Lateral lymph node dissection reduces local recurrence of locally advanced lower rectal cancer in the absence of preoperative neoadjuvant chemoradiotherapy: A systematic review and meta-analysis

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Abstract

Background: The role of lateral lymph node dissection (LLND) in the treatment of locally advanced lower rectal cancer remains controversial. The present study was conducted to compare total mesorectal excision (TME) with or without LLND in clinical stage II/III lower rectal cancer.

Methods: Studies published in PubMed, Embase, Ovid, Cochrane Library, Google Scholar and the ClinicalTrials.gov databases were systematically searched for studies that compared TME with or without LLND in clinical stage II/III lower rectal cancer. Subgroup analysis was performed based on whether preoperative neoadjuvant chemoradiotherapy (nCRT) was undertaken. The hazard ratios (HR), relative risk (RR) and weighted mean difference (WMD) were pooled.

Results: Twelve studies that included 4458 patients were identified in the current meta-analysis. Pooled data demonstrated that TME with LLND was associated with significantly longer operation time (WMD 90.73 min, P<0.001), more intraoperative blood loss (WMD 303.20 mL, P<0.001) and postoperative complications (RR=1.35, P=0.02). Urinary dysfunction (RR 1.44, P=0.38), sexual dysfunction (RR 1.41, P=0.17), and postoperative mortality (RR=1.52, P=0.70) were similar between the two groups. No statistically significant differences were observed in OS (HR 0.93, P=0.62), DFS (HR 0.99, P=0.96), total recurrence (RR 0.98, P=0.83), lateral recurrence (RR 0.49, P=0.14) or distant recurrence (RR 0.95, P=0.78) between the two groups regardless the use of nCRT. LLND significantly reduced local recurrence rate of patients who did not receive nCRT (RR 0.71, P=0.004); while the difference was not significant when nCRT was performed (RR 0.70, P=0.36).

Conclusions: Our study found LLND could not significantly improve survival in locally advanced lower rectal cancer, but could reduce the local recurrence in the absence of preoperative nCRT. The advantage of controlling local recurrence might be replaced with nCRT.

Registration: The protocol for this meta-analysis was registered prospectively with PROSPERO (CRD42020135575) in 16 May 2019.

1. Background

Total mesorectal excision (TME) technique has significantly improved the pathological and oncological outcomes, and has become the standard surgical procedure for rectal cancer. While, approximately 14%-30% of patients with clinical stage II/III lower rectal cancer develop lateral pelvic lymph node (LLN) metastasis, which is outside the surgical field of TME and is associated with a greater incidence of local recurrence and decreased survival [1, 2]. In Japan, lateral lymph node dissection (LLND) has been recommended as the standard treatment for the patients with stage II/III lower rectal cancer and has routinely been performed since the 1970s [3, 4]. However, in the West, LLN metastasis was considered to be a sign of distant metastasis and could not be entirely eliminated by surgery only [5]. Moreover, preoperative neoadjuvant chemoradiotherapy (nCRT) provides acceptable local control and has a lower incidence of postoperative complications [6]. Therefore, preoperative nCRT instead of LLND is the standard regimen in Western countries. However, studies have shown preoperative nCRT cannot completely eradicate metastatic LLN, which suggests that the combination of nCRT and LLND may be more effective in the management of locally advanced lower rectal cancer [7, 8].

The efficiency and safety of LLND in locally advanced lower rectal cancer remain controversial. Some studies reported LLND significantly reduced the local recurrence rate and improved the 5-year overall survival (OS) rate [9, 10]. In contrast, other studies showed LLND did not improve survival or decrease local recurrence but significantly increased urinary and sexual dysfunction [11, 12]. To demonstrate the effects of LLND, two previous meta-analyses were performed approximately ten years ago [13, 14]. The results indicated that LLND had no advantage in controlling recurrence or improving survival and appeared to be associated with increased urinary and sexual dysfunction. Confined by the quality of the included studies, the two meta-analyses did not explicitly restrict the anatomical location or stage of the tumors, and high rectal cancers (tumors located in the upper third of the rectum) and early-stage rectal tumors (clinical stage TNM I) were included in these studies. However, the application of LLND in high rectal and early-stage rectal cancer was practically abandoned, and LLND has been primarily performed for locally advanced lower rectal cancer since 2000 [4]. Besides, nCRT is currently the primary treatment regimen for locally advanced rectal cancer, but neither study separately assessed the effects of LLND on patients who received nCRT.

Several studies over the past decade, including large RCTs and well-designed cohort studies, were performed to clarify the value of LLND in stage II/III lower rectal cancer but provided controversial results [9, 15, 16]. Thus, a new meta-analysis is needed to integrate the results of previous studies and draw a clearer conclusion. Therefore, we performed the current meta-analysis to assess the efficacy and safety of LLND in locally advanced lower rectal cancer. We also evaluated the value of LLND in patients who underwent preoperative nCRT using subgroup analyses.

2. Methods

2.1. Literature search:

A systematic search of all peer-reviewed literature was performed in electronic databases, including MEDLINE (via PubMed), Embase, Ovid, and the Cochrane Library up to December 22, 2019. Related literature in the first ten pages of the Google Scholar database was also reviewed. The following MeSH search headings and their synonyms were used: “total mesorectal excision”, “lateral lymph node dissection”, “extended lymphadenectomy”, “lateral pelvic wall lymph-node dissection”, “rectal neoplasms”, “rectal cancer”, “comparative study” and “treatment outcome”. The related-articles function was used to broaden the search, and reference lists of relevant studies and related systematic reviews were screened manually. All abstracts, studies, and citations were reviewed irrespective of language. Full-text review was performed after a screening of the title and abstract. Data were only extracted from the arms matching the eligibility criteria for comparative studies with multiple arms.

2.2. Selection criteria:

All comparative studies evaluating the efficiency or safety of TME combined with LLND versus TME alone in the treatment of stage II/III lower (middle or low) rectal cancer were included. Studies with the following inclusion criteria were eligible: (1) Patients with locally resectable clinical stage II or III rectal cancer without evidence of metastatic disease at the time of surgery and tumor location within 8 cm from the anal verge, or the major part of the tumor was located at or below the peritoneal reflection; (2) Patients between the two arms with similar clinical characteristics and therapeutic schemes. The following exclusion criteria were used: (1) Tumor lesions located in the upper third of the rectum, or the major part of tumor was located above the peritoneal reflection; (2) Patients with significantly different clinical characteristics or distinct therapeutic protocols(except for LLND) between the two arms; (3) Patients with distant metastasis at the time of treatment or other malignant diseases or fixed tumors; And (4) Animal studies, letters, comments, and editorials. In cases of considerable overlap in subjects between studies published on a single clinical trial, the most recent or most informative study was included, and the results were used complementary.

2.3. Data extraction:

Two reviewers independently performed data extraction and study quality assessment. Extraction data that were consistent between the two reviewers were used directly for the final analysis, and disagreements between the two reviewers were discussed and resolved via consensus. The corresponding authors of the respective trials were contacted for clarification if the extracted data were ambiguous. If available, data were supplemented with additional, unpublished data (e.g., conference proceedings). The following data were extracted from each study: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, matching criteria, number of patients enrolled in each arm, and the reported outcomes. The primary endpoints were 5-year overall survival (OS) and disease-free survival (DFS). Secondary endpoints included total recurrence, local recurrence, lateral recurrence, distant recurrence, operation time, intraoperative blood loss, postoperative complications and mortality, urinary dysfunction and sexual dysfunction.

2.4. Study quality assessment

The Newcastle-Ottawa scale criteria recommended by the Cochrane Library for included trials was used to evaluate the quality of the cohort studies. This was assessed by examining three factors: method of patient selection, comparability of the study groups, and number of outcomes reported. A star rating of 0–9 was allocated to each study based on these parameters. Studies achieving seven or more stars were considered higher quality and were included in the current study [17]. The quality of RCTs was measured using the Cochrane Collaboration's risk for bias assessment tool, which contains seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each item was assessed as having a high, low, or uncertain risk of bias [18]. Two reviewers assessed the quality of the studies. Where discrepancies arose, papers were re-examined, and consensus was reached via discussion.

2.5. Statistical analysis

The meta-analysis was performed consistent with the recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines [19, 20]. Hazard ratios (HRs) and the respective 95% confidence intervals (CIs) were assessed as effective measures for time-to-event data (5-year OS and DFS). If a study reported adjusted and unadjusted HRs, the adjusted HR was used for the primary analysis. If HRs were not reported but adequate information (e.g., Kaplan-Meier plots) was available, the estimation methods described by Parmar and Tierney were used to estimate HRs and the respective 95% CIs [21, 22]. The risk ratio (RR) was used as the summary statistic for statistical analyses of dichotomous variables, and the weighted mean difference (WMD) was used to analyze continuous variables. P-values for the overall effects were calculated based on a two-sided Z-test for independent samples for effect measures on a log scale. A P-value < 0.05 was considered statistically significant. Meta-analytic results are graphically displayed in Forest plots.

Heterogeneity was tested using chi-squared analyses and defined as present in cases of a P-value < 0.10. To assess the impact of heterogeneity on the meta-analysis, I^2 (the percentage of variability in effect estimates that is due to heterogeneity rather than chance) was calculated. $I^2 > 40\%$ was considered statistically significant heterogeneity, and the random-effects model was used to calculate overall effect estimates after examining the causes of heterogeneity. Otherwise, the fixed-effects model was used. Subgroup analysis was performed based on whether preoperative nCRT was undertaken. Review Manager version 5.3 was used for the meta-analysis (Copenhagen, the Nordic Cochrane Centre) [23].

3. Results

3.1. Study selection

A total of 1564 citations were identified using the predefined search strategy (Fig. 1). After screening the titles and abstracts, 1499 of the studies were excluded due to lack of relevance. Sixty-five articles were further evaluated for eligibility. Thirty-two studies were excluded because they did not meet the selection criteria. Two studies were excluded because they were meta-analyses, and 14 additional studies were excluded because they were reviews. Three studies were excluded because the data were not extractable, and three studies with overlapping data were also excluded. Four studies based on one same randomized trial were included because they reported different outcomes. Full manuscripts were available for 11 studies, but the results of one RCT were available as a conference proceeding presented on the 2017 ECCO European Cancer Congress [15]. Twelve studies published from 2001 to 2019 and involving a total of 4458 patients (1952 in the TME + LLND group and 2506 in the TME alone group) fulfilled the selection criteria and were included in the current meta-analysis. The flow diagram is shown in Fig. 1.

3.2. Characteristics of the included studies

Six of the included studies were RCTs, and the other six studies were non-RCTs. According to the Cochrane bias assessment, all of the RCTs mentioned “randomization”, but only four studies (based on the same research) reported the generation of an adequate randomized sequence and mentioned that the allocation procedure was not masked to investigators or patients. Another two RCTs failed to report the randomization procedure or mentioned whether blinding was adopted (Fig. 2 and Fig. 3). The six non-RCTs were all cohort studies, including five retrospective studies and one prospective study with prospectively collected data. The quality of the non-RCTs was evaluated using the Newcastle-Ottawa criteria. As shown in Table 1, the total number of stars of the six non-RCTs was not less than seven for each study. The basic information of the eligible studies included in our meta-analysis is listed in Table 2. Study outcomes are shown in Table 3.

Table 1
Scores of 6 cohort studies using Newcastle-Ottawa Criteria

Study	Selection				Comparability	Outcomes			Total
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of the follow-up of cohorts	
Fujita, S. 2003	1	1	1	1	0	1	1	1	7
Kusters, M. 2009	1	1	1	1	2	0	1	1	8
Watanabe, T. 2002	1	1	1	1	1	1	1	1	8
Oki, Eiji 2019	1	1	1	1	1	1	1	1	8
Ozawa, H. 2016	1	1	1	1	2	0	1	1	8
Ogura 2019	1	1	1	1	0	1	1	1	7

Table 2
Characteristics of the 12 included studies

Study	Study year(region)	Research type	Group name	Sample size	Mean age(years)	Sex ratio(M:F)	Median follow-up time	Tumor location	Clinical stage	Preoperative adjuvant therapy	Postope adjuvan
Nagawa, H	2001(Japan)	RCTs	TME + LLND	23	59.1(± 10.1)※	17:6	N/A	Middle, Low	Stage B, C Ω	50gy	Adjuvan chemoth
			TME alone	22	60.1(± 8.8)※	16:6					
Fujita, S	2003(Japan)	Retrospective	TME + LLND	204	57(± 10)※	133:71	59 months	Middle, Low	TNM II/III	NO	NO
			TME alone	42	64(± 12)※	24:18					
Kusters, M	2009(Japan & Netherlands)	Retrospective	TME + LLND	324	58(± 11)※	215:109	7.9 years	Middle, Low	TNM II/III	NO	Partial re chemora
			TME alone	376	64(± 11)※	234:142	7.0 years				
Watanabe, T	2002(Japan)	Retrospective	TME + LLND	75	N/A	N/A	N/A	Middle, Low	Stage B, C Ω	50gy	N/A
			TME alone	40	N/A	N/A					
Fujita, S	2012(Japan)	RCTs	TME + LLND	351	61(54–67)Ψ	236:115	N/A	Middle, Low	TNM II/III	NO	TNM II = chemoth
			TME alone	350	62(55–68)Ψ	236:114					TNM III = chemoth
Dev, K	2017(India)	RCT	TME + LLND	163	N/A	N/A	N/A	Middle, Low	TNM II/III	Short-course radiotherapy	NA
			TME alone	77	N/A	N/A					
Saito, S	2016(Japan)	RCTs	TME + LLND	351	61(55–66)Ψ	N/A	N/A	Middle, Low	TNM II/III	NO	TNM II = chemoth
			TME alone	350	62(56–69)Ψ	N/A					TNM III = chemoth
Fujita, S	2017(Japan)	RCTs	TME + LLND	351	61(26–75)@	236:115	72.2 months	Middle, Low	TNM II/III	NO	TNM II = chemoth
			TME alone	350	62(26–75)@	236:114					TNM III = chemoth
Ito, Masaaki	2018(Japan)	RCTs	TME + LLND	351	61(26–75)@	236:115	N/A	Middle, Low	TNM II/III	NO	TNM II = chemoth
			TME alone	350	62(26–75)@	236:114					TNM III = chemoth
Oki, Eiji	2019(Japan)	Prospective	TME + LLND	215	60.7(± 9.4)※	159:56	5 years	Middle, Low	TNM II/III	NO	Partial re chemoth
			TME alone	230	63.5(± 8.9)※	151:79					
Ozawa, H	2016(Japan)	Retrospective	TME + LLND	499	N/A	356:143	N/A	Middle, Low	TNM II/III	NO	Partial re chemoth
			TME alone	499	N/A	334:165					

Study	Study year(region)	Research type	Group name	Sample size	Mean age(years)	Sex ratio(M:F)	Median follow-up time	Tumor location	Clinical stage	Preoperative adjuvant therapy	Postope adjuvan
Ogura	2019(Japan)	Retrospective	TME + LLND	98	N/A	N/A	56.0 (55.0-58.1) @	Middle, Low	TNM II/III	All received neoadjuvant radiotherapy, partial received neo-chemotherapy	Partial re chemoth
			TME alone	870	N/A	N/A					

For matching criteria A = year, B = sex, C = tumor location, D = neo-adjuvant, E = adjuvant, F = lateral lymph-node status G = lymph and vessel invasive H = tumo staging system; @: Values are presented as the median (range); Ψ: Values are presented as the median (IQR); ※: Values are presented as the mean ± standard anterior resection; APR: Abdominoperineal resection; Hartmann: Hartmann's procedure.

Table 3
Results of meta-analysis comparing TME + LLND versus TME alone

	Number of studies	TME + LLND patients	TME patients	Total patients	HR/RR/WMD (95% CI)	P value	Study heterogeneity			
							χ^2	df	I^2	p-value
Survival										
5-year survival	4	1088	1101	2189	0.93*(0.71–1.22)	0.62	6	3	50%	0.11
5-year disease-free survival	5	868	684	1552	0.99*(0.74–1.34)	0.96	9.93	5	50%	0.08
Recurrence										
Total recurrence	4	653	454	1107	0.98(0.81–1.18)	0.83	2.37	4	0%	0.67
Local recurrence	7	1290	1930	3220	0.71(0.56–0.89)	0.003	9.22	7	24%	0.24
Lateral recurrence	3	773	1596	2369	0.49(0.18–1.28)	0.14	5.87	2	66%	0.05
Distant recurrence	5	615	1204	1819	0.95(0.68–1.34)	0.78	8.84	5	43%	0.12
Peri-operative outcomes										
Length of operation (min)	4	716	479	1195	97.03†(75.35-118.72)	P < 0.001	82.14	3	96%	P < 0.001
Blood loss (mL)	4	716	479	1195	303.20†(156.82–449.58)	P < 0.001	201.99	3	99%	P < 0.001
Peri-operative mortality	2	578	414	992	1.52(0.18–12.65)	0.7	0.47	1	0%	0.49
Postoperative complications	3	578	414	992	1.35(1.05–1.74)	0.02	0.53	2	0%	0.77
Functional outcomes										
Urinary dysfunction	2	374	372	746	1.44(0·63–3.28)	0·38	4.93	1	80%	0.03
Sexual dysfunction	2	108	92	200	1.41(0.87–2.31)	0·17	2.23	1	55%	0.13

HR = hazard ratio. RR = risk ratio. WMD = weighted mean difference. df = degrees of freedom. *HR. †WMD.

3.3. Primary endpoints: 5-year OS and DFS.

Four studies reported the 5-year OS [9–12]. Three studies directly provided HR values for OS [9, 10, 12], and another study presented the results as a step-like survival curve [11]. We extracted the statistics according to the method provided by Tierney et al. using Engauge Digitizer software [21]. Four studies, with a total of 2189 patients, were pooled for analysis, and the random effects model was used because high heterogeneity was observed (I^2=50%, P = 0.11). The results showed no significant difference between the TME with LLND group and TME alone group (pooled HR 0.93, 95% CI 0.71–1.22, P = 0.62). Subgroup analysis showed no significant difference between the two arms regardless of the use of preoperative nCRT (HR = 1.41, 95% CI 0.56–3.55, P = 0.47 vs HR = 0.90, 95% CI 0.68–1.20, P = 0.42, respectively). The details are shown in Fig. 4a.

Data on 5-year DFS were reported in six studies. Three studies provided HR values of 5-year DFS directly [2, 9, 12], and the results of another two studies were extracted from the step-like survival curve provided by the authors [11, 24], We excluded the study of Dev, K because the results were 2-year disease-free survival [15]. Ultimately, five studies that included 1552 patients were pooled into the analysis [2, 9, 11, 12, 24]. The random effects model was used because of the high between-study heterogeneity (I^2=50%, P = 0.08). The results indicated no significant difference between the TME with LLND group and TME alone group (pooled HR 0.99, 95% CI 0.74–1.34, P = 0.96). The subgroup analysis showed no significant difference between the two arms regardless of the use of nCRT (HR = 0.71, 95% CI 0.40–1.25, P = 0.23 vs HR = 1.08, 95% CI 0.75–1.55, P = 0.69, respectively). The details are shown in Fig. 4b.

3.4. Secondary endpoints: total, local, lateral, and distant recurrence, operation time, intraoperative blood loss, postoperative complications, peri-operative mortality, sexual and urinary dysfunction.

Four studies with a total of 1107 patients were eligible for the analysis of total recurrence [2, 9, 11, 24]. Two of these studies were RCTs [9, 11], and the other two studies were retrospective [2, 24]. The fixed effects model was used to pool the statistics (I^2=0%, P = 0.67). No significant difference in total recurrence was found between the two groups (pooled RR 0.98, 95% CI 0.81–1.18, P = 0.83). The subgroup analysis showed no significant difference between the two arms with or without nCRT (RR = 1.46, 95% CI 0.76–2.81, P = 0.25 vs RR = 0.94, 95% CI 0.77–1.14, P = 0.53, respectively). The details are shown in Fig. 5a.

Seven studies with a total of 3220 patients were included in the study of local recurrence [2, 6, 9, 11, 12, 16, 24]. The fix effects model was used to pool the statistics (I^2=24%, P = 0.24). The results indicated that local recurrence rate was significantly lower in the TME with LLND group than the TME alone group (pooled RR 0.71, 95% CI 0.56–0.89, P = 0.003). The subgroup analysis found that the LLND group had a significantly lower incidence of local recurrence than the TME alone group when preoperative nCRT was not performed (RR 0.71, 95% CI 0.56–0.89, P = 0.004). However, the difference was not significant once preoperative nCRT was introduced (RR 0.70, 95% CI 0.32–1.51, P = 0.36). The details are shown in Fig. 5b.

Data on lateral recurrences rate were extracted from three studies of 2369 patients [6, 9, 16]. The random effects model was used because of the high heterogeneity (I^2=66%, P = 0.05). The results demonstrated no significant difference in lateral recurrence rate between the two groups (pooled RR 0.49, 95% CI 0.18–1.28, P = 0.14). The subgroup analysis indicated no significant difference between the two arms regardless the introduction of nCRT (RR = 0.72, 95% CI 0.27–1.97, P = 0.53 vs RR = 039, 95% CI 0.08–1.89, P = 0.24, respectively). The details are shown in Fig. 5c.

Distant recurrence was reported in five studies that investigated 1819 patients [2, 11, 12, 16, 24]. There was no significant difference between the two groups (pooled RR 0.95, 95% CI 0.68–1.34, P = 0.78). The random effects model was used because of moderate between-study heterogeneity (I^2=43%, P = 0.12). The subgroup analysis revealed no significant difference between the two arms regardless of the use of preoperative nCRT (RR = 0.74, 95% CI 0.41–1.33, P = 0.32 vs RR = 1.14, 95% CI 0.89–1.47, P = 0.29, respectively). The details are shown in Fig. 5d.

Four studies were included in the meta-analysis that assessed the length of operation in 1195 patients [2, 11, 15, 25]. The results demonstrated a significant difference that favored the non-LLND group (WMD 90.73 min, 95% CI 75.35-118.72, P < 0.001) with significant between-study heterogeneity (I^2=96%, P < 0.001), and the random effects model was used. The subgroup analysis revealed that the TME with LLND group needed a longer operation time than the TME alone group regardless of the use of preoperative nCRT (WMD = 79.85, 95% CI 74.81–84.88, P < 0.001 vs WMD = 110.74, 95% CI 93.55-127.95, P < 0.001, respectively). The details are shown in Fig. 6a.

Four studies were included in the meta-analysis to assess intraoperative blood loss in 1195 patients [2, 11, 15, 25]. The random effects model was used because of the high between-study heterogeneity (I^2=99%, P < 0.001). The results indicated that the TME alone group showed significantly lower intraoperative blood loss than the TME with LLND group (WMD 303.20 mL, 95% CI 156.82–449.58, P < 0.001). The subgroup analysis found that the TME alone group had significantly lower intraoperative blood loss than the TME with LLND group when nCRT was not performed, but the difference was not significant when nCRT was introduced (WMD = 434.84, 95% CI 34.39–835.30, P = 0.03 vs WMD = 256.86, 95% CI -211.92-725.64, P = 0.28, respectively). The details are shown in Fig. 6b.

Three studies assessed 992 patients and reported postoperative complications [2, 11, 25]. A fixed effects model was used because of the low between-study heterogeneity (I^2=0%, P = 0.77). The TME with LLND group was associated with a higher rate of postoperative complications than the TME alone group (pooled RR = 1.35, 95% CI 1.05–1.74, P = 0.02). The subgroup analysis demonstrated more postoperative complications in the TME with LLND group than the TME alone group when nCRT was not undertaken, but the difference was not significant when neoadjuvant therapy was introduced (RR = 1.39, 95% CI 1.05–1.83, P = 0.02 vs RR = 0.1.13, 95% CI 0.65–1.96, P = 0.66, respectively). The details are shown in Fig. 7a.

Peri-operative mortality was reported in three studies that investigated 992 patients [2, 11, 25]. The data extracted from one of the studies was not suitable for meta-analysis because no events occurred in either group [11]. Ultimately, two studies including 947 patients without neoadjuvant therapy were pooled into the analysis [2, 25]. A fixed effects model was used because of the low between-study heterogeneity (I^2=0%, P = 0.49). The results indicated no significant difference between the two groups (pooled RR = 1.52, 95% CI 0.18–12.65, P = 0.70). The details are shown in Fig. 7b.

Two RCTs studies assessed 200 patients and reported sexual dysfunction [11, 26]. The random effects model was used because of high between-study heterogeneity (I^2=55%, P = 0.13). The results indicated no significant difference between the two groups (pooled RR 1.41, 95% CI 0.87–2.31, P = 0.17). The subgroup analysis demonstrated that the sexual dysfunction rate was lower in the TME alone group when nCRT was introduced, but the difference was not significant when preoperative nCRT was not performed (RR = 2.03, 95% CI 1.00-3.95, P = 0.04 vs RR = 1.19, 95% CI 0.95–1.49, P = 0.13, respectively). The details are shown in Fig. 7c.

Two RCTs studies assessed 746 patients and reported urinary dysfunction [11, 27]. The random effects model was used because of the high between-study heterogeneity (I^2=80%, P = 0.03). The results demonstrated no significant difference between the two groups (pooled RR 1.44, 95% CI 0.63–3.28, P = 0.38). The subgroup analysis demonstrated that the urinary dysfunction rate was lower in the TME alone group when nCRT was introduced, but the difference was not significant when nCRT was not performed (RR = 2.39, 95% CI 1.14–5.04, P = 0.02 vs RR = 1.02, 95% CI 0.90–1.16, P = 0.74, respectively). The details are shown in Fig. 7d.

4. Discussion

The present study is the first meta-analysis evaluating the efficiency and safety of LLND in stage II/III lower rectal cancer. The aggregated data demonstrated that LLND did not decrease total or distant recurrence rates, but it significantly reduced the local recurrence rate at the cost of a longer operation time, greater intraoperative blood loss and higher incidence of postoperative complications. The benefit in controlling local recurrence did not translate to a better 5-year DFS or OS rate. Notably, LLND did not increase postoperative mortality or pose an additional risk for sexual and urinary dysfunction. The results of subgroup analysis showed that LLND significantly reduced the local recurrence of patients who received no preoperative nCRT but not in patients who received. The results also demonstrated that LLND did not improve the survival outcomes of the patients regardless the use of nCRT.

The results of our study are different from the previous two meta-analyses, which were performed by Georgiou et al. and Chen et al. approximately 10 years ago [13, 14]. Both of these studies reported the safety and efficiency of LLND in rectal cancer. Their results indicated that LLND did not decrease the recurrence rate or increase the survival rate. They also summarized that urinary and sexual function were significantly worse in patients who received LLND. However, confined by the limited quality of the studies included in their meta-analyses, there were inherent flaws in their results. For example, the clinical characteristics were significantly different between the two arms, and the LLND group had more advanced tumors, i.e., larger (higher T stage) [28], node-positive [28, 29], and more aggressive pathology [30] compared to the non-LLND group. Furthermore, high rectal cancers and early stage rectal tumors (T1) were included in their studies [30, 31–34]. However, the Japanese guidelines recommended the application of LLND limited to the cT3-4 tumors with a lower edge lying at or below the peritoneal reflection, regardless of lymphatic node metastasis, since the 2000s [4]. In addition, in the study performed by Chen and colleagues, the time-to-event data were analyzed as dichotomous outcomes instead of the generally recommended method of log HRs and its standard error [14]. Therefore, there were certain limitations in the application of their results to guide the use of LLND in present clinical practice. The current study included more high-quality trials than the previous two meta-analyses, and all of the included studies had similar clinical baselines between the two arms. Only studies with clinical stage II/III middle or low rectal cancer were included. Therefore, our study provides more powerful and valid results than the previous two meta-analyses.

The aggregated data in the current study demonstrated that LLND significantly reduced the local recurrence rate of patients who did not receive nCRT. However, this difference was not significant when preoperative nCRT was performed in both groups. These results indicated that the advantage of LLND in controlling local recurrence may be replaced with preoperative nCRT. Caution should be taken when interpreting these results because no subgroup analysis was performed based on the pretreatment size of LLNs. Previous studies indicated that patients with positive LLNs have a higher rate of local recurrence, and nCRT followed by TME only was not sufficient to completely eradicate the metastatic LLNs and avoid local recurrence [35, 36]. Akiyoshi et al. also reported that 30–40% of patients with pretreatment-positive LLN developed pathological metastasis in the lateral pelvis even after nCRT and eventually developed local recurrence, but the local recurrence rate was reduced to almost zero when additional LLND was performed [37]. Ogura et al. noted that 25.6% of patients with pretreatment-positive LLN developed local recurrence even after receiving nCRT and radical resection, but the local recurrence rate was reduced to 5.7% when extra LLND was performed [16]. Therefore, for patients with pretreatment-positive LLNs, nCRT followed by TME alone may not be sufficient, and selective LLND should probably be considered [7, 35]. The value of selective LLND in patients who received nCRT remains controversial. A current phase III Chinese randomized controlled trial (NCT02614157) to demonstrate the safety and efficacy of selective LLND after nCRT in the treatment of advanced lower rectal cancer bearing enlarged LLNs is being performed and may provide more reliable evidence [38].

The pattern of local recurrence can be divided into 3 categories: central pelvis recurrence, anastomosis recurrence and lateral recurrence. The current study found that LLND reduced the incidence of lateral recurrence, but without significant difference. The reason may be the different local recurrence patterns in the patients pooled in our studies. Several studies indicated that the most common sites of local recurrence were different between patients in different regions. A Dutch trial indicated that the most common site of recurrence was the central pelvis, and only 24% of the local recurrence originated from the lateral pelvis in the TME alone group [6]. A study from Sweden also demonstrated that lateral recurrence was not a major cause of local recurrence, and only 6% (2/33) of patients with local recurrence exhibited lateral pelvic recurrence [39]. While, a study by Nagasaki et al. from Japan suggested that the most common site of local recurrence was the lateral pelvis, and approximately 50% of the patients with local recurrence developed lateral recurrence [40]. In addition, a study by Kim et al. from Korea also demonstrated that approximately 65% (42/65) of patients with local recurrence had lateral pelvic recurrence even after receiving nCRT and radical dissection [41]. Analogously, Fujita et al. reported a much higher rate of lateral pelvic recurrence (57%) in TME alone group than Kusters and colleagues (24%) in the current meta-analysis, which may be the reason for the high between-study heterogeneity [6, 9]. Therefore, patients in East Asia tend to have a higher incidence of lateral pelvic recurrence, and LLND may play a more important role in East Asian patients than patients in Europe.

We also demonstrated that LLND did not improve the 5-year OS or DFS rates regardless of preoperative nCRT was performed or not. The results indicated that LNN metastasis may be a sign of systemic disease with a dismal prognosis rather than a regional disease, which cannot be entirely eliminated with surgery only [5]. Previous studies demonstrated that the 5-year survival rate of patients with metastatic LLNs was poor (20–45%), even when local control was achieved using LLND [42, 1, 43]. Oki et al. also indicated that LLND did not improve the 5-year DFS or OS rates of patients who received no preoperative nCRT [12]. Japanese randomized trials also demonstrated no significant differences in 5-year OS and DFS between patients who received or did not receive LLND [9]. The latest tumor-node-metastasis classification (AJCC 8th edition) has classified LLN involvement as a distant disease, and preoperative nCRT followed by TME are recommended as the standard regimens [44]. However, whether LLND provides additional benefits to patients who have received nCRT remains controversial. The current meta-analysis did not find significant differences in 5-year OS and DFS between the two groups after receiving preoperative nCRT. Notably, these results were obtained using no restriction on the pretreatment size of the LLN, and studies with negative LLNs were also included in our study. The pretreatment size of LLN was significantly associated with survival outcomes, and patients with positive LLNs have significantly worse survival rates [41, 45]. The MERCURY study showed that patients with enlarged LLNs had significantly lower 5-year DFS rates than patients with negative LLNs (42% vs. 70.7%) after surgery [45]. Furthermore, Kim et al. also identified that LLN short-axis diameter ≥ 10 mm was significantly associated with lower 5-year OS and DFS, even after nCRT and TME [41]. A subgroup analysis based on the pretreatment size of LLNs was planned during the design phase of the present meta-analysis, but no sufficiently detailed information was provided in the included trials to perform this subgroup analysis. Therefore, whether LLND provides additional survival benefits to patients with pretreatment-positive LLNs who received nCRT remains unknown, and the phase III Chinese randomized controlled trial (NCT02614157) mentioned above may provide strong evidence [38].

The aggregated data also demonstrated that TME followed by LLND required a significantly longer operation time and resulted in greater blood loss than TME alone, but a high between-study heterogeneity was observed, and these results are expected. It is not difficult to understand that LLND combined with TME required more operation time because LLND is a meticulous and systemic procedure. Two trials performed approximately 2000 indicated that the mean difference in intraoperative blood loss was greater than 500 mL between the two groups [2, 11]. However, two recent RCTs by Fujita et al. and Dev et al. showed that the mean differences were 239 ml and 70 ml, respectively [15, 25]. A reasonable explanation may be due to improvements in the surgical techniques, and blood loss may have been minimized compared with the earlier studies.

Our study also found that LLND was associated with more frequent and serious postoperative complications, but LLND did not produce additional risks for postoperative mortality. Caution should be taken when interpreting these results for use in clinical practice because all three trials included in the current meta-analysis reported extremely low incidence rates of postoperative mortality in both groups [2, 11, 25]. Notably, the aggregated data demonstrated that LLND did not bring additional risks of sexual or urinary dysfunction. One possible explanation is that complete autonomic neuroprotection was not used in early studies [11], but once the technology was introduced, there was no significant difference in urinary or sexual dysfunction between the two groups [26, 27]. Therefore, the potential damage to urinary and sexual function cannot be a stumbling block to prevent the use of LLND for the treatment of rectal cancer.

The limitations of the current study should not be neglected because six RCTs and six non-RCTs were included in our meta-analysis. Four of the six RCTs studies reported different outcomes based on the same randomized trial. The results of another study were extracted from conference proceedings [15]. However, all of the included studies were of high quality (achieving more than seven stars) according to the Newcastle-Ottawa Scale (for non-RCTs) [17] or the Cochrane Collaboration's risk of bias tool (for RCTs) [18]. The follow-up times were different across studies, but the time was sufficient for outcomes to occur, and subjects lost to follow-up were unlikely to introduce bias. Despite meeting the inclusion criteria, clinical heterogeneity was present due to the different pretreatment statuses of LLNs between the included studies, which may have introduced bias. The specific surgical methods and quality were different across studies, which presents another possibility to introduce bias. Despite these limitations, the current study provides the most comprehensive and up-to-date information on the frequently discussed value of the routine use of LLND in the treatment of stage II/III lower rectal cancer.

5. Conclusions

In conclusion, our study demonstrated that the general use of LLND in locally advanced lower rectal cancer could not improve 5-year OS or DFS but only could reduce the local recurrence rate in the absence of nCRT at the cost of longer operative time, greater intraoperative blood loss and more postoperative complications. Furthermore, the routine use of LLND did not provide additional benefits in controlling recurrence or improving survival in patients who had received preoperative nCRT. LLND should be selectively performed in patients with more risk factors, for example, patients with positive lateral lymph nodes. Future studies are needed to demonstrate whether selective LLND provides additional benefits for patients who have received preoperative nCRT.

Abbreviations

TME: Total Mesorectal Excision; LLND: Lateral Lymph Node Dissection; nCRT: Neoadjuvant Chemoradiotherapy; HR: Hazard Ratio; RR: Relative Risk; WMD: Weighted Mean Difference; OS: Overall Survival; DFS: Disease Free Survival; RCT: Randomised Controlled Trial; CI: Confidence Interval;

Declarations

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Not applicable.

Authors' contributions

XG, CW, and YYY made substantial contributions to conception and design, acquisition, analysis, and the interpretation of data; XG, CW, YYY and LY participated in drafting the article; XG, LY and ZGZ participated in revising it critically for important intellectual content; All of the authors gave final approval of the version to be published.

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Availability of data and materials

No additional data is available.

Ethics approval and consent to participate

All analyses were based on previously published studies. Therefore, no ethical approval or patient consent were required.

Consent for publication

Not applicable.

Competing interests

There are no conflicts of interest of any authors in relation to the submission of this manuscript.

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Figures

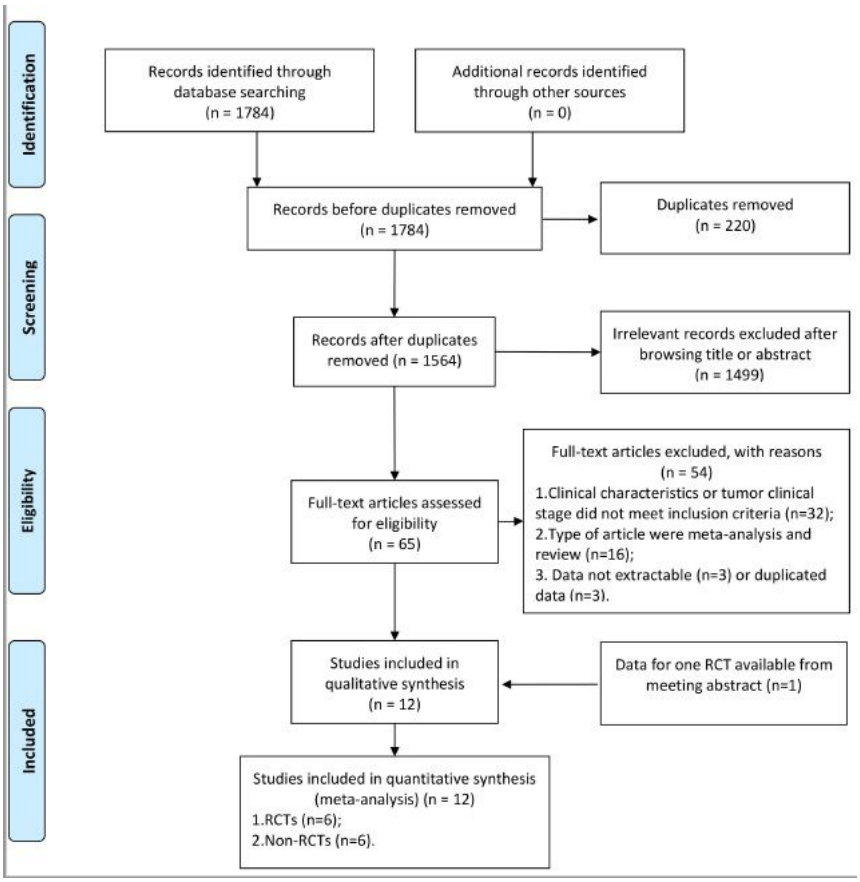

Figure 1

PRISMA flow chart.

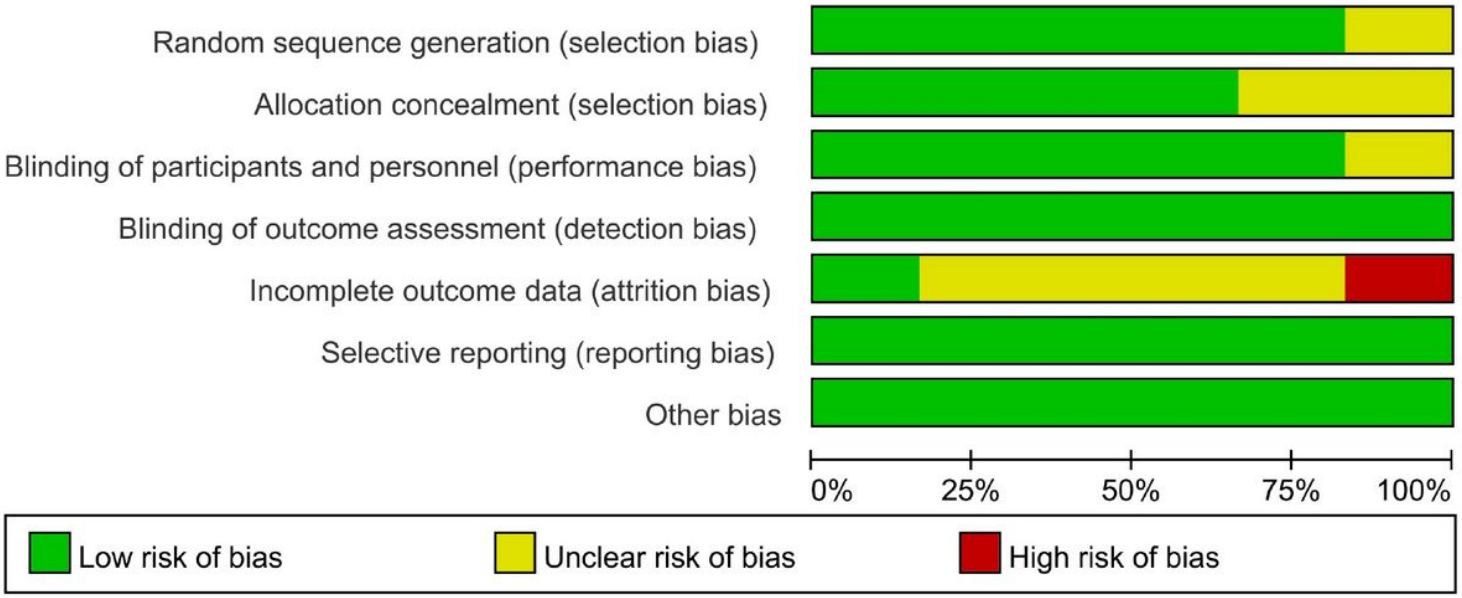

Figure 2

Risk of bias graph of RCTs: review authors' judgments about each risk of bias item presented as percentages across all included studies.

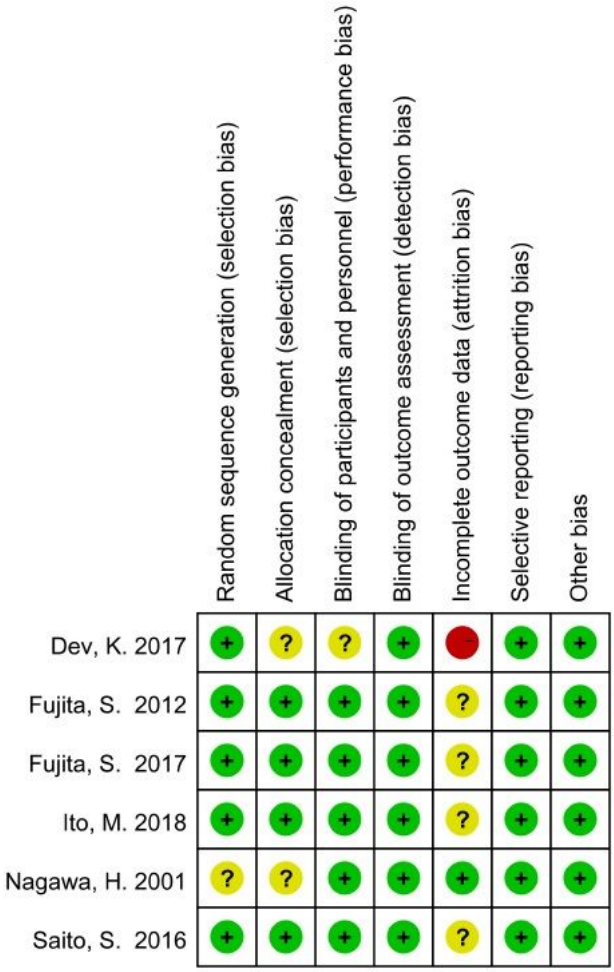

Figure 3

Risk of bias graph of RCTs: review authors' judgments about each risk of bias item presented as percentages across all included studies.

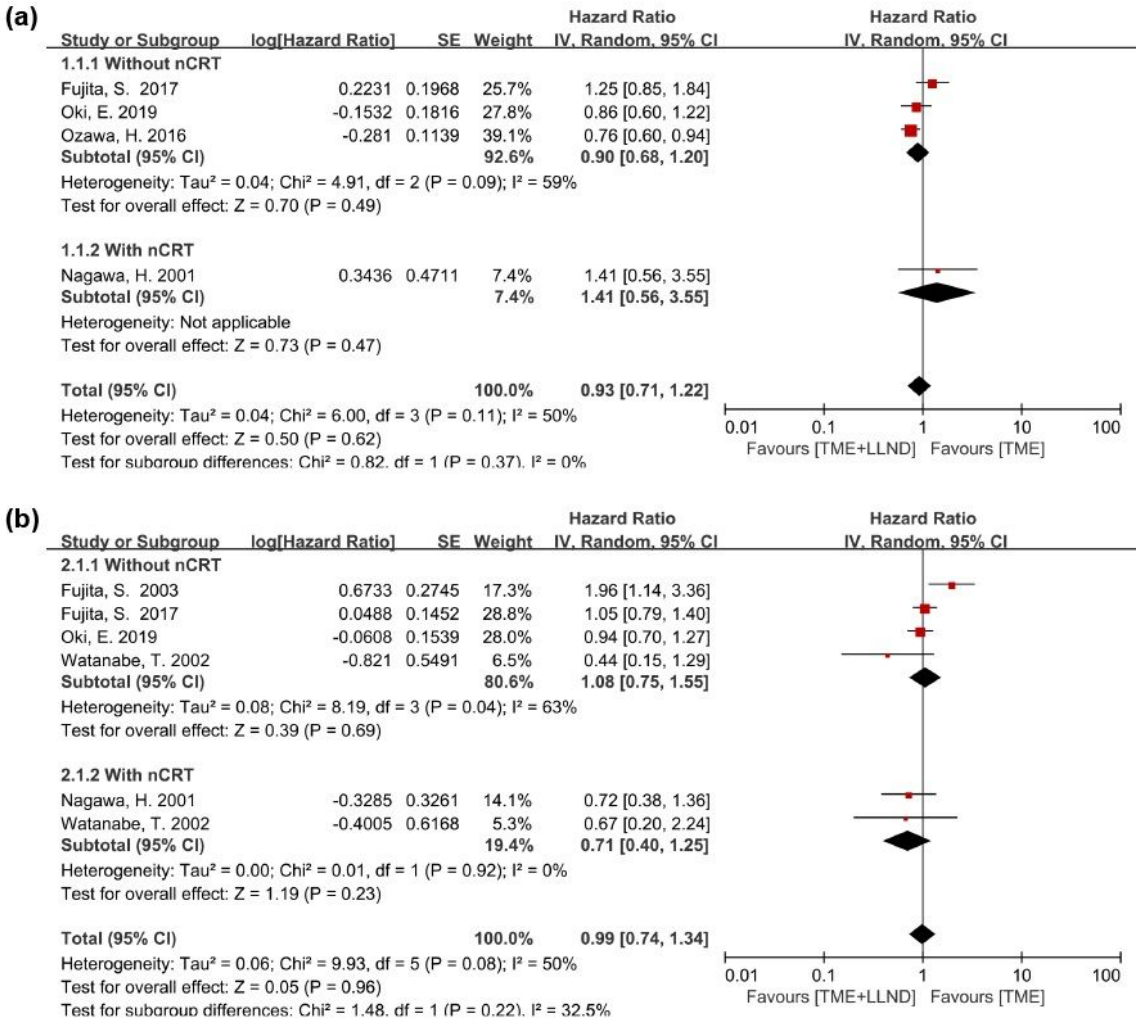

Figure 4

Total mesorectal excision and lateral lymph node dissection versus total mesorectal excision alone in 5-year overall survival (4a), and 5-year disease-free survival (4b); nCRT neoadjuvant chemoradiotherapy.

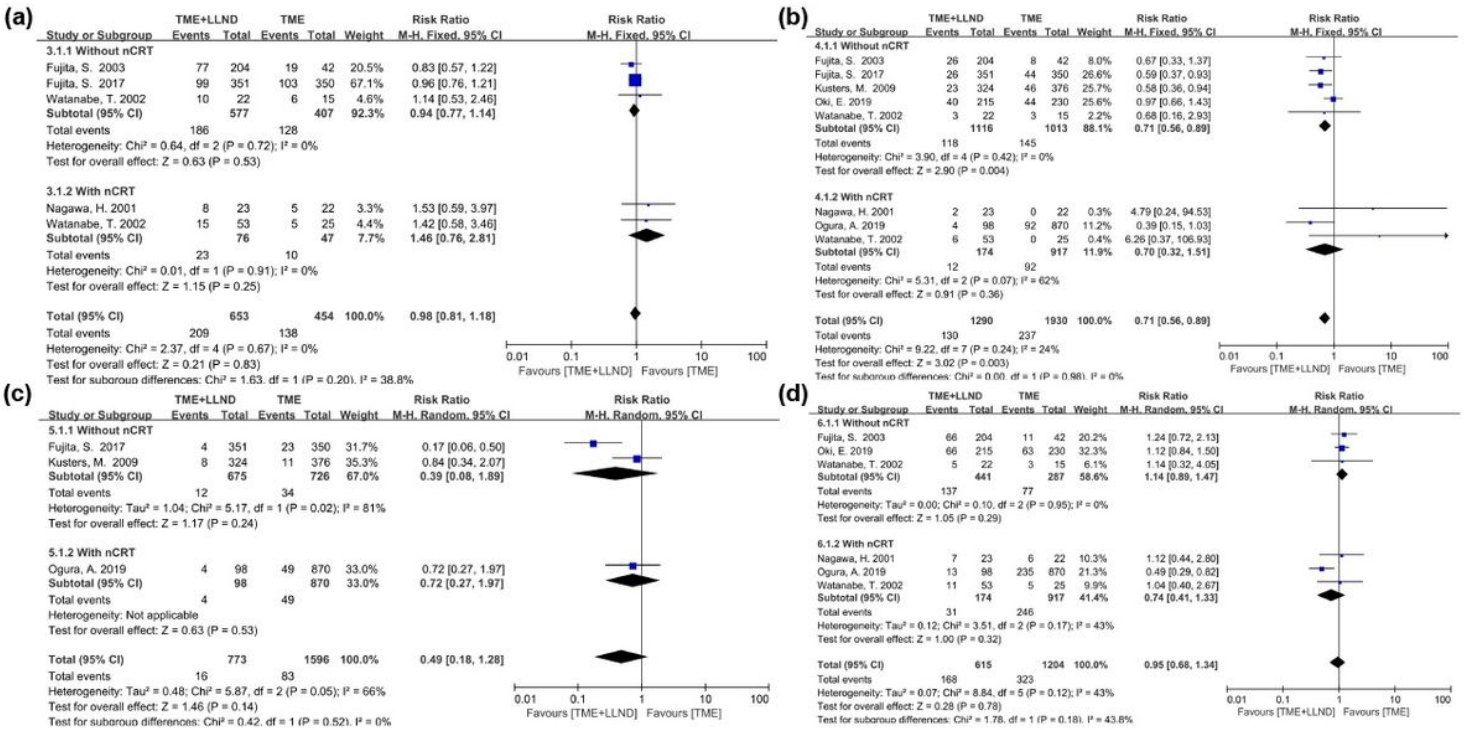

Figure 5

Total mesorectal excision and lateral lymph node dissection versus total mesorectal excision alone in 5-year total recurrence (5a), local recurrence (5b), lateral recurrence (5c), and distant recurrence (5d); nCRT neoadjuvant chemoradiotherapy.

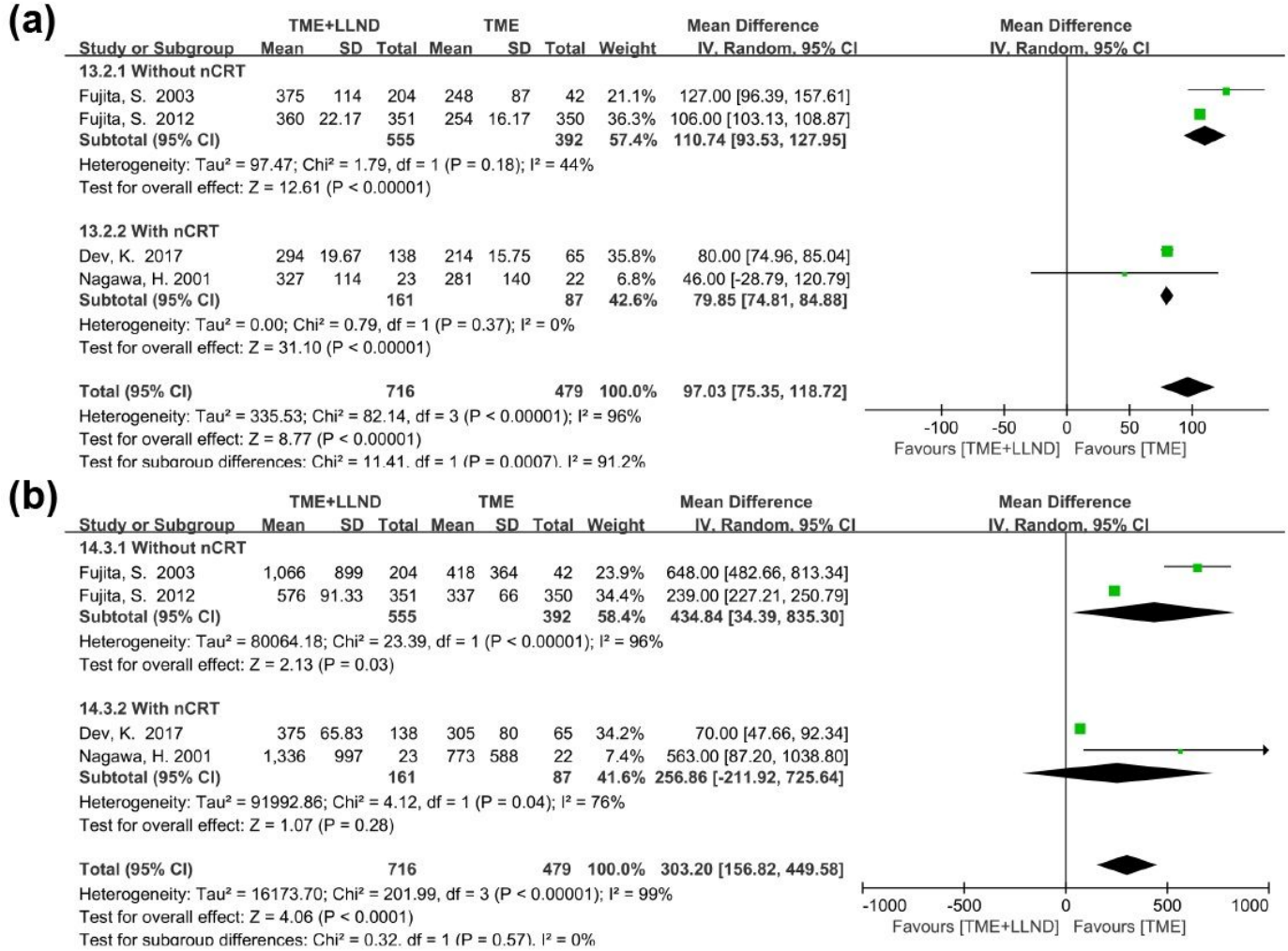

Figure 6

Total mesorectal excision and lateral lymph node dissection versus total mesorectal excision alone in operation time (6a), and intraoperative blood loss (6b); nCRT neoadjuvant chemoradiotherapy.

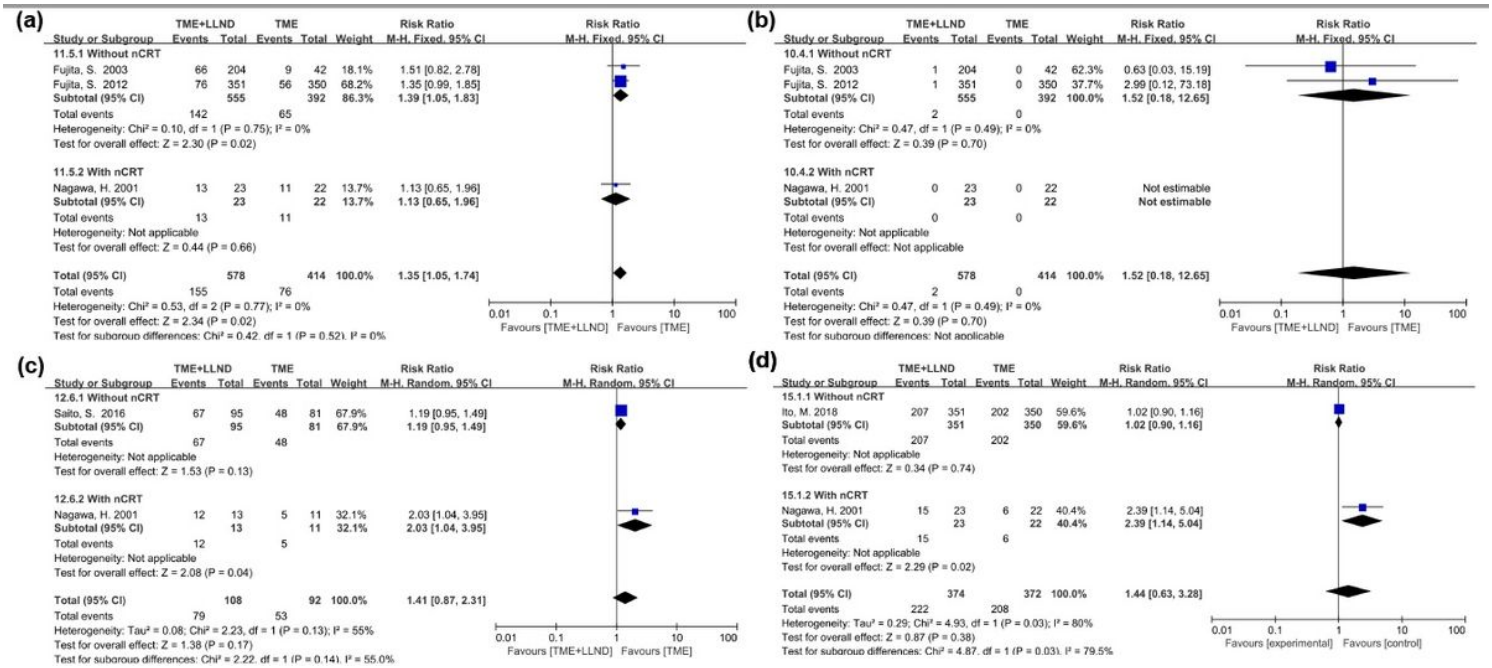

Figure 7

Total mesorectal excision and lateral lymph node dissection versus total mesorectal excision alone in postoperative complications (7a), peri-operative mortality (7b), postoperative sexual dysfunction (7c), and postoperative urinary dysfunction (7d); nCRT neoadjuvant chemoradiotherapy.