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ORIGINAL ARTICLE – COLORECTAL CANCER

Malignant Features in Pretreatment Metastatic Lateral Lymph Nodes in Locally Advanced Low Rectal Cancer Predict Distant Metastases

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ABSTRACT

Introduction. Pretreatment enlarged lateral lymph nodes (LLN) in patients with locally advanced low rectal cancer are predictive for local recurrences after neoadjuvant (chemo)radiotherapy (n(C)RT) followed by total mesorectal excision (TME). Not much is known of the impact on oncological outcomes when in addition malignant features are present in enlarged LLN.

Patients and Methods. A multicenter retrospective cohort study was conducted at five tertiary referral centers in the Netherlands and Australia. All patients were diagnosed with locally advanced low rectal cancer with LLN on pretreatment magnetic resonance imaging (MRI) and underwent n(C)RT followed by TME. LLN were considered enlarged with a short axis of ≥ 5 mm. Malignant features were defined as nodes with internal heterogeneity and/or border irregularity. Outcomes of interest were local recurrence-free survival (LRFS), distant metastatic-free survival (DMFS), and overall survival (OS).

Results. Out of 115 patients, the majority was male (75%) and the median age was 64 years (range 26–85 years). Median pretreatment LLN short axis was 7 mm (range 5–28 mm), and 60 patients (52%) had malignant features. After a median follow-up of 47 months, patients with larger LLN (7 + mm) had a worse LRFS ($p = 0.01$) but no difference in DMFS ($p = 0.37$) and OS ($p = 0.54$) compared with patients with smaller LLN (5–6 mm). LLN patients with malignant features had no difference in LRFS ($p = 0.20$) but worse DMFS ($p = 0.004$) and OS ($p = 0.006$) compared with patients without malignant features in the LLN. Cox regression analysis identified LLN short axis as an independent factor for LR. Malignant features in LLN were an independent factor for DMFS.

Conclusion. The current study suggests that pretreatment enlarged LLN that also harbor malignant features are predictive of a worse DMFS. More studies will be required to further explore the role of malignant features in LLN.

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Technical progress of magnetic resonance imaging (MRI) has greatly improved diagnostic and staging accuracy in patients with rectal cancer, allowing better identification of high-risk disease.[1,2] Specifically

pretreatment abnormal lateral lymph nodes (LLN) can now more accurately be detected.[3] On staging MRI, LLN are defined as enlarged nodes in one of the lateral nodal basins with or without malignant features, such as border irregularity or internal heterogeneity.[4,5] LLN are present in approximately 20% of patients with locally advanced low rectal cancer (AJCC stage III), and are associated with worse oncological outcomes after treatment, which in the West normally consists of neoadjuvant (chemo)radiotherapy (n(C)RT) followed by total mesorectal excision (TME).[6–8]

Previous studies, mainly focused on size, have shown that larger pretreatment LLN are predictive for local recurrences.[5,9–11] Interestingly, not much is known about the impact on oncological outcomes when malignant features are present in LLN.[4,7,8] Therefore, the aim of the current study was to investigate the effects on long-term oncological outcomes when malignant features are present in pretreatment LLN in patients with locally advanced low rectal cancer.

PATIENTS AND METHODS

The "Strengthening the Reporting of Observational Studies in Epidemiology" guideline was used for this paper.[12]

A retrospective cohort study was conducted at five tertiary referral centers in the Netherlands (NL: Antoni van Leeuwenhoek-Netherlands Cancer Institute in Amsterdam, Catharina Hospital in Eindhoven, and Leiden University Medical Center in Leiden) and Australia (AUS: Royal Adelaide Hospital and St. Andrew's Hospital, both in Adelaide). The study was approved by the human research ethics committee at each site.

Included were patients $\geq$ 18 years with a primary locally advanced (AJCC stage III) rectal cancer, $\leq$ 9 cm of the anal verge with pretreatment LLN on MRI.[6] All patients were treated with curative intent, by n(C)RT followed by TME, between January 2009 and December 2016. Exclusion criteria were patients with a high rectal cancer (> 9 cm), those with distant metastatic disease at the time of diagnosis (AJCC stage IV), patients in whom lateral lymph nodes were resected during surgery, patients requiring pelvic exenteration surgery and other patients who did not undergo TME, patients who did not receive n(C)RT, and patients with locally recurrent disease after a previous rectal resection.

MRI assessment guidelines as published by the Lateral Node Study Consortium were followed.[8] In short, pretreatment MRIs were reviewed by the same dedicated radiologist at each center using a color map atlas of the pelvis for re-evaluation of the LLN status as described previously.[4] In addition to the AJCC TNM staging, circumferential resection margin, and tumor height, radiologists were asked to assess LLN status, based on the node with the largest short axis. LLN were considered enlarged with a short axis of $\geq$ 5 mm located in the following compartments: obturator, internal iliac, and external iliac basins. Furthermore, the presence of malignant features in the LLN, e.g., internal heterogeneity and/or border irregularity, was noted (Fig. 1).

Neoadjuvant therapy consisted of either short-course radiotherapy (5 $\times$ 5 Gy) or long-course chemoradiotherapy (45–50.4 Gy in 28 fractions over 6 weeks with one of the following concomitant chemotherapy regimens: FOLFOX (folinic acid, fluorouracil, and oxaliplatin), capecitabine, or 5-fluorouracil. Radiotherapy fields were routinely extended to include LLN basins. TME with curative intent was carried out after n(C)RT. Following surgery, routine oncological follow-up was performed, with a minimum of 3 years for all patients.

De-identified data were collected from the participating hospitals' departmental prospective databases, and electronic and paper medical records, forming a new database that was collectively analyzed. Preoperative collected data included age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, cTNM stage, height of tumor from the anal verge on MRI, clinical circumferential resection margin (cCRM), side of LLN, LLN basin involved, short-axis and malignant features of LLN, and type of neoadjuvant therapy. Perioperative collected data included: type of resection and operative time,

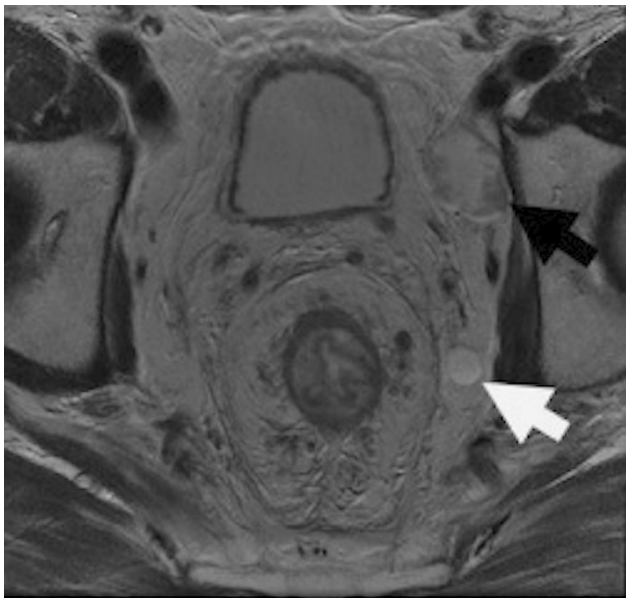

FIG. 1 Pretreatment pelvic MRI of patient with locally advanced rectal cancer with enlarged lateral lymph nodes with (black arrow) and without (white arrow) malignant features

Clavien–Dindo complication grade, length of stay (LOS), ypTNM stage, resection margins, lymphovascular invasion, number of mesorectal lymph nodes resected, and adjuvant chemotherapy.[13]

Lateral local recurrences (LLR) were defined as tumor regrowth in one of the LLN basins. Local recurrences (LR) were defined as tumor regrowth in the pelvis at the site of the anastomosis, in the previously resected mesorectal tissues, or in one of the LLN basins. Distant metastases were defined as tumor growth in the para-aortic lymph nodes and/or distant organs. For each patient, all events were recorded during follow-up. Outcomes of interest were: lateral local recurrence-free survival (LLRFS), local recurrence-free survival (LRFS), distant metastatic-free survival (DMFS), and overall survival (OS). For this analysis, patients with malignant features in LLN were compared with patients without malignant features. Two groups according to LLN size were also created: 5–6 mm and 7 + mm.[4,8]

Continuous variables are shown as medians with range, and categorical variables are presented as absolute numbers with percentages. Differences in characteristics between groups were evaluated with the Mann–Whitney *U*-test for continuous variables, and the χ^2 or the Fisher's exact test (in tables indicated with *) for categorical variables.[14] Three-year oncological outcomes (lateral local recurrence, local recurrence, distant metastases, and mortality rates) were evaluated with the χ^2 or the Fisher's exact test (indicated in tables with *). LLRFS, LRFS, DMFS, and OS were estimated using the Kaplan–Meier method, with the Cochran–Mantel–Haenszel test from the day of surgery.[15] Multivariate survival analysis was performed using the Cox proportional hazard model with stepwise backward method. A p value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 8.0.2 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

A total of 124 patients were identified. In 9 patients enlarged LLN were removed during surgery, leaving 115 patients for inclusion in the study (Table 1). The median age of the complete cohort was 64 years (range 26–85 years), and the majority was male (75%). Most patients had a clinical tumor stage 3 (cT3; 63%), and clinical nodal stage 1 (cN1) and 2 (cN2) were equally distributed (50% each). Median short axis of the LLN was 7 mm (range 5–28 mm).

Malignant features in the LLN were present in 60 patients (52%), and 55 patients had no malignant features (48%). Compared with patients without malignant features, patients with malignant features in the LLN had higher rates of cT4a-stage disease (27% versus 45%, respectively; not reaching significance: $p = 0.08$) and cN-stage disease (40% versus 60%, respectively; $p = 0.04$). Median short axis of LLN in patients with malignant features was 8 mm, and 6 mm for patients without malignant features ($p = 0.01$). Other baseline characteristics between groups were not significantly different.

Most frequent malignant features present in LLN were heterogeneity (38%) or both irregular borders and heterogeneity (43%).

None of the perioperative and postoperative histopathology outcomes was significantly different between both groups (Table 2). Patients with malignant features underwent more frequently an abdominoperineal resection (APR; 62% versus 45% for patients without malignant features; not reaching significance: $p = 0.08$) and had a wider range of tumor positive mesorectal nodes (0–14 nodes versus 0–8 nodes for patients without malignant features; not reaching statistical significance: $p = 0.09$).

Type of neoadjuvant therapy and the rate of adjuvant chemotherapy administered were not significantly different between LLN groups with or without malignant features (Tables 1, 2), or by LLN size (Online Appendix Table A).

Three years after surgery, LLR and LR rates were worse for patients with larger LLN (7 + mm; $p = 0.06$ and $p = 0.03$, respectively), while there was no significant difference in distant metastatic and mortality rates ($p = 0.67$ and $p = 0.54$, respectively; Table 3a). Similarly, after a median follow-up of 47 months, patients with larger LLN (7 + mm) had worse LLRFS ($p = 0.02$) and LRFS ($p = 0.01$), but no significant difference in DMFS ($p = 0.36$) and OS ($p = 0.30$; Fig. 2). In contrast, 3 years after surgery, LLR and LR rates were not different for LLN patients with and patients without malignant features ($p = 0.28$ and $p = 0.37$, respectively; Table 3b), while distant metastatic and mortality rates were worse for LLN patients with malignant features ($p = 0.02$ and $p = 0.0003$, respectively). Also, LLRFS ($p = 0.23$) and LRFS ($p = 0.20$) were not significantly different for LLN patients with or without malignant features, but DMFS ($p = 0.004$) and OS ($p = 0.006$) were worse for LLN patients with malignant features (Fig. 3). When analyzing LLN with malignant features by size, DMFS and OS were also worse for LLN with 5–6 mm short axis compared with LLN without malignant features ($p = 0.02$ and $p = 0.01$, respectively) (Fig. 4).

TABLE 1 Baseline patient and tumor characteristics

Variable	Complete cohort ($n = 115$)	Malignant features − ($n = 55$)	Malignant features + ($n = 60$)	p value
Age in years, median (range)	64 (26–85)	65 (30–82)	62 (26–85)	0.17
Sex (%)				
Male	86 (75)	43 (78)	43 (72)	0.52*
Female	29 (25)	12 (22)	17 (28)	
BMI, median (range)	26.6 (16.9–46.2)[a]	26.8 (20.4–39.5)[a]	26.3 (16.9–46.2)[a]	0.60
ASA classification (%)				
1	9 (16)	5 (16)	4 (17)	0.94
2	32 (58)	18 (58)	14 (58)	
3	14 (26)[b]	8 (26)[b]	6 (25)[b]	
4	0	0	0	
cT stage (%)				
cT2	1 (1)	0	1 (2)	0.08
cT3	72 (63)	40 (73)	32 (53)	
cT4a	42 (36)	15 (27)	27 (45)	
cN stage (%)				
cN1	57 (50)	33 (60)	24 (40)	0.04
cN2	58 (50)	22 (40)	36 (60)	
Height of tumor in cm, median (range)	3.2 (0.0–9.0)	3.6 (0.0–9.0)	2.8 (0.0–8.5)	0.11
cCRM involvement (%)				
Yes	48 (42)	20 (36)	28 (47)	0.26
No	67 (58)	35 (64)	32 (53)	
Side of LLN (%)				
Left	57 (50)	28 (51)	29 (48)	0.67
Right	49 (42)	24 (44)	25 (42)	
Both	9 (8)	3 (5)	6 (10)	
Involved LLN basin (%)				
External iliac	10 (14)	4 (12)	6 (16)	0.65
Obturator	39 (55)	17 (52)	22 (58)	
Internal iliac	22 (31)[c]	12 (36)[c]	10 (26)[c]	
Short-axis LLN in mm, median (range)	7 (5–28)	6 (5–21)	8 (5–28)	0.01
Short axis of LLN by size group (%)				
5–6 mm	57 (50)	38 (69)	19 (32)	< 0.0001*
7 + mm	58 (50)	17 (31)	41 (68)	
Type of malignant features LLN (%)				
Heterogeneity	–	–	23 (38)	–
Irregular border			11 (19)	
Both			26 (43)	
Neoadjuvant therapy (%)				
Short-course RT	20 (17)	11 (20)	9 (15)	0.62*
Long-course CRT	95 (83)	44 (80)	51 (85)	

LLN lateral lymph nodes, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *cT stage* clinical tumor stage, *cN stage* clinical nodal stage, *cCRM* clinical circumferential resection margin, *RT* radiotherapy, *CRT* chemoradiotherapy

*Fisher's exact test

[a]Two patients missing (1 malignant feature −, 1 malignant feature +)

[b]60 patients missing (24 malignant features −, 36 malignant features +)

[c]71 sites (33 malignant features −, 38 malignant features +)

TABLE 2 Perioperative characteristics and postoperative histopathology

Variable	Complete cohort ($n = 115$)	Malignant features − ($n = 55$)	Malignant features + ($n = 60$)	p value
Type of resection (%)				
LAR	53 (46)	30 (55)	23 (38)	0.08
APR	62 (54)	25 (45)	37 (62)	
Operation time in min, median (range)	255 (78–675)[a]	223 (117–675)[a]	262 (78–595)[a]	0.82
Clavien–Dindo grade (%)[13]				
0/1	19 (34)	11 (39)	8 (30)	0.74
2	23 (42)	11 (39)	12 (44)	
3	8 (15)	3 (11)	5 (19)	
4	4 (7)	2 (7)	2 (7)	
5	1 (2)[a]	1 (3)[a]	0[a]	
Length of hospital stay in days, median (range)	11 (4–62)[a]	11 (4–35)[a]	12 (6–62)[a]	0.63
ypT stage (%)				
ypT0	12 (11)	8 (15)	4 (7)	0.74
ypT1	6 (5)	3 (5)	3 (5)	
ypT2	30 (26)	14 (25)	16 (26)	
ypT3	54 (47)	24 (44)	30 (50)	
ypT4a	13 (11)	6 (11)	7 (12)	
ypN stage, mesorectal nodes only (%)				
ypN0	72 (63)	37 (67)	35 (58)	0.29
ypN1	29 (25)	14 (26)	15 (25)	
ypN2	14 (12)	4 (7)	10 (17)	
Lymphovascular invasion (%)				
Yes	22 (22)	11 (22)	11 (23)	0.99*
No	76 (78)[b]	39 (78)[b]	37 (77)[b]	
Total number of mesorectal LN harvested, median (range)	13 (2–46)	16 (6–46)	16 (5–45)	0.24
Range tumor-positive mesorectal lymph nodes	0–14	0–8	0–14	0.09
Resection margins (%)				
R0	103 (89)	51 (93)	52 (87)	0.39
R1	11 (10)	4 (7)	7 (11)	
R2	1 (1)	0	1 (2)	
Adjuvant chemotherapy (%)				
No	80 (70)	40 (73)	40 (66)	0.54*
Yes	35 (30)	15 (27)	20 (33)	

LLN lateral lymph nodes, *LAR* low anterior resection, *APR* abdominoperineal resection, *ypT stage* post-neoadjuvant pathological tumor stage, *ypN stage* post-neoadjuvant nodal stage, *LN* lymph nodes, *N/A* nonapplicable

*Fisher's exact test

[a]60 patients missing (27 malignant features −, 33 malignant features +)

[b]17 patients missing (5 malignant features −, 12 malignant features +)

Cox regression analysis showed that short-axis size of the LLN remained an independent significant factor for LR ($p = 0.02$). Malignant features in LLN remained an independent significant factor for DMFS ($p = 0.04$) (Table 4).

DISCUSSION

In rectal cancer, size criteria for LLN are well established to predict locoregional recurrences.[4,5,9–11] Using LLN size criteria helps to identify patients who may benefit

TABLE 3 (a) Three-year oncological outcomes for metastatic lateral lymph nodes according to short-axis size. (b) Three-year oncological outcomes for metastatic lateral lymph nodes with or without malignant features

	5–6 mm $n = 57$	7+ mm $n = 58$	p value
(*a*)			
Lateral local recurrence (%)	1 (2)	7 (12)	0.06*
Local recurrence (%)	2 (4)	10 (17)	0.03*
Distant metastases (%)	14 (25)	17 (29)	0.67*
Mortality (%)	16 (28)	20 (34)	0.54*
	Malignant features − $n = 55$	Malignant features + $n = 60$	p value
(*b*)			
Lateral local recurrence (%)	2 (4)	6 (10)	0.28*
Local recurrence (%)	4 (7)	8 (13)	0.37*
Distant metastases (%)	9 (16)	22 (37)	0.02*
Mortality (%)	8 (15)	28 (47)	0.0003*

*Fisher's exact test

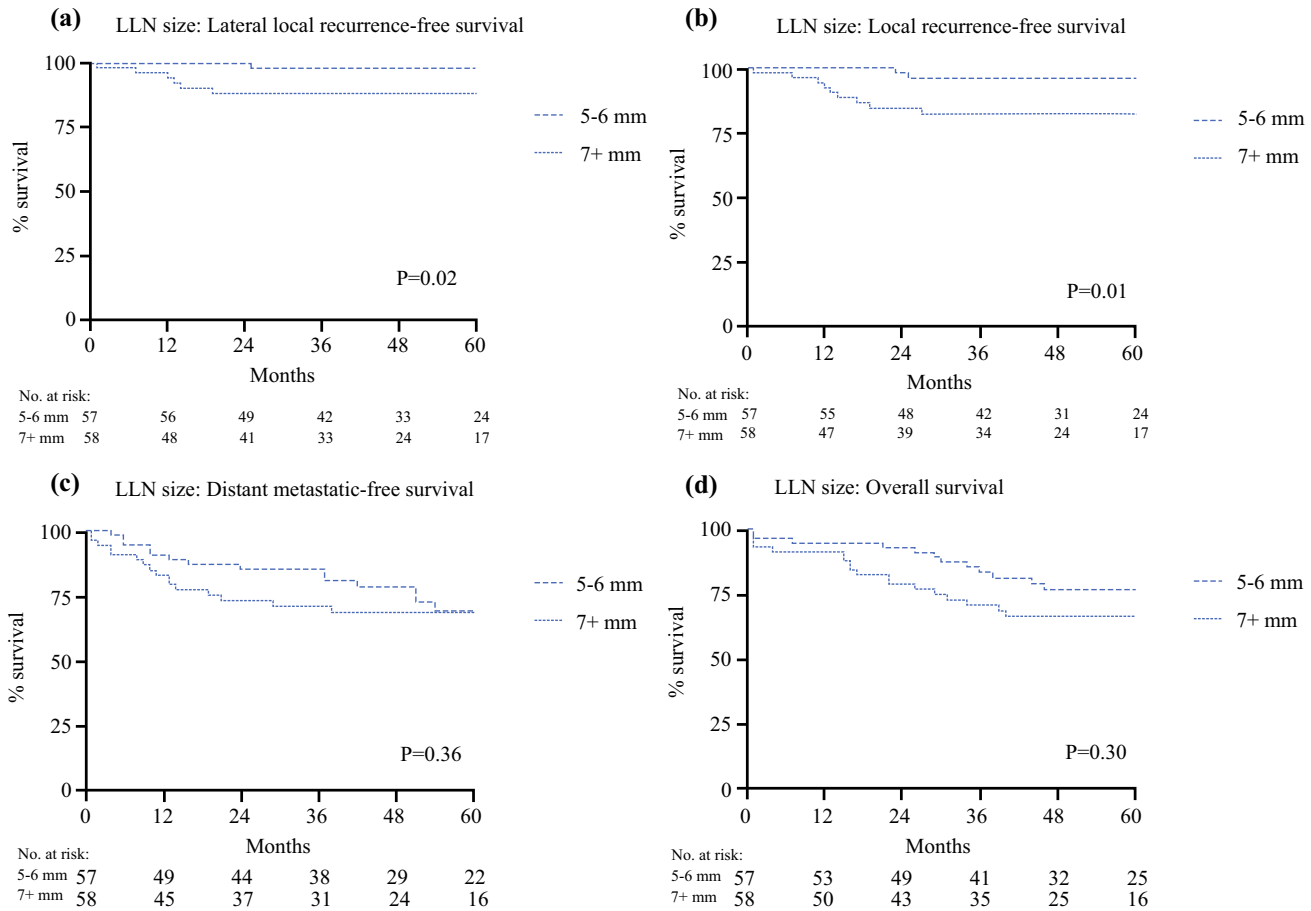

FIG. 2 **a** Kaplan–Meier survival curves of lateral local recurrence-free survival ($p = 0.02$), **b** local recurrence-free survival ($p = 0.01$), **c** distant metastatic-free survival ($p = 0.36$), and **d** overall survival ($p = 0.30$) by size of lateral lymph nodes

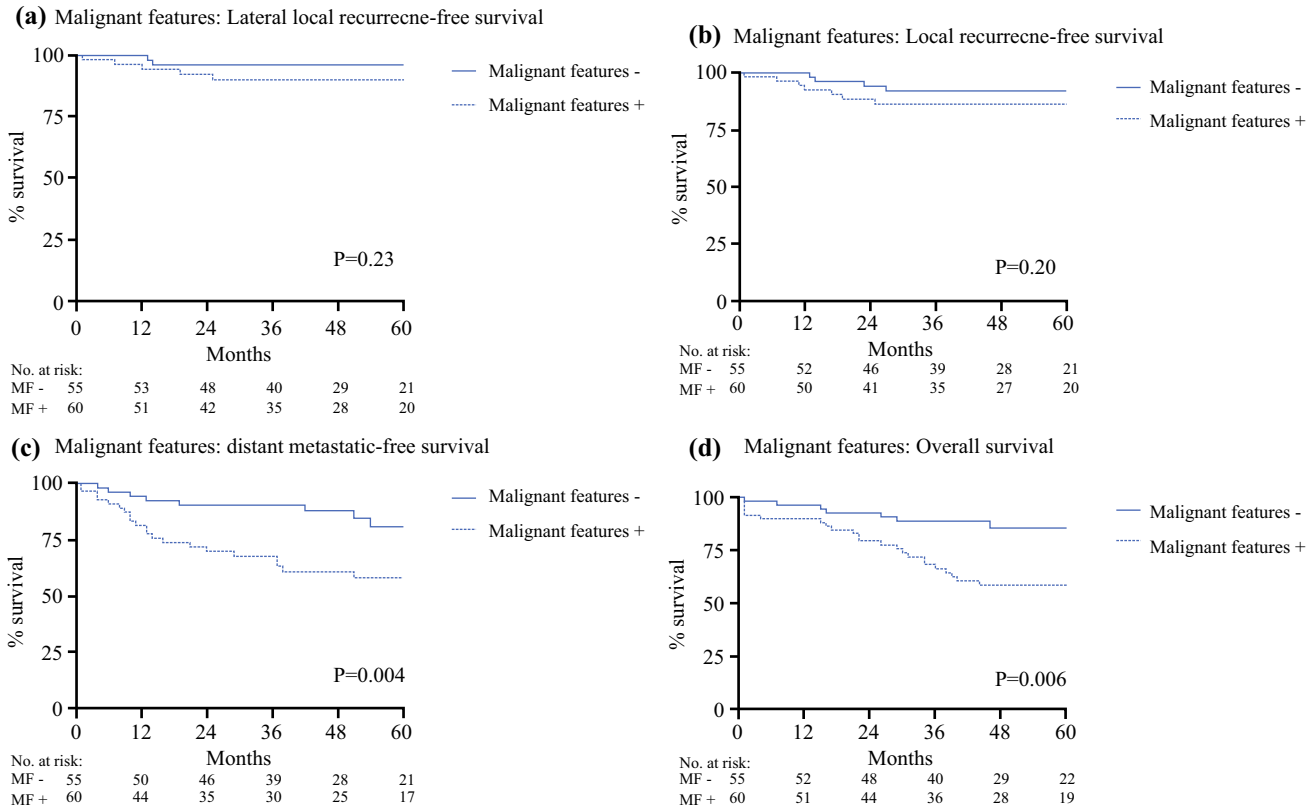

FIG. 3 **a** Kaplan–Meier survival curves of lateral local recurrence-free survival ($p = 0.23$), **b** local recurrence-free survival ($p = 0.20$), **c** distant metastatic-free survival ($p = 0.004$), and **d** overall survival ($p = 0.006$) of lateral lymph nodes with or without malignant features

from local treatment.[8] The current study suggests that additional malignant features present in enlarged LLN are predictive for worse DMFS. This could represent a poorer biology of the tumor and helps to select patients for systemic treatment.

Current knowledge about the clinical significance of enlarged LLN also harboring malignant features is limited. In a recent publication, the Lateral Node Study Consortium has been one of the few to investigate oncological outcomes of malignant features also.[4,7,8] In contrast to the current study, this consortium found that malignant features were associated with a worse LLR and LR, but not DMFS. In this study, a large number of patients from the East were included, 12% of whom underwent a lateral lymph node dissection (LLND), while 20% did not undergo any neoadjuvant treatment. To create a more homogeneous cohort, only Western patients were included in the current analysis, of whom all underwent neoadjuvant therapy, and none underwent an LLND, making the results more applicable to Western practices.

A study conducted in Oxford suggested that LLN with malignant features do not result in different LLR rates, DMFS, or cancer-specific survival.[7] However, this study only included 13 LLN patients (10%) with malignant features, meaning that it likely underestimated the true impact of LLN harboring malignant features. Furthermore, 40 patients (31%) did not undergo any neoadjuvant therapy. Since increased LLN size was significantly related to poorer cancer-specific survival and OS, it was concluded that LLN size might be a better measure than assessment of malignant features. Additionally, Japanese surgeons mainly base their judgement of LLN on size, and less on malignant features.[7]

Indeed, LLN size is one of the most important prognostic factors for long-term oncological outcomes.[4,8] Additionally, the current study suggests that patients with enlarged LLN harboring malignant features have poorer DMFS compared with those without these features. This means that, additionally to using LLN short-axis size, taking malignant features into consideration may result in improved diagnosis of smaller nodes.[16–20]

In the analyzed cohort, patients with malignant features in enlarged LLN had higher cN stages and had larger LLN compared with patients without malignant features. This

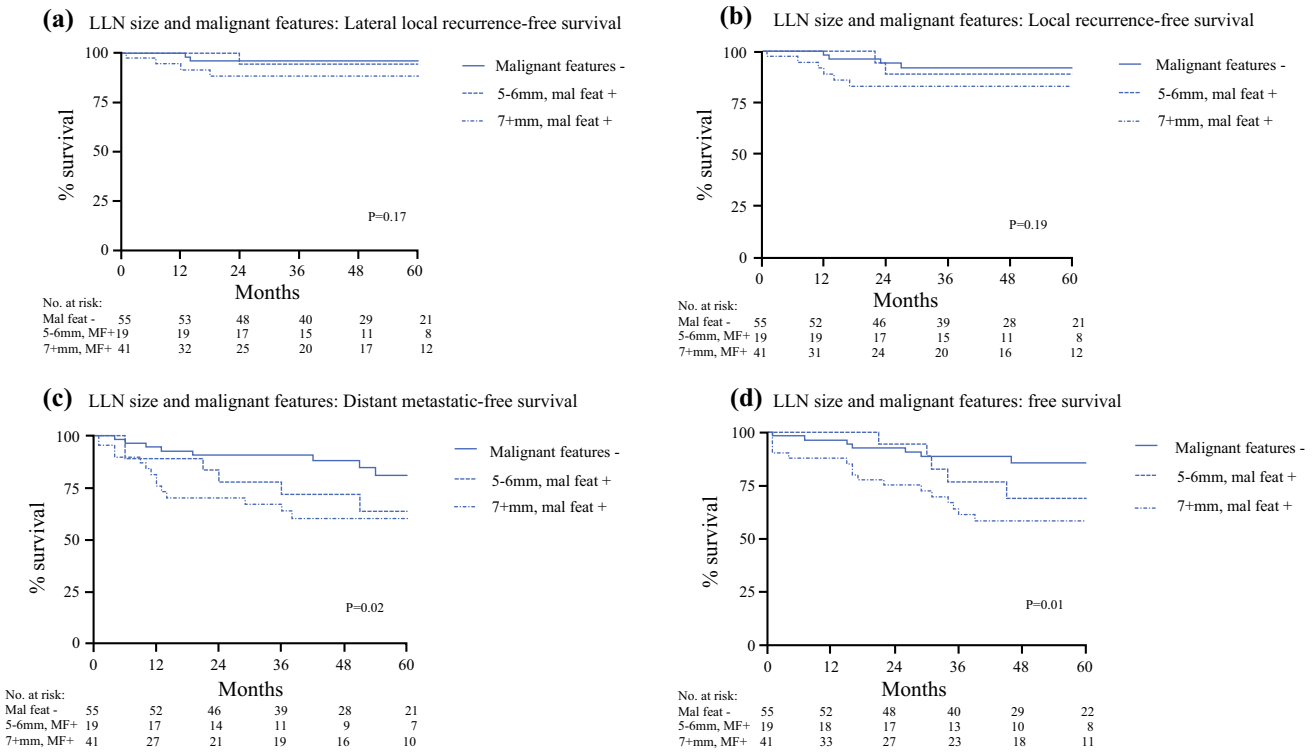

FIG. 4 **a** Kaplan–Meier survival curves of lateral local recurrence-free survival ($p = 0.17$), **b** local recurrence-free survival ($p = 0.19$), **c** distant metastatic-free survival ($p = 0.02$), and **d** overall survival ($p = 0.01$) of enlarged lateral lymph nodes without malignant features and by size groups with malignant features

TABLE 4 Summary of Cox regression analysis

Endpoint variable	*p* value	HR	95%CI
Lateral local recurrence			
ypN stage	0.04	2.94	1.43–4.56
Local recurrence			
cT stage	0.03	4.06	2.66–6.23
cN stage	0.05	3.32	1.67–7.32
Short-axis size LLN	0.02	1.31	1.21–2.12
Distant metastasis			
cN stage	0.02	3.19	2.18–8.63
Malignant features LLN	0.04	1.89	1.20–4.04
Overall survival			
Age	0.03	2.31	1.52–5.96
ypN stage	0.05	2.14	1.35–4.90
Lymphovascular invasion	0.03	4.42	1.11–10.53
Resection margins	0.02	3.54	2.15–10.91

HR hazard ratio, *95%CI* 95% confidence interval

could have impacted the distant metastatic rate, but in the Cox regression analysis, malignant features remained an independent factor for DMFS.

In the current cohort, no LLNDs were performed as the Western standard treatment of n(C)RT followed by TME was conducted. It is therefore unclear if enlarged LLN, with or without malignant features, actually were metastatic or if they were inflammatory only, as no postoperative histopathology was available. Previous studies have shown that LLN harboring metastases upon postoperative pathology are associated with decreased survival.[21–23] In light of this, another interpretation of the results of the current study could be that malignant features identified true metastatic LLN more accurately, while those that were enlarged only could have been either inflammatory or metastatic, resulting in increased distant metastatic rates in LLN with malignant features. For this reason, performing an additional LLND after nCRT in patients with enlarged LLN could be of benefit, all the more because some Western centers have recently reported reduced local recurrence rates after LLND, but evidence is limited.[8,9,24] In the future, more robust results from the currently recruiting multicenter Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) study are expected.[25]

Some limitations of the current study have to be addressed. Firstly, this is a retrospective cohort series conducted at multiple centers, resulting in unavailability of parameters, such as extramural vascular invasion and number of LLN, and in heterogeneity of patients and

treatment modalities, such as n(C)RT and adjuvant chemotherapy regimens used. Particularly in the Netherlands, adjuvant chemotherapy is used sparingly in rectal cancer and reserved for patients who develop recurrences. However, all patients in the current study were treated according to the local protocol, independently of their LLN status. Secondly, for each patient all events were recorded during follow-up to reflect the real-life setting of the study. This could have resulted in altered identification of a potential second recurrence due to adjuvant treatment that had been initiated following the first recurrence. Thirdly, due to differences in interpretation, radiologists at the participating institutions, although all with a special interest in rectal cancer imaging, may have interpreted the presence of malignant features variably, especially in smaller LLN.[19,20] Also, we were not able to evaluate the LLN response to n(C)RT as patients did not undergo a restaging MRI routinely. Lastly, despite including patients treated at five tertiary referral centers, the number of patients meeting the inclusion criteria was relatively low.

In conclusion, the current study suggests that pretreatment enlarged LLN that also harbor malignant features are predictive of a worse DMFS. More studies will be required to further explore the role of malignant features in LLN.

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