Prognostic implications of lateral lymph nodes in rectal cancer: a population-based cross-sectional study with standardized radiological evaluation after dedicated training

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ORIGINAL CONTRIBUTION

Prognostic Implications of Lateral Lymph Nodes in Rectal Cancer: A Population-Based Cross-Sectional Study with Standardized Radiological Evaluation after Dedicated Training

Running Head: Implications of lateral lymph nodes

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ABSTRACT

BACKGROUND: There is an ongoing discussion regarding the prognostic implications of the presence, short-axis diameter and location of lateral lymph nodes.

OBJECTIVE: To analyze lateral lymph node characteristics, the role of downsizing on restaging MRI and associated local recurrence rates for patients with cT3-4 rectal cancer after MRI re-review and training.

DESIGN: Retrospective population-based cross-sectional study.

SETTINGS: This collaborative project was led by local investigators from surgery and radiology departments in 60 Dutch hospitals.

PATIENTS: A total of 3057 patients underwent rectal cancer surgery in 2016: 1109 had cT3-4 tumor located ≤8 cm from the anorectal junction of which 890 received neoadjuvant therapy.

MAIN OUTCOME MEASURES: Local recurrence and ipsilateral local recurrence rates.

RESULTS: Re-review identified 314 patients (35%) with visible lateral lymph nodes. 30 of these patients had either only long-stretched obturator (n = 13) or external iliac (n = 17) nodes and both did not lead to any lateral local recurrences. The presence of internal iliac/obturator lateral lymph nodes (n = 284) resulted in 4-year local recurrence and lateral local recurrence rates of 16.4% and 8.8%, respectively. Enlarged (≥7 mm) lateral lymph nodes (n = 122) resulted in higher 4-year local recurrence (20.8%, 13.1%, 0%, $p < .001$) and lateral local recurrence (14.7%, 4.4%, 0%, $p < 0.001$) rates compared to smaller and no lateral lymph nodes, respectively. Visible lateral lymph nodes (hazard ratio 1.8 [1.1-2.8]) and enlarged lateral lymph nodes (hazard ratio 1.9 [1.1-3.5]) were independently associated with local recurrence in multivariable analysis. Enlarged lateral lymph nodes with malignant features had higher 4-year LLR rates of 17.0%. Downsizing had no impact on lateral local recurrence rates. Enlarged lateral lymph nodes were associated with higher univariate 4-year distant metastasis rates (36.4% 24.4%, p = 0.021), but not in multivariable analysis (hazard ratio 1.3 [0.9-1.]), and did not worsen overall survival.

LIMITATIONS: This study was limited by the retrospective design and total number of patients with lateral lymph nodes.

CONCLUSIONS: The risk of lateral local recurrence due to (enlarged) lateral lymph nodes was confirmed, but without prognostic impact of downsizing after neoadjuvant therapy. These results point towards the incorporation of primary lateral lymph node size into treatment planning.

IMPLICACIONES PRONÓSTICAS DE LOS GANGLIOS LINFÁTICOS LATERALES EN EL CÁNCER DE RECTO: UN ESTUDIO TRANSVERSAL DE BASE POBLACIONAL CON EVALUACIÓN RADIOLÓGICA ESTANDARIZADA DESPUÉS DE UN ENTRENAMIENTO ESPECÍFICO

ANTECEDENTES: Hay una discusión en curso sobre las implicaciones pronósticas de la presencia, el diámetro del eje corto y la ubicación de los ganglios linfáticos laterales.

OBJETIVO: Analizar las características de los ganglios linfáticos laterales, el papel de la reducción de tamaño en la RM de reestadificación y las tasas de recurrencia local asociadas para pacientes con cáncer de recto cT3-4 después de una nueva revisión y entrenamiento de RM.

DISEÑO: Estudio transversal retrospectivo de base poblacional.

CONFIGURACIÓN: Este proyecto de colaboración fue dirigido por investigadores locales de los departamentos de cirugía y radiología en 60 hospitales holandeses.

PACIENTES: 3057 pacientes fueron operados de cáncer de recto en 2016: 1109 tenían tumor cT3-4 ubicado a ≤8 cm de la unión anorrectal de los cuales 890 recibieron terapia neoadyuvante.

PRINCIPALES MEDIDAS DE RESULTADO: recurrencia local y tasas de recurrencia local ipsolateral.

RESULTADOS: Una nueva revisión identificó a 314 pacientes (35 %) con ganglios linfáticos laterales visibles. 30 de estos pacientes tenían solo ganglios obturadores estirados (n=13) o ilíacos externos (n=17) y ambos no provocaron recurrencias locales laterales. La presencia de ganglios linfáticos laterales ilíacos internos/obturadores (n = 284) dio como resultado tasas de recurrencia local y recurrencia local lateral a los 4 años del 16,4 % y el 8,8 %, respectivamente. Los ganglios linfáticos laterales agrandados (≥7 mm) (n = 122) dieron lugar a una mayor recurrencia local a los 4 años (20,8 %, 13,1 %, 0 %, p < 0,001) y recurrencia local lateral (14,7 %, 4,4 %, 0 %, p < 0,001) en comparación con ganglios linfáticos más pequeños y sin ganglios linfáticos laterales, respectivamente. Los ganglios linfáticos laterales visibles (índice de riesgo 1,8(1,1-2,8)) y los ganglios linfáticos laterales agrandados (índice de riesgo 1,9 [1,1-3,5]) se asociaron de forma independiente con la recurrencia local en el análisis multivariable. Los ganglios linfáticos laterales agrandados con características malignas tuvieron tasas de LLR a 4 años más altas del 17,0 %. La reducción de tamaño no tuvo impacto en las tasas de recurrencia local lateral. Los ganglios linfáticos laterales agrandados se asociaron con tasas univariadas más altas de metástasis a distancia a los 4 años (36,4 % 24,4 %, p = 0,021), pero no en el análisis multivariable (índice de riesgo 1,3 (0,9-1,8)), y no empeoró la supervivencia general.

LIMITACIONES: Este estudio estuvo limitado por el diseño retrospectivo y el número total de pacientes con ganglios linfáticos laterales.

CONCLUSIONES: Se confirmó el riesgo de recurrencia local lateral debido a los ganglios linfáticos laterales (agrandados), pero sin el impacto pronóstico de la reducción después de la

terapia neoadyuvante. Estos resultados apuntan hacia la incorporación del tamaño del ganglio linfático lateral primario en la planificación del tratamiento. *(Pre-proofed version)*

KEY WORDS: Lateral lymph nodes; MRI re-review; Rectal cancer.

INTRODUCTION

The adoption of adequate neoadjuvant therapy followed by total mesorectal excision (TME) surgery has helped reduce overall local recurrence (LR) rates for patients with locally advanced rectal cancer.[1–3] However, despite an absolute reduction, there has been a proportional increase in lateral local recurrences (LLR), most likely due to inadequate treatment of lateral lymph nodes (LLNs).[4] LLNs are situated outside the mesorectum and are not removed during standard TME surgery.

An international guideline for the appropriate treatment of LLNs is lacking. The recent, large-scale Lateral Node Consortium Study investigated oncological outcomes for patients with LLNs, and suggested that ≥7 mm (short-axis) LLNs should be considered clinically suspicious. These enlarged LLNs resulted in a 5-year LLR rate of 19.5%.[5] Furthermore, internal iliac LLNs remaining >4 mm and obturator LLNs remaining >6 mm on restaging MRI, had 5-year LLR rates of 52.3% and 17.8%, respectively, while LLNs which shrunk below these thresholds resulted in 0% LLR.[6] This suggests that primary and restaging sizes are needed to make appropriate treatment decisions, and that internal iliac LLNs had the highest absolute risk. Oncological outcomes for primarily, and persistently, enlarged LLNs found by the Consortium study, require validation. Additionally, the role of malignant features (heterogeneity, irregular border, loss of fatty center, round shape) is still unclear: while Ogura et al. found no significant association, Kroon et al. indicated a role for malignant features in smaller LLNs.[6,7]

The objective was to analyze prognostic implications of LLNs in patients with cT3-4 rectal cancer ≤8 cm from the anorectal junction after standardized MRI re-review and dedicated training.

MATERIALS AND METHODS

This population-based, cross-sectional cohort study examined all patients treated for primary rectal cancer between January 1 and December 31, 2016, in the Netherlands. A dataset of these patients was registered in the Dutch ColoRectal Audit (DCRA) during that period, and was expanded with additional variables collected between 15-10-2020 and 28-02-2022. A similar method is described elsewhere.[8] Each participating hospital formed a team of collaborators from Surgery, Radiology and Radiation oncology departments.

In part one, the surgical team from each hospital recorded diagnostic, therapeutic and follow-up variables based on patient-chart review. All data were verified centrally once collection was completed. A subset of patients (≤12 cm anorectal junction (ARJ: where the levator ani muscle meets the rectum on MRI), ≥cT2 stage, available MR-images) was extracted for review by the local participating radiologist(s). Based on MRI re-review, patients with a tumor ≤8 cm from the ARJ and ≥cT3 stage were included. Due to their influence on oncological outcomes, patients with synchronous metastases (≤3 months) were excluded (Fig. 1). Appendix 1 at https://links.lww.com/DCR/CXX provides details regarding data management and privacy.

Preassessment training

One or two consultant abdominal radiologist(s) per hospital participated in part two of this study and underwent a dedicated 2-hour training regarding LLNs, provided by expert radiologists (KH, RBT) with 17- and 24-years' experience, respectively. Significant improvements were seen for measurements and anatomical classifications of LLNs after training.[9] During this training, the color atlas by Ogura et al.[5,6] was explained in detail. Lateral compartments were defined as follows: the lateral border of the main trunk of the internal iliac artery separates the obturator compartment (lateral) from the internal iliac compartment (medial). Once the internal iliac artery exits the pelvis, all remaining lymphatic tissue is considered obturator compartment. External iliac LLNs were located ventral of the external iliac vessels. Afterwards, participants received an additional 23-minute Webinar describing the definitions of LLNs, and regarding extramural venous invasion (mr-EMVI) and tumor deposits.

After this, re-review commenced. A color atlas of an entire rectal MRI depicting the lateral compartments was created by the study team and distributed for use during re-review (Appendix 2 at https://links.lww.com/DCR/CXX). Participants reported LLN details such as the primary and restaging SA diameter, location according to the aforementioned definitions, and whether malignant features were present. If applicable, imaging of a (L)LR was also reviewed. The central coordinating researcher was often physically present to support the MRI re-review.

Outcome Analysis

Analyses were structured as follows (Fig. 2). Patients were divided into those who received neoadjuvant treatment (5x5Gy or 2x25Gy with concomitant oral capecitabine (825 mg/m^2), which is generally considered to be essential treatment for patients with LLNs, and those who did not. Main outcome parameters were 4-year LR and lateral LR (LLR) rates. Secondary outcomes were 4-year distant metastases (DM) and overall survival (OS). For all analyses, the largest LLN ipsilateral to the LLR was used. One patient developed an LLR on the contralateral side to the LLN due to a tumor deposit at the CRM. This patient was classified as developing LR, but not LLR due to LLN. Analyzes were first performed for all present LLNs and then for enlarged LLNs. Enlarged LLNs were defined as ≥7mm short-axis.

Then, all patients with visible LLNs on MRI (internal iliac, externa iliac and obturator) were examined. Stretched-out obturator nodes were considered benign in Ogura et al. and not included for analyses in the Consortium study.[5] Therefore, these LLNs (SA <5.0 mm, long-axis at least twice the length of the SA, without malignant features or growth on restaging MRI) were also evaluated separately.

After this, clinically relevant LLNs (internal iliac/obturator LLNs) were analyzed further based on the anatomical location of their largest LLN. Patients with only external iliac or stretched-out obturator nodes were analyzed in the "no LLN" group. For these analyses, outcomes were examined per location (internal iliac/obturator) and according to size (<5.0, 5.0-6.9, ≥7.0). Additionally, the influence of downsizing on restaging MRI according to cut-off values (≤4 mm internal and ≤6 mm obturator), and presence and influence of malignant features on primary MRI, were evaluated.[5,6]

Statistics

Analyses were conducted in SPSS Statistics, version 26.0 (SPSS, Chicago, IL). Categorical data are presented as number with percentages and continuous variables as mean with standard deviation or median with an interquartile range. Subgroups were analyzed using chi-squared, Fisher's exact or independent t-tests. Univariable analysis identified predictors of (L)LR and included visible LLN(s), enlarged (≥7 mm) LLN(s), location (internal iliac, external iliac, obturator), malignant features, and restaging diameters. Overall (L)LR, distant metastases and survival rates were analyzed with Kaplan-Meier analysis and compared with the log-rank test. Multivariable Cox regression model examined covariates with a p-value <.10 from univariable analysis, to determine independent associations of LLN characteristics with LR. This could not be performed for LLR due to low event rates. Surgical treatment of LLNs was not routine practice, and only incidentally performed without standardized technique, therefore, LLN-surgery was not included in the prognostic models (details of patients who underwent LLN-surgery are described elsewhere). Statistical significance was a p value <0.05.

Ethics

Central approval was obtained by the ethics board of Amsterdam UMC, the Netherlands, on 30th June, 2020. Local approval from each participating center was obtained before the study commenced. Each center decided whether their patients provided written informed consent or the opportunity to opt-out of the study.

RESULTS

Sixty-seven of the 69 Dutch hospitals providing rectal cancer care in 2016 participated in this study, resulting in 3107/3178 eligible patients (97.8%, Fig. 1). Of the 3057 patients included in part one, 60 hospitals participated in part two and resulted in 1109 patients (Table 1, Fig. 2). Median follow-up was 48 months (IQR 26-54 months).

Non-irradiated Patients

In total, 218/1109 (19.7%) of the patients with low, locally advanced rectal cancer did not receive any form of neoadjuvant radiotherapy. According to re-review, 58 of these patients (26.6%) had a LLN present. Eleven of these were ≥7 mm (19.0%): six (54.5%) internal iliac/obturator LLNs, and five external LLNs (45.5%). Three patients (all with an enlarged internal iliac LLN) developed a LLR.

Oncological Outcomes for External, Internal Iliac, and Obturator Nodes

A total of 891/1109 (80.3%) patients received neoadjuvant radiotherapy, of which 301 (33.8%) patients had visible internal iliac, external iliac or obturator nodes. LLNs increased the LR-rate from 7.2% to 15.8% ($p < 0.001$), LLR-rate from 0.0% to 8.2% ($p < 0.001$, Fig. 3A) and DM-rate from 24.6% to 32.5% ($p = 0.029$), compared to those without LLNs. Enlarged LLNs (n=125) further increased the LR-, LLR- and DM-rates respectively to 20.2% ($p < 0.001$), 14.3% ($p <$ 0.001, Fig. 3B) and 35.4% ($p = 0.044$).

“Stretched-out” and external iliac nodes

Thirteen patients only had “stretched-out” obturator LLNs. One patient developed a LR on the rectal stump (4-yr LR 11.1%) and no LLRs occurred. Seventeen patients had only visible external iliac LLNs; one patient developed an anterior pelvic LR, encroaching on both vesicles and bladder (4-yr LR 6.2%), but no LLR (Fig. 2, Appendix 3 https://links.lww.com/DCR/CXX).

Oncological Outcomes for Internal Iliac and Obturator Nodes

Patients with internal iliac or obturator LLNs (n = 284, 31.9%, Appendix 3 at https://links.lww.com/DCR/CXX) had 4-year LR rates of 16.4% versus 7.0% without LLNs ($p <$ 0.001) and 4-year LLR rates of 8.8% and 0%, respectively ($p < 0.001$). Present LLNs remained independently associated with an increased LR-risk in multivariable analysis (HR 1.787 (CI 95% 1.130-2.827), $p = 0.013$) (Table 2).

Explorative univariable analyses were performed to determine the most appropriate cut-off value for SA diameter of LLNs (Appendix 4 at https://links.lww.com/DCR/CXX). Enlarged LLNs (≥7.0 mm, n =122) were associated with significantly higher 4-year LR and LLR rates compared to <7.0 mm (n = 162) or no visible LLNs (n = 607), respectively (LR 20.8%, 13.1%, 7.0%: $p <$ 0.001; LLR 14.7%, 4.4%, 0%: $p < 0.001$, Fig. 3). LLNs ≥7.0 mm remained a significant predictor of LR in multivariable analyses (HR 1.948 [CI 95% 1.085-3.495], $p = 0.041$, Table 3). Higher 4-year univariate DM rates were found for patients with enlarged LLNs (36.4% ≥7 mm, 30.8% <7 mm, 24.4% no LLN, $p = 0.021$), but this was not significant in multivariable analyses (HR 1.270, CI 0.881-1.830, $p = 0.395$). Four-year DM rates did not significantly differ between internal iliac and obturator nodes (24.6% vs. 35.5%, $p = 0.076$), respectively. Of the 23 patients who developed LLR, 16 developed distant metastases (30.4%). Four-year OS was not influenced by the presence of enlarged LLNs versus smaller or no nodes (71.1%, 79.4%, 78.3%, $p = 0.071$ [Appendices 5 and 6 at https://links.lww.com/DCR/CXX]).

Internal Iliac Versus Obturator LLNs

Fifty-eight patients had their largest LLN the internal iliac compartment (20.4%) and 226 in the obturator compartment (79.6%). Four-year LR rates were 9.2% and 18.2% ($p = 0.211$) and LLR-rates were 3.6% and 10.3% ($p = 0.288$), for internal iliac and obturator LLNs, respectively. Enlarged (≥7 mm) internal iliac LLNs (n = 32) and obturator LLNs (n=90) had mean SA diameters of 9.8 mm (SD 3.2) and 9.2mm (SD 2.9) ($p = 0.192$), respectively. Four-year LR rates for enlarged LLNs were 13.8% for the internal iliac compartment and 23.2% for the obturator compartment ($p = 0.310$), with 4-year LLR rates of 6.6% and 17.7%, respectively ($p = 0.226$) (Appendix 7 at https://links.lww.com/DCR/CXX).

Restaging MRI

In total, 77/90 enlarged obturator (85.6%) and 30/32 enlarged internal iliac LLNs (93.8%) underwent restaging MRI after neoadjuvant treatment. Nineteen internal iliac LLNs (19/30, 63%) remained >4 mm on the restaging MRI and resulted in 4-year LR and LLR rates of 22.6% and 11.1%, respectively, compared to 0% and 0% when shrinking to ≤4 mm ($p = 0.127$, $p = 0.273$). For enlarged obturator LLNs which remained >6 mm (n = 32), compared to ≤6 mm (n = 45), 4-year LR rates were 44.5% and 12.8% ($p = 0.003$), and 4-year LLR rates 28.9% and 15.0% ($p = 0.406$), respectively. Obturator nodes, which downsized to ≤4 mm (n = 18), still had a 4-year LLR rate of 18.9% and for 6 patients where LLNs fully disappeared on restaging MRI; 2 developed LLR.

Malignant Features

At least one malignant feature was present in 157 patients with visible internal iliac/obturator LLNs (157/284, 55.3%). The presence of malignant features, regardless of LLN size or location, was associated with increased 4-year LR (20.3% vs. 11.3%, $p = 0.126$) and LLR (12.9% vs. 3.6%, $p = 0.024$) rates, versus those without.

Ninety-eight patients with enlarged LLNs had at least one malignant feature present (98/122, 80.3%). Enlarged LLNs with malignant features resulted in higher 4-year LR (23.4% vs. 9.1%, $p = 0.196$) and LLR (17.0% vs. 5.6%, $p = 0.189$) rates compared to those without malignant features.

Of the 91 patients with intermediate LLNs (SA 5.0-6.9 mm), 43 (47.3%) had malignant features present. Higher 4-year LR and LLR rates were found for these intermediate LLNs and malignant features compared to those without malignant features (LR 17.5% vs. 11.4% $p = 0.648$; LLR 8.2% vs. 2.1%, $p = 0.561$). Patients with small LLNs (SA <5 mm) had similar LR (6.7% vs 10.2%, $p = 0.716$) and LLR rates (0 vs. 4.4%, $p = 0.735$) in the presence or absence of malignant features, respectively.

DISCUSSION

This national, cross-sectional study included 1109 patients with cT3-4 rectal cancer located ≤8 cm from the anorectal junction and incorporated training with lateral compartment standardization to provide novel results for the prognostic impact of LLNs. The presence of LLNs, regardless of other characteristics, was associated with a 4-year LLR rate of 8.2%, which increased to 14.3% for enlarged (≥7 mm) external-, internal iliac or obturator LLNs. These outcomes largely verify the Consortium study, which found that enlarged LLNs were associated with 5-year LLR rates of 19.5%.[5] In contrast, different results were found regarding anatomical location and restaging LLN size, indicating the importance of primarily enlarged LLNs for prognosis and treatment planning. Enlarged LLNs were also associated with a higher risk of distant metastases, but this association was not statistically significant after correcting for primary tumor- and margin characteristics.

The definition of lateral nodal disease is important when comparing studies. For example, external iliac nodes were included in the Consortium study which found an 19.5% 5-yr LLR rate.[5,6] However, that study and the current study showed that isolated external iliac nodes did not result in LLR, meaning that the LLR rates for obturator/internal iliac nodes were even higher. Other studies do not specify whether external iliac nodes were excluded.[10–14] Similarly, isolated stretched-out nodes were confirmed to be 'benign' in both studies, supporting their exclusion from further analyses.

Anatomical location was noteworthy, with almost 7% 4-year LLR rates for enlarged internal iliac LLNs compared to more than 17% for enlarged obturator LLNs. Recurrence rates for internal iliac LLNs were lower than in the Consortium study and cannot purely be explained by LLN size, as mean short-axis diameters were not hugely different (9.8 mm vs. 11.7bmm). Two other factors may explain these differences. Firstly, mandatory training with detailed explanation regarding the anatomical classification of LLNs for participating radiologists has likely influenced the categorization of LLNs. This may have led to a stricter interpretation of the lateral borders, meaning that fewer LLNs may have been considered as internal iliac LLNs. In clinical practice, the internal iliac area is usually proportionally narrower than shown in the color atlas of Ogura et al. when adhering to the lateral border of the main trunk of the internal iliac artery. This atlas was the only guideline provided in the Consortium study and radiologists may have relied more on the 'color' in the atlas than following the internal iliac main trunk on MRI. Therefore, LLNs located in the transition area may have been defined as internal iliac in the Consortium, but as obturator LLNs in the current study. Secondly, due to the national design, there were less LLNs in total (34% vs. 58% in the Consortium study), with only 58 internal iliac (20%) and 226 (80%) obturator LLNs, compared to 198 internal iliac (31%) and 448 obturator LLNs (69%) in the Consortium study. Overall, classification of LLNs into separate anatomical compartments remains challenging. Even after dedicated training, consensus rates between 53 Dutch radiologists for determining LLN location ranged from 75-85% in this study.[9] The current findings and the Consortium study suggest that both compartments can contain aggressive LLNs and we should predominantly consider primary size in combination with malignant features for clinical suspiciousness.

Important patterns were deduced for the presence of malignant features. Intermediate (5-7 mm) LLNs with at least one malignant feature had higher LR and LLR rates (LR 17.5% and LLR 8.2%) compared to those without malignant features (LR 11.4% and LLR 2.1%), respectively. Just as mesorectal nodes are currently classified according to a combination of size and malignant features,[15-20] upcoming research may indicate a similar possibility for LLNs.[7] Additionally, the importance of restaging sizes could not be confirmed by this study. While potentially due to limited group numbers, 15% LLR rate was found for patients with obturator LLNs that decreased in size (≤6 mm), and 29% when remaining >6 mm. Japanese traditions have favored basing treatment decisions on the primary LLN size,[10,11,14] and the current results appear to support this. Considering that additional lateral lymph node dissection (LLND) might be indicated for patients with primarily enlarged LLNs, an important next step is to ascertain whether LLNs received proper irradiation doses. Our research group is examining the irradiation doses received by patients with LLNs ≥5 mm and the outcomes after LLN-surgery (not LLND) (separate manuscripts). We hypothesize that the majority of LLNs received an adequate dose, meaning that surgical treatment might be imperative to improve oncological outcomes for this population in the future.

The therapeutic implications of this study suggest that patients with primarily enlarged internal iliac and/or obturator LLNs should be treated as suspicious, with 4-year LLR rates of almost 15%. Patients without LLNs displayed rates of around 5%, implying the tangible implications of LLNs. Although enlarged LLNs mainly occur in low, advanced cases, it is important to realize only one-third of these metastasize in the future, so the majority can be treated curatively, avoiding of the morbidity of LLR. Furthermore, there may be a role of LLND in preventing DM.[21]

There are several limitations. The total number of (enlarged) LLNs was limited, meaning that certain features were challenging to examine, which require further exploration in extended datasets. The low number of LLRs meant that multivariable analysis was not possible. Furthermore, the retrospective design means that some data were missing, even though thorough verification processes limited this as much as possible. Radiologists were not blinded to the outcome of recurrence, which may be impacted their revision and finally, inter-physician variability during MRI-review process was inevitable, even though this was tackled by mandatory training, an extra webinar, and two visual atlases.

CONCLUSION

This national, cross-sectional study of 1109 patients with low, cT3/4 rectal cancer from 60 Dutch hospitals in 2016 with standardized MRI-assessment after dedicated training, displayed high 4-year ipsilateral LR rates when LLNs were present, with even higher recurrence rates for patients with ≥7mm LLNs. The presence of (enlarged) LLNs was a significant predictor of LR in multivariable analysis. The results provide a realistic impression of the significance of LLNs at a population-level and advocate for the careful consideration of LLNs during clinical practice.

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LEGENDS

1. Flow chart of participants.

2. Continuation of flow chart of participants.

3. *A*, Lateral local recurrence rates for the presence of external-, internal iliac, and obturator lateral lymph nodes (LLNs). *B*, Enlarged (≥7 mm) external-, internal iliac, and obturator LLNs (3B).

Table 1. Baseline characteristics of patients with cT3-4M0 rectal cancer located ≤8cm from the anorectal junction based on MRI re-review (n=1109) who received neoadjuvant radiotherapy (n=891) and those who did not (n=218).

*SD: standard deviation, mrEMVI: on MRI identified extramural venous invasion. LOREC: low rectal cancer development program – lower border of the tumor is located beneath the attachment of the levator ani (seen on coronal plane). MRF: mesorectal fascia. TME: total mesorectal excision. PME: partial mesorectal excision. *Tumors were initially staged higher according to clinical staging, but later confirmed lower by pathology.*

Table 2. Multivariable analysis of **local recurrence** in 891 patients with cT3-4 rectal cancer ≤8cm from the anorectal junction, who were treated with neoadjuvant radiotherapy (short course or chemoradiotherapy). These patients were included in the analysis based on visibility on primary staging MRI, independent of size.

Table 1. Baseline characteristics of patients with cT3-4M0 rectal cancer located ≤8cm from the anorectal junction based on MRI re-review (n=1109) who received neoadjuvant radiotherapy (n=891) and those who did not (n=218).

Variable	*n = 891 (%)*	*n = 218 (%)*
Gender: male	581 (65.2)	157 (72.0)
Mean age in years (SD)	72.1 (10.6)	74.9 (11.3)
Mean distance of tumor from anorectal junction, cm (SD)	3.3 (2.5)	4.1 (2.3)
Tumor according to LOREC criteria		
On/below	541 (60.7)	104 (47.7)
Above	350 (39.3)	114 (52.3)
Clinical T-stage		
T3a (<1mm beyond muscularis propria)	174 (19.5)	87 (39.9)
T3b (1-4.9mm beyond muscularis propria)	287 (32.2)	91 (41.7)
T3c (5-15mm beyond muscularis propria)	221 (24.8)	30 (13.8)
T3d (>15mm beyond muscularis propria)	56 (6.3)	2 (0.9)
T4a (invasion of peritoneum)	53 (6.0)	7 (3.2)
T4b (invasion surrounding organs/structures)	100 (11.2)	1 (0.5)
Threatened mesorectal fascia (MRF) or T4 on primary MRI (tumor ≤1mm of the MRF)	439 (49.3)	32 (14.7)
Mesorectal clinical N-stage		
N0	183 (20.5)	167 (76.6)
N1	400 (44.9)	46 (21.1)
N2	308 (34.6)	5 (2.3)
Extramural venous invasion (mrEMVI) on primary MRI	314 (35.2)	32 (14.7)
Tumor deposits on primary MRI	143 (16.0)	4 (1.8)
All LLNs visible on primary MRI	314/891 (35.2)	58/218 (26.6)
Largest LLN in obturator compartment	226/314 (72.0)	40/58 (69.0)
Largest LLN in internal iliac compartment	58/314 (18.5)	8/58 (13.8)
Patients with LLNs only in external iliac compartment	17/314 (5.4)	10/58 (17.2)
Patients with only stretched-out 'benign' obturator LLNs	13/314 (4.1)	-
LLN characteristics		
One or more internal iliac/obturator LLN with SA ≥7mm	122 (13.7)	6 (2.8)
Any LLN with at least one malignant feature	157 (17.6)	18 (8.3)
Neoadjuvant treatment		
None	-	216 (99.1)
Short-course radiotherapy	338 (37.9)	-
Chemoradiotherapy	553 (62.1)	-
Chemotherapy alone	-	2 (0.9)
Resection of primary tumor		
Local excision*	5 (0.6)	7 (0.5)
Local excision followed by TME	-	2 (0.2)
Low anterior resection/TME	411 (46.1)	123 (56.9)
Abdominoperineal resection	338 (37.9)	49 (22.7)
Hartmann procedure	134 (15.0)	34 (15.7)
Proctocolectomy	2 (0.2)	1 (0.1)
Total exenteration	1 (0.1)	0
Underwent some form of additional surgery for LLN		
Yes	33 (3.7)	-
No	858 (96.3)	-

SD: standard deviation, mrEMVI: on MRI identified extramural venous invasion. LOREC: low rectal cancer development program – lower border of the tumor is located beneath the attachment of the levator ani (seen on coronal plane). MRF: mesorectal fascia. TME:

Resection margins (%)			*total*
R0	823 (92.4)	206 (94.5)	
R1	68 (7.6)	12 (5.5)	

*mesorectal excision. PME: partial mesorectal excision. *Tumors were initially staged higher according to clinical staging, but later confirmed lower by pathology.*

Table 2. Multivariable analysis of **local recurrence** in 891 patients with cT3-4 rectal cancer ≤8cm from the anorectal junction, who were treated with neoadjuvant radiotherapy (short course or chemoradiotherapy). These patients were included in the analysis based on visibility on primary staging MRI, independent of size.

Variable	No.	HR	95% CI	P	HR	95% CI	P
LLN of any size present				**<0.001**			**0.013**
No	607	1			1		
Yes	284	2.414	1.556-3.744		1.787	1.130-2.827	
Gender				0.839			
Male	581	1					
Female	310	0.953	0.600-1.515				
Age in years				0.736			
<55	50	1					
55-75	472	0.849	0.336-2.147				
75+	369	1.014	0.396-2.598				
Neoadjuvant radiotherapy				0.103			
5x5	338	1					
CRT	553	1.496	0.922-2.428				
Clinical T stage				**<0.001**			0.231
T3a	174	1			1		
T3b	287	1.474	0.645-3.367		0.994	0.427-2.312	
T3c	221	2.138	0.941-4.854		1.085	0.463-2.546	
T3d	56	2.637	0.915-7.601		0.920	0.304-2.782	
T4a	53	5.913	2.378-14.704		2.484	0.942-6.549	
T4b	100	4.460	1.907-10.430		1.155	0.453-2.941	
Mesorectal clinical N stage				**0.003**			0.059
N0	183	1			1		
N1	400	0.669	0.349-1.281		0.641	0.327-1.255	
N2	308	1.618	0.897-2.917		1.208	0.646-2.258	
Extramural venous invasion (mrEMVI)				**<0.001**			**0.003**
Absent							
Present	577	1			1		
	314	2.543	1.635-3.956		2.102	1.283-3.444	
Tumor deposits				**<0.001**			0.056
Absent	748	1			1		
Present	143	2.569	1.592-4.146		1.676	0.986-2.850	
Surgery*				**0.003**			**0.027**
Sphincter non-sparing	340	1			1		
Sphincter sparing	551	0.508	0.328-0.789		0.580	0.358-0.940	
Margin status				**<0.001**			**<0.001**
R0	823	1			1		
R1	68	6.837	4.176-11.193		5.820	3.410-9.932	
		Univariable analysis			*Multivariable analysis*		

*LOREC: low rectal cancer development program – lower border of the tumor is located beneath the attachment of the levator ani (coronal plane). *Sphincter non-sparing includes abdominoperineal resections (APR) and proctocolectomy cases, Sphincter sparing cases include (low) anterior resections and local excisions. mrEMVI: on MRI identified extramural venous invasion.*

Table 3. Multivariable analysis of **local recurrence** in 891 patients with cT3-4 rectal cancer ≤8cm from the anorectal junction, who were treated with neoadjuvant radiotherapy (short course or chemoradiotherapy). Lateral lymph nodes were included in the analysis based on visibility on primary staging MRI, and stratified for short-axis diameter with a cut-off value of 7mm.

Variable	No.	HR	95% CI	P	HR	95% CI	P
Enlarged (≥7mm) LLN				**<0.001**			**0.041**
No LLN	607	1			1		
≥7mm	122	3.017	1.784-5.101		1.948	1.085-3.495	
<7mm	162	1.979	1.152-3.401		1.669	0.962-2.898	
Gender				0.839			
Male	581	1					
Female	310	0.953	0.600-1.515				
Age in years				0.736			
<55	50	1					
55-75	472	0.849	0.336-2.147				
75+	369	1.014	0.396-2.598				
Neoadjuvant radiotherapy				0.103			
5x5	338	1					
CRT	553	1.496	0.922-2.428				
Clinical T stage				**<0.001**			0.227
T3a	174	1			1		
T3b	287	1.474	0.645-3.367		0.987	0.424-2.297	
T3c	221	2.138	0.941-4.854		1.080	0.460-2.535	
T3d	56	2.637	0.915-7.601		0.912	0.301-2.760	
T4a	53	5.913	2.378-14.704		2.474	0.938-6.525	
T4b	100	4.460	1.907-10.430		1.105	0.424-2.878	
Mesorectal clinical N stage				**0.003**			0.077
N0	183	1			1		
N1	400	0.669	0.349-1.281		0.642	0.328-1.259	
N2	308	1.618	0.897-2.917		1.185	0.630-2.229	
Extramural venous invasion (mrEMVI)				**<0.001**			**0.003**
Absent	577	1			1		
Present	314	2.543	1.635-3.956		2.115	1.290-2.467	
Tumor deposits				**<0.001**			0.050
Absent	748	1			1		
Present	143	2.569	1.592-4.146		1.715	0.999-2.942	
Surgery*				**0.003**			**0.030**
Sphincter non-sparing	340	1			1		
Sphincter sparing	551	0.508	0.328-0.789		0.584	0.360-0.949	
Margin status				**<0.001**			**<0.001**
R0	823	1			1		
R1	68	6.837	4.176-11.193		5.767	3.370-9.870	
			Univariable analysis			*Multivariable*	

*LOREC: low rectal cancer development program – lower border of the tumor is located beneath the attachment of the levator ani (coronal plane). *Sphincter non-sparing includes abdominoperineal resections (APR) and proctocolectomy cases, Sphincter sparing cases include (low) anterior resections and local excisions. mrEMVI: on MRI identified extramural venous invasion.*

Figure 1. Flowchart of participants

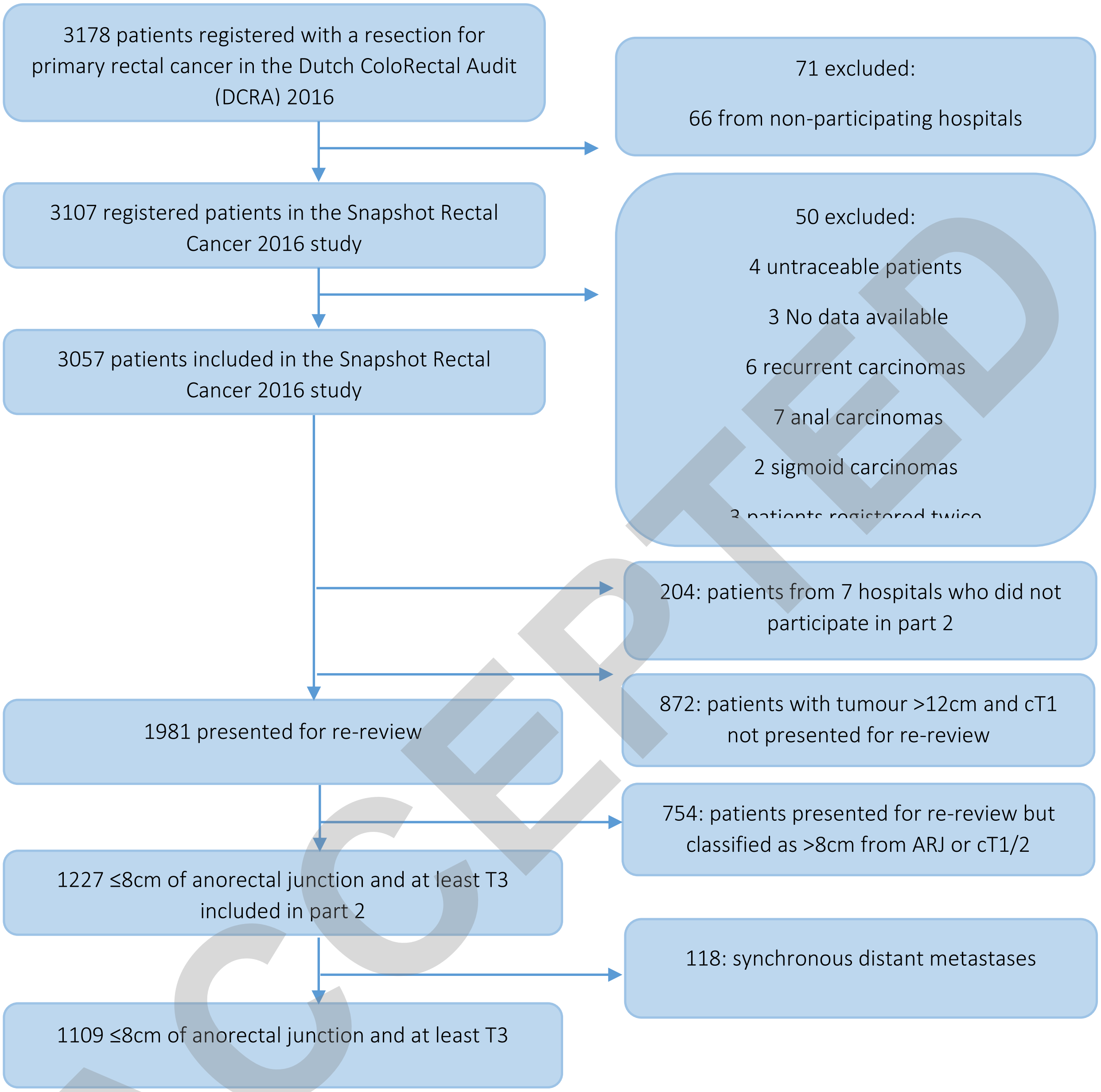
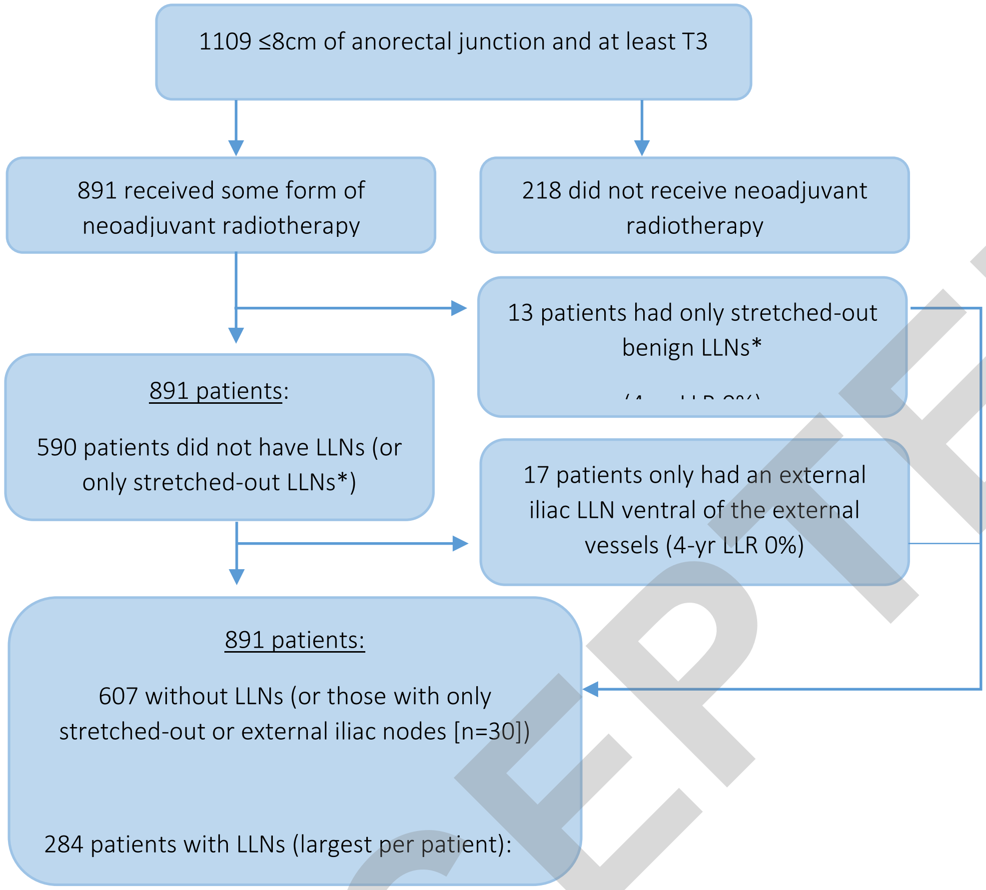
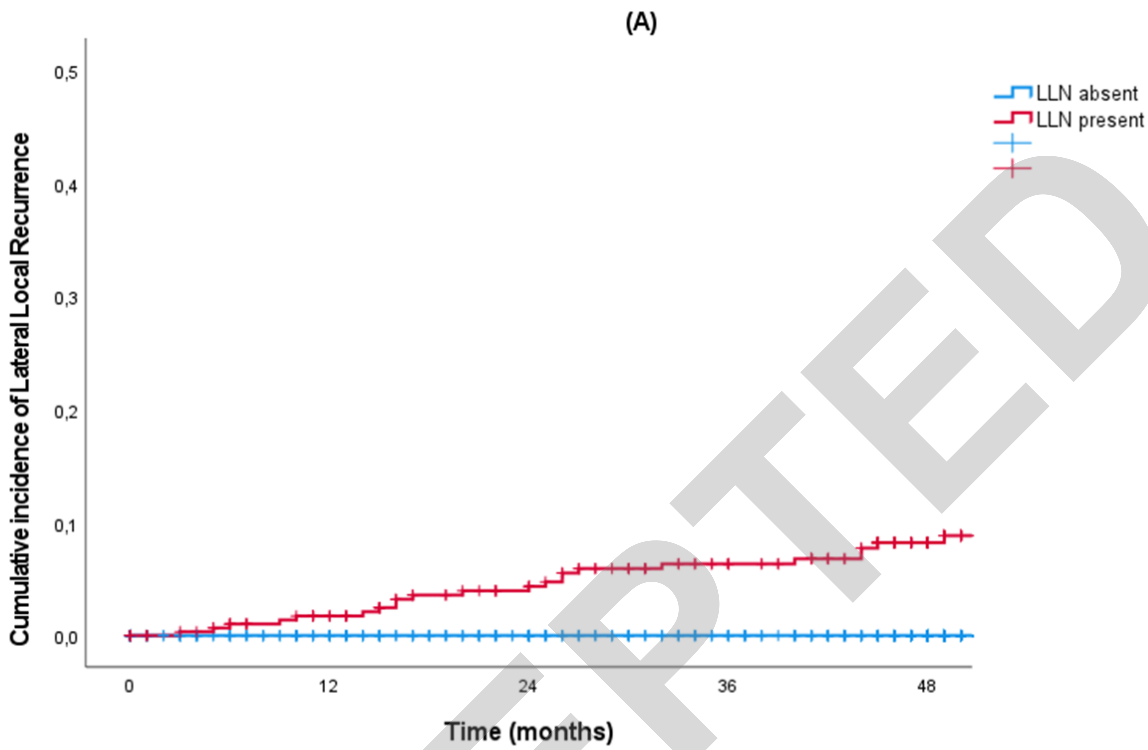


Figure 2: Continuation of flowchart of participants

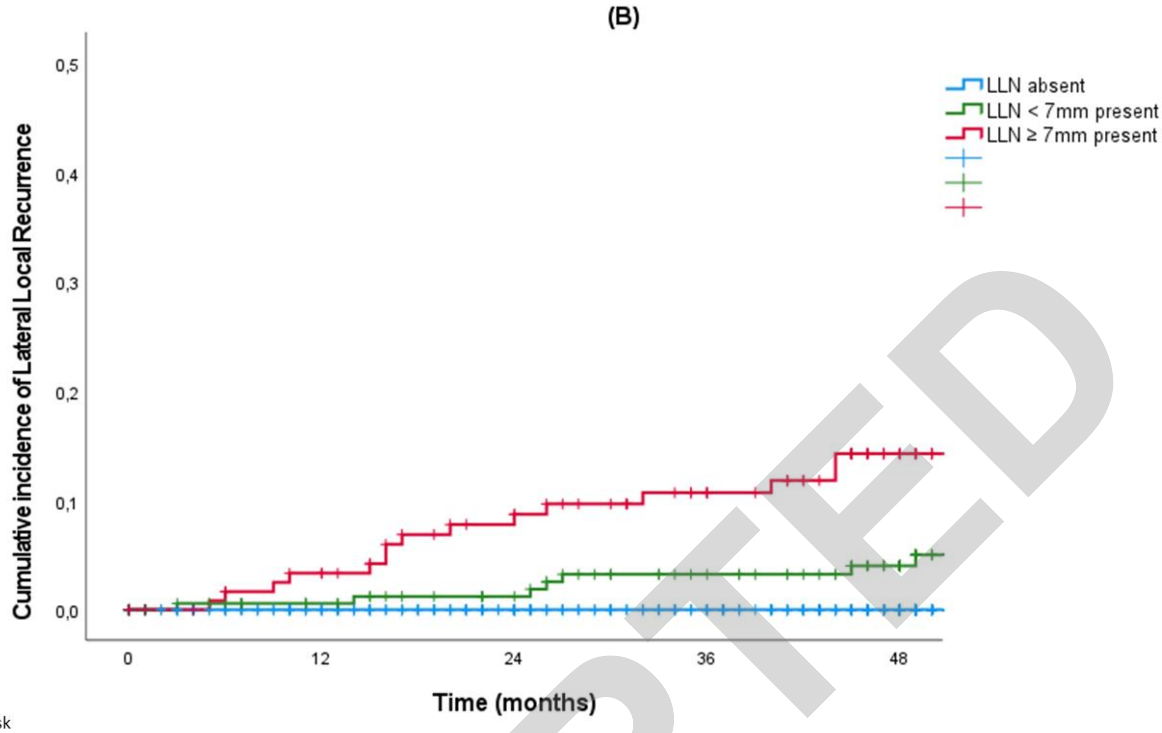


*Definition: subtype of obturator LLNs, dorsal of external iliac vessels in which the long-axis at least twice the length of the short-axis, maximum short-axis diameter of 5mm, no malignant features present and no change/increase in the restaging MRI.

Figures 3A & B. Lateral local recurrence rates for the presence of external-, internal iliac and obturator LLNs (3A) and enlarged (≥7mm) external-, internal iliac and obturator LLNs (3B).



	0	12	24	36	48
LLN absent	590	531	483	437	354
LLN present	301	274	248	217	164



No. at risk					
LLN absent	590	531	483	437	354
LLN <7.0mm present	176	160	149	132	110
LLN ≥7.0mm present	125	113	99	84	54

Appendix 1: Data management & privacy

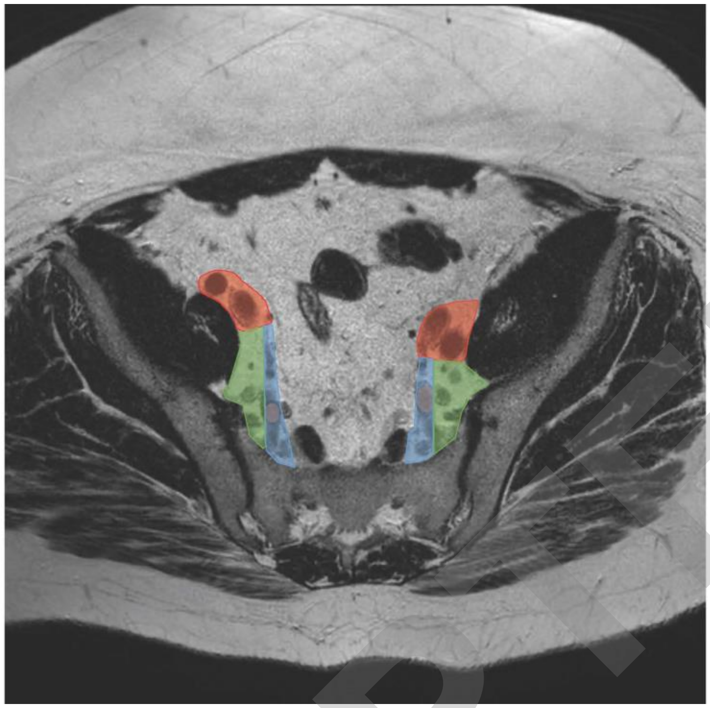
The Dutch ColoRectal Audit (DCRA) has all baseline and short-term oncological outcomes registered for patients who were treated for rectal carcinoma in the Netherlands. This Snapshot study expanded the available data in the DCRA for 3107 of the 3178 potentially eligible patients who were treated for primary rectal carcinoma in the Netherlands in 2016.

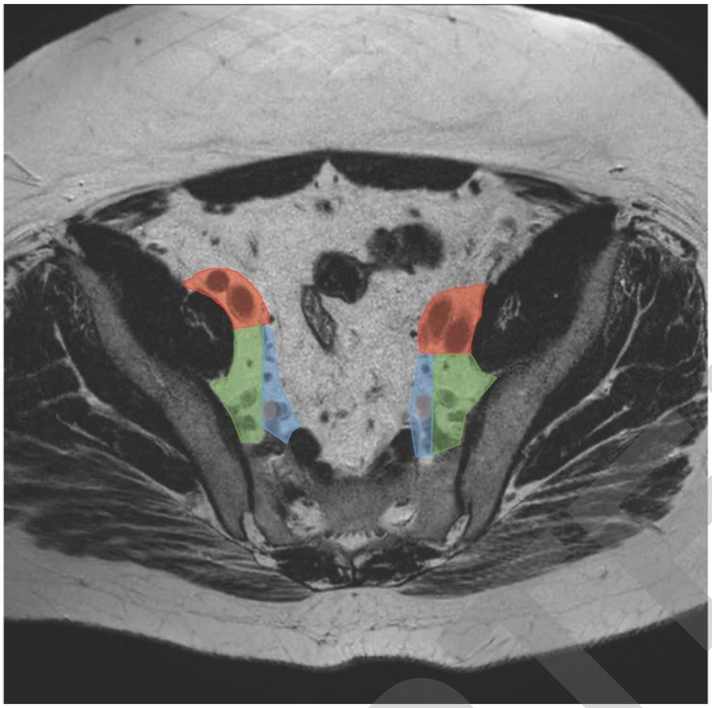
Data collection consisted of three parts, of which only the first two parts are relevant to the present study. In part 1, the surgical team collected all additional information per patient, such as baseline characteristics, procedural data, and the short- and long-term oncological and surgical outcomes. The local surgical team only had access to data for patients in their center within part 1. Once part 1 was completed, MRDM imported eligible patients to part 2 in a completely separate data collection location. This meant that local collaborators could not access any information about their patients outside their specific part or center. Sixty centers also participated in part 2. In this section, abdominal radiology consultants were asked to re-review all primary and restaging MR-images for the selected patients.

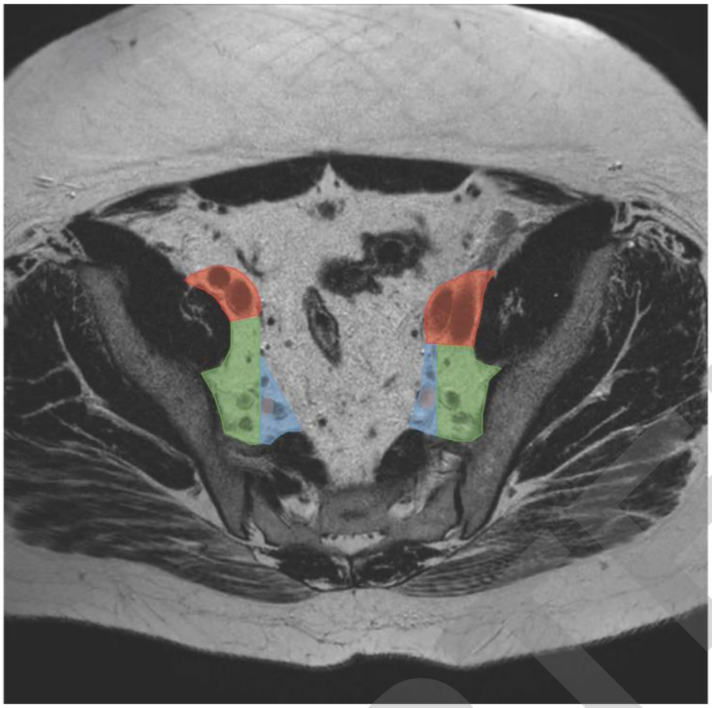
The project data was processed and stored anonymously by Medical Research Data Management (MRDM, Deventer, the Netherlands). MRDM is responsible for the data processing of the DCRA and is NEN7510 and ISO27001 certified.

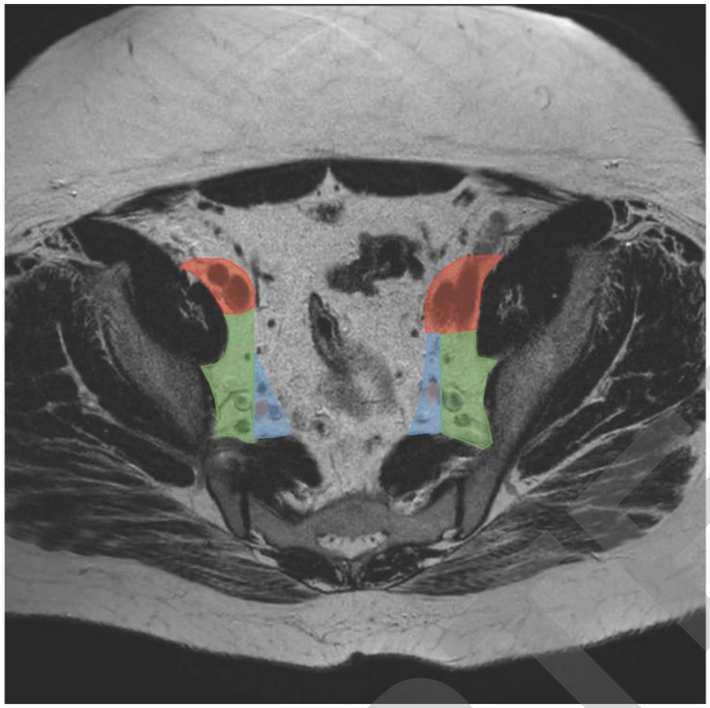
The central coordinating researchers received fully anonymized data and dates of birth were only provided as a year of birth. All other dates, such as the date of the primary MRI, were provided with a possible 10-day spread, to minimize any risk of breach in privacy. MRI-reports were copied by the local collaborative team into the database anonymously and did not include any patient-specific information.

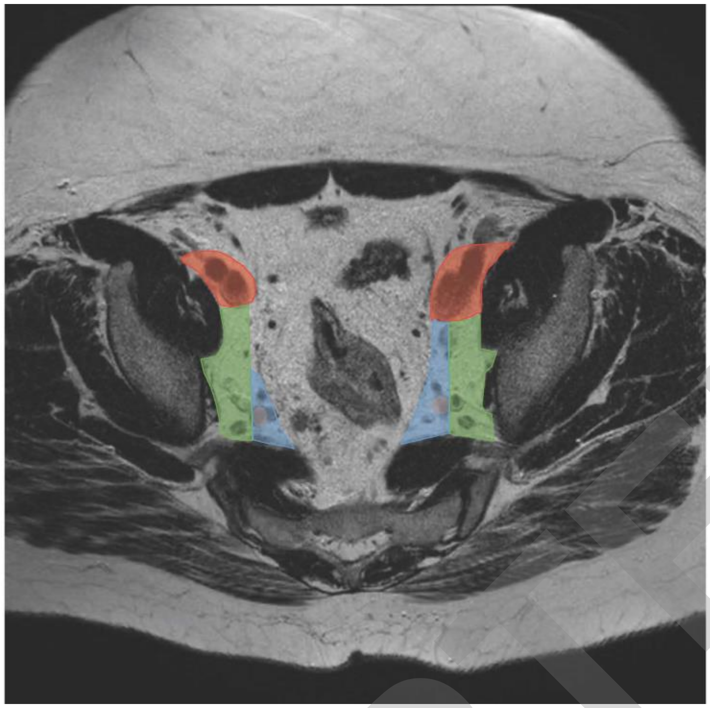
Appendix 2

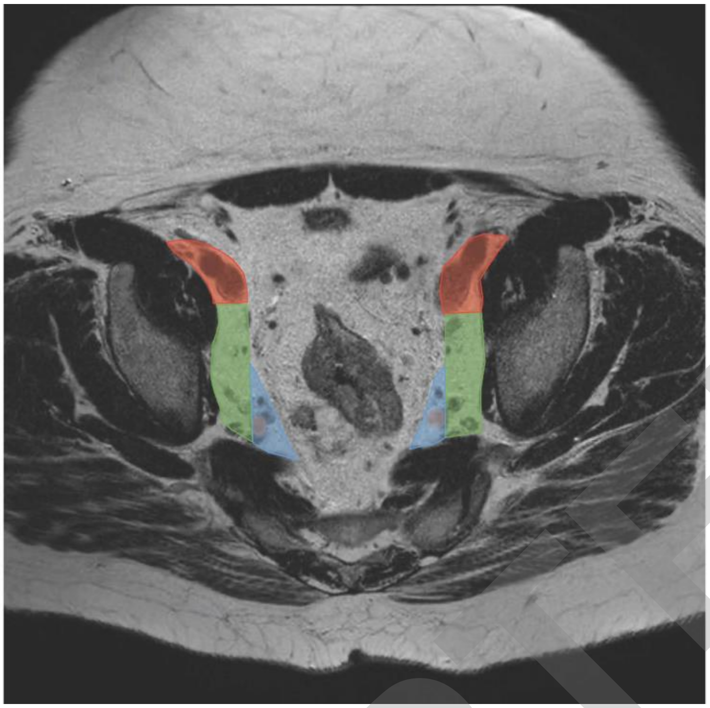


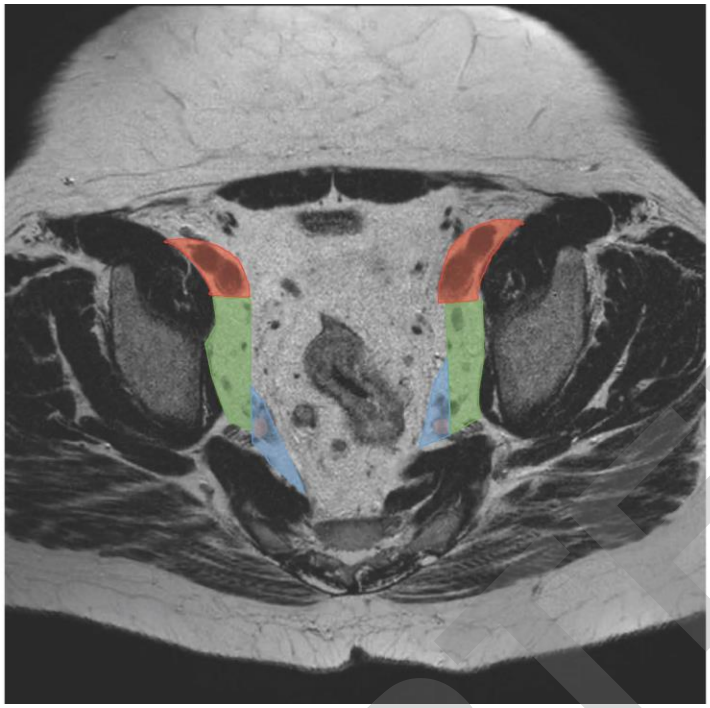


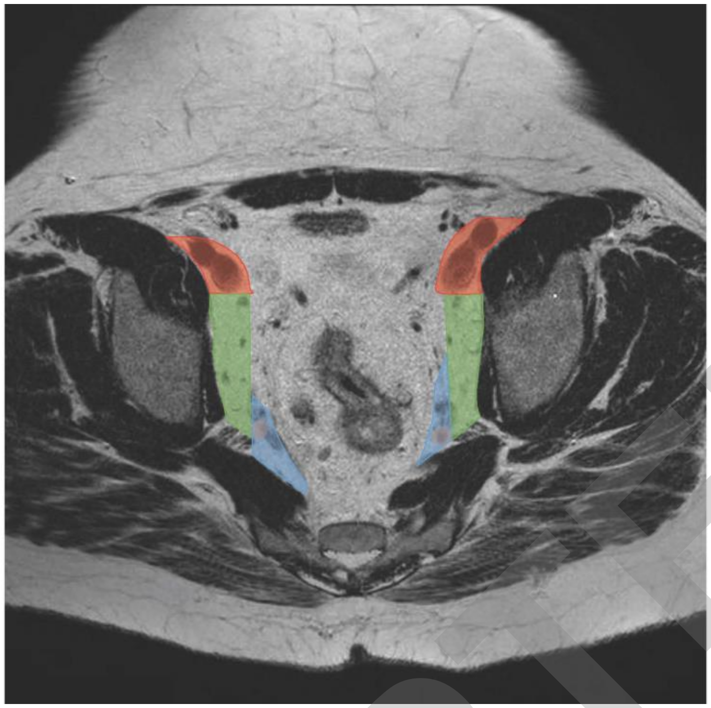


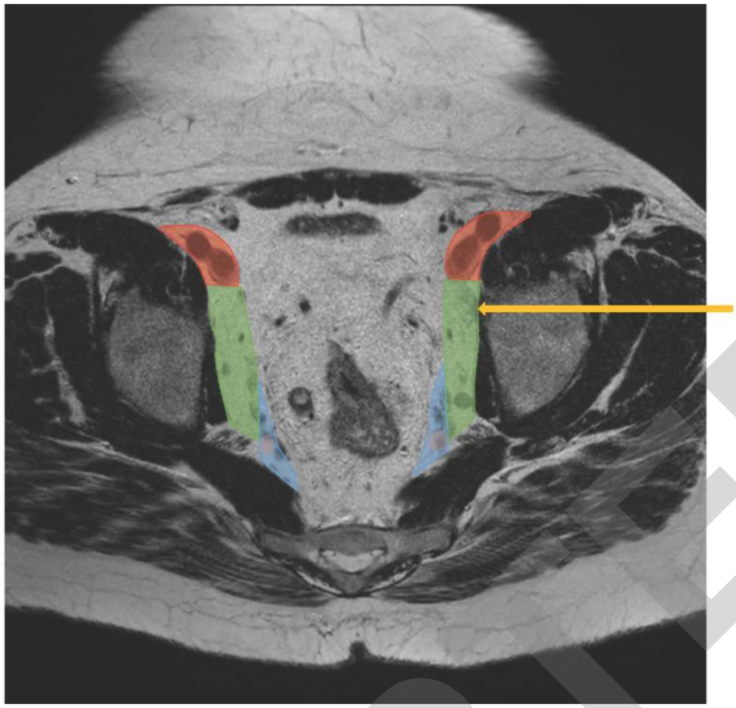


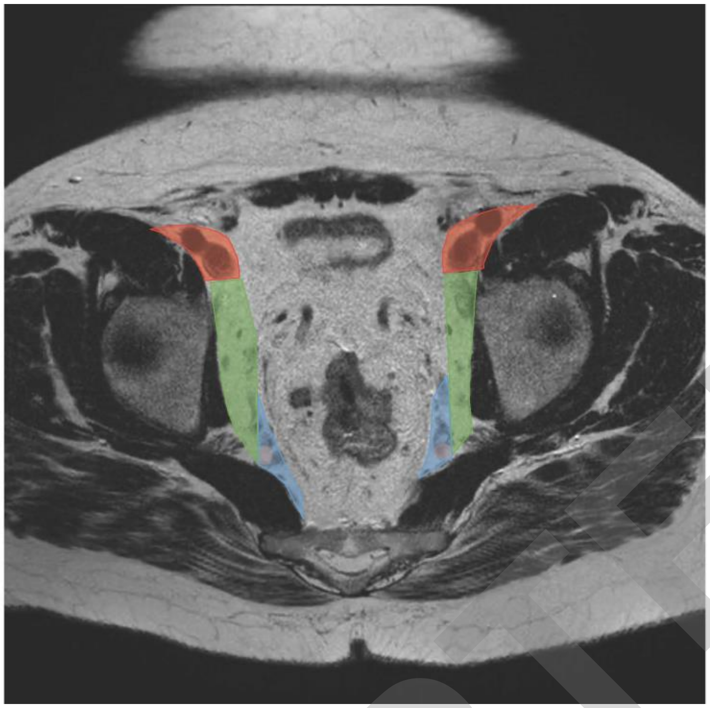


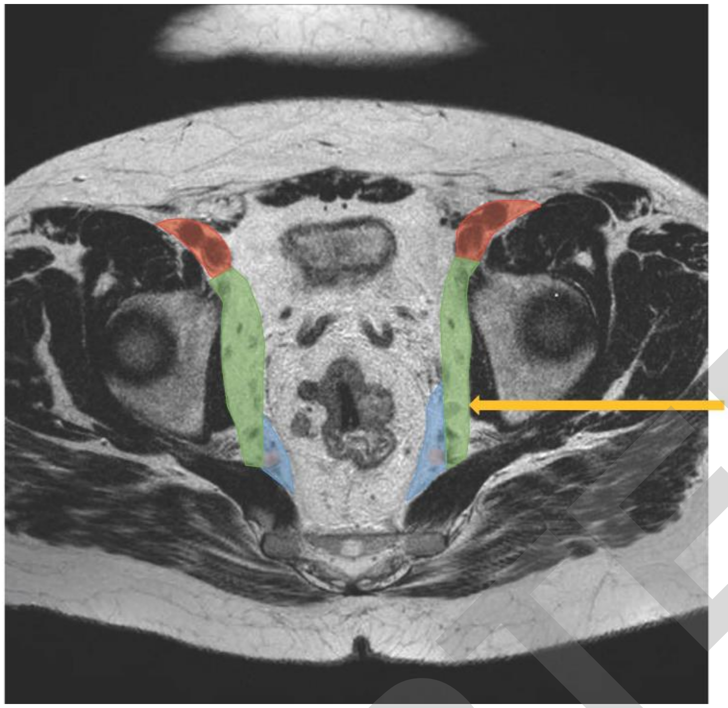


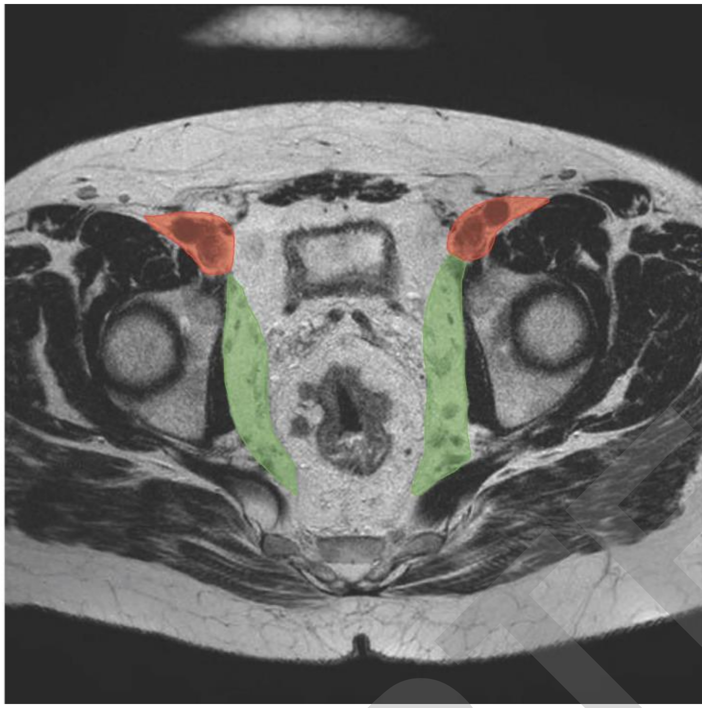


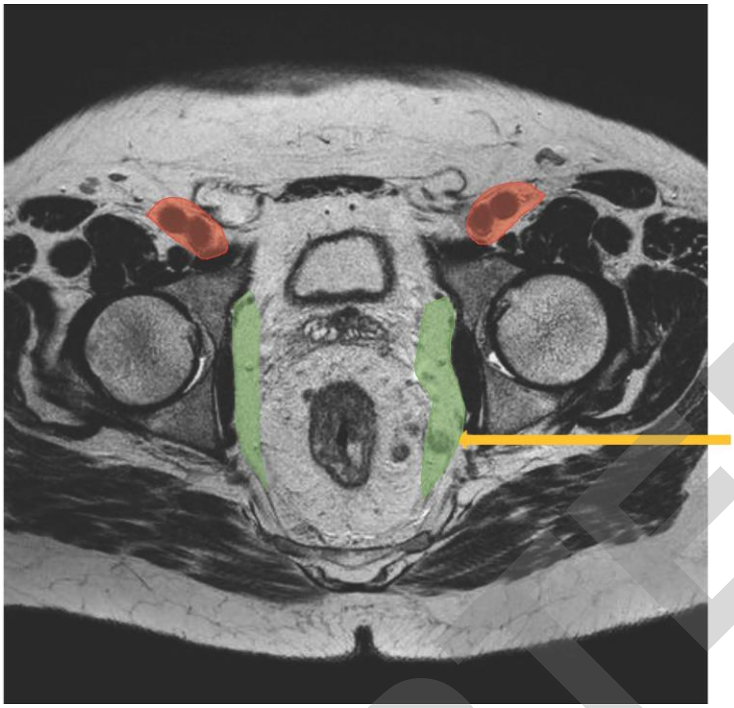












Appendix 2. 4-year LR and LLR rates for 314 patients with LLNs in different anatomical locations from the total cohort of 890 patients with low, locally advanced rectal cancer who received neoadjuvant therapy.

N = 314 patients with LLNs	N (%)	N with LR	4-yr LR, %	N with LLR	4-yr LLR, %
External iliac LLNs	17 (5.4)	1	6.2%	0	0
Obturator LLNs					
Obturator LLNs	226 (72.0)	36	18.2%	20	10.2%
Stretched-out LLNs*	13 (4.1)	1	11.1%	0	0
Internal iliac LLNs	58 (18.5)	6	9.2%	3	3.6%

*Subtype of obturator LLNs, defined as follows: long-axis at least twice the length of the short-axis, maximum short-axis diameter of 5mm, no malignant features present and no change/increase in the restaging MRI.

Appendix 4: Explorative univariable analysis to determine the most appropriate cut-off value for SA diameter of internal iliac and obturator LLNs in patients (n=284) who received neoadjuvant treatment.

N = 284	N (%)	4-yr LR	p-value	N (%)	4-yr LLR	*p* value
SA ≥1 mm SA <1 mm	284 (100) 0	16.4%	-	284 (100) 0	8.8%	-
SA ≥2 mm SA <2 mm	284 (100) 0	16.4%	-	284 (100) 0	8.8%	.
SA ≥3 mm SA <3 mm	273 (96) 11 (4)	16.2% 22.2%	.567	273 (96) 11 (4)	8.6% 11.1%	.722
SA ≥4 mm SA <4 mm	253 (89) 31 (11)	15.7% 21.9%	.343	253 (89) 31 (11)	9.3% 3.8%	.791
SA ≥5 mm SA <5 mm	213 (75) 71 (25)	18.0% 10.9%	.256	213 (75) 71 (25)	10.4% 3.4%	.199
SA ≥6 mm SA <6 mm	168 (59) 116 (41)	20.3% 10.5%	.107	168 (59) 116 (41)	11.8% 4.2%	.147
SA ≥7 mm SA <7 mm	122 (43) 162 (57)	20.8% 13.1%	.165	122 (43) 162 (57)	14.7% 4.4%	**.018**
SA ≥8 mm SA <8 mm	69 (24) 215 (76)	26.8% 13.1%	**.020**	69 (24) 215 (76)	19.4% 5.5%	**.003**
SA ≥9 mm SA <9 mm	48 (17) 236 (83)	33.8% 12.9%	**.001**	48 (17) 236 (83)	23.6% 6.0%	**.001**

Appendix 5. Multivariable analysis of **distant metastases** in 891 patients with cT3-4 rectal cancer ≤8 cm from the anorectal junction, who were treated with neoadjuvant radiotherapy (short course or chemoradiotherapy). Lateral lymph nodes were included in the analysis based on visibility on primary staging MRI, and stratified for short-axis diameter with a cut-off value of 7mm.

Variable	No.	HR	95% CI	P	HR	95% CI	P
Enlarged (≥7mm) LLN				**0.021**			0.389
No LLN	607	1			1		
≥7mm	122	1.590	1.131-2.235		1.268	0.880-1.829	
<7mm	162	1.261	0.907-1.752		1.145	0.821-1.596	
Gender				0.281			
Male	581	1					
Female	310	1.156	0.888-1.506				
Age in years				**0.033**			**0.015**
<55	50	1			1		
55-75	472	0.805	0.462-1.403		1.003	0.570-1.766	
75+	369	1.146	0.656-2.001		1.483	0.835-2.632	
Neoadjuvant radiotherapy				0.731			
5x5	338	1					
CRT	553	1.048	0.803-1.367				
Clinical T stage				**<0.001**			**0.015**
T3a	174	1			1		
T3b	287	1.027	0.666-1.584		0.949	0.611-1.472	
T3c	221	1.785	1.175-2.712		1.456	0.940-2.254	
T3d	56	1.991	1.121-3.537		1.139	0.620-2.094	
T4a	53	3.145	1.858-5.323		2.151	1.231-3.758	
T4b	100	2.790	1.754-4.438		1.567	0.934-2.632	
Mesorectal clinical N stage				0.120			
N0	183	1					
N1	400	1.010	0.705-1.447				
N2	308	1.325	0.924-1.901				
Extramural venous invasion (mrEMVI)				**0.001**			0.166
Absent	577	1			1		
Present	314	1.548	1.195-2.004		1.227	0.918-1.641	
Tumor deposits				**<0.001**			**<0.001**
Absent	748	1			1		
Present	143	2.323	1.737-3.107		1.935	1.406-2.663	
Surgery*				**<0.001**			**<0.001**
Sphincter non-sparing	340	1			1		
Sphincter sparing	551	0.545	0.422-0.705		0.578	0.439-0.762	
Margin status				**<0.001**			**<0.001**
R0	823	1			1		
R1	68	3.235	2.264-4.622		2.265	1.549-3.311	
		Univariable analysis			*Multivariable analysis*		

Appendix 6. Multivariable analysis of **overall survival** in 891 patients with cT3-4 rectal cancer ≤8cm from the anorectal junction, who were treated with neoadjuvant radiotherapy (short course or chemoradiotherapy). Lateral lymph nodes were included in the analysis based on visibility on primary staging MRI, and stratified for short-axis diameter with a cut-off value of 7mm.

Variable	No.	HR	95% CI	P	HR	95% CI	P
Enlarged (≥7mm) LLN				**0.074**			0.623
No LLN	607	1			1		
≥7mm	122	1.506	1.053-2.153		1.183	0.80671.734	
<7mm	162	1.021	0.709-1.470		0.955	0.660-1.381	
Gender				0.696			
Male	581	1					
Female	310	1.058	0.797-1.404				
Age in years				**<0.001**			**<0.001**
<55	50	1			1		
55-75	472	0.853	0.427-1.702		0.964	0.480-1.936	
75+	369	2.109	1.072-4.151		2.474	1.241-4.934	
Neoadjuvant radiotherapy				0.296			
5x5	338	1					
CRT	553	0.863	0.654-1.138				
Clinical T stage				**<0.001**			**0.002**
T3a	174	1			1		
T3b	287	1.264	0.782-2.043		1.340	0.823-2.180	
T3c	221	1.861	1.158-2.990		1.709	1.044-2.798	
T3d	56	3.201	1.804-5.680		2.501	1.357-4.608	
T4a	53	2.920	1.608-5.304		2.327	1.239-4.369	
T4b	100	3.443	2.076-5.710		2.829	1.617-4.949	
Mesorectal clinical N stage				0.254			
N0	183	1					
N1	400	0.743	0.523-1.057				
N2	308	0.841	0.586-1.207				
Extramural venous invasion (mrEMVI)				**0.033**			0.552
Absent	577	1			1		
Present	314	1.351	1.025-1.782		1.098	0.806-1.496	
Tumor deposits				**0.001**			0.062
Absent	748	1			1		
Present	143	1.735	1.257-2.396		1394	0.983-1.977	
Surgery*				**0.001**			0.060
Sphincter non-sparing	340	1			1		
Sphincter sparing	551	0.641	0.488-0.841		0.754	0.562-1.012	
Margin status				**<0.001**			**<0.001**
R0	823	1			1		
R1	68	3.614	2.519-5.185		2.285	1.556-3.356	
		Univariable analysis			*Multivariable analysis*		

Appendix 7. Baseline criteria of the 891 patients with cT3-4M0 rectal cancer located ≤8cm from the anorectal junction based on MRI re-review who received neoadjuvant radiotherapy divided into four groups: no LLNs, small (<7mm) LLNs, enlarged (≥7mm) internal iliac LLNs and obturator LLNs.

Primarily enlarged (≥7mm) internal iliac or obturator LLNs versus smaller (<7mm) LLNs or no LLNs	Internal iliac LLNs, N=32 (%)	Obturator LLNs N=90 (%)	<7 mm LLNs N=162 (%)	No LLNs N=607 (%)	*p* value
Gender: male	22 (68.8)	59 (65.6)	107 (66.0)	393 (64.7)	0.966
Age					**0.020**
<55 years	4 (12.5)	10 (11.1)	7 (4.3)	29 (4.8)	
55-74 years	22 (68.8)	46 (51.1)	87 (53.7)	317 (52.2)	
>75 years	6 (18.8)	34 (37.8)	68 (42.0)	261 (43.0)	
Distance of tumor from ARJ					**<0.001**
0.0-4.0cm	22 (68.8)	72 (80.0)	97 (59.9)	338 (55.7)	
4.1-8.0cm	10 (31.3)	18 (20.0)	65 (40.1)	269 (44.3)	
Tumor according to LOREC criteria					0.055
On/below	21 (65.6)	66 (73.3)	99 (61.1)	355 (58.5)	
Above	11 (34.4)	24 (26.7)	63 (38.9)	252 (41.5)	
Clinical T-stage					**<0.001**
T3a (<1mm beyond muscularis propria)	6 (18.8)	5 (5.6)	24 (14.8)	139 (22.9)	
T3b (1-4.9mm beyond muscularis propria)	10 (31.3)	26 (28.9)	58 (35.8)	193 (31.8)	
T3c (5-15mm beyond muscularis propria)	3 (9.4)	29 (32.2)	42 (25.9)	147 (24.2)	
T3d (>15mm beyond muscularis propria)	2 (6.3)	4 (4.4)	11 (6.8)	29 (6.4)	
T4a (invasion of peritoneum)	3 (9.4)	2 (2.2)	12 (7.4)	36 (5.9)	
T4b (invasion surrounding organs/structures)	8 (25.0)	24 (26.7)	15 (9.3)	53 (8.7)	
Positive mesorectal fascia (MRF) or T4 on primary MRI (tumor ≤1mm of the MRF)	19 (59.4)	57 (63.3)	82 (50.6)	281 (46.3)	**0.014**
Mesorectal clinical N-stage					**<0.001**
N0	4 (12.5)	9 (10.0)	30 (18.5)	140 (23.1)	
N1	12 (37.5)	31 (34.4)	75 (46.3)	282 (46.5)	
N2	16 (50.0)	50 (55.6)	57 (35.2)	185 (30.5)	
mrEMVI on primary MRI	11 (34.4)	37 (41.1)	56 (34.6)	210 (34.6)	0.668
Tumor deposits on primary MRI	5 (15.6)	15 (16.7)	33 (20.4)	90 (14.8)	0.483
Neoadjuvant treatment					**0.026**
Short-course radiotherapy	7 (21.9)	26 (28.9)	57 (35.2)	248 (40.9)	
Chemoradiotherapy	25 (78.1)	64 (71.1)	105 (64.8)	359 (59.1)	
Resection of primary tumor					**<0.001**
Non-sphincter sparing (APR/proctocolectomy)	15 (46.9)	54 (60.0)	62 (38.3)	209 (34.4)	
Sphincter sparing (LAR/TME/local excision)	17 (53.1)	36 (40.0)	100 (61.7)	398 (65.6)	
Resection margins (%)					**0.002**
R0	30 (93.8)	74 (82.2)	151 (93.2)	568 (93.6)	
R1	2 (6.2)	16 (17.8)	11 (6.8)	39 (6.4)	