original report

Neoadjuvant (Chemo)radiotherapy With Total Mesorectal Excision Only Is Not Sufficient to Prevent Lateral Local Recurrence in Enlarged Nodes: Results of the Multicenter Lateral Node Study of Patients With Low cT3/4 Rectal Cancer

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abstract

PURPOSE Improvements in magnetic resonance imaging (MRI), total mesorectal excision (TME) surgery, and the use of (chemo)radiotherapy ([C]RT) have improved local control of rectal cancer; however, we have been unable to eradicate local recurrence (LR). Even in the face of TME and negative resection margins (R0), a significant proportion of patients with enlarged lateral lymph nodes (LLNs) suffer from lateral LR (LLR). Japanese studies suggest that the addition of an LLN dissection (LLND) could reduce LLR. This multicenter pooled analysis aims to ascertain whether LLNs actually pose a problem and whether LLND results in fewer LLRs.

PATIENTS AND METHODS Data from 1,216 consecutive patients with cT3/T4 rectal cancers up to 8 cm from the anal verge who underwent surgery in a 5-year period were collected. LLND was performed in 142 patients (12%). MRIs were re-evaluated with a standardized protocol to assess LLN features.

RESULTS On pretreatment MRI, 703 patients (58%) had visible LLN, and 192 (16%) had a short axis of at least 7 mm. One hundred eight patients developed LR (5-year LR rate, 10.0%), of which 59 (54%) were LLRs (5-year LLR rate, 5.5%). After multivariable analyses, LLNs with a short axis of at least 7 mm resulted in a significantly higher risk of LLR (hazard ratio, 2.060; $P = .045$) compared with LLNs of less than 7 mm. In patients with LLNs at least 7 mm, (C)RT plus TME plus LLND resulted in a 5-year LLR of 5.7%, which was significantly lower than that in patients who underwent (C)RT plus TME (5-year LLR, 19.5%; $P = .042$).

CONCLUSION LLR is still a significant problem after (C)RT plus TME in LLNs with a short axis at least 7 mm on pretreatment MRI. The addition of LLND results in a significantly lower LLR rate.

J Clin Oncol 37:33-43. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Diagnostic and treatment strategies for rectal cancer have dramatically changed in the last decades, with the universal acceptance of the total mesorectal excision (TME) technique[1] and improved imaging with magnetic resonance imaging (MRI),[2-4] which allows better selection of high-risk patient categories; however, developments in treatment have gone in different directions in the East and the West. In Western countries, several trials have been conducted that have demonstrated increased local control with preoperative (chemo)radiotherapy ([C]RT),[5-8] resulting in the adoption of (C)RT followed by TME as the standard treatment of clinical stage II and III rectal cancer.[9,10] In contrast, in the East (predominantly in Japan) a surgical approach without (C)RT that combines TME with prophylactic lateral lymph node dissection (LLND) has been the standard treatment in low cT3/4 rectal cancers,[11,12] as it has been demonstrated in anatomic studies that advanced tumors below the peritoneal reflection are at a higher risk of spreading to lateral nodes.[13-15] Standard strategies in both Eastern and Western countries have resulted in similar local recurrence (LR) rates,[16] which has provided a rationale for Western surgeons to rely on (C)RT to sterilize the lateral compartment, alleviating fears of operative morbidity and long-term sexual and urinary dysfunction associated with LLND.[17] This may be particularly relevant in the more obese Western patients in whom LLND is technically more difficult.

Recent evidence suggests, however, that in select cases, (C)RT is not sufficient to prevent lateral LR (LLR).

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on June 12, 2018 and published at jco.org on November 7, 2018: DOI https://doi.org/10.1200/JCO.18.00032

Three Korean studies, in which no LLNDs were performed, demonstrated increased LLR rates in patients who underwent (C)RT with TME when enlarged lateral lymph nodes (LLNs) were identified on primary MRI, showing an almost linear relationship between nodal size and LLR.[18-20] Moreover, a recent Oxford series showed similar 30% to 40% LLR rates in nodes greater than 10 mm in short axis on pretreatment imaging and concluded that size might be a better measure in LLNs than assessment of malignant features.[21] Both the Korean and the Oxford studies demonstrated that more than 50% of all LRs were only in the lateral compartment and that even in the recurrent cases, approximately one half of the patients had no distant metastases at the time of recurrence diagnosis, which suggests that it was still localized disease.

Still, there is a debate over whether an LLND would prevent these LLRs from occurring or whether lateral nodal spread is more a sign of systemic disease.[22,23] Several Japanese centers have begun offering indicated LLNDs in patients with enlarged (generally 7 mm or larger) LLNs after neoadjuvant (C)RT. This approach has shown excellent disease-free survival rates,[24,25] which strongly suggests that lateral nodal disease is rather a local, than a distant issue. Eastern and Western management of LLNs is already showing signs of converging. Eastern surgeons are adopting neoadjuvant (C)RT with indicated LLNDs to prevent overtreatment,[24,25] and Western surgeons are gradually recognizing that LLR is a significant issue in certain patients.[21] This raises the challenge that if we wish to optimize treatment in this group of patients with rectal cancer—with acceptable morbidity—how do we select patients for LLND? Single-center studies do not provide sufficient patient numbers to be able to perform reliable statistics to formulate specific guidelines regarding lateral nodal disease, because it is relatively uncommon and only a proportion of these patients develop recurrence.

The current study is a multicenter pooled analysis of patients with low, locally advanced rectal cancer from referral centers in both Eastern and Western countries. The purpose of this study is to ascertain whether LLNs actually pose a problem after (C)RT plus TME and to study whether the addition of an indicated LLND results in fewer LLRs.

PATIENTS AND METHODS

Study Participants and Patient Selection

This study included patients from 12 hospitals in seven countries (Table 1). All participating hospitals were asked to collect the data and re-review MRIs of all consecutive patients who underwent operation for cT3/4 rectal cancer between January 2009 and December 2013 (Appendix Tables A1 and A2, online only). Only patients with low rectal cancers (within 8 cm of the anal verge on MRI) were included. Exclusion criteria were the absence of good-quality primary MRIs, the presence of distant metastases at initial

TABLE 1. Patient and Tumor Characteristics and Pathologic Results

Characteristic	Value (N = 1,216)
Center, No. of patients	
Cancer Institute Hospital, Tokyo, Japan	249
Catharina Hospital, Eindhoven, the Netherlands	192
Karolinska Institutet, Stockholm, Sweden	117
Leiden University Medical Center, Leiden, the Netherlands	17
Memorial Sloan-Kettering Cancer Center, New York, NY	125
Nagoya University Hospital, Nagoya, Japan	46
Netherlands Cancer Institute, Amsterdam, the Netherlands	66
Oxford University Hospitals NHS, Oxford, United Kingdom	127
Royal Adelaide Hospital, Adelaide, SA, Australia	50
Royal Prince Alfred Hospital, Sydney, NSW, Australia	25
St Mary's Hospital, Seoul, Korea	99
Toranomon Hospital, Tokyo, Japan	103
Age, years, mean ± SD	62 ± 12.9
Sex	
Male	774 (63.7)
Female	442 (36.3)
cT stage	
cT3	923 (75.9)
cT4	293 (24.1)
cN stage	
cN0	394 (32.4)
cN1	471 (38.7)
cN2	351 (28.9)
Tumor location (LOREC criteria)	
Above	427 (35.1)
Below	789 (64.9)
Tumor location (Japanese criteria)	
Above	156 (12.8)
Below	1,060 (87.2)
Preoperative radiotherapy	
No	248 (20.4)
Short-course	171 (14.1)
Long-course	797 (65.5)
Operation	
Low anterior resection	574 (47.2)
(Extended) abdominoperineal resection	458 (37.7)
Intersphincteric resection	135 (11.1)
Hartmann's operation	32 (2.6)
Pelvic exenteration	17 (1.4)

(continued on following page)

TABLE 1. Patient and Tumor Characteristics and Pathologic Results (continued)

Characteristic	Value (N = 1,216)
Procedure for lateral lymph node	
None	1,062 (87.3)
Sampling	12 (1.0)
Lateral lymph node dissection	142 (11.7)
Adjuvant chemotherapy	
No	655 (53.9)
Yes	449 (36.9)
Missing	112 (9.2)
(y)pT stage	
(y)pT0	157 (12.9)
(y)pT1	68 (5.6)
(y)pT2	317 (26.1)
(y)pT3	600 (49.3)
(y)pT4	74 (6.1)
Median No. of harvested mesorectal lymph nodes (IQR)	16 (12-23)
(y)pN stage	
(y)pN0	822 (67.6)
(y)pN1	261 (21.5)
(y)pN2	133 (10.9)
R status	
R0	1,142 (93.9)
R1	74 (6.1)

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; LOREC, Low Rectal Cancer National Development Program; SD, standard deviation.

staging, or a noncurative resection (R2 resection). Each center used a specific guideline with a color map atlas of the pelvis (Appendix Fig A1, online only) for re-evaluation of pretreatment and, if available, post-treatment MRIs by a local expert radiologist. Each center received institutional review board approval, according to local policies.

Re-Evaluation of MRIs

In addition to recording the standard TNM staging and circumferential resection margin assessment, radiologists were asked to specifically rereview two MRI features—the height of the tumor and LLN status. Tumor height was assessed according to both the English Low Rectal Cancer National Development Program (LOREC) and the Japanese definition of low rectal cancer. LOREC criteria[26] defines low rectal cancer as a tumor of which the distal part is located below the origin of the levator muscles. In Japanese terminology, low rectal cancers are defined as those where the majority of the tumor is situated at or below the peritoneal reflection.[12]

Assessment of LLN status was based on the largest LLN identified on pretreatment MRI. Both long- and short-axis (LA and SA, respectively) size and site—internal iliac, external iliac, or obturator compartment—were recorded. The benign long-stretched nodes, located just behind the distal portion of the external iliac vein, were not included in the assessment (Appendix Fig A1C). Furthermore, the presence of malignant features—for example, internal heterogeneity or border irregularity—was also noted. Potential changes in the size and presence of malignant features of this same LLN after (C)RT were also evaluated for cases in which a restaging MRI was available. Shrinkage was defined as any reduction in SA size, whereas disappearance was defined as no visible node left in the compartment.

Preoperative Treatment

Treatment strategies for individual patients were determined during multidisciplinary team meetings in each hospital. All patients who received any type of neoadjuvant radiotherapy, with or without chemotherapy, were defined as having received. Each center provided information on the general radiation fields for cT3/4 rectal tumors situated within 8 cm of the anal verge. It was confirmed for each center that, in general, both the obturator and internal iliac compartments were located in the standard irradiated field for these types of tumors.

Surgical Resection

In most patients, LLNs were not resected. In a few cases, only sampling of a suspected LLN was performed. For the purposes of this study, a formal LLND was defined as the complete resection of lymphatic tissue from the lateral compartment, both from the internal iliac and the obturator area.[11] Prophylactic LLND, which was the standard treatment of clinical stage II and III low rectal cancer in Japan, irrespective of LLN size, was performed in one Japanese hospital (Nagoya). The other two Japanese hospitals performed LLND selectively (indicated LLND) after neoadjuvant treatment in patients with LLNs equal or greater than 7 mm in the LA on primary imaging. Memorial Sloan Kettering Cancer Center and the Karolinska Institutet performed LLNDs for patients with suggestive findings on MRI after (C)RT, generally applying a size of equal or greater than 5 mm in combination with malignant features as an indication for LLND.

LR

Follow-up was performed according to local follow-up schemes. In patients with an LR, imaging was rereviewed and the site was categorized as one of the types—lateral, presacral, anastomotic site, anterior, or perineal—for which definitions have been previously described.[16,27]

Statistical Analyses

Statistical analyses were performed using Statistical Package for the Social Sciences for Windows, version 23 (SPSS, Chicago, IL). For median values, interquartile ranges (IQRs) were given. Individual variables were compared using

t tests and χ^2 tests. A *P* value $< .05$ was considered significant. Survival curves for LR, LLR, and distant recurrence (DR) rates, as well as cancer-specific survival (CSS), were calculated using the Kaplan-Meier method. To determine the risk factors, effects of covariates were analyzed using a univariable Cox proportional hazards regression model. Subsequently, a multivariable analysis using covariates with a significant effect ($P < .10$) was performed in which a *P* value of $< .05$ was considered significant. In this study, cN stage and (y)*p*-N stage always refer to mesorectal node stage.

RESULTS

Patients

Table 1 lists the patient and tumor characteristics and pathologic results of the total cohort; 1,216 patients with cT3/4 rectal cancer within 8 cm of the anal verge were

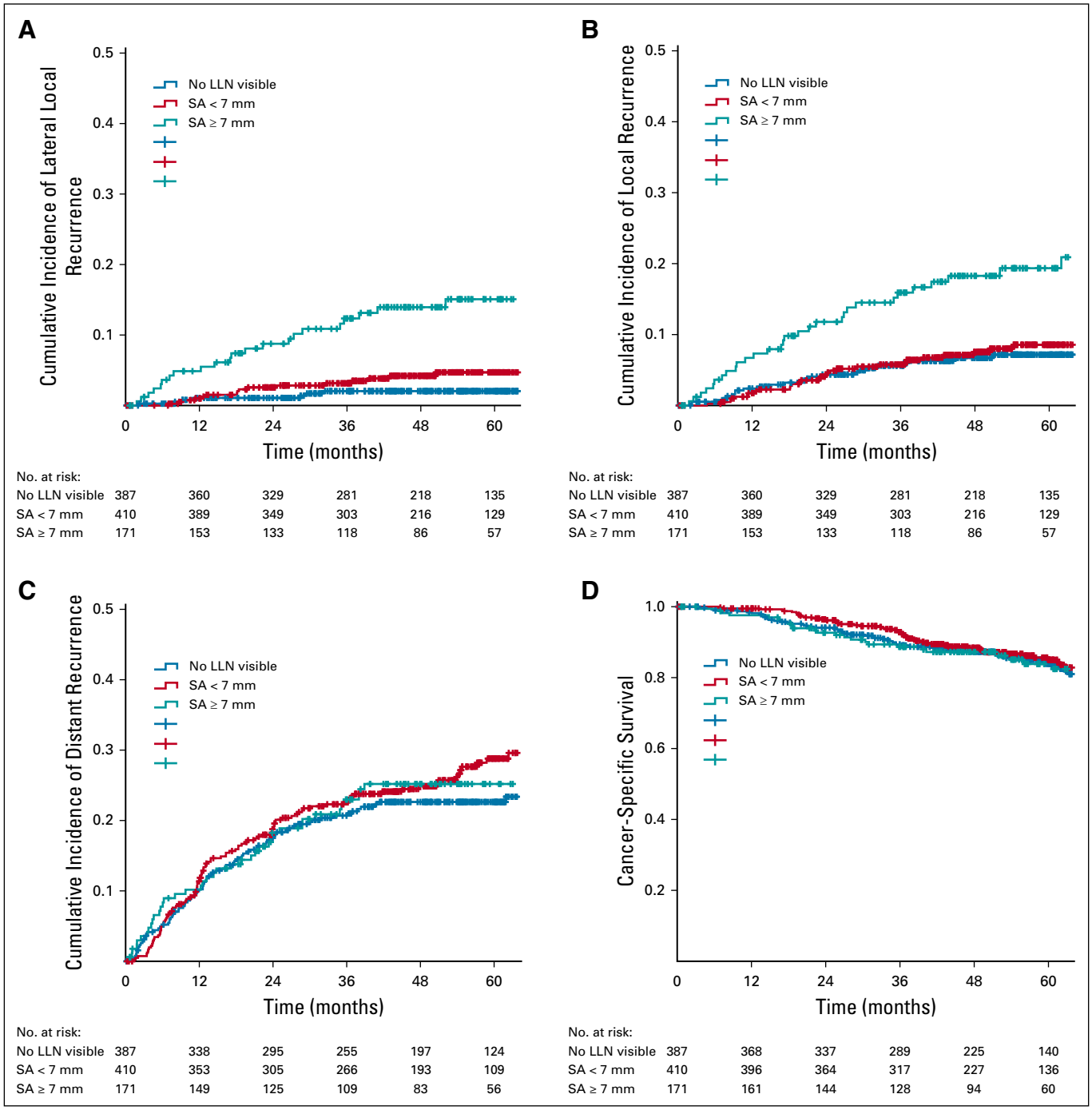

FIG 1. (A) Lateral local recurrence rate, (B) local recurrence, (C) distant recurrence, and (D) cancer-specific survival according to lateral lymph node (LLN) short axis (SA) size in patients who received (chemo)radiotherapy.

included. Median follow-up duration after surgery was 56.5 months (IQR, 55.0 to 58.1 months).

Primary and Restaging MRI

At least one visible LLN was detected in 703 patients (57.8%) on initial MRI, 448 (63.7%) of which were located in the obturator compartment and 198 (28.2%) in the internal iliac compartment. The median size of the largest LLN was 7.0 mm in LA (IQR, 5.0 to 9.9 mm) and 5.0 mm in SA (IQR, 4.0 to 7.0 mm) before (C)RT. Malignant features were evident in 208 patients (17.1%) of the total cohort.

Of 968 patients who received (C)RT, 741 patients (76.5%) had a restaging MRI. LLN size significantly declined both in LA ($P < .001$) and in SA ($P < .001$), reducing median size to 5.0 mm (IQR, 3.0 to 7.1 mm) and 3.8 mm (IQR, 2.0 to 5.0 mm), respectively.

Surgery and Pathology

R0 resection was achieved in 1,142 patients (93.9%; Table 1). In 12 patients in whom LLN sampling was performed, nine (75.0%) were shown to have pathologic involvement. Mean harvest was two nodes (range, one to seven nodes). LLND was performed in 142 patients (11.7%) in five hospitals, which resulted in 35 patients (24.6%) with pathologically positive LLN. Mean harvest from the lateral compartment was 16 nodes (range, 0 to 62 nodes). In 87 patients who had restaging MRI after (C)RT and who underwent LLND, there was a similar rate of positive LLNs in the those with shrinkage of the nodes ($P = .897$); however, there was a trend toward lower LLN-positive rates if the nodes had disappeared completely (12.5% *v* 34.2% if still present; $P = .211$).

LR

A total of 108 patients developed LR; 59 patients (54%) developed LR in the lateral compartment, 24 (22%) in the presacral site, 17 (16%) in the anastomotic site, four (4%) in the anterior, and four (4%) in the perineal site. Five-year general LR rate was 10.0% and the 5-year LLR rate was 5.5%. Table 2 lists LLR rates for different cutoff values in SA and LA in patients with visible LLNs who received (C)RT without LLND. An SA cutoff value of 7 mm was chosen as a future reference value, as the LLR rate of approximately 20% was considered too high.

SA Cutoff of 7 mm

Of the 1,216 total patients, 192 (16%) had LLNs equal to or greater than 7 mm in SA on primary MRI. Appendix Table A3 (online only) lists the characteristics according to SA of the LLN in the patients who received (C)RT. Patients with LLNs ≥ 7 mm had more advanced cT stage and cN stage ($P < .001$) than did patients with smaller or absent nodes. Nodes in these patients also had a significantly higher rate of malignant features ($P < .001$) and were more often located in the internal iliac compartment ($P < .001$). R status was not significantly different between the three groups ($P = .106$).

TABLE 2. LLR Rates for Different Cutoff Values in SA and LA in Patients With Visible Lateral Nodes Who Received (Chemo)radiotherapy ([C]RT) Without Lateral Lymph Node Dissection

SA, mm	No. (%)	5-Year LLR, %	*P*	LA, mm	No. (%)	5-Year LLR, %	*P*
SA 5			< .001	LA 5			.079
< 5	316 (65)	4.6		< 5	95 (20)	4.0	
≥ 5	171 (35)	15.9		≥ 5	392 (80)	9.6	
SA 6			< .001	LA 6			.148
< 6	316 (65)	4.6		< 6	179 (37)	6.0	
≥ 6	171 (35)	15.9		≥ 6	308 (63)	9.9	
SA 7			< .001	LA 7			.005
< 7	369 (76)	4.9		< 7	267 (55)	5.0	
≥ 7	118 (24)	19.5		≥ 7	220 (45)	12.6	
SA 8			< .001	LA 8			.002
< 8	410 (84)	5.3		< 8	311 (64)	5.5	
≥ 8	77 (16)	25.5		≥ 8	176 (36)	13.9	
SA 9			< .001	LA 9			< .001
< 9	425 (87)	5.4		< 9	356 (73)	5.2	
≥ 9	62 (13)	30.3		≥ 9	131 (27)	17.8	
SA 10			< .001	LA 10			< .001
< 10	441 (91)	5.7		< 10	385 (79)	5.4	
≥ 10	46 (9)	35.6		≥ 10	102 (21)	20.6	

Abbreviations: LA, long axis; LLR, lateral local recurrence; SA, short axis.

TABLE 3. Multivariable Analyses for Risk Factors for LLR, LR, DR, and CSS in the Total Cohort

	LLR			LR			DR			CSS		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Sex						.115						
Male				1								
Female				1.362	0.927 to 2.001							
Age, years												.015
< 62										1		
≥ 62										1.478	1.080 to 2.022	
Tumor location (LOREC criteria)						.266						.544
Above				1						1		
Below				1.288	0.825 to 2.012					1.118	0.780 to 1.602	
Tumor location (Japanese criteria)												
Above												
Below												
cT stage			.488			.228			.055			.067
cT3	1			1			1			1		
cT4	1.236	0.679 to 2.253		1.315	0.843 to 2.050		1.311	0.995 to 1.728		1.377	0.978 to 1.941	
cN stage			.140			.061			.006			.008
cN0	1			1			1			1		
cN1	0.768	0.387 to 1.526		1.073	0.653 to 1.764		1.166	0.861 to 1.578		1.087	0.732 to 1.614	
cN2	1.463	0.767 to 2.791		1.688	1.029 to 2.768		1.606	1.184 to 2.178		1.729	1.175 to 2.543	
(C)RT									.652			
Yes							1					
No							0.928	0.671 to 1.284				
Location of LLN			.007			.180						.302
No LLN visible or external iliac	1			1						1		
Obturator	1.297	0.639 to 2.632		0.777	0.480 to 1.256					0.900	0.646 to 1.254	
Internal iliac	2.952	1.384 to 6.293		1.259	0.717 to 2.110					0.668	0.399 to 1.117	
SA before (C)RT			.045			.013						
No LLN visible, SA < 7 mm	1			1								
SA ≥ 7 mm	2.060	1.017 to 4.173		2.010	1.157 to 3.495							

(continued on following page)

TABLE 3. Multivariable Analyses for Risk Factors for LLR, LR, DR, and CSS in the Total Cohort (continued)

	LLR			LR			DR			CSS		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Malignant feature(s) before (C)RT			.951			.549						
No LLN visible or absent	1			1								
Present	1.023	0.495 to 2.116		0.835	0.462 to 1.507							
Operation			.197			.478			.042			.005
Sphincter preserving	1			1			1			1		
Nonsphincter preserving	1.450	0.824 to 2.550		1.169	0.759 to 1.802		1.300	1.010 to 1.674		1.645	1.165 to 2.322	
LLN dissection									.027			.195
Yes							1			1		
No							1.680	1.062 to 2.657		1.518	0.808 to 2.853	
R status			.005			< .001			< .001			< .001
R0	1			1			1			1		
R1	2.876	1.377 to 6.006		2.976	1.713 to 5.168		2.696	1.857 to 3.913		4.251	2.789 to 6.480	

Abbreviations: (C)RT, (chemo)radiotherapy; CSS, cancer-specific survival; DR, distant recurrence; HR, hazard ration; LLN, lateral lymph node; LLR, lateral local recurrence; LOREC, Low Rectal Cancer National Development Program; LR, local recurrence; SA, short axis.

TABLE 4. Effect of LLND on LLR, LR, DR, and CSS According to SA of the LLN on Pretreatment MRI in Patients Who Received (C)RT

SA Before (C)RT	No.	5-Year LLR, %	*P*	5-Year LR, %	*P*	5-Year DR, %	*P*	5-Year CSS, %	*P*
No LLN visible			.777		.597		.311		.419
No LLND	383	2.1		7.2		22.9		83.7	
LLND	4	0		0		0		100	
SA < 7 mm			.621		.243		.132		.344
No LLND	369	4.9		9.2		30.1		84.4	
LLND	41	2.5		2.5		15.8		91.5	
SA ≥ 7 mm			.042		.005		.028		.032
No LLND	118	19.5		25.6		30.8		79.4	
LLND	53	5.7		5.7		13.5		94.1	

Abbreviations: (C)RT, (chemo)radiotherapy; CSS, cancer-specific survival; DR, distant recurrence; LLN, lateral lymph node; LLND, lateral lymph node dissection; LLR, lateral local recurrence; LR, local recurrence; MRI, magnetic resonance imaging, SA, short axis.

Patients with LLNs equal to or greater than 7 mm in SA had a significantly higher 5-year rates of LLR (15.0%) and LR (19.2%) than did patients with smaller LLNs, as shown in Figure 1 ($P < .001$). There were no significant differences in terms of DR and CSS ($P = .540$ and .756, respectively). There was no difference in 5-year rates for LLR and LR among patients with LLNs equal to or greater than 7 mm in SA between the short- versus long-course radiotherapy ($P = .667$ and .909, respectively).

In patients without LLND who underwent restaging MRIs after (C)RT, there was no influence from the shrinkage or disappearance of LLNs with SA less than 7 mm on LLR ($P = .482$ and .305, respectively). In 96 patients without LLND with LLNs equal to or greater than 7 mm in SA and restaging MRIs, in five patients (5%) the nodes disappeared and in 74 (77%) there was shrinkage, whereas in 17 (18%) there was unchanged size or growth. LLR rates in the latter two categories were 17.3% and 25.4%, respectively ($P = .440$). In the five patients in whom nodes disappeared, there was no LLR but all cases were censored at 54 months.

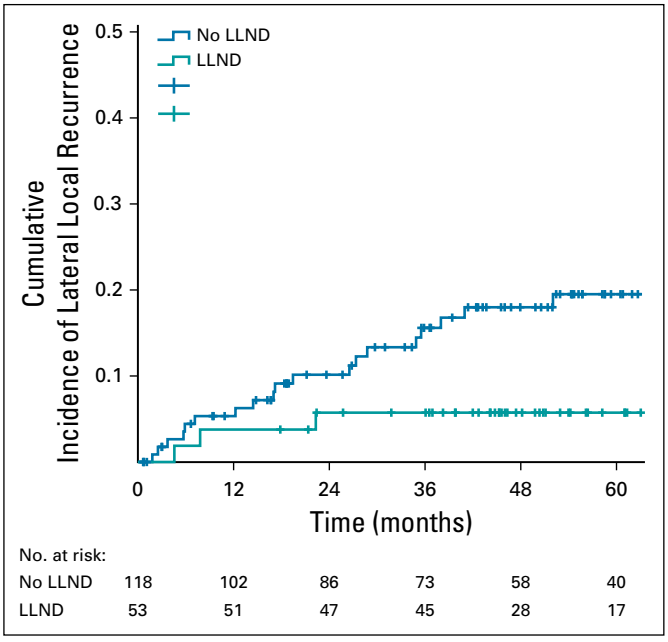

FIG 2. Effect of lateral lymph node dissection (LLND) on lateral local recurrence in patients with a short axis ≥ 7 mm on pretreatment magnetic resonance imaging in patients who received (chemo)radiotherapy.

Univariable and Multivariable Analyses

Appendix Table A4 (online only) and Table 3 show the uni- and multivariable analyses. Patients with LLNs equal to or greater than 7 mm in SA had a significantly higher risk of LR (hazard ratio [HR], 2.010; 95% CI, 1.157 to 3.495; $P = .013$) and LLR (HR, 2.060; 95% CI, 1.017 to 4.173; $P = .045$) compared with those with LLNs less than 7 mm in SA. In addition, LLNs in the internal iliac region were significantly associated with a higher risk of LLR (HR, 2.952; 95% CI, 1.384 to 6.293; $P = .007$). None of the LLN features were significantly associated with DR or CSS.

Effect of LLND

In 12 patients with LLN sampling, the 5-year LR rate was 51.1%. All LRs were located in the lateral compartment. Table 4 shows the effects of a formal LLND on LLR, LR, DR and CSS according to SA sizes of the LLN in patients who received (C)RT. After LLND, 5-year LLR and LR rates were significantly lower in patients with LLNs equal to or greater than 7 mm in SA ($P = .042$ and .0005, respectively) compared with patients who did not undergo LLND (Fig 2). In 27 (51%) of 53 patients who underwent LLND, pathologically positive LLNs were found.

DISCUSSION

To our knowledge, this is the largest multi-institutional retrospective study of a cohort of patients with low cT3/4 rectal cancer who underwent operation in a 5-year period, with rereview of all MRIs on LLN features using a standardized protocol. In 1,216 total patients, results demonstrate that enlarged nodes result in high LR rates, despite (C)RT, with a 19.5% 5-year LLR rate in nodes with SA of equal to or greater than 7 mm after (C)RT plus TME. LLR is reduced to only 5.7% if (C)RT plus TME is combined with

LLND in patients with similarly enlarged nodes in whom 51% pathologically proven LLN metastases were found.

Although this the largest cohort reported, to our knowledge, it is retrospective and multi-institutional, leading to heterogeneity in patients and treatments. Results therefore have to be interpreted with caution. LLND was performed in a subgroup of hospitals, so comparisons were across institutions. Acknowledging these limitations, we can conclude that lateral nodal disease imposes an undeniable problem if nodes are enlarged, irrespective of the exact cutoff value. Furthermore, LLN enlargement does not influence DR rate, which suggests that it is a local issue that must be addressed through targeted treatment in the pelvis rather simply representing a marker of poor prognosis and distant disease. Moreover, it can be stated that in patients in whom (C)RT and TME is combined with LLND, good local control can be achieved.

A cutoff value of 7 mm in SA on primary MRI was selected for several reasons. First, choosing SA rather than LA seemed logical as it is more reliable to standardize this measurement and reduce variation with different MRI protocols and reporting radiologists. In addition, concentrating on SA size redirected focus from the typically long-stretched benign lymph nodes that are often present in the pelvis to those with prognostic significance. Finally, analysis of the effect of SA indicated that a size equal to or greater than 7 mm was associated with an unacceptably high rate of LLR of approximately 20% compared with the more generally reported rate of 5% to 10%. However, this is a subjective measure and Table 2 can be used to adequately assess risk for separate LLN sizes.

There are several points for discussion with regard to optimizing the treatment of patients with enlarged LLN. First, this study demonstrates that limiting resection to the affected node(s) is of little benefit. More than one half of these patients will develop LR in the same compartment, which suggests that complete LLND is required. Second, this work focuses on lateral nodal features on primary MRI. There is a dilemma over the value of restaging MRI; shrinkage of enlarged LLNs reduces the risk of pathologic involvement, but does not significantly reduce the likelihood of recurrence after (C)RT plus TME in this series. However, in cases in which nodes disappear completely, there was no LR but the numbers were too small to state this with any certainty.

This study indicates that in patients with enlarged nodes, LLND after (C)RT can reduce the risk of LLR. This is an area of practice with a paucity of evidence. The randomized study from Japan, Mesorectal Excision With or Without Lateral Node Dissection for Clinical Stage II/III Lower Rectal Cancer: A Multicenter, Randomized Controlled, Non-inferiority Trial (JCOG0212),[28] considered patients with nodes up to 10 mm in SA who did not have any neoadjuvant treatment. Adding LLND to TME reduced rates of LLR from 12.6% to 7.4%, which is similar to the LLR rate in this study of approximately 5% to 6% in patients who received (C)RT plus TME with nodes with SA up to 10 mm (Table 2). However, the JCOG2012 study does not answer the question of how to deal with patients with larger nodes, as LLND is unlikely to be sufficient.

Is there enough evidence to convince Western surgeons that LLND should be added to their treatment in patients who are at risk for LLR, as defined by the presence of enlarged LLNs? Alternatively, should these patients receive more aggressive neoadjuvant treatment, perhaps starting with induction chemotherapy or increasing radiotherapy dose to the lateral compartment to induce a complete response of the nodes? This study suggests that lateral nodal disease is a local problem and that the addition of systemic chemotherapy will not suffice. Increasing the radiotherapy boost up to 60 Gy on pathologic nodes has already been established in gynecologic cancers and does not result in increased morbidity[29]; however, if nodes are resistant, performing an LLND after can be more hazardous. In addition, as the radiologic complete response rate of the nodes in this study was only 5%, the additional benefit of 60 Gy may be limited in terms of complete response. These important factors may only be resolved through a large prospective multicenter study, with high-volume referral centers for locally advanced rectal cancers, where expertise in optimal radiotherapy regimens and surgical expertise in LLND can be standardized and quality controlled. This may bring a convergence of practices in the East and West to eradicate LLR in the future.

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SUPPORT

The Nagoya Surgical Support Organization financed the travel and living expenses of A.O. during a research fellowship in the Netherlands.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABLITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.00032.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Neoadjuvant (Chemo)radiotherapy With Total Mesorectal Excision Only Is Not Sufficient to Prevent Lateral Local Recurrence in Enlarged Nodes: Results of the Multicenter Lateral Node Study of Patients With Low cT3/4 Rectal Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Consulting or Advisory Role: Medtronic

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Research Funding: Medtronic

No other potential conflicts of interest were reported.

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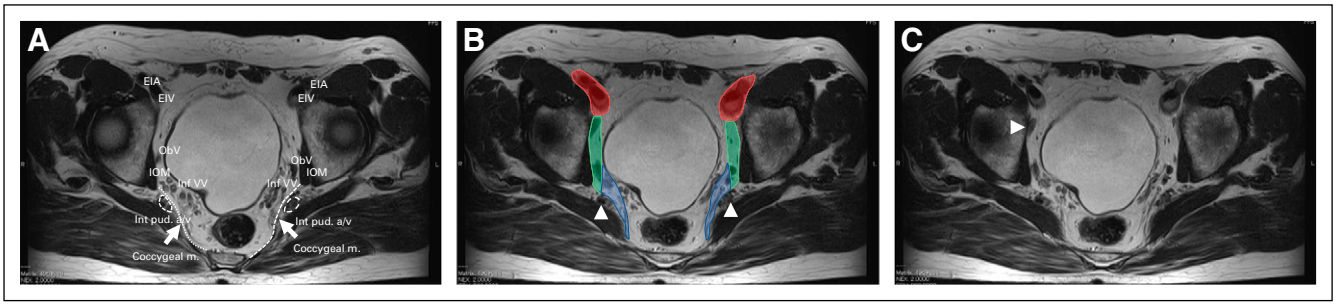

FIG A1. An example slide of the color map atlas of the pelvis. (A) Atlas of the pelvis. (B) The obturator and internal iliac areas are divided by the lateral border of the main trunk of the internal iliac vessels. External iliac region (red); obturator region (green); internal iliac region (blue); internal iliac artery (arrow head). (C) Benign long-stretched node just behind distal portion of the external iliac vein that should not be included in the assessment (arrow head). EIA, external iliac artery; EIV, external iliac vein; ObV, obturator vein; IOM, internal obturator muscle; Inf VV, inferior vesical vein; Int pud. a/v, internal pudendal artery/vein; Coccygeal m., coccygeal muscle (arrow).

TABLE A1. Participating Institutes and Investigators

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University of Sydney	Sydney, Australia	Surgical Outcomes Research Center	P. Lee, M. J. Solomon, K. G. Brown

TABLE A2. Overview of Baseline Characteristics Per Institution

Characteristic	CIH (JPN)	Catharina (NED)	Karolinska (SWE)	Leiden (NED)	MSKCC (US)	Nagoya (JPN)	NCI (NED)	Oxford (ENG)	RAH (AUS)	RPA (AUS)	St Mary (KOR)	Toranomon (JPN)
No. of patients	249	192	117	17	125	46	66	127	50	25	99	193
Age (mean ± SD)	59 ± 12.7	65 ± 10.9	66 ± 12.6	64 ± 15.7	53 ± 12.6	60 ± 13.5	60 ± 11.6	64 ± 12.9	65 ± 13.5	68 ± 12.1	61 ± 11.8	64 ± 12.8
Sex, male	162 (65.1)	122 (63.5)	69 (59.0)	13 (76.5)	80 (64.0)	32 (69.6)	42 (63.6)	76 (59.8)	32 (64.0)	15 (60.0)	62 (62.6)	69 (67.0)
cT stage												
cT3	213 (85.5)	105 (54.7)	61 (52.1)	17 (100)	103 (82.4)	37 (80.4)	57 (86.4)	86 (67.7)	44 (88.0)	21 (84.0)	81 (81.8)	98 (95.1)
cT4	36 (14.5)	87 (45.3)	56 (47.9)	0	22 (17.6)	9 (19.6)	9 (13.6)	41 (32.3)	6 (12.0)	4 (16.0)	18 (18.2)	5 (4.9)
cN stage												
cN0	117 (47.0)	66 (34.4)	20 (17.1)	3 (17.6)	18 (14.4)	18 (39.1)	10 (15.2)	57 (44.9)	10 (20.0)	9 (36.0)	14 (14.1)	52 (50.5)
cN1	112 (45.0)	50 (26.0)	45 (38.5)	5 (29.4)	66 (52.8)	18 (39.1)	35 (53.0)	41 (32.3)	18 (36.0)	13 (52.0)	36 (36.4)	32 (31.1)
cN2	20 (8.0)	76 (39.6)	52 (44.4)	9 (53.0)	41 (32.8)	10 (21.8)	21 (31.8)	29 (22.8)	22 (44.0)	3 (12.0)	49 (49.5)	19 (18.4)
Tumor location (LOREC criteria)												
Above	106 (42.6)	59 (30.7)	70 (59.8)	12 (70.6)	42 (33.6)	10 (21.7)	17 (25.8)	54 (42.5)	4 (8.0)	4 (16.0)	20 (20.2)	29 (28.2)
Below	143 (57.4)	133 (69.3)	47 (40.2)	5 (29.4)	83 (66.4)	36 (78.3)	49 (74.2)	73 (57.5)	46 (92.0)	21 (84.0)	79 (79.8)	74 (71.8)
Tumor location (Japanese criteria),												
Above	41 (16.5)	21 (10.9)	2 (1.7)	12 (70.6)	3 (2.4)	7 (15.2)	9 (13.6)	21 (16.5)	2 (4.0)	0	7 (7.1)	31 (30.1)
Below	208 (83.5)	171 (89.1)	115 (98.3)	5 (29.4)	122 (97.6)	39 (84.8)	57 (86.4)	106 (83.5)	48 (96.0)	25 (100)	92 (92.9)	72 (69.9)
Preoperative radiotherapy												
No	31 (12.4)	17 (8.9)	15 (12.8)	0	15 (12.0)	46 (100)	0	41 (32.3)	1 (2.0)	0	36 (36.4)	46 (44.6)
Short-course radiotherapy	7 (2.8)	32 (16.7)	56 (47.9)	7 (41.2)	1 (0.8)	0	13 (19.7)	0	11 (22.0)	6 (24.0)	20 (20.2)	18 (17.5)
Long-course radiotherapy	211 (84.8)	143 (74.4)	46 (39.3)	10 (58.8)	109 (87.2)	0	53 (80.3)	86 (67.7)	38 (76.0)	19 (76.0)	43 (43.4)	39 (37.9)
Operation												
Low anterior resection	113 (45.4)	93 (48.4)	19 (16.2)	8 (47.1)	62 (49.6)	13 (28.3)	29 (43.9)	75 (59.1)	27 (54.0)	12 (48.0)	54 (54.6)	69 (67.0)
(Extended) abdominoperineal resection	74 (29.7)	80 (41.7)	98 (83.8)	9 (52.9)	28 (22.4)	12 (26.1)	32 (48.5)	44 (34.7)	21 (42.0)	10 (40.0)	31 (31.3)	12 (11.7)
Intersphincteric resection	54 (21.7)	0	0	0	30 (24.0)	13 (28.3)	1 (1.5)	4 (3.1)	0	0	14 (14.1)	19 (18.4)
Hartmann's operation	5 (2.0)	19 (9.9)	0	0	1 (0.8)	4 (8.7)	1 (1.5)	0	0	0	0	2 (1.9)
Pelvic exenteration	3 (1.2)	0	0	0	2 (1.6)	2 (8.3)	3 (3.0)	4 (3.1)	3 (12.0)	3 (12.0)	0	1 (1.0)
Others	0	0	0	0	2 (1.6)	2 (4.3)	1 (1.5)	0	0	0	0	0
Procedure for LLN(s)												
LLN dissection	73 (29.3)	0	8 (6.8)	0	5 (4.0)	35 (76.1)	0	0	0	0	0	21 (20.4)
Adjuvant chemotherapy	125 (50.2)	27 (14.1)	29 (24.8)	2 (11.8)	62 (49.6)	12 (26.1)	3 (4.5)	16 (12.6)	37 (74.0)	15 (60.0)	79 (79.8)	42 (40.8)
Missing	0	0	0	0	0	0	0	109 (85.8)	0	3 (12.0)	0	0

(continued on following page)

TABLE A2. Overview of Baseline Characteristics Per Institution (continued)

Characteristic	CIH (JPN)	Catharina (NED)	Karolinska (SWE)	Leiden (NED)	MSKCC (US)	Nagoya (JPN)	NCI (NED)	Oxford (ENG)	RAH (AUS)	RPA (AUS)	St Mary (KOR)	Toranomon (JPN)
(y)pT												
(y)pT0-2	126 (50.6)	89 (46.4)	42 (35.9)	7 (41.2)	79 (63.2)	15 (32.6)	28 (42.4)	46 (36.2)	20 (40.0)	9 (36.0)	41 (41.4)	40 (38.8)
(y)pT3-4	123 (49.4)	103 (53.6)	75 (64.1)	10 (58.8)	46 (36.8)	31 (67.4)	38 (57.6)	81 (63.8)	30 (60.0)	16 (64.0)	58 (58.6)	63 (61.2)
(y)pN positive	82 (32.9)	63 (32.8)	45 (38.5)	8 (47.1)	27 (21.6)	11 (23.9)	25 (37.9)	41 (32.3)	18 (36.0)	7 (28.0)	34 (34.3)	33 (32.0)
R1 resection (yes)	3 (1.2)	13 (6.8)	9 (7.7)	2 (11.8)	15 (12.0)	1 (2.2)	6 (9.1)	15 (11.8)	5 (10.0)	3 (12.0)	2 (2.0)	0
Visible LLN	169 (67.9)	116 (60.4)	50 (42.7)	11 (64.7)	76 (60.8)	12 (26.1)	41 (62.1)	74 (58.3)	18 (36.0)	16 (64.0)	53 (53.5)	67 (65.0)
Location of LLN												
External iliac	7 (4.1)	6 (5.2)	6 (12.0)	0	1 (1.3)	0	5 (12.2)	17 (23.0)	7 (38.9)	0	4 (7.5)	4 (6.0)
Obturator	78 (46.2)	86 (74.1)	34 (68.0)	8 (72.7)	61 (80.3)	6 (50.0)	29 (70.7)	37 (50.0)	8 (44.4)	16 (100)	39 (73.6)	46 (68.6)
Internal iliac	84 (49.7)	24 (20.7)	10 (20.0)	3 (27.3)	14 (18.4)	6 (50.0)	7 (17.1)	20 (27.0)	3 (16.7)	0	10 (18.9)	17 (25.4)
Median size of visible LLN, mm (IQR)												
LA before (C)RT	6.0 (5.0-8.5)	7.0 (5.5-9.6)	9.0 (7.0-12.0)	7.1 (5.9-10.4)	8.0 (6.0-11.0)	10.5 (9.0-12.8)	6.0 (4.5-8.0)	7.0 (5.0-11.0)	7.0 (5.9-10.1)	6.0 (5.0-8.8)	7.5 (5.3-9.5)	5.0 (4.0-7.1)
SA before (C)RT	4.0 (3.0-6.5)	5.6 (3.4-7.6)	6.5 (5.0-9.0)	4.7 (3.9-7.6)	6.0 (5.0-7.0)	8.4 (6.5-11.0)	5.0 (4.0-6.0)	5.0 (3.0-7.3)	5.0 (4.8-7.1)	4.5 (3.3-5.8)	4.7 (3.7-7.0)	3.6 (2.9-5.6)
LA after (C)RT	4.0 (3.0-6.0)	4.0 (2.9-5.6)	6.0 (3.0-8.0)	6.4 (5.2-7.0)	6.0 (3.0-9.0)	—	5.0 (3.0-7.0)	5.0 (3.5-8.5)	—	—	5.3 (4.2-7.1)	3.7 (3.0-5.5)
SA after (C)RT	3.0 (2.0-4.0)	4.1 (3.0-5.6)	4.0 (2.0-7.0)	4.9 (4.0-5.9)	4.0 (3.0-5.0)	—	4.0 (2.8-5.0)	3.0 (2.5-6.0)	—	—	3.7 (2.3-4.3)	3.0 (2.0-4.0)
Malignant feature(s) before (C)RT	32 (18.9)	48 (41.4)	35 (70.0)	3 (27.3)	29 (38.2)	3 (25.0)	10 (24.4)	11 (14.9)	1 (5.6)	13 (81.3)	15 (28.3)	8 (11.9)
Malignant feature(s) after (C)RT	17 (13.4)	30 (35.3)	12 (29.3)	1 (14.3)	11 (31.4)	—	9 (29.0)	5 (10.2)	—	—	5 (16.1)	4 (14.3)
5-year LLR rate, %	5.2	6.5	4.8	0	5.9	9.1	6.6	10.2	0	4.2	6.0	0
5-year LR rate, %	6.9	13.3	8.8	0	10.9	13.3	14.3	16.0	2.0	4.2	15.5	4.1
5-year DR rate, %	18.3	34.0	32.6	28.1	19.3	15.3	35.1	26.6	12.7	14.5	24.6	19.0
5-year CSS rate, %	92.1	74.6	78.0	90.0	94.3	88.9	72.9	81.0	89.9	85.6	85.2	92.2

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: AUS, Australia; CIH, Cancer Institute Hospital; (C)RT, (chemo)radiotherapy; CSS, cancer-specific survival; DR, distant recurrence; IQR, interquartile range; JPN, Japan; KOR, Korea; LA, long axis; LLN, lateral lymph node; LLR, lateral local recurrence; LOREC, Low Rectal Cancer National Development Program; LR, local recurrence; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, Netherlands Cancer Institute; NED, the Netherlands; RAH, Royal Adelaide Hospital; RPA, Royal Prince Alfred Hospital; SA, short axis; SD, standard deviation; SWE, Sweden; US, United States.

TABLE A3. Patient Characteristics According to SA of the LLN in Patients Who Received (C)RT

Characteristic	No LLN Visible (n = 387)	SA < 7 mm (n = 410)	SA ≥ 7 mm (n = 171)	*P*
Sex				.090
Male	246 (63.6)	278 (67.8)	100 (58.5)	
Female	141 (36.4)	132 (32.2)	71 (41.5)	
Age, years				.487
< 62	198 (51.2)	203 (49.5)	94 (55.0)	
≥ 62	189 (48.8)	207 (50.5)	77 (45.0)	
cT stage				< .001
cT3	288 (74.4)	317 (77.3)	101 (59.1)	
cT4	99 (25.6)	93 (22.7)	70 (40.9)	
ypN stage				< .001
cN0	113 (29.2)	141 (34.4)	33 (19.3)	
cN1	171 (44.2)	156 (38.0)	52 (30.4)	
cN2	103 (26.6)	113 (27.6)	86 (50.3)	
Tumor location (LOREC criteria)				.433
Above	141 (36.4)	135 (32.9)	54 (31.6)	
Below	246 (63.6)	275 (67.1)	117 (68.4)	
Tumor location (Japanese criteria)				.936
Above	42 (10.9)	42 (10.2)	17 (9.9)	
Below	345 (89.1)	368 (89.8)	154 (90.1)	
Preoperative radiotherapy				.004
Short-course radiotherapy	86 (22.2)	66 (16.1)	19 (11.1)	
Long-course radiotherapy	301 (77.8)	344 (83.9)	152 (88.9)	
Location of LLN				< .001
No LLN visible or external iliac	387 (100)	32 (7.8)	11 (6.4)	
Obturator	—	283 (69.0)	91 (53.2)	
Internal iliac	—	95 (23.2)	69 (40.4)	
Median LA size before (C)RT, mm (IQR)	—	6.0 (5.0-7.0)	11.7 (9.1-16.0)	< .001
Malignant feature(s) before (C)RT				< .001
No LLN visible	387 (100)	—	—	
Absent	—	339 (82.7)	53 (31.0)	
Present	—	71 (17.3)	118 (69.0)	
Operation				.002
Sphincter preserving	241 (62.3)	255 (62.2)	81 (47.4)	
Nonsphincter preserving	146 (37.7)	155 (37.8)	90 (52.6)	
R status				.106
R0	358 (92.5)	390 (95.1)	155 (90.6)	
R1	29 (7.5)	20 (4.9)	16 (9.4)	
LLN dissection				< .001
No	383 (99.0)	369 (90.0)	118 (69.0)	
Yes	4 (1.0)	41 (10.0)	53 (31.0)	
Adjuvant chemotherapy				.283
No	218 (56.4)	229 (55.9)	81 (47.4)	
Yes	136 (35.1)	151 (36.8)	72 (42.1)	
Unknown	33 (8.5)	30 (7.3)	18 (10.5)	

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: (C)RT, (chemo)radiotherapy; IQR, interquartile range; LA, long axis; LLN, lateral lymph node; LOREC, Low Rectal Cancer National Development Program; SA, short axis.

TABLE A4. Univariable Analyses for Risk Factors for LLR, LR, DR, and CSS in the Total Cohort

		LLR			LR			DR			CSS		
Variable	**No.**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Sex				.127			.046			.235			.822
Male	774	1			1			1			1		
Female	442	1.490	0.893 to 2.486		1.471	1.007 to 2.148		0.859	0.669 to 1.104		0.964	0.702 to 1.324	
Age, years				.949			.750			.145			.008
< 62	589	1			1			1			1		
≥ 62	627	1.017	0.610 to 1.694		1.063	0.729 to 1.551		1.192	0.941 to 1.510		1.525	1.118 to 2.082	
Tumor location (LOREC criteria)				.377			.073			.330			.055
Above	427	1			1			1			1		
Below	789	1.284	0.738 to 2.235		1.469	0.964 to 2.239		1.132	0.882 to 1.454		1.390	0.994 to 1.944	
Tumor location (Japanese criteria)				.526			.777			.671			.986
Above	156	1			1			1			1		
Below	1,060	1.314	0.565 to 3.057		1.087	0.609 to 1.941		1.081	0.755 to 1.547		0.996	0.636 to 1.560	
cT stage				.011			.001			< .001			< .001
cT3	923	1			1			1			1		
cT4	293	1.989	1.173 to 3.371		1.899	1.282 to 2.812		1.712	1.334 to 2.196		2.101	1.539 to 2.869	
cN stage				.023			.013			.002			.005
cN0	394	1			1			1			1		
cN1	471	0.805	0.407 to 1.593		1.102	0.673 to 1.806		1.174	0.868 to 1.588		1.079	0.728 to 1.597	
cN2	351	1.812	0.983 to 3.339		1.868	1.163 to 3.000		1.682	1.247 to 2.269		1.747	1.196 to 2.551	
(C)RT				.534			.488			.083			.211
Yes	968	1			1			1			1		
No	248	1.210	0.664 to 2.204		1.171	0.749 to 1.832		0.756	0.551 to 1.038		0.772	0.514 to 1.158	
Location of LLN				< .001			.087			.343			.186
No LLN visible or external iliac	570	1			1			1			1		
Obturator	448	1.863	0.967 to 3.592		0.998	0.645 to 1.543		1.123	0.871 to 1.449		1.008	0.729 to 1.395	
Internal iliac	198	4.260	2.210 to 8.212		1.643	1.016 to 2.657		0.864	0.604 to 1.237		0.642	0.390 to 1.057	

(continued on following page)

TABLE A4. Univariable Analyses for Risk Factors for LLR, LR, DR, and CSS in the Total Cohort (continued)

		LLR			LR			DR			CSS		
Variable	**No.**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
SA before (C)RT				< .001			< .001			.621			.226
No LLN visible or SA < 7 mm	1,024	1			1			1			1		
SA ≥ 7 mm	192	3.866	2.300 to 6.499		2.490	1.654 to 3.751		1.083	0.789 to 1.486		1.269	0.863 to 1.865	
Malignant feature(s) before (C)RT				< .001			.015			.515			.349
No LLN visible or absent	1,008	1			1			1			1		
Present	208	3.052	1.801 to 5.174		1.716	1.110 to 2.653		1.107	0.815 to 1.504		1.202	0.818 to 1.768	
Operation				.019			.023			.001			< .001
Sphincter preserving	741	1			1			1			1		
Nonsphincter preserving	475	1.841	1.104 to 3.069		1.551	1.063 to 2.263		1.475	1.165 to 1.868		2.044	1.507 to 2.772	
LLN dissection				.457			.545			.009			.037
Yes	142	1			1			1			1		
No	1,074	0.764	0.376 to 1.553		1.213	0.650 to 2.262		1.834	1.163 to 2.890		1.916	1.039 to 3.532	
R status				.005			< .001			< .001			< .001
R0	1,142	1			1			1			1		
R1	74	3.564	1.750 to 7.260		3.514	2.063 to 5.984		2.933	2.037 to 4.224		4.823	3.204 to 7.260	
Adjuvant chemotherapy				.779			.940			.760			.601
Yes	449	1			1			1			1		
No	655	1.085	0.613 to 1.919		1.016	0.669 to 1.554		1.040	0.810 to 1.335		0.916	0.658 to 1.274	

Abbreviations: (C)RT, (chemo)radiotherapy; CSS, cancer-specific survival; DR, distant recurrence; HR, hazard ratio; LLN, lateral lymph node; LLND, lateral lymph node dissection; LLR, lateral local recurrence; LOREC, Low Rectal Cancer National Development Program; LR, local recurrence; SA, short axis.