Magnetic Resonance Imaging-Based Scoring Systems for Selective Lateral Lymph Node Dissection in Locally Advanced Low Rectal Cancer After Neoadjuvant Chemoradiotherapy

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ABSTRACT

Magnetic Resonance Imaging-Based Scoring Systems for Selective Lateral Lymph Node Dissection in Locally Advanced Low Rectal Cancer After Neoadjuvant Chemoradiotherapy

Purpose

To develop scoring systems to predict the need for selective lateral lymph node dissection (LLND) alongside total mesorectal excision (TME) in patients with locally advanced low rectal cancer after neoadjuvant chemoradiotherapy (nCRT), focusing on lateral local recurrence (LLR) and lateral lymph node (LLN) metastasis.

Materials and Methods

This retrospective study included 607 patients with mrT3/T4 rectal cancer located within 8 cm of the anal verge who underwent nCRT and TME. A development group was used to develop a scoring system predicting the necessity of LLND using logistic regression analysis, incorporating primary tumor and LLN features observed on rectal magnetic resonance imaging (MRI). External validation was conducted by comparing the model with established criteria and in an independent group of 144 patients. We also analyzed risk factors for recurrence and residual LLNs after LLND.

Results

Model 1 included pretreatment LLN size and extramural venous invasion (EMVI). Model 2 incorporated pretreatment internal iliac and obturator lymph node sizes, EMVI, and nonresponsive LLN on restaging MRI. In the development group, Models 1 and 2 exhibited high performance (area under the curve [AUC] = 0.92 and 0.90, respectively). Compared with the established criterion, which focused solely on nonresponsive LLNs on restaging MRI, Model 1 demonstrated the highest sensitivity, while Model 2 showed moderate sensitivity and specificity. Among patients who underwent LLND, the distal internal iliac compartment had more residual lymph nodes than other compartments ($p = 0.02$).

Conclusion

Scoring systems utilizing LLN features and EMVI on MRI could aid in decision-making for selective LLND following nCRT in locally advanced low rectal cancer.

Key words : rectal cancer; lateral lymph node; lateral lymph node dissection; total mesorectal excision; neoadjuvant chemoradiotherapy; lateral local recurrence

1. INTRODUCTION

Lateral lymph nodes (LLNs) are important in locally advanced low rectal cancer, particularly in managing lateral local recurrence (LLR).[1-4] The pattern of local recurrence (LR) changed after the adoption of total mesorectal excision (TME) surgery, placing more importance on LLR.[5,6] LLN metastasis has unfavorable oncological outcomes, including LLR and survival rate.[6-8] Although TME has become the gold standard surgery for rectal cancer because of reduced LR rate,[9] the treatment strategy for controlling LLNs is controversial and varies geographically.[10-12] Traditionally, Western countries considered LLN metastasis a systemic disease, favoring neoadjuvant chemoradiotherapy (nCRT) with TME.[13,14] In contrast, the Japanese Society for Cancer of the Colon and Rectum Guidelines recommend lateral lymph node dissection (LLND) alongside TME as the standard treatment, considering LLN as a locoregional disease.[4,10,15] However, neither approach alone adequately controls LLN metastasis or LLR,[2,16,17] leading to both strategies being adopted.

Selective LLND combined with nCRT shows oncological benefits while minimizing operative morbidity and nerve function disorders associated with LLND.[14,18-20] Recent studies discussed selecting high-risk patients for additional LLND, based mainly on preoperative radiological findings, especially LLN size.[21-23] However, no consensus has been reached for selecting high-risk patients for LLND. In addition, most proposals have focused on the largest LLN size as the solitary factor in determining LLND. We hypothesized it would be beneficial to determine LLND necessity based on various tumor features and the specific LLN status.

The surgical extent of LLND is another issue in LLN control. Because of the lack of standardized surgical techniques, differences in surgeon preferences, and anatomical accessibility, the extent of LLN removal after LLND can vary from node picking to full-extent LLND.[24] Despite LLND, targeted lymph nodes (LNs) observed in preoperative imaging may persist after incomplete LLND. This result could lead to insufficient treatment of LLNs and affect oncological outcomes.

Therefore, this study aimed to identify the clinical and radiological factors associated with LLR and develop scoring systems for selective LLND after nCRT in locally advanced low rectal cancer. In addition, we assessed the completeness of LLND by analyzing targeted LLNs through imaging studies.

2. MATERIALS AND METHODS

2.1. Patient selection

The Institutional Review Board of Severance Hospital approved this retrospective study and waived the requirement for informed consent. Patients with rectal cancer who underwent nCRT and curative TME at Severance Hospital, Seoul, Republic of Korea, between January 2010 and December 2018 were retrospectively reviewed via electronic medical records. During the study period, when LLND was performed at our institution, there was no established criteria for enlarged LLN size. As a result, LLND was additionally performed based on magnetic resonance imaging (MRI) findings or the surgeon's preference. Subsequently, 1185 patients who underwent both pretreatment and restaging rectal MRIs were selected. The study included patients with locally advanced rectal cancer (i.e., mrT3 or mrT4) within 8 cm of the anal verge on MRI and excluded patients with distant metastasis or short-course preoperative radiotherapy. Accordingly, 607 patients were eligible for the main study population and the development group for the scoring systems. During the same period, same criteria were applied to patients at the Gangnam Severance Hospital, Seoul, Republic of Korea, resulting in 144 patients to be an independent validation group (Fig. 1).

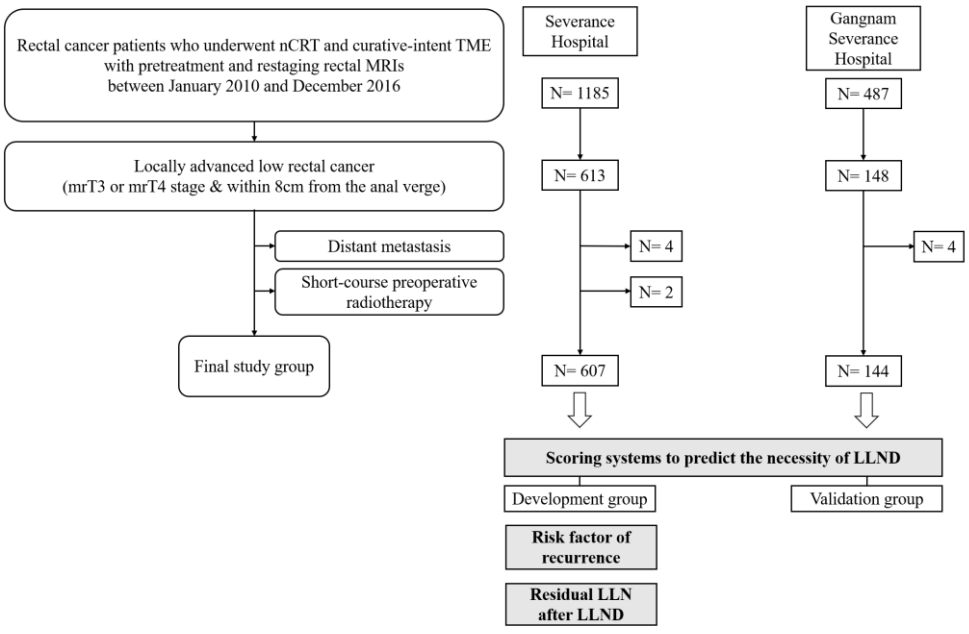

Fig. 1. Flow diagram illustrating the patient selection process. The numbers denoted by N represent the respective patient counts.

2.2. Treatments and follow-up

nCRT consists of standard, long-course radiotherapy with a total dose of 50.4 Gy of external beam radiation and concurrent chemotherapy, including 5-fluorouracil/leucovorin, capecitabine, or paclitaxel plus ifosfamide. Typically, our institute includes the internal iliac and obturator nodes in the standard irradiation field. In our institution, LLND generally involves standardized resection including the internal iliac and obturator compartments. The external iliac compartment is included in the extended dissection field only when enlarged LLNs are observed on pretreatment MRI. Curative-intent surgery was performed 6–8 weeks after completing nCRT. Adjuvant chemotherapy was also administered based on the pathological results and National Comprehensive Cancer Network guidelines.[25] Patient follow-ups were conducted at 3-month intervals for the first 3 years, at 6-month intervals for the next 2 years, and annually after that. Follow-up tests included physical examination, endoscopy, chest radiography, serum carcinoembryonic antigen (CEA), and abdominopelvic CT (APCT). If recurrence was suspected, histological confirmation, MRI, or fluorodeoxyglucose-positron emission tomography were performed for further assessment. Disease recurrence was diagnosed using radiological imaging or histologically, if possible.

2.3. Data collection

Clinical, laboratory, and pathological data were collected. The primary endpoints for the development group were LLR (any tumor recurrence in the lateral compartment bearing the LLN), distant recurrence (DR; any tumor recurrence outside the pelvic cavity), and recurrence-free survival (RFS); the presence and duration of each event were recorded. The criteria used for the scoring models to predict the necessity of LLND were 1) the LLN metastasis was confirmed pathologically if LLND was conducted with TME, and 2) LLR occurred within 3 years after the initial treatment regardless of whether LLND was performed. The variables related to LLN and LLR were categorized into right and left sides to convey that the features of the corresponding side of the LLN influence specific pelvic side LLN metastasis or LLR.

2.4. Imaging protocol

Pretreatment and restaging rectal MRI scans were conducted using a 3.0-T MR scanner (Magnetom Tim Trio, Siemens Medical Solutions, Germany; or Ingenia, Philips Medical Systems, The Netherlands) equipped with a pelvic phased-array surface coil. To minimize bowel peristalsis, 20 mg of scopolamine butyl bromide was injected intramuscularly approximately 5 min before the MRI examination. If the mass was presumed to be located at the middle or lower rectum level, an

endorectal administration of 50–100 mL of sonographic transmission gel was performed. T2-weighted images were acquired in the sagittal, axial, oblique-axial, and oblique-coronal planes. The scan protocol for the T2-weighted fast spin-echo sequence had a repetition time/echo time of 4714–6000 msec/110–113 msec, using a 320×320 mm matrix with a section thickness/gap of 3 mm/3 mm. Restaging MRIs were conducted 3–6 weeks after completion of nCRT and 2–6 weeks before surgery.

The first postoperative follow-up APCTs were performed using various machines with intravenous contrast agents and included the portal venous phase covering the pelvic cavity. These scans were analyzed to determine whether LLND was performed along with curative-intent TME. The mean duration between surgery and the first follow-up APCT was 13 weeks (range, 1–48 weeks).

2.5. Image analysis

All images were analyzed using a Picture Archiving and Communication System (Centricity, Version 4.0; GE Healthcare, Chicago, IL, USA). The image analysis used a computerized radiological database of rectal MRI scans, containing structured formats for rectal cancer interpretations from routine clinical practice. Throughout the study period, this database was produced by six radiologists, each with more than five years of experience in interpreting rectal MRIs.

For each patient, the investigator blinded to clinical information and outcomes, extracted the primary tumor features from MRI records in the database. The following tumor features were determined: distance from tumor distal margin to the anal verge, location of the tumor distal margin according to anatomical landmarks (below the line connecting the symphysis pubis mid-point and sacral promontory/peritoneal reflection/sacrococcygeal junction, respectively), MR tumor stage (mrT and mrN, according to the standard American Joint Committee on Cancer 7th and 8th edition criteria),[26,27] circumferential resection margin (CRM) status, extramural venous invasion (EMVI), and MRI-based tumor regression grade (mrTRG). The CRM status was categorized into 3 groups based on the distance between the tumor deposits and the CRM: >2 mm (negative), 0–2 mm (threatening), and abutment or penetration (involvement). EMVI indicates an intravenous tumor that extends beyond the muscularis propria. Positive EMVI corresponded to an MRI-EMVI score of 3 (slightly expanded contour or caliber of tumor-involved vessels) or 4 (obvious irregular vessel contour or nodular expansion of tumor-involved vessels) in the MRI-EMVI scoring system of Smith et al.[28] The mrTRG consists of five scales from grades 1 to 5

assessing the tumor response after nCRT on restaging MRI.[29] All features, except mrTRG, were recorded based on pretreatment MRI.

Detailed LLN features were not included in the database and were retrospectively analyzed by the investigator. The LLNs were assessed by recording the short axis (SA) size and location of the enlarged LLNs (sides and compartments). Enlarged LLNs were defined as those with a SA of ≥7 mm, according to recently suggested criteria.[21,23] The SA size of LLN was categorized as <7 mm, 7-12 mm, and ≥12 mm. The 12 mm criterion was added for more detailed analysis of LLNs ≥7 mm. LLNs were considered nonresponsive if any node had an SA >4 mm on restaging MRI after nCRT.[21] If multiple LLNs were present in a single compartment, the largest was recorded. Patients with enlarged LLNs on both right and left sides were counted as two cases of pelvic sides, each having the same clinical and primary tumor features but differing LLN features per side. Patients with none or only one-sided LLNs were counted as one pelvic side. The final numbers of analyzed pelvic sides were 629 and 154 in development and validation groups, respectively (Fig. 1, Fig. 2).

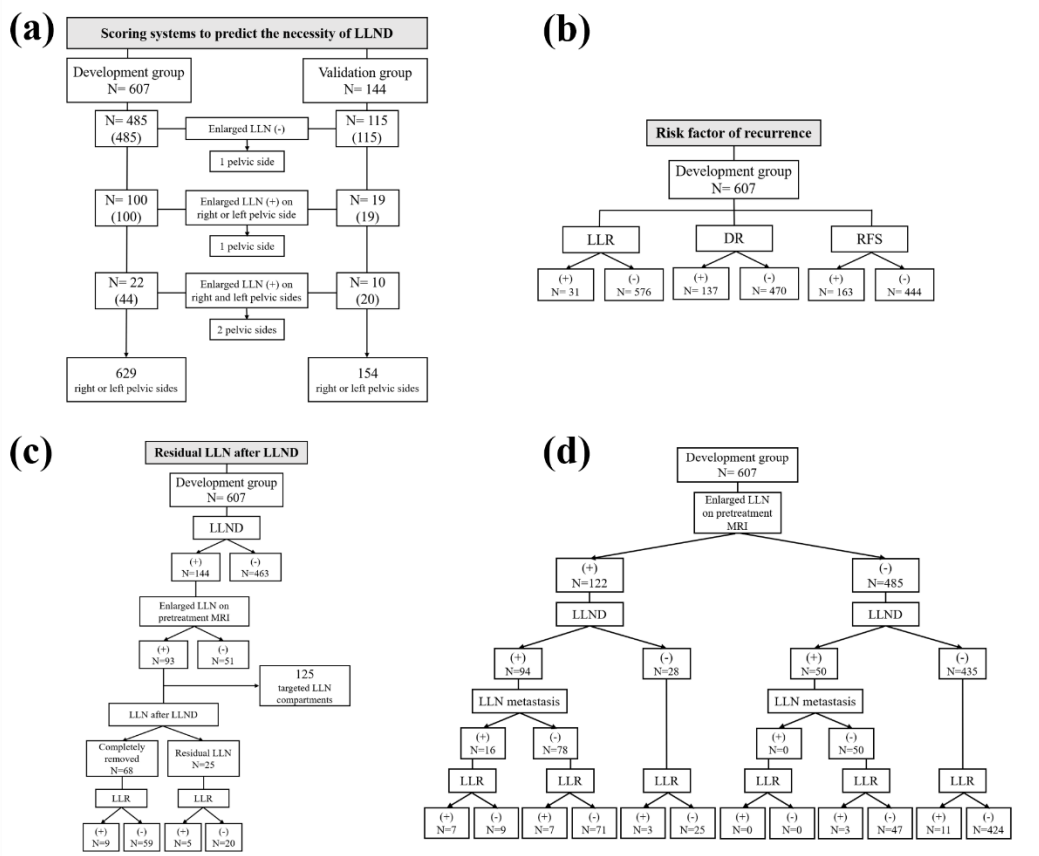

Fig. 2. Detailed flowchart for each analysis (A), (B), (C), and overview of patients with enlarged LLN in development group (D). The numbers denoted by N represent the respective patient counts. In (A), the number in parentheses indicates the number of analyzed pelvic sides. In (D), each group is detailed by the presence of enlarged LLNs, specifying whether LLND was performed, LLN metastasis was surgically confirmed, and LLR occurred.

LLN locations were further divided into five compartments: external iliac, proximal internal iliac, distal internal iliac, proximal obturator, and distal obturator (Fig. 3) to evaluate LLND extent. The external iliac compartment is located close to the external iliac vessels from the bifurcation of the common iliac vessels to the inguinal ligament. The internal iliac and obturator compartments were divided into proximal and distal compartments bordered by the infrapiriformis foramen. The proximal internal iliac compartment was located medial to the lateral border of the main trunk of the internal iliac vessels at the level of the bifurcation of the common iliac vessels to the upper

margin of the infrapiriformis foramen. The distal internal iliac compartment was located at the level of the infrapiriformis foramen and below, close to the internal iliac vessel branches (superior/inferior vesical, vaginal, and uterine vessels). The proximal obturator compartment was located lateral to the proximal internal iliac compartment at the same level. The distal obturator compartment was located at the infrapiriformis foramen level and below, close to the obturator vessels and nerves. In cases where LLND was performed with TME, each enlarged LLN observed on pretreatment MRI was analyzed on postoperative APCT to confirm its surgical removal. LLND was considered incomplete if the LLN was still visible on postoperative APCT. The compartment of the residual LLN was recorded in these cases.

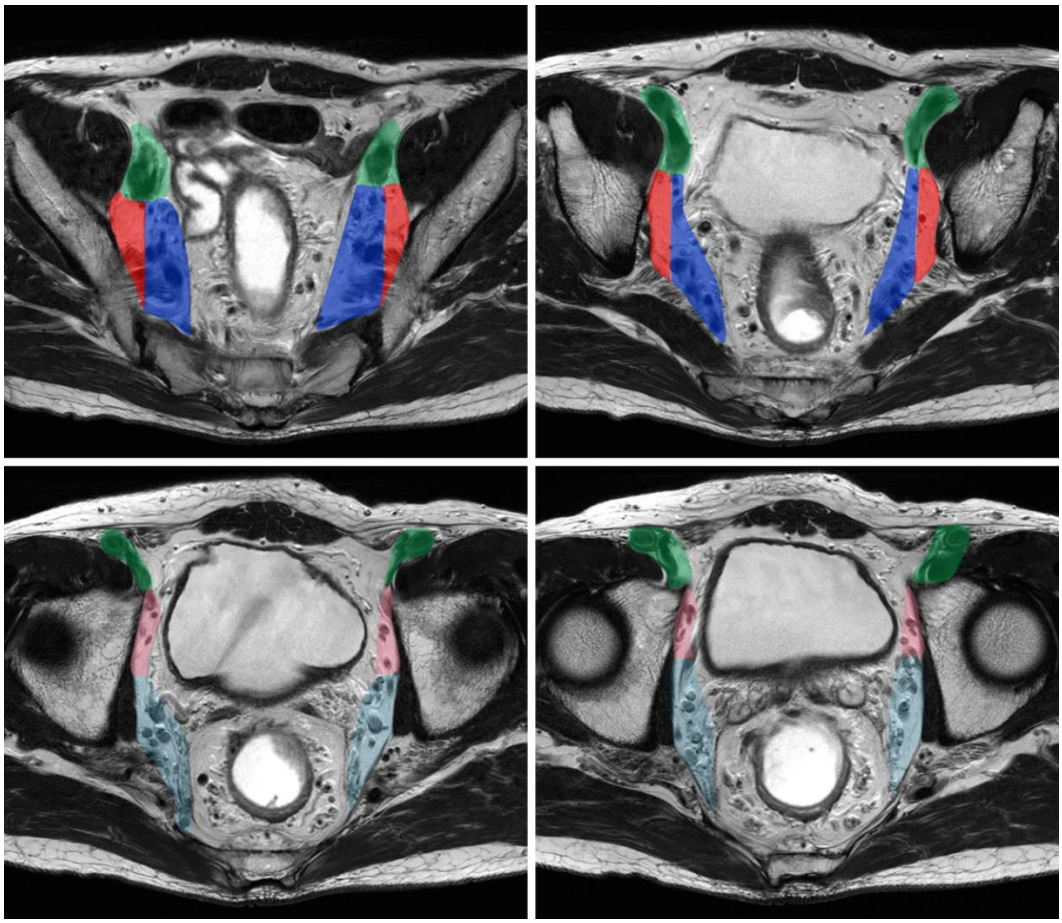

Fig. 3. Compartments of LLNs (green: external iliac, deep blue: proximal internal iliac, light blue: distal internal iliac, deep red: proximal obturator, light red: distal obturator). The

infrapiriformis foramen divides the proximal and distal compartments of the internal iliac and obturator lymph nodes.

2.6. Statistical analysis

Baseline characteristics were presented as the median (interquartile range [IQR]) or number (%). Fisher's exact or chi-squared tests compared categorical variables, and Mann–Whitney U test compared continuous variables between development and validation groups. Fisher's exact test compared compartments of residual LLNs after LLND. Univariable Cox regression analyses identified variables associated with LLR, DR, and RFS in the development group, with significant variables undergoing multivariable analyses.

Logistic regression developed scoring systems in the development group, and Bootstrap backward selection with 1000 resamples prioritized variables with the highest selection frequency for multivariable analyses.[30] Scoring points were calculated by the ratio of each variable's beta regression coefficient to the reference category.[31] Discrimination ability was assessed with receiver operating characteristic (ROC) curve and area under the curve (AUC). Optimal cut-off values were determined based on the highest sum of sensitivity and specificity. The external validation with same analyses were conducted in the validation group. To develop scoring systems, a side-specific analysis was performed, with the 44 pelvic sides of 22 patients with bilateral enlarged LLNs counted independently. Since the number of duplicate cases was small, we assumed accounting for correlation would not significantly affect the results, so any consideration for correlation was not taken.

Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA) and R package (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

3. RESULTS

3.1. Patient baseline characteristics

The study included 607 (median age, 60 years [IQR, 51–68]; 379 male) patients in the development group. The detailed clinical characteristics are presented in Table 1. On pretreatment rectal MRI, 122 patients (20.1%) had enlarged LLNs, and 144 patients (23.7%) underwent concomitant LLND with curative-intent TME after CRT. The median follow-up duration was 48 months (IQR 31–64). During follow-up, 31 patients (5.1%) developed LLR, and 137 (22.6%)

developed DR. The validation group comprised 144 patients (median age, 60 years [IQR, 51–67]; 97 male). None of the baseline characteristics in the validation group differed significantly from those in the development group, except for the type of surgery and ypN stage, and 12 patients (8.3%) underwent LLR.

Table 1. Baseline characteristics of the development and validation groups

Characteristics	**Development group (n = 607)**	**Validation group (n = 144)**	***p***
Age (years)*	60.00 (51.00–68.00)	59.50 (51.00–66.75)	0.49
Sex			0.27
Male	379 (62.4%)	97 (67.4%)	
Female	228 (36.6%)	47 (32.6%)	
Pre-CRT CEA (ng/mL)*	3.54 (1.91–8.12)	3.80 (2.03–7.08)	0.89
Tumor location (from distal margin to the anal verge; cm)*	5.50 (3.70–6.90)	5.00 (4.00–7.00)	0.57
Tumor location (distal margin)			0.70
below the peritoneal reflection	204 (33.6%)	46 (31.9%)	
below the sacrococcygeal junction	403 (66.4%)	98 (68.1%)	
mrT stage			0.70
mrT3a–b	306 (50.4%)	70 (48.6%)	
mrT3c–d/cT4	301 (49.6%)	74 (51.4%)	
mrN stage			0.10
cN0	173 (28.5%)	30 (20.8%)	
cN1	206 (33.9%)	48 (33.3%)	
cN2	228 (37.6%)	66 (45.8%)	
LLN SA ≥7 mm on pretreatment MRI			0.99
No	485 (79.9%)	115 (79.9%)	

Yes	122 (20.1%)	29 (20.1%)	
Type of surgery			
uLAR	250 (41.2%)	64 (44.4%)	<0.01
LAR	283 (46.6%)	75 (52.1%)	
APR	74 (12.2%)	5 (3.5%)	
LLND			0.20
No	463 (76.3%)	117 (81.2%)	
Yes	144 (23.7%)	27 (18.8%)	
Adjuvant chemotherapy			0.06
No	112 (18.5%)	17 (11.8%)	
Yes	495 (81.5%)	127 (88.2%)	
ypT stage			0.11
ypT0	122 (20.1%)	23 (16.0%)	
ypTis	7 (1.2%)	2 (1.4%)	
ypT1	35 (5.8%)	2 (1.4%)	
ypT2	149 (24.5%)	34 (23.6%)	
ypT3	277 (45.6%)	77 (53.5%)	
ypT4	17 (2.8%)	6 (4.2%)	
ypN stage			0.03
ypN0	446 (73.5%)	95 (66.0%)	
ypN1	136 (22.4%)	36 (25.0%)	
ypN2	25 (4.1%)	13 (9.0%)	
R status			0.66
R0	547 (90.1%)	128 (88.9%)	
R1	60 (9.9%)	16 (11.1%)	

uLAR, ultra-low anterior resection; LAR, low anterior resection; APR, abdominoperineal resection
*Continuous variables are presented as medians with ranges in parentheses.

3.2. Risk factors for LLR, DR, and RFS in the development group

Table 2 shows univariable and multivariable Cox regression analyses results for the risk factors associated with LLR, DR, and RFS in the development group. In univariable analyses, the largest LLN size on pretreatment MRI correlated significantly with LLR. When analyzed by location, this association extended to the external iliac, internal iliac, and obturator LNs.

Nonresponsive LLN on restaging MRI, cases where LLND was performed, and the absence of adjuvant chemotherapy were also associated with higher LLR risk. In multivariable analysis, LLNs with an SA of ≥12 mm and non-administration of adjuvant chemotherapy exhibited a significant association with LLR.

Shorter tumor distance from the anal verge, CRM distance ≤2 mm, positive EMVI, and non-administration of adjuvant chemotherapy were significant risk factors for DR and RFS in the multivariable analyses. However, none of the LLN features, except for external iliac LN with an SA of ≥12 mm, were significantly associated with DR. External and internal iliac LN sizes, and nonresponsive LLN were not significant risk factors for RFS in multivariable analysis despite their association in univariable analyses.

Table 2. Univariable and multivariable Cox regression analyses of risk factors for LLR, DR and RFS in the development group

	Univariable analysis		**Multivariable analysis**	
Variables	**HR (95% CI)**	***p****	**HR (95% CI)**	***p***
<< Lateral local recurrence>>				
<Clinical features>				
Age	0.99 (0.96, 1.02)	0.38		
Sex				
Male	Ref	-		
Female	1.10 (0.53, 2.30)	0.80		
Pre-CRT CEA (ng/mL)	1.00 (1.00, 1.01)	0.71		
LLND				
No	Ref	-	Ref	-
Yes	4.23 (2.08, 8.59)	**<0.01**	1.75 (0.61, 4.98)	0.30
Adjuvant chemotherapy				
No	Ref	-	Ref	-
Yes	0.37 (0.18, 0.79)	**0.01**	0.37 (0.17, 0.80)	**0.01**
<Primary tumor features on MRI>				
Tumor location (from distal margin to the anal verge; cm)	0.87 (0.73, 1.04)	0.12		

Tumor location (distal margin)				
below the peritoneal reflection	Ref	-		
below the sacrococcygeal junction	1.49 (0.67, 3.33)	0.33		
mrT stage				
mrT3a–b	Ref	-		
mrT3c–d/cT4	1.75 (0.85, 3.61)	0.13		
mrN stage				
mrN0	Ref	-		
mrN1	0.63 (0.20, 2.00)	0.44		
mrN2	2.09 (0.85, 4.80)	0.11		
CRM status				
Negative	Ref	-		
Threatening	1.12 (0.42, 2.94)	0.82		
Involvement	1.670 (0.63, 4.46)	0.31		
EMVI				
No	Ref	-		
Yes	2.02 (0.98, 4.18)	0.06		
mrTRG grade				
TRG1–2	Ref	-		
TRG3–5	2.96 (0.70, 12.39)	0.14		
<LLN features on MRI>[†]				
LLN size (SA)				
<7 mm	Ref	-	Ref	-
7–12 mm	3.13 (1.35, 7.23)	**<0.01**	1.48 (0.40, 5.42)	0.56
≥12 mm	17.30 (7.25, 41.29)	**<0.01**	6.06 (1.36, 26.99)	**0.02**
External iliac LN size (SA)				
<7 mm	Ref	-		
7–12 mm	0.78 (0.05, 13.53)	0.86		
≥12 mm	70.17 (10.97, 448.93)	**<0.01**		
Internal iliac LN size (SA)				
<7 mm	Ref	-		

7–12 mm	3.21 (1.38, 7.44)	**<0.01**		
≥12 mm	18.71 (7.33, 47.73)	**<0.01**		
Obturator LN size (SA)				
<7 mm	Ref	-		
7–12 mm	3.62 (1.48, 8.86)	**<0.01**		
≥12 mm	4.00 (0.54, 29.69)	0.17		
Nonresponsive LLN (SA>4 mm) on restaging MRI				
Absence	Ref	-	Ref	-
Presence	6.46 (3.14, 13.32)	**<0.01**	1.97 (0.64, 6.08)	0.24
<<Distant recurrence>>				
<Clinical features>				
Age	0.85 (0.78, 0.92)	**<0.01**	0.87 (0.78, 0.98)	**0.02**
Sex				
Male	Ref	-		
Female	0.87 (0.62, 1.23)	0.43		
Pre-CRT CEA (ng/mL)	1.00 (0.99, 1.00)	0.59		
LLND				
No	Ref	-		
Yes	1.07 (0.72, 1.57)	0.74		
Adjuvant chemotherapy				
No	Ref	-	Ref	-
Yes	0.62 (0.42, 0.92)	**0.02**	0.54 (0.36, 0.82)	**<0.01**
<Primary tumor features on MRI>				
Tumor location (from distal margin to the anal verge; cm)	0.85 (0.78, 0.92)	**<0.01**	0.87 (0.78, 0.98)	**0.02**
Tumor location (distal margin)				
below the peritoneal reflection	Ref	-	Ref	-
below the sacrococcygeal junction	1.56 (1.06, 2.29)	**0.02**	0.89 (0.53, 1.49)	0.65
mrT stage				
mrT3a–b	Ref	-		

mrT3c–d/cT4	1.28 (0.92, 1.79)	0.15		
mrN stage				
mrN0	Ref	-		
mrN1	0.99 (0.63, 1.55)	0.95		
mrN2	1.35 (0.89, 2.04)	0.16		
CRM status				
Negative	Ref	-	Ref	-
Threatening	2.22 (1.31, 3.78)	**<0.01**	1.78 (1.01, 3.16)	**0.048**
Involvement	2.62 (1.52, 4.53)	**<0.01**	1.87 (1.02, 3.43)	**0.04**
EMVI				
No	Ref	-	Ref	-
Yes	1.49 (1.04, 2.13)	**0.03**	1.48 (1.02, 2.15)	**0.04**
mrTRG grade				
TRG1–2	Ref	-		
TRG3–5	0.99 (0.63, 1.56)	0.95		
<LLN features on MRI>				
LLN size (SA)				
<7 mm	Ref	-		
7–12 mm	1.15 (0.74, 1.77)	0.54		
≥12 mm	1.91 (0.93, 3.93)	0.08		
External iliac LN size (SA)				
<7 mm	Ref	-	Ref	-
7–12 mm	1.69 (0.66, 4.36)	0.27	1.57 (0.58, 4.28)	0.37
≥12 mm	14.73 (4.14, 52.46)	**<0.01**	4.94 (1.14, 21.40)	**0.03**
Internal iliac LN size (SA)				
<7 mm	Ref	-		
7–12 mm	1.22 (0.76, 1.96)	0.42		
≥12 mm	2.22 (0.98, 5.05)	0.06		
Obturator LN size (SA)				
<7 mm	Ref	-		
7–12 mm	0.78 (0.37, 1.63)	0.51		

≥12 mm	0.35 (0.02, 5.70)	0.46		
Nonresponsive LLN (SA>4 mm) on restaging MRI				
Absence	Ref	-		
Presence	1.55 (0.95, 2.51)	0.08		
<<Recurrence-free survival>>				
<Clinical features>				
Age	0.84 (0.78, 0.91)	**<0.01**	0.86 (0.77, 0.96)	**<0.01**
Sex				
Male	Ref	-		
Female	0.91 (0.66, 1.24)	0.53		
Pre-CRT CEA (ng/mL)	1.00 (0.99, 1.00)	0.48		
LLND				
No	Ref	-		
Yes	1.26 (0.89, 1.78)	0.19		
Adjuvant chemotherapy				
No	Ref	-	Ref	-
Yes	0.62 (0.43, 0.90)	**0.01**	0.56 (0.39, 0.82)	**<0.01**
<Primary tumor features on MRI>				
Tumor location (from distal margin to the anal verge; cm)	0.84 (0.78, 0.91)	**<0.01**	0.86 (0.77, 0.96)	**<0.01**
Tumor location (distal margin)				
below the peritoneal reflection	Ref	-	Ref	-
below the sacrococcygeal junction	1.67 (1.17, 2.39)	**<0.01**	0.98 (0.61, 1.57)	0.92
mrT stage				
mrT3a–b	Ref	-	Ref	-
mrT3c–d/cT4	1.41 (1.03, 1.92)	**0.03**	1.27 (0.88, 1.83)	0.20
mrN stage				
mrN0	Ref	-		
mrN1	0.92 (0.61, 1.39)	0.69		
mrN2	1.31 (0.90, 1.91)	0.16		

CRM status				
Negative	Ref	-	Ref	-
Threatening	2.31 (1.42, 3.77)	**<0.01**	1.81 (1.07, 3.06)	**0.03**
Involvement	2.76 (1.67, 4.57)	**<0.01**	1.67 (0.93, 3.00)	0.08
EMVI				
No	Ref	-	Ref	-
Yes	1.54 (1.11, 2.13)	**0.01**	1.43 (0.98, 2.06)	0.06
mrTRG grade				
TRG1–2	Ref	-		
TRG3–5	1.10 (0.72, 1.70)	0.66		
<LLN features on MRI>				
LLN size (SA)				
<7 mm	Ref	-	Ref	-
7–12 mm	1.27 (0.82, 1.96)	0.29	1.30 (0.52, 3.24)	0.58
≥12 mm	2.63 (1.29, 5.37)	**<0.01**	4.39 (0.50, 38.36)	0.18
External iliac LN size (SA)				
<7 mm	Ref	-	Ref	-
7–12 mm	1.35 (0.53, 3.47)	0.53	1.28 (0.40, 4.12)	0.68
≥12 mm	12.99 (3.66, 46.07)	**<0.01**	8.59 (0.69, 107.52)	0.10
Internal iliac LN size (SA)				
<7 mm	Ref	-	Ref	-
7–12 mm	1.27 (0.82, 1.96)	0.29	1.30 (0.52, 3.24)	0.58
≥12 mm	2.63 (1.29, 5.37)	**<0.01**	4.39 (0.50, 38.36)	0.18
Obturator LN size (SA)				
<7 mm	Ref	-		
7–12 mm	0.90 (0.47, 1.70)	0.74		
≥12 mm	0.62 (0.09, 4.45)	0.64		
Nonresponsive LLN (SA>4 mm) on restaging MRI				
Absence	Ref	-	Ref	-
Presence	1.79 (1.17, 2.74)	**<0.01**	1.33 (0.64, 2.74)	0.44

HR, hazard ratio

*Significant values with $p < 0.05$ are indicated in bold.

†All LLN features, except for nonresponsive LLN, were evaluated using pretreatment MRI.

3.3. Development of scoring systems to predict the necessity of LLND

In the development group, 629 pelvic sides were analyzed for LLN status. Among them, 24 (3.8%) required LLND due to LLN metastasis on surgical dissection or developed ipsilateral LLR within 3 years. The largest LLN size (overall and by compartment), positive EMVI, and nonresponsive LLN were significant ($p < 0.05$) in univariable logistic regression. Multivariable analyses derived scoring systems (Table 3, Table 4). Model 1 included LLN size and EMVI. Model 2 was obtained by selecting variables other than overall LLN size to reflect more detailed factors, including internal iliac and obturator LN sizes, EMVI, and nonresponsive LLN.

Table 3. Univariable and multivariable logistic regression analyses of risk factors for the necessity of LLND in the development group

	Univariable analysis		**Multivariable analysis**			
			Model 1		**Model 2**	
Variables	**OR (95% CI)**	***p****	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
<Clinical features>						
Age	0.97 (0.94, 1.01)	0.12				
Sex						
Male	Ref	-				
Female	1.44 (0.63, 3.27)	0.38				
Pre-CRT CEA (ng/mL)	1.00 (0.98, 1.01)	0.69				
<Primary tumor features on MRI>						
Tumor location (from distal margin to the anal verge; cm)	1.03 (0.84, 1.27)	0.78				
Tumor location (distal margin)						
below the peritoneal reflection	Ref	-				
below the sacrococcygeal junction	0.81 (0.35, 1.89)	0.63				

mrT stage						
mrT3a–b	Ref	-				
mrT3c–d/cT4	1.17 (0.52, 2.65)	0.71				
mrN stage						
mrN0	Ref	-				
mrN1	0.66 (0.18, 2.50)	0.54				
mrN2	2.26 (0.81, 6.34)	0.12				
CRM status						
Negative	Ref	-				
Threatening	0.95 (0.35, 2.64)	0.93				
Involvement	0.82 (0.27, 2.48)	0.72				
EMVI						
No	Ref	-	Ref	-	Ref	-
Yes	4.17 (1.82, 9.59)	**<0.01**	2.32 (0.92, 5.99)	0.08	2.99 (1.13, 8.27)	**0.03**
mrTRG grade						
TRG1–2	Ref	-				
TRG3–5	2.02 (0.47, 8.75)	0.35				
<LLN features on MRI>†						
LLN size (SA)						
<7 mm	Ref	-	Ref	-		
7≤ <12 mm	62.17 (8.09, 477.79)	**<0.01**	56.54 (11.12, 1031.93)	**<.001**		
≥12 mm	363.00 (42.54, >999.99)	**<0.01**	287.93 (47.63, 5578.22)	**<.001**		
External iliac LN size (SA)						
<7 mm	Ref	-				
7≤ <12 mm	5.10 (1.19, 21.91)	**0.03**				

≥12 mm	27.53 (1.67, 454.96)	**0.02**		
Internal iliac LN size (SA)				
<7 mm	Ref	-	Ref	-
7≤ <12 mm	5.98 (2.36, 15.17)	**<0.01**	2.92 (0.86, 9.41)	0.07
≥12 mm	28.78 (8.17, 101.41)	**<0.01**	6.12 (1.12, 32.61)	**0.03**
Obturator LN size (SA)				
<7 mm	Ref	-	Ref	-
7≤ <12 mm	6.69 (2.44, 18.34)	**<0.01**	3.90 (1.14, 12.11)	**0.02**
≥12 mm	56.90 (8.85, 365.95)	**<0.01**	42.18 (5.05, 411.14)	**<0.01**
Nonresponsive LLN (SA>4 mm) on restaging MRI				
Absence	Ref	-	Ref	-
Presence	21.27 (8.92, 54.70)	**<0.01**	4.74 (1.43, 16.65)	**0.01**

OR, odds ratio

*Significant values with $p < 0.05$ are indicated in bold.

†All LLN features, except for nonresponsive LLN, were evaluated using pretreatment MRI.

Table 4. Scoring systems predicting the necessity of LLND after nCRT in locally advanced low rectal cancer

		Score
Model 1		
LLN size (SA)	<7 mm	0
	7–12 mm	5
	≥12 mm	7
EMVI	No	0
	Yes	1
Model 2		
Internal iliac LN size (SA)	<7 mm	0
	7–12 mm	1
	≥12 mm	2
Obturator LN size (SA)	<7 mm	0
	7–12 mm	1
	≥12 mm	3
EMVI	No	0
	Yes	1
Nonresponsive LLN (SA>4 mm) on restaging MRI	Absence	0
	Presence	1

The AUCs of Models 1 and 2 were 0.92 (95% confidence interval [CI]: 0.86–0.97) and 0.90 (95% CI: 0.84–0.96), with no significant difference according to DeLong's method (p = 0.16) (Fig. 4). Model 1 showed the highest sensitivity (95.83%), followed by Model 2 (79.17%) using optimal cut-offs of 3 and 2, respectively (Table 5). Specificities of Models 1 and 2 were 80.00% and 88.26%, respectively. These results were compared with the established criterion currently in use, which considers only nonresponsive LLNs on restaging MRI. While this criterion demonstrated the highest specificity (91.4%), it showed the lowest sensitivity (66.67%).

In the validation group, the ROC curves showed AUCs of 0.96 (95% CI: 0.93–0.99), 0.96 (95% CI: 0.92–0.99) for Models 1 and 2, respectively (Fig. 4). AUCs were not significantly different between Models 1 and 2 (p = 0.97), as in the development group. The sensitivities and specificities of the scoring models with the same optimal cut-offs in the development group demonstrated similar tendencies; Model 1 had the highest sensitivity (100%) and the lowest specificity (84.56%) (Table 5).

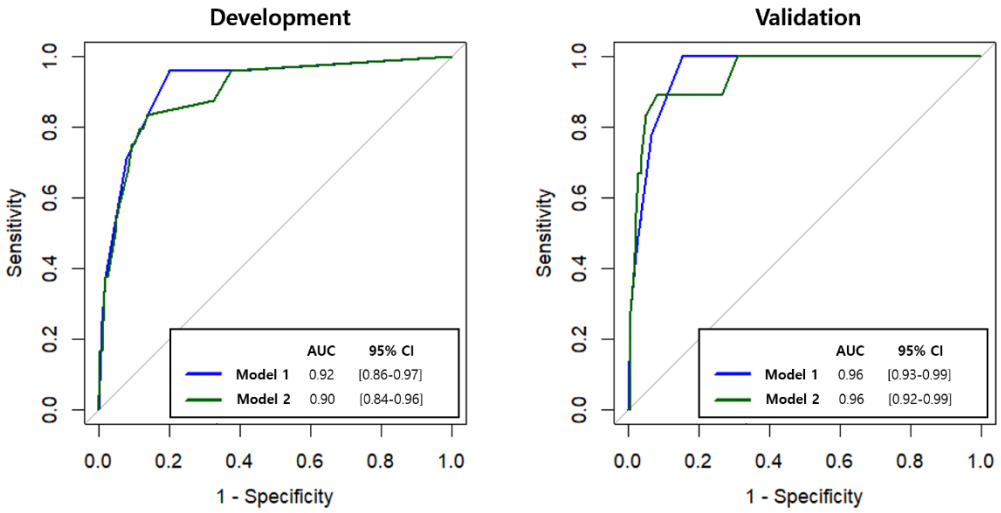

Fig. 4. Performances of the two scoring models in the development and validation groups, presenting the receiver operating characteristic curves and area under the curves. AUC, area under the curves; CI, confidence interval.

Table 5. Comparisons of sensitivity and specificity in scoring models according to the optimal cut-offs and established criterion to perform LLND

	Cut-off	Development group		Validation group	
		Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
Model 1	≥3	95.83% (23/24)	80.00% (484/605)	100.00% (18/18)	84.56% (115/136)
Model 2	≥2	79.17% (19/24)	88.26% (534/605)	88.89% (16/18)	91.91% (125/136)
Established criterion*	N/A	66.67% (16/24)	91.40% (553/605)	77.78% (14/18)	94.85% (129/136)

N/A, not applicable

*The established criterion relies solely on the presence of nonresponsive LLNs on restaging MRI.

3.4. Assessment of residual LLNs after LLND

Of 607 patients in the development group, 144 (23.7%) underwent LLND on one or both pelvic sides during curative surgery; 93 patients had enlarged targeted LLNs on pretreatment MRI. In 68 (73.1%) patients, all targeted LLNs seen on preoperatively were absent on postoperative APCT along with postoperative changes, indicating complete removal by LLND (Fig. 5). However, in 25 (26.9%) patients, LLNs remained intact on postoperative APCT despite LLND on

that side (Fig. 5). The targeted LLN compartments on the right and left sides were counted separately. Among the 5 compartments, the distal internal iliac compartment had the highest rate (14/34, 41.2%) of residual LLNs after LLND (Table 5). The rate of residual LLNs after LLND differed significantly across compartments (p = 0.02).

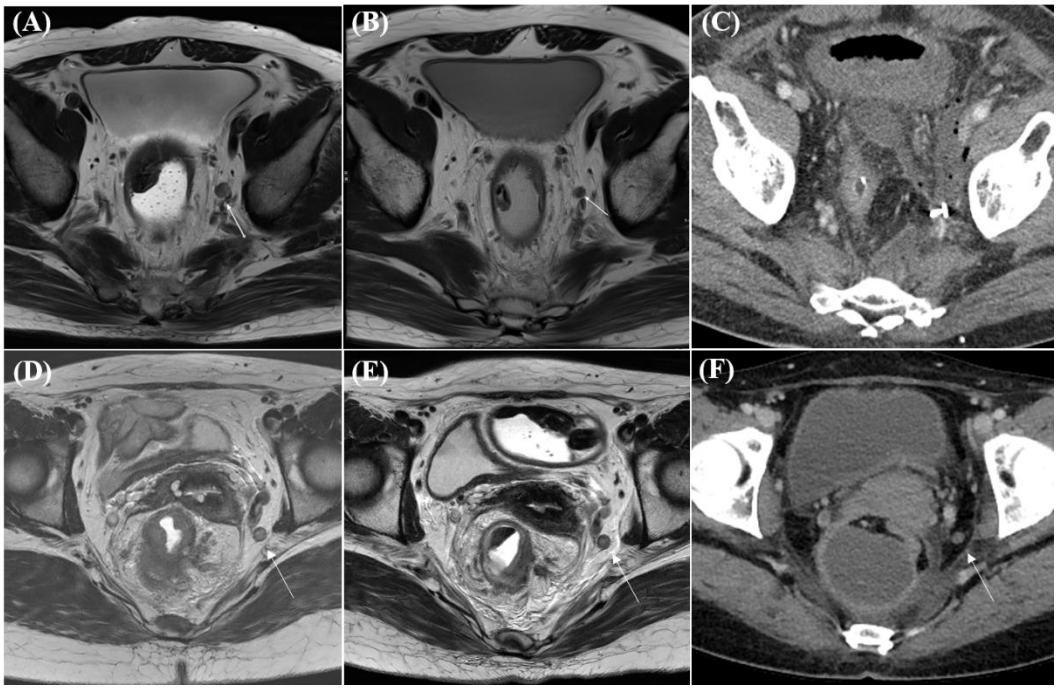

Fig. 5. Assessment of residual LNs after LLND. (A), (B), and (C) show case where LLNs were successfully removed through LLND, while (D), (E), and (F) display case where LLNs remained after the procedure. The left proximal internal iliac LN (arrows) in pretreatment MRI (A) and restaging MRI (B) was not visualized in the postoperative APCT (C), leaving postoperative change with fluid and air bubbles. This proximal internal iliac LN was dissected and the left LLN metastasis was reported in the pathologic report. Another case of left distal internal iliac LN (arrows) showed a remaining LLN in the postoperative APCT (F), compared with pretreatment MRI (D) and restaging MRI (E). The surgical record included the full extent of LLND, and pathology reported no LLN metastasis despite the residual distal internal iliac LN.

Table 6. Assessment of LLN removal among the patients who underwent LLND and had targeted LLNs (LLN with a SA ≥7 mm) on pretreatment MRI in the development group, according to the targeted LLN compartments

	Total	Completely removed LLN	Residual LLN	*p*
Patients who underwent LLND and had targeted LLNs on pretreatment MRI	93	68 (73.1%)	25 (26.9%)	
Targeted LLN compartment*	125			0.02
External iliac	12	8 (66.7%)	4 (33.3%)	
Proximal internal iliac	44	38 (86.3%)	6 (13.6%)	
Distal internal iliac	34	20 (58.8%)	14 (41.2%)	
Proximal obturator	28	23 (82.1%)	5 (17.9%)	
Distal obturator	7	7 (100%)	0 (0%)	

*The targeted LLN compartments were counted separately on each patient's right and left pelvic sides.

4. DISCUSSION

This study developed MRI-based scoring systems to assist in the decision-making process for LLND, specifically immediately before surgery. These systems, tailored to the left and right pelvic sidewalls, enable risk assessment on each side to inform surgical decisions regarding LLND. Model 1 focused on overall LLN size and EMVI on pretreatment MRI. Model 2 provided a detailed analysis based on internal iliac and obturator LN sizes and additionally included the LLN size change from restaging MRI, which served as the single variable in the established criterion. Application of the optimal cut-off revealed that Models 1 had the highest sensitivity, and Model 2 demonstrated moderate sensitivity and specificity, compared with the established criterion, which showed the highest specificity.

The endpoint of LLND was determined by considering both pathologically proven LLN metastasis or LLR within 3 years, encompassing all cases with or without LLND, which differs from previous studies that focused only on LLR or LLN metastasis separately.[21,23,32-34] Persistent LLN metastases after nCRT indicate the need for LLND. LLR within 3 years post-surgery suggests that LLND should have been considered during the initial TME because short-term LLR is more likely to originate from preexisting viable tumor tissue in the LLNs at the time of curative-intent TME.

Notable imaging-based predictors for LLN metastasis and LLR are LLN sizes before and after nCRT. Recent studies identified an SA of ≥7 mm in the LLNs on pretreatment MRI significantly predicts LLR and LLN metastasis,[21,23,34,35] which was adopted to identify enlarged LLN in our study. Furthermore, we introduced an additional size cut-off of 12 mm, noting larger LLNs correlated with higher recurrence risk and higher scores in our models. Model 2 further differentiated obturator and internal iliac LNs. The obturator LNs with a larger size (SA ≥12 mm) had higher scores and greater predicted values than internal iliac LNs with the same size range. Compared with the internal iliac compartment, positive nodes in the obturator compartment may indicate more upward lymphatic spread and metastatic progression, thereby increasing the likelihood of LLND.[20]

On restaging MRI following nCRT, persistent enlargement of LLNs correlates with LLR or positive pathological LLN using an SA size cut-off of 4–5 mm.[21,22] As Model 2 identified it as a significant factor, nonresponsive LLN on restaging MRI are noteworthy and served as a criterion for determining the need for LLND.[22] We additionally compared the models with the established criterion to assess the validity of using nonresponsive LLNs as the sole criterion. However, it showed a significant drawback in terms of sensitivity compared with the other models. Rather than relying solely on the nonresponsive LLN to determine the necessity for LLND, combining it with other factors was more helpful in making decisions, as demonstrated in Model 2.

We found that aside from LLNs' inherent characteristics, only EMVI significantly influenced the decision to perform LLND, leading to its inclusion in Models 1 and 2. This finding is consistent with previous studies that reported an association between EMVI and LLN metastasis.[32,33,36] Recent studies proposed nomograms for predicting LLN metastasis in low rectal cancer, incorporating the LLN SA size and EMVI as factors, similar to our study.[34,36] These two nomograms also included distance from the anal verge to the tumor as a predictive factor. In contrast, our study found that the tumor location did not significantly influence the decision to perform LLND.

Other factors we found associated with recurrence were comparable to the findings of previous studies. Although the external iliac LN was not regarded as distant metastasis in our study or in Eastern countries, the American Joint Committee on Cancer classifies external LNs as sites of distant disease rather than regional disease.[27] The association between DR and external iliac LNs with an SA ≥12 mm supports that they serve as distant metastasis sites, as none of the other LLN features exhibited an association with DR. A lower tumor location has been proposed to be associated with a higher rate of distant metastasis,[37] consistent with our results when measuring

tumor location from the anal verge. CRM status is another recognized prognostic factor for LR, survival, and distant metastasis.[38,39] Our analyses did not find CRM to significantly affect LLR risk, but CRM threatening and involvement increased DR. Adjuvant chemotherapy lowered LLR and DR incidences and enhanced RFS, contrasting previous studies suggesting its limited impact on recurrence.[40]

LLN locations were classified prioritizing vascular territory and the surgical procedure of LLND. During LLND, internal iliac LNs are dissected along the internal iliac artery until they reach the pudendal canal.[41] Thus, the LNs around the pudendal canal and distal internal iliac branches are removed as internal iliac LNs, corresponding to the internal iliac chain drainage. This contrasts with studies grouping them as obturator LNs.[21] We subdivided the internal iliac and obturator compartments into proximal and distal portions to confirm different levels of surgical accessibility, revealing a higher incidence of residual LLNs in the distal internal iliac compartment. This highlights surgical challenges in LLND around the pudendal canal, emphasizing the need for standardized surgical protocols for consistent LLN removal.

This study had limitations. First, Models 1 and 2 were more likely than the established criterion to lead to unnecessary LLND, although LLND with higher sensitivity could enhance oncological safety. Second, despite the large population, LLR events and the need for LLND were relatively rare, limiting further subgroup analyses. Additionally, one-to-one matching of LLNs on MRI with pathologic results was not possible due to the retrospective study design, which could result in false positive or negative matches from the perspective of individual LLNs. However, our evaluation of LLNs focused on selecting the side for LLND rather than the diagnostic accuracy of individual LLN metastases. Therefore, we believe one-to-one matching was not essential for our study. Meanwhile, indirect assessment of LLND, by identifying the presence of preexisting targeted LLNs on the postoperative CT, may potentially lead to an underestimation of incomplete LLND prevalence. Finally, relying on a single radiologist for MRI feature analysis limited the evaluation of interobserver variation and its potential effect on model development and validation. However, LLN size measurement by a single radiologist was based on the relatively clear criterion of the short axis. Additionally, the involvement of each of the six radiologists using a structured report form has some advantage of reflecting a real prospective clinical situation.

5. CONCLUSION

Using combined assessment of LLN size and EMVI on pretreatment and restaging MRI, our scoring systems can help decide whether to perform selective LLND along with TME after nCRT

in locally advanced low rectal cancer. Our findings are exploratory and should be interpreted cautiously due to potential biases and confounders, underscoring the need for further research to establish standardized protocols.

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ABSTRACT IN KOREAN

선행 화학방사선치료 후 국소 진행성 저위 직장암에서 선택적 측부 림프절 절제를 위한 자기공명영상 기반 점수 모델

목적

선행 화학방사선치료 후 국소 진행성 저위 직장암 환자에서 전직장간막절제술과 함께 시행하는 선택적 측부 림프절 절제술의 필요성을 예측하기 위하여 측부 국소 재발 및 측부 림프절 전이에 초점을 맞추어 점수 모델을 개발한 연구이다.

재료 및 방법

본 후향적 연구는 항문연에서 8cm 이내에 위치한 mrT3/T4 직장암으로 진단받고 선행 화학방사선치료 및 전직장간막절제술을 시행한 607명의 환자를 대상으로 하였다. 점수 모델 개발을 위해, 직장 자기공명영상(MRI)에서 관찰된 원발 종양 및 측부 림프절의 특징을 반영하여 로지스틱 회귀 분석을 수행하였다. 외부 검증은 모델들을 기존의 기준과 비교하고, 독립적인 114명 환자군에서 추가로 수행되었다. 선택적 측부 림프절 절제술 후 재발 위험 인자 및 잔존 측부 림프절에 대한 분석도 수행하였다.

결과

모델 1은 치료 전 측부 림프절 크기와 벽외 혈관 침윤을 포함하였다. 모델 2는 치료 전 내장골 및 폐쇄 림프절 크기, 벽외 혈관 침윤, 그리고 재평가 MRI에서 반응이 없는 측부 림프절을 반영하였다. 개발 집단에서 모델 1과 2는 높은 예측 성능(AUC = 0.92 및 0.90)을 보였다. 재평가 MRI에서 비반응성 측부 림프절 여부만을 고려한 기존 기준과 비교했을 때, 모델 1은 가장 높은 민감도를 보였으며, 모델 2는 중간 수준의 민감도와 특이도를 나타냈다. 이러한 소견들은 독립된 검증 집단에서도 일관되게 나타났다. 선택적 측부 림프절 절제술을 시행한 환자들 중, 원위부 내장골 구획에서 다른 구획보다 더 많은 잔존 림프절이 확인되었다($p = 0.02$).

결론

MRI에서 확인된 측부 림프절의 특징과 벽외 혈관 침윤을 활용한 점수 모델은 국소 진행성 저위 직장암에서 선행 화학방사선치료 후 선택적 측부 림프절 절제술 여부를 결정하는 데 도움을 줄 수 있다.

핵심되는 말 : 직장암; 측부 림프절; 측부 림프절 절제술; 전직장간막절제술; 선행 화학방사선치료; 측부 국소 재발