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ORIGINAL ARTICLE

Prediction model of the risk for lateral local recurrence in locally advanced rectal cancer without enlarged lateral lymph nodes: Lessons from a Japanese multicenter pooled analysis of 812 patients

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Abstract

Aim: Although the oncological impact of lateral lymph node dissection on enlarged lateral lymph nodes has been gradually accepted over the last decade, that on lateral lymph nodes without swelling remains doubtful. This study aimed to develop a prediction model for the future risk of lateral local recurrence and to clarify the value of adding lateral lymph node dissection in locally advanced rectal cancer without enlarged lateral lymph nodes.

Methods: This retrospective, multi-institutional study recruited 812 patients with cStage II/III low rectal cancer without enlarged lateral lymph nodes <7 mm. Total lateral local recurrence was a hypothetical value of future risk of lateral local recurrence when lateral lymph node dissection was never performed.

Results: Overall, total lateral local recurrences were observed in 67 patients (8.3%). In the multivariate analyses, the strongest risk factor for total local recurrences was no preoperative chemoradiotherapy (odds ratio [OR][95%CI]: 33.2 [4.56–241.7], $P < 0.001$), followed by tumor distance ≤40 mm (OR [95%CI]: 2.71 [1.51–4.86], $P < 0.001$) and lateral lymph node 5–7 mm (OR[95%CI]: 2.38 [1.26–4.48], $P = 0.007$). In patients with lateral lymph nodes of 5–7 mm, the total lateral recurrence rate was 4.8% after preoperative chemoradiotherapy. Lateral lymph node dissection could reduce from a total lateral local recurrence of 21.6% to an actual lateral local recurrence of 8.0% in patients without preoperative treatment.

Conclusion: We introduce a novel prediction model of future risk of lateral local recurrences, which has the potential to enable us to indicate lateral lymph node dissection selectively according to the patients' risks.

KEYWORDS
lateral local recurrence, lateral lymph node, lateral lymph node dissection, prediction model, rectal cancer

1 | INTRODUCTION

Western and Japanese practices for lateral nodal disease in rectal cancer have gone in different directions. While Western clinicians have valued preoperative chemoradiotherapy (CRT) for local control, including the lateral pelvis, Japanese surgeons have preferred adding systematic lateral lymph node dissection (LLND) to total mesorectal excision (TME).[1,2] However, in the past 5 y, these situations have been gradually changing, and we are going in the same direction toward achieving favorable local control and survival with risk-adapted and tailor-made strategies using CRT, systemic chemotherapy, and/or LLND. The authors analyzed a total of 1216 patients from 11 international referral hospitals and reported that adding LLND could decrease lateral local recurrence (LLR) in patients with enlarged LLNs,[3] leading to increasing evidence that LLND should be considered even after CRT in patients with enlarged LLNs from not only Eastern[4–6] but also Western[7–9] countries. On the other hand, the value of LLND for patients without enlarged LLNs remains doubtful.

A Japanese multicenter randomized controlled noninferiority trial (JCOG0212) included patients with lateral nodes up to 10 mm in the short-axis (SA) who did not have any neoadjuvant treatment and evaluated the value of adding LLND to TME.[10] Adding LLND successfully reduced LLR rates from 7.4% to 2.3%; however, LLND failed to demonstrate additional benefit for central local control and survival. They concluded that additional LLND should not be recommended for stage II, but instead for stage III patients without enlarged LLNs when any preoperative treatments were not performed.[11] However, little is known about the benefit of adding LLND when patients have no enlarged LLNs and undergo any preoperative treatment, although it seems to be ineffective and unnecessary.

Considering the tendency toward the recent complicated and tailored strategy for locally advanced rectal cancer,[12,13] the risk-adapted indications of LLND should be established. Of several risk factors for lateral lymph node metastasis (LLNM) reported up to now,[14–16] the cut-off size of an "enlarged LLN" remains controversial, the SA size is in the spotlight due to its simplicity and usefulness. In the present study, we aimed to develop a new prediction model that estimates the risk of future LLR and helps determine the optimal indication of LLND, focusing on patients with locally advanced rectal cancer without enlarged LLNs.

2 | MATERIALS AND METHODS

2.1 | Study population and data collection

This study was approved by the local Ethics Committees at the Nagoya University Hospital (reference No. 2019–0220). This study included patients who gave informed consent from five referral hospitals in Japan (Table S1). All patients were diagnosed with cStage II/III low rectal cancer within 8 cm from the anal verge (AV) and underwent curative-intent surgery with or without LLND between January 2009 and December 2016. Each participating hospital rereviewed the initial magnetic resonance imaging (MRI) and/or multidetector computed tomography (CT) (MDCT) findings with a focus on LLNs using a colored map of the lateral pelvis, as previously reported.[3] In patients who underwent preoperative treatment, LLNs were assessed before preoperative treatment. The assessment of LLNs was based on the largest LLN, and the SA size and location (internal iliac or obturator compartment) were recorded. Benign long-stretched LLNs just behind the external iliac vein were excluded from the assessment, as previously reported.[3,17] The "enlarged" LLNs were defined as those that were 7 mm or larger in the SA, and the patients with enlarged LLNs were excluded from the analyses in this study. When no subjective LLNs were detected in any slices of the imaging findings, the patients were defined as having invisible LLNs. Assessment of tumor distance was based on the lower edge of the tumor on the sagittal view of the initial MRI and/or MDCT. If the lower edge was difficult to assess on the images, the data measured by digital examination were tolerated.

2.2 | Preoperative treatment

The treatment strategies for individual patients were determined in the multidisciplinary meeting at each hospital; therefore, there were various types of preoperative treatment. Irradiation with fluorouracil was defined as CRT, and neoadjuvant chemotherapy (NAC) indicated intensive oxaliplatin-based doublet chemotherapy without radiotherapy for at least one cycle before surgery. No patients received irradiation alone or total neoadjuvant therapy in this cohort. Neoadjuvant treatment was routinely indicated for patients with cStage II/III low rectal cancer in two hospitals, whereas it was selectively indicated only for patients with high-risk factors for local recurrence (e.g. suspected mesorectal or lateral LN metastasis,[18] threatened circumferential resection margin,[19] or extramural vascular invasion[20]) in the other three institutions.

2.3 | Lateral lymph node dissection

Lateral lymph node dissection (LLND) was defined as complete removal of fat tissue from the bilateral or unilateral lateral compartment (i.e. the internal iliac and obturator compartments) in the pelvis. Because the Japanese guidelines recommended LLND for the

subjects of this study,[21] LLND was actually indicated on at least one side, with a rate of 65%–74% in three hospitals. In contrast, the other two institutions did not principally perform LLND for patients without enlarged LLNs during this study period.

2.4 | Lateral local recurrence and total lateral lymph node metastasis

Not only initial recurrent sites but also all recurrent sites during the follow-up period were reviewed from the patients' records in this study. Local recurrence (LR) developed in various sites of the pelvis, and LRs in the lateral compartment were particularly defined as LLRs. As previous reports described,[5,22] "total lateral local recurrences (tLLRs)" were built to neutralize the effect of LLND and to estimate the risk of future LLR. The hypothetical tLLR included the following three situations of lateral events—A: actual LLRs developed in the untouched lateral compartments, B: actual LLRs in the touched ones without pathological LLN metastases (pLLNMs), and C: pLLNMs in the touched lateral ones. In short, $tLLRs = A + B + C$ (Figure 1).

2.5 | Statistical analysis

All the statistical analyses were performed using the IBM SPSS Statistics package (v. 28: SPSS, IBM, Armonk, NY, USA) except for the bootstrap analysis performed with the SAS for Windows, v. 9.4 (SAS Institute, Cary, NC, USA). Individual variables were compared with the use of chi-square tests. A P value of less than 0.05 was considered significant. A prediction model of tLLRs was developed using risk factors identified using uni- and multivariate logistic regression models, the accuracy of which was evaluated by the area under the curve (AUC) analyzed using the receiver operating characteristic curve (ROC). The validity of the prediction model was then validated using 1000 bootstrap samples.

3 | RESULTS

3.1 | Patients

Data from 936 patients with cStage II/III low rectal cancer who underwent curative-intent surgery were collected from five referral hospitals (Table S2). A total of 124 patients (13.2%) who had enlarged LLNs ≥7 mm were excluded, and a total of 812 patients without enlarged LLNs were analyzed in this study (Figure 2). Table 1 summarizes the patient and tumor characteristics of the total cohort, including 269 patients (33.1%) who underwent CRT, 82 patients (10.1%) who received NAC, and the remaining 461 patients (56.8%) who underwent upfront surgery. At least one visible LLN was detected in 278 patients (34.3%) on the initial imaging; conversely, no LLNs were detected in the remaining 65.7% of patients. Bilateral and unilateral LLNDs were performed in 334 patients (41.1%) and 50 patients (6.2%), respectively. The rate of undergoing LLND was significantly higher in patients with upfront surgery and NAC than in those with CRT (65.8% and 57.4% vs. 19.4%, $P < 0.001$).

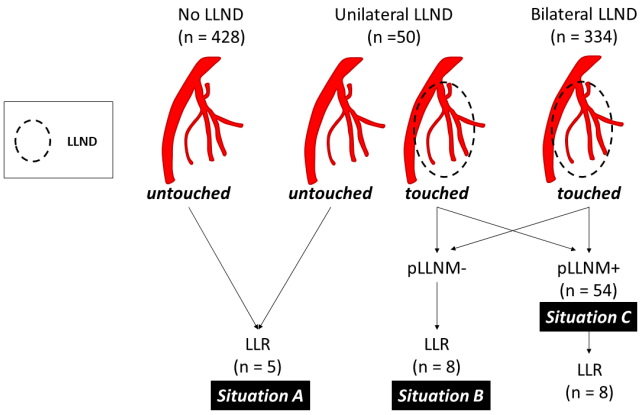

FIGURE 2 Overview of the situations in the lateral compartment and the associated information, including the rates of lateral lymph node dissection, pathological LLN metastases, and actual lateral local recurrence.

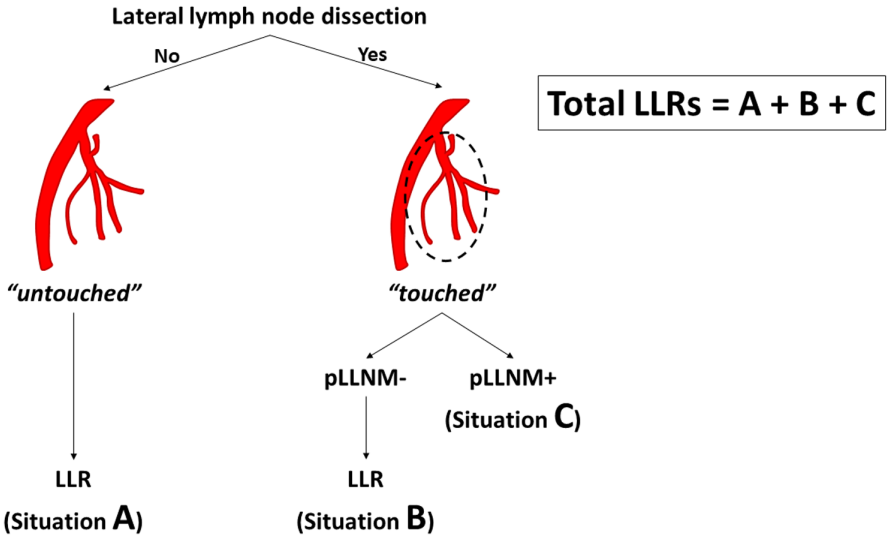

FIGURE 1 Definition of total lateral local recurrence consisting of three situations.

TABLE 1 Patient and tumor characteristics.

	Total (*N* = 812)	Surgery alone (*N* = 461)	CRT (*N* = 269)	NAC (*N* = 82)	*P*-Value
Sex, man (%)	564 (69.5)	317 (68.8)	247 (70.4)	56 (68.3)	0.794
Age ≥ 65 y (%)	398 (49.0)	224 (48.6)	144 (53.5)	30 (36.6)	0.026
Distance from anal verge ≤40 mm	410 (50.5)	232 (50.3)	146 (54.3)	32 (39.0)	0.053
MRI (%)	503 (61.9)	362 (78.5)	71 (26.4)	70 (85.4)	<0.001
cT4b disease (%)	98 (12.1)	42 (9.1)	39 (14.5)	17 (20.7)	0.004
cN+ (%)	442 (54.4)	232 (50.3)	153 (56.9)	57 (69.5)	0.004
LLN visibility (%)					<0.001
Invisible	534 (65.7)	266 (57.7)	204 (75.8)	64 (78.0)	
<5.0 mm	159 (19.6)	107 (23.2)	44 (16.4)	8 (9.8)	
5.0–7.0 mm	119 (14.7)	88 (19.1)	21 (7.8)	10 (12.2)	
Operative procedure					<0.001
Low anterior resection	439 (53.0)	216 (46.8)	180 (67.0)	34 (41.5)	
Intersphincteric resection	134 (16.5)	98 (21.3)	17 (6.3)	19 (23.2)	
Abdominoperinieal resection	209 (25.7)	122 (26.5)	64 (23.8)	23 (28.0)	
Pelvic exenteration	24 (3.0)	14 (3.0)	4 (1.5)	6 (7.3)	
Hartmann's operation	13 (1.6)	11 (2.4)	2 (0.7)	0	
Local resection	2 (0.2)	0	2 (0.7)	0	
Lateral lymph node dissection (LLND) (%)	384 (47.3)	316 (68.5)	21 (7.8)	47 (57.4)	<0.001
Unilateral	50 (6.2)	28 (6.1)	4 (1.5)	18 (22.0)	
Bilateral	334 (41.1)	288 (62.5)	17 (6.3)	29 (35.4)	
Any complications (%)	356 (43.8)	206 (44.7)	99 (36.8)	51 (62.2)	<0.001
Complications CD ≥3 (%)	119 (14.7)	68 (14.8)	34 (12.6)	17 (20.7)	0.192
Urinary dysfunction (%)	80 (9.9)	60 (13.0)	9 (3.3)	11 (13.4)	<0.001
(y)pT4 disease (%)	60 (7.4)	46 (10.0)	9 (3.3)	5 (6.1)	0.004
(y)pN+ (%)	309 (38.1)	220 (47.7)	72 (26.8)	17 (20.7)	<0.001
Pathological LLNM (%[a])	54 (14.0)	52 (16.5)	0	2 (4.3)	<0.001
R0 resection (%)	791 (97.4)	449 (97.4)	264 (98.1)	78 (95.1)	0.321
Adjuvant chemotherapy (%)	339 (41.7)	175 (38.0)	118 (43.9)	175 (38.0)	0.006
Actual LLR (%)	21 (2.6)	15 (3.3)	1 (0.4)	5 (6.1)	0.007
Estimated LLR (%)	67 (8.3)	60 (13.0)	1 (0.4)	1 (10.0)	<0.001

Abbreviations: CD, Clavien–Dindo; LLN, lateral lymph node; LLNM, lateral lymph node metastasis; LLR, lateral local recurrence.
[a]Rate in patients who received LLND.

3.2 | Composition of estimated future LLR (tLLR)

There were no patients with bilateral LLRs or pLLNMs, and LLRs never developed combined with central LRs in this cohort. Figure 2 summarizes the overview of the situations in the lateral compartment and the associated information, including the rate of LLND, pLLNM, and actual LLR. Situation A included five actual LLRs that developed in the untouched lateral compartment during the follow-up period. Situation B included eight actual LLRs that developed in the touched lateral compartment without pLLNMs. Situation C included a total of 54 patients with pLLNMs, which were hypothesized to develop future LLR if LLND was not given. Briefly, tLLRs were seen in 67 patients (8.7%) in this cohort. It is supplementary information that eight LLRs (14.8%) were detected in 54 patients in situation C, despite performing LLND. In addition, preoperative treatment was not given for seven (87.5%) in eight LLRs.

3.3 | Impact of preoperative treatment and initial LLN size on estimated future LLR (tLLR)

Table 2 summarizes the clinical impact of the preoperative treatment and initial LLN size on tLLR. tLLR was quite high, at 13.0%, even in patients without enlarged LLNs if any preoperative treatment was never indicated, whereas it was reduced to

0.4% after preoperative CRT and 7.3% after NAC. However, tLLR size-dependently increased in the CRT group, and the tLLR rate reached 4.8% in patients with LLNs of 5–7 mm, even after preoperative CRT. For patients who received NAC, although LLND was performed in 47 patients (57.3%), only two patients (4.3%) had pLLNMs. On the other hand, for patients with upfront surgery, LLND was given for 68.5% of the patients, resulting in a comparable actual LLR rate of 3.3%. For patients with LLNs 5–7 mm, despite the high rate of LLNDs at 80.7%, the actual LLR rate remained high at 8.0%.

3.4 | Univariate and multivariate analyses of clinical risk factors for the estimated future LLR (tLLR)

Table 3 shows the uni- and multivariate analyses of clinical risk factors for tLLR. Patients without preoperative CRT had a significantly higher risk of tLLR than those with preoperative CRT (OR: 33.2 [4.56–241.7], $P < 0.001$). Patients with LLNs 5–7 mm in the SA also had a significantly higher risk of tLLR (OR: 2.38 [1.26–4.48], $P = 0.007$) than those with LLNs <5.0 mm. Additionally, a tumor distance ≤40 mm was also significantly associated with a higher risk of tLLR (OR: 2.71 [1.51–4.86], $P < 0.001$).

3.5 | A prediction model of the estimated future LLR (tLLR)

Probabilities using three risk factors derived from multivariate logistic regression analysis, tumor distance ≤40 mm, no preoperative treatment, and LLNs 5–7 mm, are shown as a percentage risk of tLLR in Table 4. The formula was as follows:

$$\sum_{i=0}^{p} \beta i\mathrm{Xi} = -6.282 + 3.500\,X1 + 1.015\,X2 + 0.780\,X3, X1: [\textit{preoperative CRT}\,(0), \textit{no preoperative CRT}\,(1)], X2: [\textit{tumor distance} > 40\,\textit{mm}\,(0), \textit{tumor distance} \le 40\,\textit{mm}\,(1), X3: \textit{LLN} < 5\,\textit{mm}\,(0), \textit{LLN}\ 5 - \neg 7\,\textit{mm}\,(1)].$$

$$\text{Probability (tLLR rate for individual)} = \frac{1}{1 + \exp\left(-\sum_{i=0}^{p} \beta i Xi\right)}.$$

The AUC of the prediction model was 0.7713 (95% confidence interval [CI]: 0.7253, 0.8174; Figure 3). The internal validation of the model, using 1000 bootstrap samples, revealed an AUC of 0.7708 (95% CI: 0.7229–0.8187).

Of the 812 patients, 138 patients (17.0%) with no risk factors had just a 0.2% risk for tLLR. When preoperative CRT was performed, 131 patients (16.1%) who had another risk factor for tumors (i.e. distance within 40 mm and/or LLN 5–7 mm) were also at low risk, around 1% for tLLR. On the other hand, when preoperative CRT was not given, 226 patients (27.8%) without the other two factors remained at intermediate risk of 5.8%. Additionally, 257 patients (31.7%) who had another risk factor had a high risk for tLLR (risk 15%), and the tLLR rate of 60 patients (7.4%) with all risk factors reaching an extremely high value of 27%.

4 | DISCUSSION

This is the first study of a prediction model of the estimated future LLR (i.e. tLLR) in patients with cStage II/III low rectal cancer without enlarged LLNs, which consists of three key clinical risk factors for tLLR, including preoperative CRT, maximum SA size of LLN, and the distance from the AV. This prediction model of tLLR clarified the future risk of LLR if LLND was never indicated and may help to consider the value of adding LLND under various situations.

The JCOG0212 study demonstrated that the additional LLND reduced LLR in patients with LLNs <10 mm when any preoperative treatment was not given.[10,11] In our cohort, although the estimated future risk of LLR (tLLR) was estimated to be 13.0% in patients who underwent surgery alone, the high LLND rate of 68.5% could suppress the actual LLR rate to be 3.3%. On the other hand, another finding was that the tLLR was almost equivalent to the actual LLR in patients who underwent preoperative CRT. Although the rate of undergoing LLND was 7.8%, no pLLNM was found in only 2.9%, confirming that LLND might be unnecessary for patients without enlarged LLNs after preoperative CRT, which could sterilize some LLNMs. The effect on lateral local control should be different between CRT and NAC. It was clearly evidenced that LLND was not beneficial in patients with LLNs <7 mm who received preoperative CRT.[3] Although tLLR was observed in only one patient (1.8%) out of 57 patients with LLNs <7 mm who received NAC alone in the previous report,[22] the actual LLR rate remained 6.1% after NAC in this study. Briefly, preoperative CRT would be stronger than NAC in terms of local control and may enable us to omit LLND in patients with LLNs <7 mm.

Among patients with LLNs of 5–7 mm in the SA, however, a high tLLR rate of 21.6% and actual LLR rate of 8.0% in patients who underwent upfront surgery and a slightly high rate of tLLR and actual LLR of 6.1% in those who indicated NAC alone for the management of lateral local control. Hida et al recently reported that patients with LLNs of 5–10 mm had a higher risk of LLNM (24.1% vs. 9.9%) than those with LLNs <5 mm and significantly achieved prognostic benefits from LLND on OS (OS: 81.9% vs. 67.3%, $P = 0.012$) and relapse-free survival (69.4% vs. 51.6%, $P = 0.021$).[23] Further analyses of JCOG0212 reported that

TABLE 2 Clinical impact of preoperative treatment and initial LLN size on the estimated future LLR (tLLR).

	Total cohort (N = 812)	Surgery alone				CRT				NAC			
		Invisible (N = 266)	<5.0 (N = 107)	5.0–7.0 (N = 88)	Total (N = 461)	Invisible (N = 204)	<5.0 (N = 44)	5.0–7.0 (N = 21)	Total (N = 269)	Invisible (N = 64)	<5.0 (N = 8)	5.0–7.0 (N = 10)	Total (N = 82)
Estimated future LLR (tLLR)	67 (8.3)	27 (10.2)	14 (13.1)	19 (21.6)	60 (13.0)	0	0	1 (4.8)	1 (0.4)	4 (6.3)	1 (12.5)	1 (10.0)	6 (7.3)
LLND (%)	384 (47.3)	164 (61.7)	81 (75.7)	71 (80.7)	316 (68.5)	8 (3.9)	8 (18.2)	5 (23.8)	21 (7.8)	33 (51.6)	6 (75.0)	8 (80.0)	47 (57.3)
Pathological LLNM (%)[a]	54 (14.1)	22 (13.4)	14 (17.3)	16 (22.5)	52 (16.5)	0	0	0	0	2 (6.1)	0	0	2 (4.3)
Actual LLR (%)	21 (2.6)	6 (2.3)	2 (1.9)	7 (8.0)	15 (3.3)	0	0	1 (4.8)	1 (0.4)	3 (4.7)	8 (12.5)	1 (10.0)	5 (6.1)

Abbreviations: LLND, lateral lymph node dissection; LLNM, lateral lymph node metastasis; LLR, lateral local recurrence.

[a]Rate in patients who received LLND.

LLR-free survival decreased at 7 y after surgery according to the SA size of LLNs: 85.1% in patients with LLNs <7 mm and 70.0% in those with LLNs 7–10 mm.[11] Kim et al[6] analyzed a total of 900 Korean patients with cStage II/III rectal cancer within 10 cm from the AV who underwent CRT without LLND and demonstrated that LLR-free survival in patients with LLNs 5–10 mm was significantly worse than those with LLNs <5 mm (91.7% vs. 98.2%, $P < 0.001$). LLNs 5–7 mm should be treated with additional caution for lateral local control compared to those with LLNs <5 mm. The definition of an "enlarged LLN" may need to be shifted from LLNs with a SA ≥7 mm to a SA ≥5 mm.

There are some limitations to our study. First, this was a retrospective study including the heterogeneous strategies for LARC in terms of perioperative treatment and LLND. Although the small number of patients could not allow further analyses, the difference in the impact on lateral control between both preoperative treatments should be investigated in future studies. Second, we ignored the possibility of the eradication of cancer cells in LLNs by preoperative treatment in this study. Some LLNMs could become free from future LLRs (tLLRs) irrespective of LLND. Because it is difficult to identify the possibility of not only its eradication but also its regrowth, we have no clear answer in these small numbers up to now. However, the lower rate of 2.1% of LLRs in patients with invisible LLNs after CRT in the previous reports may be supportive for the observation and salvage LLND for them. Third, we should confirm the usefulness of this prediction model using another independent dataset for external validation in the future. Fourth, extramural venous invasion (EMVI) and CRM on MRIs were not analyzed, which were significantly important prognostic factors of rectal cancers because some patients diagnosed only by MDCT were included in this study. One recent article published by Sumii et al indicated EMVI and CRM on MRIs were not significant risk factors for potential LLNM. Instead, SA size of LLN and tumor location were also significant risk factors,[24] which justifies our prediction model based on the status of SA size of LLN and tumor location. Last, LLND could not completely avoid future LLR (i.e. LLR could develop in the touched lateral compartment); therefore, whether patients with LLNs 5–7 mm or upfront surgery should be given the additional LLND would be the subject of further research.

5 | CONCLUSION

We introduce a novel prediction model of estimated future LLR (tLLR) in patients with cStage II/III low rectal cancer without enlarged LLNs, which could neutralize the effect LLND and consists of three important clinical risk factors, including preoperative CRT, maximum SA size of the LLN, and distance from the AV. Although external validation is needed, this model could help decision-making by adding preoperative CRT and/or LLND under various situations.

TABLE 3 Univariate and multivariate analyses of clinical risk factors for total lateral local recurrence ($N = 812$).

			Univariate			Multivariate[a]		
	N	tLLR (%)	OR	95% CI	*P*-Value	OR	95%CI	*p*-Value
Age					0.138			
<65	414	10.0	1					
≥65	398	7.1	0.68	0.41–1.13				
Sex					0.669			
Man	564	8.2	1					
Woman	248	9.4	1.49	0.89–2.50				
Tumor distance from AV					<0.001			<0.001
>40 mm	410	5.3	1			1		
≤40 mm	402	11.9	3.02	1.73–5.29		2.71	1.51–4.86	
cT stage					0.058			0.303
cT1-4a	530	7.5	1			1		
cT4b	77	15.6	1.87	0.98–3.57		1.46	0.71–2.97	
cN stage					0.247			
cN0	370	7.6	1					
cN+	442	9.4	1.35	0.81–2.26				
Preoperative CRT					<0.001			<0.001
Yes	269	1.9	1			1		
No	543	13.5	37.1	5.11–268.7		33.2	4.56–241.7	
LLN status								
Invisible	534	5.7	1			1		
<5.0 mm	159	10.4	1.69	0.89–3.22	0.110	1.63	0.84–3.15	0.146
5.0–7.0	119	17.7	3.48	1.92–6.30	<0.001	2.38	1.26–4.48	0.007

Abbreviations: AV, anal verge; LLN, lateral lymph node; LLR, lateral local recurrence.

[a]This multivariate analysis was calculated by bootstrapping using 2000 samples.

TABLE 4 Prediction model of total lateral local recurrence according to three key clinical risk factors.

LLR%	Preoperative CRT			
	Done		Not done	
	SA size of LLN			
	<5.0	5.0–7.0	<5.0	5.0–7.0
AV > 40	0.2	0.4	5.8	12
AV ≤ 40	0.5	1.1	15	27

Note: Back ground colors; red: high-risk, orange: middle-risk, green: low-risk.

Abbreviations: AV, anal verge; LLN, lateral lymph node; SA, short-axis.

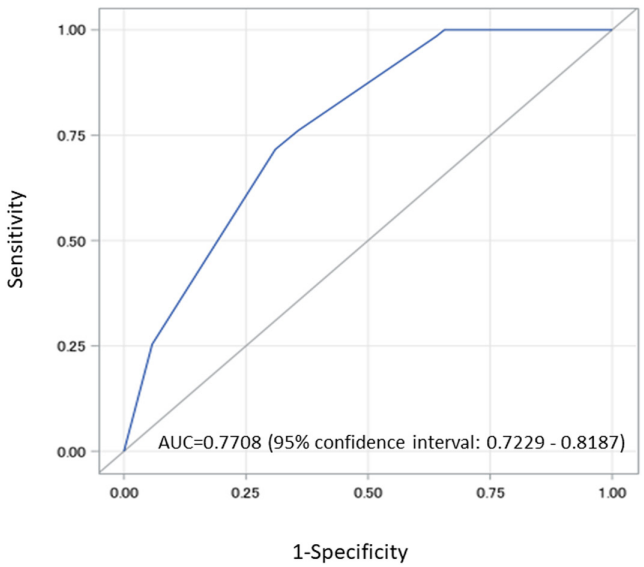

FIGURE 3 Receiver operating characteristic curve (ROC) evaluating the accuracy of the prediction model.

AUTHOR CONTRIBUTIONS

Study conception and design, drafting the article: Ogura, Uehara. Data acquisition, data analysis and interpretation, critical revision for intellectual content, final approval of the article and agree to be accountable for all aspects of the work to ensure that questions regarding accuracy and integrity investigated and resolved: All authors.

ETHICS STATEMENT

Approval of the research protocol: The protocol for this research project was approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of Nagoya University Hospital, Approval No. 2019–0220.

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

CONFLICT OF INTEREST STATEMENT

K.U. is an editorial member of the *Annals of Gastroenterological Surgery*. The other authors declare no conflicts of interest for this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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