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Clinical Relevance of Lateral Pelvic Lymph Node Dissection for Enlarged Lateral Nodes in Locally Advanced Low Rectal Cancer without Preoperative Treatment

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Abstract

Objectives: The present study aimed to investigate the clinical relevance of lateral pelvic lymph node dissection (LPLND) in low rectal cancer without preoperative treatment, with a focus on the presence of LPLN enlargement in preoperative imaging.

Methods: Consecutive patients with cT3 to T4 low rectal cancer who underwent mesorectal excision and LPLND without preoperative treatment between 2007 and 2018 at a single dedicated cancer center were included. LPLN short-axis diameter (SAD) measured using preoperative multi-detector row computed tomography (MDCT) was evaluated retrospectively.

Results: A total of 195 consecutive patients were analyzed. Overall, 101 (51.8%) and 94 (48.2%) patients had visible and no visible LPLNs in preoperative imaging, including 56 (28.7%), 28 (14.4%), and 17 (8.7%) patients had SADs of <5 mm, 5-7 mm, and ≥7 mm, respectively. Incidence of pathologically confirmed LPLN metastasis were 18.1%, 21.4%, 28.6%, and 52.9%, respectively. Overall, thirteen (6.7%) patients developed local recurrence (LR), including one patient who developed lateral recurrence, yielding a 5-year cumulative risk for LR of 7.4%. Five-year RFS and OS for all patients were 69.7% and 85.7%, respectively. No differences were observed in the cumulative risk for LR and OS between any pairs of groups.

Conclusions: No significant difference was observed in the cumulative risk for LR and OS regardless of LPLN SAD, implying the good impact of LPLND on the prevention of lateral recurrence, as well as the difficulty of predicting LPLN metastasis using only LPLN SAD in preoperative imaging.

Keywords

lateral pelvic lymph node dissection, local recurrence, preoperative chemoradiation, rectal cancer, total mesenteric excision

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Introduction

Colorectal cancer is the third most common cancer in both sexes worldwide, with approximately 1.8 million new cases reported in 2018[1]. Although rectal cancer and colon cancer share many underlying biological features, the former occurs in a specific anatomical setting (i.e., in the narrow pelvis near other organs) and thus requires a unique therapeutic approach not required for treating the latter.

There are two major concerns with treating rectal cancer: local pelvic recurrence and distant organ metastasis after surgical resection. Local pelvic recurrence is further categorized into two types: lateral recurrence due to lateral pelvic lymph node (LPLN) metastasis and central recurrence due to microscopic residual disease in the circumferential resection margin (CRM). Many colorectal surgeons have empha-

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sized preoperative pelvic radiotherapy to manage extramesorectal disease in locally advanced rectal cancer since the Dutch trial[2]. Treatment outcomes for locally advanced rectal cancer have drastically improved with the combination of (chemo)radiation and perioperative systemic chemotherapy in the last two decades[3,4]. Meanwhile, an insufficient therapeutic effect was recently reported for neoadjuvant chemoradiation alone with total mesenteric excision (TME) for enlarged LPLNs[5]. Therefore, there has been an increasing interest in the surgical management of enlarged LPLNs.

In Japan, colorectal surgeons have taken on the challenge of addressing lateral recurrence with LPLN dissection (LPLND) without preoperative treatment[6]. The autonomic nerve-preserving procedure was established in the 1990s and significantly contributed to the spread of LPLND in Japan[7]. A Japanese nationwide multi-institutional study revealed a high incidence of LPLN metastasis (approximately 15-20%) for T3 to T4 rectal cancers below the peritoneal reflection[8]. The results of that study provide support for current guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR), which recommend adding LPLND to mesorectal excision (ME) for clinical stage II or III locally advanced low rectal cancer without any preoperative treatment[9]. However, the Japan Clinical Oncology Group (JCOG) 0212 trial demonstrated that prophylactic LPLND had a minor impact on survival, although the trial did not confirm noninferiority of ME alone compared to ME with LPLND[10]. Several meta-analyses have also found that adding LPLND to TME had a minimal impact when performed for all rectal cancers[11,12], implying the need to reconsider the indications for LPLND.

Although both Western and Eastern treatment strategies have provided satisfactory control for local recurrence and survival outcomes, there is still room for improvement. We have a common goal to implement tailored strategies based on risk stratification for each recurrent pattern of lateral recurrence, central recurrence, and distant organ recurrence. Hence, in the present study, we reviewed the preoperative clinical characteristics and oncologic outcomes of patients with low rectal cancer, with a focus on the presence of LPLN enlargement in preoperative imaging, in order to better understand the clinical relevance of LPLND in low rectal cancer without preoperative treatment in Eastern countries.

Patients and Methods

Patient identification

Consecutive patients with American Joint Committee on Cancer (AJCC)[13] cT3 to T4 low rectal adenocarcinoma who underwent proctectomy with curative intent between January 2007 and December 2018 were identified from a prospectively collected database of the Aichi Cancer Center Hospital (ACCH). In the present study, patients with tumors for which the lower edge was located below the peritoneal reflection were considered to have low rectal cancer according to the JSCCR guidelines[9].

Patient characteristics were reviewed and augmented by secondary chart review. Patients were excluded if they did not receive LPLND for any reason, e.g., enrolling in a clinical trial, or having unfit performance status, low cardiopulmonary function, or severe atherosclerosis intolerable to LPLND. Patients were also excluded if they received preoperative chemotherapy primarily for unresectable tumors. Patients with recurrent or metastatic colorectal cancer, primary colon cancer spreading to the rectum, or those who had undergone urgent surgery without preoperative examination were also excluded from the present analysis.

Treatment

All rectal cancer patients received a colonoscopy, barium or gastrografin enema, and computed tomography (CT) scanning of the chest, abdomen, and pelvis for preoperative staging. Multi-detector row CT (MDCT) was used for the detailed evaluation of lymph node involvement and growth into circumferent organs or structures. Endoscopic ultrasound and pelvic magnetic resonance imaging (MRI) were also recommended for preoperative staging, but was not performed for all cases during the study period.

Standard treatment for rectal cancer at ACCH during the study period included upfront TME or tumor-specific ME with upward lymph node dissection toward the root of the inferior mesenteric artery (IMA) without preoperative CRT[14]. Multivisceral resection was included when clinical T4 tumors were detected on preoperative imaging without any preoperative treatment. Bilateral LPLND was performed for all clinical stage II or III tumors for which the lower edge of the tumor was located below the peritoneal reflection. The current JSCCR classification regards all internal iliac, hypogastric, obturator, external iliac, common iliac, lateral sacral, presacral, and sacral promontory nodes as regional LPLNs for low rectal cancer[9]; thus, the extent of LPLND included all of these nodes.

After surgical treatment and pathological evaluation, the benefit of postoperative chemotherapy was discussed in a multidisciplinary team conference for each patient. Meanwhile, some people refused postoperative chemotherapy after providing informed consent from medical oncologists.

Follow-up and survival

After surgical treatment (and postoperative chemotherapy), all patients were recommended to undergo follow-up, which entailed physical examinations and collection of laboratory data including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels every three

months for the first two years and every six months for the subsequent three years, and CT scanning of the chest, abdomen, and pelvis every six months for five years. All follow-up visits, laboratory tests, and radiological examinations were performed at ACCH.

All patients were followed for ten years postoperatively, up to when any event occurred, or up to March 2021, whichever was earlier. Survival time was defined as the time from primary rectal cancer surgery to each event. The cumulative risk for local recurrence (LR) was calculated as the time to LR as a first relapse, relapse-free survival (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.

Statistical analysis

For all patients who met the inclusion criteria, LPLN short-axis diameter (SAD) was retrospectively evaluated using preoperative MDCT at slice thickness of 5 mm or less. Patients were categorized into four groups according to LPLN diameter: No visible LPLN, LPLN SAD less that 5 mm (<5 mm), LPLN SAD 5 mm or more and less than 7 mm (5-7 mm), and LPLN SAD 7 mm or more (≥7 mm). Associations between LPLN diameter and pathologic positivity were assessed. The correlation between LPLN diameter and oncologic outcomes was also evaluated by the cumulative risk for LR, RFS, and OS.

Categorical variables were analyzed using Pearson's χ^2 test. Continuous variables were presented as medians with interquartile ranges (IQRs) and analyzed using the Kruskal-Wallis *H* test. Odds ratios (ORs) for LPLN metastasis were calculated by univariate and multivariate logistic regression analyses. Cumulative risks for LR, RFS, and OS were estimated by Kaplan-Meier survival analysis and compared with the log-rank test. Multivariate models were developed with backward selection using covariates with p values < 0.10 in the univariate analysis. P values < 0.05 were considered statistically significant. SPSS 27.0 (IBM Corporation, Armonk, NY, US) was used for all statistical analyses.

Ethical approval

The present experimental protocols were approved by the institutional review committee at Aichi Cancer Center Hospital (2020-1-297).

Results

Patient, surgical, and pathological characteristics

A total of 620 consecutive patients with early-stage rectal cancer during the study period were identified from a prospectively collected database, and 206 patients met the inclusion criteria of the present study. Eleven patients lacked preoperative imaging data and thus were excluded. Accordingly, 195 patients were included and analyzed in the present study.

Patient, surgical, and pathological characteristics are shown in Table 1. Overall, 20 (10.3%) patients had cT4 tumors, and 74 (37.9%) had clinically positive nodes in the mesorectum. One hundred and twenty-four (63.6%) and 71 (36.4%) patients underwent sphincter-preserving surgery and non-sphincter-preserving surgery, respectively. Twenty-four (12.3%) patients underwent multivisceral resection, of which the most frequent organ resected was the vagina (ten patients), followed by seminal vesicles (six patients), prostate (four patients), ovary (three patients), and ureter (one patient). R0 resection was achieved in 182 (93.8%) patients. One hundred and six (54.4%) patients had pathologically confirmed lymph node metastasis in the mesorectum or lateral pelvis, and 86 (44.1%) patients underwent postoperative chemotherapy.

There were no differences according to LPLN SAD in age, sex, tumor size, histology, tumor location, AJCC cT/N classification, surgical procedures, AJCC pN classification, R status, and postoperative chemotherapy. AJCC pT classification was earlier in the no visible LPLN group compared to the SAD <5 mm and SAD 5-7 mm groups.

Associations between LPLN diameter and pathologic positivity

Overall, 101 (51.8%) and 94 (48.2%) patients had visible and no visible LPLNs in preoperative imaging. Of those with visible LPLNs, 56 (28.7%), 28 (14.4%), and 17 (8.7%) patients had SADs of <5 mm, 5-7 mm, and ≥7 mm, respectively. The median (IQR) LPLN SAD for patients with visible LPLNs was 4.7 (3.7-6.4) mm.

Of all 195 patients, 46 (23.6%) had pathologically confirmed LPLN metastasis. The incidence of LPLN metastasis according to SAD in preoperative imaging is shown in Figure 1. Seventeen of 94 (18.1%) patients with no visible LPLN and 12 of 56 (21.4%) patients with LPLNs of less than 5 mm in preoperative imaging had positive LPLNs. Meanwhile, patients who had positive LPLNs remained 8 of 20 (28.6%) in patients with LPLNs of 5-7 mm, and 9 of 17 (52.9%) in patients with LPLNs of 7 mm or more in preoperative imaging.

The results of univariate and multivariate analyses for LPLN metastasis are shown in Table 2. In univariate analysis, AJCC cT/N classification and LPLN diameter were significantly associated with the incidence of LPLN metastasis. After backward selection and development of the multivariate model, AJCC cN classification and LPLN SAD remained significant predictors of LPLN metastasis, along with sex.

Table 1. Patient, Surgical, and Pathological Characteristics.

	All n = 195	No visible LPLN n = 94	SAD <5 mm n = 56	SAD 5-7 mm n = 28	SAD ≥7 mm n = 17	*p* value
Age, years	60 (53-67)	60 (52-67)	59 (52-66)	62 (55-67)	57 (47-72)	0.915
Sex, male (%)	130 (66.7)	58 (61.7)	39 (69.6)	12 (75.0)	12 (70.6)	0.521
Tumor size, cm	5.0 (4.1-6.3)	5.0 (4.0-6.1)	5.5 (4.2-6.4)	5.5 (4.5-6.4)	6.0 (4.9-6.5)	0.423
Histology, n (%)						0.454
tub1/tub2	181 (92.8)	89 (94.7)	50 (89.3)	27 (96.4)	15 (88.2)	
por/muc/sig	14 (7.2)	5 (5.3)	6 (10.7)	1 (3.6)	2 (11.8)	
Distance from AV, n (%)						0.187
<5 cm	124 (63.6)	62 (66.0)	28 (50.0)	21 (75.0)	13 (76.5)	
≥5 cm	70 (35.9)	31 (33.0)	28 (50.0)	7 (25.0)	4 (23.5)	
Missing	1 (0.5)	1 (1.1)	0	0	0	
AJCC cT classification, n (%)						0.648
T3	175 (89.7)	87 (92.6)	49 (87.5)	24 (85.7)	15 (88.2)	
T4	20 (10.3)	7 (7.4)	7 (12.5)	4 (14.3)	2 (11.8)	
AJCC cN classification, n (%) *						0.900
N0	121 (62.1)	61 (64.9)	32 (57.1)	19 (67.9)	9 (52.9)	
N1	51 (26.2)	22 (23.4)	17 (30.4)	6 (21.4)	6 (35.3)	
N2	23 (11.8)	11 (11.7)	7 (12.5)	3 (10.7)	2 (11.8)	
Surgical procedure, n (%)						0.811
Sphincter preserving	124 (63.6)	61 (64.9)	33 (58.9)	18 (64.3)	12 (70.6)	
Non-sphincter preserving	71 (36.4)	33 (35.1)	23 (41.1)	10 (35.7)	5 (29.4)	
Multivisceral resection, n (%)						0.216
Present	24 (12.3)	7 (7.4)	10 (17.9)	5 (17.9)	2 (11.8)	
Absent	171 (87.7)	87 (92.6)	46 (82.1)	23 (82.1)	15 (88.2)	
AJCC pT classification, n (%)						0.047
T1	2 (1.0)	2 (2.1)	0	0	0	
T2	52 (26.7)	30 (31.9)	10 (17.9)	6 (21.4)	6 (35.3)	
T3	129 (66.2)	61 (64.9)	41 (73.2)	17 (60.7)	10 (58.8)	
T4	12 (6.2)	1 (1.1)	5 (8.9)	5 (17.9)	1 (5.9)	
AJCC pN classification, n (%)						0.457
N0	89 (45.6)	49 (52.1)	22 (39.3)	13 (46.4)	5 (29.4)	
N1	60 (30.8)	28 (29.8)	19 (33.9)	7 (25.0)	6 (35.3)	
N2	46 (23.6)	17 (18.1)	15 (26.8)	8 (28.6)	6 (35.3)	
R status, n (%)						0.160
R0	182 (93.8)	90 (95.7)	51 (91.1)	24 (85.7)	17 (100.0)	
R1	13 (6.2)	4 (4.3)	5 (8.9)	4 (14.3)	0	
Postoperative chemotherapy, n (%)						0.119
Present	86 (44.1)	38 (40.4)	28 (50.0)	9 (32.1)	11 (64.7)	
Absent	109 (55.9)	56 (59.6)	28 (50.0)	19 (67.9)	6 (35.3)	

Values are presented as median (IQR).

*Regional (mesorectal, intermediate, and IMA) N status

SAD: short-axis diameter, LPLN: lateral pelvic lymph node, AV: anal verge, AJCC: the American Joint Committee on Cancer, R: resection, IMA: inferior mesenteric artery

Correlations between short-axis diameter and oncologic outcomes

Median (IQR) follow-up durations for all patients were 44.0 (20.0 - 75.0) months for recurrence and 59.0 (35.0 - 87.0) months for survival. No perioperative mortality occurred within 30 days after surgery.

Overall, 55 (28.2%) patients developed recurrence during the follow-up period. Thirteen (6.7%) patients developed LR, yielding a five-year cumulative risk for LR of 7.4%. The most frequent pattern of LR was recurrence in the central pelvis (11 patients), followed by anastomosis (one patient) and lateral pelvis (one patient). Five-year RFS and five-year OS rates for all patients were 69.7% and 85.7%, respectively.

Stratified oncologic outcomes of cumulative risk for LR,

RFS, and OS according to LPLN SAD in preoperative imaging are shown in Figure 2. Five-year cumulative risk for LR for no visible LPLN, SAD <5 mm, SAD 5-7 mm, and SAD ≥7 mm groups were 5.6%, 8.8%, 11.7%, and 6.2%, respectively. No differences were observed in the cumulative risk for LR between any pairs of groups. Five-year RFS rates for the no visible LPLN, SAD <5 mm, SAD 5-7 mm, and SAD ≥7 mm groups were 77.9%, 62.9%, 60.1%, and 60.1%, respectively. RFS for the no visible LPLN group was significantly better than those of the SAD <5 mm and SAD 5-7 mm groups (p = 0.043 and 0.048, respectively). No significant differences were observed in RFS between any other pairs of groups. Five-year OS rates for the no visible LPLN, SAD <5 mm, SAD 5-7 mm, and SAD ≥7 mm groups were 88.1%, 88.3%, 71.1%, and 84.6%, respectively. No differences were observed in OS between any pairs of groups.

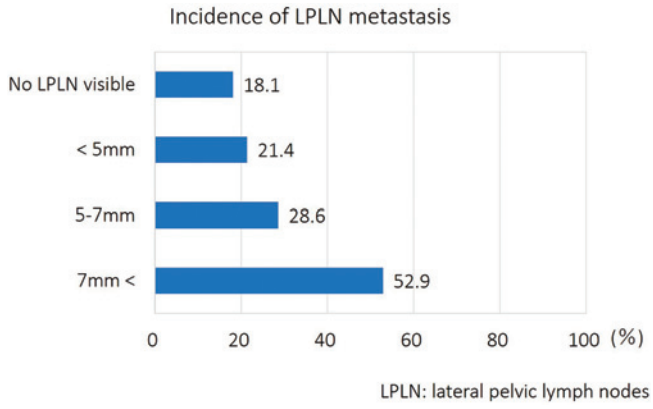

Figure 1. Lateral pelvic lymph node metastasis according to short-axis diameter in preoperative imaging.

Discussion

The present study investigated the clinical relevance of LPLND for patients with low rectal cancer without preoperative treatment. Approximately 20% of patients with LPLN SAD <5 mm in preoperative imaging had pathologically confirmed LPLN metastasis. Conversely, nearly 50% of patients with LPLN SAD ≥7 mm had no LPLN metasta-

Table 2. Univariate and Multivariate Analyses for Lateral Pelvic Node Metastasis.

	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age						
<70 years	1.000			1.000		
≥70 years	2.118	0.948-4.732	0.067	2.050	0.861-4.882	0.105
Sex						
Male	1.000			1.000		
Female	1.966	0.997-3.878	0.051	2.331	1.094-4.965	0.028
Tumor size						
<5 cm	1.000					
≥5 cm	1.272	0.631-2.563	0.501			
Distance from AV						
<5 cm	1.000					
≥5 cm	1.845	0.884-3.861	0.103			
Histology						
pap/tub	1.000			1.000		
por/muc/sig	2.606	0.854-7.951	0.092	2.565	0.759-5.851	0.130
AJCC cT classification						
cT1-3	1.000			1.000		
cT4	3.007	1.160-7.799	0.024	2.107	0.759-5.851	0.153
AJCC cN classification*						
cN0	1.000			1.000		
cN1-2	2.116	1.081-4.143	0.029	2.613	1.252-5.453	0.011
LPLN short-axis diameter						
<5 mm	1.000			1.000		
≥5 mm	2.491	1.205-5.152	0.014	2.990	1.360-6.576	0.006

Values are presented as median (IQR).

*Regional (mesorectal, intermediate, and IMA) N status

AV: anal verge, AJCC: the American Joint Committee on Cancer, IMA: inferior mesenteric artery, LPLN: lateral pelvic lymph node

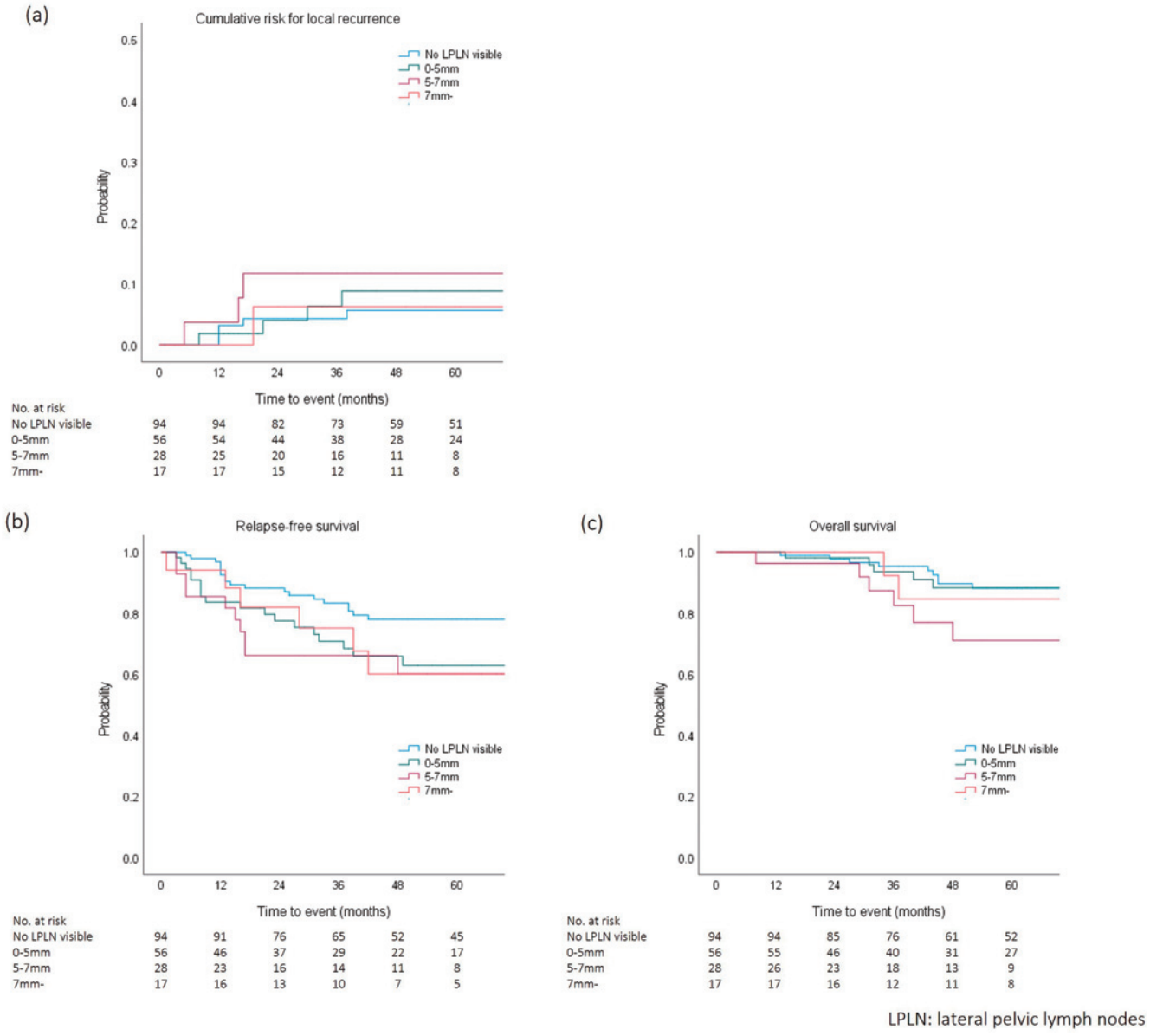

Figure 2. Cumulative risk for (a) local recurrence, (b) relapse-free survival, and (c) overall survival according to lateral pelvic lymph node diameter in preoperative imaging.

sis. It is also noteworthy that, as opposed to a previous study reporting the limited impact of neoadjuvant chemoradiation for enlarged LPLNs[5], no significant difference was observed in the cumulative risk for LR regardless of LPLN SAD. Although the present study design had some limitations, the results highlight the good impact of LPLND on the prevention of lateral recurrence, as well as the difficulty of optimizing LPLND using only LPLN SAD in preoperative imaging.

An international multicenter pooled analysis from Western countries demonstrated an increased cumulative incidence of all and lateral LR with enlarged LPLNs in pretreatment imaging after preoperative chemoradiation followed by TME[5]. Meanwhile, the present results revealed an equivalent cumulative risk for LR in patients with LPLN SAD ≥7 mm and <7 mm after mesorectal excision and LPLND without preoperative chemoradiation. The former Western analysis also revealed a regrettable radiologic complete response rate of enlarged LPNs after chemoradiation of only about 5%[15]. These results suggest that LPLND can be an option for patients with apparently enlarged LPLNs in locally advanced rectal cancer.

Malakorn et al. reported that no patient with LPLN SAD ≤5 mm in post-neoadjuvant chemoradiation imaging had LPLN metastasis after TME and selective LPLND[16], and other studies from China also revealed only 3.8% of patients with LPLN SAD ≤7 mm in post-neoadjuvant chemoradiation imaging had LPLN metastasis[17]. Meanwhile, the pre-

Table 3. Previous and Present Studies on Associations between LPLN Short-Axis Diameter and Pathologic Positivity.

Author	Year	N	Prevalence	Modality	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
Arii [18]	2006	53	28%	MRI	LA 7 mm	56%	97%	91%	81%	83%
Matsuoka [19]	2007	51	29%	MRI	SAD 5 mm	67%	83%	N/A	N/A	78%
Akasu [20]	2009	104	14%	MRI	SAD 4 mm	87%	87%	52%	97%	87%
Fujita [21]	2009	210	22%	CT	LA 5 mm	62%	90%	64%	89%	84%
Ogawa [22]	2014	77	14.9%	MRI	LA 5 mm	80.0%	56.7%	21.6%	95.0%	59.7%
Ishibe [23]	2015	84	19.9%	MRI	SAD 10 mm	75.0%	69.1%	36.4%	92.2%	70.2%
Komori [24]	2019	351	7.3%	CT	SAD 5 mm	37.5%	89.1%	21.4%	94.8%	85.3%
Hiyoshi [25]	2020	78	11.5%	CT	SAD 5 mm	66.7%	79.7%	30.0%	94.8%	78.2%
Present study	2021	195	23.6%	CT	SAD 5 mm	37.0%	81.2%	37.8%	80.7%	70.8%
					SAD 7 mm	19.6%	94.6%	52.9%	79.2%	76.9%

LA: long-axis, SAD: short-axis diameter, PPV: positive predictive value, NPV: negative predictive value

sent study found that about 20% of patients with LPLN SAD ≤5 mm in preoperative imaging had LPLN metastasis after ME and routine LPLND. These results suggest the treatment effect of preoperative chemoradiation for LPLN micrometastasis. A relatively high rate of LPLN micrometastasis and low rate after preoperative chemoradiation implies that preoperative chemoradiation might have a therapeutic effect toward micrometastases in LPLNs and, in other words, 20% of patients without enlarged LPLNs require LPLND in the absence of preoperative chemoradiation.

When preoperative chemoradiation is not performed, selecting 20% of patients who do not have enlarged LPLNs but have LPLN metastasis is not straightforward. Previous studies on the association between LPLN diameter and pathologic positivity without preoperative treatment are summarized in Table 3[18-25]. Most of these studies were retrospective studies that enrolled <100 patients, with accuracy in predicting LPLN metastasis of 59-87%. Some of them tried to define the optimal size criteria in their study for predicting LPLN metastasis; however, none of them could establish the practical cutoff values. In the present study setting, routine LPLND is performed for all patients with clinical stage II or III low rectal cancer instead of preoperative chemoradiation, given the difficulty of predicting LPLN metastasis. However, the fact remains that the other 80% of patients who have neither enlarged LPLNs nor LPLN metastasis were overtreated by invasive surgical procedures.

In the present study, RFS for patients with no visible LPLNs was significantly better than those for patients with LPLN SAD <5 mm and SAD 5-7 mm. These results may be ascribed to the earlier AJCC pT classification in no visible LPLN group than SAD < 5 mm and SAD 5-7 mm groups. Schaap et al. reported the different impact that obturator node diameter has on survival based on whether LPLND is performed[26]. However, it remains unclear whether LPLND contributes to distant metastasis control and survival. Multidisciplinary treatment, including chemotherapy or total neoadjuvant therapy (TNT) in addition to local treatment, is desirable for patients with a high risk for distant metastasis[3,4].

The main limitation in the present study relates to the imaging modalities used for preoperative diagnosis. Although recommended for preoperative staging, pelvic MRI was not performed for all patients. However, Amano et al. reported in a retrospective study, albeit with a small number of patients, that MDCT and MRI had similar detection power for LPLN metastasis[27]. Only a few studies have compared the abilities of MDCT and MRI to detect LPLN metastasis, and the superior modality of the two remains controversial. Besides, MDCT is used more often than MRI for preoperative staging of locally advanced rectal cancer. Therefore, the present study design, which used MDCT, may be desirable from the perspective of generalizability of the results.

This study has additional limitations. This study was retrospective in nature and had a small sample size. However, the present study included patients who underwent standardized follow-up in a single dedicated cancer center, enabling a detailed analysis of patient background and oncologic outcomes. Our data did not include CRM but pathological margin status due to the unique pathological diagnosis method for mesenteric lymph nodes in Japan. However, in the present study, there were no differences according to LPLN SAD in AJCC cT/N classification. Fewer patients received chemotherapy after surgery than indicated during the study period. However, the data used were real-world data, as the data were directly obtained from our clinical practice. Third, there were no uniform imaging protocols and slice thickness for preoperative CT imaging during the study period, resulting in the possible understaging of clinical LPLN status and a relatively high rate of LPLN metastasis compared to the previous studies (Table 3). However, enlarged LPLN of 5 mm or more seemed to be able to be detected by general imaging protocol with 5 mm slice thickness or less. Finally, the present results were obtained from a highly experienced, high-volume cancer center which routinely performs LPLND, and thus might not be generalizable to all practice

settings.

In conclusion, the present study revealed no significant difference in the cumulative risk for LR and OS regardless of LPLN SAD, implying the good impact of LPLND on the prevention of lateral recurrence. Meanwhile, approximately 20% of patients with LPLN SAD <5 mm in preoperative imaging had pathologically confirmed LPLN metastasis, suggesting the difficulty of predicting LPLN metastasis using only LPLN SAD in preoperative imaging and further study requirement.

Acknowledgements

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Conflicts of Interest

There are no conflicts of interest.

Author Contributions

AO and KK were responsible for the study concept. However, all authors contributed to the study design. AO, KK, TK, and YuS created the prospectively collected database, and AO collected, assembled, and analyzed the data. AO wrote the initial draft, and all authors approved the final draft of the manuscript.

Approval by Institutional Review Board (IRB)

The present experimental protocols were approved by the institutional review committee at Aichi Cancer Center Hospital (2020-1-297).

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