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Research Paper

Significance, diagnosis and treatment of lateral lymph nodes in rectal cancer: A systematic review

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ABSTRACT

Introduction: Patients with low rectal cancer are at risk for lateral lymph node metastasis (LLNM). Neoadjuvant chemoradiotherapy (CRT) is used to eradicate LLNM in the West, whereas in Japan the addition of lateral lymph node dissection (LLND) to total mesorectal excision (TME) is performed. A systematic review was conducted to assess incidence, location, risk factors and diagnosis of LLNM and lateral lymph node (LLN) treatment outcomes.
Method: The Medline, Embase and Cochrane databases were searched for English-language articles pertaining to LLNs in rectal cancer.
Results: 242 studies were identified and 15 prospective studies selected for qualitative analysis. LLNM was detected in 7–40% of patients who underwent LLND, and lower incidence occurred in patients without preoperative suspicion of LLNM. LLNs located along the middle rectal artery were most common. LLNM was associated with female sex, advanced T stage and positive mesorectal nodes. LLN short-axis diameter of ≥10 mm on preoperative imaging appeared to predict LLNM after neoadjuvant CRT. The addition of LLND to TME seemed to decrease LR and improve survival rates, with comparable results seen for CRT. LLND appeared to be associated with longer operation time, greater blood loss and increased risk of sexual and urinary dysfunction.
Conclusion: LLND could be advantageous for patients with suspected LLNM, but associated morbidities need to be considered. Further studies are needed to improve preoperative identification of LLNs and to determine how to manage persistent enlarged LLNs after CRT. Furthermore, the applicability of LLND in a Western population needs to be investigated.

1. Introduction

Total mesorectal excision (TME) is the gold standard surgery for mid- and low rectal cancer [1]. The lymphatic drainage of tumors in the upper and middle rectum occurs predominantly longitudinally. However, rectal tumors can also spread laterally to lymph nodes along the middle rectal arteries, internal iliac and obturator arteries [2–5]. Lateral lymph node metastasis (LLNM) occurs most commonly in patients with low rectal cancer [4]. Lateral lymph node (LLN) drainage, in addition to mesorectal drainage, is present in over 40% of patients with low rectal cancer [6].

Lateral lymph node dissection (LLND) and chemoradiotherapy (CRT) can be added to TME to treat potential LLNM in cases of advanced low rectal cancer [2,7]. In Japanese guidelines, LLND is indicated for low rectal tumors below the peritoneal reflection and invasion beyond the muscularis propria (T3-T4 tumors) [8–10]. In contrast, preoperative CRT followed by TME without LLND is the standard treatment of advanced rectal cancer described in American and European guidelines [1,8,11]. In Europe, LLND is not considered unless persistent enlargement of LLNs is seen on imaging following CRT, leading to selective LLND of solitary or multiple LLNs on the affected side [1,12]. According to the National Comprehensive Cancer Network Clinical Practice Guidelines for Rectal Cancer which is the standard of care in the United States, LLND is not routinely performed in the absence of clinically suspected LLNM, but suspicious LLNs detected outside the field of resection should be either biopsied or removed [11].

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Local recurrence (LR) rates have decreased substantially with the routine use of CRT and the implementation of TME [13–19]. However, LR remains a problem, and evidence suggests that lateral recurrences make up the majority of locoregional recurrences in patients with locally advanced rectal cancer undergoing preoperative CRT and TME [14,20–22]. As pelvic nodal involvement is detected despite preoperative CRT, even in cases with complete pathologic primary tumor responses, neoadjuvant therapy may be insufficient to sterilize LLNs completely [2,3,23,24]. In Japan, LLNs are sometimes removed prophylactically to potentially reduce LR and improve survival for low rectal cancer patients, but this approach is not used in the West [1,2,10,11].

The significance of LLNs in rectal cancer remains controversial, considering the use of different treatment modalities in Japan versus Europe and the United States. The overarching goal was to investigate the significance, diagnosis, and treatment of LLNs in rectal cancer. This systematic review was undertaken to determine the incidence, location, risk factors, and preoperative diagnostic assessment of LLNM, in addition to LLN treatment outcomes (e.g. complications, recurrence).

2. Method

2.1. Search strategy

A systematic review was conducted in accordance with the PRISMA guidelines [25]. The Cochrane, EMBASE and MEDLINE databases were systematically searched to February 2018. The search terms included the MeSH terms “rectal neoplasms” and “lymph nodes” or “lymphatic metastasis”, combined with following free text words: “low rectal cancer”, “rectal cancer”, “lateral lymph node”, “LLN”, “lateral pelvic lymph node metastasis”, and “nodal disease”. The searches were limited to English language and human clinical trials. Details of the full search strategy are shown in Appendix A.

2.2. Selection criteria

Titles, abstracts, and full-text articles identified through database searches were screened independently by two reviewers according to pre-determined inclusion and exclusion criteria (SG and MR). Any disagreements in the eligibility assessment of titles, abstracts and full papers were resolved by discussion with a third reviewer (PB).

Titles were screened for relevance based on inclusion of key terms related to rectal cancer nodal involvement, treatment and outcomes. Basic science studies, non-rectal cancer studies, duplicate studies, and titles without any mention of surgery or lymph nodes were excluded.

Abstracts were screened for studies related to lymph nodes in a study population of rectal cancer patients of all ages. Studies evaluating location, diagnosis and risk factors for lymph node metastasis were included. Treatment modality outcome studies were included if at least one of the following outcome measures was evaluated: LR rate, survival, short- and/or long term complications. Studies in which chemotherapy or radiotherapy (RT) was given alone, and not as CRT were included.

Inclusion criteria for the full text screening were prospective studies explicitly related to LLNs. Retrospective studies and non-full text articles were excluded. Reference lists of included studies were hand-searched for additional relevant prospective articles.

2.3. Data extraction

Data collected from the studies included first author, year of publication, study design and duration, length of follow-up, number of patients assigned to each treatment arm, eligibility criteria, tumor stage and location. With respect to data on proportion of patients with LLNM, LLNM location and risk factors, radiology imaging used and accuracy of diagnostic strategy in LLN detection were abstracted. Outcomes data were also collected when available including operation time, adverse effects of CRT, peri-operative surgical complications, survival, and LR.

2.4. Study quality assessment

Methodological quality of studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials [26] and the Methodological Index for Non-Randomized Studies (MINORS) [27]. For the Cochrane tool, a score of $\leq$3, 4 and 5 out of 6 was regarded as high, moderate and low risk of bias, respectively. MINORS contains 8 methodological points for comparative and non-comparative studies, with an additional 4 items for comparative studies. Each item is scored as 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The ideal global score is 16 for non-comparative studies, and 24 for comparative studies.

2.5. Statistical analysis

The criteria for pooling data to perform meta-analysis were homogenous studies and results presented as comparable outcome variables.

3. Results

3.1. Search results and study characteristics

The results of the systematic search are presented in Fig. 1. Details about the included studies are shown in Table 1, including eligibility criteria, tumor stage and surgical approach. Six articles primarily investigated diagnosis, incidence or risk factors for LLNM [28–33], whereas nine [34–42] were predominantly related to clinical outcomes of LLND or CRT in addition to TME. Six studies were randomized controlled trials (RCTs) of which three studies [35,37,38] were based on the same clinical trial but evaluated different outcomes such as postoperative morbidities, sexual dysfunction and LR.

Pooling of the studies through formal meta-analysis was not feasible due to heterogeneity among studies regarding patient eligibility criteria, CRT regimens as well as definitions of clinical outcomes.

3.2. Quality assessment of included studies

Assessment of risk of bias of the RCTs is shown in Appendix B. One RCT was judged to have low risk of bias, the other two were considered to have moderate and high risk of bias. None of the non-randomized studies reached the ideal global score.

3.3. Diagnosis of lateral lymph node metastasis

Studies evaluating the diagnosis of LLNM are shown in Table 2. Two studies [29,33] evaluated diagnostic criteria to predict LLNM, and three studies investigated diagnostic accuracy of LLNM in

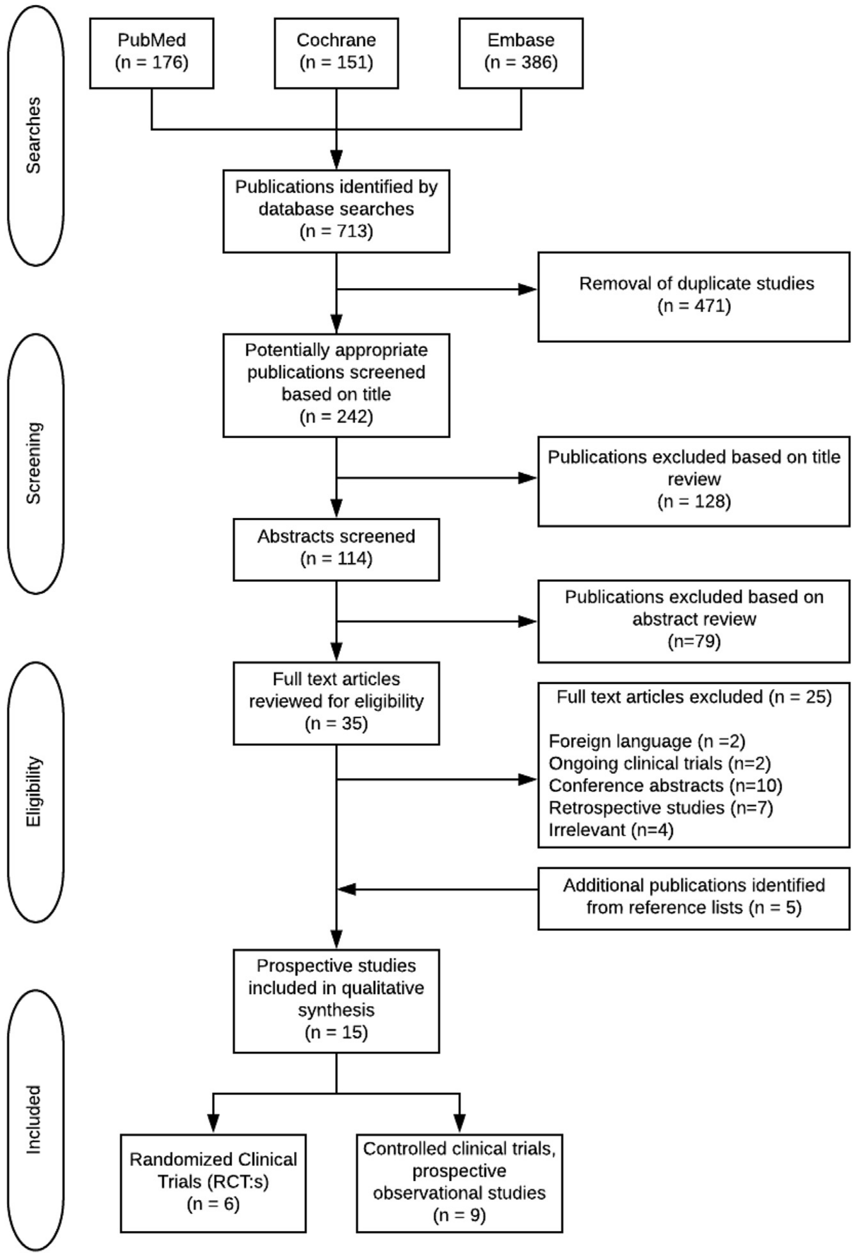

Fig. 1. Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram showing selection of articles for review.

imaging modalities [31–33]. Lim et al. [29] suspected LLNM on preoperative magnetic resonance imaging (MRI) if a node was ≥5 mm in the largest short-axis diameter, had a heterogenic pattern or irregular borders. The correlation between preoperative imaging and metastasis rates on pathological examination was analysed. Short-axis diameter of ≥10 mm was suggested to predict LLN involvement both before surgery and CRT [29]. Matsuoka et al. [33] used no predetermined criteria for preoperative detection of LLNM. Instead, the long and short-axis of the largest LLNs were measured by MRI and compared to histopathological sizes of LLNMs after LLND. The authors found that the optimal diagnostic criteria for LLNM in patients who did not undergo preoperative CRT was short-axis diameter ≥5 mm and ovoid shape [33].

The LLNM diagnostic accuracy was evaluated for computed tomography (CT) [31,32] and MRI [31,33]. The CT sensitivity in detecting LLNM was 33–95% with MRI corresponding sensitivity 56–67%. No studies were found of diagnostic accuracy for PET-CT and LLNM.

3.4. Incidence, location and risk factors of lateral lymph node metastasis

Studies presenting LLNM incidence and location are shown in Table 3. A histopathologically verified LLNM incidence of 7–40% after LLND was found across nine studies [28–33,37,40,41]. Fujita et al. [37] was the only study that excluded patients with LLN ≥ 10 mm on preoperative imaging, and showed postoperative LLNM in 7% of TME + LLND patients. Yano et al. [32] performed LLND in patients with suspected mesorectal or LLN involvement on preoperative CT, with 54% having pathologically confirmed LLNM. Postoperative LLNM in the entire study including patients without suspected LLNM was 19.3%. Lim et al. [29] reported LLNM in 40% of

Table 1
Study characteristics of studies included for review.

Author, Year	Type of study	Country	*n*	Eligibility criteria	Treatment modality (*n* in group)	Stage	Tumor height	Surgery (*n* in treatment group)	Technique	CRT
Fujita et al., 2017 [38]	RCT JCOG2012 trial	Japan	696 [38]	Clinical stage II-III, Lower tumor margin below PR, no extramesorectal LN	TME + LLND vs TME alone (348 vs 348)	II: 54% vs 56% III: 46% vs 44%	Distance from AV ≤5 cm: 56% vs 57% >5 cm: 43% vs 42%	N/A	PANP in both groups	Adjuvant CTX for stage III tumors
Saito et al., 2016 [35]			343 [35]	involvement (short axis diameter <10 mm on imaging)	TME + LLND vs TME alone (171 vs 172)	T2: 1% vs 2% T3-T4: 99% vs 98% N0: 55% vs 55% N1–N2: 45% vs 45%	Above PR: 20% vs 23% Below PR: 80% vs 76%	LAR: 78% vs 80% APR: 22% vs 20%		
Fujita *et al.*, 2012 [37]			701 [37]	Macroscopic confirmation of R0 resection and absence of LLN metastasis	TME + LLND vs TME alone (350 vs 351)	II: 45% vs 56% III: 46 vs 44%	Above PR: 23% vs 23% Below PR: 77% vs 77%	LAR: 81% vs 81% APR: 19% vs 18% Hartmann's: <1% vs <1%		
Masaki et al., 2010 [40]	RCT	Japan	55	Lower tumor margin below PR, invasion beyond muscle layer or involvement of mesorectal LN	TME + IORT + PANP + LLND - Uni (11%) - or bilateral (89%) vs TME + LLND (28 vs 27)	pT1-T2: 14% vs 19% pT3: 86% vs 81%	Distance from AV ≤2 cm: 7% vs 7% 2.1–4 cm: 25% vs 26% >4.1 cm: 68% vs 67%	SPS: 64% vs 59%	Uni- or bilateral PANP vs resection of pelvic nerves	Adjuvant CTX for patients with LLN metastasis/stage III tumors (67% vs 41%)
Masaki et al., 2008 [41]			41		TME + IORT + PANP + LLND vs TME + limited PANP + LLND (19 vs 22)	pT1-T2: 11% vs 18% pT3: 89% vs 82%	Distance from AV ≤2 cm: 5% vs 9% 2.1–4 cm: 26% vs 23% >4.1 cm: 68% vs 68%	APR: 37% vs 41% SPS: 63% vs 59%	Complete PANP vs limited PANP	Adjuvant CTX for patients with LN metastasis (37% vs 41%)
Nagawa et al., 2001 [34]	RCT	Japan	45	Tumor extending to lower rectum, invasion beyond mucle layer, LN metastasis limited to perirectal nodes	Nerve-preserving surgery (D1) vs surgery + LLND (D2) (22 vs 23)	I: 23% vs 22% II: 39 vs 22% III: 37 vs 56%	Distance from AV 4.8 (3.4–6.2) vs 4.7 (3.1–6.3) cm	LAR: 68% vs 52% APR: 32% vs 48%	PANP vs LLND with resection of autonomic nerves	Neoadjuvant RT and adjuvant CTX for all patients
Lim et al., 2013 [29]	Prospective	Korea	67	Mid- or low rectal tumors. Selective LLN excision if suspected LLN metastasis (≥5 mm in short axis diameter)	CRT + TME + selective LLND - Unilateral:52 (77.6%) - Bilateral: 15 (22.4%)	T3: 71.6% T4: 28.4% N1: 31.3% N2: 68.7%	Distance from AV ≤5 cm (low): 79.1% 5–10 cm (mid): 20.9%	APR: 38.8% SPS: 61.2%	N/A	Neoadjuvant CRT for all. Adjuvant CTX for 89.5% of patients
Tan et al., 2010 [30]	Prospective	Japan	1, 046	Low rectal cancer stage T3 and above, clinical I,II,III in the 80's. LLND if LLN >1 cm in size on imaging or clinically suspicious LLN	LLND: 1, 046	T1: 18% T2: 29% T3: 49% T4: 3%	Below PR (distal to the middle Houston valve)	N/A	N/A	Preoperative RT for clinical T4 and tumors <5 cm from the AV
Kusters et al., 2009 [36]	Prospective	Netherlands and Japan	1, 079	Tumors from 0 to 7 cm from AV (Dutch group) or below PR (Japanese group) LLND performed for suspected TNM stage II or III in Japanese group	RT + TME vs TME alone vs TME + LLND (379 vs 376 vs 324)	T1: 5 vs 6 vs 16% T2: 38 vs 35 vs 33% T3: 55 vs 56 vs 49% T4: 2 vs 4 vs 2% N0: 64 vs 61 vs 61% N1: 21 vs 22 vs 23% N2: 15 vs 17 vs 16%	At or below PR, or 0 −7 cm from AV	LAR: 42% vs 42% vs 60% APR: 51% vs 53% vs 35% Hartmann's: 6% vs 4% vs 1% PE: 1% vs 1% vs 4%	Uni- (21%) or bilateral (38%) LLND in Japanese group	Neoadjuvant RT for Dutch patients Adjuvant RT and/or CTX in a minority of patients (<15%)
Yano et al., 2007 [32]	Prospective	Japan	109[a]	Low rectal cancer. LLND if more than one LN detected in the mesorectum or at least one LN detected in the lateral pelvic area	TME alone: 60 TME + LLND: 39 LE: 10	N/A	Low (at or below middle Houston's valve): 100%	LAR: 31% APR: 41% Hartmann's: 11% PE: 7%	N/A	Preoperative therapy: 2%
Kim et al., 2007 [39]	Prospective	Korea and Japan	485	Stage II/III rectal cancer. Rectal cancer within 15 cm of the anal verge	TME + PANP + CRT (Korea) vs TME + PANP + LLND (Japan) (309 vs 176)	T1: 1% vs 3% T2: 7% vs 5% T3: 86% vs 87% T4: 6% vs 5% N0: 33% vs 53% N1: 38% vs 28% N2: 29% vs 19%	Above PR (11–15 cm from AV): 22% vs 33% Below PR: 78% vs 67%	LAR: 63% vs 81% APR: 37% vs 19%	PANP in both groups	Postoperative CRT for one group
Matsuoka et al., 2007 [33]	Prospective	Japan	51	Locally advanced rectal carcinoma	TME + LLND: 51	T3: 90% T4: 10%	Middle rectal carcinoma: 29% Lower rectal carcinoma: 71%	N/A	N/A	IORT (no effect on LN specimens)
Arii et al., 2006 [31]	Prospective	Japan	53	Lower rectal cancer	TME + LLND: 53	T1: 6% T2: 13% T3: 74% T4: 8%	N/A	SPS: 87% APR: 13% PE: 3/53	N/A	CRT not given before surgery
Ueno et al., 2001 [28]	Prospective	Japan	545			N/A				

				LLND for patients with low rectal cancer whose tumor penetrated the rectal wall. Cancers above the PR included if suspected LLN involvement	Bilateral LLND: 250/545 53/250 had LLN involvement and were analysed in this study		Upper rectum 21% Lower rectum: 43% Anal canal: 36% (tumor edge)	APR: 58% LAR: 28% Hartmann's: 4% PE: 9%	Resection of pelvic nerve plexuses	Adjuvant CTX: 91% Adjuvant RT: 6%
Ishikura et al., 1999 [42]	Prospective	Japan	50	Low rectal cancer. Tumor without bilateral LLN involvement	TME + LLND: 50	T1: 2% T2: 22% T3: 74% T4: 2%	At or belor PR: 100%	LAR: 52% APR: 48%	PANP for all	IORT for all + adjuvant RT for 92% of patients

RCT: randomized controlled trial; PR: peritoneal reflection; LN: lymph node; LLN: lateral lymph node; TME: total mesorectal excision; LLND: lateral lymph node dissection; AV: anal verge; LAR: low anterior resection; APR: abdominoperineal resection; PANP: pelvic autonomic nerve preservation; CTX: chemotherapy; IORT: intraoperative radiotherapy; SPS: sphincter preserving surgery; RT: radiotherapy; CRT: chemoradiotherapy; PE: pelvic exenteration; TNM: Tumor-Node-Metastasis; N/A: not available.

*stages converted from Astler-Coller staging system to TNM.

[a] Including patients from JCOG2012 trial.

surgical excisions after preoperative CRT in patients with LLN $\geq$ 5 mm on preoperative imaging [29].

Two studies [28,32] addressed anatomical location of LLNM. Yano et al. [32] reported the middle rectal artery and obturator regions as the most common as 90% of LLNM were found in these locations [32]. Ueno et al. [28] reported LLNM in the middle rectal, the internal iliac and obturator regions in 52.8%, 30.2% and 24.5% of patients, respectively.

Risk factors associated with LLNM are presented in Table 4. Female sex was a significant risk factor [29,30]. Lim et al. [29] identified low rectal tumors ($\leq$5 cm from anal verge), high preoperative serum carcinoembryonic antigen levels >6.8 nm/ml after neoadjuvant CRT, and advanced pT- and pN-stage after neoadjuvant CRT and surgery as significant risk factors for LLNM. Circumferential resection margin (CRM) positivity was associated with LLNM since 15.6% of patients with LLNM had positive CRM as compared to 2.0% for patients without LLNM [29]. Tan et al. [30] also found $\geq$ pT3 and positive mesorectal nodes as significant risk factors for LLNM.

3.5. Complications and perioperative outcomes following LLN treatment

All complications and perioperative outcomes are presented in Appendix C.

Three studies evaluated operation time and intraoperative blood loss for LLND [34,37,40]. Two studies compared LLND to TME alone [37] or TME with preoperative RT [34]. The operation time was longer and the intraoperative bleeding was higher for LLND. Masaki et al. [40] noted longer operation time and greater blood loss in the pelvic autonomic nerve preservation (PANP) group compared to the group where LLND included resection of the pelvic autonomic nerves.

Postoperative morbidity was reported in four studies [29,34,37,39]. In summary, complications appeared in 22–57% of LLND patients and in 15.5–50% for non-LLND patients. Fujita et al. [38] reported on postoperative grade 3–4 complications according to the National Cancer Institute-Common Toxicity Criteria during hospital stay including anastomotic leakage, urinary retention, surgical hemorrhage, infections and ileus. Nagawa et al. [34] reported on complications of surgery, including infections, anastomotic leakage and ileus, without a specified time limit.

Postoperative infections were reported in five studies [34,37,40–42]. Wound infections and/or pelvic abscesses developed in 2–21% of patients undergoing LLND compared to <1–14% for non-LLND.

Bowel complications were reported in seven publications [29,34,37,39–42]. Postoperative ileus occurred in 1–13% of patients with LLND across six studies, and in <1%–14% for non-LLND patients. Anastomotic leak was reported with a frequency of 9–11% in LLND patients vs 9–13% in TME alone patients (+/– RT) [34,37].

3.6. Postoperative sexual and urinary dysfunction

Studies evaluating sexual and urinary dysfunction are also presented in Appendix C. Two studies assessed sexual function using questionnaires before and one year after surgery and reported sexual dysfunction of 79–92% for LLND versus 45–68% for non-LLND [34,35].

Urinary dysfunction was reported across six studies [29,34,37,39,41,42]. Nagawa et al. [34] reported a significant difference in urinary dysfunction after LLND (65%) compared to TME with PANP (27%).

Table 2
Diagnostic strategies and accuracies for detection of LLN metastasis.

Reference	Imaging modality	Diagnostic criteria	Diagnostic accuracy		
			Sensitivity	Specificity	Overall accuracy
Yano *et al.* [32]	Preoperative CT	Preoperative: Lymph node involvement if any lymph nodes were identified by CT, irrespective of size or pattern of enhancement. Postoperative: Histopathological tumour nodule of 3 mm or more in diameter in the lateral pelvic area	95%	94%	–
Matsuoka *et al.* [33]	Preoperative MRI	Preoperative: LLN with largest long axis diameter. Postoperative: 10 mm or larger in the long axis, 5 mm or larger in the short axis. Ovoid shape and heterogeneity of the internal structure. The combination of ovoid shape with a transverse axis diameter 5 mm or larger on MRI had the highest diagnostic accuracy.	67% 67%	75% 83%	73% 78%
Arii *et al.* [31]	Preoperative - CT - MRI	Metastasis confirmed if round shaped lymph node > 7 mm in diameter on preoperative imaging was detected during surgery.	33% 56%	78% 97%	75% 83%
Lim *et al.* [29]	Preoperative MRI with transrectal ultrasound before CRT and reperformed before surgery	Preoperative: suspicious LLN involvement when LN size was ≥5 mm in the largest short-axis diameter, had a spiculated or indistinct border, or a mottled heterogenic pattern. Postoperative: short-axis LLN diameters predicting LLN metastasis based on comparisons of preoperative imaging with histopathologic findings (maximum Youden index in the ROC curves) - 11.7 mm before CRT - 11.4 mm before surgery 10 mm was suggested as the optimal criteria for LLN metastasis.	68.8% 62.5%	82% 92%	– –

CT: computed tomography; MRI: magnetic resonance imaging; LLN: lateral lymph node; LN: lymph node; CRT: chemoradiotherapy.

Table 3
Clinical and pathological incidence (%) of lateral lymph node involvement, and anatomical locations of lateral lymph nodes.

Author	Preoperative LLN involvement based on imaging	Postoperative incidence of LLN metastases based on pathology	Most common anatomical locations of LLN metastases
Fujita *et al.* [37]	None. Patients with extramesorectal LN involvement not included.	TME with LLND: 7% - 42% were clinical stage II - 58% were clinical stage III	Not reported
Masaki *et al.* [41]	Unknown	21% and 27% in respective group	Not reported
Masaki *et al.* [40]	Unknown	Preserved group: 19% Resected group: 23%	
Lim *et al.* [29]	Suspicious LLN metastasis	40.0%	Not reported
Tan *et al.* [30]	Suspicious LLN mestastasis on CT or MRI (size >1 cm) Unknown in the case of some low rectal cancers	11% - T1: 0.5% - T2: 15% - T3: 16% - T4: 44% - T3-T4: 17.3% - T1-T2: 3.5%	Not reported
Yano *et al.* [32]	Preoperative CT: lateral node enlargement in 54% of patients who underwent LLND (i.e. patients with mesorectal or lateral nodal involvement)	54% of patients who underwent LLND	Metastatic nodes were found in either of the obturator or middle rectal artery regions in 90% patients with LLN metastasis. The other LLN metastases were found in the common iliac region alone and the internal iliac region alone.
Matsuoka *et al.* [33]	37% had LLN on MRI	29%	Not reported
Ueno *et al.* [28]	Unknown for patients with low rectal cancer. Suspected LLN involvement on CT/MRI/ intraoperatively for high rectal cancers	21.2%	Involvement in at least one of the following lateral divisions n (%): Middle rectal artery: 28 (52.8), internal iliac: 16 (30.2), common iliac: 8 (15.1), external iliac: 8 (15.1), obturator nodes: 13 (24.5), median sacral: 8 (15.1), aortic bifurcation: 3 (5.7).
Arii *et al.* [31]	Unknown	28% 21% with both regional and LLN metastases	Not reported

LLN: lateral lymph node; LN: lymph node; TME: total mesorectal excision; LLND: lateral lymph node dissection; CT: computed tomography; MRI: magnetic resonance imaging.

3.7. Comparison of local recurrence and survival after CRT and LLND

Studies evaluating oncologic outcomes are shown in Table 5. Four comparative studies addressed LR rates [34,36,38,39]. Nagawa et al. [34] identified one recurrence in the pelvic cavity in the LLND group (1/23 = 4%). The LR rates for TME with LLND was 7.4% and 12.6% for TME alone in the study by Fujita et al. [38]. Kusters et al. [36] reported 5-year LR rates of 6.9% in the LLND group, 5.8% in the RT + TME group and 12.1% in the TME alone group. Kim et al. [39] reported a 5-year 11% LR rate in the LLND group, and no LR in the postoperative CRT group after 52 months. In the remaining non-comparative studies, LLND patients showed 5-year LR rates of 5.6–56.8%.

Eight studies reported survival rates [28,29,34,36,38,39,41,42] of which four compared LLND to TME [34,36,38,39]. Fujita et al. [38]

Table 4
Risk factors associated with LLN metastases.

Author	Risk factors associated with LLN metastases
Lim *et al.* [29] [a]	• Female sex (59.4% of + LLNs) • Tumors of the low rectum (90.6% of + LLNs) • Higher pre-surgery carcinoembryogenic levels (6.8 ng/mL in LLN(+) vs 2.3 ng/mL in LLN(−) patients • Longer short-axis of the largest LLN, both before and after CRT (16.5 mm vs 10.6 mm before CRT, 13.4 vs 7.9 mm before surgery) • Advanced ypT- and ypN-categories • CRM positivity • Poor response to CRT
Tan *et al.* [30] [b]	• Female sex • Not well differentiated tumor • pT3 • Positive microscopic lymphatic invasion • Positive mesorectal nodes Low risk of lateral node spread when fewer than three positive risk factors (out of sex, differentiation, T stage and mesorectal nodes) are present (4.7%) Three or more positive risk factors: odds 7.5 times higher (hazard ratio 7.567)

LLN: lateral lymph nodes; CRT: chemoradiotherapy; CRM: circumferential resection margin.
[a] Results based on bivariate analysis.
[b] Results based on multivariate analysis.

reported a 5-year overall survival rate of 92.6% for TME with LLND and 90.2% for TME alone. Five-year overall survival for patients with stage II/III low rectal cancer who underwent TME + CRT and TME + LLND was 85%/71.7% and 72.6%/68.2%, respectively [39]. No differences were observed in survival or disease-free survival between LLND and TME with PANP [34]. Kusters et al. [36] reported a higher cancer-specific survival in the LLND group compared to TME alone and RT + TME groups (HR 2.0 and 1.7, respectively).

4. Discussion

This systematic literature review compared LLND with TME and CRT. LLND seemed to be associated with longer operation time and greater operative blood loss, as well as higher rates of urinary and sexual dysfunctions. In terms of oncologic outcomes, survival rates tended to be better for LLND compared to TME ± neoadjuvant RT, and CRT addition to TME seemed to improve survival. LLND lowered LR rates compared to TME alone but neoadjuvant RT or postoperative CRT in addition to TME appeared just as effective.

There appears to be a strong correlation between clinical suspicion of LLNM on preoperative imaging and pathology results postoperatively. However, 7% of LLNM patients had no suspicion of extramesorectal involvement on preoperative imaging in the study by Fujita et al. [38], which is in accordance with the LLNM diagnostic accuracies of CT and MRI with relatively high specificities but lower sensitivities for LLNM. PET-CT usage for evaluation of LLN involvement could be of value but needs further investigation. Not all LLNM will be identified based on imaging size and better tools for identification are required. Risk factors such as threatened or involved CRM, advanced T-stage, and mesorectal lymph node metastasis should alert suspicion of LLNM.

LLNs that remain enlarged after CRT may contain residual metastatic disease as LLN enlargement after CRT has been associated with higher LR rates and shorter survival [43]. A poor response to CRT in terms of short-axis diameter >10 mm was identified as predictor of LLNM, suggesting that CRT may not be sufficient for some patients [29]. Even patients with suspicious LLNM who showed good response to preoperative CRT on post treatment MRI (diameter <5 mm) have been shown to develop LR, where the majority occurred in LLNs [44]. Surgical removal of LLNs that are not fully sterilized could possibly prevent lateral pelvic recurrences.

Overall morbidity and the incidence of anastomotic leakage seem similar in LLND patients and patients undergoing TME ± RT. Most studies reporting on complications used a combination of CRT and LLND or lacked an appropriate control group, making it difficult to conclude whether LLND causes more complications compared to CRT alone. Ileus and infections were more common after LLND, which may be related to longer operation time.

Although LLND seems to potentially improve survival and LR rates, complications and dysfunctions related to LLND must be taken into account. Proper patient selection where the oncological benefits outweigh the surgical risks is needed. There are indications that preoperative RT and LLND had comparable outcomes, making LLND unnecessary in patients where LLNMs have not been confirmed preoperatively [34,36]. There is currently not enough data to recommend LLND as prophylactic treatment for advanced rectal cancers. Combination therapy including CRT and LLND in addition to TME may improve the outcomes in a subgroup of rectal cancer patients with suspected or confirmed LLNM on preoperative evaluation. LLND would eliminate suspicious LLNs not fully treated by CRT, and furthermore CRT could remove micrometastases in nodes or surrounding fat tissue that could otherwise contribute to LR.

This systematic review, is to our knowledge, the only one exclusively including prospective studies. Limitations involve variations in eligibility criteria, surgical and oncological treatment given, as well as inconsistencies in follow-up durations and time of assessment after surgery, tumor stage and location, which all contribute to significant heterogeneity and affect the comparability of the studies. Most of the studies published on LLND are Asian, and apart from non-English language publication bias, it is unclear if the results are applicable to Western populations with higher BMI and LLND learning curve for Western surgeons [45].

Oncological outcomes for LLND were better compared to TME alone when LLNM was either absent or unknown preoperatively [36,38]. Although LLND may implicate potential benefits, additional randomized trials are needed. Fujita et al. [38] is the only largescale RCT verifying improved LR by LLND compared to TME alone, as opposed to previous meta-analyses [46,47]. However, many of the retrospective studies in these meta-analyses included patients with low stage rectal cancer, less likely to have LLNM and thereby benefit from LLND. Furthermore, neoadjuvant CRT is seldomly used in Japan but commonly used for stage II and III rectal cancers in the West. No RCT has compared neoadjuvant CRT with LLND for cases with suspicious LLNM to CRT alone. An ongoing Japanese RCT compares perioperative versus postoperative CRT for suspected LLNM [48], and a Chinese RCT is investigating LLND with neoadjuvant therapy in rectal cancer patients with suspicion of LLNM [49]. A European or American equivalent, including patients at high risk for LLNM is needed to explore the LLND feasibility for advanced rectal cancer in the West.

In summary, LLND could be advantageous for patients with suspected LLNM. Further studies are needed to improve preoperative identification of patients with LLNM and to determine how to manage persistent enlarged LLNs after CRT. Furthermore, the applicability of LLND in a Western population with routine use of CRT for locally advanced rectal cancer needs to be further investigated.

Table 5
Studies evaluating oncologic outcomes.

Author	Follow up time	Local Recurrence (%)	Survival (%)		
Fujita et al. [38]	Median 72.2 months	TME with LLND: 7.4% TME: 12.6%	5-year relapse-free survival TME with LLND: 73.4% TME alone: 73.3% HR 1.07	5-year overall survival TME with LLND: 92.6% TME: 90.2% HR: 1.25	5-year local-recurrence-free survival TME with LLND:87.7% TME: 82.4% HR 1.37
Masaki et al. [41]	Median 34 months	5.6% in the entire group (At 2 years and thereafter) 5.3% in IORT with PANP group 4.5% in limited PANP group	Overall survival rates and disease-free survival rates were not statistically different between the two groups		
Masaki et al. [40]	Median 37 months	10% in IORT with PANP group 11% in group with resection of pelvic autonomic nerves	Not reported		
Nagawa et al. [34]	Not reported	D1: 0% D2: 4% (one recurrence in pelvic cavity)	No differences observed in survival or disease-free survival between D1 and D2 (no numbers reported)		
Ishikura et al. [42]	Median 41 months	12% at 3 years	3-year overall survival 78%		3-year progression-free survival 70%
Kim et al. [39]	Median 68 and 64 months in CRT group and LLND group, respectively	5-year locoregional recurrence: LLND group 11% CRT group: 0% LR rates for stage III rectal cancers LLND group: 16.7% Postoperative CRT group: 7.5% Locoregional recurrence after LLND: - 5.2% with upper rectal cancer - 12.7% with lower rectal cancer	5-year OS LLND: 73.9% Postoperative CRT: 78.3%		5-year DFS LLND: 68.6% Postoperative CRT: 67.3%
Lim et al. [29]	Median 34 months	LR not reported 37.3% overall recurrence rate	3-year overall survival 90.3% for patients without LLN metastasis 60.3% for patients with LLN metastasis		3-year disease free survival rates 70.5% for patients without LLN metastasis 31.4% for patients with LLN metastasis HR 2.938
Yano et al. [32]	Median 5.7 years	LLND group: 13% Non-LLND: 7%	Not reported		
Ueno et al. [28]	Average 71 months	Locoregional recurrence in 56.8% w/o distant metastases	5-year survival rate: 26.6% for all LLND patients 5-year survival rate: 32% for patients w/o distant metastases, 0% for patients with distant metastases		
Kusters et al. [36]	Median 7.0 and 7.9 years for Japanese and Dutch patients, respectively	5-year LRR 6.9% in LLND group 5.8% in RT + TME 12.1% for TME alone (HR 1.6 compared to LLND group)	Cancer specific survival: higher for LLND than both TME group (HR 2.0 (1.2–3.3) and RT + TME group (HR 1.7)		

TME: total mesorectal excision; LLND: lateral lymph node dissection; HR: hazard ratio; IORT: intraoperative radiotherapy; PANP: pelvic autonomic nerve preservation; LR: local recurrence; OS: overall survival; CRT: chemoradiotherapy; DFS: disease-free survival; LLN: lateral lymph node; CI: confidence interval; RT: radiotherapy.

Ethical approval

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Author contribution

Stephanie Gulevski: reviewed included studies, collected and analysed data, wrote most of the manuscript.

Marcia M. Russell: reviewed included studies, reviewed and edited manuscript.

Pamela Buchwald: contributed to writing, reviewing and editing manuscript.

Conflicts of interest statement

The authors declare no conflict of interest.

Guarantor

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Appendix A. Supplementary data

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