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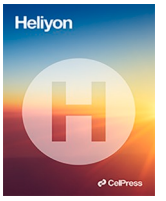

Research article

Comparison of local excision and total mesorectal excision for rectal cancer: Systematic review and meta-analysis of randomised controlled trial

Zan Meng [a], Zehong Liu [b,*]

[a] Department of Nursing, Leshan Vocational and Technical College, Leshan, 614000, China
[b] Department of Physiology, Chongqing Medical and Pharmaceutical College, Chongqing, 401331, China

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ABSTRACT

Objectives: To report the first and largest systematic review and meta-analysis of radomised controlled trials (RCTs) to compare the efficacy and safety of transanal endoscopic microsurgery (TEM) and total mesorectal excision (TME) for rectal cancer for perioperative and oncological outcomes. *Methods*: We conducted a systematic literature retrieval via PubMed, Embase, Web of Science, and Cochrane until December 2022 for RCTs which evaluated the efficacy and/or safety between TEM and TME for rectal cancer. Outcomes included operative time, blood loss, transfusion rates, hospital stay, complication rates, recurrence rates, and mortality. *Results*: A total of 5 RCTs involving 545 patients (272 TEM versus 273 TME) were included for the meta-analysis. There were no significant differences between the two groups for age, gender, and distance from lower border of tumor to anal verge. Meta-analysis found that the TEM group was significantly favorable than the TME group for blood loss (WMD: 172.01; 95 % CI: 212.78, −131.24; $P < 0.00001$), hospital stay (WMD: 2.58; 95 % CI: 3.01, −2.16; $P < 0.00001$), operative time (WMD: 81.86; 95 % CI: 87.51, −76.21; $P < 0.00001$) and transfusion rates (RR: 0.05; 95 % CI: 0.01, 0.38; $P = 0.004$). The complication rates (RR: 0.60; 95 % CI: 0.32, 1.11; $P = 0.10$), recurrence rates (RR: 1.10; 95 % CI: 0.66, 1.83; $P = 0.72$), and mortality (RR: 1.23; 95 % CI: 0.67, 2.26; $P = 0.51$) were similar in the two groups. *Conclusions*: TEM was an effective and safe approach with advantages in perioperative outcomes compared with TME approach. Caution should be exercised in interpreting the differences in surgical complications between TEM and TME group due to significant heterogeneity and instability.

1. Introduction

At present, the management of patients with stage I rectal cancer differs widely. In stage I rectal cancer without risk factors associated with recurrence or progression, local excision (LE) is effective. However, in T1 rectal cancer with several risk factors and T2 rectal cancer, the rate of lymph node invasion was 12 %–28 % [1]. Under the circumstances, radical surgery, mainly total mesorectal excision (TME), is the first-choice treatment for localized rectal cancer, with alternative application of pre-operative chemo-radiotherapy considered for patients with locally progressive tumors [2].

As reported by Heald and Ryall, the emergence of TME has changed the traditional treatment pattern of rectal cancer, which

* Corresponding author.
E-mail address: liuliuliu20160520@163.com (Z. Liu).

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reducing local relapse risk to 2 % and 11 % and systematic relapse risk to 25 % and 40 % [3,4]. Nevertheless, TME demands the establishment of a temporary or permanent ostomy, of which risk of mortality varies from 0.9 % to 1.5 % [5,6]. It is reported that between 30 % and 60 % of rectal cancer patients are affected by urogenital changes and low anterior resection syndrome secondary to TME [7,8]. In addition, long-term bowel, bladder, and sexual dysfunction following TME are observed in survivors of rectal cancer, which seriously reduces the quality of life [9–11].

Organ preservation technique, which was reported by HabrGama in 2004, is a new treatment for locally advanced rectal cancer [12]. Preserving the rectum was ground-breaking, particularly in patients with locally progressive rectal cancer, in which it could be related to a significant promotion in quality of life, mostly due to the disappearance of most postoperative complications associated with surgery, including a colostomy, genitourinary dysfunctions, or gastro intestinal disorders [13]. On the other hand, preserving the rectum was also an effective measure for cost saving of health systems, given the diagnosis of smaller tumors (good candidates of rectum preservation) is increasing. LE composed of transanal endoscopic microsurgery (TEM) techniques could preserve the rectum [14,15]. The morbidity and mortality rates of patients received TEM is 23 % and 0.3 %, respectively. Meanwhile, there is no urogenital change and lowest change of constrictor function during the procedure of TEM [16].

Although several clinical studies, especially radomised controlled trials (RCTs), have compared the efficacy of TEM and TME in the treatment of rectal cancer in recent years, it is still unclear which treatment pattern is the best choice for rectal cancer patients. Therefore, on this basis, we conducted the first and largest systematic review and meta-analysis of RCTs, aiming to evaluate the efficacy and safety of TEM and TME in the surgical management of rectal cancer for perioperative and oncological outcomes.

2. Methods

2.1. Literature search

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) 2020 statement [17] and has been prospectively registered in the PROSPERO (Registration ID: 443499). We conducted a systematic literature search via PubMed, Embase, Web of Science, and Cochrane up to December 2022 for RCTs that evaluated the efficacy and safety of local excision and TME for patients with rectal cancer. We searched the literature through the following terms: “rectal neoplasms”, “transanal endoscopic microsurgery”, “local excision”, and “total mesorectal excision”. The detailed search strategy is shown in Supplementary Table S1. Furthermore, we manually screened the bibliography lists of all included RCTs. Two authors retrieved and assessed eligible articles independently. Any differences in literature retrieval were resolved by discussion.

2.2. Inclusion and exclusion criteria

Articles were eligible when meeting the following standards: (1) study design was RCT; (2) studies were performed in patients with rectal cancer; (3) studies evaluated the efficacy and/or safety of local excision (TEM) and TME; (4) at least one primary outcome (complication, operative time, blood loss, transfusion, and hospital stay), or secondary outcome (recurrence and mortality) was evaluated; (5) complete data to analyze risk ratio (RR) and weighted mean difference (WMD). We excluded study protocols, unpublished studies, non-original studies (including letters, comments, abstracts, correction, and reply), non-RCT studies, studies without sufficient data, and reviews.

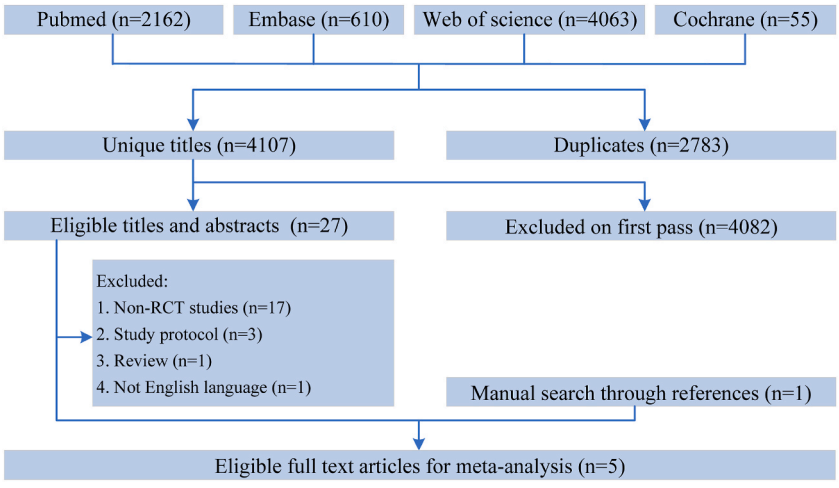

Fig. 1. Flowchart of the systematic search and selection process.

Table 1
Baseline characteristics of include RCTs.

Authors	Study period	Registration number	Country	TNM stage	Intervention	Control	Outcomes	Patients (n)	Mean follow-up
								TEM/ TME	
Serra-Aracil 2023	2010–2017	NCT01308190	Spain	cT2-cT3ab, N0	CRT (Long-term neoadjuvant chemotherapy was administered concomitantly with radiotherapy, in the form of capecitabine 825 mg/m^2 every 12 h orally on the days of radiotherapy. Radiotherapy was administered in daily fractions of 1.8 Gy 5 days a week in accordance with the standard schedule. The total dose was 45 Gy plus a boost of 5.4 Gy in the tumour area.) + TEM	TME	Local recurrence rate, adverse effects and surgical complications.	86/87	2 years
Bach 2021	2012–2014	ISRCTN14422743	UK	Staged T2 or lower, no lymph node involvement (ie, N0)	Short-course radiotherapy (25 Gy in five fractions was given over a period of 5–7 days with photon energies of at least 6 MV and a three or four field technique.) + TEM	TME	Tumor downstaging, organ preservation rate, stoma rates, tumor recurrence, disease-free survival, overall survival, HRQOL, adverse effects and surgical complications.	27/28	4.28 years
Rullier 2017	2007–2012	NCT00427375	France	Clinically staged T2 or T3, and N0-1 (none to three nodes ≤8 mm involved)	CRT (Radiotherapy consisted of 3D conformal pelvic radiotherapy delivering 50 Gy with high-energy (18 MV) photons in fractions of 2 Gy, 5 days a week over 5 weeks. Capecitabine 1600 mg/m^2 per day, 5 days per week, and oxaliplatine 50 mg/m^2 per week, were administered during radiotherapy.) + TEM	CRT (Radiotherapy consisted of 3D conformal pelvic radiotherapy delivering 50 Gy with high-energy (18 MV) photons in fractions of 2 Gy, 5 days a week over 5 weeks. Capecitabine 1600 mg/m^2 per day, 5 days per week, and oxaliplatine 50 mg/m^2 per week, were administered during radiotherapy.) + TME	Death, recurrence, major surgical morbidity, severe complications, disease-free and overall survival, clinical and pathological tumor response.	74/71	5 years
Lezoche 2012	1997–2004	NCT01609504	Italy	clinical (c) T2 N0 M0	CRT (Long-course three-dimensional four-field chemoradiotherapy in the prone position, with bladder preparation and use ofintravenous contrast. The total dose given was 50·4 Gy in 28 fractions over 5 weeks. A continuous infusion of 5fluorouracil 200 mg per m^2 per day was administered during radiotherapy treatment.) + TEM	CRT (Long-course three-dimensional four-field chemoradiotherapy in the prone position, with bladder preparation and use ofintravenous contrast. The total dose given was 50·4 Gy in 28 fractions over 5 weeks. A continuous infusion of 5fluorouracil 200 mg per m^2 per day was administered during radiotherapy treatment.) + TME	Local recurrence or distant metastases, cancer-related mortality, duration of operation, blood loss, analgesic use, morbidity, hospital stay and 30-day mortality.	50/52	5 years
Lezoche 2008	–	–	Italy	T2 N0 M0	CRT (The total dose administered was 50.4 Gy in 28 fractions over 5 weeks. The irradiated areas were the anus, rectum, mesorectum, and regional and iliac lymph-nodes. Continuous infusion of 5-flurouracil 200 mg/m^2/ day was performed during radiotherapy treatment.) + TEM	CRT (The total dose administered was 50.4 Gy in 28 fractions over 5 weeks. The irradiated areas were the anus, rectum, mesorectum, and regional and iliac lymph-nodes. Continuous infusion of 5-flurouracil 200 mg/m^2/ day was performed during radiotherapy treatment.) + TME	Local recurrence and distant metastases, morbidity, 30-day mortality, operative time, blood loss, analgesic use, and hospital stay.	35/35	5 years

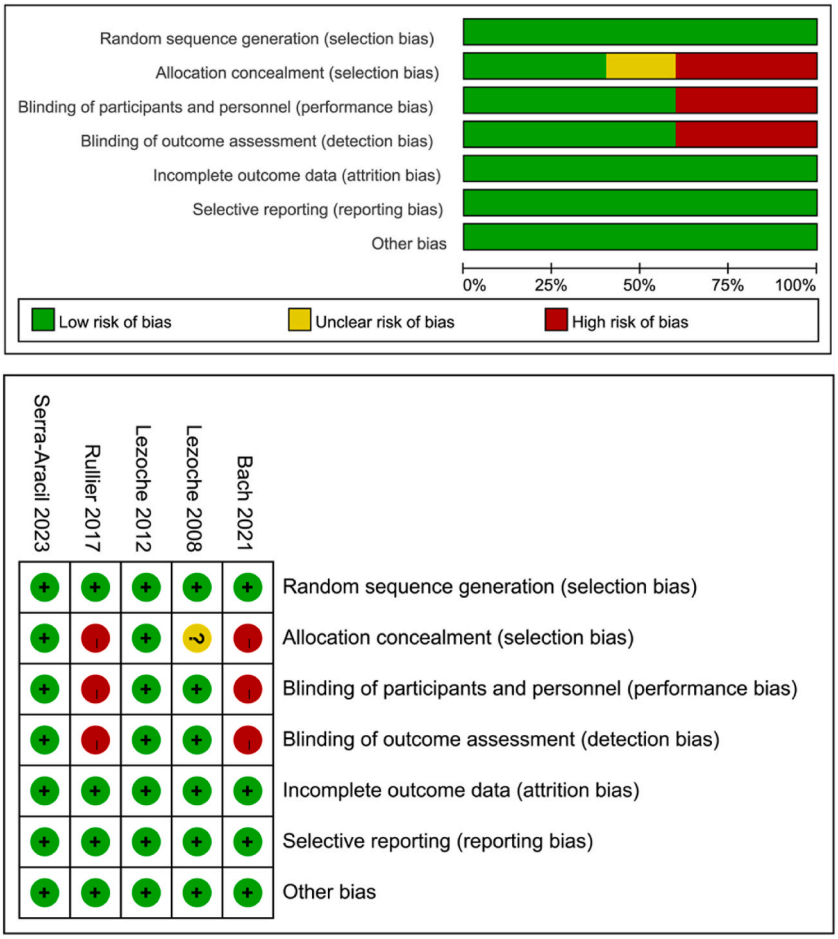

Fig. 2. Quality assessment of all eligible RCTs.

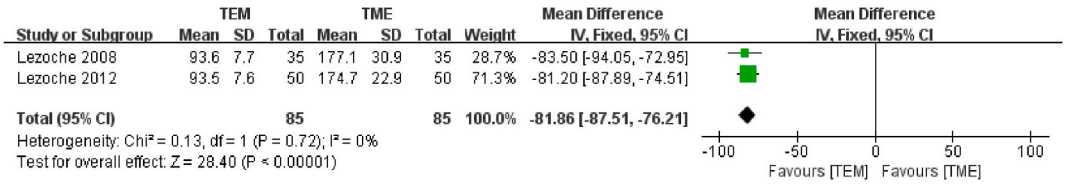

Fig. 3. Forest plots of operating time.

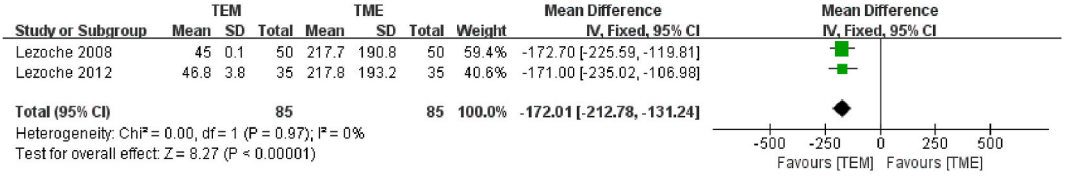

Fig. 4. Forest plots of blood loss.

2.3. Data abstraction

Data abstraction was conducted by two authors severally. Any differences were settled by another author. We abstracted following information from eligible RCTs: first author name, published year, research period, study region, study design, registration number,

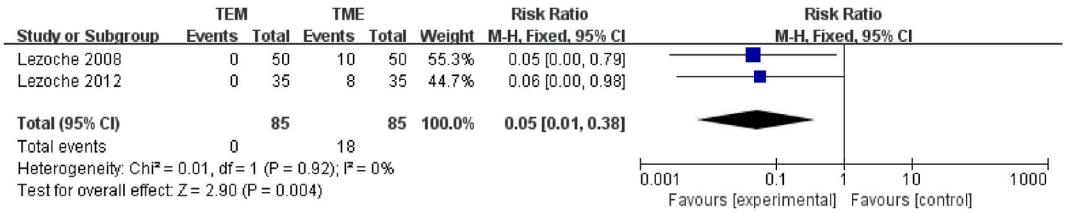

Fig. 5. Forest plots of transfusion rates.

sample size, age, gender, follow-up time, distance from lower border of tumor to anal verge, complication, operative time, blood loss, transfusion, and hospital stay, recurrence, and mortality. If the continuous data in the article was presented as median plus range or median plus interquartile range (IQR), we reanalysed the mean ± standard deviation (SD) via the methods reported by Wan et al. and Luo et al. [18,19]. If the research data is insufficient, corresponding authors were contacted for full data if available.

2.4. Quality assessment

The quality assessment of eligible RCTs was conducted following the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 based on seven terms: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias [20]. Three evaluation outcomes including low risk, high risk and unclear risk were assigned to every study aspect. Studies with more "low risk" bias evaluations were regarded as superior. Two authors severally assessed the quality of all included studies, and any disagreement was settled by discussion.

2.5. Statistical analysis

Meta-analysis was conducted in Review Manager 5.4.1 edition. For continuous data, the WMD or SMD was used for data synthesis, and the RR were used for the synthesis of dichotomous data. Each metric was presented with 95 % confidential intervals (CIs). The chi-squared (χ^2) test (Cochran's Q) and inconsistency index (I^2) were applied for the evaluation of the heterogeneity of each outcome [21]. χ^2 P value less than 0.1 or I^2 more than 50 % were regarded as high heterogeneity. The random-effects model was applied to calculate the total WMD, SMD or RR for outcomes with significant heterogeneity (χ^2 P value less than 0.1 or I^2 more than 50 %). Or else, the fixed-effects model was used. In addition, we performed subgroup analyses for efficacy outcomes with two or more included studies to evaluate the possible confounders, if data were sufficient. Besides, we conducted sensitivity analysis to assess the influence of every included RCT on the total WMD, SMD or RR for results with more than 2 included studies. Moreover, we assessed the potential publication bias by producing funnel plots through Review Manager 5.4.1 edition as well as through performing Egger's regression tests [22] through Stata 15.1 edition (Stata Corp, College Station, Texas, USA). P value < 0.05 was considered as statistically significant publication bias.

3. Results

3.1. Literature retrieval, study characteristics, and baseline

Fig. 1 shows the flowchart of the literature retrieval and selection process. A total of 6890 related studies in PubMed (n = 2162), Embase (n = 610), Web of Science (n = 4063), and Cochrane (n = 55) were identified via systematically literature search. After removing duplicate studies, a total of 4107 titles and abstracts were evaluated. Eventually, 5 RCTs including 545 patients (272 TEM versus 273 TME) were included for the meta-analysis [13,23–26]. Table 1 presents the characteristics of each eligible RCT. Details of the quality evaluation for all included RCTs are shown in Fig. 2. The two groups were comparable in age (WMD: 0.07; 95 % CI: 1.86, 2.01; $P = 0.94$), gender (male/total, RR:1.02; 95 % CI: 0.90, 1.15; $P = 0.80$), and distance from lower border of tumor to anal verge (WMD: 0.23; 95 % CI: 0.17, 0.63; $P = 0.26$). Due to the large differences in TNM stages of various studies, data synthesis was not conducted. However, TNM stages of TEM and TME groups were comparable in all studies ($P > 0.05$).

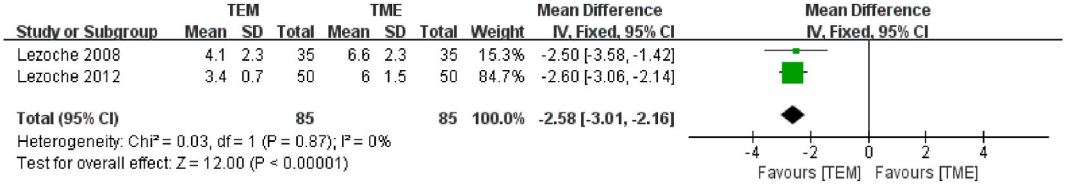

Fig. 6. Forest plots of hospital stay.

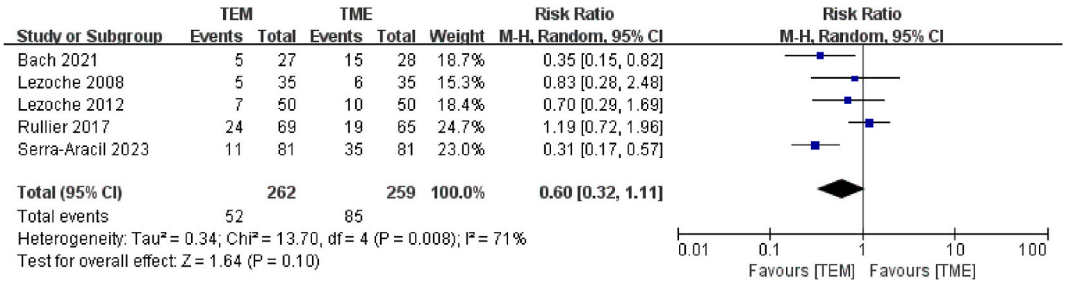

Fig. 7. Forest plots of complication rates.

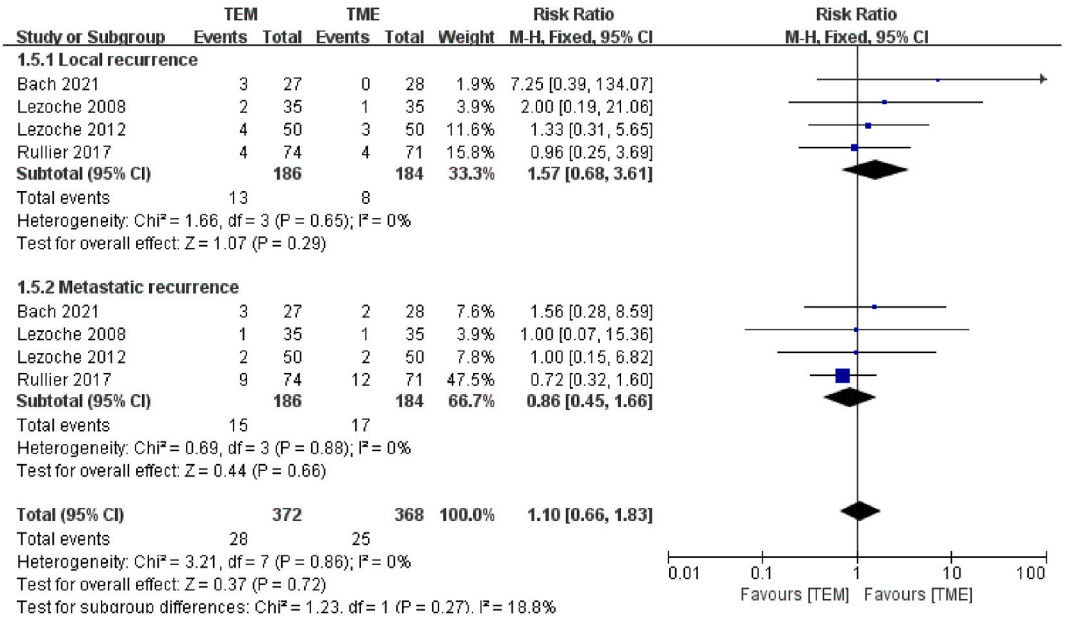

Fig. 8. Forest plots of recurrence rates.

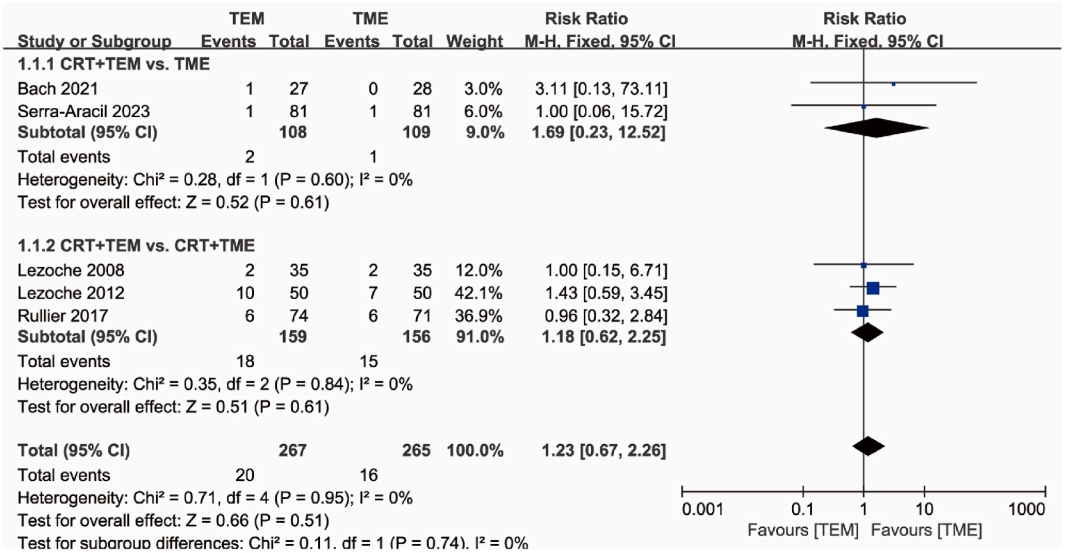

Fig. 9. Forest plots of mortality.

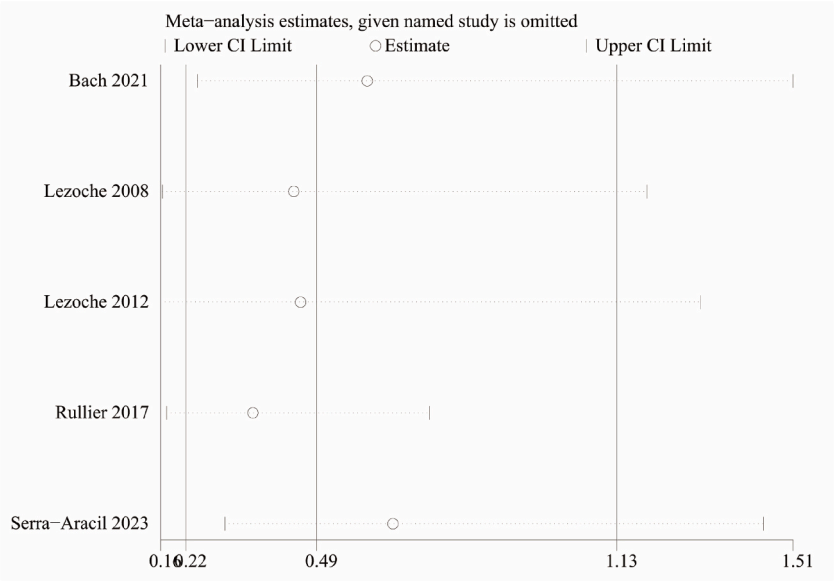

Fig. 10. Sensitivity analysis of complication.

3.2. Meta-analyses of primary outcomes

3.2.1. Operative time

Meta-analysis of operative time was conducted from 2 articles including 170 patients (85 TEM versus 85 TME) [25,26]. Evidence synthesis found a significant shorter operative time in TEM group (WMD: 81.86; 95 % CI: 87.51, −76.21; $P < 0.00001$) without significant heterogeneity ($I^2 = 0$ %, $P = 0.72$) (Fig. 3).

3.2.2. Blood loss

Meta-analysis of blood loss was performed in 2 studies with 170 patients (85 TEM versus 85 TME) [25,26]. Evidence synthesis revealed a significant lower blood loss in TEM group (WMD: 172.01; 95 % CI: 212.78, −131.24; $P < 0.00001$) without significant heterogeneity ($I^2 = 0$ %, $P = 0.97$) (Fig. 4).

3.2.3. Transfusion

There were 2 RCTs which had the data of transfusion of the two groups, including 170 patients (85 TEM versus 85 TME) [25,26]. Meta-analysis observed a significant lower transfusion rate in TEM group (RR: 0.05; 95 % CI: 0.01, 0.38; $P = 0.004$) without significant heterogeneity ($I^2 = 0$ %, $P = 0.92$) (Fig. 5).

3.2.4. Hospital stay

Two RCTs reported the data of hospital stay, including 170 patients (85 TEM versus 85 TME) [25,26]. Meta-analysis found a significant shorter hospital stay in TEM group (WMD: 2.58; 95 % CI: 3.01, −2.16; $P < 0.00001$) without significant heterogeneity ($I^2 = 0$ %, $P = 0.87$) (Fig. 6).

3.2.5. Complication

Results of complications were conducted from 5 RCTs with a total of 521 patients (262 TEM versus 259 TME) [13,23–26]. No significant difference was detected among the two groups in terms of complication rates (RR: 0.60; 95 % CI: 0.32, 1.11; P = 0.10), but statistically significant heterogeneity was observed ($I^2 = 71$ %, $P = 0.008$) (Fig. 7).

3.3. Meta-analyses of secondary outcomes

3.3.1. Recurrence

Data of recurrence (including local recurrence and metastatic recurrence) were extracted from 4 RCTs with 370 patients (186 TEM versus 184 TME) [13,24–26]. No significant difference was detected between the two groups for total recurrence rates (RR: 1.10; 95 % CI: 0.66, 1.83; $P = 0.72$), and no significant heterogeneity ($I^2 = 0$ %, $P = 0.86$) was detected (Fig. 8). Subgroup analysis found that both local recurrence (RR: 1.57; 95 % CI: 0.68, 3.61; $P = 0.29$) and metastatic recurrence (RR: 0.86; 95 % CI: 0.45, 1.66; $P = 0.66$) were comparable between the two groups without significant heterogeneity (local recurrence: $I^2 = 0$ %, $P = 0.65$; metastatic recurrence: $I^2 = 0$ %, $P = 0.88$; subgroup: $I^2 = 18.8$ %) (Fig. 8).

3.3.2. Mortality

Five RCTs were included in the meta-analysis for mortality, involving 532 patients (267 TEM versus 265 TME) [13,23–26]. Evidence synthesis showed that mortality was comparable between the two groups (RR: 1.23; 95 % CI: 0.67, 2.26; $P = 0.51$) without significant heterogeneity ($I^2 = 0$ %, $P = 0.95$) (Fig. 9). Subgroup analysis based on the treatment of control group (CRT + TME or TME alone) found that both CRT + TME (RR: 1.18; 95 % CI: 0.62, 2.25; $P = 0.61$) and TME alone (RR: 1.69; 95 % CI: 0.23, 12.52; $P = 0.61$) were comparable between the two groups without significant heterogeneity (CRT + TME: $I^2 = 0$ %, $P = 0.84$; TME alone: $I^2 = 0$ %, $P = 0.60$; subgroup: $I^2 = 0$ %) (Fig. 9).

3.4. Sensitivity analysis

We performed sensitivity analysis for the results of absolute change of body weight and adverse events to assess the effect of each RCT on the total WMD or RR via excluding eligible RCTs one by one. Sensitivity analyses observed that when the data reported by Rullier et al., in 2017 [13] was excluded, the new combined RR revealed a lower complication rates in the TEM group (RR: 0.45; 95 % CI: 0.28, 0.72; $P = 0.0008$) (Fig. 10). Meanwhile, the heterogeneity for the complication disappeared ($I^2 = 22$ %, $P = 0.28$), when we excluded this RCT, suggesting that this paper may be the main cause of the significant heterogeneity in the complication.

4. Discussion

The favorable oncological outcomes finished by TME in stage pT2-3ab,N0,M0 rectal cancer are commonly accompanied by the increased risk of perioperative complications and impairment for quality of life [7]. In the situation, several management ways have been proposed to attempt to save the rectum and meanwhile keeping the similar improvement of overall and disease-free survival recently [23,24]. Thereinto, preoperative chemoradiotherapy (CRT) followed by LE (TEM) have observed the best efficacy in several RCTs [23–26]. The TREC, a randomized, multi-center open-label, feasibility phase II clinical trial found that short-course preoperative radiotherapy combined with TEM could significantly increase the organ preservation rate, with comparatively decreased morbidity and improved quality of life compared with TME [24]. The TAU-TEM, a prospective, multicentre, randomised controlled non-inferiority trial including 173 patients diagnosed with T2-T3ab,N0,M0 rectal cancer, revealed that preoperative CRT followed by TEM obtains high pathological complete response rates (44.3 %) and a high CRT compliance rate (98.8 %). Postoperative complications and hospitalisation rates of patients in the TEM group were significantly lower than those in the TME group [23]. However, it is worth noting that several RCTs found no significant difference in either survival (overall or disease-free) or recurrence between patients received TEM and those received TME [13,23–26], which is in line with our findings.

As for perioperative outcomes, our meta-analysis found that the TEM group was significantly favorable than the TME group in terms of blood loss, hospital stay, operative time and transfusion rates. This finding may be largely due to differences in procedure and difficulty between the two types of surgical approach. On the other hand, no significant difference was observed between the two groups for complication rates in this meta-analysis (RR: 0.60; 95 % CI: 0.32, 1.11; P = 0.10), while statistically significant heterogeneity was detected ($I^2 = 71$ %, P = 0.008). For this reason, we performed one-way sensitivity analysis for the complication and observed that when the data reported by Rullier et al., in 2017 [13] was excluded, the new combined RR revealed a lower complication rates in the TEM group (RR: 0.45; 95 % CI: 0.28, 0.72; $P = 0.0008$). Meanwhile, the heterogeneity for the complication disappeared ($I^2 = 22$ %, $P = 0.28$), when we excluded this RCT, suggesting that this paper may be the main cause of the significant heterogeneity. In fact, the types of complications associated with TEM seems to be less severe than that related to TME, although they were regarded as a major morbidity according to Dindo's classification [13]. Given the significant heterogeneity and instability, caution should be exercised in interpreting the differences in surgical complications between TEM and TME.

In terms of oncological outcomes, our meta-analysis did not observe significant differences in survival and recurrence rates between the two groups. Subgroup analysis found that both local recurrence and metastatic recurrence were comparable between the two groups without significant heterogeneity. However, it is notable that the confidence intervals for risk ratios in several RCTs were very wide, reflecting the small sample size and relatively small number of events in these studies. Therefore, RCTs with larger sample sizes are needed to confirm whether there is a difference in oncological outcomes between TEM and TME when treating for rectal cancer.

We presented the first meta-analysis of RCTs to evaluate the efficacy and safety of TEM and TME for patients with rectal cancer. Nevertheless, we this meta-analysis still has several limitations. First, most of the included studies were small sample size RCTs, where the potential selection bias cannot be ignored. Besides, significant heterogeneity and instability were observed in complication. Due to the underlying confounding factors, findings of the complication should be explained with caution. Lastly, due to insufficient data in the original study, we could not analyze the differences between the two groups in patient co-morbidities, radiation protocols, post radiation interval before surgery, surgery specimen tumor downstaging and R0, duration of follow-up, anal function and quality of life. Notwithstanding several limitations of our study, our meta-analysis supported studies published previously which reported the advantage of the TEM technique in rectal cancer [23–26], particularly in patients need preservation of rectum for higher quality of life after surgery. More large-scale, multi-center, double-blind RCTs are needed to further compare the superiority in perioperative, oncological outcomes and long-term postoperative quality of life in these two surgical approaches for rectal cancer.

5. Conclusion

TEM was an effective and safe technique with superiority in blood loss, hospital stay, operative time and transfusion rates compared with TME approach for rectal cancer, although we did not observe a significant difference in oncological outcomes between the two

groups. Given the significant heterogeneity and instability, caution should be exercised in interpreting the differences in surgical complications between TEM and TME.

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Chongqing Education Science Commission (grant No. KJQN202202823) and Chongqing Medical College Research Project (grant No. ygz2021122). Academic level project of Leshan Vocational and Technical College (grant No. KY2022039).

Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

CRediT authorship contribution statement

Zan Meng: Project administration, Methodology, Investigation, Data curation. **Zehong Liu:** Resources, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30027.

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