International Journal of Colorectal Disease
https://doi.org/10.1007/s00384-020-03623-w

REVIEW

Total mesorectal excision with and without lateral lymph node dissection: a systematic review of the literature

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Accepted: 14 May 2020

Abstract

Purpose Treatment of lateral lymph node metastasis in rectal cancer is still under debate. While these nodes are routinely resected by Japanese teams, neoadjuvant radiochemotherapy alone is performed in Western countries. We aimed to systematically report the current literature assessing the overall and disease-free survivals of patients with rectal cancer treated with total mesorectal resection (TME) with or without lateral lymph node dissection (LLND).

Methods MEDLINE/Pubmed, Embase, Cochrane, and Web of Science were searched from database implementation until 19 January 2019. Studies reporting overall survival or recurrence-free survival in patients with LLND for rectal cancer were included. We excluded studies including patients with recurrent rectal cancer, multivisceral resection, and/or without control group (patients with rectal surgery without LLND).

Results Eleven studies were included, accounting for a total of 4159 patients. Overall survival ranged between 55.6 and 92.6% for TME with LLND versus 49.2 and 90.2% for TME alone, with one study reporting statistically significant benefit of LLND. Recurrence-free survival ranged between 58.3 and 74.1% for TME with LLND versus 39.5 and 76.5% for TME alone. Two studies showed statistically significant differences between the two strategies, one randomized controlled trial showed improved recurrence-free survival in TME alone group (74.5% versus 74.1% with LLND at 5 years) and one observational retrospective study reported increased recurrence-free survival with more extensive resection (65.4% versus 39.5% without LLND, at 5 years).

Conclusion Benefits of LLND are not clear and further randomized controlled trials should be performed to determine which strategy would allow improving survival in rectal cancer patients.

Trial registration The study protocol was registered in PROSPERO prior to study screening (CRD42019123181) and published in September 2019.

Keywords Rectal cancer · TME · LLND · Overall survival · Recurrence-free survival

Introduction

Colorectal cancer ranks as the third most common cancer in the world [1] and the second most common cause of cancer death [2]. Cancer of the rectum, defined as a tumor arising in the distal 15 cm of the large bowel, accounts for one-third of all large bowel neoplasms [3]. The estimated new cases in the USA were 44,180 in 2019, with a higher incidence among males and elderly [3, 4]. Total mesorectal resection (TME) introduced by Heald et al. in 1982 [5] is considered the gold standard surgical procedure allowing to reach a lower recurrence and higher survival rates [5–7].

Metastases to lateral lymph nodes defined by positive pathologic specimen [8] range between 10 and 25% and result from the lymphatic drainage of the rectum along the iliac

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00384-020-03623-w) contains supplementary material, which is available to authorized users.

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Published online: 27 May 2020

arteries and the inferior mesenteric artery [9, 10]. This leads to impaired oncologic outcomes with decreased 10-year overall survival and recurrence-free survival [11]. These lymphatic nodes need to be treated to prevent recurrence. To this end, Japanese teams consider these nodes as a local disease and treat them with lateral lymph node dissection (LLND) in addition to conventional surgery [12]. In contrast, these nodes are considered a distant disease in the last TNM classification from the American Joint Committee on Cancer (AJCC) 8th edition [13]. Therefore, Western teams use neoadjuvant radiochemotherapy instead, avoiding the morbidity associated with LLND [14].

However, neoadjuvant therapy may not be sufficient for treating enlarged lateral lymph nodes, and increased recurrence was documented (5.2–7.9% versus 3.2% recurrence rate in patients with neoadjuvant therapy and TME without or with LLND, respectively) [15, 16]. In the other hand, some studies showed increased urinary and sexual dysfunction without oncological benefits following LLND [17, 18]. Because it is not clear whether LLND could improve oncological outcomes in these patients, we aimed to review the literature by performing a systematic review to report the overall and recurrence-free survivals in rectal cancer patients treated with TME with or without LLND.

Materials and methods

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [19] checklist (Table S1). The study protocol was registered in PROSPERO prior to study screening (CRD42019123181) and published [20]. As described in the protocol, a quantitative analysis was planned. However, a meta-analysis could not be conducted because of the low quality and heterogeneity of the data. Regarding the two randomized controlled trials (RCT), one consisted of 701 patients [21] and the other of 45 patients [22]; the results would therefore be mainly reflected by the trial by Fujita et al. [21]. Concerning the nine observational studies [8, 23–30], an important confusing phenomenon would preclude a meta-analysis. Moreover, the quality of the reported results is low with no hazard ratio reported and therefore restrained from conducting statistical analysis. Therefore, we performed a qualitative analysis with a systematic review.

Literature search and studies selection

A systematic search was performed on MEDLINE/Pubmed, Embase, Cochrane, and Web of Science from database implementation to 19 January 2019 for original studies written in English or in French including patients who benefited from LLND for rectal cancer. The search strategy is reported in Table 1. Additional records were identified by manual search of the reference lists of the included publications.

Outcome of interest

The aim of the study was to determine whether LLND for rectal cancer improved oncological outcomes in comparison with TME without LLND. The main outcome was the overall survival. The secondary outcome was the recurrence-free survival. With compliance to PICO statement: Participants = patients with rectal cancer, Intervention = TME with LLND, Comparison = TME without LLND, Outcome = survival.

Inclusion criteria

Only original studies reporting overall survival or recurrence-free survival in patients with LLND for rectal cancer were included.

Exclusion criteria

Studies including patients with recurrent rectal cancer, multivisceral resection, and/or without control group (patients with rectal surgery without LLND) were excluded. Studies not reporting overall survival for patients with and without LLND were also excluded. Other exclusion criteria were case series, conference abstracts, letters to the editor, and secondary analyses of previously published papers.

Data extraction

Studies were independently selected for inclusion using the Covidence software by three authors (GL, JM, KC). Discrepancies were solved by a fourth author (FR). The following data were extracted: first author, publication year, country where the investigation took place and database used (monocentric, multicentric), study period, study design with method of randomization if applicable, number of patients included, number of patients who underwent low anterior resection (LAR) or abdominoperineal resection (APR) or another resection, number of patients who underwent open, laparoscopic, or robotic procedure, number of patients who underwent LLND (with the indication for LLND, the technic for LLND, the definition of lymph nodes dissected [common iliac, internal iliac, external iliac, obturator, middle sacral; uni-/bilateral or both]), number of patients who did not undergo LLND, demographics data (age, gender) and localization of tumor for each group, number of patients who underwent preoperative radio- and/or chemotherapy for each group, type of treatment in those patients, pathological TNM category and stage [AJCC staging [13]] of included patients (for each group), overall survival for each group, recurrence-free survival for each group. Nagawa et al. [22] reported survival

Table 1 Search strategy

Database	Search build	Occurrences
MEDLINE	((lateral lymph node dissection[Title/abstract]) OR (lateral lymph-node dissection[Title/abstract]) OR (LLND[Title/abstract]) OR (extended lymphadenectomy[Title/abstract]) OR (extended lymph node dissection[Title/abstract])) AND (rectal neoplasms[MeSH Terms])	152
Embase	("lateral lymph node metastasis":ti,ab,kw OR "extended lymphadenectomy":ti,ab,kw OR "extended lymph node dissection":ti,ab,kw) AND ("rectum cancer":ti,ab,kw OR "rectum tumor":ti,ab,kw OR "mesorectum":ti,ab,kw OR "mesorectal excision":ti,ab,kw OR "total mesorectal excision":ti,ab,kw)	41
Cochrane	(MeSH) Rectal Neoplasms AND (MeSH) Lymph Node Excision	37
Web of Science	TS=((lateral lymph node dissection) OR (LLND) OR (extended lymphadenectomy) OR (lateral lymphadenectomy) OR (extended lymph node dissection) OR (lateral lymph node)) AND TI=(cancer OR neoplasm) AND TI=(rectum OR rectal)	330

curves only; therefore, we performed extraction for numerical values.

Results

Literature search and study characteristics

Five hundred sixty-one publications were identified through database screening. One hundred and thirteen duplicates were removed. Of the 448 studies that were identified as eligible, 258 were excluded after title/abstract screening. After full text screening, 179 publications were excluded because they were lacking control group (without LLND) (105 studies), because they met exclusion criteria and should have been excluded during abstract screening (52 studies), because no overall survival or recurrence-free survival were reported for both groups (17 studies), or because they were duplicates (5 studies). Four studies [31–34] reported surgical procedures as "other," without specification of the procedure performed, but different from the category APR, LAR, or Hartmann's procedure. The proportion of these interventions was important (> 5% of the study population), and they were therefore excluded because it was considered to be more extensive surgeries or including resections of adjacent organs. One study [28] including only one total pelvic exenteration was included in the review, because the rate was negligible (0.79% of the study population). Ultimately, eleven articles [8, 21–30] were included in the qualitative synthesis (Fig. 1).

Among them, five studies [21, 27–30] were published in the last 10 years, eight [8, 22, 24–26, 28–30] were monocentric, and three [21, 23, 27] were multicentric. Six studies [21, 22, 26–28, 30] were performed in Japan, one [24] in China, one [29] in Korea, two [8, 23] in Netherlands, and one [25] in Turkey. Two studies [21, 22] were RCT and data of nine studies [8, 23–30] were retrospectively collected.

A total of 4159 patients were included with low (seven studies) [8, 22, 23, 26–28, 30] or mixed rectal cancer (four studies) [21, 24, 25, 29], representing 2098 cases with LLND. There were more males (1233 patients with LLND versus 1011 patients without LLND) than women (630 patients with LLND versus 701 patients without LLND). Preoperative therapies consisted of radiation [22, 23] or chemoradiation [28–30]. Neoadjuvant therapy was not administered in two studies [8, 26] and was not mentioned for three studies [21, 24, 25]. In six studies [8, 26–30], LLND was performed only in patients with enlarged lateral lymph nodes in preoperative imaging, whereas in two studies [23, 24], systematic LLND was performed in all included patients (TNM staging reported in Table 2). A random controlled allocation was performed in two studies [21, 22], while one study [25] did not mention the indication for LLND. In five articles [21, 24–26, 29], the autonomic nerve system was preserved, whereas one study [22] performed LLND without autonomic nerves preservation. Two other studies [8, 23] preserved the autonomic nerves only in case of unsuspicious lateral lymph node, and the technique for LLND was not described in three studies [27, 28, 30]. The definition of the dissected lymph node was not mentioned in three studies [8, 25, 26], while the obturator nodes were dissected in eight other studies [21–24, 27–30]. Other areas of lymph node dissection were the common iliac (seven studies) [21–24, 27–29], internal iliac (seven studies) [21, 22, 24, 27–30], external iliac (five studies) [24, 27–30], and middle sacral (one study) [24]. Four studies [8, 28–30] performed uni-

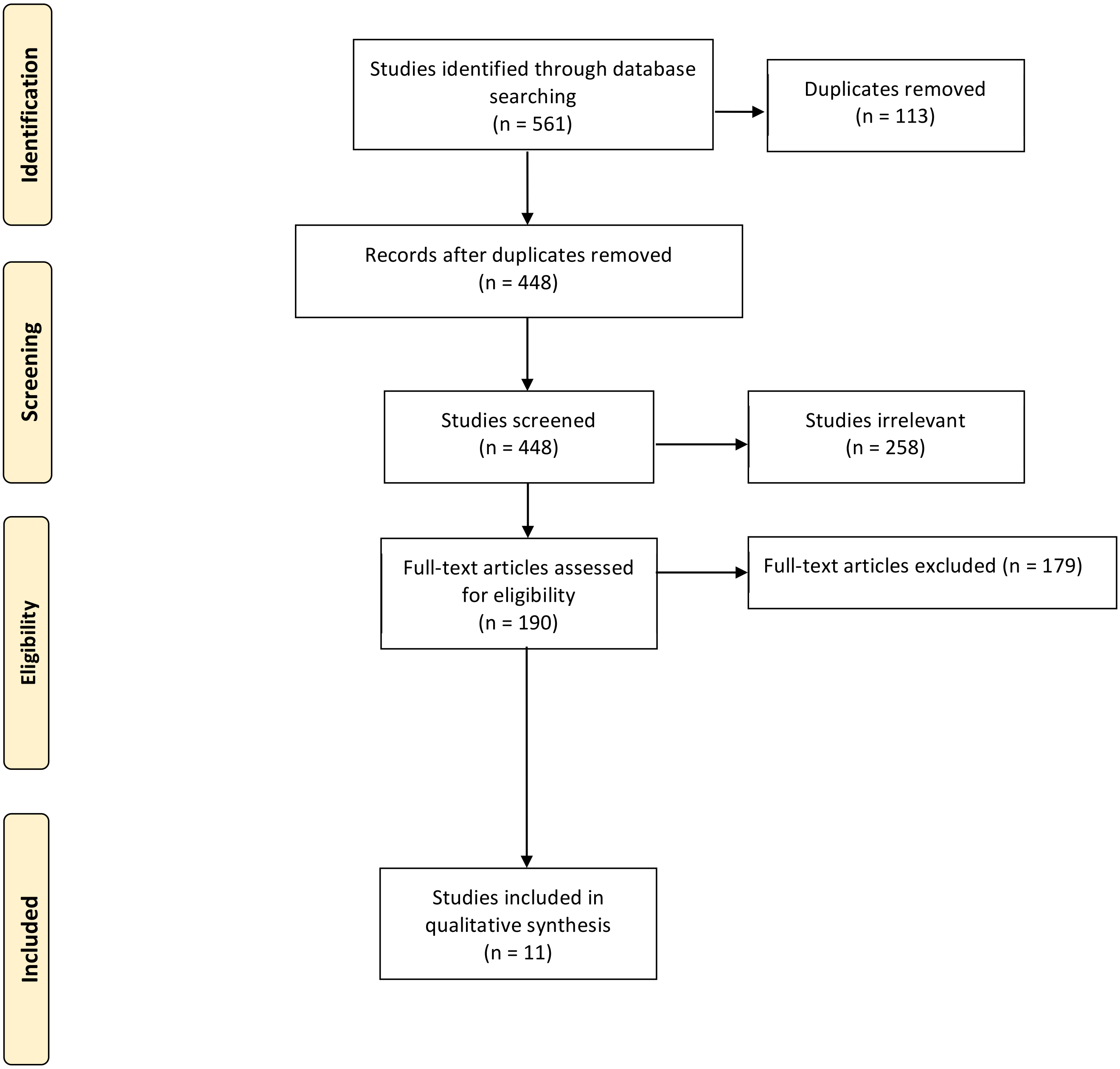

Fig. 1 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flowchart showing selection of publications for review

or bilateral LLND according to clinical and/or imaging findings and seven studies [21–27] did not report lateralization of dissection. The technique for TME resection consisted mainly of LAR and APR, with 736 patients with LLND versus 930 patients without LLND and 226 patients with LLND versus 263 patients without LLND, respectively. Other procedures included Hartmann's surgery, anterior resection, intersphincteric resection, and total pelvic exenteration in 10, 14, 34, and 1 patient, respectively, but it was not documented in 1945 cases. Resection category (R0, R1, or R2) was reported for three studies [21, 28, 29] and TNM staging for T category for seven studies [8, 21, 26–30] and N category for six studies [8, 21, 26, 28–30]. AJCC staging [13] was reported for 45% of studies [21, 23, 26, 27, 30]. Characteristics of the included studies are described in Tables 2 and 3.

Overall survival

Overall survival at 5 years was reported for eight studies [8, 21–25, 27, 29] and ranged from 55.6 to 92.6% for patients with TME + LLND and from 49.2 to 90.2% for patients with TME resection alone. The overall survival was significantly higher for TME + LLND group in one study [24] with 68.0% versus 49.2% at 5 years and 47.0% versus 25.3% at 10 years for TME with LLND versus TME alone, respectively ($p < 0.05$). The RCT by Fujita et al. [21] reported an increased

Table 2 Characteristics of included studies, part I

Study	Female	Male	Age (years in median [range])	Tumor localization (high, medium, low, mixed)	R0	R1	R2	N0	N1	N2	T0	T1	T2	T3	T4	Stade 0	Stade 1	Stade 2	Stade 3	Stade 4
Nagawa H.[22]	6/6	17/16	59.1 ± 10.1/60.1 ± 8.8*	Low	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fujita M.[21]	115/114	236/236	61 [26–75]/62 [26–75]	Mixed	344/343	6/5	1/2	184/199	99/105	68/46	0/0	4 / 8	88 / 75	248 / 258	11 / 9	0/0	70/60	114/139	165/150	2/1
Havenga K.[23]	78/294	155/254	57.7/63.7*	Low	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/0	0/0	79/120	154/238	0/0
Dong XS.[24]	N/A	N/A	N/A	Mixed	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hasdemir O.[25]	N/A	N/A	N/A	Mixed	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Shiozawa M.[26]	41/9	102/17	60.2 ± 0.9/66.4 ± 1.9*	Low	N/A	N/A	N/A	67/10	35/7	41/9	0/0	0/0	37/9	91/14	15/3	0/0	28/5	39/5	76/16	0/0
Kusters M.[8]	73/49	133/96	57/61*	Low	N/A	N/A	N/A	108/102	58/30	40/13	0/0	6/52	64/47	123/46	13/0	N/A	N/A	N/A	N/A	N/A
Kobayashi H.[27]	277/192	507/296	N/A	Low	N/A	N/A	N/A	N/A	N/A	N/A	0/0	37/196	207/127	497/157	43/8	0/0	179/282	224/86	381/120	0/0
Akiyoshi T.[28]	10/27	28/62	61 [35–75]/60 [34–81]	Low	35/87	3/2	0/0	12/61	18/17	8/11	2/9	3/3	8/29	23/46	2/2	N/A	N/A	N/A	N/A	N/A
Kim HJ.[29]	22/6	31/25	N/A	Mixed	77	0	0	29/24	20	11	0	2	21	45	6	N/A	N/A	N/A	N/A	N/A
Matsuda T.[30]	8/4	24/9	64 [39–76]/68 [40–79]	Low	N/A	N/A	N/A	21/6	7/3	4/4	5/0	0/0	8/1	16/11	2/1	4/0	5/0	12/6	11/7	0/0

Characteristics are expressed in:

• Number of patients undergoing TME with LLND/number of patients undergoing TME without LLND

• Total number of patients if the distinction is not available.

N/A not available

*Expressed in mean ± standard deviation

Table 3 Characteristics of included studies, part I

First author	Publication year	Country	Study period	Mono-/ multicentric	Study design	Number of patients included	Number of patients with neoadjuvant treatment	Number of patients with LLND (% of the total)	Indication for LLND	Nodes for LLND	Laterality of LLND (uni-/ bilateral or mixed)	Type of TME resection (number of patients from TME with LLND / TME without LLND)		
												LAR	APR	Other
Nagawa H.[22]	2001	Japan	1993–1995	Monocentric	RCT	45	45 Rt	23 (51.1%)	Random controlled allocation	IC + II + OØ	N/A	12 / 15	11 / 7	0
Fujita M.[21]	2017	Japan	2003–2010	Multicentric	RCT	701	N/A	351 (50.1%)	Random controlled allocation	IC + II + O‡	N/A	284 / 284	66 / 64	1 / 2*
Havenga K.[23]	1999	Netherlands	1978–1994	Multicentric	Observational, retrospective cohort	691	96 Rt	233 (33.7%)	Systematic	IC + O¥	N/A	142 / 366	92 / 91	0
Dong XS.[24]	2003	China	1981–1987	Monocentric	Observational, retrospective cohort	504	N/A	211 (41.9%)	Systematic	IC + II + IE + O + MS‡	N/A	N/A	N/A	N/A
Hasdemir O.[25]	2005	Turkey	2000–2005	Monocentric	Observational, retrospective cohort	170	N/A	24 (14.1%)	N/A	N/A‡	N/A	13 / 71	8 / 64	3 / 11**
Shiozawa M.[26]	2007	Japan	1990–2000	Monocentric	Observational, retrospective cohort	169	0	143 (84.6%)	Imaging (barium enema, colonoscopy, CT)	N/A‡	N/A	N/A	N/A	N/A
Kusters M.[8]	2008	Netherlands	1993–2002	Monocentric	Observational, retrospective cohort	351	0	206 (58.7%)	Imaging (CT, EUS) + intraoperative findings	N/A¥	Mixed	219 / 132	0	0
Kobayashi H.[27]	2009	Japan	1991–1998	Multicentric	Observational, retrospective cohort	1272	0	784 (61.6%)	Imaging	IC + II + IE + O	N/A	N/A	N/A	N/A
Akiyoshi T.[28]	2013	Japan	2004–2010	Monocentric	Observational, retrospective cohort	127	127 Rt + Ct	38 (29.9%)	Imaging (CT or MRI)	IC + II + IE + O	Mixed	16 / 29	15 / 27	2 / 3* 5 / 29*** 0 / 1 ****
Kim HJ.[29]	2017	Korea	2006–2013	Monocentric	Observational, retrospective cohort	84	84 Rt + Ct	53 (63.1%)	Imaging (MRI)	IC + II + IE + O ‡	Mixed	45 / 28	8 / 3	0
Matsuda T.[30]	2018	Japan	2005–2016	Monocentric	Observational, retrospective cohort	45	45 Rt + Ct	32 (71.1%)	Imaging (CT or MRI > 7 mm diameter, high-intensity by PET)	II + IE + O	Mixed	5 / 5	26 / 7	1 / 1*

LLND, lateral lymph node dissection; *TME*, total mesorectal excision; *LAR*, low anterior resection; *APR*, abdominoperineal resection; *RCT*, randomized controlled trial; *Rt*, radiotherapy; *IC*, iliac common; *II*, iliac intern; *IE*, iliac extern; *O*, obturator; *N/A*, not available; *MS*, mesenteric superior; *CT*, computed tomography; *EUS*, endoscopic ultrasound; *Ct*, chemotherapy; *MRI*, magnetic resonance imaging; *PET*, positive emission tomography

Ø Without autonomic nerves preservation

‡ With autonomic nerves preservation

¥ With autonomic nerves preservation in case of no suspicion lateral lymph node

*Hartmann's procedure

**Anterior resection

***Intersphincteric resection

****Total pelvic exenteration

survival with LLND (hazard ratio 1.25). This tendency was inversed in the other RCT by Nagawa et al. [22] (hazard ratio of 0.91), and in the study from Kobayashi et al. [27]. However, the results from these three last studies [21, 22, 27] were not significant.

Moreover, overall survival was increased in the group with LLND at 1 or 2 years [25], at 3 years [29], and at 5 years [23], contrasting with the increased overall survival without LLND at 3 [25] and at 5 years [8]. Nonetheless, the statistical value of these last results is not known as no *p* value was reported. The overall survival is reported in Table 4.

Recurrence-free survival

The recurrence-free survival at 5 years was reported for six studies [21, 22, 25, 26, 28, 29] and ranged from 58.6 to 74.1% for patient undergoing LLND and from 39.5 to 76.4% for patient with TME resection alone. The difference of 5-year recurrence-free survival was statistically significant in two studies [21, 26]. The recurrence-free survival was slightly increased at 5 years to 74.5% with TME alone versus 74.1% with LLND ($p = 0.045$) in the RCT of 701 cases by Fujita et al. [21]. In the 45 randomized controlled patients by Nagawa et al. [22], the recurrence-free survival was similar between the two groups (60.2% with LLND versus 76.4% without LLND at 5 years, hazard ratio = 1.56, $p = 0.44$). On the other hand, it was decreased at 5 years to 39.5% without LLND versus 65.4% with LLND, as well as at 10 years to 39.3% versus 64.3% ($p = 0.02$) in the observational retrospective study by Shiozawa et al. [26]. The disease-free survival was increased in patients with LLND in two other studies [28, 29], but the *p* value was statistically neither significant [28] nor reported [29]. Hasdemir et al. [25] found benefit of LLND at 1 year with increased recurrence-free survival, but this advantage did not persist over time as TME alone has increased recurrence-free survival at 2, 3, and 5 years of follow-up.

Local recurrence-free survival was another outcome reported from nine studies [8, 21, 23, 25–30], but none of them revealed a statistically significant difference between groups. At 5 years, the local recurrence-free survival was higher in patients with LLND for two studies with 87.7% versus 82.5% (statistically not significant) [21] and 100% versus 80% (*p* value not reported) [30]. This was consistent with the improved local recurrence-free survival at 3 years from the study by Akiyoshi et al. [28] and Kim et al. [29]. On the other hand, the local recurrence rate at 5 years was reduced with TME alone, with local recurrence-free survival up to 93.3% [23] and 99.2% [8] versus 90.6% with LLND and 84.6% with unilateral or 91.7% with bilateral LLND, respectively. Other investigators did not specify the timepoint of the outcome, with an either increased local recurrence-free survival with LLND [25, 26] or decreased local recurrence-free survival with LLND [27] and the *p* value was not significant [26, 27] or not reported [25]. The recurrence-free survival is reported in Table 4.

Discussion

The present systematic review included eleven articles reporting overall survival, recurrence-free survival, and local recurrence-free survival by eight [8, 21–25, 27, 29], five [21, 22, 25, 26, 28, 29], and nine studies [8, 21, 23, 25–30], respectively. Overall, only two studies [21, 22] were RCT, whereas the majority were observational retrospective studies [8, 23–30].

Regarding the overall survival, only one study [24] found benefit of performing LLND with a statically significant difference (68.0% with LLND versus 49.2% without LLND, $p < 0.05$, at 5 years). The other studies failed to report the *p* value [8, 23, 25, 29] or failed to find a statistically significant difference [21, 22, 27] with results showing superiority of TME alone [8, 25, 27] or of TME with LLND [21–23, 25, 29].

Recurrence-free survival was significantly increased with LLND in one study [26] at 5 and 10 years (65.4% and 64.3% with LLND versus 39.5% and 39.3% without LLND, respectively). These results based on retrospectively collected data were however not consistent with the improved recurrence-free survival in the TME alone group from the RCT by Fujita et al. [21] of 74.5% (versus 74.1% with LLND, $p = 0.045$). While the statistical value was not significant [22, 28] or not known [25, 29], the recurrence-free survival was reported to increase with LLND [25, 28, 29] or without LLND [22, 25]. No statistically significant difference was reported for local recurrence-free survival for both groups. This outcome was improved with LLND from some studies [21, 25, 26, 28–30] ranging from 81.2 to 100%; nonetheless, other investigators found increased local recurrence-free survival in the TME alone group [8, 23, 27] with rate from 92.6 to 99.2%.

A meta-analysis by Georgiou et al. published in 2009 [17] found a greater blood loss, longer operative time, increased male sexual dysfunction, and urinary dysfunction in patients undergoing LLND. However, perioperative mortality and morbidity were similar, as well as the long-term oncological outcomes with no significant difference in 5-year overall survival (hazard ratio 1.1, 95%CI 0.8–1.5, $p = 0.62$) and 5-year disease-free survival (hazard ratio 1.2, 95%CI 0.8–2.0, $p = 0.41$) [17]. Our present review reported five additional studies [8, 21, 23, 24, 29] reporting the overall survival with four of them [21, 23, 24, 29] in favor of TME + LLND including one RCT [21] and only one [24] with statistically significant difference. Concerning the recurrence-free survival, we identified three supplementary articles [21, 28, 29], with only one of them [21] showing statistical difference with benefit of TME alone versus TME + LLND (hazard ratio 1.0, $p = 0.045$).

Table 4 Reported survivals of included studies

Study	Overall survival					Recurrence-free survival					Local Recurrence-free survival				
	With LLND	Without LLND	Timepoint	HR	*p* value	With LLND	Without LLND	Timepoint	HR	*p* value	With LLND	Without LLND	Timepoint	HR	*p* value
Nagawa H.[22]	77.6%	74.5%	5 years	0.9	NS	60.2%	76.4%	5 years	1.6	NS	N/A				
Fujita M.[21]	92.6%	90.2%	5 years	1.3	NS	74.1%	74.5%	5 years	1.1	0.04	87.7%	82.4%	5 years	1.4	NS
Havenga K.[23]	75.3%	66.6%	5 years	N/A		N/A					90.6%	93.3%	5 years	N/A	
Dong XS.[24]	68.0%	49.2%	5 years	N/A	< 0.05	N/A					N/A				
	47.0%	25.3%	10 years	N/A	< 0.05										
Hasdemir O.[25]	90.2%	88.7%	1 year	N/A		85.7%	82.0%	1 year	N/A		87.5%	85.0%	N/A		
	78.9%	76.8%	2 years			68.4%	71.6%	2 years							
	55.8%	63.9%	3 years			58.6%	63.4%	3 years							
	55.8%	58.9%	5 years			58.6%	59.7%	5 years							
Shiozawa M.[26]	N/A					65.4%	39.5%	5 years	N/A	0.01	82.5%	76.9%	N/A	N/A	NS
						64.3%	39.3%	10 years							
Kusters M.[8]	78.0%U, 77.0%B	89.0%	5 years	N/A		N/A					84.6%U, 91.7%B	99.2%	5 years	N/A	
Kobayashi H.[27]	75.8%	79.5%	5 years	N/A	NS	N/A					89.5%	92.6%	N/A	N/A	NS
Akiyoshi T.[28]	N/A					83.8%	74.6%	3 years	N/A	NS	97.3%	92.9%	3 years	N/A	
Kim HJ.[29]	83.6%	80.1%	3 years	N/A		57.8%	53.7%	3 years	N/A		81.2%	76.9%	3 years	N/A	
Matsuda T.[30]	N/A					N/A					100%	80.0%	5 years	N/A	

LLND, lateral lymph node dissection; *HR*, hazard ratio; *N/A*, not available; *NS*, not significant

[U] For unilateral LLND

[B] For bilateral LLND

Another meta-analysis by Cheng et al. published in 2011 [35] was consistent with the previous one, with increased operating time, male urinary, and sexual dysfunction associated with LLND. The intraoperative blood loss was also increased but not statistically significant. Moreover, the perioperative morbidity was increased with extensive resection (odds ratio 1.6, 95%CI 1.1–2.3, p = 0.02) [35]. In regard to oncological outcomes, 5-year survival rate was similar between LLND group and non-LLND group (odds ratio 0.9, 95%CI 0.8–1.1, p = 0.48). Compared with this meta-analysis [35], the present systematic review assembled five new articles [8, 21, 23, 24, 29].

The main limitation of the study is the inherent risk of bias from retrospective studies representing the majority of the included studies (nine studies). Secondly, the indication for LLND differed among studies, as well as the surgical technique for LLND, number and laterality of nodes removed, as well as autonomic nerve preservation. Thirdly, heterogeneity existed among participant characteristics (tumor location, TNM and AJCC staging, neoadjuvant therapy). Fourthly, bias may exist, because we only selected articles in English, despite LLND is widely performed in Asian countries. Therefore, some studies written in native language may have been excluded.

Conclusions

In conclusion, the overall survival was increased with LLND by the majority of the included studies [21–25, 29], but with only one of them [24] showing a statically significant difference. The result of recurrence-free survival was balanced between the two groups with improvement with TME alone [21, 22, 25] or with TME and LLND [25, 26, 29, 30], but it was statistically significant only in two studies [21, 26]. Regarding the local recurrence, the results were similar among studies [8, 21, 23, 25–30]. Overall, benefits of the LLND are not clear and further RCT should be performed to determine which strategy, LLND versus radiochemotherapy, or a combination of both would allow improving survival in rectal cancer patients. Furthermore, the target population should be better defined, as some patients with advanced rectal cancer and lateral lymph node on preoperative imaging might benefit from LLND added to conventional Western treatment.

Acknowledgments The authors thank Christophe Combescure (Division of Epidemiology, University Hospitals of Geneva) for his contribution to data acquisition and interpretation.

Authors' contribution GL, JM, and NC conceived and designed the study. GL, JM, and NC acquired the data. GL, JM, NC, SP, ER, CT, NB, and FR interpreted the data. GL, JM, NC, SP, ER, CT, NB, and FR contributed to the writing of the manuscript and to its critical revision. GL, JM, NC, SP, ER, CT, NB, and FR approved the final version of the manuscript.

Data availability The authors confirm that the data supporting the findings of this study are available within the article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval Not applicable

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

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