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European Journal of Surgical Oncology 48 (2022) 1475–1482

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Review Article

Systematic review and meta-analysis of long-term oncological outcomes of lateral lymph node dissection for metastatic nodes after neoadjuvant chemoradiotherapy in rectal cancer

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A R T I C L E I N F O

Article history:
Accepted 19 April 2022
Available online 29 April 2022

Keywords:
Rectal cancer
Locally advanced rectal cancer
Lateral lymph nodes
Lateral pelvic nodes
Neoadjuvant chemoradiotherapy
Lateral lymph node dissection

A B S T R A C T

Background: Standard Western management of rectal cancers with pre-treatment metastatic lateral lymph nodes (LLNs) is neoadjuvant (chemo)radiotherapy (nCRT) followed by total mesorectal excision (TME). In recent years, there is growing interest in performing an additional lateral lymph node dissection (LLND). The aim of this systematic review and meta-analysis was to investigate long-term oncological outcomes of nCRT followed by TME with or without LLND in patients with pre-treatment metastatic LLNs.

Methods: PubMed, Ovid MEDLINE, Embase, Cochrane Library and Clinicaltrials.gov were searched to identify comparative studies reporting long-term oncological outcomes in pre-treatment metastatic LLNs of nCRT followed by TME and LLND (LLND+) vs. nCRT followed by TME only (LLND-). Newcastle-Ottawa risk-of-bias scale was used. Outcomes of interest included local recurrence (LR), disease-free survival (DFS), and overall survival (OS). Summary meta-analysis of aggregate outcomes was performed.

Results: Seven studies, including 946 patients, were analysed. One (1/7) study was of good-quality after risk-of-bias analysis. Five-year LR rates after LLND+ were reduced (range 3–15%) compared to LLND- (11–27%; RR = 0.40, 95%CI [0.25–0.62], $p < 0.0001$). Five-year DFS was not significantly different after LLND+ (range 61–78% vs. 46–79% for LLND-; RR = 0.72, 95%CI [0.51–1.02], $p = 0.143$), and neither was five-year OS (range 69–91% vs. 72–80%; RR = 0.72, 95%CI [0.45–1.14], $p = 0.163$).

Conclusion: In rectal cancers with pre-treatment metastatic LLNs, nCRT followed by an additional LLND during TME reduces local recurrence risk, but does not impact disease-free or overall survival. Due to the low quality of current data, large prospective studies will be required to further determine the value of LLND.

1. Introduction

Between 15 and 20% of patients with locally advanced rectal cancer have metastases to the lateral lymph nodes (LLNs) in the pelvic side-wall at diagnosis at diagnosis [1]. Historically, treatment paradigms for these pre-treatment metastatic LLNs differs between the East and the West [2,3]. Standard treatment in the East does not include neoadjuvant (chemo)radiotherapy (nCRT), but consists of upfront rectal resection adhering to total mesorectal excision (TME) principles and a lateral lymph node dissection (LLND) to remove

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https://doi.org/10.1016/j.ejso.2022.04.016

the tumour and the metastatic LLNs [1,4]. In contrast, standard treatment in the West consists of nCRT followed by only TME, without a LLND [5,6].

This difference in approach to similar disease finds its origin in the definition of LLNs. In the East, LLNs are considered regional, surgically treatable disease, while historically the West has defined LLNs as distant metastatic disease, with the assumption that outcomes are not altered by a LLND [7–9]. However, there is growing debate as to whether TME and nCRT adequately treats LLNs given studies have shown that nCRT sterilises metastatic LLNs in less than 50% of patients, and therefore, whether a LLND should be performed in addition for optimal long-term oncological outcomes and local control [2,6,10–12].

On the other hand, a LLND is associated with increased operation time, blood loss, and potential postoperative morbidity such as urinary, sexual, and lower limb movement dysfunction [13–15]. Furthermore, the incidence of these complications is potentially higher in the West than that reported in the East, as LLND is technically more complex in patients with a higher BMI and after pelvic radiotherapy [2]. As a result, there has been reluctance to perform a LLND in the West when metastatic LLNs are present.

Recently, however, some Western centres have reported favorable outcomes of LLND after nCRT in patients with pre-treatment metastatic LLNs [10,12,16]. Likewise, a number of Eastern centres are now administering nCRT before TME and LLND to patients these patients [3,17]. Therefore, the aim of this systematic review and meta-analysis was to investigate long-term oncological outcomes in patients with rectal cancer and pre-treatment metastatic LLNs, treated with nCRT followed by TME with or without an additional LLND.

2. Methods

A comprehensive systematic review of the literature was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Supplementary Tables 1 and 2) [18,19]. The study protocol was registered prospectively at the PROSPERO database of systematic reviews (CRD42021275927).

2.1. Search strategy

Searches to identify relevant publications were performed independently by two reviewers (HK and LH) on PubMed, Ovid MEDLINE, Embase, Cochrane Library and Clinicaltrials.gov. Searches were conducted from January 1, 1985 (since the first publications on neoadjuvant therapy for rectal cancer) to September 30, 2021 [20,21]. Medical Subject Headings (MeSH) terms and key words that were used included:'rectal neoplasm', 'pelvic neoplasm', 'rectal cancer', 'lymphatic metastasis', 'lateral lymph node', 'lateral pelvic lymph node', 'pelvic side wall node', 'neoadjuvant therapy', 'chemoradiotherapy', 'proctectomy', 'rectal resection', 'total mesorectal excision', 'lymph node dissection', 'extended lymphadenectomy', 'lateral lymph node dissection', 'lateral pelvic lymph node dissection', 'pelvic side wall dissection', 'comparative study'.

Supplementary Table 3 provides the search strategies. Boolean AND/OR operators were used to combine MeSH terms and keywords. The related-articles function was used to broaden the searches.

2.2. Eligibility criteria for including studies

Included studies were those describing outcomes of patients with rectal cancer with pre-treatment metastatic LLNs, without distant metastatic disease, who underwent a LLND during TME surgery after nCRT compared to patients who underwent nCRT and TME only: nCRT + TME + LLND (LLND + group) vs. nCRT + TME (LLND-group). Randomised controlled trials (RCTs) as well as prospective and retrospective cohort studies were considered for inclusion.

Excluded were non-English studies, letters, short communications, reviews, commentaries, and case reports. Also excluded were studies describing treatment of malignancies other than rectal cancer, single-arm non-comparative studies (e.g. nCRT + TME or nCRT + TME + LLND only), studies in which no nCRT was used, studies including rectal cancer patients without metastatic LLNs, those including patients with distant metastases, recurrent rectal cancer and multivisceral resection studies, and those describing other surgical procedures (e.g. LLN sampling or pelvic exenterations).

2.3. Study selection

Following the searches, all identified titles and abstracts were reviewed independently by two reviewers (HK and LH), followed by full-text review of potentially eligible studies. Reference lists of full-text articles were manually searched to identify additional eligible studies. Any differences in study selection were resolved by consensus and, if needed, discussed with a third reviewer (NHR) to reach agreement.

2.4. Risk of bias assessment

The methodological quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS) independently by two reviewers (HK and NHR), examining three factors: method of patient selection, comparability of the study groups, and number of outcomes reported [22]. A rating of 0–9 was allocated to each study based on these parameters. Publications with a score of *$\geq$7 were considered good-quality studies.

2.5. Data extraction

A predefined spreadsheet (Supplementary Table 4) was used to extract data from the included studies independently by two reviewers (HK and LH). Any discrepancies were discussed and resolved by a third author (NHR). The data extracted from each article included first author, country, publication year, study design, single or multi-centre, number of patients in each arm, population characteristics, tumour characteristics, surgical procedures, postoperative pathology, adjuvant therapy, follow-up times, and survival analyses.

2.6. Outcomes of interest and statistical analysis

The primary outcomes of interest were local recurrence, disease-free survival, and overall survival. Secondary outcomes included lateral local recurrences and distant metastases in LLND + vs. LLND-groups. Descriptive statistics were used for individual patient data analysis. No assumptions for missing data were made. Summary meta-analysis of aggregate data, using relative risk (RR), was performed on the outcomes of interest using StatsDirect software Version 3 (StatsDirect Ltd, Birkenhead, Wirral, United Kingdom) as only summary statistics were provided or able to be extracted from the included studies [23]. Survival data extracted from Kaplan-Meier curves and hazard ratios (HR) were used for the corresponding quantitative analysis using the method of inverse of the invariance (fixed effect model) in absence of sensitive heterogeneity. Results are presented as RR with 95% confidence intervals (95%CI) and in forest plots. For overall effect $p < 0.05$ was considered statistically significant. Cochran's Q test and I^2 results were used to estimate heterogeneity. Heterogeneity was considered statistically significant when $p < 0.05$ for the Cochran's Q test and I^2>50%. Risk of bias was analysed using the Eggar method, in which $p < 0.05$ indicated significant bias [24].

3. Results

The search identified 689 studies. After removing duplicate entries (n = 137), 552 article titles and abstract were screened. Ninety-seven articles were selected for full-text analysis, after which seven were eligible for this systematic review, with one additional article included from the reference list (Fig. 1) [2,10,16,25–28].

Table 1 demonstrates the patient characteristics and preoperative management of the included studies. All studies were retrospective observational in design. Four were multi-centre studies [2,10,16,27], and three single-centre [25,26,28]. The seven studies included a total of 946 patients who all underwent neoadjuvant therapy: 266 underwent a LLND during TME (LLND + group), and 640 underwent TME only (LLND-group) One study did not report size of the groups [27].

Tumour height was reported with a range of 3.3–5.2 cm from the anal verge in three studies reporting median distance [10,26,27]. and four studies reported the majority of tumours were located in the lower rectum (range 53–81%) [2,16,25,28]. Three studies used short-axis of ≥5 mm as LLNs size selection criteria for suspicion of metastases [10,25,28], Ogura et al. used short-axis cut-off of ≥7 mm, and Shiratori used LLNs long-axis cut-off of ≥6 mm [2,26]. Five studies described the anatomical location of metastatic LLNs as enlarged nodes in the internal iliac, external iliac and obturator basins. Three studies included the common iliac basin

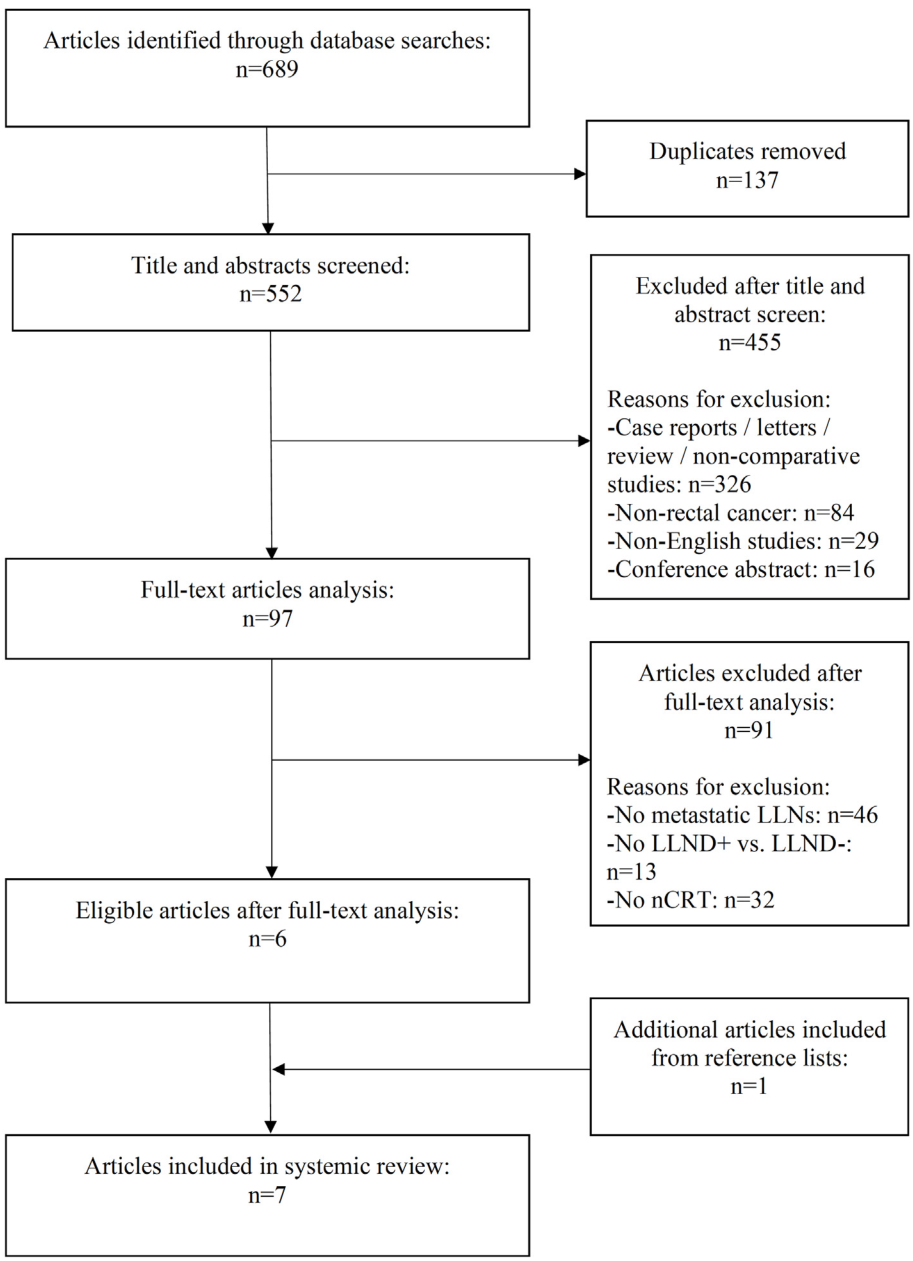


Fig. 1. PRISMA chart outlining the selection of included articles.
LLNs, lateral lymph nodes; LLND, lateral lymph node dissection; nCRT, neoadjuvant (chemo)radiotherapy.

Table 1
Patient characteristics and preoperative management included studies.

Author, country, year	Study design	Single/multi centre	No. of patients		Male/female (%)		Age (median)	
			LLND+	LLND-	LLND+	LLND-	LLND+	LLND-
Kim HJ, Korea, 2017 [25]	Retrospective observational	Single	53	31	58/42	81/19	13% ≥ 70 yr	15% ≥ 70 yr
Shiratori, Japan, 2018 [26]	Retrospective observational	Single	34	206	65/35[1]	–	63 yr[1]	–
Ogura, international collaborative, 2018 [2]	Retrospective observational	Multi	53	118	58/42[2]	–	45% ≥ 62 yr[2]	–
Nishizaki, Japan, 2019 [27]	Retrospective observational	Multi	40[4]	–	–	–	–	–
Jones, UK, 2020 [16]	Retrospective observational	Multi	13	68	54/46	76/24[5]	57 yr	64 yr[5]
Kim MJ, Korea, 2020 [28]	Retrospective observational	Single	69	102	–	–	58 yr	55 yr
Kroon, US/AUS/NL, 2021 [10]	Retrospective observational	Multi	44	115	48/52	75/25	56 yr	64 yr

Author	Tumour height (median/%)		cT-stage (%)		LLNs size criteria (mm)	Site of LLNs	Neoadjuvant CRT/RT (%)	
	LLND+	LLND-	LLND+	LLND-			LLND+	LLND-
Kim HJ [25]	81% <5 cm	65% <5 cm	T2: 7 T3: 76 T4: 17	T2: 12 T3: 76 T4: 12	≥5 SA	Internal iliac External iliac Obturator Common iliac Aortic bifurcation	100/0	100/0
Shiratori [26]	4.4 cm[1]	–	T2: 1 T3: 92 T4: 7[1]	–	≥6 LA	Internal iliac External iliac Obturator Common iliac	100/0[1]	–
Ogura [2]	68% low[2,3]	–	T3: 59 T4: 41[2]	–	≥7 SA	Internal iliac External iliac Obturator	89/11[1]	–
Nishizaki [27]	5.2 cm[1]	–	–	–	≥5	–	100/0	100/0
Jones [16]	54% ≤5 cm	53% ≤5 cm[5]	Mean cT: 3.25	Mean cT: 3.3	–	Internal iliac External iliac Obturator	100/0	100/0
Kim MJ [28]	60% ≤5 cm	60% ≤5 cm	–	–	≥5 SA	–	100/0	100/0
Kroon [10]	5.0 cm	3.3 cm	T2: 7 T3: 73 T4: 20	T2: 1 T3: 63 T4: 36	≥5 SA	Internal iliac External iliac Obturator Common iliac	100/0	83/17

LLND, lateral lymph node dissection; LLNs, lateral lymph nodes; CRT, chemoradiotherapy; RT, radiotherapy; SA, short-axis; LA, long-axis - not reported; [1] reported for complete cohort; [2] reported for complete cohort with LLNs ≥7 mm; [3] according to LOREC criteria [29]; [4] number of patients per group not reported; [5] reported for standard TME cohort (no CRT n = 24, CRT n = 68).

Table 2
Operative, postoperative and pathological outcomes of included studies.

Author	Operation performed: LAR/APR, (%)		LLND: single/bilateral (%)		Adjuvant therapy (%)	
	LLND+	LLND-	LLND+	LLND-	LLND+	LLND-
Kim HJ [25]	85/15	90/10	25/75	N/A	95[1]	–
Shiratori [26]	–	–	–	N/A	–	–
Ogura [2]	47/53[1]	–	–	N/A	43[3]	–
Nishizaki [27]	–	–	–	N/A	–	–
Jones [16]	–	–	100/0	N/A	–	–
Kim MJ [28]	97/3	79/21	–	N/A	84	98
Kroon [10]	43/50	46/54	73/27	N/A	100	30

Author	ypT-stage (%)		ypN+ (%)		Positive resection margins (%)		Tumour positive LLNs (%)	
	LLND+	LLND-	LLND+	LLND-	LLND+	LLND-	LLND+	LLND-
Kim HJ [25]	T0-2: 34 T3-4: 66	T0-2: 48 T3-4: 52	45	23	8[1]	–	38	N/A
Shiratori [26]	T0-2: 50 T3-4: 50[1]	–	23[1,2]	–	–	–	56	N/A
Ogura [2]	T0-2: 45 T3-4: 55[1]	–	81[4]	–	9[4]	–	–	N/A
Nishizaki [27]	–	–	–	–	–	–	–	N/A
Jones [16]	Mean: 2.55	Mean: 2.45	Mean: 0.62	Mean: 0.66	23	9	8	N/A
Kim MJ [28]	T0-2: 30 T3-4: 70	T0-2: 42 T3-4: 58	52	37	22	12	35	N/A
Kroon [10]	T0-2: 38 T3-4: 62	T2-3: 42 T3-4: 58	61	43	11	11	0.5[5]	N/A

LLND, lateral lymph node dissection; LLNs, lateral lymph nodes; N/A, not applicable; LAR, low anterior resection; APR, abdominoperineal resection; - not reported; [1] reported for complete cohort; [2] reported as mesenteric ypN; [3] reported for complete cohort with LLNs ≥7 mm; [4] reported for complete cohort with LLNs ≥7 mm; [5] median number of positive LLNs resected per patient.

Table 3
Postoperative survival outcomes of included studies.

Author	Follow-up in months (median)		5-year lateral local recurrence rate (%)		5-year local recurrence rate (%)		5-year distant metastatic rate (%)	
	LLND+	LLND-	LLND+	LLND-	LLND+	LLND-	LLND+	LLND-
Kim HJ [25]	34[1]	–	–	–	8[2,3]	23*[,3]	41[2,3]	26[3]
Shiratori [26][4]	47[1]	–	–	–	–	–	–	–
Ogura [2]	57[1]	–	6	20*	6	26*	14	31*
Nishizaki [27]	–	–	–	–	–	–	–	–
Jones [16]	–	–	–	–	15	12	–	–
Kim MJ [28]	37	54	–	–	5	27*	–	–
Kroon [10]	47	59	0	7	3	11	29	30

Author	5-year disease-free survival (%)		5-year cancer-specific survival (%)		5-year overall survival (%)	
	LLND+	LLND-	LLND+	LLND-	LLND+	LLND-
Kim HJ [25]	61[2,3]	54*[,3]	–	–	84[2,3]	80[3]
Shiratori [26][4]	–	–	–	–	–	–
Ogura [2]	–	–	94	79*	–	–
Nishizaki [27]	78	46*	–	–	–	–
Jones [16]	69	79	–	–	69	80
Kim MJ [28]	74	61*	–	–	91	77
Kroon [10]	68	64	–	–	74	72

- not reported; *significant difference between rates was reported; [1] reported for complete cohort; [2] combined for reported groups (LLND + after response to nCRT) and (LLND+ with no response to nCRT); [3] 3-year rates; [4] Shiratori did not report survival analysis for LLND + vs. LLND-.

Table 4
Newcastle Ottawa quality assessment for included studies.

Author	Selection (0–4)	Comparability (0–2)	Outcome (0–3)	Total (0–9)
Kim HJ [25]	****	*	*	6
Shiratori [26]	***	–	**	5
Ogura [2]	**	*	**	5
Nishizaki [27]	***	*	–	4
Jones [16]	****	*	*	6
Kim MJ [28]	****	*	**	7
Kroon [10]	**	*	***	6

also and one study included enlarged LLNs at the aortic bifurcation [10,25,26]. In five studies all patients underwent nCRT, and in two studies a small percentage underwent radiotherapy only: 11% of patients in the study by Ogura et al. and 17% of the LLND-group in the study by Kroon et al. [2,10,16,25–28].

Five studies reported details of the operative management (Table 2) [2,10,16,25,28]. A low anterior resection was performed in the majority of patients in the two Korean studies [25,28], while in the two studies including Western patients an abdominoperineal resection was performed more often [2,10]. Single side LLND was performed mostly in two studies [10,16], and in one study a bilateral LLND was performed in 75% of the patients [25]. Operating time was reported in one study, which was longer in the LLND + group (436 vs. 255 min for LLND-group) with higher postoperative complication rates (Clavien-Dindo grade ≥3: 22% vs. 14%), but with shorter hospital stay (8 vs. 11 days) [10]. There was a wide range in the use of adjuvant chemotherapy in both groups: LLND + range 43–100%, LLND-range 30–98% [2,10,25,28]. No study reported long-term morbidity.

Range of pathological (yp)T3/4 stage for the LLND + group was 50–70% and 52–58% in the LLND-group [2,10,25,26,28]. Pathological (yp)N+ was present in 23–81% of the LLND + group, and in 23–43% of the LLND-group [2,10,25,26,28]. Resection margins were positive in 8–23% of the LLND + group, and 9–12% of the LLND-group [2,10,16,25,28]. Of the LLNs resected, 8–56% were tumour positive [16,25,26,28].

Table 3 lists survival outcomes. Follow-up ranged between 34 and 59 months. Two studies reported five-year lateral local recurrence rates with ranges of 0–6% for LLND+ and 7–20% for LLND- [2,10]. Local recurrence rates were reported in five studies and ranged from 3 to 15% for LLND+ and 11–27% for LLND- [2,10,16,25,28]. Five-year distant metastatic rate was reported in three studies with a range of 14–41% for LLND+ and 26–31% for LLND- [2,10,25]. Five-year disease-free survival was reported in five studies with a range of 61–78% for LLND+ and 46–79% for LLND- [10,16,25,27,28]. Ogura et al. reported five-year cancer-specific survival rates of 94% and 79% for LLND+ and LLND-, respectively [2]. Range of five-year overall survival was 69–91% for LLND+ and 72–80% for LLND- [10,16,25,28].

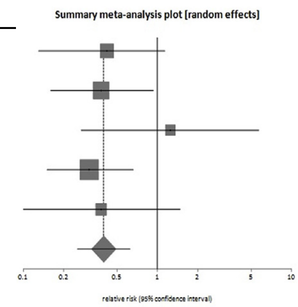
Risk of bias assessment of the included studies using the NOS is listed in Table 4. One article qualified as a good-quality study (*≥7). Most studies were retrospective comparative series, and no RCTs were available. Selection bias was present in three studies [2,10,26]. Issues pertaining to follow-up (e.g. no follow-up, short follow-up, or high number of patients lost to follow-up) were a common recurrent theme in the studies [2,10,16,25–28].

Meta-analysis could be performed for local recurrence, disease-free survival, and overall survival with respectively five, four and four studies reporting on these outcomes (Table 5). This showed that local recurrence was significantly lower in the LLND + group (RR = 0.40, 95%CI [0.25–0.62], $p < 0.0001$) compared to the LLND-group [2,10,16,25,28]. Disease-free survival (RR = 0.72, 95%CI [0.51–1.02], p = 1.43) and overall survival (RR = 0.72, 95%CI [0.45–1.14], p = 0.163) were not significantly different between both groups [10,16,25,28]. Meta-analysis on lateral local recurrences and distant metastases could not be performed due to

Table 5
Meta-analysis of (A) local recurrences, (B) disease-free survival and (C) overall survival of included studies.

A. Summary meta-analysis for local recurrence.

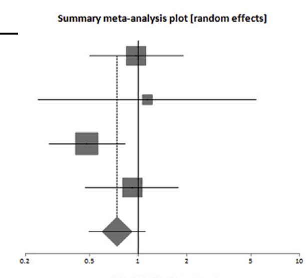
Study	Log (HR)	SE	Weight (%)	RR (fixed 95%CI)
Kim HJ [25]	−0.86	0.62	17.1	0.42 (0.13–1.14)
Ogura [2]	−0.96	0.49	26.2	0.38 (0.16–0.93)
Jones [16]	0.22	0.78	8.7	1.25 (0.27–5.71)
Kim MJ [28]	−1.16	0.37	36.9	0.31 (0.15–0.66)
Kroon [10]	−0.96	0.69	11.1	0.38 (0.10–1.48)
Total			**100**	**0.40 (0.25–0.62)**



Heterogeneity: Cochran Q=2.62 (df=4), p=0.622, I^2=0%
Test for overall effect: Z=4.02 (p<0.0001)
Egger: bias=2.26 (95%CI=-0.86 to 5.38), p=0.104

B. Summary meta-analysis for disease-free survival.

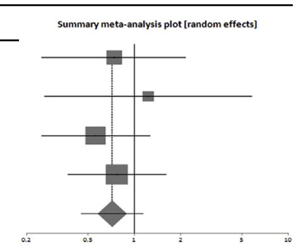
Study	Log (HR)	SE	Weight (%)	RR (fixed 95%CI)
Kim HJ [25]	−0.03	0.34	26.8	0.97 (0.50–1.91)
Jones [16]	0.13	0.79	5.0	1.14 (0.24–5.38)
Kim MJ [28]	−0.73	0.28	40.8	0.48 (0.28–0.83)
Kroon [10]	−0.09	0.34	27.4	0.92 (0.47–1.77)
Total			**100**	**0.72 (0.51–1.02)**



Heterogeneity: Cochran Q=3.76 (df=3), p=0.289, I^2=20.2%
Test for overall effect: Z=1.47 (p=0.143)
Egger: bias=1.75 (95%CI=-6.21 to 9.72), p=0.442

C. Summary meta-analysis for overall survival.

Study	Log (HR)	SE	Weight (%)	RR (fixed 95%CI)
Kim HJ [25]	−0.30	0.55	18.6	0.74 (0.25–2.16)
Jones [16]	0.21	0.79	8.9	1.23 (0.26–5.8)
Kim MJ [28]	−0.57	0.41	32.6	0.56 (0.25–1.27)
Kroon [10]	−0.26	0.37	39.9	0.77 (0.37–1.61)
Total			**100**	**0.72 (0.45–1.14)**



Heterogeneity: Cochran Q=0.86 (df=3), p=0.835, I^2=0%
Test for overall effect: Z=1.40 (p=0.163)
Egger: bias=1.19 (95%CI=-2.89 to 5.28), p=0.341.

lack of studies reporting these outcomes (two and three, respectively).

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis of current literature specifically looking at the role of adding a LLND at the time of TME in patients with pre-treatment metastatic LLNs who all had nCRT. The results show that local recurrence rates are significantly reduced when a LLND is performed, but no difference in disease-free survival or overall survival was observed.

Lymphatic spread of rectal cancer occurs in two directions: medially along the inferior mesenteric artery and laterally along the internal iliac artery into the lateral nodal basins. In lateral spread, the Mercury study has shown that patients with metastatic LLNs on pre-treatment MRI, have lower five-year disease-free survival rates than patients without metastatic LLNs on MRIs [30]. Therefore, to reduce the chance of recurrences, metastatic LLNs should proactively be treated [31]. In most Western centres, nCRT is considered adequate treatment to sterilise LLNs after which TME is performed to remove the tumour, while in the East, LLND is performed during TME, however, often without nCRT [7,8,31,32]. Because of this difference in management of rectal cancer with pre-treatment metastatic LLNs between the East and West, it is difficult to compare both treatment approaches.

In recent years, emerging evidence has shown that local recurrences are a significant clinical issue in patients with pre-treatment metastatic LLNs, due to the risk of failure of nCRT followed by TME only [2,11,33]. Also, surgeons from Japan are re-evaluating the role of nCRT, as this may reduce the need for prophylactic LLNDs, reserving the procedure for patients with metastatic LLNs [14,32]. Therefore, the treatment philosophies of the East and West are moving closing together, highlighting the concept that LLND after nCRT in locally advanced rectal cancer can be complementary in the management of metastatic LLNs [2,34].

A number of systematic reviews on the benefits of LLND in rectal cancer have been published over the past years. However, none have addressed the clinically relevant question of the benefit of the addition of LLND in patients with pre-treatment metastatic LLNs after nCRT. Three reviews, for instance, examined recurrence and survival outcomes, but also included studies that did not use nCRT and studies in which a prophylactic LLND was performed in patients without metastatic LLNs [35–37]. It was therefore not surprising that, similarly to the early landmark systematic review on this topic by Georgiu et al. none of these studies found local recurrence or survival benefits of LLND [38]. Overall, the null findings of these previous reviews can be explained by the broad selection of studies reporting on rectal cancers with heterogeneous stages, overshadowing the group of patients in whom a LLND after nCRT could be of added value; those with pre-treatment metastatic LLNs. Including patients without metastatic LLNs is likely to have diluted the findings of these reviews as it has previously been shown that these patients do not have local recurrence or survival benefit from a LLND after nCRT [39–41]. The current systematic review and meta-analysis is the first to report local recurrence benefit of LLND after nCRT in patients with pre-treatment metastatic LLNs, and thus the first to answer this clinical dilemma.

Some limitations of the current study have to be addressed. Firstly, the number of studies in current literature that report on long-term oncological outcomes of LLND during TME after nCRT vs. TME only after nCRT is low. As shown in the PRISMA chart of study selection (Fig. 1), most studies that report on oncological outcomes after LLND had to be excluded as patients did not receive nCRT or had no pre-treatment metastatic LLN. Furthermore, all included studies are retrospective series, with a high risk of bias, mainly in patient selection. There are currently no prospective series or RCTs available. Thirdly, the studies included relatively low patient numbers and limited follow-up times with medians of less than 5 years for the survival analyses. Fourthly, details on operative management, especially the technical aspect of how a LLND was performed, in-hospital recovery, and long-term morbidity were not reported in the majority of studies. A LLND is a complex procedure without international agreement on the technical aspects. In some cases, this could lead to not resecting LLNs that do harbour metastases, resulting in higher local recurrence rates, and lower DFS and OS rates between studies. Standardisation of the LLND procedure is therefore important to allow comparison outcomes between surgical teams. Finally, for the study by Nishizaki et al. only an abstract was available with to date no full article published, and Shiratori et al. reported the combined survival outcomes for the complete cohort without reporting long-term oncological outcomes for LLND + vs. LLND-separately [26,27].

Considering the outcomes of this systematic review and meta-analysis, an argument could be made to perform a LLND following nCRT in rectal cancers with metastatic LLNs to reduce local recurrence rates. However, because data is limited, more robust prospective results are eagerly awaited, including larger patients numbers with sufficient follow-up times for more accurate survival analyses. In view of this, it is unfortunate the RCT by Wei et al. (NCT02614157) has been recently terminated, leaving the multi-centre Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) study as the only currently recruiting prospective study to in the future provide more evidence on the value of an additional LLND after nCRT in rectal cancers with metastatic LLNs [42,43].

In conclusion, this systematic review and meta-analysis suggests that in rectal cancer patients with pre-treatment metastatic LLNs, nCRT followed by an additional LLND during TME results in a lower local recurrence rate. Due to the low quality of current literature, future higher quality studies will determine the true value of a LLND in this setting.

Funding

None.

Declaration of competing interest

No conflict of interest.

Acknowledgement

This project was undertaken whilst holding a Royal Adelaide Hospital Florey Fellowship by Hidde M. Kroon.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.04.016.

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