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ORIGINAL ARTICLE

Optimal treatment strategy for rectal cancer based on the risk factors for recurrence patterns

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Abstract

Background For rectal cancer, multimodality therapeutic approach is necessary to prevent local recurrence and distant metastasis. However, the efficacy of additional treatments, such as neoadjuvant chemoradiotherapy (nCRT), neoadjuvant chemotherapy (NAC), and lateral pelvic lymph node dissection (LPLND), has not been scrutinized.

Methods Recurrence patterns were categorized into local recurrence and distant metastasis. Local recurrence was classified into two types: (1) pelvic cavity recurrence and (2) LPLN recurrence. First, we analyzed the risk factors for each recurrence pattern. Second, based on the status of clinically suspected involvement of circumferential resection margin (cCRM), the efficacy of additional treatments was investigated.

Results A total of 240 patients was enrolled. nCRT was performed for 25 (10%), NAC was for 46 (19%), and LPLND was for 35 patients (15%). As the recurrence patterns, pelvic cavity recurrence occurred in 15 (6%), LPLN recurrence in 8 (3%), and distant metastasis in 42 patients (18%). Five-year overall survival and relapse-free survival were 87% and 70%, respectively. Multivariate analysis indicated that pelvic cavity recurrence was associated with cCRM status and tumor histology, that LPLN recurrence was with serum carcinoembryonic antigen level and LPLN swelling, and that distant metastasis was with clinical N category. In the cCRM-positive subgroup ($n=66$), cumulative rate of pelvic cavity recurrence was lower in the nCRT group than in the NAC or non-NAC/nCRT group ($P=0.02$ and 0.09, respectively).

Conclusion cCRM status was associated with pelvic cavity recurrence, and LPLN swelling was with LPLN recurrence. nCRT could reduce pelvic cavity recurrence in cCRM-positive subgroup.

Keywords Rectal cancer · Neoadjuvant chemoradiotherapy · Neoadjuvant chemotherapy · Lateral lymph node dissection · Circumferential resection margin

Introduction

The standard surgical treatment for rectal cancer is total mesorectal excision (TME) [1]. However, local recurrence following rectal surgery was reported to be over 10% when treated by TME alone [2]. Especially, for advanced low-rectal cancer, additional treatments, such as neoadjuvant chemoradiotherapy (nCRT), neoadjuvant chemotherapy (NAC), and lateral pelvic lymph node dissection (LPLND), are considered to be important to prevent the postoperative recurrence. Although such additional treatments are beneficial for patients' prognosis, they are associated with several adverse events, such as anal dysfunction, urogenital dysfunction, sexual dysfunction, and risk of secondary cancer [3–8]. In Japan, lateral pelvic lymph node (LPLN) metastasis is considered to be regional lymph node metastasis rather than distant metastasis, and so extended surgery, including LPLND without nCRT, has been standard for locally advanced rectal cancer [9–11]. In Western countries, nCRT followed by TME without LPLND has been the standard for treating rectal cancer, because LPLNs are not targets of surgical resection [2, 12–14].

We previously reported that postoperative local recurrence should be categorized as LPLN recurrence and other types of pelvic cavity recurrence (anastomotic recurrence and dissemination) [15], because the underlying mechanism

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and risk factors for each recurrence pattern were completely different [16–18]. Furthermore, the risk factors for distant metastasis seem to be different from those for local recurrence. Considering the risk factors for postoperative recurrence as well as adverse events of additional treatments, selective use of nCRT, NAC, and LPLND is ideal. However, the optimal indication for each treatment remains unclear.

The aims of this study were to investigate the risk factors associated with different patterns of recurrence and to identify the optimal treatment strategy based on the risk factors for recurrence patterns.

Patients and methods

Patient population

We enrolled consecutive 240 rectal cancer patients with cStage II and III who underwent curative resection in our hospital between July 2005 and June 2017. Patients with distant metastasis or who underwent non-curative resection were excluded. The lower edge of the tumor was within 10 cm from the anal verge in all cases. Tumor location was categorized according to the Japanese Rule for Staging of Cancer of the Colon and Rectum [19]. "Ra" (upper rectum) was defined as the portion between the inferior border of the second sacral vertebra and peritoneal reflection, "Rb" (lower rectum) was between the peritoneal reflection and upper border of the anal canal, and "P" was the anal canal. Pre-treatment clinical staging was determined using magnetic resonance imaging (MRI), colonoscopy, and computed tomography (CT). Positron emission tomography with ^{18}F-fluorodeoxyglucose was used when necessary. On the pre-treatment MRI and CT, we generally diagnosed LPLN $\geq$ 5.0 mm in short-axis diameter as suspected metastasis, and the final assessment of metastasis was determined at the multidisciplinary team meeting. Clinically suspected circumferential resection margin involvement (cCRM) was defined as "positive" when the invasion front of the tumor was within 1 mm from the mesorectal fascia on the pre-treatment MRI and CT [20, 21]. The study protocol was approved by the institutional review board of Kyoto University (reference no. R1404).

Treatment protocol

All of the surgical procedures included lymphadenectomy using a standard TME technique. Treatment strategy of individual cases was determined at the multidisciplinary team meeting. Basically, neoadjuvant treatment (NAC or nCRT) was performed for the cases with high-risk of recurrence, such as bulky tumor or marked swelling of mesorectal lymph nodes. Because the study period extended over 12 years, our treatment strategy was inevitably subjected to certain chronological changes; namely, NAC and nCRT were more widely applied in the later period. In the NAC group, modified FOLFOX6-based chemotherapy, FOLFIRI-based chemotherapy, or S-1 plus CPT-11 regimen was performed.

Chemotherapy regimens were finally determined through the discussion between the patients and the attending physicians, in consideration of the risk factors including age, past medical history, and performance status. In addition, some patients were enrolled in clinical trials, and for them, the regimens were determined based on the protocol of the trials. In the nCRT group, radiation therapy (total 45 Gy in 25 fractions) with concomitant S-1 and CPT-11 was performed [22–24]. LPLND was selectively performed for patients with LPLNs clinically suspected of having metastasis. Prophylactic dissection of non-swollen LPLNs (i.e., clinically negative) was not performed.

Outcome measures

Oncological outcomes were evaluated by assessing overall survival (OS), relapse-free survival (RFS), and cumulative local recurrence rate. Local or distant recurrence was counted as an event when it emerged as the first site of recurrence. Follow-up examinations were performed according to the Japanese Society for Cancer of Colon and Rectum Guidelines [11]. To determine the risk factors for LPLN recurrence, we defined "potential LPLN recurrence" as both LPLN recurrence, and as the pathological LPLN metastasis in patients treated with LPLND [15, 25].

Statistical analysis

Continuous variables are presented as median [range]. The Fisher's exact test or Chi-square test was used for the comparison of categorical variables. To determine factors associated with "potential LPLN recurrence", multivariate logistic regression analysis was used and factors with a P value of <0.05 were included in the model. The Kaplan–Meier method and log-rank test were used for the estimation and comparison of OS, RFS, and cumulative local recurrence rate. Multivariate analysis of the prognostic factors was carried out using the Cox's proportional hazard regression model. All analyses were two-sided, and a P value of <0.05 was considered statistically significant. All statistical analyses were conducted using JMP Pro, Version 13 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics and outcomes

In total, 240 patients were enrolled for analysis. Median follow-up duration was 57 months [3.1–152]. Table 1 shows the clinicopathological characteristics of the study population, consisting of 164 males and 76 females with a median age of 66 years old (21–90). The patients were staged as follows: cStage II, $n = 73$ (30%) and III, $n = 167$ (70%). On the pre-treatment MRI and/or CT, cCRM was positive in 66 patients (27%). As additional preoperative treatments, nCRT was performed in 25 patients (10%) and NAC in 46 patients (19%). Swollen LPLN (i.e., ≥ 5.0 mm in short-axis diameter) was found in 35 patients (15%), all of whom underwent LPLND. In detail, LPLND was performed in 9 patients who underwent nCRT, and in 15 patients who underwent NAC. The remaining 158 patients (66%) were treated by TME without LPLND.

As the recurrence patterns, pelvic cavity recurrence occurred in 15 (6%), LPLN recurrence in 8 (3%), and distant metastasis in 42 patients (18%). Figure 1 shows OS, RFS, pelvic cavity recurrence rate, and distant metastasis rate in all patients. Five-year OS and RFS were 87% and 70%, respectively.

Risk factors for each recurrence pattern

Local recurrence was divided into the following two types: pelvic cavity recurrence (anastomotic recurrence and dissemination of the pelvic cavity) and LPLN recurrence. Among the clinical factors that could be determined before preoperative treatment, we investigated the risk factors associated with each type of recurrence (Table 2). On univariate analysis, pelvic cavity recurrence was significantly associated with cCRM (positive) and tumor histology (por/muc). In addition, there was a tendency for serum carcinoembryonic antigen (CEA) level (≥ 5.0) to increase pelvic cavity recurrence, with P value less than 0.10. Multivariate analysis indicated that only cCRM (positive) and tumor histology (por/muc) remained significantly associated with pelvic cavity recurrence (hazards ratio [HR], 4.92; 95% confidence interval [CI], 1.70-15.89; $P = 0.003$ and HR, 4.13; 95% CI, 1.12–12.56; $P = 0.035$, respectively).

Among the 35 patients treated by LPLND, nine (26%; 9/35) were pathologically diagnosed as positive for lymph node metastasis (Table 3). Postoperative LPLN recurrence was observed in three patients (8.6%; 3/35), and 5-year recurrence rate of LPLN was 9.0% (Fig. 2a). All LPLN recurrences occurred at the side in which LPLND was

Table 1 Patients' characteristics

Variables	$n = 240$
Age, median [range]	66 [21–90]
Sex	
Male	164 (68)
Female	76 (32)
Tumor location	
Ra	117 (49)
Rb–P	123 (51)
CEA[a] (ng/mL)	
≥ 5.0	103 (43)
< 5.0	137 (57)
cCRM[b]	
Positive	66 (27)
Negative	174 (73)
cT category	
cT1	2 (1)
cT2	19 (8)
cT3	171 (71)
cT4a	26 (11)
cT4b	22 (9)
cStage	
II	73 (30)
III	167 (70)
LPLN[c] swelling	
Positive	35 (15)
Negative	205 (85)
Preoperative treatment	
None	169 (70)
nCRT[d]	25 (10)
NAC[e]	46 (20)
FOLFOX6-based/FOLFIRI-based/S-1 plus CPT-11	38/1/7
Operative procedure	
LAR[f]	155 (65)
ISR[g]	35 (14)
APR[h]	39 (16)
TPE[i]	4 (2)
Hartmann	7 (3)
LPLND[j]	
Yes	35 (15)
No	205 (85)
Approach	
Lap	207 (86)
Open	10 (4)
Robot	23 (10)
Lymphatic invasion (+)	56 (23)
Venous invasion (+)	139 (58)
Histology	
Well/moderate	224 (93)
Por/muc	15 (6)
pT category	
pCR	8 (3)

Table 1 (continued)

Variables	$n=240$
pT0	2 (1)
pT1	9 (4)
pT2	55 (23)
pT3	139 (58)
pT4a	21 (9)
pT4b	6 (2)
pN category	
pN0	159 (66)
pN1	62 (26)
pN2	19 (8)
LPLN[c] metastasis	9 (4)
Adjuvant chemotherapy	107 (45)
Recurrence pattern	
Pelvic cavity	15 (6)
LPLN[c]	8 (14)
Distant	42 (18)

Data are presented as median [range], or *n* (%)

[a]*CEA* carcinoembryonic antigen

[b]*cCRM* clinical circumferential resection margin

[c]*LPLN* lateral pelvic lymph node

[d]*nCRT* neoadjuvant chemoradiotherapy

[e]*NAC* neoadjuvant chemotherapy

[f]*LAR* low anterior resection

[g]*ISR* intersphincteric resection

[h]*APR* abdominoperineal resection

[i]*TPE* total pelvic exenteration

[j]*LPLND* lateral pelvic lymph node dissection

not performed. Meanwhile, in the non-LPLND group ($n=205$), five patients (2.4%; 5/205) developed LPLN recurrence, and 5-year recurrence rate of LPLN was 2.9% (Fig. 2a). When patients treated with and without LPLND were compared, 5-year OS was 93.5% in the LPLND group and 86.5% in the non-LPLND group (Fig. 2b). A total of 14 patients were defined as "potential LPLN recurrence" [15, 25] (see method section); nine pathologically positive patients were initially treated by TME plus LPLND, and five patients experienced postoperative LPLN recurrence following TME alone. Regarding the clinicopathological features of these 14 patients with "potential LPLN recurrence", univariate analysis indicated that "potential LPLN recurrence" was significantly associated with tumor location (Rb–P), serum CEA level (≥ 5.0), cCRM (positive), LPLN swelling, and tumor histology (por/muc). In the multivariate analysis including factors with a *P* value less than 0.05, only serum CEA level (≥ 5.0) and LPLN swelling remained statistically significant (Table 2; odds ratio [OR], 4.79; 95% CI, 1.25–20.59; $P=0.018$ and OR, 8.45; 95% CI, 2.56–33.99; $P=0.002$, respectively).

On the other hand, among the same variables, only clinical N category (positive) was significantly associated with distant metastasis on multivariate analysis (HR, 2.44; 95% CI, 1.15–5.98; $P=0.018$), which indicates that the risk factors for local recurrence were completely different from those for distant metastasis.

Subgroup analyses

Based on the status of cCRM, 240 patients were stratified into two subgroups: cCRM-positive ($n=66$) and cCRM-negative ($n=174$). We investigated the influence of the NAC and nCRT on patients' prognosis in each subgroup. In the cCRM-positive subgroup, the cumulative rate of pelvic cavity recurrence was significantly lower in the nCRT group than in the NAC group ($P=0.022$), and tended to be lower than in the non-NAC/nCRT group ($P=0.089$) (Fig. 3a). The 5-year cumulative rate of pelvic cavity recurrence was 0% in the nCRT group, 32% in the NAC group, and 20% in the non-NAC/nCRT group. Meanwhile, no significant difference was observed among the three groups in LPLN recurrence (Fig. 3b) and distant metastasis (Fig. 3c). In the cCRM-negative subgroup, there was no significant difference among the three groups in the rate of pelvic cavity recurrence, LPLN recurrence, and distant metastasis (Fig. 3d–f).

Among the total of 240 patients, 152 patients (63.3%) exhibited all of the following 3 factors: cCRM-negative, differentiated type (tub1/2), and non-swollen LPLN. These patients showed significantly lower rate of local recurrence compared with the remaining 88 patients (4.7% vs. 22%, log-rank $P<0.001$), although the rate of distant metastasis was not different (21% vs. 22%, log-rank $P=0.940$). Namely, 5-year cumulative rates of pelvic cavity recurrence and LPLN recurrence were 2.7% and 2.1%, respectively. Furthermore, the majority of these patients (136/152: 89%) were treated by TME alone.

Discussion

Although TME remains the mainstay for controlling local recurrence following rectal cancer surgery, multimodality therapeutic approach is important because of the high rate of local recurrence. In Western countries, nCRT followed by TME has been widely used to reduce local recurrence [13, 14]. In a Dutch randomized controlled trial (RCT), 5-year local recurrence rate of the TME plus nCRT group was significantly lower than that of the TME alone group (5.8% vs. 12.1%) [2]. Similarly, a German RCT trial that compared preoperative and postoperative CRT showed the advantage of the preoperative CRT in preventing local recurrence [12]. However, these reports did not distinguish between pelvic cavity recurrence and LPLN recurrence. LPLN recurrence is

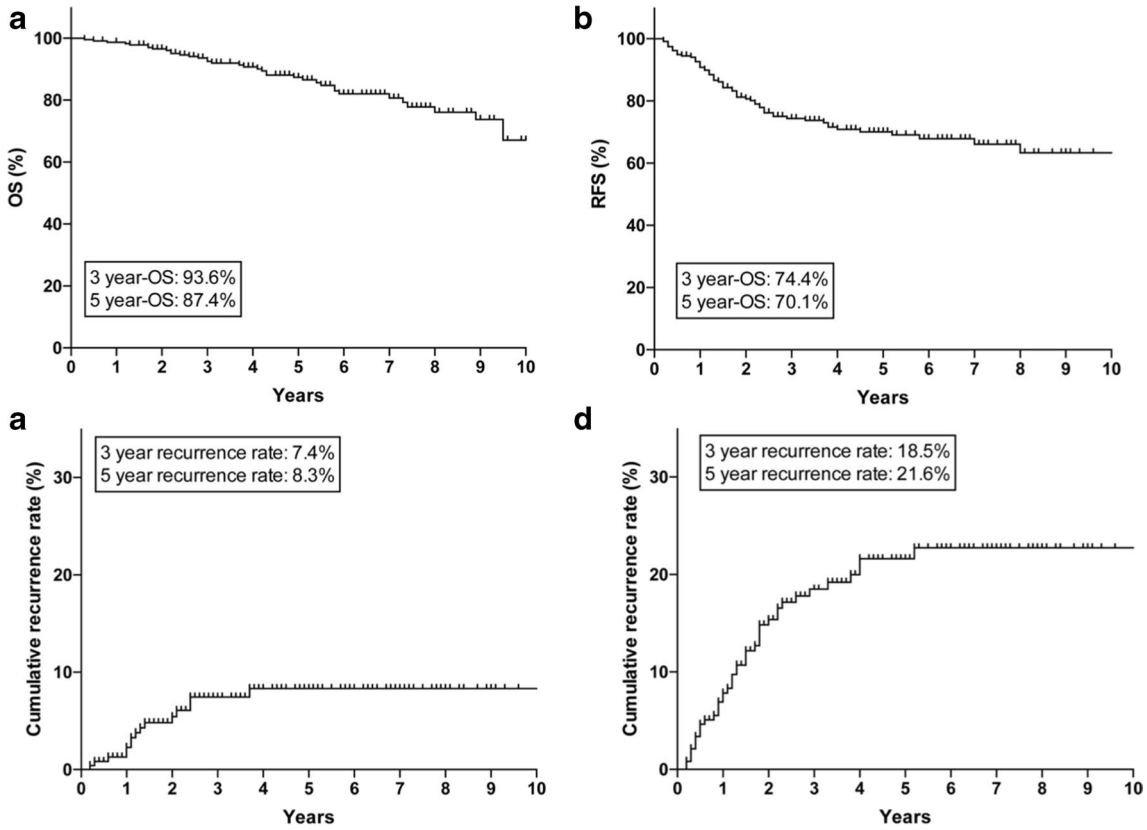

Fig. 1 Overall survival (OS), relapse-free survival (RFS), and the cumulative rate of pelvic cavity recurrence and distant metastasis among all 240 study patients. **a** OS. **b** RFS. **c** Pelvic cavity recurrence rate. **d** Distant metastasis rate

developed through lymphatic flow to the LPLN region [26], whereas pelvic cavity recurrence is considered for residual cancer cells to grow at a local pelvic site [16, 17]. In the present study, we categorized local recurrence into pelvic cavity recurrence and LPLN recurrence, and found that pelvic cavity recurrence was associated with cCRM (positive) and tumor histology (por/muc), while LPLN recurrence was associated with serum CEA level (≥5.0) and LPLN swelling (Table 2). The risk factors for these two recurrences were different, and so an optimal therapeutic strategy to prevent each type of recurrence is mandatory. In fact, we conducted subgroup analysis based on the status of cCRM, and found that nCRT was significantly effective for reducing pelvic cavity recurrence in the cCRM-positive subgroup, not the cCRM-negative subgroup (Fig. 3). This result suggests that cCRM-positive could be one of the important factors for selecting the patients who need to undergo nCRT.

Instead of nCRT, LPLND has long been adopted for cStage II–III rectal cancer in Japan [11]. LPLN metastasis has been reported to occur in 15–20% of patients with locally advanced rectal cancer [27–29]. One prospective RCT (JCOG 0212) was conducted to compare TME alone with TME plus LPLND [6, 28]. TME plus LPLND was associated with significantly longer operation time and greater blood loss compared with TME alone [6, 30]. Although 5-year RFS of the TME alone and TME plus LPLND groups were similar (73.4% vs. 73.3%), LPLND was found to be effective in preventing LPLN recurrence [30]. Several previous studies reported that approximately 30–40% of LPLN metastasis was pathologically observed after nCRT plus LPLND in patients with clinically suspected LPLN metastasis [18, 31–33], which suggests that nCRT cannot eradicate LPLN metastasis and that LPLND is needed if LPLN metastasis is suspected even after nCRT.

LPLND remains technically demanding, because the autonomic nerves need to be preserved while performing lymphadenectomy in the narrow pelvis. In the JCOG 0212 trial, the rate of ≥ grade III complications (Clavien–Dindo classification) was significantly higher in the TME plus LPLND group than in the TME alone group (22% vs. 16%) [6]. Yamaguch et al. reported that the rate of ≥ grade III complications in the laparoscopic LPLND group was almost similar to that in the open LPLND group (24% vs. 23%) [8]. On the other hand, nCRT can cause the increase in the rate of adverse events, such as anal/urogenital dysfunction, sexual dysfunction, risk of secondary cancer, bowel obstruction, and constipation [3–5]. Furthermore, nCRT can decrease the compliance to

Table 2 Factors associated with pelvic cavity recurrence, potential LPLN recurrence, and distant metastasis

Variables			Pelvic cavity recurrence				Potential LPLN recurrence				Distant metastasis			
			Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
$n=240$		n	5-year recurrence rate	P value	HR	P value	n	P value	OR	P value	5-year recurrence rate	P value	HR	P value
Age	≥ 70	83	3.5				3				26.2			
	≤ 69	157	10.3	0.154			11	0.626			19.6	0.314		
Sex	Male	164	9.8				8				19.0			
	Female	76	5.3	0.419			6	0.354			27.8	0.158		
Location	Ra	117	8.6				3				16.7			
	Rb–P	123	8.3	0.835			11	0.008*		0.066	26.8	0.164		
CEA[a]	< 5	103	6.4				4				19.9			
	≥ 5	137	11.2	0.073		0.219	10	0.006*	4.79	0.018*	24.3	0.250		
cCRM[b]	negative	174	3.9				6				20.2			
	positive	66	20.5	< 0.001*	4.92	0.003*	8	0.011*		0.346	26.8	0.527		
cT category	cT1/2	21	0.0				0				37.2			
	cT3/4a/4b	219	8.4	0.237			14	0.233			18.6	0.072		0.121
cN category	cN- (cStage II)	81	3.5				1				12.4			
	cN+ (cStage III)	159	10.7	0.112			13	0.051			25.8	0.023*	2.44	0.018*
LPLN[c] swelling	Negative	205	7.8				5				22.5			
	Positive	35	11.6	0.556			9	< 0.001*	8.45	0.002*	17.1	0.596		
Histology	well / moderate	224	6.9				11				20.9			
	por/muc	15	30.9	0.002*	4.13	0.035*	3	0.016*		0.971	38.8	0.229		

*$p < 0.05$

[a]*CEA* carcinoembryonic antigen

[b]*cCRM* clinical circumferential resection margin

[c]*LPLN* lateral pelvic lymph node

Table 3 Data on the rate of pathological LPLN metastasis, and the comparison of the rate of postoperative LPLN recurrence between the LPLND group and non-LPLND group

	LPLN ≥ 5 mm	LPLN < 5 mm
Pathological LPLN metastasis		
(+)	9	
(−)	26	
Postoperative LPLN recurrence		
(+)	3	5
(−)	32	200

adjuvant chemotherapy [34]. Therefore, optimal selection of patients who can benefit from additional treatments, such as nCRT and LPLND, and who can be cured by TME alone is essential in terms of reducing the adverse events and postoperative complications.

Although several reports on the diagnosis of LPLN metastasis have been published, the optimal cut-off value of the diameter of LPLN remains controversial [35–37]. In our institution, LPLN ≥ 5.0 mm in short-axis diameter on the pre-treatment MRI and/or CT has been adopted for LPLND. In the present study, nine (26%) of 35 patients treated by LPLND were diagnosed as pathologically positive, and the LPLN recurrence rate in the non-LPLND group was as low as 2.4% (5/205). In the JCOG 0212 trial, the inclusion criterion for LPLN size was < 10 mm in short-axis diameter, and the LPLN recurrence rate in the TME alone group was 6.6% (23/350). Although the backgrounds of the study patients were different, the results of our study might indicate that our criterion for LPLND is favorable for the optimal selection of patients who need to undergo LPLND. In contrast, the LPLN recurrence rate following LPLND was higher in the present study than that in the JCOG 0212 trial (8.6% vs. 1.1%). The comparatively higher rate of LPLN recurrence in the present

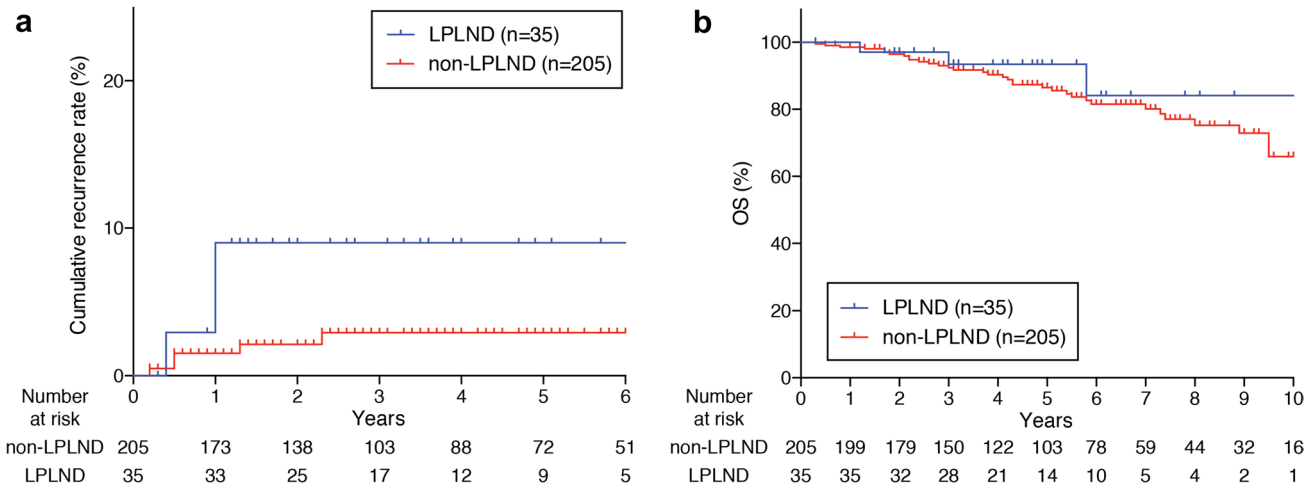

Fig. 2 Comparison of the cumulative LPLN recurrence rate and OS between the LPLND group ($n=35$) and the non-LPLND group ($n=205$). **a** LPLN recurrence rate in the LPLND group and in the non-LPLND group. **b** OS in the LPLND group and in the non-LPLND group

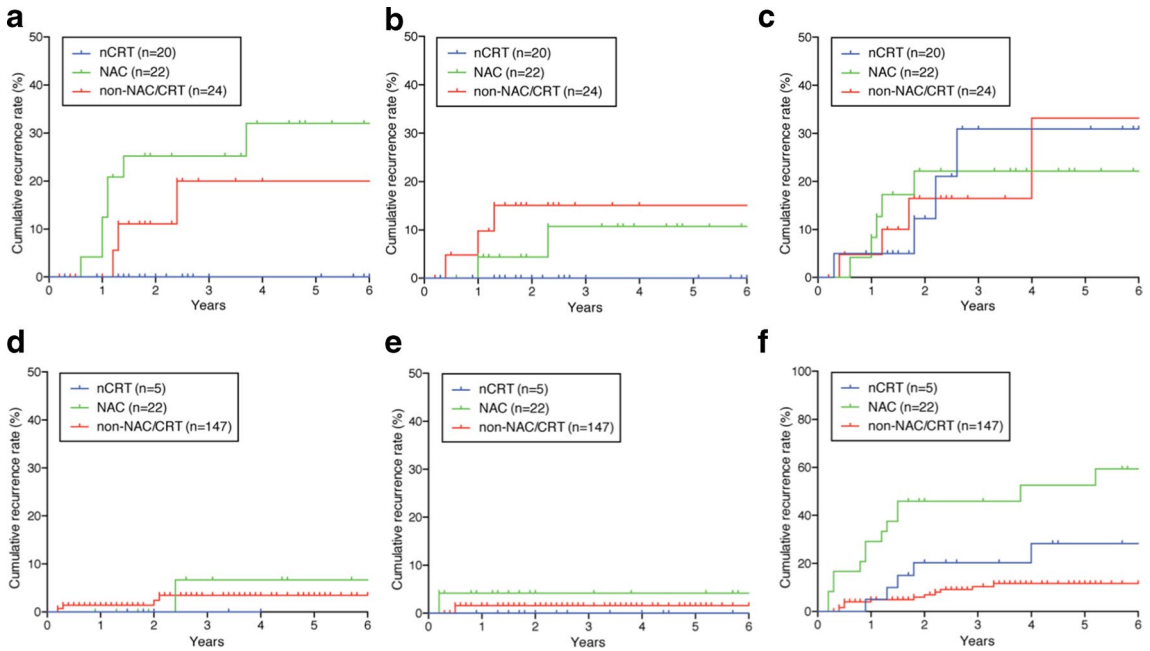

Fig. 3 Cumulative incidence of three recurrence patterns; pelvic cavity recurrence, LPLN recurrence, and distant metastasis, among the three groups (i.e., nCRT, NAC, and non-NAC/nCRT groups) in the cCRM-positive subgroup ($n=66$) (**a**–**c**) and in the cCRM-negative subgroup ($n=174$) (**d**–**f**). **a, d** Pelvic cavity recurrence rate. **b, e** LPLN recurrence rate. **c, f** Distant metastasis rate

study might be explained by the facts that the eligibility of the JCOG 0212 trial did not include the patients with swollen LPLN ≥ 10 mm in short-axis diameter, and that in our institution, LPLND was performed only for the side in which the LPLN swelling was identified. However, 5-year OS in the LPLND group was 93.5% and equivalent to the result of the JCOG 0212 trial (92.6%). All postoperative LPLN recurrences occurred at the side in which LPLND was not performed, which could enable the reoperation for recurrent cases to be safely performed. This might be attributable to the better 5-year OS, despite the higher recurrence rate.

The MERCURY study showed that high-resolution MRI increased the accuracy in precise pre-treatment staging of rectal cancer patients [38]. In the European Society for Medical Oncology guideline [13], pelvic MRI is used for decision-making, and rectal cancer patients are categorized as high-risk ("Ugly"), intermediate-risk ("Bad") and

low-risk ("Good") based on distance from mesorectal fascia, depth of mesorectal invasion, lymph node metastases, or extramural venous invasion [39, 40]. "Good" tumors are considered ideal candidates for TME alone, "Bad" tumors are for short-course RT followed by TME, and "Ugly" tumors are for long-course CRT followed by surgery (TME plus more extended surgery). Considering the results of the present study, we can recommend nCRT for cCRM-positive cases, LPLND for LPLN-positive cases, and NAC for clinical N-positive cases.

There are some limitations in the present study. First, pre- and postoperative management, including chemotherapy regimens, was inconsistent. This was the inevitable selection bias of the retrospective study. Second, our treatment strategy underwent certain chronological changes. Finally, the present study was conducted at a single center with a relatively small population. A larger multicenter study is needed to confirm our findings.

Conclusions

The therapeutic strategy for rectal cancer should be determined based on the pre-treatment MRI; nCRT is recommended for the cCRM-positive patients, while LPLND is recommended for the patients with LPLN swelling.

Conflict of interest The authors declare that they have no conflicts of interest.

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