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CLINICAL INVESTIGATION

Coverage of Lateral Lymph Nodes in Rectal Cancer Patients with Routine Radiation Therapy Practice and Associated Locoregional Recurrence Rates

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Purpose: Involved internal iliac and obturator lateral lymph nodes (LLNs) are a known risk factor for the occurrence of ipsilateral local recurrences (LLR) in rectal cancer. This study examined coverage of LLNs with routine radiation therapy practice in the Netherlands and associated LLR rates.

Methods and Materials: Patients with a primary tumor ≤8 cm of the anorectal junction, cT3-4 stage, and at least 1 internal iliac or obturator LLN with short axis ≥5 mm who received neoadjuvant (chemo)radiation therapy, were selected from a national, cross-sectional study of patients with rectal cancer treated in the Netherlands in 2016. Magnetic resonance images and radiation therapy treatment plans were reviewed regarding segmented LLNs as gross tumor volume (GTV), location of LLNs within clinical target volume (CTV), and received proportion of the planned radiation therapy dose.

Results: A total of 223 out of 3057 patients with at least 1 LLN ≥5 mm were selected. Of those, 180 (80.7%) LLNs were inside the CTV, of which 60 (33.3%) were segmented as GTV. Overall, 202 LLNs (90.6%) received ≥95% of the planned dose. Four-year LLR rates were not significantly higher for LLNs situated outside the CTV compared with those inside (4.0% vs 12.5%, $P = .092$) or when receiving <95% versus ≥95% of the planned radiation therapy dose (7.1% vs 11.3%, $P = .843$), respectively. Two of 7 patients who received a dose escalation of 60 Gy developed an LLR (4-year LLR rate of 28.6%).

Conclusions: This evaluation of routine radiation therapy practice showed that adequate coverage of LLNs was still associated with considerable 4-year LLR rates. Techniques resulting in better local control for patients with involved LLNs need to be explored further.

Introduction

Despite improvements in rectal cancer treatment through neoadjuvant (chemo)radiation therapy and total mesorectal excision (TME) surgery, an increasing proportion of local recurrences (LR) are occurring in the lateral compartments.[1,2] These ipsilateral local recurrences (LLR) are most likely due to insufficient treatment of lateral lymph nodes (LLNs) in that compartment.[3-6] Unfortunately, consensus on the appropriate treatment of LLNs is lacking.[7] Globally, differences exist concerning the adequate treatment of LLNs. While Japanese physicians have historically omitted neoadjuvant therapy and favored the prophylactic lateral lymph node dissection (LLND) for advanced rectal cancer,[8-12] Western physicians considered neoadjuvant radiation therapy as sufficient treatment for the lateral compartments.[9,13,14] Furthermore, involved LLNs were often regarded as a sign of metastatic disease from the Western perspective, thereby not appreciating the potential benefits of LLND.[15] Some reconciliation has occurred, with an increase in research concerning neoadjuvant therapy and selective LLND in cases of primarily enlarged LLNs, or those with inadequate response to neoadjuvant treatment.[3,16-18]

A recent survey revealed that 33 of 62 Dutch colorectal surgeons (53.2%) would choose radiation therapy with dose escalation as ideal treatment of suspicious LLNs,[19] along with 63% (138/220) amongst American radiation oncologists.[20] However, there is currently no conclusive evidence to support this, with very few studies providing mixed results. Alternatively, selective LLND after neoadjuvant therapy might be considered, which is supported by recent studies.[21,22]

An unresolved issue is whether radiation therapy with sufficient dose can prevent LLR. The radiation therapy dose

to individual LLNs during routine radiation therapy has never been investigated, nor whether there is a dose-effect relationship with LLR as a clinically relevant parameter. Such data will provide valuable answers to further determine the role of radiation therapy in the treatment of LLNs. The objective of this study was to determine the coverage of LLNs and received doses during routine radiation therapy practice in the Netherlands, and correlate these with LLR rates.

Methods and Materials

Patients were selected from a national, cross-sectional cohort study that included all patients who underwent rectal cancer surgery between January 1, 2016, and December 31, 2016, in the Netherlands. Patients were identified from the Dutch ColoRectal Audit (DCRA), which registers short-term oncological outcomes for these patients. Additional diagnostic, therapeutic, and long-term follow-up variables were collected to expand this DCRA data.

This "Snapshot" design allowed for the compilation of population-based data in a short period. A research team in each participating center, including a surgeon with supervised residents, abdominal radiologist, and radiation oncologist, collected data regarding their patients. This project had 3 parts. Once surgical and oncological data were gathered (part 1), participating radiologists, after additional training, identified and re-reviewed the low (≤8 cm from the anorectal junction) tumors of at least clinical T3 stage in their own hospital (part 2). Those with a LLN (short axis ≥5 mm) were selected for review by radiation oncologists (part 3) (Fig. 1). As only patients undergoing resection are registered in the DCRA, it was not expected that the presence of distant metastases would influence radiation therapy target volumes, and thus patients with metastases were not excluded. Appendix 1 describes additional privacy details.

Terminology

The gross tumor volume (GTV) denotes delineations around the primary tumor and/or macroscopically involved lymph nodes. The clinical target volume (CTV) contains the GTV plus a margin, as well as areas with possible microscopic tumor spread. Received dose was the calculated dose based on the planning computed tomography (CT) scan and was not corrected for possible uncertainties as a result of organ motion. Radiation therapy doses were divided into ≥95%, 50% to 94%, and <50% of the received dose (Fig. 2).

LLN location was classified according to surgical definitions. The lateral edge of the main internal iliac artery trunk forms a border between the internal iliac compartment (medial) and obturator compartment (lateral). Once the artery exits the pelvis, only the obturator compartment remains. External iliac areas are not included in lateral compartment delineation guidelines, so patients with only external iliac nodes were excluded.[23] Furthermore, analyses from part 2 demonstrated that patients who only had external nodes did not have any long-term lateral local recurrences.[24]

In total, 30 patients in the current cohort underwent some form of additional LLN surgery, including 23 node sampling and 7 incomplete LLND. None were formal LLND. A separate analysis of patients undergoing LLN-surgery in 2016 revealed similar long-term LLR rates for these patients compared with those who did not undergo additional surgery (around 15%),[25] highlighting the inexperience of Western surgeons with these procedures. Because additional LLN surgery was not standard in the Netherlands in 2016 and did not positively influence LLR rates, it has not been considered separately.

Preparation and assessment

All Dutch radiation oncology centers participated and examined the included patients selected from part 2. During an initial preparatory meeting (January 2021), anatomic borders of the lateral compartments were discussed. Surgical definitions (mentioned previously) were compared with radiation oncology definitions, in which the compartments lie ventrally and dorsally of each other (Fig. 3).[7] This led to an amendment of the Dutch radiation oncology delineation guideline for the names of the lateral compartments to reduce ambiguity. After this, all participating radiation oncologists completed an e-learning to test these definitions. Radiation oncologists had a mean accuracy of 90% when classifying compartments according to surgical definitions. A second meeting (December 2021) regarded logistics of the current study. After this, data entry of part 3 started. LLN size and location as reviewed by the local radiologist were provided along with magnetic resonance imaging series/slide numbers, allowing radiation oncologists to identify the same LLN on their planning CT scan with delineated target volumes and isodose lines of the given treatment. No other imaging was evaluated. Radiation oncologists reported the anatomic compartment (surgical definitions), whether located inside/outside the CTV, if a GTV was delineated, and the point-dose according to the dose distribution on the planning CT scan for that LLN. This was done for all visible LLNs, after which the largest LLN per patient was selected for most analyses. A central coordinator was present at 17 of 19 centers and available for questions by all participants.

Statistics

Analyses were conducted in SPSS Statistics, version 26.0 (IBM). Continuous variables are presented as the mean with standard deviation or median with an interquartile range (IQR); categorical data are numbers with percentages. Subgroups were examined with χ^2 or independent t tests. LLRs were only correlated to ipsilateral LLNs. Univariate analysis investigated a priori selected variables assumed to be

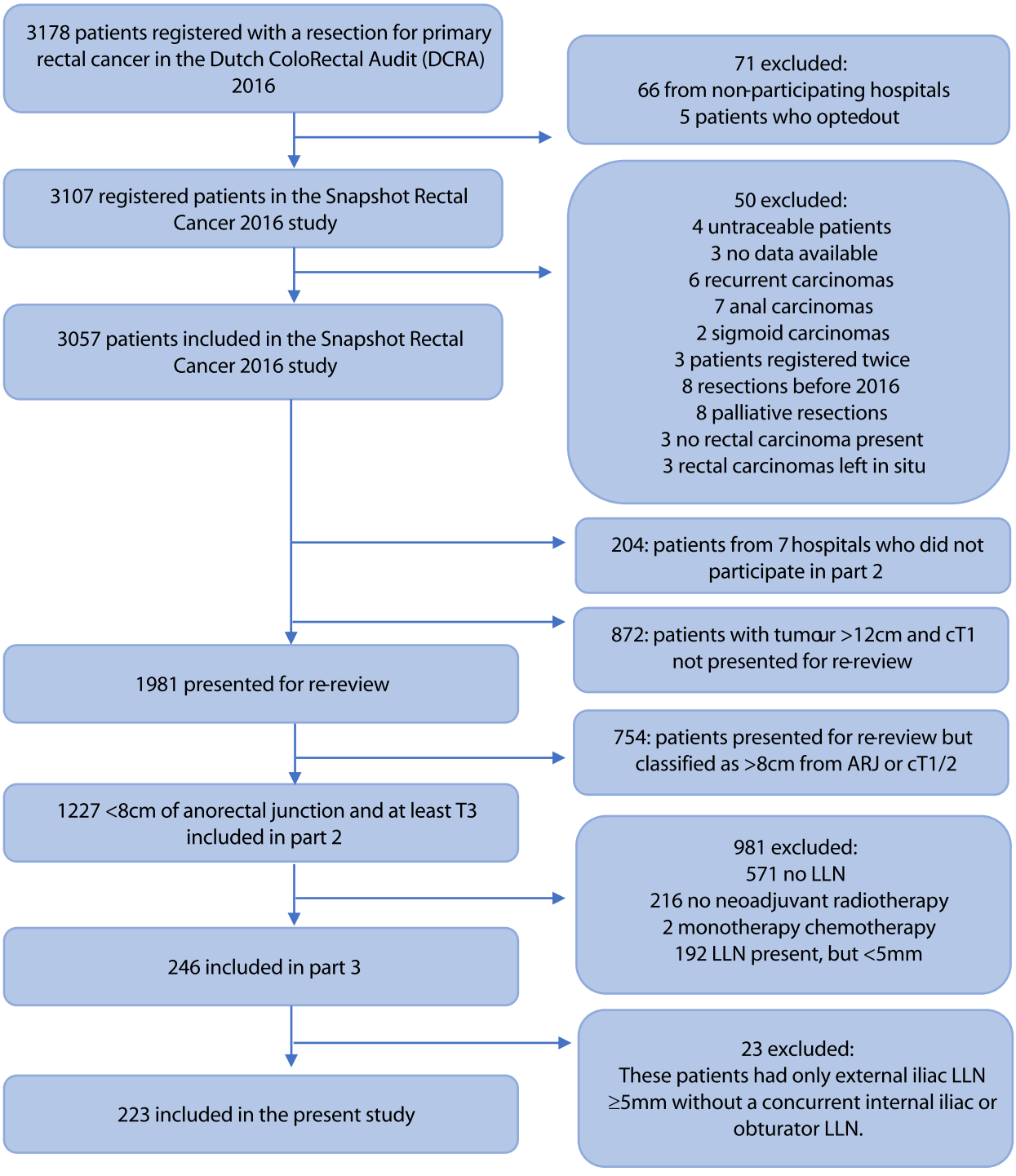

Fig. 1. Study participation flowchart.

predictors of oncological outcomes: LLN located inside/outside the CTV, radiation therapy dose (≥95%, 50%-94%, <50%), anatomic location, and LLN size. Four-year LR and LLR rates were examined for the different subgroups of patients and analyzed using Kaplan-Meier analysis with the log-rank test for comparison. A *P* value <.05 was considered statistically significant.

Ethics

The medical ethics board approved the study on June 30, 2020. Participating centers received local approval before commencing and each center decided whether their patients should provide written informed consent or an opportunity to opt out.

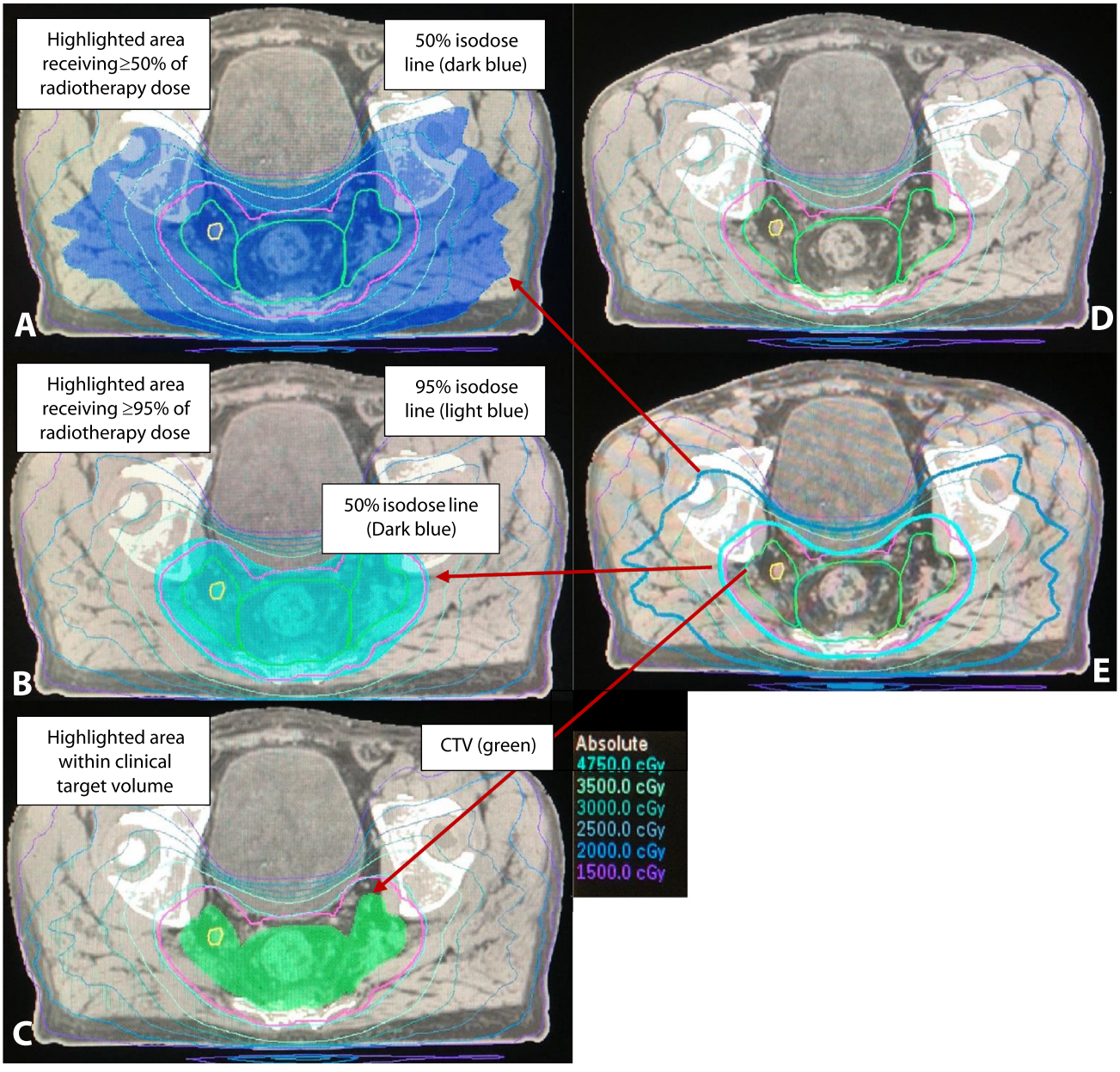

Fig. 2. Axial rectum computed tomography scan showing an enlarged lateral lymph node with the corresponding target volumes and isodose lines. The gross tumor volume (GTV; yellow circle) is the area delineation of a lateral lymph node. The clinical target volume (CTV; green) denotes the volume containing all GTVs with an additional margin for subclinical microscopic disease. The planning target volume (PTV; pink) is a fixed margin around the CTV to allow for possible variation such as bowel movements. Isodose lines represent percentages of the prescribed dose. (A) The area receiving ≥50% of the prescribed dose (within dark blue colour wash). (B) The area receiving ≥95% of the prescribed dose (within light blue colour wash). (C) The area inside the CTV (light green colour wash). (D) The standard setting with isodose lines, GTV, and CTV. (E) The 50% and 95% isodose lines are thickened.

Results

Sixty-seven of the 69 Dutch hospitals that performed rectal cancer surgery in 2016 participated, resulting in 3107 of 3178 (97.8%) eligible patients. The current study included 223 patients (Fig. 1). The largest LLN per patient was an internal iliac node in 35 cases and an obturator node in 188. The location following surgical definitions scored by the radiation oncologists was in accordance with radiologists in 75% of cases. Baseline characteristics are displayed in Table 1. Median follow-up was 48 months (IQR, 27-54 months).

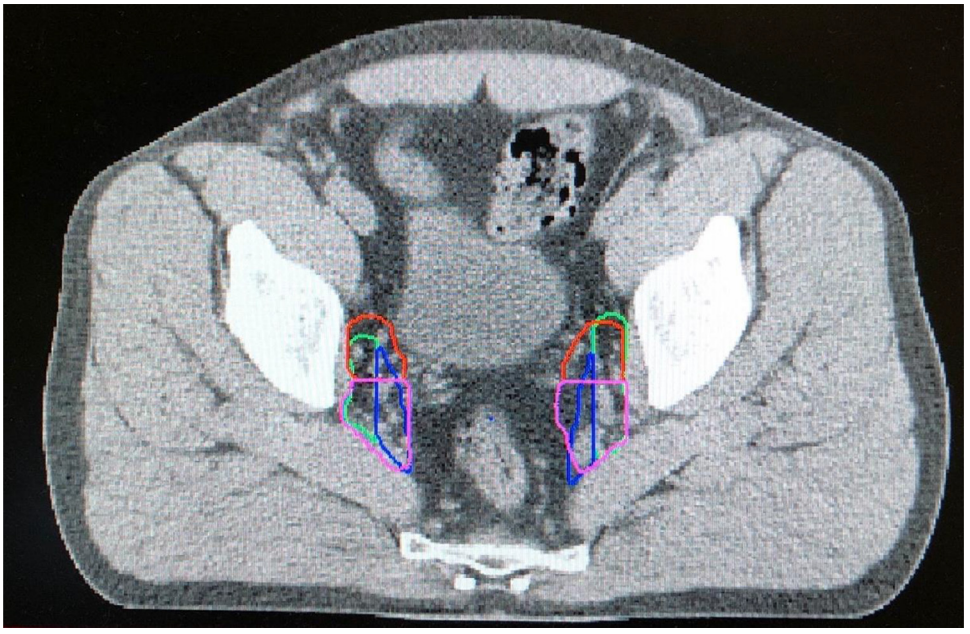

Fig. 3. Anatomic borders of lateral compartments per specialty. Differences in lateral border definitions for surgery versus radiation oncology. Red: radiation oncology obturator compartment. Pink: radiation oncology internal iliac compartment. Green: surgery obturator compartment. Blue: surgery internal iliac compartment. Surgical definitions adhere to the lateral border of the main trunk of the internal iliac artery as border between the obturator (lateral of this) and internal iliac (medial to this) compartments. Once the internal iliac artery exits the pelvis, all remaining lymphatic tissue is considered obturator compartment. According to radiation oncology definitions, the internal iliac compartment surrounds the internal iliac vessels (7 mm) and follows the internal iliac artery as it progresses through the pelvis. After exiting the pelvis, only the obturator compartment remains. The obturator compartment is located ventral of the internal iliac compartment.

Target volumes and doses

Thirty-three of 35 internal iliac LLNs (94.3%) and 147 of 188 obturator LLNs (78.2%) were within the CTV (Fig. 4A, 4B). Therefore, 41 obturator nodes (21.8%) and 2 (5.7%) internal iliac nodes were outside the CTV. Obturator nodes outside the CTV were predominantly located dorsal of the external iliac vessels (48.6%, Fig. 5A) or caudal of where the internal iliac artery leaves the pelvis (42.8%, Fig. 5B). The remaining 8.6% were against the lateral pelvic side-wall. For obturator nodes outside the CTV, 63.4% received ≥95% of the planned dose (26/41), 24.4% received 50% to 94% (10/41), and 12.2% received <50% (5/41).

Of the 180 LLNs inside the CTV, 60 LLNs (33.3%) had a separate GTV delineated, whereas 120 LLNs (66.7%) were in the CTV but not identified with a GTV. Two hundred two LLNs (90.6%) received ≥95% of the planned dose (including 7 that received 120% [60 Gy]), 16 (7.2%) received 50% to 94%, and 5 (2.2%) received <50%.

Ipsilateral local recurrence

Overall, 4-year LR and LLR rates for patients with LLNs were 19.4% and 10.8%, respectively. There was no significant difference in LR and LLR rates between short-course and chemoradiotherapy (CRT) or those with or without synchronous distant metastases (Appendix 2). Twenty-two patients (9.9%) had a pathological complete response (pCR: ypT0N0). One patient still developed a LLR (5.6%), compared with LR and LLR rates of 21.5% and 10.9%, respectively, for patients without pCR. These rates were not statistically significantly lower (LR: $P = .077$, LLR: $P = .374$), most likely due to the limited cohort size.

For patients with LLNs located inside or outside the CTV, 4-year LR rates were 20.5% versus 15.0% ($P = .333$) and LLR rates were 12.5% versus 4.0% ($P = .092$), respectively. LLNs were not significantly larger inside CTV (mean, 7.9 mm) versus outside (7.2 mm) ($P = .158$). Subanalyses according to size and compartment did not reveal significant differences in oncological outcomes (Figs. 4A, 4B, 5A, 5B). For the 41 obturator nodes located outside the CTV, 1 patient developed a LLR (4-year LLR 4.3%) and the 4-year LR rate was 18.3% (Appendix 3). According to the proportion of radiation therapy dose received (<50%, 50%-94%, and ≥95%), 4-year LR rates were 0%, 14.3%, and 20.1% ($P = .333$), and 4-year LLR rates were 0%, 7.1%, and 11.3% ($P = .843$), respectively. Again, subanalyses revealed no significant differences in LR or LLR rates (Figs. 4C, 4D, 5C, 5D).

Twenty patients developed an LLR. The median LLN size was 8.8 mm (IQR, 7.2-10.9 mm). Seven LLNs (35.0%) had a GTV delineation, and in 19 of the 20 cases (95.0%), the largest LLN was inside the CTV and received ≥95% of the planned dose. Similar results were found when analyzing only LLNs ≥7 mm (Appendix 4).

Table 1 Baseline characteristics (N = 233)

Characteristic	Number, mean, or median	Percentage, SD, or IQR
Male	143	64.1
Mean age (y)	63.2	SD, 11.0
Mean distance of tumor from anorectal junction (cm)	2.7	SD, 2.6
Tumor according to LOREC criteria*		
On or below	149	66.8
Above	74	33.2
Clinical T stage		
T3a (<1 mm beyond muscularis propria)	23	10.3
T3b (1-5 mm beyond muscularis propria)	65	29.1
T3c (5-15 mm beyond muscularis propria)	56	25.1
T3d (>15 mm beyond muscularis propria)	16	7.2
T4a (invasion of peritoneum)	15	6.7
T4b (invasion surrounding organs/structures)	48	21.5
Mesorectal clinical N stage		
N0	23	10.3
N1	83	37.2
N2	117	52.5
Threatened MRF on primary MRI or cT4 stage (tumor ≤1 mm of the MRF)	129	67.8
Extramural venous invasion on primary MRI	95	52.6
Tumor deposits on primary MRI	44	19.7
Synchronous distant metastases	25	11.2
Neoadjuvant radiation therapy		
Short-course radiation therapy†	68	30.5
Chemoradiotherapy	155	69.5
Dose escalation		
Only on primary tumor	2	0.9
On lateral lymph nodes	7	3.3
Median total volume of clinical tumor volume (cc)	642	IQR, 527-830
Median total volume of planning tumor volume (cc)	1347	IQR, 1190-1563
Mean time from end of neoadjuvant therapy to surgical resection (wk)	12	SD, 8.3
Resection of primary tumor		
Anterior resection/PME	5	2.2
Low anterior resection/TME	115	51.6
Abdominoperineal resection	103	46.2
Resection margins (%)		
R0	195	87.4
R1	28	12.6

Abbreviations: IQR = interquartile range; MRF = mesorectal fascia; MRI = magnetic resonance imaging; PME = partial mesorectal excision; SD = standard deviation; TME = total mesorectal excision.

* The English National Low Rectal Cancer Development program: the distal edge of the tumor is located on or below where the levator ani muscles meet the pelvic wall as seen on coronal MRI.

† Four patients also received some form of preoperative chemotherapy as participants in the RAPIDO trial.[26]

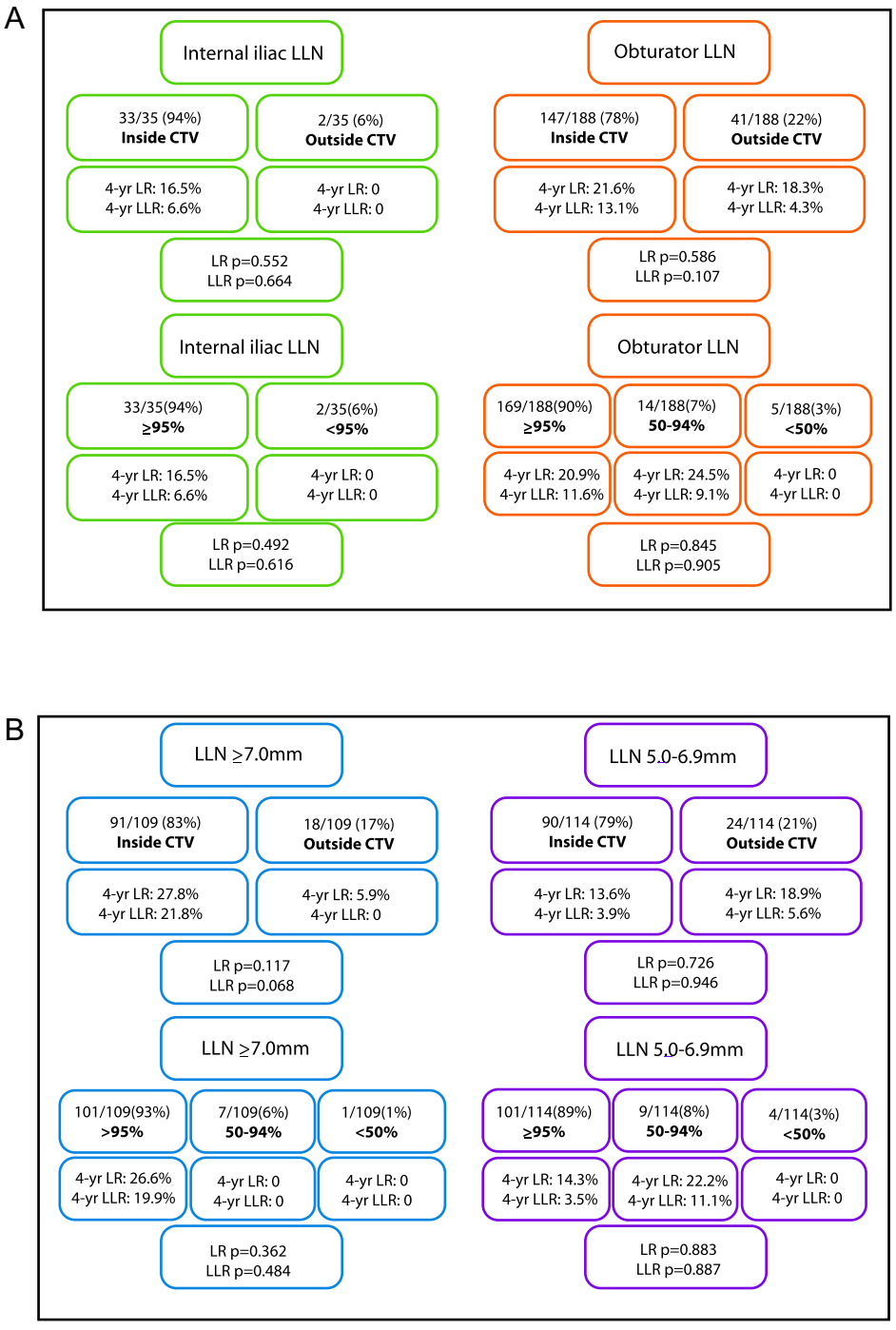

Fig. 4. (A) Number of internal iliac and obturator nodes inside and outside the clinical target volume (CTV) and receiving radiation therapy doses ≥95%, 50% to 94%, or <50% with correlated 4-year local recurrence (LR) and lateral local recurrence (LLR) rates. (B) Number of ≥7.0-mm and 5- to 6.9-mm nodes inside and outside the CTV and receiving radiation therapy doses ≥95%, 50% to 94%, or <50% with correlated 4-year LR and LLR rates.

Dose escalation

Seven patients received a dose escalation on the enlarged LLN. Four received 25 × 2 Gy CRT plus a simultaneous integrated boost (SIB) up to 60 Gy and 3 received an additional 10 Gy in 5 fractions after 25 × 2 Gy CRT. Two of the 7 developed an LLR (4-year LLR rate of 28.6%). Patients with dose escalation had the same median size LLN (6.9 mm [5.4-15.0 mm]) compared with 216 patients without (6.9 mm [5.7-8.3 mm]).

Multiple LLNs

In total, 100 patients (45%) had more than one LLN visible during radiation therapy delineation planning. The individual

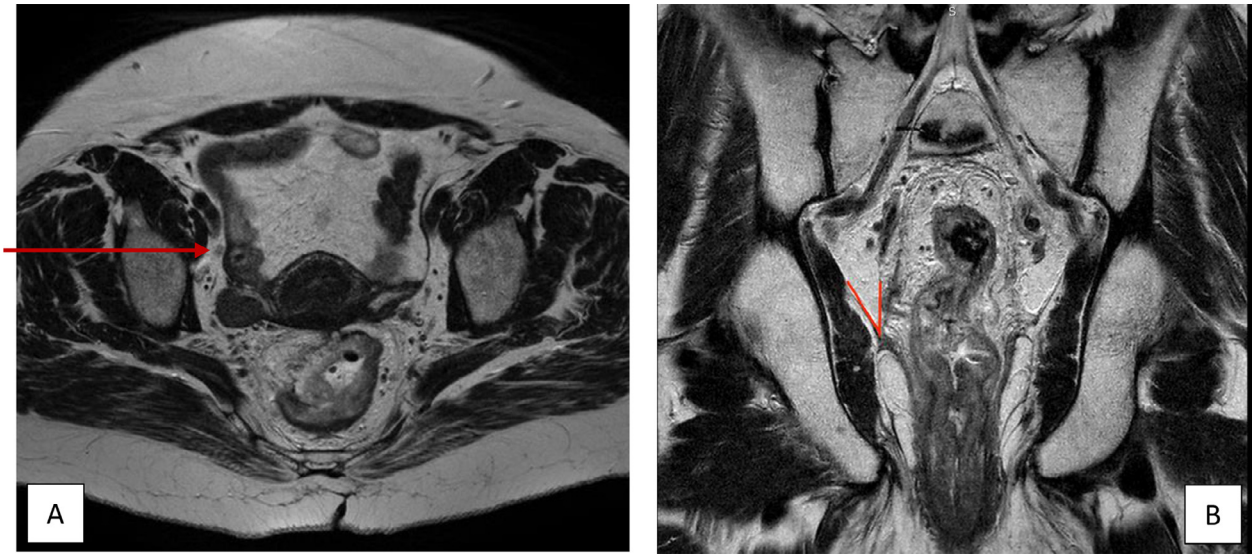

Fig. 5. Axial (A) and coronal (B) T2 magnetic resonance images displaying sections of the obturator compartment. These two areas were often left out of irradiation delineations. (A) Axial T2-weighted slice with red arrow showing an anterior obturator lateral lymph node located just behind the external iliac vessels. (B) Coronal T2-weighted slice in which red lines denote a deep section of the obturator compartment, which extends toward the levator ani muscle. This is the section caudal of where the internal iliac artery leaves the pelvis.

position within the CTV and point doses was evaluated for all visible LLNs per patient. Long-term LR and LLR rates were not statistically significant different for patients with multiple LLNs compared with patients with only one LLN. Similarly, cases where all LLNs were inside the CTV, or received ≥95% of the planned dose, did not result in significantly different 4-year LR or LLR rates compared with patients with a portion of LLNs outside the CTV or receiving lower doses (Table 2, Fig. 6).

When only considering patients with enlarged (≥7 mm short axis) LLNs (n = 122), 68 patients (56%) had multiple LLNs present (of all sizes). Again, both the presence of multiple LLNs, and their individual dose did not result in statistically significant differences in LR or LLR rates (Table 2). However, patients with multiple LLNs inside the CTV (48/68) did result in statistically higher LLR rates compared with patients with multiple LLNs situated both inside and outside the CTV (20/68) (25.1% vs 0%, $P = .029$).

For the 68 patients with multiple LLNs, more than half had at least 2 LLNs that were both ≥7 mm (38/68, 56%). The presence of multiple enlarged LLNs significantly increased the LLR rate (26% vs 4%, $P = .050$) compared with those with just 1 enlarged LLN (30/68). Again, the LLR rate was higher for patients with multiple enlarged LLN inside the CTV (24/38) compared with those with LLNs inside and outside the CTV (14/38) (42% vs 0%, $P = .014$). Furthermore, LLR rates were significantly higher for patients with multiple enlarged LLNs that all received ≥95% of the dose compared with those where lower doses were also given (37.9% vs 0%, $P = .034$) (Table 2, Fig. 6).

Discussion

This national, cross-sectional, cohort study assessed radiation therapy doses given to LLNs in patients with low, cT3-4 rectal cancer. Although 81% of LLNs were inside the clinical target volume (CTV), the vast majority of those outside the CTV still received ≥95% of the planned radiation therapy dose. These equivalent dose levels might explain why no significant differences were found in 4-year LR and LLR rates between patients. Dose escalation aiming for better control was applied in only 7 cases, limiting the ability to analyze the effects of this within this cohort.

One might hypothesize that LLNs located outside the CTV, or those receiving <95% of the planned radiation therapy dose, would more frequently lead to LLR compared with LLNs with optimal coverage. However, the present data do not support such a hypothesis. There was no statistical difference in LR or LLR rates for LLNs located inside or outside the CTV, or depending on the proportion of received dose. One explanation could be that LLNs inside the CTV might have a higher a priori risk of recurrent disease (these were also slightly larger, though not significantly so), were more often adequately identified on imaging due to their larger size (although not significant), and as a consequence more often included in target volumes. This is mirrored by the fact that boosted LLNs, which were on average larger LLNs, and therefore likely deemed most suspicious and aggressive, resulted in higher LLR rates than the smaller, nonsuspicious LLNs outside the CTV. This inverse relationship, though not statistically significant, implies that LLNs within the CTV are adequately identified as suspicious compared with LLNs not included in the CTV, and that radiation therapy,

Table 2 Four-year LR and LLR rates for patients with or without multiple LLNs, the positions of (multiple) LLNs with the CTV, and the received irradiation dose by (multiple) LLNs

Four-year LR and LLR rates for patients with or without multiple LLNs				
Factor	**4-y LR rate**	***P* value**	**4-y LLR rate**	***P* value**
Of the total 223 patients				
123 patients with only one LLN	16.6%	.206	7.3%	.152
100 patients with multiple LLNs	23.8%		13.2%	
Of the 122 patients with enlarged LLNs				
54 patients with only one LLN	20.8%	.876	12.2%	.802
68 patients with multiple LLNs (all sizes)	24.8%		17.1%	
Of the 68 patients with multiple LLNs				
30 patients with one enlarged LLN	12.0%	.089	26.0%	.050
38 patients with multiple enlarged LLNs	33.4%		4.0%	
Positions of (multiple) LLNs with the CTV				
Factor	**4-y LR rate**	***P* value**	**4-y LLR rate**	***P* value**
Of the 100/223 patients with multiple LLNs				
66 patients with LLNs all inside the CTV	27.3%	.247	19.1%	.051
34 patients with LLNs inside and outside the CTV	16.9%		4.5%	
Of the 68/122 patients with enlarged LLNs				
48 patients with LLNs all inside the CTV	31.6%	.116	25.1%	.029
20 patients with LLNs inside and outside the CTV	10.5%		0%	
Of the 38/68 patients with multiple enlarged LLNs				
24 patients with LLNs all inside the CTV	49.0%	.023	42.0%	.014
14 patients with LLNs inside and outside the CTV	7.7%		0%	
Received irradiation dose by (multiple) LLNs				
Factor	**4-y LR rate**	***P* value**	**4-y LLR rate**	***P* value**
Of the 100/223 patients with multiple LLNs				
72 patients with LLNs all receiving ≥95%	24.8%	.581	17.6%	.110
28 patients with LLNs receiving mixed doses	21.3%		5.6%	
Of the 68/122 patients with enlarged LLNs				
50 patients with LLNs all receiving ≥95%	29.2%	.248	23.1%	.059
18 patients with LLNs receiving mixed doses	12.5%		0%	
Of the 38/68 patients with multiple enlarged LLNs				
25 patients with LLNs all receiving ≥95%	44.6%	.065	37.9%	.034
13 patients with LLNs receiving mixed doses	9.1%		0%	

Abbreviations: CTV = clinical tumor volume; LLN = lateral lymph node; LLR = ipsilateral local recurrence; LR = local recurrence.

even a boost in its current form of 60 Gy, may not be enough to adequately treat suspicious LLNs. This is further supported by the evidence that cases with multiple LLNs that all LLNs received ≥95% of the dose and/or were in the CTV resulted in the highest LLR rates, insinuating that these were the most aggressive cases, in contrast to those in which LLNs were left outside the CTV or received lower doses.

Another explanation is that most patients in 2016 were treated with 3-dimensional (3D) conformal radiation therapy, explaining why LLNs outside the CTV still received a relatively high dose. An unpublished survey of all Dutch radiation oncology centers in 2020 revealed that ≥50% used 3D conformal techniques and PTV margins ranged from 0.5 to 2.5 cm, with a median of 1 cm, except for the anterior margin, which ranged up to 2.5 cm in some centers (with a median of 1.5 cm). Similar margins in 2016 would explain the broad coverage of LLNs, regardless of whether they were deliberately identified and included. However, this may change with an increase in more

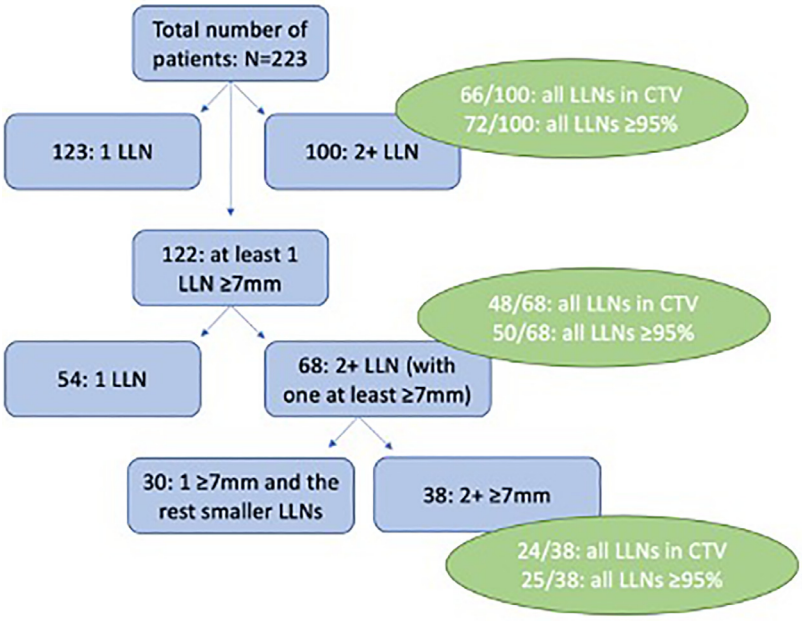

Fig. 6. Flowchart for selection of patients with multiple lateral lymph nodes (LLNs) for evaluation.

conformal techniques such as image-guided online adaptive radiation therapy, resulting in smaller CTV-PTV margins and a steeper dose decline for surrounding areas outside the CTV, which can hold unidentified LLNs. Although this may be advantageous for reducing radiation therapy—related toxicity, unidentified and thus untreated malignant LLNs pose a risk for local recurrence. Identification and delineation of a GTV for suspicious LLNs is therefore extremely important to guarantee inclusion in the CTV, especially for those located in vulnerable areas (Fig. 5A, 5B).

Of the 20 of 223 patients (9%) who developed an LLR after 4-year follow-up, 19 (95%) received ≥95% of the planned radiation therapy dose, implying that 50 Gy may be insufficient to prevent LLR. Based on a presumed dose-response effect, some dose escalation studies have examined whether radiation therapy on LLNs can be optimized. Importantly, very few studies have specifically investigated dose escalation on LLNs. One study of 12 patients with enlarged LLNs (≥10 mm) with dose escalation on LLNs (total dose of 59.4 Gy) showed similar overall survival rates compared with 41 patients without LLNs (total dose of 50.4 Gy).[27] However, considering the proven influence of LLNs on increased local recurrence rates, overall survival is not an ideal endpoint. A larger study of 202 patients with LLNs ≥5 mm examined the 3-year LLR rate for 48 patients who received CRT with dose escalation on LLNs (total dose of 58 Gy), 94 patients who received only neoadjuvant chemotherapy (without radiation therapy), and 60 patients who received CRT (total dose of 50 Gy). LLR rates were 2.3%, 31.6%, and 20.4%, respectively.[28] Another study compared 78 patients with simultaneous integrated boost to LLNs and the primary tumor (total dose of 55 Gy) to 94 patients without LLNs (71 received 55 Gy to primary tumor, 23 received 25 Gy).[29] Five-year local control rate was significantly better in the boost group (97% vs 86%, P = .026). These 2 larger studies imply that improvements may be achieved with dose escalation; however, current escalation up to 60 Gy may be insufficient. For example, Appelt et al established a relationship between dose and tumor regression for 222 patients and suggested that a >90 Gy dose is needed to achieve a pathologic complete response in 50% of patients.[30] This could explain why dose escalation up to 60 Gy in the current study still resulted in almost 30% LLR. However, further dose escalation may also influence the rate of fibrosis in the lateral compartments. This would theoretically make a subsequent lateral lymph node dissection (LLND) more difficult, with a higher risk of complications. Considering the limited amount of evidence specific for LLNs, future research concerning dose escalation is required, and it is hoped this will provide additional information necessary to aid in treatment decisions regarding radiation therapy and surgical options.

This study has several limitations, such as the retrospective design. The planning CT scan was often acquired separately from the magnetic resonance images, so LLNs were sometimes challenging to identify. Furthermore, it was assumed that the dose from the planning CT scan was the received dose. Classification of anatomic location can be difficult; one study found that consensus for location among radiologists after training was still limited to 75% to 85%.[31] In 2016, the majority of radiation therapy used 3D conformal/box techniques; currently, it is predominantly intensity modulated radiation therapy, dynamic-arc therapy, or image-guided online adaptive radiation therapy, which have steeper dose fall-offs outside the CTV. Present-day results may therefore provide different outcomes.

Conclusion

This national retrospective cross-sectional study investigated the individual radiation therapy doses of 223 patients

with low, cT3-4 stage rectal cancer with at least 1 LLN ≥5 mm. LLNs outside the CTV, or receiving <95% of the dose, did not result in higher 4-year LLR rates, and adequate coverage was associated with 4-year LLR rates of 11% to 13%. In an era in which online adaptive radiation therapy is increasing, suitable delineations should help ensure LLNs are not missed. In the current study, a GTV was delineated for only 60 LLNs, which can be improved. Further research is needed to investigate whether any additional reduction in LLR can be achieved with a lateral lymph node dissection or increased dose escalation.

References

1. Iversen H, Martling A, Johansson H, Nilsson PJ, Holm T. Pelvic local recurrence from colorectal cancer: Surgical challenge with changing preconditions. *Colorectal Dis* 2018;20:399-406.
2. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: Long-term follow-up of a population-based study. *Cancer* 2001;92:896-902.
3. Malakorn S, Yang Y, Bednarski BK, et al. Who should get lateral pelvic lymph node dissection after neoadjuvant chemoradiation? *Dis Colon Rectum* 2019;62:1158-1166.
4. Kusters M, Slater A, Muirhead R, et al. What to do with lateral nodal disease in low locally advanced rectal cancer? A call for further reflection and research. *Dis Colon Rectum* 2017;60:577-585.
5. Christou N, Meyer J, Toso C, Ris F, Buchs NC. Lateral lymph node dissection for low rectal cancer: Is it necessary? *World J Gastroenterol* 2019;25:4294-4299.
6. Williamson JS, Quyn AJ, Sagar PM. Rectal cancer lateral pelvic sidewall lymph nodes: A review of controversies and management. *Br J Surg* 2020;107:1562-1569.
7. Sluckin TC, Couwenberg AM, Lambregts DMJ, et al. Lateral lymph nodes in rectal cancer: Do we all think the same? A review of multidisciplinary obstacles and treatment recommendations. *Clin Colorectal Cancer* 2022;21:80-88.
8. Fujita S, Mizusawa J, Kanemitsu Y, et al. Mesorectal excision with or without lateral lymph node dissection for clinical stage II/III lower rectal cancer (JCOG0212): A multicenter, randomized controlled, noninferiority trial. *Ann Surg* 2017;266:201-207.
9. Watanabe T, Matsuda K, Nozawa K, Kobunai T. Lateral pelvic lymph node dissection or chemoradiotherapy: Which is the procedure of choice to reduce local recurrence rate in lower rectal cancer? *Ann Surg* 2008;248:342-343 author reply 3.
10. Yang X, Hu T, Gu C, et al. The prognostic significance of isolated tumor cells detected within lateral lymph nodes in rectal cancer patients after laparoscopic lateral lymph node dissection. *J Laparoendosc Adv Surg Tech A* 2019;29:1462-1468.
11. Yang X, Yang S, Hu T, et al. What is the role of lateral lymph node dissection in rectal cancer patients with clinically suspected lateral lymph node metastasis after preoperative chemoradiotherapy? A meta-analysis and systematic review. *Cancer Med* 2020;9:4477-4489.
12. Kanemitsu Y, Komori K, Shida D, et al. Potential impact of lateral lymph node dissection (LLND) for low rectal cancer on prognoses and local control: A comparison of 2 high-volume centers in Japan that employ different policies concerning LLND. *Surgery* 2017;162:303-314.
13. Kusters M, Beets GL, van de Velde CJ, et al. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. *Ann Surg* 2009;249(2):229-235.
14. Kim TH, Jeong SY, Choi DH, et al. Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. *Ann Surg Oncol* 2008;15:729-737.
15. Sluckin TC, Hazen SJA, Kusters M. From "east vs west" towards international multidisciplinary collaboration: An appraisal of lateral lymph nodes in rectal cancer. *Ann Gastroenterol Surg* 2021;5:731-737.
16. Akiyoshi T, Matsueda K, Hiratsuka M, et al. Indications for lateral pelvic lymph node dissection based on magnetic resonance imaging before and after preoperative chemoradiotherapy in patients with advanced low-rectal cancer. *Ann Surg Oncol* 2015;22(suppl 3):S614-S620.
17. Akiyoshi T, Ueno M, Matsueda K, et al. Selective lateral pelvic lymph node dissection in patients with advanced low rectal cancer treated with preoperative chemoradiotherapy based on pretreatment imaging. *Ann Surg Oncol* 2014;21:189-196.
18. Akiyoshi T, Watanabe T, Miyata S, Kotake K, Muto T, Sugihara K. Results of a Japanese nationwide multi-institutional study on lateral pelvic lymph node metastasis in low rectal cancer: Is it regional or distant disease? *Ann Surg* 2012;255:1129-1134.
19. Hazen SM, Sluckin T, Beets G, et al. Current practices concerning the assessment and treatment of lateral lymph nodes in low rectal cancer: A survey among colorectal surgeons in the Netherlands. *Acta Chir Belg* 2021;1-9.
20. Yahya JB, Herzig DO, Farrell MJ, et al. Does a fine line exist between regional and metastatic pelvic lymph nodes in rectal cancer-striking discordance between national guidelines and treatment recommendations by US radiation oncologists? *J Gastrointest Oncol* 2018;9:441-447.
21. Ogura A, Konishi T, Beets GL, et al. Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. *JAMA Surg* 2019;154 e192172.
22. Ogura A, Konishi T, Cunningham C, et al. 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. *J Clin Oncol* 2019;37:33-43.
23. Valentini V, Gambacorta MA, Barbaro B, et al. International consensus guidelines on clinical target volume delineation in rectal cancer. *Radiother Oncol* 2016;120:195-201.
24. Sluckin TC, van Geffen EGM, Hazen SJA, et al. Prognostic Implications of Lateral Lymph Nodes in Rectal Cancer: A Population-Based Cross-Sectional Study with Standardized Radiological Evaluation after Dedicated Training. [e-pub ahead of print]. *Dis Colon Rectum* 2023 2023. https://doi.org/10.1097/DCR.0000000000002752. Accessed June 5, 2023.
25. Sluckin T C, Kusters M. Evaluation of national surgical practice for lateral lymph nodes in rectal cancer in an untrained setting. *Ann Surg Oncol* 2023. https://doi.org/10.1245/s10434-023-13460-0.
26. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): A randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22:29-42.
27. Chen H, Nguyen KNB, Huang H, et al. Effect and safety of radiation therapy boost to extramesorectal lymph nodes in rectal cancer. *Pract Radiat Oncol* 2020;10:e372-e377.
28. Pang X, Huang L, Ma Y, et al. Management of clinically involved lateral lymph node metastasis in locally advanced rectal cancer: A radiation dose escalation study. *Front Oncol* 2021;11 674253.
29. Meldolesi E, Chiloiro G, Giannini R, et al. The role of simultaneous integrated boost in locally advanced rectal cancer patients with positive lateral pelvic lymph nodes. *Cancers (Basel)* 2022;14(7):1643.
30. Appelt AL, Pløen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2013;85:74-80.
31. Sluckin TC, Hazen SJA, Horsthuis K, et al. Significant improvement after training in the assessment of lateral compartments and short-axis measurements of lateral lymph nodes in rectal cancer. *Eur Radiol* 2022;33:483-492.