JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2024-102
http://journal-arc.jp

Original Research Article

Lateral Pelvic Recurrence in Rectal Cancer Is Not Local Recurrence but Lymphatic Metastasis

Shigeo Toda[1)3)], Naoko Inoshita[2)], Shuichiro Matoba[1)], Yusuke Maeda[1)], Kosuke Hiramatsu[1)], Yudai Fukui[1)], Yutaka Hanaoka[1)], Masashi Ueno[1)], Hiroya Kuroyanagi[1)], Fumihiko Ishikawa[3)] and Kenichi Ohashi[4)]

1) Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan
2) Department of Pathology, Moriyama Memorial Hospital, Tokyo, Japan
3) Department of Comprehensive Pathology, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo, Tokyo, Japan
4) Department of Human Pathology, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo, Tokyo, Japan

Abstract

Objectives: Complete resection of advanced rectal cancer is challenging, with local recurrence rates ranging from 4% to 12%. Local recurrence is often categorized as central, anastomotic, or lateral, with lateral lymph node (LLN) metastasis being the primary driver of lateral recurrence. Although preoperative radiotherapy effectively manages nonlateral recurrences, it is less effective for lateral recurrences, and LLN dissection significantly reduces lateral recurrence rates. This study aimed to clarify the clinicopathological characteristics associated with lateral and nonlateral recurrences.

Methods: We retrospectively analyzed 232 patients (156 males and 76 females; median age, 64 years) who underwent preoperative radiotherapy followed by curative-intent surgery for clinical T3/4 rectal adenocarcinoma located below the peritoneal reflection between April 2010 and December 2017. In total, 40% of the patients underwent LLN dissection. Univariate and multivariate analyses of clinicopathological data were performed to identify the independent risk factors for lateral and nonlateral recurrences.

Results: Local recurrence occurred in 19 (8%) patients: 7 had lateral recurrence, 13 had nonlateral recurrence, and 1 had both. Multivariate analysis identified mesorectal lymph node metastasis as a significant risk factor for lateral recurrence, whereas positive circumferential resection margin was a significant risk factor for nonlateral recurrence.

Conclusions: The identification of different risk factors for lateral and nonlateral recurrence suggests that lateral recurrence is more strongly associated with lymphatic permeation than nonlateral recurrence. These findings highlight the importance of LLN dissection in minimizing the risk of lateral recurrence.

Keywords

rectal cancer, preoperative radiotherapy, lateral lymph node dissection, local recurrence, lateral lymph node metastasis, laparoscopic surgery

J Anus Rectum Colon 2025; 9(2): 225-236

Corresponding author: Shigeo Toda, shigeo-toda@toranomon.gr.jp
Received: November 18, 2024, Accepted: January 23, 2025

Introduction

Colorectal cancer is a common malignancy worldwide, and surgical resection is its primary treatment. Local recurrence after curative resection is more common in rectal cancer than in colon cancer, primarily because of the anatomical complexity of the rectum and technical challenges of surgery in the narrow pelvis.

Preoperative radiotherapy followed by total mesorectal excision (TME) has been shown to reduce local recurrence in randomized trials, making it a widely recommended approach[1,2]. In contrast, some Asian countries, particularly Japan, have used lateral lymph node dissection (LLND) to reduce local recurrence. A randomized trial in Japan, JCOG 0212, demonstrated that TME plus LLND significantly reduced local recurrence rates in patients with advanced rectal cancer who did not receive preoperative radiotherapy[3,4].

Local recurrence is often classified according to pelvic subsites, such as central, anastomotic, and lateral recurrences. Some studies have suggested that patients with lateral recurrence generally have a poorer prognosis[5,6], likely because of the lower curative resection rate compared with central or anastomotic recurrence. Additionally, one study identified lateral recurrence as the major pattern of local recurrence after TME following preoperative radiotherapy[7]. An international retrospective study revealed that radiotherapy alone was insufficient in preventing local recurrence in patients with enlarged lateral lymph nodes (LLNs)[8]. However, data from the JCOG 0212 trial indicated that although LLND reduced lateral recurrence, it did not affect nonlateral local recurrence, such as central or anastomotic recurrence[3]. Collectively, these findings suggest that the pathologies underlying lateral and nonlateral local recurrences differ, underscoring the need to understand these differences to improve recurrence control.

Since 2010, our institution has adopted a harmonized strategy that combines preoperative radiotherapy with selective LLND. Preoperative radiotherapy is performed for advanced low rectal cancer located below the peritoneal reflection, and LLND is performed on the side with LLN enlargement.

This study aimed to identify the factors that contribute to lateral and nonlateral local recurrence in rectal cancer and provide insights to help reduce local recurrence rates.

Methods

Patient inclusion and exclusion criteria

Patients who underwent preoperative radiotherapy followed by surgery for clinical T3 or T4 low rectal adenocarcinoma located below the peritoneal reflection (approximately 7 cm from the anal verge) between April 2010 and December 2017 were included in this study. The exclusion criteria were the presence of other simultaneous malignancies and cases in which only palliative surgery was performed. Patients with resectable distant metastases were included if surgery was performed with curative intent for both local and distant diseases. This study was approved by our hospital's institutional review board (approval number: 1661-H,B), and all participants were informed of their right to opt out.

Treatment strategy for rectal cancer in our institution

Our treatment approach for rectal cancer comprises four main components: preoperative radiotherapy, selective LLND, neoadjuvant chemotherapy, and laparoscopic surgery.

For patients with clinical T3/T4 or N+ adenocarcinoma located in the lower rectum below the peritoneal reflection, we administered preoperative (chemo-)radiotherapy. Patients with prior pelvic irradiation, uncontrollable infections, or those declining preoperative radiotherapy were excluded. Preoperative radiotherapy has two options, long-course chemoradiotherapy (LCCRT) and short-course radiotherapy (SCRT). Our standard approach, LCCRT, consists of 45 Gy of radiotherapy (25 fractions of 1.8 Gy per day) combined with concomitant oral fluoropyrimidines (capecitabine or tegafur-uracil), followed by surgery 6-8 weeks after completion of radiotherapy. SCRT consisted of 25 Gy (five fractions of 5 Gy per day) without chemotherapy, with surgery scheduled 1 week later. This option is selected for patients with an estimated clear resection margin who do not require tumor shrinkage for organ preservation, or those requiring prompt treatment for resectable distant metastases.

Selective LLND is performed for all patients with enlarged LLNs, defined by a long-axis diameter of ≥7 mm on pretreatment computed tomography (CT) and magnetic resonance imaging (MRI). We performed LLND regardless of the response to preoperative treatment; even if the enlarged LLN shrank after neoadjuvant therapy, LLND was still performed.

Neoadjuvant chemotherapy, typically an oxaliplatin-based regimen (FOLFOX or CAPOX), is administered to patients with tumors that threaten resection margins. The standard treatment duration was 12 weeks (six cycles of FOLFOX or four cycles of CAPOX). Patients selected for preoperative chemotherapy generally received preoperative radiotherapy, with chemotherapy typically preceding radiotherapy (induction chemotherapy).

We routinely perform laparoscopic surgery in patients with rectal cancer because it allows meticulous dissection under magnified vision. We prefer using a three-dimensional flexible laparoscope because its stereoscopic perception of organ structures is particularly advantageous in a narrow pelvic space.

Adjuvant chemotherapy was generally recommended and

administered based on the physician's recommendations and patient's will. Chemotherapy regimens included oral fluoropyrimidines (capecitabine or tegafur uracil) with oxaliplatin, when feasible, or FOLFOX. Our intensive postoperative surveillance protocol for advanced rectal cancer included alternating CT and MRI every 3 months for the first 3 years (CT and MRI every 6 months with a 3-month offset), followed by imaging every 6 months for at least 5 years postoperatively. Colonoscopy was performed at least once every 12 months during the first 3 years and once every 24 months thereafter.

Local recurrence was resected by salvage surgery, if the patient was fit for surgery, the recurrence was technically resectable and other metastasis was not detected or controlled.

Surgical procedures

Laparoscopic surgery was the standard procedure during the study period, and all surgeries were performed or supervised by board-certified surgeons qualified by the Endoscopic Surgical Skill Qualification System of the Japan Society for Endoscopic Surgery.

The inferior mesenteric artery was ligated at its root, and the inferior mesenteric vein was ligated at the same level. The splenic flexure was mobilized when an additional proximal colon length was required for anastomosis. Rectal mobilization was initiated posteriorly to reveal and preserve the hypogastric nerves. A deep dissection layer was selected posteriorly between the left and right hypogastric nerves, whereas a shallow dissection was performed laterally and anteriorly to preserve the autonomic nervous system. For anterior resections, the distal rectum was transected laparoscopically with an endostapler, followed by double-stapling anastomosis using a circular stapler. Diverting ileostomy was performed when neoadjuvant treatment was administered.

For abdominoperineal resections, the levator ani muscle was divided laparoscopically, considering the tumor localization. Perineal dissection was performed to meet the transabdominal dissection posteriorly in front of the coccyx. The specimen was extracted through a perineal wound, and a permanent colostomy was created in the left lower abdomen.

LLND involved the removal of adipose tissue containing lymph nodes in the lateral pelvic compartment, bounded by the external iliac vessels and obturator internus muscle laterally; the pelvic plexus, ureter, and urinary bladder medially; the internal iliac vessels, lumbosacral trunk, and coccygeus muscle dorsally; and the levator ani muscle caudally. Detailed procedural methods have been described elsewhere[9].

Pathological evaluation

Pathological evaluation of resected specimens followed the Japanese classification of colorectal carcinoma by the Japanese Society for Cancer of the Colon and Rectum (JSCCR)[10] and American Joint Committee on Cancer staging criteria. Typically, rectal specimens were opened anteriorly along the long axis of the rectum. If the tumor was located along the intended incision line, the specimen was opened. Longitudinal and perpendicular sections were prepared on the intestine containing the tumor to prepare slides. The entire tumor was sectioned at 4-5-mm intervals, and the cross-sections (longitudinal and perpendicular) were examined to determine the depth of invasion.

For microscopic evaluation, the following parameters were carefully assessed: histological type and differentiation of the tumor, tumor depth (T), lymph node metastasis (N) (including both the mesorectal and LLNs), lymphatic invasion, venous invasion, circumferential resection margin (CRM), and JSCCR response to preoperative therapy. Immunohistochemical staining with D2-40 for lymphatic invasion and Elastica van Gieson staining for venous invasion were routinely performed. Lymphatic and venous invasions were classified into four groups: ly0-ly3 and v0-v3 (0, none; 1, minimal; 2, moderate; 3, severe invasion). For this study, the patients were categorized into two groups for each invasion type: ly0 (absent) and ly1-ly3 (present). The same classification approach was applied to venous invasion, categorizing patients into the v0 and v1-v3 groups.

CRM was considered positive if tumor cells were located within 1 mm of the resection margin. Inking the resection margin to aid CRM evaluation was not performed during the study period.

The JSCCR classifies responses to preoperative therapy into four grades: 0 (no effect), 1 (mild effect), 2 (moderate effect), and 3 (marked effect)[10]. For the analysis, we grouped these into two categories: grades 0-1 versus grades 2-3. Grade 2 indicates tumor reduction in more than two-thirds of the lesions, whereas grade 3 indicates complete remission. The Dworak classification[11] was not assessed in this study; however, JSCCR grades 2-3 approximately correspond to Dworak grades 3-4.

If needed, an experienced pathologist (N.I.) and a surgeon (S.T.) jointly reevaluated the specimens.

Data collection

We retrospectively collected the clinicopathological data for each patient, focusing on factors associated with local recurrence in previous studies[12-14]. Collected data included age, sex, body mass index, tumor distance from the anal verge (≤4 cm vs. >4 cm), preoperative clinical tumor depth (T3 vs. T4), preoperative clinical lymph node (LN) metastasis (N- vs. N+), serum carcinoembryonic antigen (CEA) level (categorized as elevated or not), LLN enlargement (equivalent to LLND, as it was performed for all patients with LLN enlargement), preoperative radiotherapy, preoperative chemotherapy, sphincter preservation, cancer histology (well- and moderately differentiated adenocarcinoma vs. poorly differentiated and mucinous adenocarci-

noma), pathological tumor depth (T0-T2 vs. T3-T4), mesorectal lymph node metastasis, LLN metastasis, lymphatic invasion (ly0 vs. ly1-ly3), venous invasion (v0 vs. v1-v3), distant metastasis, CRM status, JSCCR response to preoperative therapy, and adjuvant chemotherapy.

Two experienced surgeons (S.T. and S.M.) analyzed the clinical and radiological findings of patients with local recurrence and categorized each case into one of two groups based on the recurrence localization: lateral or nonlateral (including central and anastomotic). Local recurrence that developed after distant recurrence was also recorded.

Statistical analyses

Continuous variables are presented as median values with interquartile ranges (IQRs). For the univariate analysis, Fisher's exact test was used to assess the association between clinicopathological variables and local recurrence (lateral and nonlateral) for categorical variables. Kaplan-Meier methods with log-rank test was used to calculate survival and its difference. Multivariate logistic regression analysis was then performed on factors with a p-value of <0.1 in the univariate analysis. Differences were considered statistically significant at $p < 0.05$. Variance inflation factors (VIFs) were calculated for each variable in the logistic regression model to assess multicollinearity, with a VIF <5 indicating no significant multicollinearity.

All statistical analyses were performed using EZR[15] (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a modified version of R Commander (The R Foundation for Statistical Computing, Vienna, Austria) designed to include statistical functions commonly used in biostatistics.

Results

A total of 268 patients underwent curative-intent surgery for T3/4 lower rectal cancer. Thirty-six patients who did not receive preoperative radiotherapy because of prior pelvic irradiation, uncontrollable infection, other medical conditions, or refusal to participate were excluded from the analysis. A total of 232 patients were included in this study. Figure 1 illustrates the flowchart of this study. Table 1 presents the clinicopathological characteristics of the patients, comprising 156 males and 76 females with a median age of 64 years. All 232 patients underwent preoperative radiotherapy (163 received LCCRT and 69 received SCRT). Preoperative chemotherapy was administered to 21 patients before preoperative radiotherapy. Sphincter-preserving surgery was performed in 190 (82%) patients, and LLND was performed in 92 (40%) patients (Table 2).

All the patients underwent laparoscopic surgery. Conversion to open surgery was not required. The median operative time was 387 min, and the median blood loss was 70 mL. Morbidity of Clavien-Dindo grade 2 or higher was observed in 52 (22%) patients.

Table 2 shows the pathological characteristics of the patients. Well- and moderately differentiated adenocarcinomas were found in 90% of the patients. Seventeen patients achieved a complete pathological response of primary tumor (including 2 patients with residual LN metastasis) and showed no local recurrence. Among 92 patients who underwent LLND, LLN metastasis was pathologically confirmed in 34.

Local recurrence was diagnosed in 19 patients, with seven classified as lateral recurrence and 13 as nonlateral recurrence (11 central and two anastomotic). The relationships between each clinicopathological factor and recurrence patterns are summarized in Table 3, 4. One patient developed lateral and central recurrences. The median follow-up period was 84 (IQR, 62-103) months.

Univariate analysis identified mesorectal LN metastasis as a significant risk factor for lateral recurrence. Multivariate analysis indicated that mesorectal LN metastasis was the only significant risk factor. The VIFs for each variable were <2, indicating no multicollinearity (Table 3).

For nonlateral recurrence, univariate analysis revealed significant risk factors, including pretreatment clinical T4, pathological T3/4, mesorectal lymph node metastasis, venous invasion, positive CRMs, and poor response to preoperative therapy. Multivariate analysis identified positive CRM as the sole significant risk factor. The VIFs for each variable were <2, ruling out multicollinearity (Table 4).

Table 5 clarify the sidedness of dissected, metastasized LLD and lateral recurrence. Among the four patients who had undergone LLND and developed lateral recurrence, two experienced ipsilateral recurrence and the other two had contralateral recurrence. Three patients without LLND developed lateral recurrence. More than half patients (four out of seven) with lateral recurrence could undergo salvage surgery. Figure 2 illustrates the application of salvage surgery based on the site of local recurrence. Salvage surgery was performed in eight out of 19 patients with local recurrence. The figure also presents overall survival after local recurrence, calculated using the Kaplan-Meier method. The 3-year survival rate was 11% for patients who did not undergo salvage surgery, compared to 100% for those who did (p= 0.0003).

Table 6 outlines clinical outcomes in relation to the strategies employed for LCCRT and SCRT, with or without preoperative chemotherapy. Notably, none of the patients who underwent SCRT achieved a pathological complete response (pCR).

Discussion

Our data differed from previous reports, showing a lower

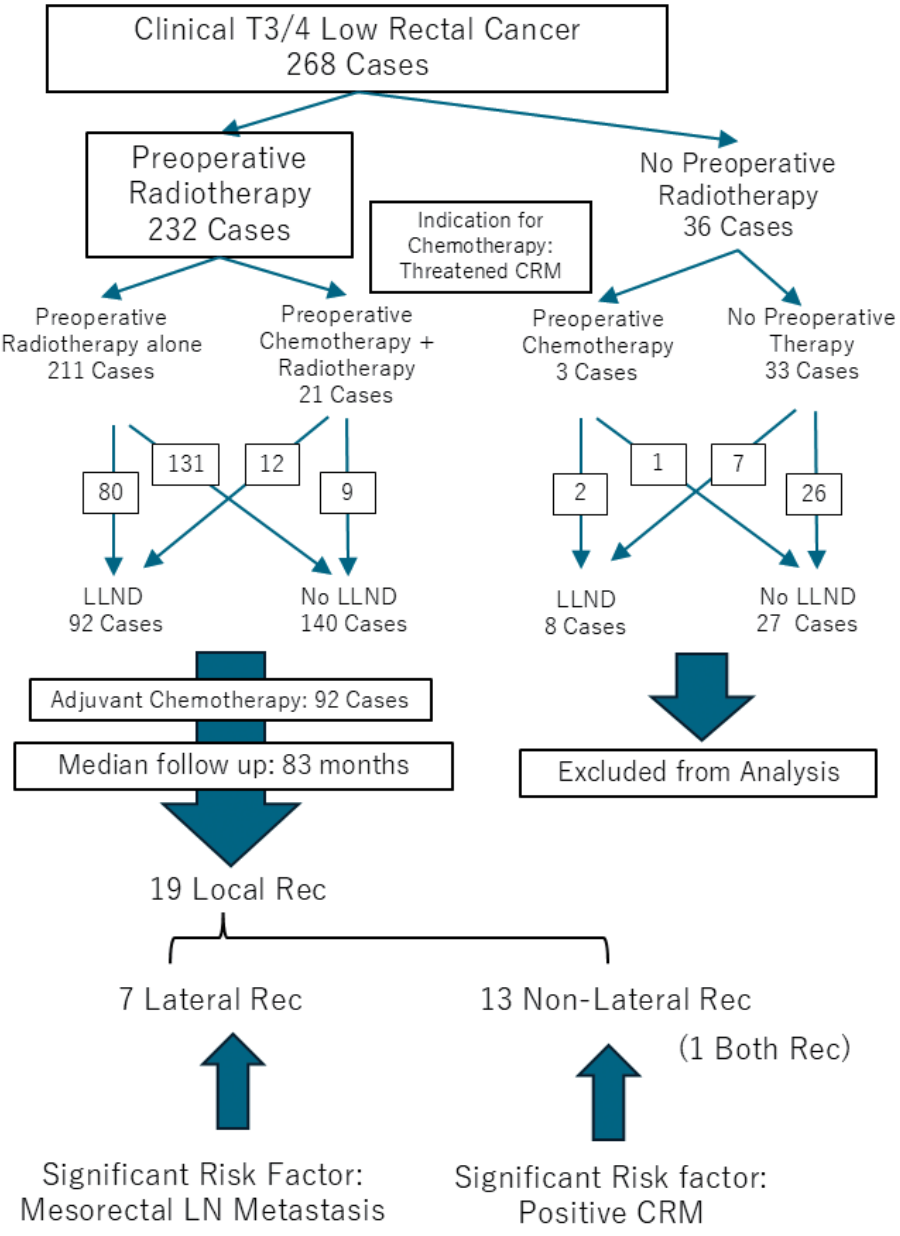

Figure 1. Study flow.
M/F, male/female; LLND, lateral lymph node dissection; Rec, recurrence; LN, lymph node; CRM, circumferential resection margin

pCR rate and a higher LLN metastasis rate.

The pCR rate in our study was lower than the rates reported in previous studies. We believe this can be attributed to the following reasons. Firstly, approximately 30% of our patients received SCRT, which seldom achieves pCR because surgery is performed within one week after completing radiotherapy. No patients with SCRT had pCR in our data. A study comparing SCRT and LCCRT[16] revealed that SCRT is related with lower pCR rate, but the local recurrence rate is similar between the two groups. Secondly, during the study period, our LCCRT protocol included a total irradiation dose of 45 Gy combined with oral tegafur-uracil or capecitabine. Additionally, the interval between the completion of CRT and surgery was typically six weeks during the study period. Extending this interval beyond six weeks has been associated with higher pCR rates in previous reports; however, longer waiting periods can result in stiffer tissues, complicating surgical procedures. For cases requiring extensive tumor regression to achieve negative resection margins or for non-operative management, we now consider adding consolidation chemotherapy or extending the waiting period.

The higher rate of LLN metastasis in our study can be attributed to application of SCRT and inclusion of high risk

Table 1. Preoperative Clinical Characteristics of the Patients, Surgical Findings, and Follow-Up Periods.

	Number of the patients N=232
Age (years)	64 (54–71)†
Sex (male:female)	156:76
Body mass index (kg/m^2)	21.4 (19.9–24.2)†
Tumor distance from anal verge (cm)	4 (3-5)†
≤4 cm/>4 cm	121/111
Pretreatment clinical tumor depth T3/T4	213/19
Pretreatment clinical LN metastasis N-/N+	91/141
Preoperative treatment	232 (100)
Radiotherapy	232 (100)
Long-course/short-course	163/69
Chemotherapy and radiotherapy	21 (9.1)
Serum CEA (ng/mL)	3.5 (2–6.4)†
Lateral lymph node enlargement (=lateral lymph node dissection)	92 (40)
Sphincter-preserving surgery	190 (82)
Laparoscopic surgery	232 (100)
Conversion to open surgery	None
Operative time (min)	387 (302–468)†
Blood loss (mL)	70 (10–160)†
Postoperative hospital stay (days)	16 (12–22)†
Morbidity ≥C–D grade 2	52 (22)
Adjuvant chemotherapy	92 (40)
Median follow-up (months)	84 (62–103)†

*With percentages in parentheses unless indicated otherwise; † values are median (interquartile range [IQR]). LN, lymph node; CEA, carcinoembryonic antigen; C–D, Clavien–Dindo

Table 2. Pathological Characteristics of Resected Materials.

	Number of the patients N=232
Histology	
Well- and moderately differentiated adenocarcinoma	209 (90)
Poorly differentiated and mucinous adenocarcinoma	23 (10)
Tumor depth	
CR (T0)/T1/T2/T3/T4	17/12/71/118/14
Lymph node metastasis	88 (38)
Mesorectal LN metastasis	76 (33)
Lateral LN metastasis	34 (15)
Lymphatic invasion	
ly0/ly1/ly2/ly3	152/63/12/5
Venous invasion	
v0/v1/v2/v3	82/85/49/16
Distant metastasis	15 (6.5)
Positive Circumferential resection margin	11 (4.7)
JSCCR response to preoperative therapy	
Grade 0/1/2/3	0/128/89/15

*Percentages are in parentheses unless indicated otherwise; CR, complete response; LN, lymph node

patients: As SCRT is associated with a lower pCR rate, it is also unlikely to achieve pCR in LLN metastases, contributing to the observed high LLN metastasis rate. The inclusion of high-risk patients, such as those with resectable distant

Table 3. Relationship between Each Clinicopathological Factor and Lateral Local Recurrence.

Variables		Lateral Local recurrence (–)	Lateral Local recurrence (+)	Univariate analysis	Multivariate logistic regression analysis		
				Fisher's exact test p-value	Odds ratio (95% CI)	p-value	Variance inflation factors (VIFs)
Sex:	Male	149	7	0.10			
	Female	76	0				
Tumor distance from anal verge:	≤4 cm	118	3	0.712			
	>4 cm	107	4				
Pretreatment clinical tumor depth:	T3	207	6	0.455			
	T4	18	1				
Pretreatment clinical LN metastasis:	N -	89	2	0.707			
	N +	136	5				
Serum CEA level:	≥5.0 ng/mL	66	1	0.676			
	<5.0 ng/mL	159	6				
Preoperative radiotherapy:	Long-course	158	5	1			
	Short-course	67	2				
Preoperative chemotherapy:	Present	19	2	0.124			
	Absent	206	5				
Sphincter preservation:	Present	183	7	0.356			
	Absent	42	0				
LLN enlargement:	Present	88	4	0.44			
(=LLND)	Absent	137	3				
Well-/moderately differentiated adenoca.		203	6	0.523			
Poorly differentiated/mucinous adenoca.		22	1				
Pathological tumor depth:	T0–T2	98	2	0.702			
	T3–T4	127	5				
Mesorectal LN metastasis:	Present	70	6	0.00554	9.6 (1.04–88.8)	0.0463	1.08
	Absent	155	1				
Lymphatic invasion:	Present	77	3	0.695			
	Absent	148	4				
Venous invasion:	Present	145	5	1			
	Absent	80	2				
LLN metastasis:	Present	31	3	0.0666	1.88 (0.325–10.9)	0.482	1.23
	Absent	194	4				
Distant metastasis:	Present	13	2	0.068	2.19 (0.311–15.5)	0.430	1.21
	Absent	212	5				
CRM:	Negative	214	7	1			
	Positive	11	0				
JSCCR response to preoperative therapy:	G2–3	101	3	1			
	G0–1	124	4				
Adjuvant chemotherapy:	Present	90	2	0.706			
	Absent	135	5				

LLN, lateral lymph node; LLND, lateral lymph node dissection; LN, lymph node; CRM, circumferential resection margin, JSCCR, Japanese Society for Cancer of the Colon and the Rectum

metastases, as well as patients with peritumoral abscesses or obstruction, may have contributed to the higher LLN metastasis rate. All consecutive patients were included in this study as long as surgery was performed with curative intent.

This study revealed that different pathological mechanisms were involved in the risk of rectal cancer recurrence. The risk factor for lateral local recurrence is mainly lymphatic spread, whereas the risk factor for nonlateral local recurrence is positive CRM. This finding underscores the need to address lateral and nonlateral recurrences separately for effective local control.

Reducing the local recurrence of rectal cancer is a primary challenge. Rectal cancer can spread through the lymphatics, veins, and along nerves and often metastasizes to

Table 4. Relationship between Each Clinicopathological Factor and Nonlateral Local Recurrence.

Variables		Nonlateral Local recurrence (–)	Nonlateral Local recurrence (+)	Univariate Analysis	Multivariate Logistic Regression Analysis		
				Fisher's exact test p-value	Odds ratio (95% CI)	p-value	Variance inflation factors (VIFs)
Sex:	Male	146	10	0.554			
	Female	73	3				
Tumor distance from anal verge:	≤4 cm	115	6	0.778			
	>4 cm	104	7				
Pretreatment clinical tumor depth:	T3	204	9	0.0145	1.40 (0.206-9.58)	0.729	1.15
	T4	15	4				
Pretreatment clinical LN metastasis:	N -	86	5	1			
	N +	133	8				
Serum CEA Level:	≥5.0 ng/mL	62	5	0.529			
	<5.0 ng/mL	157	8				
Preoperative radiotherapy:	Long-course	155	8	0.535			
	Short-course	64	5				
Preoperative chemotherapy:	Present	19	2	0.333			
	Absent	200	11				
Sphincter preservation:	Present	182	8	0.0638	1.09 (0.182-6.54)	0.99	1.18
	Absent	37	5				
LLN enlargement:	Present	86	6	0.772			
(=LLND)	Absent	133	7				
Well-/moderately differentiated adenoca.		198	11	0.624			
Poorly differentiated/mucinous adenoca.		21	2				
Pathological tumor depth:	T0–T2	100	0	0.000727	2.69 ($0^{-\infty}$)	0.992	1.0
	T3–T4	119	13				
Mesorectal LN metastasis:	Present	67	9	0.0111	2.59 (0.551–12.2)	0.228	1.09
	Absent	152	4				
Lymphatic invasion:	Present	72	8	0.0666	0.785 (0.165–3.73)	0.76	1.15
	Absent	147	5				
Venous invasion:	Present	138	12	0.0362	0.924 (0.0908–9.4)	0.947	1.15
	Absent	81	1				
LLN metastasis:	Present	30	4	0.104			
	Absent	189	9				
Distant metastasis:	Present	13	2	0.201			
	Absent	206	11				
CRM:	Negative	215	6	<0.0001	48.2 (6.81–342)	0.000104	1.32
	Positive	4	7				
JSCCR response to preoperative therapy:	G2–3	102	2	0.0415	0.202 (0.0213–1.92)	0.164	1.37
	G0–1	117	11				
Adjuvant chemotherapy:	Present	85	7	0.382			
	Absent	134	6				

LLN, lateral lymph node; LLND, lateral lymph node dissection; LN, lymph node; CRM, circumferential resection margin, JSCCR, Japanese Society for Cancer of the Colon and the Rectum

the lymph nodes within the mesorectum. TME, the complete removal of the mesorectum, reduces local recurrence and is accepted as the standard of care worldwide[17]. CRM status and TME quality are crucial risk factors for recurrence[12,18,19]. Preoperative radiotherapy can shrink tumors and improve CRM status, thereby reducing local recurrence rates in patients with stage II/III rectal cancer undergoing TME[1] and is considered a standard treatment in Western countries. In contrast, in Japan, TME combined with selective LLND without neoadjuvant radiotherapy reduces local recurrence[3,20] and is recommended as a standard treatment[4]. An international collaborative study comparing oncological outcomes between the Netherlands and Japan revealed similar local recurrence rates after preoperative radio-

Table 5. Proportions of Lateral Recurrence according to the Status of Radiotherapy, LLND and Pathological LLN Metastasis.

			Long-course CRT	Short-course RT
LLND performed	Pathological LLN metastasis	Positive	1/19 Ipsilateral lateral recurrence: 1 case → Unresectable	2/15 Contralateral lateral recurrence: 2 cases → One underwent salvage surgery
		Negative	1/45 Ipsilateral lateral recurrence: 1 case → One underwent salvage surgery	0/13
LLND not performed			3/99 Undissected side: 3 cases → Two underwent salvage surgery	0/41

CRT, chemoradiotherapy; RT, radiotherapy; LLND, lateral lymph node dissection; LLN, lateral lymph node

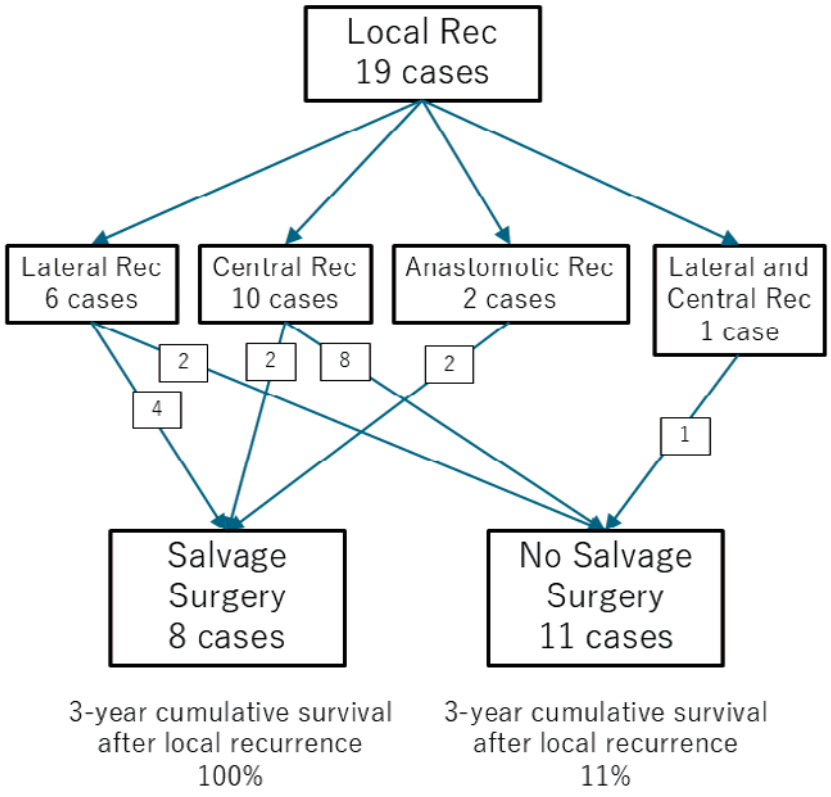

Figure 2. Application of salvage surgery according to the subsite of local recurrence.
Rec, recurrence

therapy and LLND (5.8% in the Netherlands and 6.9% in Japan)[21]. However, many Western and Japanese surgeons remain reluctant to adopt each other's treatment modalities, citing concerns regarding increased early and late complications. Our institution is among the few that offers both LLND and preoperative radiotherapy under clear indications.

Kim et al. reported that LLN metastasis was the major cause of local recurrence in patients with rectal cancer who underwent preoperative radiotherapy, followed by TME without LLND. They identified a pretreatment LLN short-axis diameter of ≥5 mm as a risk factor for lateral local recurrence[7]. Ogura et al. conducted an international collaborative study involving 12 institutions from eight countries and found that LLN enlargement, defined as a short-axis diameter of ≥7 mm, was a significant risk factor for lateral local recurrence. In their study, the lateral recurrence rate was 5.7% in patients undergoing preoperative radiotherapy followed by TME and LLND, compared with 19.5% in those receiving preoperative radiotherapy followed by TME alone. They concluded that preoperative (chemo-)radiotherapy

Table 6. Clinical Outcomes according to the Mode of Radiotherapy and Addition of Preoperative Chemotherapy.

Preoperative chemotherapy	Long-course CRT n=163		Short-course RT n=69	
	CRT alone n=152	CRT with chemotherapy n=11	RT alone n=59	RT with chemotherapy n=10
Pretreatment Tumor depth T4	12 (7.9)	2 (18)	2 (3.4)	3 (30)
Distant metastasis	4 (2.6)	1 (9)	5 (8.5)	5 (50)
LLN enlargement (=LLND)	60 (39)	4 (36)	20 (34)	8 (80)
Pathological CR	14 (9.2)	1 (9)	0 (0)	0 (0)
LLN metastasis	17 (11)	2 (18)	10 (17)	5 (50)
Positve CRM	8 (5.2)	1 (9)	1 (1.7)	1 (10)
Lateral recurrence	4 (2.6)	1 (9)	1† (1.7)	1 (10)
Nonlateral recurrence	7 (4.6)	1 (9)	4† (6.8)	1 (10)

*With percentages in parentheses unless indicated otherwise; † Including one case with both lateral and nonlateral recurrence, CRT, chemoradiotherapy; RT, radiotherapy; LLND, lateral lymph node dissection; LLN, lateral lymph node; CR, complete response; CRM, circumferential resection margin

alone was insufficient to reduce lateral recurrence in patients with LLN enlargement[8]. The JCOG 0212 trial further demonstrated that TME with LLND significantly reduced local recurrence rates compared with TME alone in patients without preoperative radiotherapy (7.4% vs. 12.6%, p= 0.024). The lateral recurrence rates in the TME with LLND and TME alone groups were 2.0% and 7.1%, respectively, whereas the nonlateral recurrence rates were similar (6.3% vs. 6.0%). These findings from independent studies highlight the differing pathologies of lateral and nonlateral recurrences, necessitating distinct management approaches.

In the present study, we aimed to elucidate these differences and identify strategies to improve local recurrence rates using data from our institution, which integrates both preoperative radiotherapy and LLND. Pathological factors play a critical role in rectal cancer recurrence, and TNM staging, which is the most widely recognized and effective indicator of recurrence, depends on these parameters. Our analysis included various pathological factors, such as CRM status, lymphovascular invasion, and tumor differentiation, along with clinical factors, including sex, serum CEA levels, and sphincter-preserving surgery, in line with previous studies[12-14].

As anticipated, the risk factors for lateral and nonlateral local recurrence significantly differed. Mesorectal lymph node metastasis has emerged as a key risk factor for lateral recurrence, suggesting that the tendency for discontinuous lymphatic metastasis plays a critical role as most lateral recurrences originate from LLN metastases. Conversely, the CRM was identified as a significant risk factor for nonlateral recurrence, underscoring the importance of maintaining continuity in tumor resection to minimize nonlateral local recurrences.

To effectively manage recurrence, strategies should focus on controlling continuous tumor spread to decrease nonlateral recurrence and managing discontinuous extension to reduce lateral recurrence. Approaches, such as preoperative radiotherapy for tumors threatening the resection margins and multivisceral extended resection for tumors invading adjacent organs, may help address continuous spread, whereas selective LLND can mitigate lateral recurrence. Establishing the optimal criteria for LLND remains challenging. At our institution, LLN enlargement, defined as a long-axis diameter of ≥7 mm, is an indication for LLND. Approximately one-third of patients (92 of 232, 40%) underwent LLND, and one-third (34 of 92, 37%) were found to have pathological LLN metastasis. MRI findings, such as internal heterogeneity and irregularity of the LLN, may provide additional insights; however, the pretreatment diameter of the LLN remains the most practical parameter for preoperative evaluation. Each institution must determine whether to use long- or short-axis measurements and establish appropriate cut-off lengths based on local experience, risks, and benefits of LLND.

An alternative approach could involve the application of radiomics for selective LLND. Refining the criteria represents a promising strategy to improve outcomes. One study demonstrated that a radiomics-based approach was significantly more effective than diameter-based criteria in predicting pathological LLN metastasis[22]. This method may provide a more accurate solution for predicting LLN metastasis. Intensive surveillance of high-risk patients, particularly those with mesorectal lymph node metastasis, as indicated by our study findings, is essential because early detection of LLN recurrence may allow for salvage resection. Akiyoshi et al. reported that salvage surgery could be safely performed for LLN recurrence[23]. Our data show that more than half of the lateral recurrences can be successfully resected via sal-

vage surgery. Patients with resectable local recurrence demonstrated better prognoses, although resectable disease likely reflects less aggressive tumor biology.

Although our data indicate that pathological mesorectal lymph node (LN) metastasis is an independent risk factor for lateral recurrence, we do not consider prophylactic LLND necessary for patients with suspected mesorectal LN metastasis. According to previous studies[24,25], the accuracy of diagnosing mesorectal LN metastasis is approximately 70%, which is insufficient to warrant prophylactic LLND given the associated increase in postoperative complications. Instead, we recommend intensive surveillance for patients with mesorectal LN metastasis to detect lateral recurrence at an early stage and facilitate salvage surgery. As noted earlier, more than half of the patients with lateral recurrence (four out of seven) underwent salvage surgery, achieving favorable long-term outcomes based on our data.

Unlike mesorectal LN metastasis, a positive CRM can be more effectively predicted using imaging studies, typically MRI, as reported in previous studies[24]. Therefore, total neoadjuvant therapy (TNT), consisting of radiotherapy either preceding or following systemic chemotherapy, is recommended for patients with threatened CRM to promote tumor shrinkage.

In summary, we recommend intensive surveillance with alternating CT and MRI every 3 months to detect local recurrence at an early stage especially for patients with pathological mesorectal LN metastasis, enabling salvage surgery for lateral recurrence with favorable outcomes. TNT is recommended for patients with threatened CRM on MRI to reduce the positive CRM rate and, consequently, the nonlateral local recurrence rate.

This study has some limitations. The variability in the pathological examination methods, retrospective design, lengthy study period, and inclusion of patients with resectable distant metastases may have affected the findings. First, our pathological assessment utilized longitudinal sectioning of specimens based on Japanese guidelines, whereas circumferential sectioning was the international standard. This may affect CRM evaluation; however, Matsunaga et al. reported that longitudinal sectioning did not compromise the accuracy of CRM and distal margin assessments[26]. Second, the retrospective nature of this study introduced a potential bias. Third, a 7-year study period was necessary to enroll a sufficient number of patients; however, our treatment strategy remained consistent throughout, minimizing bias. Finally, including patients with resectable distant metastasis is crucial, as curative resection can still be achieved even in the presence of distant metastasis. Notably, tumors with distant metastases tend to be biologically aggressive and frequently develop local recurrences. Thus, including these patients is vital for improving the prognosis of patients with advanced rectal cancer.

Conclusion

This study has shown two types of local recurrence in rectal cancer: lateral local recurrence is mainly associated with lymphatic spread, and nonlateral local recurrence is associated with CRM. This distinction underscores the need for tailored management strategies that account for the differing pathogeneses of each type of recurrence, and LLND is effective in fully controlling lateral recurrence of rectal cancer.

Acknowledgements

We would like to thank Editage (www.editage.jp) for English language editing.

Conflicts of Interest

There are no conflicts of interest.

Source of Funding

This work was supported by the Okinaka Memorial Institute for Medical Research.

Author Contributions

Toda: conception and design of the study; collection, analysis, and interpretation of the data; and manuscript writing and editing

Inoshita: study conception and design, data interpretation, and manuscript review and editing

Matoba: study conception and design, data collection and interpretation, and manuscript review and editing

Maeda: data collection and manuscript review

Hiramatsu: data collection and manuscript review

Fukui: data collection and manuscript review

Hanaoka: data collection and manuscript review

Ueno: data collection and manuscript review

Kuroyanagi: data collection and manuscript review

Ishikawa: manuscript review

Ohashi: manuscript review

All authors contributed to the critical revisions. All the authors have read and approved the final version of the manuscript.

Approval by Institutional Review Board (IRB)

This study was approved by the Institutional Review Board of Toranomon Hospital (approval code: 1661-H,B).

References

1. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001 Aug;345(9):638-46.
2. Abraha I, Aristei C, Palumbo I, et al. Preoperative radiotherapy and curative surgery for the management of localised rectal carcinoma. Cochrane Database Syst Rev. 2018 Oct;10:Cd002102.

3. Fujita S, Mizusawa J, Kanemitsu Y, et al. Mesorectal Excision With or Without Lateral Lymph Node Dissection for Clinical Stage II/III Lower Rectal Cancer (JCOG0212): A Multicenter, Randomized Controlled, Noninferiority Trial. Ann Surg. 2017 Aug;266(2):201-7.
4. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020 Jan;25(1):1-42.
5. Kusters M, Marijnen CA, van de Velde CJ, et al. Patterns of local recurrence in rectal cancer; a study of the Dutch TME trial. Eur J Surg Oncol. 2010 May;36(5):470-6.
6. Enríquez-Navascués JM, Borda N, Lizerazu A, et al. Patterns of local recurrence in rectal cancer after a multidisciplinary approach. World J Gastroenterol. 2011 Apr;17(13):1674-84.
7. Kim TH, Jeong SY, Choi DH, et al. Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. Ann Surg Oncol. 2008 Mar;15(3):729-37.
8. Ogura A, Konishi T, Cunningham C, et al. Neoadjuvant (Chemo) radiotherapy With Total Mesorectal Excision Only Is Not Sufficient to Prevent Lateral Local Recurrence in Enlarged Nodes: Results of the Multicenter Lateral Node Study of Patients With Low cT3/4 Rectal Cancer. J Clin Oncol. 2019 Jan;37(1):33-43.
9. Toda S, Kuroyanagi H, Matoba S. Appendix, Colon, and Rectum: Oxford University Press; 2024. Chapter 13, Rectal Cancer Surgery; p. 103-114
10. Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3d English Edition [Secondary Publication]. J Anus Rectum Colon. 2019 Oct;3(4):175-95.
11. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis. 1997;12(1):19-23.
12. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol. 2008 Jan;26(2):303-12.
13. Compton CC, Fielding LP, Burgart LJ, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med. 2000 Jul;124(7):979-94.
14. Ganeshan D, Nougaret S, Korngold E, et al. Locally recurrent rectal cancer: what the radiologist should know. Abdom Radiol (NY). 2019 Nov;44(11):3709-25.
15. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013 Mar; 48(3):452-8.
16. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol. 2012 Nov 1;30(31):3827-33.
17. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg. 1982 Oct;69 (10):613-6.
18. Quirke P, Durdey P, Dixon MF, et al. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet. 1986 Nov;2(8514):996-9.
19. Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. Lancet. 2009 Mar;373 (9666):821-8.
20. Sugihara K, Kobayashi H, Kato T, et al. Indication and benefit of pelvic sidewall dissection for rectal cancer. Dis Colon Rectum. 2006 Nov;49(11):1663-72.
21. Kusters M, Beets GL, van de Velde CJ, et al. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. Ann Surg. 2009 Feb;249(2):229-35.
22. Nakanishi R, Akiyoshi T, Toda S, et al. Radiomics Approach Outperforms Diameter Criteria for Predicting Pathological Lateral Lymph Node Metastasis After Neoadjuvant (Chemo)Radiotherapy in Advanced Low Rectal Cancer. Ann Surg Oncol. 2020 Oct;27 (11):4273-83.
23. Akiyoshi T, Nagata J, Nagasaki T, et al. Laparoscopic salvage lateral pelvic lymph node dissection for locally recurrent rectal cancer. Colorectal Dis. 2015 Oct;17(10):O213-6.
24. Al-Sukhni E, Milot L, Fruitman M, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol. 2012 Jul;19(7):2212-23.
25. Group MS. Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. Radiology. 2007 Apr;243(1):132-9.
26. Matsunaga R, Kojima M, Nishizawa Y, et al. The utility of longitudinal slicing method for rectal specimen: pathological analysis of circumferential resection margin of intersphincteric resection for low-lying rectal cancer. Pathol Int. 2019 May;69(5):272-81.