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Local recurrences in western low rectal cancer patients treated with or without lateral lymph node dissection after neoadjuvant (chemo) radiotherapy: An international multi-centre comparative study

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ABSTRACT

Background: In the West, low rectal cancer patients with abnormal lateral lymph nodes (LLNs) are commonly treated with neoadjuvant (chemo)radiotherapy (nCRT) followed by total mesorectal excision (TME). Additionally, some perform a lateral lymph node dissection (LLND). To date, no comparative data (nCRT vs. nCRT + LLND) are available in Western patients.

Methods: An international multi-centre cohort study was conducted at six centres from the Netherlands, US and Australia. Patients with low rectal cancers from the Netherlands and Australia with abnormal LLNs (≥5 mm short-axis in the obturator, internal iliac, external iliac and/or common iliac basin) who underwent nCRT and TME (LLND-group) were compared to similarly staged patients from the US who underwent a LLND in addition to nCRT and TME (LLND + group).

Results: LLND + patients (n = 44) were younger with higher ASA-classifications and ypN-stages compared to LLND-patients (n = 115). LLND + patients had larger median LLNs short-axes and received more adjuvant chemotherapy (100 vs. 30%; $p < 0.0001$). Between groups, the local recurrence rate (LRR) was 3% for LLND + vs. 11% for LLND- ($p = 0.13$). Disease-free survival (DFS, $p = 0.94$) and overall survival (OS, $p = 0.42$) were similar. On multivariable analysis, LLND was an independent significant factor for local recurrences ($p = 0.01$). Sub-analysis of patients who underwent long-course nCRT and had adjuvant chemotherapy (LLND-n = 30, LLND + n = 44) demonstrated a lower LRR for LLND + patients (3% vs. 16% for LLND-; $p = 0.04$). DFS ($p = 0.10$) and OS ($p = 0.11$) were similar between groups.

Conclusion: A LLND in addition to nCRT may improve loco-regional control in Western patients with low rectal cancer and abnormal LLNs. Larger studies in Western patients are required to evaluate its contribution.

Introduction

Pre-treatment abnormal lateral lymph nodes (LLNs; ≥5 mm

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short-axis in the obturator, internal iliac, external iliac and/or common iliac basin) are present in 16–23% of patients with a primary locally advanced low rectal cancer [1]. These LLNs are associated with increased risk of developing local recurrences (LR) [2]. In most Western centres, standard treatment for patients with LLNs is similar to the treatment of those without LLNs and consists of neoadjuvant (chemo)radiotherapy (nCRT), mostly with extended beam radiotherapy to include the LLNs basins, followed by total mesorectal excision (TME) [3–5]. This means that, in the West, abnormal LLNs are normally not resected but are assumed to be sterilized by nCRT. It is, however, unclear how effective this Western treatment approach in neutralizing LLNs [6–9].

In contrast, for similarly staged patients, the treatment strategy in the East (mainly Japan) has evolved in a different direction, consisting of TME, often without nCRT, but with a lateral lymph nodal dissection (LLND) [1,10]. Recent data from primarily Eastern centres and two Western centres performing LLNDs have suggested oncological benefit in terms of lower local recurrence rates (LRR), when, after nCRT, a LLND is carried out at the time of TME compared to nCRT and TME alone [11]. This is likely due to residual disease in the LLNs after nCRT [8,9]. For this reason, some centres in the West now treat patients with low rectal cancer and LLNs with nCRT and LLND [12,13].

To date, however, no studies exist in Western LLNs patients comparing those undergoing a TME with LLND to TME only after nCRT. It remains therefore unclear whether a LLND after nCRT leads to lower LRR in this population. In order to investigate its value, we conducted an international multi-centre study including Western patients only with locally advanced low rectal cancers and LLNs who underwent nCRT followed by a LLND at the time of TME, or TME only, with the hypothesis that an additional LLND results in a lower LRR.

Methods

The 'Strengthening the Reporting of Observational Studies in Epidemiology' guideline was used for this paper [14].

A retrospective comparative cohort study was conducted at six international tertiary referral centres from the Netherlands (NL: Antoni van Leeuwenhoek-Netherlands Cancer Institute in Amsterdam, Catharina Hospital in Eindhoven and Leiden University Medical Centre in Leiden), Australia (AUS: Royal Adelaide Hospital and St. Andrew's hospital both in Adelaide) and the MD Anderson Cancer Centre in Houston (MDACC), Texas, USA. Patients from MDACC underwent nCRT and a LLND with TME and were compared to NL/AUS patients who were treated with nCRT and TME only (without LLND). The study was approved by the human research ethics committee at each site.

For the current study, patient inclusion criteria from the Lateral Node Study Consortium were adopted [11]. Included were consecutive patients from each centre, $\geq$18 years with a primary locally advanced rectal cancer $\leq$8 cm of the anal verge with abnormal pre-treatment lateral lymph nodes on staging MRI, without distant metastases, who were treated with curative intent between January 2009 and December 2016, with a minimum of three-year follow-up [1,11]. LLNs were considered abnormal in case of a short-axis of $\geq$5 mm in the following anatomical locations: the obturator, internal iliac, external iliac and/or common iliac basins [1,15–17]. The MRI's were re-reviewed and reported by dedicated radiologists. All patients underwent neoadjuvant therapy which consisted of either short-course radiotherapy (5 $\times$ 5 Gray) or long-course chemoradiotherapy (45–50.4 Gy in 28 fractions over 5.5 weeks) with one of the following concomitant chemotherapy regimens: FOLFOX (folinic acid, fluorouracil and oxaliplatin), capecitabine, or 5-fluorouracil. In all participating centres, radiotherapy routinely a boost and fields were extended to include LLNs basins. Restaging after nCRT was not performed routinely at all participating sites. A TME with curative intent was carried out 6–8 weeks after completion of nCRT. Additionally, MDACC patients underwent an indicated LLND at the time of TME to remove the pre-treatment abnormal LLN basins according to a previously described technique [3,6,18]. None of the AUS/NL patients underwent a LLND. All operations were performed by two to five senior attending surgeons per centre at least three years before data analysis. Following surgery, routine oncological follow-up took place. LR was defined as tumour regrowth in the pelvis at the site of the anastomosis, the previously resected mesorectal tissues, or in one or more of the LLNs basins. Lateral local recurrence (LLR) was defined as tumour regrowth in one or more of the LLNs basins. Distant metastases were defined as tumour growth in inguinal and/or para-aortic lymph nodes, peritoneum and/or in distant organs. Excluded were patients with a high rectal cancer (>8 cm), those with distant metastatic disease beyond the LLNs at the time of diagnosis, patients with LR after previous rectal resections, patients who did not receive nCRT, and patients who did not undergo TME.

Preoperative data collected included age, sex, body mass index (BMI), ASA-classification, cTNM-stage, height of tumour from the anal verge on MRI, clinical circumferential resection margin (cCRM), side of LLNs, short-axis and malignant features (defined as nodes with internal heterogeneity and/or border irregularity; Fig. 1) of LLNs and type of neoadjuvant therapy. Peri-operative data included: type of resection, operation time, side and sites of LLNs resected (MDACC only), Clavien-Dindo complication grade [19], Length of hospital stay (LOS), ypTNM-stage, resection margins, lymphovascular invasion, number of lymph nodes resected, and adjuvant chemotherapy. Primary outcomes were LLR and LR. Secondary outcomes were: postoperative complications, 30-day mortality, distant metastatic-free survival (DMFS), disease-free survival (DFS) and overall survival (OS). Time to LLR and LR, and DMFS, DFS and OS were all calculated from time of surgery until occurrence of event. Data were collected at the six participating hospitals using departmental prospective colorectal databases, and electronic and paper medical records.

De-identified data of all participating centres were collected, forming a new database which was collectively analysed. Patients

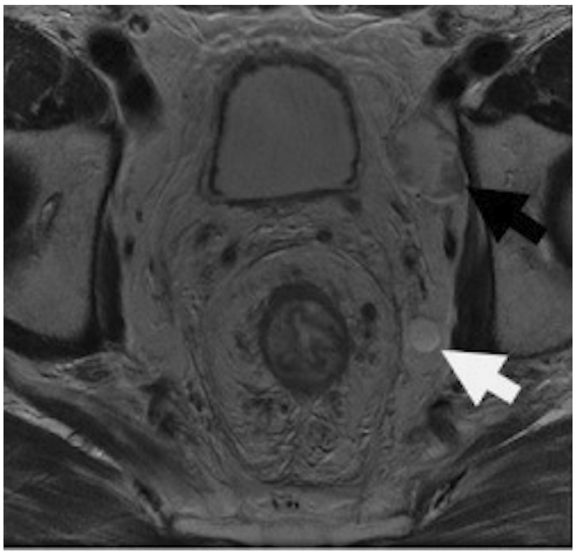

Fig. 1. Pre-treatment staging MRI of a patient with locally advanced rectal cancer and abnormal enlarged lateral lymph nodes, with (black arrow) and without (white arrow) malignant features.

Table 1
Baseline patient and tumour characteristics of complete cohort of low rectal cancer patients with pre-treatment abnormal lateral lymph nodes either undergoing neoadjuvant (chemo)radiotherapy followed by lateral lymph node dissection at the time of total mesenteric excision (TME), or had neoadjuvant (chemo)radiotherapy and TME only.

	Abnormal LLNs not resected (n = 115)	Abnormal LLNs resected (n = 44)	P-value
Age in years, median (range)	64 (26–85)	56 (20–82)	**0.0009**
Sex (%)			
Male	86 (75)	21 (48)	**0.002**
Female	29 (25)	23 (52)	
BMI, median (range)	26.6 (16.9–46.2)	26.7 (17.2–48.5)	0.36
ASA-classification (%)			
1	9 (16)	1 (2)	**<0.0001**
2	32 (58)	5 (11)	
3	14 (26)	38 (87)	
4	0 (0)[a]	0 (0)	
cT-stage (on MRI) (%)			
cT1	0 (0)	0 (0)	**0.023**
cT2	1 (1)	3 (7)	
cT3	72 (63)	32 (73)	
cT4	42 (36)	9 (20)	
cN-stage mesenteric (on MRI) (%)			
cN0	19 (17)	2 (5)	**0.032**
cN1	38 (33)	23 (52)	
cN2	58 (50)	19 (43)	
Height of tumour in cm, median (range)	3.3 (0.0–9.5)	5.0 (0.0–10.0)	**0.016**
cCRM-involvement (on MRI) (%)[d]			
Yes	48 (42)	17 (39)	0.86
No	67 (58)	27 (61)	
Side of LLNs (%)			
Left	49 (43)	15 (34)	**0.001**
Right	59 (51)	17 (39)	
Both	7 (6)	12 (27)	
Site of LLNs (%)			
External iliac	9 (8)	1 (2)	**<0.0001**
Internal iliac	34 (29)	35 (60)	
Obturator	73 (61)	16 (28)	
Common iliac	3 (2)[c]	6 (10)[b]	
Short-axis LLNs in mm, median (range)	7.0 (5–28)	11.0 (5–70)	**<0.0001**
Malignant features LLNs (%)[d]			
Yes	61 (52)	13 (29)	**0.012**
No	54 (48)	31 (71)	
Malignant features LLNs (%)			
No	54 (47)	31 (71)	**0.009**
Heterogeneity	24 (21)	7 (16)	
Irregular border	11 (9)	5 (11)	
Both	26 (23)	1 (2)	
Neoadjuvant therapy (%)[d]			
Short-course RT	20 (17)	0 (0)	**0.001**
Long-course CRT	95 (83)	44 (100)	

LLNs: lateral lymph nodes, BMI: body mass index, ASA: American Society of Anaesthesiologists, cT-stage: clinical tumour stage, MRI: magnetic resonance imaging, cN-stage: clinical nodal stage, cCRM: clinical circumferential resection margin, RT: radiotherapy, CRT: chemoradiotherapy.
[a] 60 patients missing.
[b] 58 sites involved.
[c] 119 sites involved.
[d] Fisher's exact test.

were divided into two groups: LLND + group (MDACC data) and LLND-group (NL/AUS data). Two analyses were performed: one including the complete cohort and one including only those patients receiving adjuvant chemotherapy. 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 Chi-square or the Fisher's exact test for categorical variables [20]. Lateral local recurrence rate (LLRR), LRR, DMFS, DFS, and OS were estimated using the Kaplan-Meier method, with the Mantel-Haenszel tests from the day of surgery [21]. For LLRFS, an event was defined as tumour recurrence in one or more of the LLNs basins. For LRFS, this was defined as tumour recurrence in the pelvis at the site of the anastomosis, the previously resected mesorectal tissues, or in one or more of the LLNs basins. For DMFS, an event was defined as distant tumour recurrence in liver, lung, peritoneum, or any other distant organ site. For DFS, this was defined as lateral and local tumour recurrence, and distant metastases. For OS, an event was defined as death from all causes. Multivariable survival analysis was performed using the Cox proportional hazard model with stepwise backward method. A p-value of $\leq$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

Complete cohort

In total, 159 rectal cancer patients with pre-treatment abnormal LLNs met the inclusion criteria; 44 of whom in the LLND + group

Table 2
Peri-operative characteristics and postoperative histopathology of complete cohort of low rectal cancer patients with pre-treatment abnormal lateral lymph nodes either undergoing neoadjuvant (chemo)radiotherapy followed by lateral lymph node dissection at the time of total mesenteric excision (TME), or had neoadjuvant (chemo)radiotherapy and TME only.

	Abnormal LLNs not resected (n = 115)	Abnormal LLNs resected (n = 44)	P-value
Type of resection (%)			
LAR	53 (46)	19 (43)	0.30
APR	62 (54)	22 (50)	
Exenteration	0 (0)	3 (7)	
Approach (%)[f]			
Open	48 (46)	34 (77)	**0.0005**
Minimally invasive	56 (54)[a]	10 (23)	
Operation time in minutes, median (range)	255 (78–675)[b]	436 (176–898)[c]	**<0.0001**
Side of LLNs resected (%)			
Left	N/A	15 (34)	N/A
Right		17 (39)	
Both		12 (27)	
Clavien-Dindo grade (%) [19]			
0	19 (41)	20 (46)	0.64
1	0 (0)	1 (2)	
2	21 (45)	13 (30)	
3	3 (6)	9 (20)	
4	3 (6)	1 (2)	
5	1 (2)[d]	0 (0)	
Length of hospital stay in days, median (range)	11 (4–62)[b]	8 (2–58)	**0.0004**
ypT-stage (%)			
ypT0	12 (11)	4 (9)	0.85
ypT1	6 (5)	4 (9)	
ypT2	30 (26)	9 (20)	
ypT3	54 (47)	21 (48)	
ypT4	13 (11)	6 (14)	
ypN-stage (%)			
ypN0	72 (63)	17 (39)	**0.018**
ypN1	29 (25)	16 (36)	
ypN2	14 (12)	11 (25)	
Resection margins (%)			
R0	103 (89)	39 (89)	0.78
R1	11 (10)	5 (11)	
R2	1 (1)	0 (0)	
Lympho-vascular invasion (%)[f]			
Yes	23 (22)	13 (30)	0.30
No	83 (78)[e]	31 (70)	
Total number of mesorectal LN harvested, median (range)	16 (5–46)	22.5 (6–60)	**0.004**
Total number of LLNs harvested, median (range)	N/A	3 (0–15)	N/A
Tumour positive mesorectal lymph nodes, median (range)	0 (0–14)	0 (0–13)	0.15
Tumour positive LLNs, median (range)	N/A	0.5 (0–3)	N/A
Adjuvant chemotherapy (%)[f]			
No	80 (70)	0 (0)	**<0.0001**
Yes	35 (30)	44 (100)	

LLNs: lateral lymph nodes, LAR: low anterior resection, APR: abdomino-perineal resection, ypT-stage: post-neoadjuvant pathological tumour stage, ypN-stage: post-neoadjuvant nodal stage, LN: lymph nodes, N/A: non-applicable.
[a] 11 patients missing.
[b] 60 patients missing.
[c] 10 patients missing.
[d] 68 patients missing.
[e] 9 patients missing.
[f] Fisher's exact test.

and 115 in the LLND-group.

LLND + patients were significantly younger (median 56 vs. 64 years; p = 0.0009), included more female patients (52 vs. 25%; p = 0.002) and had higher ASA-classifications (p < 0.0001; Table 1). The tumour was located more proximally in the LLND + patients (median 5.0 vs. 3.3 cm from the anal verge; p = 0.016) with significantly fewer having cT4 disease (20 vs. 36%; p = 0.023) but more with advanced mesenteric nodal stages (cN1/2 in 95 vs. 83%; p = 0.032). The LLNs in LLND + patients had a larger median short-axis diameter (11.0 vs. 7.0 mm; p < 0.0001), but showed fewer malignant features on MRI compared to LLND-patients (29 vs. 52%; p = 0.012). Furthermore, LLND + patients had more LLNs located in multiple nodal basins (34 vs. 7%; p < 0.0001). All LLND + patients received long-course nCRT, whereas 17% of the LLND-patients received a short-course regimen (p = 0.001).

There was an equal distribution in the procedure type between groups (Table 2). The surgery was performed more often by an open approach (77 vs. 46%; p = 0.0005) and took longer in LLND + patients (median 436 vs. 255 min; p < 0.0001) but they had a shorter median hospital stay (8 vs. 11 days; p = 0.0004). On pathological analysis, LLND + patients had more advanced nodal (ypN)-stage (ypN I/II in 61 vs. 37%; p = 0.018). In the LLND + group, the median number of LLNs removed was 3, with a median of 0.5 being tumour positive upon histopathology. In 22 (50%) of the LLND + patients, metastases were found in the LLNs upon histopathology. Two out of the eight patients (25%) with LLNs with a short-axis of 5–6 mm had metastatic nodes upon histopathology. Adjuvant chemotherapy was administered to significantly more

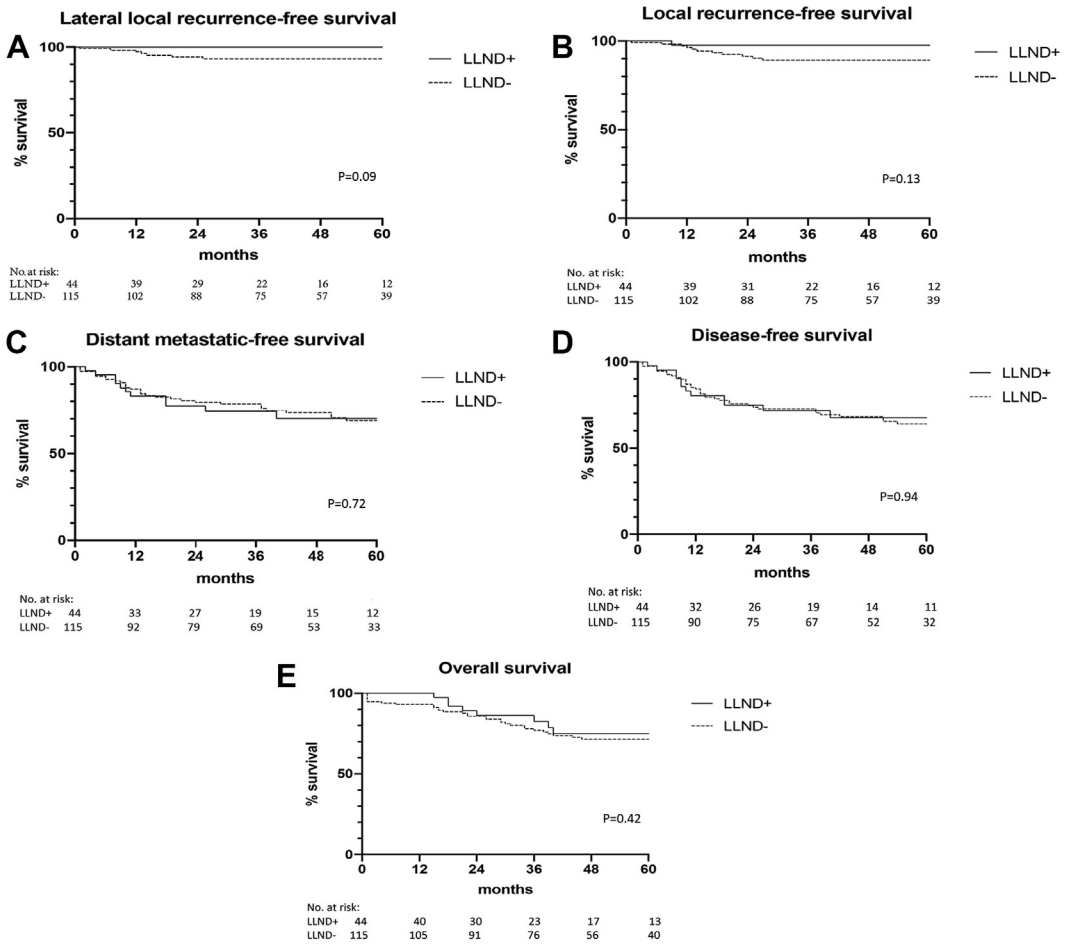

Fig. 2. Kaplan-Meier survival curves of complete cohort showing lateral local recurrence-free survival (2a; p = 0.09), local recurrence-free survival (2b; p = 0.13), distant metastatic-free survival (2c; p = 0.72), disease-free survival (2d; p = 0.94) and overall survival (2e; p = 0.42) for LLND + vs. LLND-patients.

Table 3
Complete cohort - Cox regression analysis summary.

Endpoint - Variable	p-value	HR	95%CI
Lateral local recurrence			
ypN-stage	0.04	4.26	1.28–14.74
Local recurrence			
Age	0.02	0.91	0.84–0.99
Short-axis	0.02	1.33	1.06–1.68
ypN-stage	0.04	9.89	1.06–22.75
LLND	0.01	8.34	3.07–32.94
Distant metastasis			
cCRM involved	0.04	2.37	1.04–5.40
Malignant features	0.03	0.35	0.14–0.91
Resection margin	0.01	4.20	1.39–12.76
Adjuvant chemotherapy	0.04	4.63	1.64–13.04
Overall survival			
Age	0.05	1.03	1.01–1.06
Resection margin	0.04	4.89	1.68–14.27

HR: hazard ratio, 95%CI: 95% confidence interval, ypN-stage: post-neoadjuvant pathological nodal stage, LLND: lateral lymph node dissection, cCRM: clinical circumferential resection margin.

LLND + patients (100 vs. 30%; p < 0.0001).

Median follow-up for LLND + patients was 47 months (range 1–141), and 59 months (range 1–106) for LLND-patients. No patients were lost to follow-up. There were no significant differences between groups in three-year LLRR (0% for LLND + vs. 7% for LLND-; p = 0.09), LRR (3% for LLND + vs. 11% for LLND-; p = 0.13), DMFS (p = 0.72), DFS (p = 0.94) and OS (p = 0.42). (Fig. 2).

Cox multivariable analysis showed that LLND was an independent significant factor for LRs (p = 0.01). (Table 3).

Adjuvant chemotherapy cohort

Table 4 shows the analysis of the baseline patient and tumour characteristics of patients who all underwent long-course nCRT and had adjuvant chemotherapy (n = 44 for the LLND + group; n = 30 for the LLND-group). The LLND + group consisted of more female patients (52 vs. 30%; p = 0.09) and consisted of more patients with ASA grade 3 (87 vs. 29%; p < 0.0001). Patient groups had similar ages, BMI, cT- and mesenteric cN-stages, height of tumour from the anal verge and cCRM involvement. The LLND + group had larger median short-axis diameter of the LLNs (11.5 vs. 7.5 mm; p = 0.05) but a lower percentage of LLNs with malignant features (29 vs. 60%; p = 0.02).

The surgery was performed more often by an open approach (77 vs. 40%; p = 0.004) and median operation time was longer in LLND + patients (436 vs. 255 min; p < 0.0001) but they had a shorter hospital stay (8 vs. 13 days; p = 0.004). All other peri-operative and histopathology results were similar between both groups (Table 5).

Median follow-up for LLND + patients was 47 months (range 1–141), and 64 months (range 1–98) for LLND-patients. Three-year LLRR was 0% for LLND + vs. 8% for LLND-patients (p = 0.05), and LRR was 3% for LLND + vs. 16% for LLND- (p = 0.04). DMFS was 74%

Table 4
Baseline patient and tumour characteristics of low rectal cancer patients with pre-treatment abnormal lateral lymph nodes who had adjuvant chemotherapy after either undergoing long-course neoadjuvant chemoradiotherapy followed by lateral lymph node dissection at the time of total mesenteric excision (TME), or had long-course neoadjuvant chemoradiotherapy and TME only.

	Abnormal LLNs not resected (n = 30)	Abnormal LLNs resected (n = 44)	P-value
Age in years, median (range)	58 (26–80)	56 (20–82)	0.78
Sex (%)[e]			
Male	21 (70)	21 (48)	0.09
Female	9 (30)	23 (52)	
BMI, median (range)	27.2 (20.8–40.1)	26.7 (17.2–48.5)	0.90
ASA-classification (%)			
1	2 (8)	1 (2)	**<0.0001**
2	15 (63)	5 (11)	
3	7 (29)	38 (87)	
4	0 (0)[a]	0 (0)	
cT-stage (on MRI) (%)			
cT1	0 (0)	0 (0)	0.58
cT2	1 (3)	3 (7)	
cT3	21 (70)	32 (73)	
cT4	8 (27)	9 (20)	
cN-stage mesenteric (on MRI) (%)			
cN0	1 (3)	2 (5)	0.69
cN1	13 (43)	23 (52)	
cN2	16 (53)	19 (43)	
Height of tumour in cm, median (range)	3.4 (0.0–9.5)	5.0 (0.0–10.0)[b]	0.29
cCRM-involvement (on MRI) (%)[e]			
Yes	14 (47)	17 (39)	0.63
No	16 (53)	27 (61)	
Side of LLNs (%)			
Left	14 (47)	15 (34)	0.54
Right	10 (33)	17 (39)	
Both	6 (20)	12 (27)	
Site of LLNs (%)			
External iliac	2 (6)	1 (2)	0.12
Internal iliac	13 (39)	35 (60)	
Obturator	16 (49)	16 (28)	
Common iliac	2 (6)[d]	6 (10)[c]	
Short-axis LLNs in mm, median (range)	7.5 (5–26)	11.5 (5–70)	**0.05**
Malignant features LLNs (%)[e]			
Yes	18 (60)	13 (29)	**0.02**
No	12 (40)	31 (71)	
Malignant features LLNs (%)			
No	12 (40)	31 (71)	**0.04**
Heterogeneity	9 (30)	7 (16)	
Irregular border	5 (17)	5 (11)	
Both	4 (13)	1 (2)	

LLNs: lateral lymph nodes, BMI: body mass index, ASA: American Society of Anaesthesiologists, cT-stage: clinical tumour stage, MRI: magnetic resonance imaging, cN-stage: clinical nodal stage, cCRM: clinical circumferential resection margin, RT: radiotherapy, CRT: chemoradiotherapy.
[a] 6 patients missing.
[b] 1 patient missing.
[c] 58 sites involved.
[d] 33 sites involved.
[e] Fisher's exact test.

for LLND + vs. 55% for LLND- (p = 0.12), DFS was 72% for LLND + vs. 51% for LLND- (p = 0.10), and OS was 86% vs. 62%, respectively (p = 0.11). (Fig. 3).

Discussion

The current study suggests beneficial oncological outcomes when a LLND is performed in addition to TME surgery after nCRT in Western patients with pre-treatment abnormal LLNs in terms of lower LLRR and LRR.

A recent international multi-centre study in 223 patients comparing those with mesorectal nodes only to those with LLNs showed a lower LRR and a longer DFS in patients with mesorectal nodes only [2]. Another study showed that four years after treatment, 33% of LLNs patients developed a LR when treated with nCRT only [22]. These studies show that pre-treatment abnormal LLNs are more advanced disease than metastatic mesorectal lymph nodes and that they may have been undertreated with nCRT alone.

In the East, mainly Japan, treatment differs from the West, as most patients with LLNs undergo a LLND at the time of TME, however, often without nCRT [10]. Despite these differences in treatment between the East and the West, comparable LRRs have been reported [23]. Interestingly, it has been shown that if LLNs harbour tumour upon pathology, a LLND alone, without nCRT, may not be adequate treatment to prevent LRs [24].

Multiple centres, again mainly from the East, have published their experience combining both treatment strategies, performing a LLND after nCRT. Similarly to the current study, in these series, metastatic disease was found upon histopathology in 22–66% of the resected LLNs, demonstrating that LLNs are not eradicated completely by nCRT only [6–8,17]. Furthermore, Ishihara et al. reported that a LLND after nCRT resulted in a 0% LRR and improved OS [7]. Similar results have been presented by a large multi-centre LLNs analysis, showing a reduction of the 5-year LRR from 19.5% for those treated with nCRT only, to 5.7% after an additional LLND [11]. These studies, however, included almost exclusively Eastern

Table 5
Peri-operative characteristics and postoperative histopathology of low rectal cancer patients with pre-treatment abnormal lateral lymph nodes who had adjuvant chemotherapy after either undergoing long-course neoadjuvant chemoradiotherapy followed by lateral lymph node dissection at the time of total mesenteric excision (TME), or had long-course neoadjuvant chemoradiotherapy and TME only.

	Abnormal LLNs not resected (n = 30)	Abnormal LLNs resected (n = 44)	P-value
Type of resection (%)			
LAR	13 (43)	19 (43)	0.33
APR	17 (57)	22 (50)	
Exenteration	0 (0)	3 (7)	
Approach (%)[e]			
Open	10 (40)	34 (77)	**0.004**
Minimally invasive	15 (60)[a]	10 (23)	
Operation time in minutes, median (range)	255 (78–675)[b]	436 (176–898)[c]	**<0.0001**
Side of LLNs resected (%)			
Left	N/A	15 (34)	N/A
Right		17 (39)	
Both		12 (27)	
Clavien-Dindo grade (%) [19]			
0	5 (23)	20 (46)	0.38
1	0 (0)	1 (2)	
2	14 (64)	13 (30)	
3	2 (9)	9 (20)	
4	1 (4)	1 (2)	
5	0 (0)[d]	0 (0)	
Length of hospital stay in days, median (range)	13 (6–35)[b]	8 (2–58)	**0.004**
ypT-stage (%)			
ypT0	2 (6)	4 (9)	0.84
ypT1	1 (3)	4 (9)	
ypT2	8 (27)	9 (20)	
ypT3	14 (47)	21 (48)	
ypT4	5 (17)	6 (14)	
ypN-stage (%)			
ypN0	14 (47)	17 (39)	0.47
ypN1	12 (40)	16 (36)	
ypN2	4 (13)	11 (25)	
Resection margins (%)			
R0	24 (80)	39 (89)	0.36
R1	5 (17)	5 (11)	
R2	1 (3)	0 (0)	
Lympho-vascular invasion (%)[e]			
Yes	10 (30)	13 (30)	0.80
No	20 (70)	31 (70)	
Total number of mesorectal LN harvested, median (range)	20 (6–46)	22.5 (6–60)	0.18
Total number of LLNs harvested, median (range)	N/A	3 (0–15)	N/A
Tumour positive mesorectal lymph nodes, median (range)	0.5 (0–13)	0 (0–13)	0.84
Tumour positive LLN, median (range)	N/A	0.5 (0–3)	N/A

LLNs: lateral lymph nodes, LAR: low anterior resection, APR: abdomino-perineal resection, ypT-stage: post-neoadjuvant pathological tumour stage, ypN-stage: post-neoadjuvant pathological nodal stage, LN: lymph nodes, N/A: non-applicable.
[a] 5 patients missing.
[b] 7 patients missing.
[c] 10 patients missing.
[d] 8 patients missing.
[e] Fisher's exact test.

patients in the dissected group, which may represent significant bias. Since it is not clear whether the biological behaviour of rectal cancer is different in Eastern patients, or whether there are other geographical confounders impacting outcomes, the current study contributes as the first to directly compare outcomes in only Western patients with pre-treatment abnormal LLNs undergoing nCRT with or without a LLND. Interestingly, we found a reduction in the three-year LRR: from 14% to 3%, but this difference did not reach statistical significance in the adjuvant chemotherapy cohort, likely due to low patient numbers, but the 3% LRR in LLND + patients is lower than would be expected and in the Cox multivariable analysis a LLND was a significant factor for less LRs [11]. This is an interesting finding, as LRs after rectal cancer are challenging to treat and associated with significant morbidity, and reduce quality of life and OS [25].

In the complete cohort analysis, differences in baseline characteristics were found between both groups. These differences may have had an influence on the LRRs and other outcome measures. In particular, there was a higher rate of adjuvant chemotherapy use in the LLND + group. It is unclear whether this was due to a higher rate of ypN + disease or due to institutional differences in indications for adjuvant treatment. Anecdotally, particularly in the Netherlands, adjuvant chemotherapy is used sparingly and reserved for patients who are more likely to develop recurrences. To overcome the difference in adjuvant chemotherapy between groups, the analysis only including patients who underwent adjuvant chemotherapy was performed. In this subset analysis, most of the previously significant baseline characteristics, such as the cTNM-stage, were now more similar between both cohorts.

A LLND is a complex procedure with associated risks of intra- and postoperative complications [26–28]. Although the operating time was longer in the LLND group, complications were similar to patients who underwent TME only, and LOS was shorter. While LOS may have been influenced by the hospital's local protocols, the

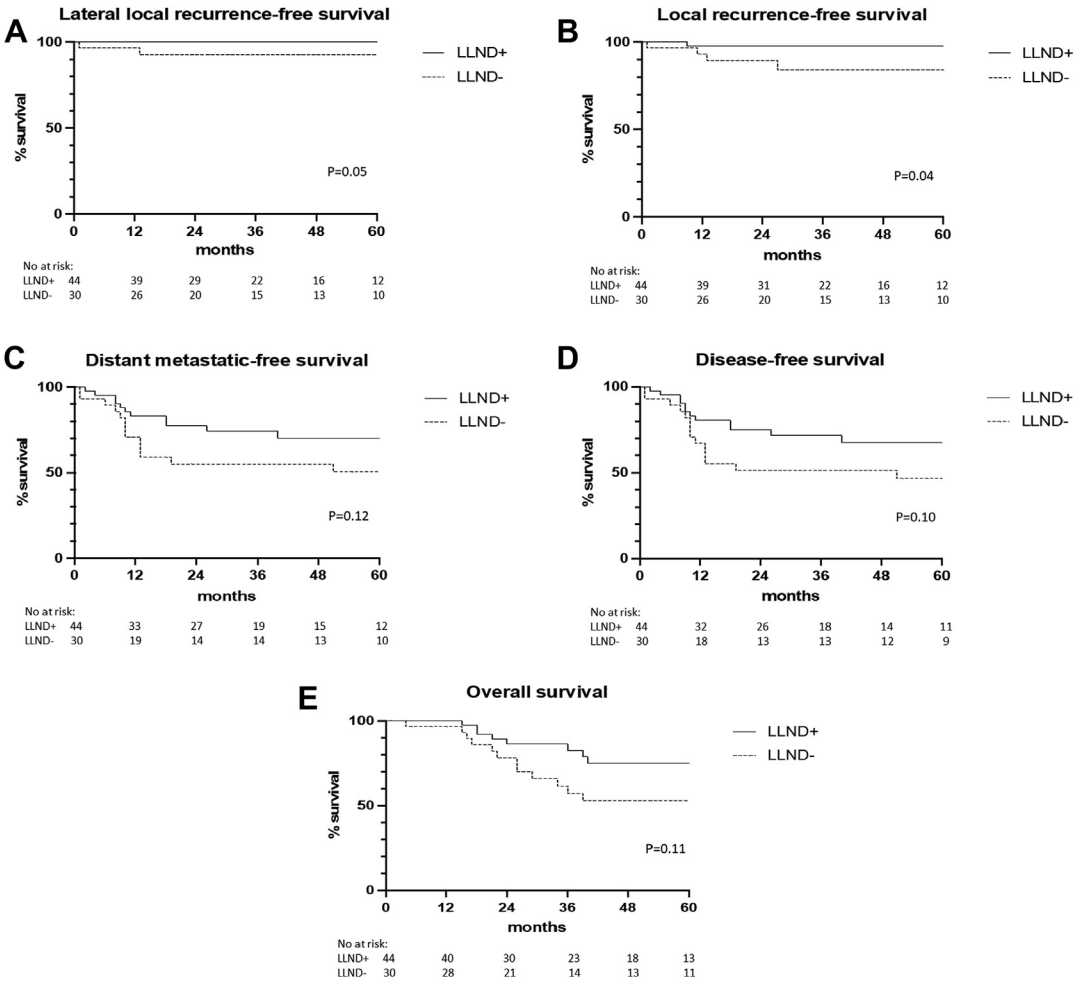

Fig. 3. Kaplan-Meier survival curves of long-course nCRT and adjuvant chemotherapy cohort showing lateral local recurrence-free survival (3a; p = 0.05), local recurrence-free survival (3b; p = 0.04), distant metastatic-free survival (3c; p = 0.12), disease-free survival (3d; p = 0.10) and overall survival (3e; p = 0.11) for LLND + vs. LLND-patients.

current results suggest that a LLND is not associated with significant short-term adverse events.

Some limitations of the current study have to be mentioned. Firstly, due to the retrospective nature of the study, exact details of radiotherapy could not be retrieved. However, all participating centres include LLNs during radiotherapy. Interpretation of the results is also limited by the retrospective nature of the study, heterogeneity between centres and of the patient populations, (neoadjuvant) treatment strategies and surgical technique. We did not capture functional outcomes and therefore cannot report on long-term morbidity such as sexual and urinary dysfunction. The results of the JCOG0212 trial suggested similar morbidity and functional outcomes after LLND [29]. Furthermore, there was variability in the median length of follow-up, however, as a minimum 3-year follow-up was mandated for inclusion in the study, most recurrences are likely to have been captured [30]. The sites of the involved LLNs basins were different between LLND+ and LLND- cohorts, which may have been the results of a difference in definition between the participating centres [11]. Interestingly, a recent multi-centre cohort study showed a difference in LRR between internal iliac and obturator LLNs, indicating the need for uniform definition [9]. Similar to the definition of the anatomical location of the LLNs, a cut-off short-axis size of ≥5 mm for LLNs was chosen based on previous publications and threshold of surgical management, yet, in literature the definition of LLNs varies between a short-axis of 5–10 mm, making comparisons challenging [9,11,15–17]. Lastly, despite including patients treated at tertiary referral centres, the number of patients meeting the inclusion criteria was relatively low. This could indicate that patients with low rectal cancer and abnormal LLNs are missed at diagnosis as the incidence of abnormal LLNs is estimated to be 16–23% [1].

In future studies it would be beneficial if more Western centres could participate, especially those centres performing LLNDs, although this may be difficult considering the number of Western centres who have experience performing the procedure. For this reason, it is unlikely that a randomised trial in Western patients will be conducted in the foreseeable future. Therefore, the results of the soon to open Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) study and the currently recruiting trial by Wei et al. randomising Chinese LLNs patients after nCRT for a LLND at the time of TME to TME only, are eagerly awaited [31,32].

In conclusion: A lateral lymph node dissection at the time of total mesorectal excision in addition to neoadjuvant (chemo) radiotherapy may improve loco-regional control in Western patients with low rectal cancer and abnormal lateral lymph nodes. Larger studies in Western patients are required to evaluate its contribution.

CRediT authorship contribution statement

Hidde M. Kroon: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation,

Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Songphol Malakorn:** Methodology, Validation, Investigation, Resources, Data curation, Writing – review & editing. **Nagendra N. Dudi-Venkata:** Validation, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Project administration. **Sergei Bedrikovetski:** Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Visualization. **Jianliang Liu:** Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Visualization. **Tim Kenyon-Smith:** Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Visualization. **Brian K. Bednarski:** Methodology, Validation, Investigation, Resources, Data curation, Writing – review & editing. **Atsushi Ogura:** Methodology, Validation, Investigation, Resources, Data curation, Writing – review & editing, Project administration. **Cornelis J.H. van de Velde:** Methodology, Validation, Investigation, Resources, Data curation, Writing – review & editing, Project administration. **Harm J.T. Rutten:** Methodology, Validation, Investigation, Resources, Data curation, Writing – review & editing, Project administration. **Geerard L. Beets:** Methodology, Validation, Investigation, Resources, Data curation, Writing – review & editing, Project administration. **Michelle L. Thomas:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Miranda Kusters:** Methodology, Validation, Investigation, Resources, Data curation, Writing – review & editing, Project administration. **George J. Chang:** Methodology, Validation, Investigation, Resources, Data curation, Writing – review & editing, Project administration. **Tarik Sammour:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

None.

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