNM (+) and (-) groups, respectively.

Conclusion: LLND would lead to comparable local control in the pLLNM (+) and (-) groups if the clinicopathological characteristics except for LLNM are similar.

KEYWORDS

lateral lymph node dissection, lateral lymph node metastasis, local recurrence, rectal cancer, total mesorectal excision

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1 | INTRODUCTION

The management of lateral lymph node metastasis (LLNM) is crucial for treating rectal cancer. LLNM incidence in patients with T3 or T4 lower rectal cancer is 18.1%.¹ In Japan, total mesorectal excision (TME) with lateral lymph node dissection (LLND) is the standard treatment strategy for locally advanced lower rectal cancer.^{2,3} However, in Western countries, neoadjuvant chemoradiotherapy (nCRT) followed by TME is the standard strategy.^{4,5} The incidence of local recurrence (LR) was 7.9% in patients treated with nCRT and TME, of whom 82.7% had lateral pelvic recurrence, suggesting that nCRT and TME without LLND may be insufficient to control LLNM.⁶ More recently, studies have revealed that LLND can improve local control of rectal cancer, even in patients who undergo nCRT.^{7,8} Therefore, LLND has been focused on as an important treatment strategy, even in Western countries.^{9,10}

However, the efficacy of LLND in the local control of rectal cancer according to the presence or absence of pathological LLNM has not been fully investigated. Although previous reports have demonstrated poorer prognosis in patients with pathological LLNM than in those without LLNM after LLND,^{11,12} prognostic-related factors other than LLNM were different between the groups in these reports. Thus, factors other than LLNM may have affected prognosis. This study aimed to evaluate the impact of pathological LLNM in local control of patients with rectal cancer treated with LLND while adjusting for prognostic-related factors other than LLNM. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) MRI study group recently conducted a multicenter prospective study to establish the optimal diagnostic indications for LLND using MRI.¹³ In the MRI study, prognostic data of patients who underwent TME and LLND were prospectively collected. Here, as a secondary outcome of the MRI study, we compared the incidence of LR and lateral lymph node recurrence (LLNR) after TME and LLND between patients with and without pathological LLNM, using multicenter prospective data to assess the impact of LLND on the local control of rectal cancer.

2 | MATERIALS AND METHODS

2.1 | Patient selection

We reviewed data collected from 13 institutes participating in the JSCCR MRI study.¹³ This database included 212 patients who underwent TME and LLND for rectal cancer between January 2017 and December 2019. Patients with and without preoperative treatment, such as neoadjuvant chemotherapy or nCRT, were allowed to register. Twenty-three patients were excluded from this study owing to the presence of distant metastasis, lack of MRI data, or concomitant prostate cancer. Consequently, 189 patients were included in this study. The recorded variables included age, sex, distance from the anal verge, LLND extent, surgical approach, neoadjuvant treatment, adjuvant chemotherapy, histology, (y)

pathological T stage, (y)pathological mesenteric lymph node metastasis, recurrence, and overall survival (OS). The patients were divided into two groups based on the presence or absence of pathological LLNM. The pLLNM (+) and (-) groups included patients with and without pathological LLNM, respectively. The Institutional Review Board of Shizuoka Cancer Center approved the study protocol (institutional code: T28-42-2021-1).

2.2 | Treatments and surveillance

The indications and extent of LLND were determined at each institution. Lateral lymph node numbers and locations were recorded according to the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma.¹⁴ In this classification, the lateral pelvic nodes included the aortic bifurcation nodes (#280), common iliac nodes (#273), internal iliac nodes proximal (#263P) and distal (#263D) to the superior vesical artery, obturator nodes (#283), and external iliac nodes (#293). Bilateral dissection of the internal iliac (#263P and D) and obturator (#283) nodes was classified as LD2. In this study, all patients underwent a minimum of unilateral dissection of the internal iliac (#263P and #263D) and obturator (#283) nodes. Open, laparoscopic, and robotic surgeries were performed. Indications and regimens for neoadjuvant chemotherapy or nCRT were determined at each institution. Adjuvant chemotherapy and surveillance were performed per the standards of the study institutions and the JSCCR guideline.²

2.3 | Outcome measurements

In addition to the LR and LLNR rates, OS and relapse-free survival (RFS) rates in both groups were assessed in the entire and propensity score-matched cohorts. OS was the time between surgery and death. The RFS was the time from surgery to recurrence or death. LR was recurrence within the pelvic cavity. LLNR was defined as recurrence in the lateral lymph nodes.

2.4 | Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables were presented as medians (ranges). Categorical variables were compared using the χ^2 test. Continuous variables were compared using the Mann-Whitney *U* test. We used propensity score-based methods to adjust for differences in baseline characteristics between the pLLND (+) and (-) groups. To estimate the propensity score, logistic regression analysis was performed using the following nine variables: age, sex, distance from the anal verge, LLND extent, surgical approach, neoadjuvant treatment, histology, (y)pathological T stage, and (y)pathological mesenteric lymph node metastasis. After propensity score estimation, patients in the pLLND (+) and (-) groups were matched according to the propensity

score in a 1:1 ratio without replacement using a caliper with a width of 0.2 of the standard deviation. The LR and LLNR were calculated and compared using the cumulative incidence function and Gray's test, respectively. Death without recurrence was considered a competing event. OS and RFS were calculated and compared using the Kaplan–Meier method and log-rank test, respectively. All statistical analyses were performed using EZR software, version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Patient characteristics

We analyzed data from 189 patients. The pLLNM (+) and (–) groups comprised 39 and 150 patients, respectively. The baseline characteristics of the patients in both groups are presented in Table 1. Significant differences were observed between both groups in terms of distance from the anal verge, LLND extent, surgical approach, histology, (y)pathological T stage, and (y)pathological mesenteric lymph node metastasis. After propensity score matching, 31 pairs of patients were matched from the pLLNM (+) and (–) groups. All characteristics were comparable between both groups.

3.2 | Long-term outcomes

In the entire cohort, the median postoperative follow-up was 39.2 (20.0–64.0) and 38.3 (18.2–66.5) months in the pLLNM (+) and (–) groups, respectively. Figure 1 presents the LR and LLNR curves of the entire cohort. The 3-year LR and LLNR rates were 18.3% and 4.0% and 7.7% and 3.3% in the pLLNM (+) and (–) groups, respectively. The cumulative incidence of LR was significantly higher in the pLLNM (+) group than in the pLLNM (–) group ($p=0.01$). The cumulative incidence of LLNR was higher in the pLLNM (+) group than in the pLLNM (–) group, although the difference was not significant. Figure 2 illustrates the OS and RFS curves for the entire cohort. The OS was higher in the pLLNM (–) group than in the pLLNM (+) group, although the difference was not significant, while RFS was significantly worse in the pLLNM (+) group ($p < 0.01$).

After propensity score matching, the median postoperative follow-up was 39.1 (20.0–64.0) and 38.3 (18.2–51.5) months in the pLLNM (+) and (–) groups, respectively. Figure 3 presents the LR and LLNR curves of the propensity score-matched cohort. No significant differences existed in LR or LLNR between both groups. In the pLLNM (+) and (–) groups, the 3-year LR and LLNR rates were 16.4% and 9.8% and 9.7% and 9.8%, respectively. Figure 4 illustrates the OS and RFS curves of the propensity score-matched cohorts. No significant differences were observed in the OS or RFS between both groups.

TABLE 1 Baseline characteristics of study patients.

		Full cohort (n = 189)			Propensity score-matched cohort (n = 62)		
		pLLNM (+) (n = 39)	pLLNM (–) (n = 150)	p value	pLLNM (+) (n = 31)	pLLNM (–) (n = 31)	p value
Age, years [median (range)]		58 (29–82)	64 (35–82)	0.09	58 (35–82)	69 (36–78)	0.65
Sex	Male	24 (59.0)	100 (66.7)	0.45	19 (61.3)	17 (54.8)	0.80
	Female	16 (41.0)	50 (33.3)		12 (36.7)	14 (45.2)	
Distance from AV, cm [median (range)]		4.0 (0–7.0)	5.0 (0–12.0)	<0.01	4.0 (0–7.0)	3.5 (0–7.0)	0.43
Extent of LLND	Unilateral	13 (33.3)	23 (15.3)	0.02	7 (22.6)	7 (22.6)	1.00
	Bilateral	26 (66.6)	127 (84.7)		24 (77.4)	24 (77.4)	
Approach	Open	9 (23.1)	13 (8.7)	0.03	8 (25.8)	6 (19.4)	0.48
	Laparoscopic	22 (56.4)	86 (57.3)		15 (48.4)	20 (64.5)	
	Robotic	8 (20.5)	51 (34.0)		8 (25.8)	5 (16.1)	
Neoadjuvant treatment	Present	19 (48.7)	61 (40.7)	0.37	15 (48.4)	13 (41.9)	0.80
Histology	Well or mod	32 (82.1)	143 (95.3)	0.01	27 (87.1)	27 (87.1)	1.00
	Others	7 (17.9)	7 (4.7)		4 (12.9)	4 (12.9)	
(y)Pathological T stage	0–3	31 (79.5)	137 (91.3)	0.047	25 (80.6)	25 (80.6)	1.00
	4	8 (20.5)	13 (8.8)		6 (19.4)	6 (19.4)	
(y)Pathological mesenteric LN metastasis	Present	23 (59.0)	50 (33.3)	<0.01	18 (48.1)	14 (45.2)	0.45

Note: Values in parentheses represent percentages unless otherwise noted.

Abbreviations: AV, anal verge; LLND, lateral lymph node dissection; LN, lymph node; Well or moderately, well or moderately differentiated adenocarcinomas.

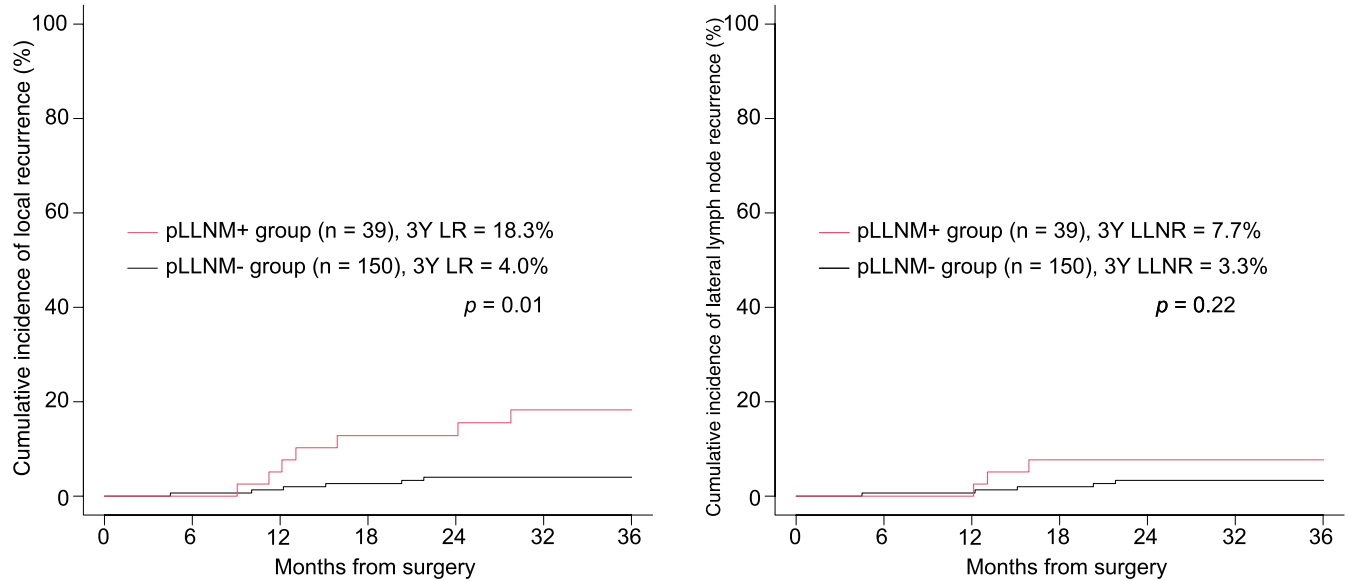


FIGURE 1 Local and lateral lymph node recurrence in the entire cohort. LLNR, lateral lymph node recurrence; LR, local recurrence.

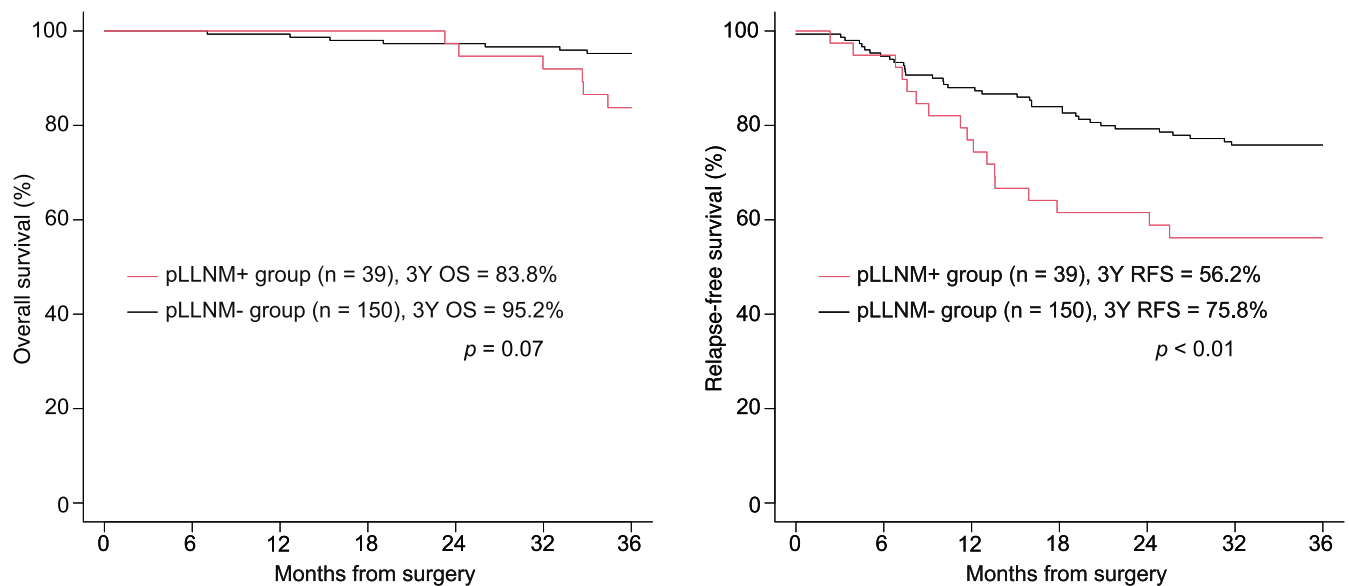


FIGURE 2 Overall and relapse-free survival in the entire cohort. OS, overall survival; RFS, relapse-free survival.

The site of recurrence and the relationship between LR and distant metastasis are presented in Tables 2 and 3, respectively. Six (42.9%) of the 14 patients with LR and 40 (22.9%) of the 175 without LR had distant metastasis. Although the incidence of distant metastasis tended to be higher in patients with LR, it was not statistically significant.

3.3 | Patients with LLNR

Details of patients with LLNR after TME with LLND in the full cohort are presented in Table 4. Eight (4.2%) patients had LLNR: three and five in the pLLNM (+) and (-) groups, respectively. In all eight cases,

LD2 or greater dissection was performed. The LLNR site was within and outside the dissected area in six and two patients, respectively. LLNR outside the dissected area was detected in the common iliac nodes (#273) in both cases, with one in the LLNM (+) group and the other in the LLNM (-) group.

4 | DISCUSSION

LLNR is a major cause of LR after lower rectal cancer resection.⁶ Previous reports have revealed the efficacy of LLND in reducing LR risk,^{1,3,7} and LLND has recently been considered an important strategy for lower rectal cancer worldwide.¹⁰ LR incidence after LLND

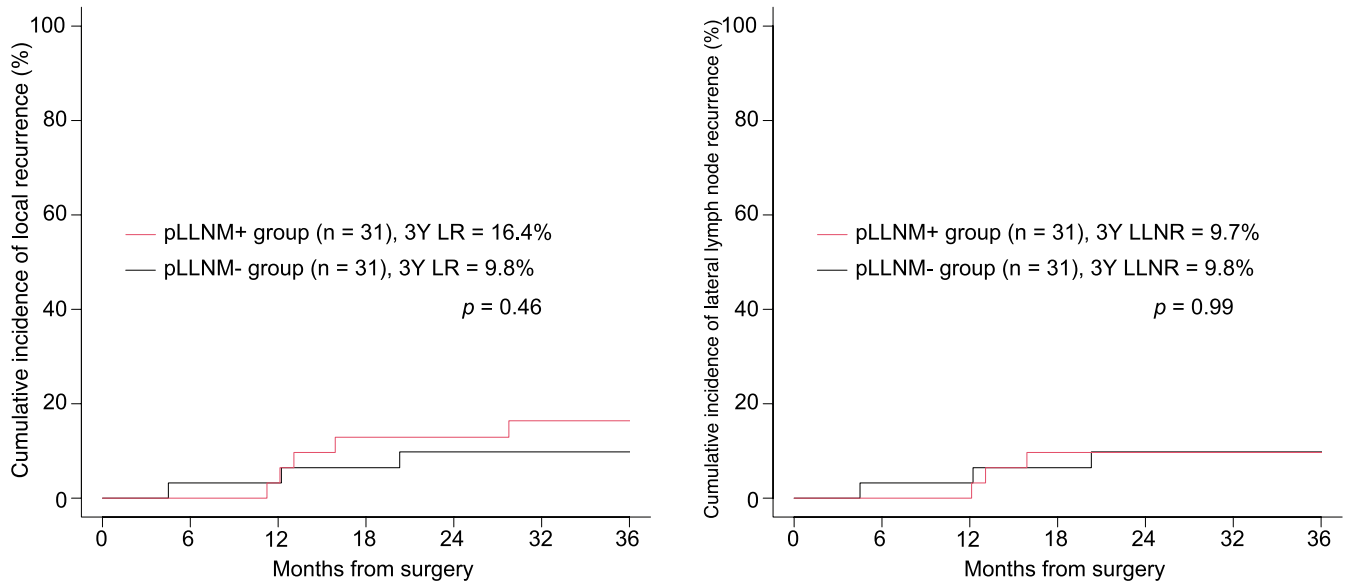


FIGURE 3 Local and lateral lymph node recurrence in the propensity score-matched cohort. LLNR, lateral lymph node recurrence; LR, local recurrence.

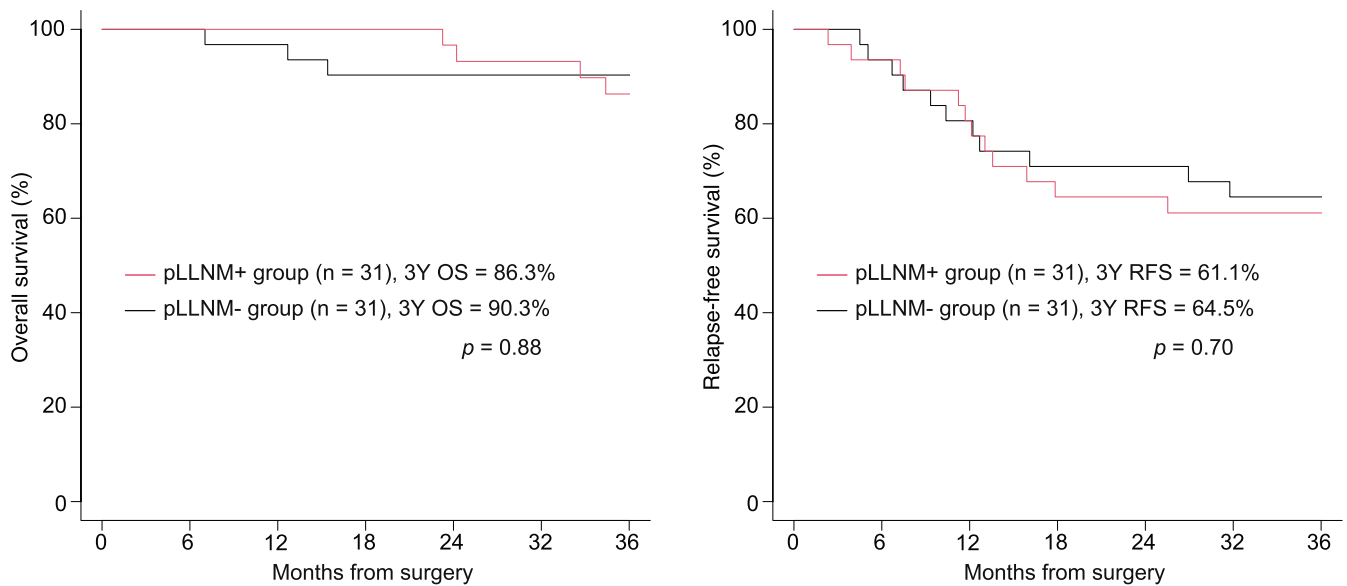


FIGURE 4 Overall and relapse-free survival in the propensity score-matched cohort. OS, overall survival; RFS, relapse-free survival.

has been reported in several studies as 2.7–21.4%.^{3,7,15–20} However, the frequencies of LR and LLNR based on the presence or absence of pathological LLNM after LLND remain unclear.

The prognosis and local control of patients with pathological LLNM after LLND were poorer than those of patients without LLNM.^{11,12} In these studies, tumors with LLNM had more advanced factors except for LLNM than those without LLNM, and these factors may impact prognosis.^{12,21,22} In this study, LR was significantly higher, while LLNR was higher in the pLLNM (+) group than in the pLLNM (–) group in the entire cohort. In addition, the RFS was significantly worse in the pLLNM (+) group. However, the pLLNM (+) group had more cases with lower tumors, T4 tumors, and mesenteric lymph node metastasis, and a smaller proportion of differentiated

TABLE 2 Site of recurrence.

	n = 189
Recurrence	57 (30.2)
Lung	25 (13.2)
Liver	17 (9.0)
Local recurrence	14 (7.4)
Lateral lymph node	8 (4.2)
Distant lymph node	6 (3.2)
Peritoneum	4 (2.1)
Bone	1 (0.5)

Note: Values in parentheses represent percentages unless otherwise noted.

		Local recurrence (+) (n = 14)	Local recurrence (-) (n = 175)	p value
Distant metastasis	Present	6 (42.9)	40 (22.9)	0.11
	Absent	8 (57.1)	135 (77.1)	

Note: Values in parentheses represent percentages unless otherwise noted.

TABLE 3 Relationship between local recurrence and distant metastasis.

TABLE 4 Patients with lateral lymph node recurrence in the entire cohort.

No.	pLLNM	Number of LLNM	Distribution of LLNM	Extent of LLND	Region of LLNR	(y)pT stage	Number of mesenteric LNM	NAT	AC	Approach
1	+	1	283Rt	LD2	283Rt	3	0	+	+	Laparoscopic
2	+	14	263Rt,283Rt	LD2+293Rt, 273Rt, 293Lt, 273Lt	263D Rt	3	23	-	+	Open
3	+	3	263Rt,263Lt,283Lt	LD2+293Rt	273Lt	3	30	-	+	Robotic
4	-	0	-	LD2+273Rt, 273Lt	263D Rt	4b	4	-	+	Robotic
5	-	0	-	LD2	263Lt	3	3	+	+	Laparoscopic
6	-	0	-	LD2	263D Lt	3	1	+	+	Laparoscopic
7	-	0	-	LD2	273Lt	3	1	-	+	Laparoscopic
8	-	0	-	LD2	263D Rt	4b	5	+	+	Robotic

Abbreviations: AC, adjuvant chemotherapy; LLND, lateral lymph node dissection; LLNM, lateral lymph node metastasis; LLNR, lateral lymph node recurrence; NAT, neoadjuvant treatment.

tumors was observed in the entire cohort. Furthermore, significant differences were observed in LLND extent and surgical approach between both groups. These factors could affect the long-term outcomes, making it challenging to determine whether local control after LLND differs based on the presence of pathological LLNM in the entire cohort. Therefore, we performed propensity score matching and adjusted for prognostic-related factors other than LLNM to evaluate the prognostic impact of pathological LLNM in patients who underwent LLND. After matching, no significant differences existed in LR and LLNR between the pLLNM (+) and (-) groups. Of particular note, the 3-year LLNR rates were almost the same between the groups: 9.7% and 9.8% in the pLLNM (+) and (-) groups, respectively. These results suggest that LLND would provide the same local control for patients with and without pathological LLNM if the clinicopathological characteristics, except for LLNM, are comparable. Therefore, our study findings support the efficacy of LLND in patients with LLNM. In addition, both groups had no significant differences in the OS or RFS. Whether LLND can control distant metastasis remains unclear; nonetheless, if prognostic-related factors other than LLNM are comparable between patients with and without LLNM, the prognosis after LLND might also be comparable. In this study, the incidence of distant metastasis tended to be higher in patients with LR. Further studies are needed to determine whether the management of LR leads to the control of distant metastasis.

In this study, the 3-year LR and LLNR rates in patients without pathological LLNM after LLND were 4.0% and 3.3%, respectively. No patients had LLNR after unilateral lymph node dissection. Eight (4%) patients had LLNR, and all underwent bilateral dissection of the internal iliac and obturator nodes (LD2) or greater. However,

two (1%) patients had LLNR outside the dissection area, and both recurrences were confirmed in the common iliac nodes. Further studies are required to clarify the appropriate LLND extent. The other six (3%) patients had LLNR in the dissected area, such as the internal iliac or obturator nodes. These results suggest that despite performing LLND, not all lateral lymph nodes with metastatic potential are resected. This may be due to the technical difficulties associated with LLND. Local control may be improved if the technical difficulties are overcome. Recently, robotic LLND has increased. Robotic surgery allows precise surgical manipulation, even in a narrow pelvic space, with favorable results.^{23,24} In this study, no significant differences were found in LLNR between surgical approaches. However, some differences may have existed in patient characteristics between approaches, making it difficult to compare the local controls. Although some single-center studies have shown the usefulness of robotic surgery,²³⁻²⁵ multicenter studies including a large number of patients are needed to verify this. Further development of surgical devices may lead to more precise dissections and improved surgical outcomes. Additionally, a detailed understanding of pelvic vascular anatomy based on preoperative imaging is crucial^{26,27} and is expected to lead to a more accurate dissection.

This study had several limitations. First, patient selection may have been biased. This was a multicenter study, and LLND indications were determined at each institution. Furthermore, the indications and regimens for preoperative treatment differed between the institutions. Second, the generalizability of this study's findings for all institutions is limited because the participating institutions were university hospitals or high-volume centers that performed LLND daily and were extensively experienced. Third, since propensity score matching was performed, patients with tumors with

extremely high malignant potential who were likely to be pLLNM (+) or extremely low malignant potential who were likely to be pLLNM (-) may have been excluded from the matched cohort. Fourth, the number of patients with LLNR in this study may have been relatively low to draw a definitive conclusion. Only eight patients had LLNR: three and five in the pLLNM (+) and (-) groups, respectively.

In conclusion, we determined the local control of patients with rectal cancer treated with LLND based on pathological LLNM. When patient characteristics, except for LLNM, are comparable, LLND would lead to similar local control, regardless of a pathological LLNM.

AUTHOR CONTRIBUTIONS

Yusuke Tanaka: conceptualization, analysis, methodology, writing—original draft. Hitoshi Hino: conceptualization, methodology, and writing—original draft. Akio Shiomi: conceptualization, methodology, resources, supervision, writing, review, and editing. Kazushige Kawai: conceptualization, data curation, funding acquisition, investigation, project administration, writing, review, and editing. Kay Uehara, Jun Watanabe, Takeshi Nishikawa, Hideki Ueno, Yusuke Kinugasa, and Yoichi Ajioka: conceptualization, resources, supervision, writing, review, and editing.

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CONFLICT OF INTEREST STATEMENT

Jun Watanabe, Hideki Ueno, and Dr. Yusuke Kinugasa are editorial board members of *Annals of Gastroenterological Surgery*.

ETHICS STATEMENT

The Institutional Review Board of the Shizuoka Cancer Center approved the study protocol (institutional code: T28-42-2021-1).

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