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Possibilities for and limits of upfront surgical strategy with lateral pelvic node dissection for low rectal cancer

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Abstract

Background: Metastatic lateral pelvic nodes represent an important cause of pelvic recurrence in low rectal cancer patients even after preoperative chemoradiotherapy. This study aimed to evaluate the prognostic benefit of an upfront lateral pelvic nodes dissection strategy.

Methods: A total of 175 consecutive patients with stage II/III low rectal adenocarcinoma who underwent mesorectal excision with lateral pelvic nodes dissection between 1998 and 2013 were identified. Regional lateral pelvic nodes were categorized as LD2 nodes (internal iliac, hypogastric and obturator) and LD3 nodes (external iliac, common iliac, lateral sacral, presacral and sacral promontory) according to the current Japanese Society for Cancer of the Colon and Rectum classification.

Results: Five-year cumulative risks of local recurrence and recurrence-free survival were 4.8% and 78.1% for stage II patients, and 11.8% and 61.7% for stage III patients, respectively. Among stage III patients, no differences were observed in cumulative risks of local recurrence (5 years: 9.3% vs 14.7%, $P = 0.463$) and recurrence-free survival (5 years: 65.1 vs 61.2%, $P = 0.890$) between lateral pelvic nodes (−) and LD2 (+) patients. In multivariate analyses, metastatic lateral pelvic nodes had no impact on cumulative risks of local recurrence (hazard ratio$_{adj}$: 1.389; 95% confidence interval: 0.409–4.716) and recurrence-free survival (hazard ratio$_{adj}$: 0.884; 95% confidence interval: 0.425–1.837).

Conclusions: Metastatic lateral pelvic nodes had no impact on cumulative risks of local recurrence and recurrence-free survival based on an upfront lateral pelvic nodes strategy. Lateral pelvic nodes can improve recurrence and survival outcomes in locally advanced low rectal cancer patients with metastatic lateral pelvic nodes.

Key words: lateral pelvic node dissection, rectal cancer, metastatic lateral pelvic nodes

Introduction

Colorectal cancer is the third most common cancer worldwide, currently affecting ~1.3 million new patients each year globally (1). Although colon cancer and rectal cancer share many underlying biological features, the latter has a specific anatomical setting (i.e. narrow pelvis near other organs) and thus requires unique therapeutic approaches not necessary for the former.

The concept of total mesorectal excision (TME) to achieve complete excision of the intact mesorectum has been broadly accepted in rectal cancer surgery, resulting in the reduction of local recurrence (LR) rates from 30% to 50% to single digit percentages (2). However, TME cannot sufficiently address the issue of pelvic recurrence, which arises from tumours with circumferential resection margin (CRM) involvement or extramesorectal lymph node metastasis. Whereas Western surgeons have attempted to improve local control through multidisciplinary therapies such as preoperative radiotherapy and chemoradiotherapy ((C)RT) (3–6), Japanese surgeons have sought to overcome pelvic recurrence with extended lymphadenectomy to the pelvic wall (i.e. lateral pelvic node dissection [LPND]) without preoperative treatment (7,8).

Metastatic lateral pelvic nodes (LPN) represent an important cause of pelvic recurrence in low rectal cancer patients and are associated with increased risks of LR and shorter survival (9,10). Even among patients who underwent preoperative (C) RT followed by TME, those with enlarged LPN on pretreatment pelvic magnetic resonance imaging (MRI) had higher LR rates (11,12). Meanwhile, in the Japan Clinical Oncology Group (JCOG) 0212 trial, non-inferiority of omitting LPND was not demonstrated in terms of relapse-free survival (RFS), and LPND was found to reduce the incidence of LR in the lateral pelvis from 7.1% to 1.9% with an acceptable adverse event profile (13–17).

Despite advances in upfront surgical strategy with LPND (hereafter, the upfront LPND strategy) for rectal cancer in Japan, the extent to which advanced approaches influence contemporary factors associated with the risk of recurrence requires further evaluation. In particular, the prognostic benefit of LPND in patients with metastatic LPN remains controversial. Therefore, in the present study, we reviewed oncologic outcomes of patients with locally advanced (i.e. stage II/III) low rectal cancer who were treated with upfront LPND, with the aim of identifying risk factors for recurrence and survival associated with the current upfront LPND strategy.

Patients and methods

Standard treatment at Aichi Cancer Center Hospital

All rectal cancer patients at Aichi Cancer Center Hospital (ACCH) were recommended to undergo preoperative staging with colonoscopy, endoscopic ultrasound, barium or gastrografin enema and computed tomography (CT) scanning of the chest, abdomen and pelvis during the present study period. MRI examinations were also recommended for advanced rectal cancer patients to improve the accuracy of preoperative staging.

The standard treatment for locally advanced rectal cancer at ACCH is upfront TME or tumour-specific ME with upward lymph node dissection towards the root of the inferior mesenteric artery (IMA) without preoperative treatment (18). Additional multivisceral resection is performed for clinical T4 tumours detected on preoperative imaging, without preoperative treatment. Bilateral LPND is also routinely performed for clinical stage II or III tumours when the lower edge of the tumour is located below the peritoneal reflection. Autonomic nerves are preserved as long as a negative CRM is ensured. The current Japanese Society for Cancer of the Colon and Rectum (JSCCR) classification regards all of the internal iliac, hypogastric, obturator, external iliac, common iliac, lateral sacral, presacral and sacral promontory nodes as regional LPN in low rectal cancer (19). Thus, the extent of LPND included all of these regional LPN (Fig. 1).

For all patients, benefits of postoperative chemotherapy were discussed in a multidisciplinary team conference after surgery. The actual postoperative chemotherapy indication and regimen were finally selected by patients. Informed consent was obtained by medical oncologists.

Patient identification

Consecutive patients with JSCCR stage II/III low rectal adenocarcinoma who underwent proctectomy with curative intent between January 1998 and December 2013 at ACCH were identified from a prospectively collected database. In the present study, patients with tumours for which the lower edge was located below the peritoneal reflection were included as low rectal cancer patients. Patients who underwent total pelvic exenteration (TPE) were excluded, as accurate LPN examination is difficult to perform due to different pathological examination processes. All patients who required LPND underwent open surgery during the study period.

Collected variables of patients were reviewed and augmented by secondary chart review. Patients were excluded if they did not receive the standard treatment at ACCH for various reasons, such as conversion surgery for primarily unresectable tumours, clinical trials (including JCOG0212), or unfit performance status, such as that observed in elderly patients, those with low cardiopulmonary function, and those with severe atherosclerosis intolerable to LPND. Patients with recurrent or metastatic colorectal cancer, primary colon cancer, or synchronous multiple or double cancer, or those who had undergone urgent surgery or palliative (R2) resection, were also excluded.

Patients with metastatic disease within regional LPN defined by the current JSCCR classification were included, whereas those with distant metastatic nodes, such as the paraaortic or superficial inguinal nodes, were excluded.

Follow-up and survival

All patients were recommended to be followed up with physical examinations and laboratory data collection, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19–9), every 3 months for the first 2 years and every 6 months for the following 3 years, and radiological examinations of the chest, abdomen and pelvis every 6 months for 5 years.

All patients were followed up to 10 years after primary rectal cancer surgery, or until any event or December 2017. Survival time was defined as the time from primary rectal cancer surgery to each event. Cumulative risk of LR was calculated as the time to LR as a first relapse, RFS was calculated as the time to first recurrence or death from any cause, and overall survival (OS) was calculated as the time to death from any cause.

Patient categorization and statistical analysis

Pathological staging, which had been recorded according to the JSCCR classification 7th edition, was converted to that according to the current (9th) edition (19,20). CRM was not measured in most

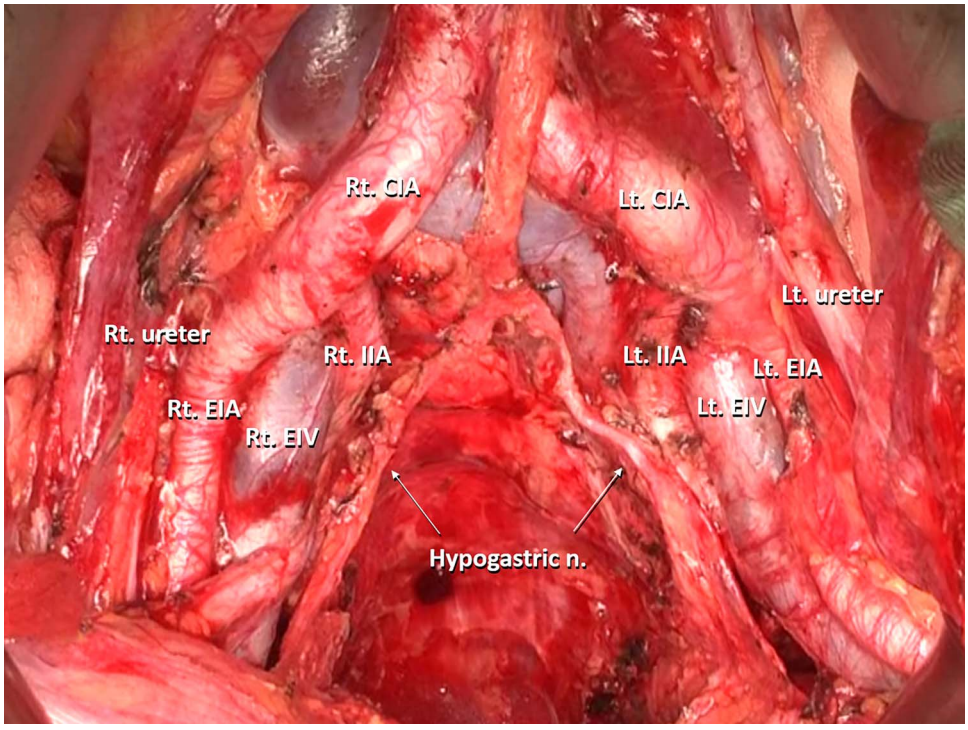


Figure 1. LD3 lateral pelvic node dissection with open total mesorectal excision at Aichi Cancer Center Hospital. CIA, common iliac artery; IIA, internal iliac artery; EIA/EIV, external iliac artery/vein; LD3, internal iliac, hypogastric, obturator, external iliac, common iliac, lateral sacral, presacral, and sacral promontory nodes.

cases, and only resected margin status (RM: positive/negative) was recorded. Recorded N categories included N1 (1–3 metastatic nodes), N2 (4 or more metastatic nodes), and N3 (metastatic IMA nodes and/or regional LPN). The current JSCCR classification categorizes regional LPN as LD2 nodes (internal iliac, hypogastric and obturator nodes) and LD3 nodes (external iliac, common iliac, lateral sacral, presacral and sacral promontory nodes). Accordingly, stage III patients were further stratified into the following three groups: no metastatic LPN [LPN (−)), metastatic LD2 nodes (LD2 (+)), and metastatic LD3 nodes (LD3 (+)].

Categorical variables were analysed using Pearson's χ^2 test. Continuous variables were analysed using Mann–Whitney's *U* test and presented as medians with interquartile ranges (IQRs). Cumulative risks of LR, RFS and OS were calculated using Kaplan–Meier survival analysis, and hazard ratios (HRs) were calculated by univariate and multivariate Cox proportional hazards regression models. Multivariate models were developed with backwards selection using covariates with *P* values <0.10 in the univariate analysis. *P* values <0.05 were considered statistically significant. SPSS 25.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses.

Ethical approval

The present experimental protocols were approved by the institutional review committee of ACCH.

Results

Patient, surgical and pathological characteristics

A total of 175 consecutive patients who met the inclusion criteria were analysed. Patient, surgical and pathological characteristics are summarized in Table 1. In total, 108 (61.7%) and 67 (38.9%) patients underwent sphincter-preserving surgery and non–sphincter-preserving surgery, respectively. Twenty-eight (16.0%) patients underwent multivisceral resection, of which the most frequent viscera resected were the seminal vesicles in 10 patients, vagina in seven patients, uterus in five patients, internal iliac artery in four patients, prostate and colon in two patients each, and ovary and bladder in one patient each.

Overall, 91 (52.0%) patients experienced more than one complication. The most frequent complication was surgical site infection (n = 32, 18.2%), followed by urinary dysfunction (n = 25, 14.3%) and ileus (n = 17, 9.7%). Seven of 108 (6.4%) patients with sphincter-preserving surgery developed anastomotic leakage. Twenty-four (13.7%) patients experienced more than one major complication of Clavien–Dindo Grade 3a or more. There was no postoperative mortality within 30 days after surgery.

T and N classifications and JSCCR stage are as shown in Table 1. With regard to LPN metastasis, 57 (32.6%) patients had metastatic disease in regional LPN, including 49 (28.0%) within LD2 nodes and eight (4.6%) spread to LD3 nodes. Seven (3.0%) patients experienced incomplete surgical resection with positive resection margins.

Overall, 87 (49.7%) patients underwent postoperative chemotherapy, including 26 (14.9%) who received oxaliplatin doublet therapy. Among patients with stage III disease, 83/127 (65.4%) underwent postoperative chemotherapy, including 26/127 (20.5%) who received oxaliplatin doublet therapy.

RFS, RFS and OS

Median follow-up durations were 60 (35–86) months for recurrence and 68 (48–90) months for survival for all patients. No postoperative mortality occurred within 30 days after surgery.

Table 1. Patient, surgical and pathological characteristics for all patients

	$n = 175$		$n = 175$
Age, years	59 (28–79)	JSCCR T classification, *n* (%)	
Gender, male (%)	115 (65.7)	T1–3	165 (94.3)
BMI, kg/m^2	22.0 (15.0–29.7)	T4a/b	10 (5.7)
Surgical procedure, *n* (%)		JSCCR N classification, *n* (%)	
Sphincter-preserving	108 (61.7)	N0	48 (27.4)
Non–sphincter-preserving	67 (38.3)	N1	48 (27.4)
Multivisceral resection, *n* (%)		N2	19 (10.9)
Present	28 (16.0)	N2	60 (34.3)
Absent	147 (84.0)	JSCCR stage, n (%)	
Operation time, min	386 (209–642)	Stage II	48 (27.4)
Blood loss, ml	630 (75–3110)	Stage IIa	47 (26.9)
Any complications, *n* (%)	91 (52.0)	Stage IIb/c	1 (0.6)
SSI	32 (18.2)	Stage III	127 (72.6)
Superficial	10 (5.7)	Stage IIIa	14 (8.0)
Deep/organ	23 (13.1)	Stage IIIb	59 (33.7)
Urinary dysfunction	25 (14.3)	Stage IIIc	54 (30.9)
Ileus	17 (9.7)	Metastatic LPN, *n* (%)	
Anastomotic leakage	7 (4.0)	Present	57 (32.6)
Others	5 (2.9)	LD2 (+)	49 (28.0)
Major complications*, *n* (%)	24 (13.7)	LD3 (+)	8 (4.6)
Hospital stay, day	25 (19–36)	Absent	118 (67.4)
Mortality, *n*	0	R status, *n* (%)	
Harvested total nodes, *n*	44 (13–115)	R0	168 (96.0)
Harvested LPN, *n*	22 (1–62)	R1	7 (4.0)
Pathological grade, *n* (%)		Postoperative chemotherapy, *n* (%)	
G1/2	156 (89.1)	Present	87 (49.7)
G3/4	19 (10.9)	5-FU alone	61 (34.9)
		Oxaliplatin doublet	26 (14.9)
		Absent	76 (43.4)
		Missing	12 (6.9)

Values are median (interquartile ranges).

*Clavien–Dindo Grade > 3a **Within 30 days after surgery.

BMI, body mass index; LPN, lateral pelvic nodes; SSI, surgical site infection; G, Grade; JSCCR, the Japanese Society for Cancer of the Colon and Rectum; T, tumour; N, lymph nodes; LD2 (+), metastatic LPN within internal iliac, hypogastric and/or obturator nodes; LD3 (+), metastatic LPN spread to external iliac, common iliac, lateral sacral, presacral and/or sacral promontory nodes; R, resection; 5-FU, 5-fluorouracil.

Overall, 54 (30.9%) patients developed recurrence during the follow-up period, including one (0.6%) with simultaneous occurrence of LR and distant metastasis. Fifteen (8.6%) patients developed LR, corresponding to a 5-year cumulative risk of 9.9%. The 5-year cumulative risk of LR was 4.8% for stage II patients and 11.8% for stage III patients. Forty (22.9%) patients developed distant metastases, and 33 (18.9%) died during the follow-up period. The 5-year RFS was 67.2% overall, 78.1% for stage II patients, and 61.7% for stage III patients. The 5-year OS was 81.0% overall, 91.3% for stage II patients, and 75.6% for stage III patients.

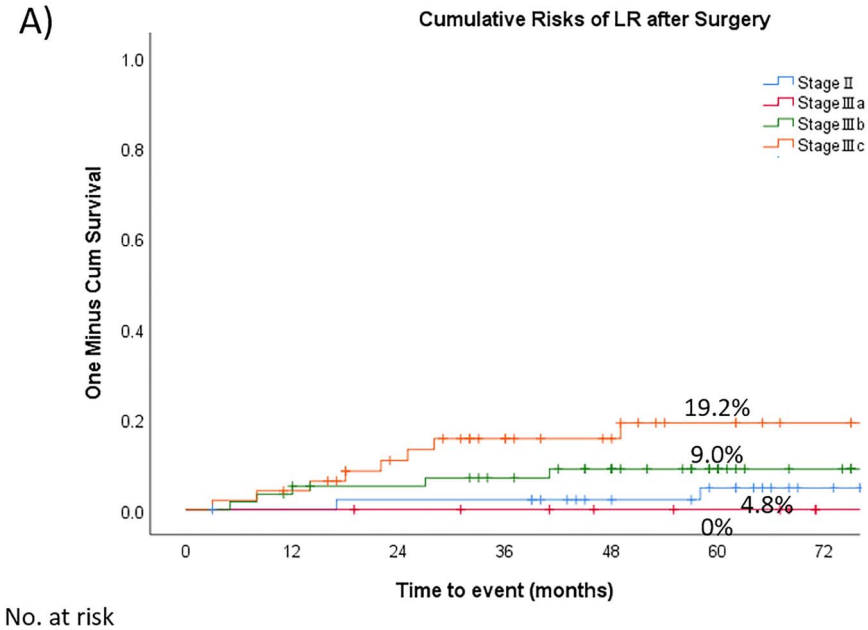
Cumulative risks of LR and RFS for stage II and III patients stratified according to substage are shown in Fig. 2. Although not significant, a higher cumulative risk of LR and lower RFS were observed in more advanced substages. Cumulative risks of LR and RFS were similar between stage II and IIIa patients.

Cumulative risks of LR and RFS for stage III patients stratified according to LPN status are shown in Fig. 3. Despite the presence of metastatic LPN, no significant differences were observed in the cumulative risk of LR between LPN (−) patients and LD2 (+) or LD3 (+) patients ($P = 0.463$ and 0.371, respectively). Although RFS was significantly worse for LD3 (+) patients compared with LPN (−) patients ($P = 0.006$), no significant difference was observed between LPN (−) and LD2 (+) patients ($P = 0.890$).

Factors associated with the risk of recurrence and survival

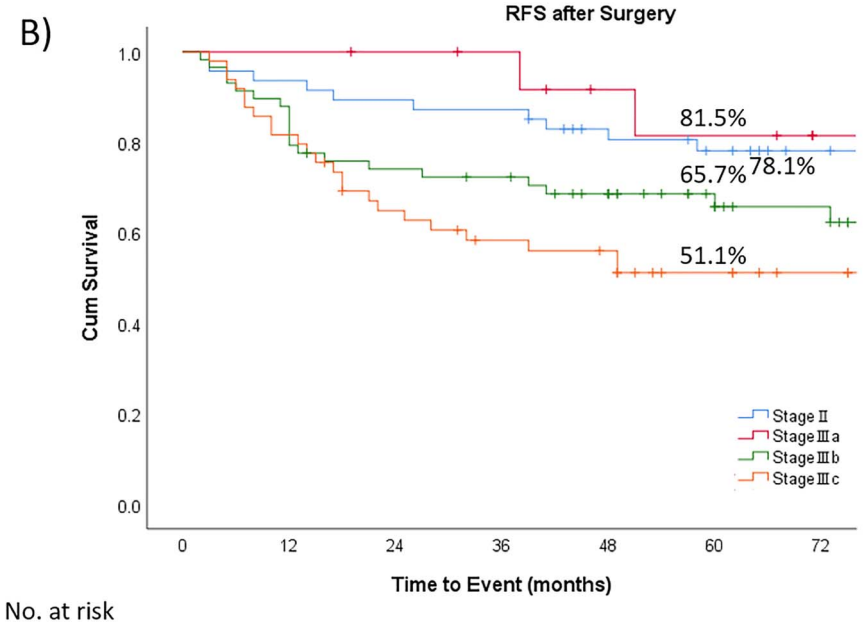
Results of multivariate analyses of cumulative risks of LR, RFS and OS for all patients are shown in Table 2. R status was significantly correlated with cumulative risks of LR [HR_{adj}: 16.18; 95% confidence interval (CI): 1.275–110.5; $P = 0.005$], RFS (HR_{adj}: 5.965; 95% CI: 1.621–22.07; $P = 0.007$), and OS (HR_{adj}: 23.15; 95% CI: 5.355–100.1; $P < 0.001$), whereas the depth of invasion was not.

The number of metastatic lymph nodes was correlated with cumulative risks of RFS (HR_{adj}: 4.773; 95% CI: 2.222–10.25; $P < 0.001$) and OS (HR_{adj}: 3.641; 95% CI: 1.501–8.829; $P = 0.004$), but not LR. The presence of metastatic SRA/IMA nodes was not correlated with recurrence or survival. In the present series, no significant correlations were observed between metastatic LPN and cumulative risks of LR (HR_{adj}: 1.389; 95% CI: 0.409–4.716), RFS (HR_{adj}: 0.884; 95% CI: 0.425–1.837), and OS (HR_{adj}: 1.753; 95% CI: 0.766–4.012).



No. at risk

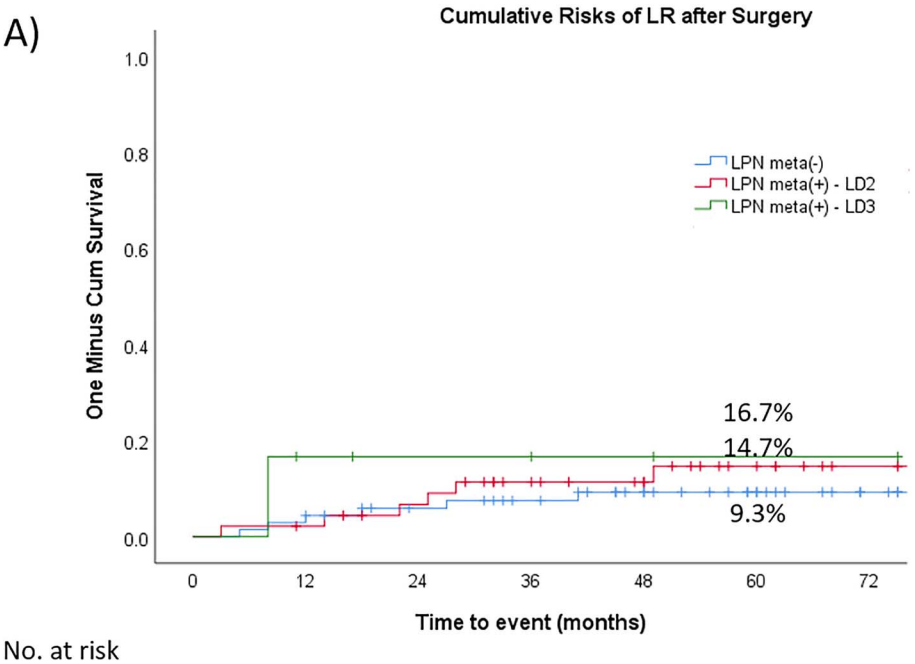
Stage Ⅱ	48	46	45	45	38	35	28
Stage Ⅲa	14	14	13	12	10	9	5
Stage Ⅲb	59	55	52	48	43	33	26
Stage Ⅲc	54	45	37	30	25	19	15



No. at risk

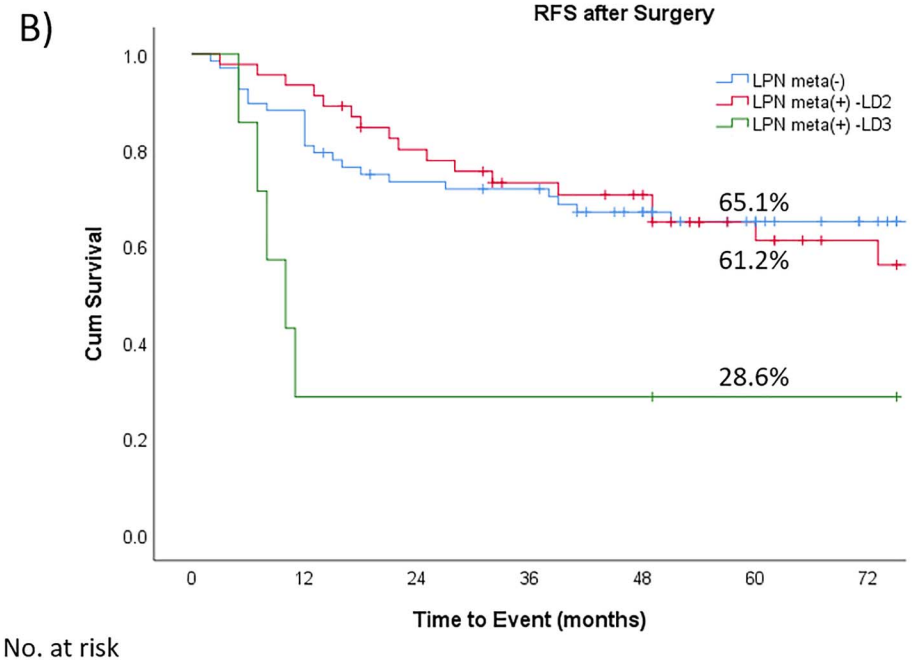
Stage Ⅱ	48	44	42	41	34	31	26
Stage Ⅲa	14	14	13	12	9	8	5
Stage Ⅲb	59	51	42	40	34	24	19
Stage Ⅲc	54	40	30	25	23	16	12

Figure 2. (A) Cumulative risks of local recurrence (LR) and (B) relapse-free survival (RFS) for stage II and III patients stratified by substage. *P* values for patients with stage II—IIIa, II—IIIb, II—IIIc, IIIa—IIIb, IIIa—IIIc, and IIIb—IIIc disease were 0.459, 0.338, 0.028, 0.264, 0.101, and 0.170, respectively (overall $P = 0.066$). *P* values for patients with stage II—IIIa, II—IIIb, II—IIIc, IIIa—IIIb, IIIa—IIIc, and IIIb—IIIc disease were 0.634, 0.093, 0.004, 0.143, 0.030, and 0.202, respectively (overall $P = 0.012$).



No. at risk

LPN (-)	70	66	59	54	47	39	30
LD2 (+)	49	44	40	33	29	21	15
LD3 (+)	8	4	3	3	2	1	1



No. at risk

LPN (-)	70	57	48	46	38	30	23
LD2 (+)	49	43	35	29	26	17	12
LD3 (+)	8	2	2	2	2	1	1

Figure 3. (A) Cumulative risks of local recurrence (LR) and (B) relapse-free survival (RFS) for stage III patients stratified according to lateral pelvic node (LPN) status. LD2 (+): metastatic disease within the internal iliac, hypogastric, and obturator nodes; LD3 (+), metastatic disease spread to the external iliac, common iliac, lateral sacral, presacral, or sacral promontory nodes. *P* values for patients with LPN (−)—LD2 (+), LPN(−)—LD3 (+), and LD2 (+)—LD3 (+) were 0.463, 0.371, and 0.582, respectively (overall $P = 0.566$). *P* values for patients with LPN (−)—LD2 (+), LPN(−)—LD3 (+), and LD2 (+)—LD3 (+) were 0.890, 0.006, and 0.006, respectively (overall $P = 0.012$).

Table 2. Multivariate analysis of cumulative risk for local recurrence (LR), relapse-free survival (RFS) and overall survival (OS) for Stage III patients

	Cumulative risk for LR			RFS			OS		
	HR	95% CI	*P* values	HR	95% CI	*P* values	HR	95% CI	*P* values
Preoperative CEA									
<5 ng/ml							1		
≥5 ng/ml							1.218	0.531–2.795	0.642
Surgical procedure									
Sphincter-preserving							1		
Non–sphincter-preserving							1.208	0.541–2.699	0.645
Multivisceral resection									
Absent				1			1		
Present				1.497	0.647–3.467	0.346	1.944	0.725–5.214	0.186
Operation time									
<7 hours	1			1			1		
≥7 hours	3.636	1.275–10.37	0.016	1.439	0.812–2.551	0.212	1.025	0.464–2.265	0.952
Pathological grade									
G1/2							1		
G3/4							1.885	0.633–5.616	0.255
Depth of invasion									
pT1–3	1			1			1		
pT4	2.073	0.431–9.966	0.363	1.617	0.577–4.531	0.360	1.872	0.551–6.356	0.315
No. of metastatic lymph nodes									
≤3	1			1			1		
≥4	1.491	0.426–5.226	0.532	4.773	2.222–10.25	<u>< 0.001</u>	3.641	1.501–8.829	<u>0.004</u>
Metastatic SRA/IMA nodes									
Absent				1					
Present				0.663	0.275–1.598	0.360			
Metastatic LPN									
Absent	1			1			1		
Present	1.389	0.409–4.716	0.599	0.884	0.425–1.837	0.740	1.753	0.766–4.012	0.184
R status									
R0	1			1			1		
R1	16.18	2.369–110.5	<u>0.005</u>	5.965	1.612–22.07	<u>0.007</u>	23.15	5.355–100.1	<u><0.001</u>
Adjuvant chemotherapy									
Present				1					
Absent				1.240	0.619–2.485	0.544			

CEA, carcinoembryonic antigen; R, resection; G, Grade; T, tumour; SRA, superior rectal artery; IMA, inferior mesenteric artery; LPN, lateral pelvic nodes Multivariate Cox regression models were developed with backwards selection using covariates with *P* values <0.10 in the univariate analysis: age, gender, obesity, preoperative CEA, surgical procedure, operation time, blood loss, multivisceral resection, R status, pathological grade, depth of invasion, no. of metastatic lymph nodes, SRA/IMA node status, LPN status, and adjuvant chemotherapy.

Discussion

The present study evaluated the risks of recurrence and survival in locally advanced low rectal cancer patients who were treated with the upfront LPND strategy at a single dedicated cancer centre in Japan. Overall, the current strategy achieved good local control and survival with acceptable complication rates, which compared favourably with results of previous clinical trials in Japan (15) and the West (3–6). Survival analysis revealed similar cumulative risks of LR and RFS between LD2 (+) patients and LPN (−) patients, and in multivariate analyses, metastatic LPN had no impact on cumulative risks of LR and RFS. These results suggest that LPND can improve recurrence and survival outcomes in low rectal cancer patients with metastatic LPN, even without preoperative treatment.

In the West, locally advanced rectal cancer with metastatic LPN is generally considered a systemic disease with poor prognosis. In fact, several studies have reported a higher incidence of LR and worse survival in patients with metastatic LPN (9,10). It is often assumed that lateral LR after TME can be prevented by preoperative CRT, although preoperative (C) RT reportedly did not reduce the incidence of LR in patients with enlarged LPN on pretreatment imaging (11,12). On the other hand, the results of the present study revealed that oncologic outcomes of patients with metastatic LD2 nodes are not inferior to those of patients without metastatic LPN in terms of LR and RFS after treatment with the upfront LPND strategy.

A nationwide multi-institutional study in Japan previously reported similar survival rates between patients with metastatic LD2 nodes and those with 4–6 metastatic mesentery nodes (21). Consistently, our previous study also revealed a favourable therapeutic value index of internal iliac, hypogastric and obturator nodes compared with that of superior hemorrhoidal (rectal) nodes (22). Thus, metastatic LPN can be considered a regional disease that can be cured by strict lymph node dissection in addition to TME. Although a concern still remains regarding patients with metastatic disease spread to LD3 nodes, the present results suggest the possibility that LPND may improve the prognosis in patients with metastatic LD2 nodes.

Although the upfront LPND strategy was associated with satisfactory outcomes in many patients, the results of the present study cast doubt on the feasibility of the current total upfront surgical strategy with routine LPND. One issue is the wide range of indications for LPND. In the present cohort, only one-third of stage II and III low rectal cancer patients had metastatic LPN. That is, two-thirds of patients could be treated without LPND. Difficulties in the preoperative diagnosis of metastatic LPN are underlying issues; even in patients with LPN $\leq$ 5 mm in the short axis on preoperative MRI, about 10% of metastatic LPN is reportedly confirmed pathologically after surgery (23). There appears to be a limitation in the prediction of metastatic LPN based only on the diameter of LPN in preoperative imaging, Unfortunately, we could not find a good predictive factor for metastatic LPN in the present study, and even now, we routinely perform LPND for all locally advanced low rectal cancer patients. We are starting to establish optimal diagnostic criteria for metastatic LPN to narrow down the range of indications for LPND, investigating many more and complex variables.

Another issue is that patients in advanced stages did not achieve satisfactory outcomes in the present study. Specifically, the cumulative risks of LR and RFS for stage IIIc patients were 19.2% and 51.1%, respectively. There are three concerns in the treatment of locally advanced rectal cancer: lateral recurrence due to metastatic LPN, central recurrence due to microscopic residual disease in CRM, and distant metastasis. In the present study, microscopic residual tumours were correlated with both LR and survival, i.e. the risk of central recurrence is a concern especially for tumours with a threatened CRM or those requiring intersphincteric resection. Widespread lymph node metastasis was also correlated with survival, suggesting that the risk of distant metastasis is another concern. Furthermore, although the depth of invasion was not correlated with either recurrence or survival in the present study, the higher rate of multivisceral resection, even after the exclusion of TPE, should be noted. Additional local and/or systemic treatment, including preoperative (C) RT or systemic chemotherapy, might decrease the rate of multivisceral resection, improve the risk of LR at the central pelvis, and the risk of distant recurrence of these patients based on the upfront LPND strategy.

Although both Japanese and Western treatment strategies, including LLND or preoperative CRT, are associated with acceptable outcomes, the outcomes have slightly distinct features. Japan and Western countries are converging in terms of additional treatment based on their respective strategies these days; however, the purpose of these treatments seems to differ somewhat. In Japan, the aim is to reduce recurrence rates and improve the survival of patients with an advanced disease that cannot be cured solely with postoperative chemotherapy after ME with LLND. In contrast, in Western countries, additional preoperative systemic chemotherapy (total neoadjuvant therapy) aims to improve the outcomes of patients to boost up the impact of preoperative CRT with pre-CRT systemic chemotherapy (24). The present study revealed favourable outcomes of the upfront LPND strategy in Japan, especially in patients with metastatic LPN, which is the absolute advantage of this strategy to improve the survival of patients with metastatic LPN. Meanwhile, our results also suggest the two limitations: the range of indications for LPND can be narrowed down for patients at low risk of metastatic LPN, and additional local treatment might lead to a decreased rate of multivisceral resection and reduced risk of LR at the central pelvis. This may render management decisions for locally advanced low rectal cancer more complex (i.e. involving preoperative chemotherapy and/or radiotherapy, LPND, both or neither); however, it will be desirable to organize not a uniform but structured treatment strategy to optimize the treatment for locally advanced low rectal cancer.

In discussing optimal surgical strategies, the concern about the quality of surgery cannot be ignored. Even in Japan, quality dispersion in LPND is a major problem, which might prevent generalization of our results to a wider population. The current JSCCR classification recommends adding LPND to ME for clinical stage II or III low rectal cancer below the peritoneal reflection; however, there is no clear recommendation regarding the extent of LPND (25). Thus, LPND to dissect within LD2 nodes and hemilateral LPND are rampant in the absence of preoperative treatment in many institutions in Japan. It should be noted, however, that the present results were obtained in patients who underwent complete removal of bilateral regional LPN without any preoperative treatment.

There are also several limitations in this study. First, the lack of original images in some patients and specific pathological examination processes unique to Japan made it difficult for us to analyse clinical and pathological CRM. Second, there were limitations inherent to the retrospective study design. However, the present study included both prospectively and retrospectively collected data from patients who underwent standardized follow-up in a dedicated cancer center. Third, despite the current use of postoperative chemotherapy worldwide, a limited number of patients received postoperative chemotherapy during the study period. However, we evaluated outcomes after adjusting for postoperative chemotherapy. Fourth, surgical skills widely varied from surgeon to surgeon, which should be taken into consideration when evaluating outcomes by surgical strategy. Nevertheless, the rate of LR was similar to those reported previously in randomized controlled trials in Japan. Finally, regarding the quality of LPND, the results of the present study, which were obtained in a highly experienced, high-volume cancer center, may not be generalizable to all practice settings.

The upfront LPND strategy achieved good local control and survival, with favourable outcomes compared with those of historically reported cases of locally advanced low rectal cancer. Metastatic LPN had no impact on cumulative risks of LR and RFS in multivariate analysis, suggesting that LPND can improve recurrence and survival outcomes in low rectal cancer patients with metastatic LPN. Meanwhile, these results also suggest that the indications for LPND can be narrowed down for patients at low risk of metastatic LPN, and that additional treatment might improve LR and survival outcomes in advanced-stage patients under the current strategy.

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Conflict of interest statement

Akira Ouchi, Koji Komori, Takashi Kinoshita, Taihei Oshiro, Aina Kunitomo, Seiji Ito, Tetsuya Abe, Yasuhiro Shimizu declare no relationships to disclose.

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