

# Lateral Nodal Features on Restaging Magnetic Resonance Imaging Associated With Lateral Local Recurrence in Low Rectal Cancer After Neoadjuvant Chemoradiotherapy or Radiotherapy

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**IMPORTANCE** Previously, it was shown in patients with low rectal cancer that a short-axis (SA) lateral node size of 7 mm or greater on primary magnetic resonance imaging (MRI) resulted in a high lateral local recurrence (LLR) rate after chemoradiotherapy or radiotherapy (CRT) with total mesorectal excision (TME) and that this risk was lowered by a lateral lymph node dissection (LLND). The role of restaging MRI after CRT with regard to LLR risk and which specific patients might benefit from an LLND is not fully understood.

**OBJECTIVE** To determine the factors on primary and restaging MRI that are associated with LLR in low rectal cancer after CRT and to formulate specific guidelines on which patients might benefit from an LLND.

**DESIGN, SETTING, AND PARTICIPANTS** In this retrospective, multicenter, pooled cohort study, patients who underwent surgery for cT3 or cT4 low rectal cancer with a curative intent from 12 centers in 7 countries from January 2009 to December 2013 were included. All patients' MRIs were rereviewed according to a standardized protocol, with specific attention to lateral nodal features. The original cohort included 1216 patients. For this study, patients who underwent CRT and had a restaging MRI were selected, leaving 741 for analyses across 10 institutions, including 651 who underwent CRT with TME and 90 who underwent CRT with TME and LLND.

**MAIN OUTCOMES AND MEASURES** The main purpose was to identify the factors on primary and restaging MRI associated with LLR after CRT with TME. Whether high-risk patients might benefit in terms of LLR reduction from an LLND was also studied.

**RESULTS** Of the 741 included patients, 480 (64.8%) were male, and the mean (SD) age was 60.4 (12.0) years. An SA lateral node size of 7 mm or greater on primary MRI resulted in a 5-year LLR rate of 17.9% after CRT with TME. At 3 years, there were no LLRs in 28 patients (29.2%) with lateral nodes that were 4 mm or less on restaging MRI. Nodes that were 7 mm or greater on primary MRI and greater than 4 mm on restaging MRI in the internal iliac compartment resulted in a 5-year LLR rate of 52.3%, significantly higher compared with nodes in the obturator compartment of that size (9.5%; hazard ratio, 5.8; 95% CI, 1.6-21.3;  $P = .003$ ). Compared with CRT with TME alone, treatment with CRT with TME and LLND in these unresponsive internal nodes resulted in a significantly lower LLR rate of 8.7% (hazard ratio, 6.2; 95% CI, 1.4-28.5;  $P = .007$ ).

**CONCLUSIONS AND RELEVANCE** Restaging MRI is important in clinical decision making in lateral nodal disease. In patients with shrinkage of lateral nodes from an SA node size of 7 mm or greater on primary MRI to an SA node size of 4 mm or less on restaging MRI, which occurs in about 30% of cases, LLND can be avoided. However, persistently enlarged nodes in the internal iliac compartment indicate an extremely high risk of LLR, and an LLND lowered LLR in these cases.

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Local recurrence rates in rectal cancer have reduced dramatically since the introduction of the total mesorectal excision (TME) technique.<sup>1</sup> These rates have been lowered further with the use of neoadjuvant chemoradiotherapy or radiotherapy (C)RT regimens in appropriate cases, decreasing overall rates of 5-year local recurrence to 5% to 10%.<sup>2-4</sup> Western surgeons have always relied on (C)RT to sterilize the lateral compartment, containing internal iliac and obturator lymph nodes, and to alleviate fears of operative morbidity and nerve function disorders associated with a lateral lymph node dissection (LLND), which is mainly performed in the East.<sup>5</sup> Furthermore, most Western clinicians consider lateral nodal disease to represent metastatic disease not amendable to cure.<sup>5,6</sup>

Single-center studies in 2015<sup>7</sup> and 2017<sup>8</sup> have shown that (C)RT with TME is not sufficient to eradicate lateral nodal disease in enlarged nodes, resulting in 30% to 40% 5-year lateral local recurrence (LLR) rates in nodes that are 10 mm or greater, with about half of patients presenting with only localized disease at the time of local recurrence diagnosis. Also, some Japanese centers that combine (C)RT with TME and LLND show excellent disease-free survival rates, suggesting that patients with lateral nodal disease can be cured.<sup>9,10</sup>

The Lateral Node Study Consortium<sup>11</sup> undertook a multicenter study including 12 centers from 7 countries, collecting data over a 5-year period and including all consecutive patients who underwent an operation for cT3 or cT4 low rectal cancer. In all patients, every series of magnetic resonance imaging (MRI) was rereviewed by a standardized protocol, examining lateral pelvic nodes and defining these according to size and the presence of malignant features and relating these to the development of locally recurrent disease. In the first publication of the Lateral Node Study Consortium with a total of 1216 patients,<sup>11</sup> it was shown that pretreatment lateral lymph node (LLN) size of 7 mm or greater resulted in an unacceptably high incidence of LLR of 19.5%, despite (C)RT with TME. Within the Lateral Node Study Consortium, several centers performed LLNDs after (C)RT, which resulted in a significantly lower rate of LLR of 5.7% in nodes of 7 mm or greater ( $P = .04$ ).

In this multicenter study, 75% of the patients who had received (C)RT underwent restaging MRI following treatment. To our knowledge, there is no consensus in the literature on whether the risk of recurrence should be determined by the primary MRI (pre-[C]RT MRI) or the restaging MRI. The goal of the current study is to assess which factors on primary and restaging MRI are associated with lateral nodal recurrence and to formulate specific guidelines on which patients might benefit from an LLND.

## Methods

### Study Participants and Patient Selection

This study included patients from 12 centers in 7 countries. All participating hospitals were asked to collect the data and to rereview the MRI scans of all consecutive patients who underwent an operation for cT3 or cT4 rectal cancer within 8 cm from the anal verge measured on MRI from January 2009 to

## Key Points

**Question** What is the role of restaging magnetic resonance imaging (MRI) after chemoradiotherapy or radiotherapy, and which specific patients might benefit from a lateral lymph node dissection (LLND)?

**Findings** In this multicenter pooled cohort study including 741 patients with low rectal cancer after chemoradiotherapy or radiotherapy, shrinkage of lateral nodes from a short-axis node size of 7 mm or greater on primary MRI to a short-axis node size of 4 mm or less on restaging MRI abolished the risk of lateral local recurrence (LLR). However, in persistently enlarged nodes (greater than 4 mm) in the internal iliac compartment on restaging MRI, the risk of LLR was high, and an LLND lowered this risk significantly.

**Meaning** Persistently enlarged nodes in the internal iliac compartment indicate a high risk of LLR, and an LLND should be seriously considered in these patients.

December 2013. Exclusion criteria were the absence of (high-quality) MRI scans, the presence of distant metastases, or a non-curative resection (R2 resection status). The treatment regimens and initial results of the 1216 patients regarding primary MRI staging have been published previously.<sup>11</sup> As stated previously, each center received institutional review board approval according to local policies. For the current analyses, patients who had not received neoadjuvant (C)RT (248 patients) or had no restaging MRI (227 patients) were excluded, leaving 741 patients (60.9%) for analyses across 10 institutions (eFigure 1 in the Supplement). Informed consent was not obtained, as deidentified data were used.

### Reassessment of MRIs

Magnetic resonance imaging reassessment guidelines have been described previously.<sup>11</sup> In short, each center used a specific protocol with a color map atlas of the pelvis for reevaluation of pretreatment and posttreatment MRIs by a local expert radiologist (eFigure 2 in the Supplement). In addition to the standard American Joint Committee on Cancer TNM staging, circumferential resection, and tumor height assessment, radiologists were asked to assess LLN status. This was based on the largest LLN identified on pretreatment MRI, of which short-axis (SA) and long-axis node size and location (internal iliac, external iliac, or obturator compartment) were recorded. The stretched benign lymph nodes, located just behind the distal part of the external iliac vein, were specifically not included in the assessment. Furthermore, the presence of malignant features, eg, internal heterogeneity or border irregularity, was also noted.

The assessment was repeated by the same radiologist on restaging MRI, recording the SA and long-axis node sizes and the presence of malignant features on the same lateral nodes after (C)RT. Shrinkage was defined as any reduction in SA node size, with shrinkage size defined as the difference in millimeters and disappearance defined as no visible node left in the compartment after (C)RT. Shrinkage rate was defined as the rate of reduction in SA size of a lymph node on the restaging MRI compared with the SA node size on primary MRI. In

Table 1. Patient Characteristics and Pathological Results

Variable	No. (%)
Total, No.	741
Sex	
Male	480 (64.8)
Female	261 (35.2)
Age, mean (SD), y	60.4 (12.0)
cT stage	
cT3	515 (69.5)
cT4	226 (30.5)
cN stage	
cN0	215 (29.0)
cN1	289 (39.0)
cN2	237 (32.0)
Location of lateral lymph node	
None visible	256 (34.5)
External iliac	32 (4.3)
Obturator	304 (41.1)
Internal iliac	149 (20.1)
Preoperative radiotherapy	
Short course	89 (12.0)
Long course	652 (88.0)
Operation	
Low anterior resection	322 (43.4)
Hartmann operation	16 (2.2)
Intersphincteric resection	102 (13.8)
(Extended) abdominoperineal resection	292 (39.4)
Pelvic exenteration	9 (1.2)
LLND	
No	651 (87.9)
Yes	90 (12.1)
Adjuvant chemotherapy	
No	433 (58.4)
Yes	262 (35.4)
Missing	46 (6.2)
ypT stage	
ypT0	120 (16.2)
ypT1	45 (6.1)
ypT2	191 (25.8)
ypT3	330 (44.5)
ypT4	55 (7.4)
ypN stage	
ypN0	513 (69.3)
ypN1	150 (20.2)
ypN2	78 (10.5)
R status	
R0	697 (94.1)
R1	44 (5.9)

Abbreviations: LLND, lateral lymph node dissection; R, residual tumor.

patients with local recurrence, imaging was rereviewed, and the recurrent site was categorized into 1 of 5 types: lateral, presacral, anastomotic site, anterior, or perineal, of which the definitions have been described previously.<sup>12,13</sup>

## Statistical Analyses

Statistical analyses were conducted using SPSS Statistics version 23 (IBM) and the survival ROC package of R version 3.4.3 (The R Foundation).<sup>14,15</sup> For median values, interquartile ranges (IQRs) were given. Individual variables were compared with Mann-Whitney *U* tests, *t* tests, and  $\chi^2$  tests, as appropriate; a 2-tailed *P* value of less than .05 was considered significant. Time-dependent receiver operating characteristic (ROC) curves for survival data and area under the ROC curves (AUCs) at 3 and 5 years after surgery were used to evaluate the predictive value of LLN size variables in relation to LLR. Survival curves for LLR, overall local recurrence, distant recurrence rates, and cancer-specific survival were calculated using the Kaplan-Meier method. To determine the risk factors, the effects of covariates were analyzed using a univariate Cox regression model. Subsequently, a multivariate analysis using covariates with a significant effect (*P* < .10) was performed, in which a *P* value of less than .05 was considered significant. Regarding response classification, no response was defined as similar outcomes in pathological T staging as in clinical T staging; tumor response was defined as any reduction in pathological T stage compared with primary clinical T stage, as long as there was still tumor left; and complete response was defined as a pathologic complete response with no (viable) tumor tissue identified.

## Results

### Patients

Of the 741 included patients, 480 (64.8%) were male, and the mean (SD) age was 60.4 (12.0) years. A total 65 patients (8.8%) had a local recurrence, 185 (25.0%) had a distant recurrence, and 107 (14.4%) died of cancer recurrence over a median (IQR) follow-up duration of 52 (37-64) months after surgery. Restaging MRIs were performed a median (IQR) of 35 (29-42) days after the final date of neoadjuvant (C)RT, and resection was performed a median (IQR) of 54 (46-71) days after (C)RT. Baseline characteristics and pathological results are shown in **Table 1**.

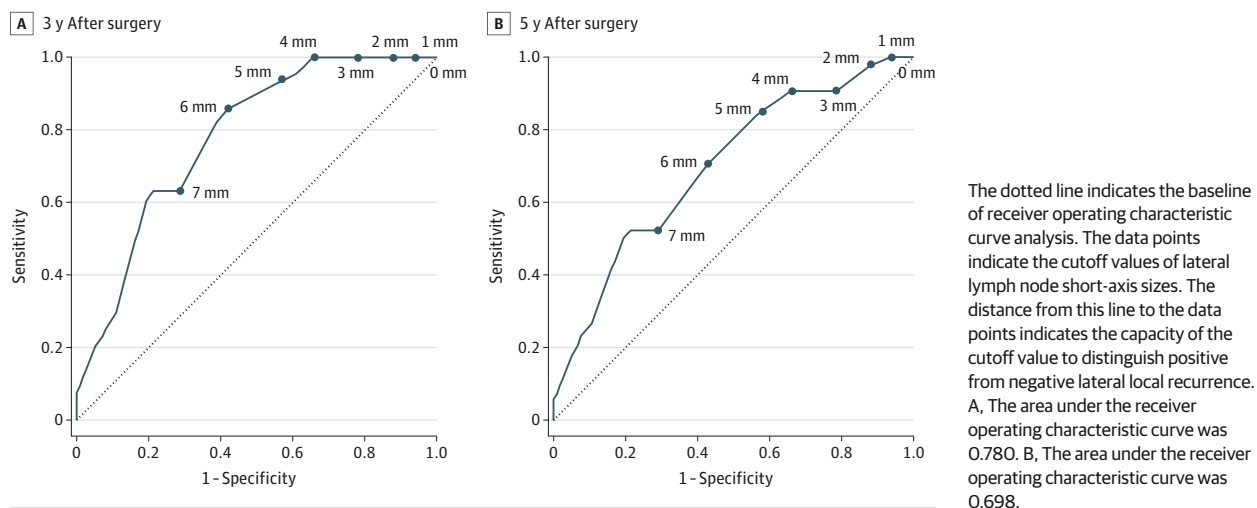
### LLN Sizes on Primary and Restaging MRI

At least 1 visible LLN was identified on primary MRI in 485 patients (65.5%). The median (IQR) SA node size of the largest LLN on primary MRI was 5.0 (4.0-7.0) mm. The LLN had disappeared on restaging MRI in 64 patients (13.2%); the chance of disappearance was 15.9% (54 of 340) in patients with pretreatment nodes smaller than 7 mm, while the chance of disappearance was only 6.9% (10 of 145) in patients with pretreatment nodes of 7 mm or greater (risk ratio, 2.3; 95% CI, 1.2-4.4; *P* = .01). Of 421 patients in whom the LLN remained visible on restaging MRI, the median (IQR) SA node size on restaging MRI was 4.0 (3.0-5.6) mm.

### Predictive Performance of SA Node Size Variables on LLR After (C)RT With TME

Of 651 patients who underwent (C)RT with TME, 33 (5.1%) developed an LLR (5-year LLR rate, 6.1%); of these, 26 (79%)

**Figure 1. Time-Dependent Receiver Operating Characteristic Curves for Short-Axis Node Size on Restaging Magnetic Resonance Imaging at 3 and 5 Years After Surgery in 651 Patients Who Underwent Chemoradiotherapy or Radiotherapy With Total Mesorectal Excision**



occurred in the first 3 years after surgery. In 96 patients (14.7%) with an SA node size of 7 mm or greater on primary MRI, the 5-year LLR rate was 17.9%, significantly higher than the 5-year LLR rate in the 555 patients (85.3%) with an SA node size smaller than 7 mm (4.1%; hazard ratio [HR], 4.6; 95% CI, 2.3-9.2;  $P < .001$ ). At 3 years after surgery, there were no LLRs in the 28 patients (29%) with an SA node size of 4 mm or less on reimaging MRI. eFigure 3 in the Supplement shows the time-dependent ROC curves for SA node size on restaging MRI, shrinkage rate, and shrinkage size at 3 and 5 years after surgery. The AUC value was the highest for SA nodes on restaging MRI; thus, this was chosen as the post-treatment reference. Figure 1 shows the time-dependent ROC curves for SA node size on restaging MRI at 3 and 5 years after surgery; in SA nodes greater than 4 mm on restaging MRI, the AUC value decreased, leaving an uncertainty in assessing risk of LLR.

### Size vs Malignant Features

In the previous Lateral Node Study Consortium publication,<sup>11</sup> it was shown that malignant features on primary MRI were not associated with LLR after multivariate analyses. In this study, malignant features on restaging MRI were present in 68 of 342 patients (19.8%) with visible nodes that underwent (C)RT with TME; they were more common in patients with an SA node size of 7 mm or greater on primary MRI (48 of 91 [53%]) than in the patients with an SA node size less than 7 mm on primary MRI (20 of 251 [8.0%]; risk ratio, 1.9; 95% CI, 1.6-2.4;  $P < .001$ ). None of the LLNs that had an SA node size of 4 mm or less on restaging MRI had any malignant features, whereas malignant features were present in 48 of 68 patients (71%) with an SA node size greater than 4 mm on restaging MRI. Univariate and multivariate analyses showed that malignant features on restaging MRI increased the risk of LLR further in LLNs with an SA node size greater than 4 mm on restaging MRI in patients that underwent (C)RT with TME (Table 2; eTable in the Supplement).

### Location of Enlarged Lateral Nodes

The location of the LLN was a significant risk factor for LLR after (C)RT with TME (Table 2; eTable in the Supplement). Enlarged external iliac nodes did not result in any LLRs (0% LLR rate) but significantly influenced distant recurrence, with a more than 2-fold risk.

Short-axis node size of 7 mm or greater on primary MRI was significantly more common in the internal iliac compartment (32 of 94 [34%]) than in the obturator compartment (56 of 274 [20.4%]; risk ratio, 1.2; 95% CI, 1.0-1.5;  $P = .008$ ). Table 3 shows LLR rates for different cutoff values in SA node size on restaging MRI for patients with LLNs of 7 mm or greater on primary MRI, separated by obturator vs internal iliac compartment. In obturator nodes, the risk of LLR was 0% in LLNs with an SA node size of 6 mm or less on restaging MRI. However, in internal iliac nodes, the 3-year LLR risk increased rapidly if SA node size was greater than 4 mm on restaging MRI. Short-axis node size of 7 mm or greater on primary MRI and greater than 4 mm on restaging MRI in the internal iliac compartment resulted in a 5-year LLR rate of 52.3%, significantly higher compared with nodes of that size in the obturator compartment (9.5%; HR, 5.8; 95% CI, 1.6-21.3;  $P = .003$ ).

To assess the value of LLND, outcomes of patients with SA node size of 7 mm or greater on primary MRI and greater than 4 mm on restaging MRI in the internal iliac compartment who underwent (C)RT with TME were compared with outcomes of patients with similar SA node sizes treated with (C)RT with TME and LLND. Treatment including LLND resulted in a significantly lower 5-year LLR rate of 8.7% compared with treatment with (C)RT with TME alone (52.3%; HR, 6.2; 95% CI, 1.4-28.5;  $P = .007$ ) (Figure 2). A total of 17 of 23 patients (74%) who underwent LLND had pathologically positive LLN. This difference was still significant when comparing patients with an SA node size of 7 mm or greater on primary MRI and greater than 4 mm on restaging MRI with malignant features in the internal compartment treated with (C)RT with TME alone with patients with similar LLR rates who underwent (C)RT with TME

**Table 2. Multivariate Analyses of Risk Factors for Lateral Local Recurrence, Local Recurrence, Distant Recurrence, and Cancer-Specific Survival Among 651 Patients Who Underwent Chemoradiotherapy or Radiotherapy With Total Mesorectal Excision<sup>a</sup>**

Variable	Lateral Local Recurrence		Local Recurrence		Distant Recurrence		Cancer-Specific Survival	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
<b>Sex</b>								
Male	NA	NA	1 [Reference]		NA	NA	NA	NA
Female	NA		1.7 (1.0-3.0)	.04	NA	NA	NA	NA
<b>Age, y</b>								
<62	NA	NA	NA	NA	1 [Reference]		1 [Reference]	
≥62	NA		NA		1.4 (1.4-1.8)	.049	1.7 (1.1-2.5)	.01
<b>cT stage</b>								
cT3	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
cT4	1.2 (0.6-2.5)	.64	1.3 (0.8-2.4)	.31	1.2 (0.8-1.7)	.29	1.4 (0.9-2.1)	.19
<b>cN stage</b>								
cN0	NA		1 [Reference]		1 [Reference]		1 [Reference]	
cN1	NA	NA	1.1 (0.5-2.3)	.08	1.5 (1.0-2.3)	.001	1.1 (0.7-1.9)	.02
cN2	NA		2.0 (1.0-3.9)		2.2 (1.4-3.3)		1.9 (1.1-3.1)	
<b>Location of lateral lymph node</b>								
None visible	1 [Reference]		1 [Reference]		1 [Reference]		NA	
External iliac	1.6 (0.2-14.5)		2.6 (0.9-7.0)		2.5 (1.4-4.4)		NA	
Obturator	2.4 (0.8-7.6)	.01	0.9 (0.5-1.8)	.08	1.0 (0.7-1.4)	.007	NA	NA
Internal iliac	5.9 (1.8-19.4)		1.7 (0.8-3.8)		0.8 (0.5-1.4)		NA	
<b>SA node size and malignant features</b>								
<7 mm on Primary MRI	1 [Reference]		1 [Reference]		NA		NA	
≥7 mm on Primary MRI and ≤4 mm on restaging MRI with no malignant features	0.6 (0.1-4.9)		1.0 (0.3-3.3)		NA		NA	
≥7 mm on Primary MRI and >4 mm on restaging MRI with no malignant features	2.8 (0.8-9.9)	.01	2.1 (0.8-5.4)	.17	NA	NA	NA	NA
≥7 mm on Primary MRI and >4 mm on restaging MRI with malignant features	4.0 (1.7-9.5)		2.1 (1.0-4.6)		NA		NA	
<b>Operation</b>								
Sphincter preserving	NA	NA	NA	NA	1 [Reference]		1 [Reference]	
Non-sphincter preserving	NA		NA		1.2 (0.9-1.7)	.18	1.5 (1.0-2.3)	.06
<b>R status</b>								
R0	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
R1	2.0 (0.7-5.9)	.21	3.1 (1.5-6.6)	.003	2.4 (1.4-4.0)	.001	3.9 (2.1-6.6)	<.001
<b>Response</b>								
Complete response	NA		1 [Reference]		1 [Reference]		1 [Reference]	
Tumor response	NA	NA	2.5 (0.8-8.5)	<.001	2.6 (1.4-4.9)	<.001	2.4 (1.0-5.9)	<.001
No response	NA		5.7 (1.7-18.7)		4.9 (2.6-9.2)		5.1 (2.1-12.1)	

Abbreviations: HR, hazard ratio; MRI, magnetic resonance imaging; NA, not applicable; R, residual tumor; SA, short-axis.

<sup>a</sup> Comparisons that were not significant on univariate analysis did not undergo multivariate analyses.

and LLND (HR, 4.3; 95% CI, 0.9-20.7;  $P = .048$ ). There was no difference in (C)RT with TME alone vs (C)RT with TME and LLND in those with an SA node size of 7 mm or greater on primary MRI and greater than 4 mm on restaging MRI in the obturator compartment (5-year LLR: 9.5% vs 0%; HR, 31.6; 95% CI, 0-∞;  $P = .32$ ), although 5 of 11 patients (45%) had positive LLNs, and there was a 0% LLR rate in the LLND group.

## Discussion

This study, including 741 patients from 10 centers who underwent operations over a 5-year period for cT3 or cT4 low rectal

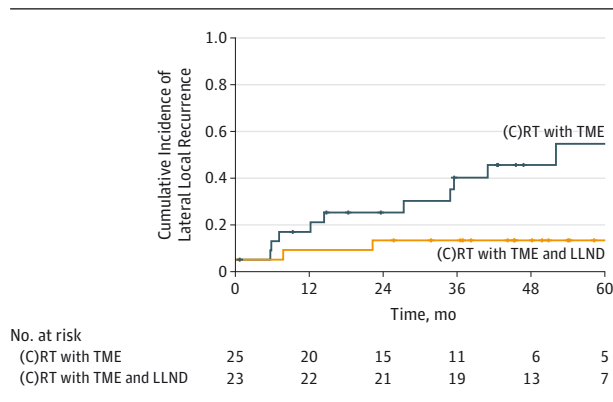
cancer, demonstrated that both primary and restaging MRI are important in clinical decision making in lateral nodal disease. Shrinkage of nodes from an SA node size of 7 mm or greater on primary MRI to 4 mm or less on restaging MRI abolishes the risk of LLR at 3 years. This occurs in 30% of patients and defines an important group in whom LLND can be avoided, as it probably offers no benefit. However, in persistently enlarged nodes in the internal iliac compartment, the risk of LLR is extremely high (52.3%), and LLND has an important role, as it lowers LLR significantly in these cases.

The first conclusion that can be made is that size matters. It was shown in the first Lateral Node Study Consortium publication<sup>11</sup> that relatively small lymph nodes (SA node size

**Table 3. Lateral Local Recurrence (LLR) Rates and Overall Recurrence (OAR) Rates for Different Cutoff Values in Short-Axis (SA) Node Size on Restaging Magnetic Resonance Imaging (MRI) Among Patients With an SA Node Size of 7 mm or Greater on Primary MRI Who Underwent Chemoradiotherapy or Radiotherapy With Total Mesorectal Excision, Separated by Compartment**

SA Node Size Cutoff on Restaging MRI	Obturator					Internal Iliac				
	No. (%)	LLR, %		OAR, %		No. (%)	LLR, %		OAR, %	
		3-y Rate	5-y Rate	3-y Rate	5-y Rate		3-y Rate	5-y Rate	3-y Rate	5-y Rate
<b>0 mm</b>										
0 mm	3 (5)	0	0	33.3	33.3	1 (3)	0	0	0	0
>0 mm	53 (95)	6.1	6.1	21.2	26.9	31 (97)	29.9	44.8	43.1	55.6
<b>1 mm</b>										
≤1 mm	3 (5)	0	0	33.3	33.3	1 (3)	0	0	0	0
>1 mm	53 (95)	6.1	6.1	21.2	26.9	31 (97)	29.9	44.8	43.1	55.6
<b>2 mm</b>										
≤2 mm	7 (13)	0	0	14.7	14.7	2 (6)	0	0	50.0	50.0
>2 mm	49 (88)	6.7	6.7	23.0	29.1	30 (94)	31.1	46.9	44.7	47.9
<b>3 mm</b>										
≤3 mm	11 (20)	0	0	9.1	9.1	6 (19)	0	20.0	16.7	33.3
>3 mm	45 (80)	7.4	7.4	25.1	31.9	26 (81)	37.0	52.3	52.8	64.6
<b>4 mm</b>										
≤4 mm	20 (36)	0	0	10.0	15.3	7 (22)	0	20.0	16.7	33.3
>4 mm	36 (64)	9.5	9.5	28.8	34.3	25 (78)	37.0	52.3	52.8	64.6
<b>5 mm</b>										
≤5 mm	26 (46)	0	0	11.5	15.8	9 (28)	12.5	30.0	25.0	40.0
>5 mm	30 (54)	11.7	11.7	31.4	37.2	23 (72)	34.7	50.6	51.5	63.6
<b>6 mm</b>										
≤6 mm	35 (63)	0	0	11.4	14.5	12 (38)	20.5	45.5	28.4	50.9
>6 mm	21 (38)	17.8	17.8	40.4	47.9	20 (63)	34.5	41.8	54.6	60.1
<b>7 mm</b>										
≤7 mm	41 (73)	4.9	4.9	17.1	19.7	18 (56)	21.2	40.0	38.6	53.2
>7 mm	15 (27)	11.1	11.1	36.5	47.1	14 (44)	38.9	47.6	52.4	60.3

**Figure 2. Kaplan-Meier Analysis of Lateral Lymph Node Dissection**



Kaplan-Meier plot of patients with a short-axis node size of 7 mm or greater on primary magnetic resonance imaging and greater than 4 mm on restaging magnetic resonance imaging located in the internal iliac compartment among patients who received chemoradiotherapy or radiotherapy [(C)RT] with total mesorectal excision (TME) alone and patients who received (C)RT with TME and lateral lymph node dissection (LLND). Crosses indicate censored events.

of 7 mm or greater) have to raise red flags with clinicians. In this study, it was shown that posttreatment size was a better predictor of LLR than the shrinkage rate or size. Shrinkage to an SA node size of 4 mm or less on restaging MRI is a safe cut-

off value that keeps the risk of recurrence at 0% after 3 years. In this study, the focus was mainly on 3-year recurrence rates, as the median follow-up duration was shorter than 5 years and because of the censoring of cases, which resulted in the AUC of the ROC curves becoming smaller and thus making risk prediction less accurate (eFigure 3 in the Supplement). When LLNs with an SA node size of 7 mm or greater on primary MRI were 4 mm or less on restaging MRI after (C)RT treatment, which occurred in 30% of the cases, surgeons probably do not need to consider LLND. However, in 70% of the cases when nodes are still present, clinicians need to start weighing the options.

The second main finding from this study is that besides size of the lateral nodes, the location is a major factor of influence. Although only around 30% of the visible nodes in this study were located in the internal iliac compartment (Table 1), the percentage of LLNs with an SA node size of 7 mm or greater on primary MRI was significantly higher in this compartment. Also, these nodes had a higher chance of being unresponsive (SA node size greater than 4 mm on restaging MRI), and they tended to behave much more aggressively than obturator nodes, with a 5-year LLR rate of 52.3%. To our knowledge, this is a new finding that has not been published previously. It is known from Japanese studies that malignant LLNs were most frequently located in the internal iliac compartment after LLND,<sup>16</sup> the rationale behind this being that they

are the first basin directly from the lateral ligament.<sup>17</sup> However, why similarly large, unresponsive nodes in the obturator compartment result in a much lower 9.5% 5-year LLR rate remains a mystery. One theory to consider is that obturator nodes generally may behave more reactively, while the internal nodes act as sentinel nodes and are more likely to contain viable tumor tissue. Another theory would be that the internal iliac nodes would not have received the full irradiation dose. As described before,<sup>11</sup> all centers have stated that in general, both the obturator and the internal iliac compartments were included in the standard irradiated fields for these low cT3 and cT4 tumors. However, in this retrospective study, it was impossible to verify this for each individual patient, but we think this latter theory is less likely, as the internal iliac nodes are closest to the mesorectum. The only way to verify this would be a prospective trial with standardized radiotherapy protocols; the Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) trial is currently being prepared in the Netherlands.

The literature varies on whether persistence (using varying criteria) of lateral nodes on restaging MRI predicts involvement of nodes. These are mainly Eastern studies where LLNDs were performed<sup>18-20</sup>; persistence tends to result in more pathologic metastases in the resected nodes, but it does not tell us whether leaving these nodes behind would actually result in LLR. A study conducted by Kim et al<sup>20</sup> including 31 patients showed that even responsive nodes can lead to LLRs after (C)RT with TME, but it does not define in which compartment the nodes were located, and more than 72% of the nodes were responsive, which suggests a selection bias.

In Japan, it is standard to perform an LLND of both the internal iliac and obturator compartment, irrespective of where the involved node is located. This is probably a pragmatic approach, as resecting the internal iliac compartment laparo-

scopically is more difficult if the obturator compartment is not resected first. Also, in this study, only the largest node was assessed; it might be possible that in some patients, there was a very large node in the obturator compartment and a smaller but more significant node in the internal iliac compartment. The method of using the largest node irrespective of compartment in this study is a representation of clinical decision making as it is currently done in Japan.

Regarding external iliac nodes, as Japanese studies have shown before,<sup>16,21</sup> involvement of these nodes is predictive for metastatic but not for local recurrence. These patients do not benefit from an LLND and might need induction chemotherapy to address systemic disease.

### Limitations

This study has limitations. As previously stated, this exploratory and hypothesis-generating study is retrospective and multi-institutional in nature, leading to a heterogeneity in patients and treatments, so the results have to be interpreted with caution.<sup>11</sup> Additionally, sample size calculation and power analyses were not performed initially, as the study was set up retrospectively, and all centers were asked to analyze all consecutive patients who underwent operations in a 5-year period. Further, to formulate practical clinical guidelines, subgroup analyses had to be performed.

### Conclusions

In conclusion, size and location of the lateral pelvic sidewall nodes on primary and restaging MRI are important and may be the key to clinical decision making. These data may provide some insight into the appropriate use of LLND in an effort to abolish preventable local recurrences after rectal cancer surgery.

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