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Significance of Lateral Pelvic Lymph Node Size in Predicting Metastasis and Prognosis in Rectal Cancer

DONGHA LEE[1], TAKERU MATSUDA[2,3], KIMIHIRO YAMASHITA[3], HIROSHI HASEGAWA[3], MASASHI YAMAMOTO[3], SHINGO KANAJI[3], TARO OSHIKIRI[3], TETSU NAKAMURA[3], SATOSHI SUZUKI[3], TAKUMI FUKUMOTO[1] and YOSHIHIRO KAKEJI[3]

[1]*Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan;*
[2]*Division of Minimally Invasive Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan;*
[3]*Division of Gastrointestinal Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan*

Abstract. *Aim: To evaluate the clinical significance of lateral pelvic lymph node (LLN) size in predicting pathological metastasis and prognosis in rectal cancer treated with preoperative chemoradiotherapy (CRT) followed by surgery. Patients and Methods: Fifty-two patients with rectal cancer who underwent curative surgery after preoperative CRT were included. Fifteen patients underwent total mesorectal excision (TME) alone, while 37 patients underwent TME with LLN dissection for clinical LLN metastasis. Results: Pathological metastasis was identified in seven (2.6%) out of 270 resected LLNs in six (16.2%) out of 37 patients. The cut-off value of the short-axis diameter was 7.0 mm before and 6.0 mm after CRT. The 5-year recurrence-free survival rate was significantly higher in patients with LLNs <7.0 mm than in those with LLNs ≥7.0 mm (85.7% versus 56.8%, p=0.038). Conclusion: Short-axis diameter of LLNs of 7.0 mm seems to be an optimal cut-off value before CRT for predicting pathological metastasis and prognosis.*

Total mesorectal excision (TME) following preoperative chemoradiotherapy (CRT) is the standard treatment for patients with locally advanced low rectal cancer in western countries because it achieves a local recurrence rate of less than 10% (1-3). However, the effect of this multimodal therapy on patients with rectal cancer with pathological lateral pelvic lymph node (LLN) metastasis is unknown because such data are unavailable. In Japan, TME with LLN dissection (LLND) is generally performed in these patients to improve local control and overall survival (OS). In fact, the Japanese Society for Cancer of the Colon and Rectum Guidelines recommend bilateral LLND for patients with locally advanced low rectal cancer that extends below the peritoneal reflection (4). In previous studies in Japan, pathologically positive LLN metastasis was found in approximately 15% of patients with rectal cancer who underwent LLND (5-8). The oncological outcomes after TME with bilateral LLND are unfortunately poor in patients with rectal cancer with LLN metastasis (9-11).

Considering these outcomes, TME combined with LLND following preoperative CRT seems to be a valid and effective approach, at least for those patients with rectal cancer with clinically positive LLNs. We performed selective LLND after preoperative CRT for such patients and reported on good oncological outcomes of this treatment strategy (12). In our treatment strategy, LLND was performed only in patients with clinically positive LLNs on the basis of pretreatment images. Patients with clinically negative LLNs underwent only TME after preoperative CRT. Our criteria for performing LLND include the presence of LLNs with a short-axis diameter of ≥8 mm on computed tomography (CT) or magnetic resonance imaging (MRI) or LLNs showing a high-intensity spot on pretreatment positron-emission tomography (PET) images. However, various size criteria to predict LLN metastasis on preoperative CT or MRI have been previously reported, and whether our criteria are valid remains to be proven.

In the present study, we therefore, intended to investigate the relationship between the size of resected LLN specimens and their pathologically confirmed metastatic status. The

Correspondence to: Takeru Matsuda, MD, Ph.D., Division of Gastrointestinal Surgery, Department of Surgery, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-chou, Chuo-ku, Kobe 650-0017, Japan. Tel: +81 783825925, Fax: +81 783825939, e-mail: takerumatsuda@nifty.com

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purpose of this study was to evaluate the validity and clinical significance of our size criteria and determine the optimal cut-off value of LLN size by receiver operating characteristic (ROC) curve analysis.

Patients and Methods

Study population. A total of 52 patients with locally advanced rectal cancer who underwent curative surgery after preoperative CRT between November 2005 and September 2017 were included in this study. Of the 52 patients included in the study, 15 underwent TME alone (TME group) because of clinically negative LLNs, while the remaining 37 underwent TME with LLND (TME with LLND group) due to clinically positive LLN metastasis. Their data were retrospectively analyzed. The median follow-up duration was 45.0 (range=6.0-151.0) months. Tumors were classified according to the seventh edition of the American Joint Committee on Cancer classification guidelines (13). Postoperative complications were assessed according to the Extended Clavien–Dindo classification of surgical complications (14).

This retrospective study was conducted with approval of the Institutional Review Board and Ethics Committee of the Graduate School of Medicine, Kobe University School of Medicine (approval number: 180267).

Treatment strategy. Our treatment strategy for locally advanced low rectal cancer was described previously (12). Briefly, preoperative CRT consisted of a total radiation dose of 45 Gy and oral 5-fluorouracil-based chemotherapy. Radiotherapy was delivered in 25 fractions over 5 weeks, and the lateral pelvic area was included in the radiation target volume. Chemotherapy was started on the first day of radiotherapy. Tegafur–uracil (200 mg/m^2/day) and leucovorin (75 mg/day) were orally administered for 28 days. The imaging studies were repeated 4-6 weeks after the completion of CRT. Patients in whom metastasis of the para-aortic lymph nodes or distant organs was suspected after CRT were excluded from the indications for curative surgery. Surgery was performed 6-8 weeks after the completion of CRT. TME was performed through an open or laparoscopic approach. LLND was performed only in patients with clinically positive LLNs on the basis of pretreatment images. LLNs with a short-axis diameter of ≥8 mm on CT or MRI or showing a high-intensity spot on PET images, regardless of any shrinkage of the lymph nodes after CRT, and LLNs that had increased in size on CT or MRI images after CRT were considered as clinically positive for metastasis. LLND was performed only on the side of clinically positive LLNs, with the internal iliac and obturator regions dissected as the standard LLND procedure. When LLN metastasis was suspected on both sides, bilateral LLND was performed. Inguinal lymph node dissection was performed following the same principle.

Determination of the cut-off value of LLN size. The short-axis diameter of each LLN was measured *via* CT or MRI images before and after CRT. All resected LLN specimens were histologically examined for their pathological status. The cut-off value of LLN size to predict pathological metastasis before and after CRT was determined by the ROC curve analysis.

Follow-up. Tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 were examined every 3 months in the first 3 years and every 6 months thereafter. CT and abdominal ultrasonography were performed every 6 months. Total colonoscopy was conducted every 12 months. Local recurrence was defined as recurrence within the pelvic cavity, and distant recurrence was defined as any recurrence outside the pelvic cavity.

Statistical analysis. Statistical analyses were performed using JMP® software 11 (SAS Institute Inc., Cary, NC, USA). Continuous variables were expressed as the median (range). Analysis of survival time from surgery was performed using the Kaplan–Meier method, and univariate survival comparison was performed using the log-rank test. Variables with a *p*-value of less than 0.15 in univariate analysis were further evaluated in multivariate analysis using the Cox proportional hazards model. A *p*-value of less than 0.05 was considered statistically significant.

Results

The patient and tumor characteristics in this study are shown in Table I. There were no significant differences in the age, sex, clinical stage, postneoadjuvant pathological (yp) TNM stage, pretreatment CEA level, histological type, and the rate of adjuvant chemotherapy between the groups. Pathologically positive LLNs were identified in six (16.2%) out of the 37 patients who underwent LLND in the TME with LLND group.

The surgical and oncological outcomes are shown in Table II. The operative time was significantly longer and the estimated blood loss tended to be larger when LLND was performed (p=0.015 and p=0.053, respectively). There was no significant difference in the rate of postoperative complications between the two groups (p=0.743). Local recurrence developed in nine patients in the TME with LLND group, but in none in the TME group (17.3% *versus* 0%; p=0.066). Distant metastasis developed in 10 patients (27.0%) in the TME with LLND group and two (13.3%) in the TME group (p=0.479).

Of the 270 LLNs resected in 37 patients, only seven (2.6%) showed pathological metastasis. The median short-axis diameter before CRT was 4.7 mm (range=2.0-15.6 mm) for LLNs without pathological metastasis and 11.5 mm (range=5.2-30.1 mm) for LLNs with pathological metastasis (p<0.001) (Figure 1). After CRT, it was 4.0 mm (range=1.7-9.8) for LLNs without pathological metastasis and 11.5 mm (range=5.8-20.7 mm) for LLNs with pathological metastasis (p<0.001). The short-axis diameter of LLNs with pathological metastasis was significantly larger than that of LLNs without pathological metastasis, both before and after CRT.

The ROC curves for the per-patient prediction of nodal status before and after CRT are shown in Figure 2. The area under the curve (AUC) before and after CRT was 0.92 and 0.97, respectively. Based on the ROC curve analysis, the cut-off value of the short-axis diameter of LLNs before and after CRT was 7.0 mm and 6.0 mm, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value were 85.7%, 84.0%, 12.5%, and 99.5% before CRT and 100%, 87.8%, 17.9%, and 100% after CRT, respectively.

Table I. *Patient and tumor characteristics*.

	TME (n=15)	TME+LLND (n=37)	*p*-Value
Age, years			
Median (range)	66 (56-77)	65 (39-79)	0.424
Gender, n (%)			
Male	10 (66.7)	25 (67.6)	0.950
Female	5 (33.3)	12 (32.4)	
cStage*, n (%)			
II	5 (33.3)	4 (10.8)	0.052
III	10 (66.7)	33 (89.2)	
ypT*, n (%)			
pT0	1 (6.7)	6(16.2)	0.134
pTis/T1	0	0	
pT2	2 (13.3)	9 (24.3)	
pT3	12 (80.0)	17 (46.0)	
pT4	0	5 (13.5)	
ypN*, n (%)			
pN0	7 (46.6)	24 (64.9)	0.307
pN1	4 (26.7)	9 (24.3)	
pN2	4 (26.7)	4 (10.8)	
ypStage*, n (%)			
0	0 (0)	6 (16.2)	0.283
I	1 (6.7)	5 (13.5)	
II	6 (40.0)	13 (35.1)	
III	8 (53.3)	13 (35.1)	
Pretreatment CEA, ng/ml			
Median (range)	4.2 (1-136)	5.5 (1-110)	0.413
Histological type			
Well/moderately	12 (80.0)	32 (86.5)	0.557
Poorly/other	3 (20.0)	5 (13.5)	
Pathological LLN metastasis, n (%)			
Present	NA	6 (16.2)	
Absent	15 (100)	31 (83.8)	
Adjuvant chemotherapy, n (%)			
Yes	9 (60.0)	22 (59.5)	0.971
No	6 (40.0)	15 (40.5)	

TME: Total mesorectal excision, LLND: lateral pelvic lymph node dissection, yp: postneoadjuvant pathological, CEA: carcinoembryonic antigen, LLN: lateral pelvic lymph node, NA: not applicable. *Tumors were classified according to the American Joint Committee on Cancer TNM system (13).

Table II. *Operative and oncological outcomes*.

	TME (n=15)	TME+LLND (n=37)	*p*-Value
Operative procedure, n (%)			
Low anterior resection	6 (40.0)	6 (16.2)	0.065
Miles/Hartmann	9 (60.0)	31 (83.8)	
Surgical approach, n (%)			
Laparoscopy	9 (60.0)	19 (51.4)	0.571
Open	6 (40.0)	18 (48.6)	
Operative time, min			
Median (range)	436 (256-583)	562 (300-1135)	0.015
Estimated blood loss, g			
Median (range)	135 (0-5345)	560 (0-4200)	0.053
Blood transfusion, n (%)			
Yes	5 (33.3)	15 (40.5)	0.628
No	10 (66.7)	22 (59.5)	
Postoperative complication, n (%)[a]			
Total	6 (42.9)	14 (37.8)	0.743
Perineal wound infection	3	5	
Perineal wound dehiscence	0	3	
Lymphorrhea	0	2	
Ileus	2	3	
Deep vein thrombosis	1	2	
Anastomotic leakage	1	1	
Other	3	6	
Recurrence, n (%)			
Local	0 (0)	9 (17.3)	0.066
Distant	2 (13.3)	10 (27.0)	0.479
Lung/Liver	1 (2.7)	7 (18.9)	
Bone	0 (0)	1 (2.7)	
Inguinal	1 (2.7)	0 (0)	
Dissemination	0 (0)	1 (2.7)	
Lung lymph node	0 (0)	1 (2.7)	

TME: Total mesorectal excision, LLND: lateral pelvic lymph node dissection. [a]Exceeding grade 2 according to the extended Clavien–Dindo classification (14).

The 5-year recurrence-free survival (RFS) rate was significantly better in patients with LLNs of <7.0 mm (n=13) than in those with LLNs of ≥7.0 mm (n=39) (85.7% *versus* 56.8%; p=0.038) (Figure 3). The 5-year OS rate also tended to be better in patients with LLNs <7.0 mm than in those with LLNs ≥7.0 mm (100% *versus* 84.1%; p=0.098).

Discussion

Recently, the Japan Clinical Oncology Group (JCOG) reported the results of a multicenter, randomized, controlled trial (JCOG0212) that aimed to confirm the non-inferiority of TME compared with TME with LLND for cStage II/III low rectal cancer (15). In JCOG0212, the OS and RFS rates for the TME with LLND group were significantly better than for the TME-only group. Accordingly, TME with LLND remains a standard treatment for locally advanced low rectal cancer in Japan. However, there have been only a limited number of studies investigating the size of LLNs as a means of predicting pathological metastasis. Ishibe *et al*. reported a cut-off value of 10 mm (AUC=0.79, sensitivity=43.8%, and specificity=98.5%) to be useful in avoiding unnecessary LLND (16). Akiyoshi *et al*. reported the optimal cut-off value as a short-axis diameter of 8.0 mm before CRT (AUC=0.86, sensitivity=68%, and specificity=85%) (17). Our criterion of ≥7.0 mm before CRT seems stricter but more adequate than these previously described criteria, because our study showed a better AUC value, sensitivity, and specificity (AUC=0.92, sensitivity= 85.7%, and specificity=84.0%). In addition, the five-year RFS

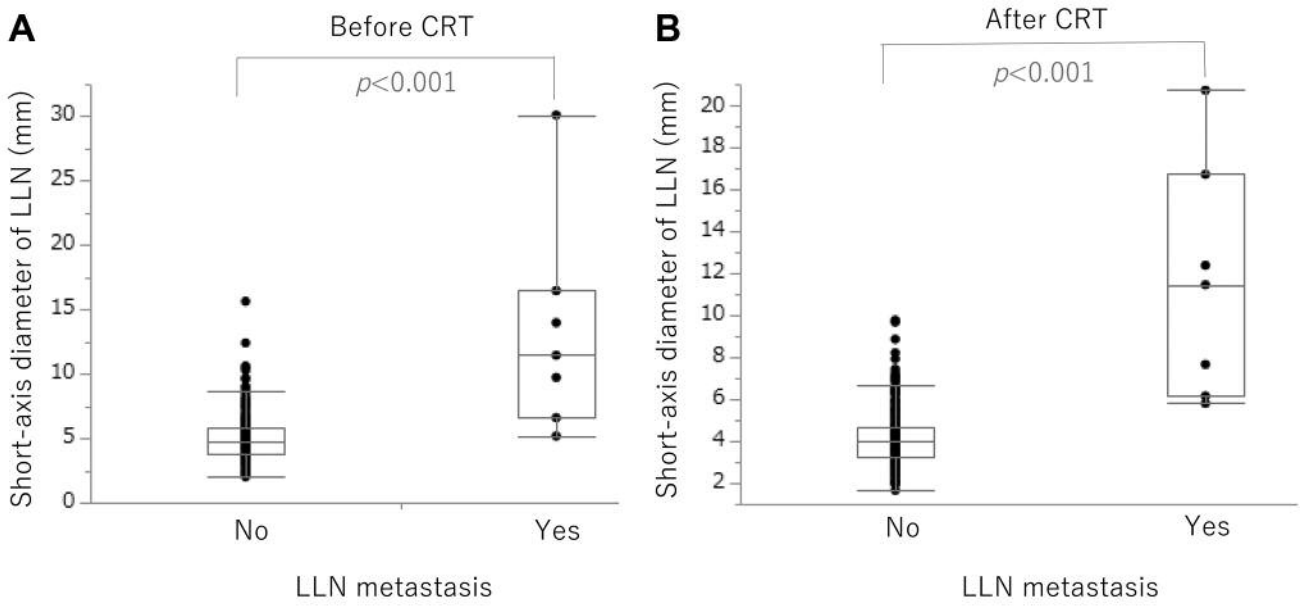

Figure 1. *Relation between the short-axis diameter and pathological metastasis of lateral lymph nodes. The short-axis diameter of lateral pelvic lymph nodes (LLNs) with pathological metastasis was significantly larger than that without pathological metastasis, both before (A) and after (B) preoperative chemoradiotherapy (CRT).*

was significantly better in patients with LLNs <7.0 mm than in those with LLNs ≥7.0 mm (85.7% *versus* 56.8%; p=0.038) in our study. Akiyoshi *et al*. found no significant correlation between the RFS and their cut-off value of 8.0 mm before CRT (p=0.2291). The 5-year OS in our study also tended to be better in patients with LLNs <7.0 mm than in those with LLNs ≥7.0 mm before CRT (p=0.098). Therefore, our new criterion of a cut-off value of 7.0 mm before CRT may predict pathological metastasis of LLNs more effectively and accurately than the previously recommended values.

Several investigators have proposed cut-off values using MRI (15, 16). The usefulness of functional MRI for predicting quantitative treatment responses in rectal cancer has also been reported (18). In our study, we mainly used CT as the evaluation tool for LLN metastasis because it allows the evaluation of lymph node size with finer slices than MRI. The sensitivity of 85.7% and specificity of 84.0% of CT in diagnosing LLN metastasis in our study were not inferior to those of previous reports using MRI. PET examination was also used in predicting the metastatic LLN status in our study. Two patients with LLNs <7.0 mm underwent LLND because of positive accumulation in PET, but neither were found to have pathologically-positive metastases. Although CT seems to be the most powerful tool for detecting pathologically positive LLNs, we still recommend a comprehensive assessment using CT, MRI, and PET.

It remains difficult to predict micrometastasis in LLNs by size alone. Yamaoka *et al*. reported that 2.3% of patients with LLNs ≤3.0 mm in short-axis diameter had pathological metastases even when they did not receive preoperative CRT (19). Brown *et al*. (20) and Park *et al*. (21) reported that LLNs <3.0 mm could not be detected on MRI. In the present study, there was no local recurrence in the group treated with TME alone, suggesting that possible micrometastases in LLNs <7.0 mm might be controlled by CRT alone.

Several investigators have reported that LLNs shrink in size after CRT. Yamaoka *et al*. reported that the cut-off value of LLN size for the determination of metastasis decreased after CRT (19), which our results is consistent with. In fact, most LLNs shrank after CRT in the present study. Only one case showed an increase in the LLN size after CRT (5.2 mm before and 12.4 mm after CRT), and this LLN was pathologically positive for metastasis. Oh *et al*. reported that patients with an unchanged size of LLNs after CRT had a significantly higher incidence of LLN metastasis than those whose LLNs were responsive to CRT in terms of decreasing in size (61% *vs*. 0%; p<0.0001) (22). Therefore, we recommend performing LLND in cases with increased LLN size after CRT, even if the short-axis diameter of LLNs before CRT was shorter than 7.0 mm.

This study had several important limitations. Firstly, it was a single-center retrospective study. Secondly, our study population diagnosed with pathologically LLN metastasis was very small. However, we believe that preoperative CRT dramatically reduced the number of metastatic LLNs after surgery because of the treatment effect. Further

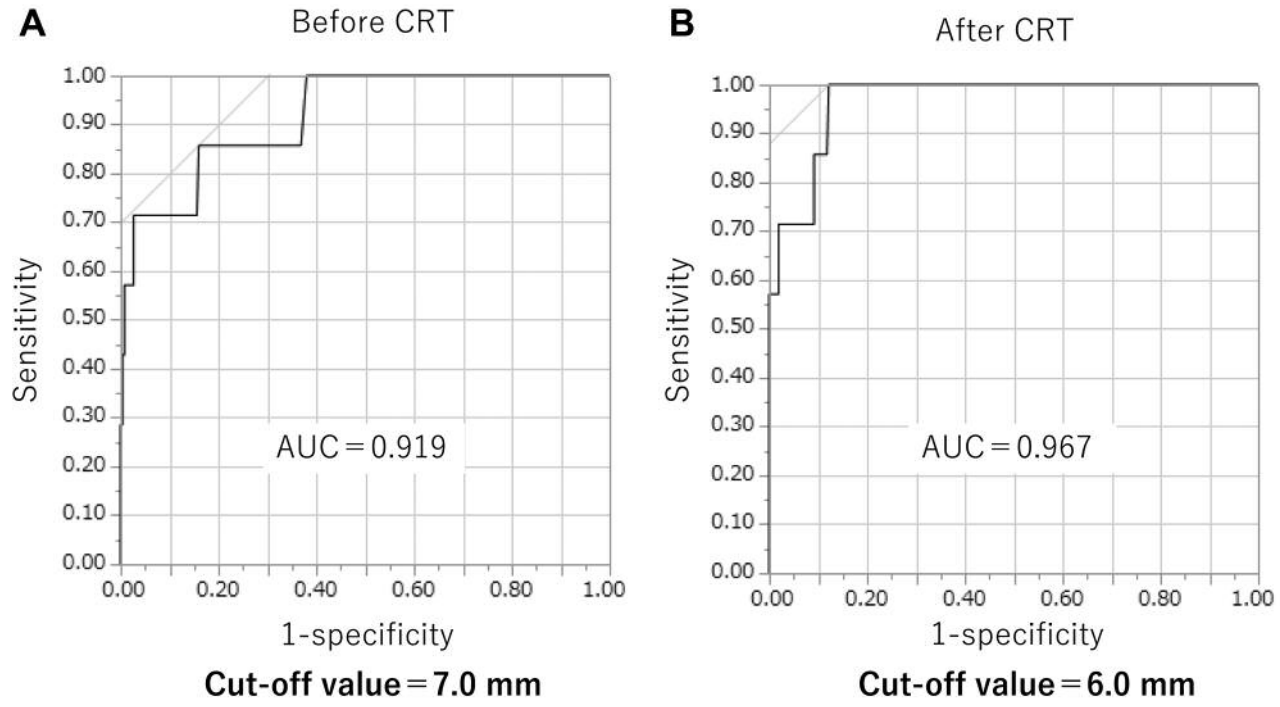

Figure 2. *Receiver operating characteristic (ROC) curve analysis. The cut-off value of the short-axis diameter of lateral pelvic lymph nodes (LLNs) before (A) and after (B) preoperative chemoradiotherapy (CRT) was 7.0 and 6.0 mm, respectively. AUC: Area under the ROC curve.*

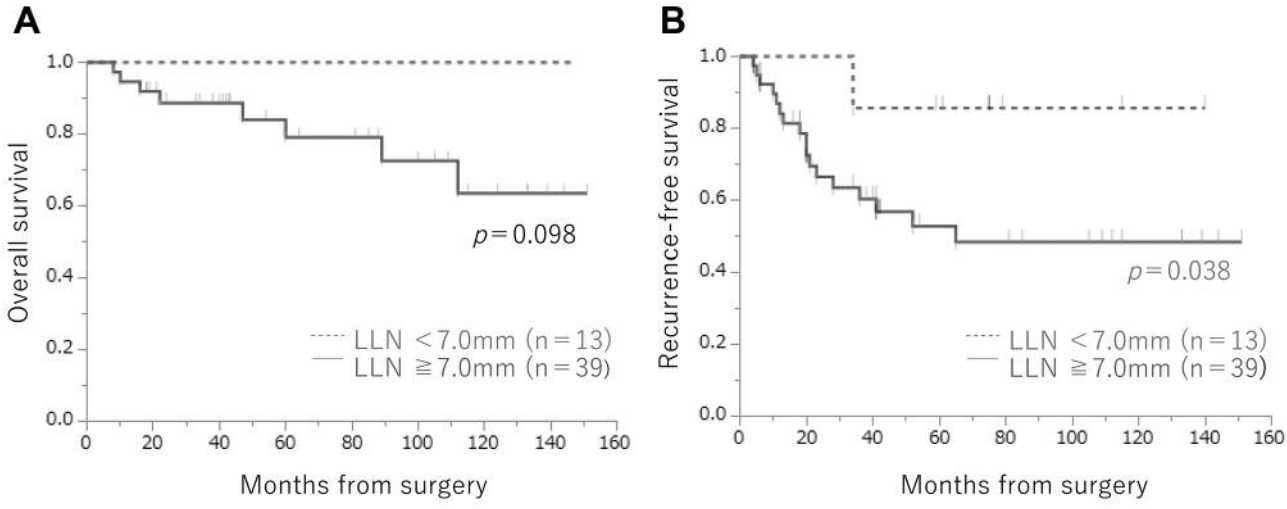

Figure 3. *Kaplan–Meier curves for overall (OS) (A) and recurrence-free (RFS) (B) survival in patients with rectal cancer according to the size of lateral pelvic lymph nodes (LLNs). The 5-year OS rate was 100% and 84.1% for patients with LLNs <7.0 mm and LLNs ≥7.0 mm, respectively (p=0.098). The corresponding 5-year RFS rates were 85.7% and 56.8%, respectively (p=0.038).*

studies employing more patients who undergo LLND without preoperative CRT are needed to confirm our results.

In conclusion, the optimal cut-off value for predicting pathological metastasis of LLNs in patients with low rectal cancer in our study was 7.0 mm before and 6.0 mm after CRT, respectively. The size of LLNs also seemed to predict the oncological outcome. The size criterion might be useful to select patients who are likely to benefit from LLND following preoperative CRT in multimodal therapy.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

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