

Preservation versus non-preservation of left colic artery in colorectal cancer surgery

An updated systematic review and meta-analysis

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Abstract

Background: It remains unclear whether or not preservation of the left colic artery (LCA) for colorectal cancer surgery. The objective of this updated systematic review and meta-analysis is to evaluate the current scientific evidence of LCA non-preservation versus LCA preservation in colorectal cancer surgery.

Methods: A systematic search was conducted in the Medline, Embase, PubMed, Cochrane Library, ClinicalTrials, Web of Science, China National Knowledge Infrastructure and Chinese BioMedical Literature Database, and reference without limits. Quality of studies was evaluated by using the Newcastle–Ottawa scale and the Cochrane Collaboration’s tool for assessing the risk of bias. Effective sizes were pooled under a random- or fixed-effects model. The funnel plot was used to assess the publication bias. The outcomes of interest were oncologic consideration including the number of apical lymph nodes, overall recurrence, 5-years overall survival, and 5-years disease-free survival (DFS); safety consideration including overall 30-day postoperative morbidity and overall 30-day postoperative mortality; anatomic consideration including anastomotic circulation, anastomotic leakage, urogenital, and defaecatory dysfunction.

Results: Twenty-four studies including 4 randomized controlled trials (RCTs) and 20 cohort studies with a total of 8456 patients (4058 patients underwent LCA non-preservation surgery vs 4398 patients underwent LCA preservation surgery) were enrolled in this meta-analysis. The preservation of LCA was associated with significantly less anastomotic leakage (odds ratio 1.23, 95% confidence interval 1.02–1.48, $P = .03$). In term of sexual dysfunction, urinary retention, the number of apical lymph nodes, and long-term oncologic outcomes, there were no significant differences between the LCA non-preservation and LCA preservation group. It was hard to draw definitive conclusions on other outcomes including operation time, blood loss, the first postoperative exhaust time, and perioperative morbidity and mortality for insufficient data and highly significant heterogeneity among studies.

Conclusions: The pooled data provided evidence to support the LCA preservation preferred over LCA non-preservation in anastomotic leakage. Future more large-volume, well-designed RCTs with extensive follow-up are needed to draw a definitive conclusion on this dilemma.

Abbreviations: BFR = the blood flow ratios, DFS = disease-free survival, I^2 = I square statistic, IMA = inferior mesenteric artery, LCA = left colic artery, MD = weighted mean differences, OR = the odds ratios, OS = overall survival, PRISMA = the Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCT = randomized controlled trial.

Keywords: colorectal cancer, high tie, inferior mesenteric artery, left colic artery, low tie, meta-analysis, preservation

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1. Introduction

Currently, there remains controversy on the management of left colic artery (LCA) in colorectal cancer resection: non-preservation of LCA (high ligation of inferior mesenteric artery [IMA] ligated at the aortic origin) or preservation of LCA (low ligation of IMA, IMA ligated below the origin of LCA). Most surgeons consider non-preservation of LCA as the IMA ligation 2 cm from the aortic origin.^[1] The LCA non-preservation has the advantage of lower anastomosis traction, more lymphatic clearance, oncological benefits, and the disadvantage of the risk of poor blood supply of the anastomosis and autonomic nerve damage around the origin of the IMA.^[2] When it comes to the concept “LCA preservation”, however, people have different views and understanding. In studies concerning the preservation of LCA, Miles stated that the IMA would be ligated at the point half an inch below the origin of the first sigmoidal branch to preserve the LCA.^[3] Dixon described an atypical low ligation on the superior haemorrhoidal artery distally from the sigmoid arteries origin.^[4] This LCA preservation technique of Miles and Dixon description

was not associated with the lymph nodes dissection round the root of IMA (apical lymph nodes dissection). Nowadays, however, most surgeons consider the LCA preservation technique as follows: apical lymph nodes dissection, preservation of LCA, ligation the IMA distally to the LCA.^[2] This LCA preservation has the advantage of better autonomic nerves protection, good blood supply of the anastomosis especially for patients with extensive arterial diseases and the disadvantage of lesser number of lymph nodes for accuracy of tumor staging.^[2,5]

There already had systematic review and meta-analysis to compare LCA non-preservation and LCA preservation technique. A recent meta-analysis conducted by Singh et al showed that LCA non-preservation had better survival benefits for the patients with IMA positive lymph nodes.^[6] In this meta-analysis, however, the identified primary studies included LCA preservation with or without apical lymph nodes dissection and it may be caused heterogeneity. Yang et al did not perform a comprehensive meta-analysis on this topic.^[7] Although Guraya, Titu et al, Langeet al, and Hida and Okuno performed a systematic review to compare these 2 techniques, there is no quantitative analysis.^[8–11] Additionally, Cirocchi et al and Chen et al also performed a meta-analysis to identify the role of the preservation of LCA in sigmoid and rectal cancer, while it needs to be updated.^[5,12]

On the other hand, nowadays, laparoscopy is widely accepted in colorectal surgery, it seems harder to achieve LCA preservation under laparoscopy and encouraged more frequent execution of LCA non-preservation. Therefore, it is necessary to make an update systematic review and meta-analysis to comprehensively appraise the real advantages of LCA non-preservation and LCA preservation with apical lymph nodes dissection.

2. Methods

This systemic review and meta-analysis were performed following the Cochrane Handbook for Systematic Reviews of Interventions 5.2.0 (updated February 2017) to ensure data quality.^[13] All aspects of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement were followed.^[14]

2.1. Information sources and search strategy

A systemic search was performed in Medline, Embase, PubMed, Cochrane Library, ClinicalTrials, Web of Science, China National Knowledge Infrastructure, and Chinese BioMedical Literature Database for any potentially relevant study comparing the LCA non-preservation versus LCA preservation in colorectal cancer without restriction to regions, publication types, or languages. To minimize retrieval bias, hand searching method was also used to identify appropriate studies from reference lists and key journals and abstracts from the major annual meetings in the field of colorectal cancer.

Combinations of the following Medical Subject Headings (MeSH) and non-MeSH terms were used: “rectal,” “rectum,” “colon,” “colorectal;” “cancer,” “carcinoma,” “tumour,” “tumor,” “neoplasms;” “left colic artery,” “mesenteric artery, inferior,” “inferior mesenteric artery,” “superior rectal artery;” “left colic artery preservation or non-preservation,” “high ligation or high tie,” “low ligation or low tie.” In addition, the following terms were also used: lymph node, circulation,

flow, stump pressure, function, autonomous, nerve, and tension. The publication time window was from 1950 to 2017.

2.2. Criteria for including studies for this review

Studies were considered for this systemic review if they concerned randomized controlled trials (RCTs) or cohort studies (prospective/retrospective), which evaluated the LCA non-preservation versus LCA preservation for left colon or rectal cancer resection. Studies were excluded if any of the following factors were identified:

- (1) case report, letter, reply, comment, conference proceeding, and review article;
- (2) benign lesion or inflammatory disease;
- (3) animal trial;
- (4) cadaveric study;
- (5) insufficient information concerning the outcomes of interest or it was impossible to extrapolate them from the published results;
- (6) single arm study;
- (7) full-text not available.

The following outcomes of interest were observed:

- (1) oncologic consideration including the number of apical lymph nodes dissection, overall recurrence, 5-years overall survival, and 5-years DFS;
- (2) safety consideration including overall 30-day postoperative morbidity and overall 30-day postoperative mortality;
- (3) anatomic consideration including anastomotic circulation, anastomotic leakage, bowel, and urogenital dysfunction.

2.3. Study selection

The main search and the evaluation of titles, abstracts and full-text articles of all identified studies were completed independently by 2 investigators (YYY and XBZ). All irrelevant studies were excluded. Any discrepancy was solved by discussion or consultation of the corresponding author (ZQW).

2.4. Data collection process

Two reviewers (YYY and PFM) independently extracted data from all eligible studies. Any disagreement was solved through discussion or consulting the corresponding author (ZQW). The following information was extracted: first author, publication year, country, study design, surgical procedure, tumor location, number of patients in each arm, and outcomes of interest. For studies with insufficient information, when possible, the reviewers contacted the primary author to acquire and verify the data.

2.5. Quality assessment

The methodological quality of the enrolled cohort studies was assessed by the modified Newcastle–Ottawa Scale, which consists of 3 factors: selection, comparability, and outcome assessment.^[15,16] A score of 0 to 9 (allocated as stars) was allocated to each study. Studies achieved 7 or more stars were considered to be of high quality. The methodological quality of RCTs was assessed by the Cochrane Collaboration’s tool for assessing the risk of bias, which consists of 7 domains: random sequence generation, allocation concealment, blinding of participants and

personnel, blinding of outcome assessment, attrition bias, reporting bias, and other bias.^[13] Each domain can be rated as “yes” (low risk of bias), “no” (high risk of bias), “unclear” (unclear risk).

3. Statistical analysis

According to the recommendations from the PRISMA statement and the Cochrane Handbook for systematic reviews, 2 reviewers (XYY and PFM) performed the statistical analysis. Statistical analysis was performed using Review Manager (Version 5.3) (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

The Mantel–Haenszel method (fixed or random model) combined with the odds ratios (OR) was used to analyze the dichotomous data. Continuous outcomes measured on the same scale were expressed as a mean value and standard deviation and were analyzed by using weighted mean differences (MD). When study only reported the median, range, and the size of the trial, the mean and the standard deviation could be estimated referring to the formulas reported by Hozo et al.^[17] In order to estimate survival outcomes, data would be extracted from the survival curve by previous recommended method and hazard ratio (HR) was used for the quantitative analysis.^[18] The χ^2 test with *I* square statistic (I^2) was used to assess the heterogeneity across studies, with I^2 values of 0%, 25%, 50%, and 75% representing no, low, moderate, and high heterogeneity, respectively. *P* value < .05 was considered statistically significant. If severe heterogeneity was present at $I^2 > 50\%$, the

following strategies were used to quantitatively assess heterogeneity. First, data were reanalyzed by using random effect models. Second, subgroup analyses were performed according to the type of study design (RCTs or cohort studies). Moreover, a sensitivity analysis was undertaken by the following subgroups:

- (1) by deleting each study individually to evaluate the quality and consistency of the pooled results;
- (2) high-quality studies with 7 or more stars;
- (3) studies published in or after 2000;
- (4) studies containing more than 20 patients in each group.

If there still existed highly significant heterogeneity after subgroup analysis, we would carry out a narrative review rather than a meta-analysis. Publication bias was assessed by visual inspection of the funnel plot.

4. Results

A flowchart of the literature screening, exclusion, and inclusion process was shown in Figure 1. A total of 1032 studies were obtained according to the initial search algorithm. After removing duplicates, 619 studies remained. After reviewing the titles and abstracts, 107 studies were further evaluated. Among these studies, 83 studies were excluded for the following reasons: 3 cadaver studies; 1 study included benign disease; 15 studies just reported 1 surgical regimen; 49 studies were reviews, letters, conference proceedings, editorials, or technical materials; 15 studies were lack of full text. Finally, 24 studies including

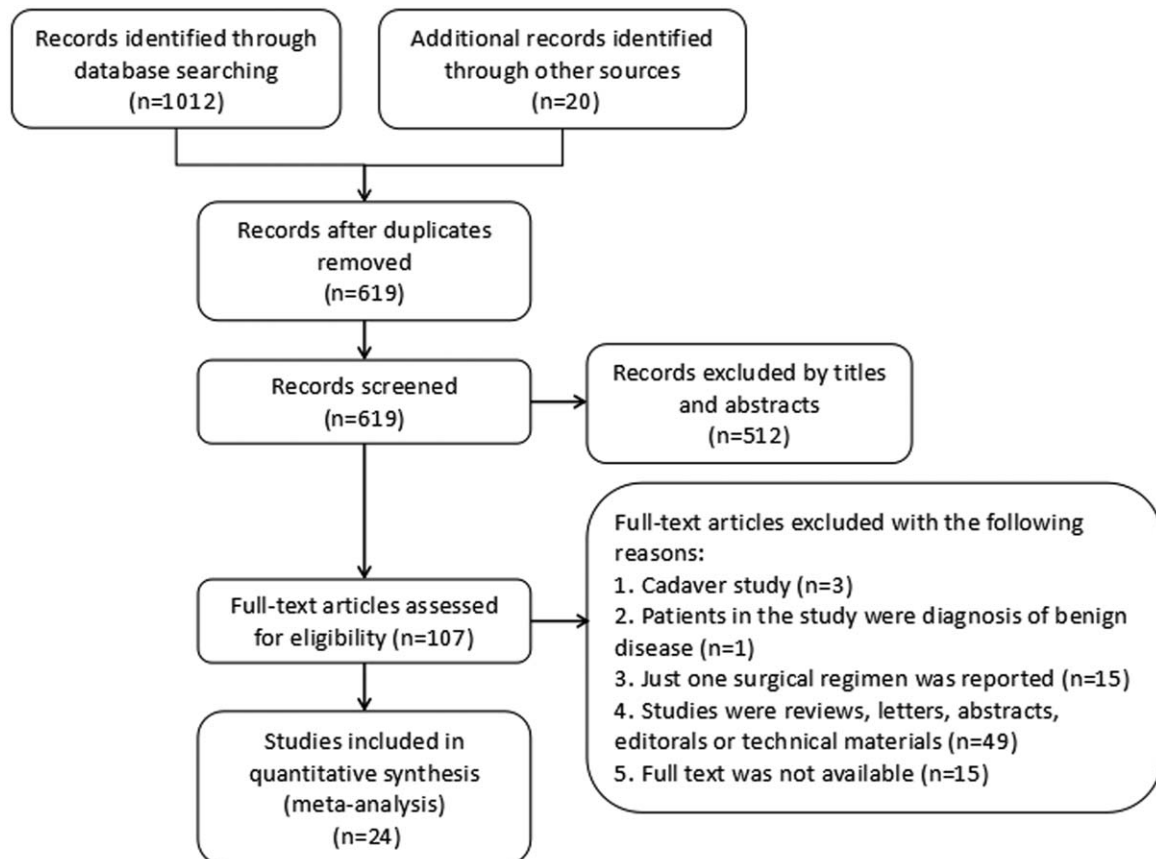


Figure 1. The flowchart of the literature screening, exclusion and inclusion process.

Table 1

The basic characteristics of studies included in the meta-analysis.

First author, yr	Years of the study	Country	Type of study	Surgical treatment of LCA (n)		Tumor location	Procedure	Quality assessment (NOS score)
				LCA non-preservation	LCA preservation			
Bostrom, ^[19] 2015	Between 2007 and 2010	Sweden	Retrospective cohort	334	388	Rectum	Laparoscopy or open	★★★★★★
Charan, ^[20] 2014	Between 2007 and 2008	India	Prospective cohort	44	16	Left colon and rectum	–	★★★★★★
Corder, ^[21] 1992	Between 1982 and 1992	United Kingdom	Retrospective cohort	91	52	Rectum	Open	★★★★★
Guo, ^[22] 2017	Between 2013 and 2013	China	RCT	29	28	Rectum	Laparoscopy	–
Hall, ^[23] 1995	Between 1994 and 1994	United Kingdom	Prospective cohort	30	32	Left colon	Open	★★★★★
Han, ^[24] 2013	Between 2007 and 2008	China	Retrospective cohort	76	80	Rectum	–	★★★★★★★
Hinoi, ^[25] 2013	Between 1994 and 2006	Japan	Retrospective cohort	256	155	Rectum	Laparoscopy or open	★★★★★★★
Komen, ^[26] 2011	Between 2011 and 2011	Netherlands	Prospective cohort	16	17	Rectum	Open	★★★★★★
Kverneng Hultberg, ^[27] 2017	Between 2011 and 2012	Sweden	Retrospective cohort	373	432	Rectum	Laparoscopy or open	★★★★★
Lee, ^[28] 2018	Between 2008 and 2013	Korea	Retrospective cohort	51	83	Sigmoid or rectosigmoid colon	laparoscopy	★★★★★★★
Luo, ^[29] 2017	Between 2015 and 2016	China	Retrospective cohort	320	203	Rectum	Laparoscopy	★★★★★★
Matsuda, ^[30] 2015	Between 2008 and 2011	Japan	RCT	51	49	Rectum	Laparoscopy or open	–
Matsuda, ^[31] 2017	Between 2008 and 2011	Japan	RCT	51	49	Rectum	Laparoscopy or open	–
Pezim, ^[32] 1984	Between 1953 and 1972	Canada	Retrospective cohort	586	784	The rectum or rectosigmoid colon	–	★★★★★★★
Rutegard, ^[33] 2012	Between 2007 and 2009	Sweden	Retrospective cohort	818	1101	Rectum	Laparoscopy or open	★★★★★★
Rutegard, ^[34] 2016	Between 2012 and 2013	Sweden	Prospective cohort	5	18	Rectum	Open	★★★★★★★
Shen, ^[35] 2014	Between 2009 and 2012	China	Retrospective cohort	41	72	Rectum	Laparoscopy	★★★★★★
Shen, ^[36] 2017	Between 2007 and 2011	China	Retrospective cohort	154	168	Rectum	Laparoscopy	★★★★★★★
Surtees, ^[37] 1990	Between 1948 and 1983	United Kingdom	Retrospective cohort	150	100	Rectosigmoid and rectum	–	★★★★★★★
Tsujinaka, ^[38] 2012	Between 2004 and 2009	Japan	Retrospective cohort	302	107	Sigmoid colon and rectum	Laparoscopy or open	★★★★★★
Wang, ^[39] 2015	Between 2012 and 2013	China	RCT	63	65	Rectum	Laparoscopy or open	–
Yamamoto, ^[40] 2014	Between 1998 and 2009	Japan	Retrospective cohort	91	120	Sigmoid and rectosigmoid colon	Laparoscopy	★★★★★★★
Yasuda, ^[41] 2016	Between 1997 and 2007	Japan	Retrospective cohort	42	147	Sigmoid colon and rectum	Open	★★★★★★★
Zhang, ^[42] 2016	Between 2010 and 2015	China	Retrospective cohort	84	132	Rectum	Laparoscopy	★★★★★★

–=data not available, LCA=left colic artery, NOS=the modified Newcastle–Ottawa Scale, RCT=randomized controlled trials.

4 RCTs and 20 cohort studies published between 1948 and 2018 were included in this systematic review and meta-analysis.^[19–42] A total of 8456 patients were included in our analysis, 4058 forming the group underwent the LCA non-preservation versus 4398 patients underwent the LCA preservation. The characteristics of the eligible studies were summarized in Table 1.

5. Quality judgment of studies

The methodological quality assessment of RCTs was shown in Table 2 and the scores of the enrolled prospective/retrospective cohort studies were shown in Table 1. Of the 20 cohort studies, 11 studies had high quality with achieving 7 or more stars.^[19,20,24,25,28,32,34,36,37,40,41] The 4 RCTs had medium or high quality.^[22,30,31,39]

6. Effects of interventions

6.1. Operation time and blood loss

There were 9 studies reported the operation time (939 patients in LCA non-preservation group, 859 patients in LCA preservation group) and 5 studies reported blood loss (759 patients in LCA non-preservation group, 599 patients in LCA preservation group) (Table 3). Meta-analysis for overall operation time effect showed that significant difference between LCA non-preservation and LCA preservation group (MD –7.92, 95% confidence interval [CI] –15.47 to –0.37, *P*=.04) with highly significant heterogeneity (*I*²=85%) (figure not shown). On the other hand, meta-analysis for overall blood loss effect showed that no significant difference between 2 groups (MD –4.09, 95% CI –11.64 to 3.45, *P*=.29) with highly significant heterogeneity (*I*²=99%) (figure not shown). According to the study design

Table 2

Quality assessment of RCTs in the meta-analysis based on the Cochrane Collaboration’s tool for assessing risk of bias.

First author, yr	Selection bias		Blinding bias		Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment			
Matsuda, ^[30] 2015	Yes	Unclear	Unclear	No	Yes	Yes	Yes
Guo, ^[22] 2017	Yes	Unclear	Yes	No	Yes	Yes	Yes
Wang, ^[39] 2015	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes

No=high risk, RCTs=randomized controlled trials, Unclear=unclear risk, Yes=low risk.

Table 3
Study reporting operative parameters in patients underwent LCA non-preservation or LCA preservation surgery.

First author, yr	Design	No. patients		Procedure	Operation time, min		Blood loss, ml			The first postoperative exhaust time, d			
		LCA non-preservation	LCA preservation		LCA non-preservation	LCA preservation	LCA non-preservation	LCA preservation	LCA non-preservation	LCA preservation			
Guo, ^[22] 2017	RCT	29	28	Laparoscopy	166.00±9.15	180.00±10.80	NS	-	-	-	-	-	-
Han, ^[24] 2013	Retrospective cohort	76	80	-	-	-	-	-	-	3.9±0.4	3.4±0.4	*	
Hinoi, ^[25] 2013	Retrospective cohort	256	155	Laparoscopy or open	262±83	303±84	*	152±198	140±158	NS	-	-	-
Komen, ^[26] 2011	Prospective cohort	16	17	open	190±60	140±45	NS	-	-	-	-	-	-
Lee, ^[28] 2018	Retrospective cohort	51	83	Laparoscopy	212.74±59.92	183.20±53.91	*	-	-	-	-	-	-
Luo, ^[29] 2017	Retrospective cohort	320	203	Laparoscopy	140.40±2.17	149.80±2.77	*	113.10±4.02	121.50±5.35	NS	3.24±0.04	3.07±0.05	*
Matsuda, ^[30] 2015	RCT	51	49	Laparoscopy or open	265±94.5	247±102	NS	30±262.5	20±180	NS	-	-	-
Shen, ^[35] 2014	Retrospective cohort	41	72	Laparoscopy	128.3±21.1	133.8±14.6	NS	55.7±22.7	60.8±23.8	NS	2.8±0.9	2.6±0.8	NS
Yamamoto, ^[40] 2014	Retrospective cohort	91	120	Laparoscopy	Stage II: 230±81.25 Stage III: 217±86.25	Stage II: 230±67.5 Stage III: 195±47.5	NS	Stage II: 10±234.75 Stage III: 10±60	Stage II: 10±177.5 Stage III: 10±70	NS	-	-	-
Zhang, ^[42] 2016	Retrospective cohort	84	132	Laparoscopy	141.7±31.0	159.3±33.5	NS	-	-	-	1.9±0.39	1.52±0.32	*

* = significant difference, -- = data not available, LCA = left colic artery, NS = no significant difference, RCT = randomized controlled trial.

(RCTs, prospective or retrospective cohort studies), a subgroup analysis was conducted to quantitatively assess heterogeneity. However, there was still highly heterogeneity across studies with regard to operation time and blood loss. Thus, these studies were included in the qualitative synthesis (Table 3). In term of operation time and blood loss, most studies did not find a significant difference between 2 groups. All 3 studies but 1 study showed operation time in LCA preservation group longer than that of LCA non-preservation group. With regard to blood loss, no studies found a significant difference between 2 groups.

6.2. The first postoperative exhaust time

Four retrospective cohort studies reported the first postoperative exhaust time, and meta-analysis showed that significant difference between the 2 groups (MD 0.32, 95% CI 0.13–0.51, *P* < .01) with highly significant heterogeneity (*I*² = 93%) (figure not shown). Thus, the 4 studies were included in qualitative synthesis shown in Table 3. Three studies showed that shorter

postoperative exhaust time in LCA preservation group than that of LCA non-preservation group.

6.3. Meta-analysis for safety consideration

Due to the lack of data regarding the safety consideration including overall 30-day postoperative morbidity and overall 30-day postoperative mortality amenable to pooling in the meta-analysis, the meta-analysis was not performed.

6.4. Perfusion of the proximal limb of anastomosis

Four studies concerned the influence of the preservation of LCA on anastomotic perfusion (Table 4). Hall et al reported the tissue oxygen tension change (ptO₂) proximal to the resection margin before and after either preservation or non-preservation of LCA in patients underwent colorectal resection.^[2,3] They found that, regardless of the ligation level, ptO₂ was maintained or improved when the transverse and descending colon were used for the

Table 4
Studies concerning the influence of the level of arterial ligation on anastomotic circulation.

First author, yr	Design	No. patients		Procedure	Outcome measure	Results
		LCA non-preservation	LCA preservation			
Guo, ^[22] 2017	Prospective Cohort study	29	28	Rectal resection with LCA non-preservation or LCA preservation	Marginal artery stump pressure	MASP: 41.30±1.92 mm Hg in high tie group; 49.55±1.96 mm Hg in low tie group. Significant MASP reduction after high tie
Hall, ^[23] 1995	Prospective cohort study	30	32	Colorectal resection with LCA non-preservation or LCA preservation	Tissue oxygen tension	Median ptO ₂ change after versus before resection: transverse colon in low tie +9mm Hg, high tie +8 mm Hg; descending colon in low tie +7 mm Hg, high tie +1mm Hg; sigmoid anastomoses in low tie -4 mm Hg, high tie -9 mm Hg. No significant ptO ₂ change between high tie and low tie. Tissue oxygen tension of sigmoid not adequate after both techniques
Komen, ^[26] 2011	Prospective cohort study	16	17	Rectal resection with LCA non-preservation or LCA preservation	Colonic blood flow; blood flow ratios	BFR in the afferent loop after laparotomy and before construction of the anastomosis: 0.91±0.24 in high tie group; 1.48±0.32 in low tie group. Significant BFR lower after high tie independent of the blood pressure
Rutegard, ^[34] 2016	Prospective cohort study	5	18	Rectal resection with LCA non-preservation or LCA preservation	Colonic limb perfusion; blood flow ratios	Mean colonic blood flow: 158.7 PU in high tie; 45.5 PU in low tie; Mean colonic blood flow ratio: 1.71 in high tie; 1.19 in low tie; No significant difference between high tie and low tie

BFR = blood flow ratios, LCA = left colic artery, MASP = marginal artery stump pressure, PU = perfusion unit.

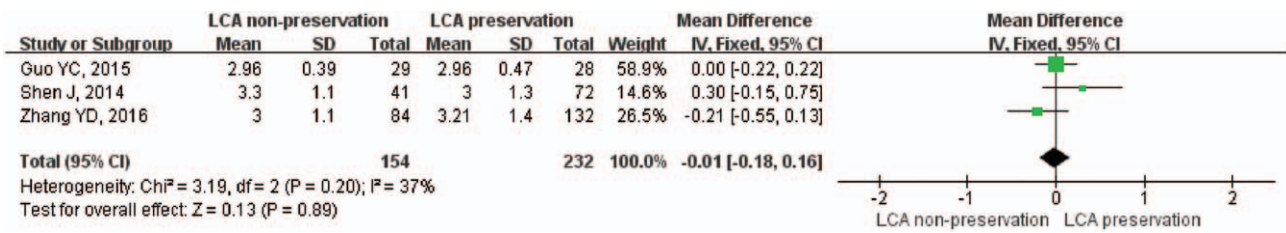


Figure 2. Forest plot of the number of apical lymph nodes dissected.

anastomosis but diminished for sigmoid anastomosis. They concluded that change in oxygenation was significantly affected by the location of proximal resection site rather than whether the LCA preservation or not.

Laser Doppler flowmetry was used by Komen to measure the blood flow on the antimesenteric side of the proximal colon loop after laparotomy and before construction of the anastomosis in patients underwent rectal resection.^[26] The blood flow ratios (BFR) were compared between LCA non-preservation group and LCA preservation group. The results suggested that significant BFR lower after LCA non-preservation surgery independent of the blood pressure. Rutegard also used the Laser Doppler flowmetry to evaluate the impact of LCA preservation on colonic limb perfusion.^[34] They found that the mean blood flow ratio was not decreased after LCA non-preservation surgery compared to LCA preservation surgery (1.71 vs 1.19; P=.28). Guo used angiocatheter to measure the marginal artery stump pressure and found that LCA preservation surgery could provide better anastomotic blood supply.^[22]

6.5. Meta-analysis for the number of apical lymph nodes harvested

A total of 3 studies reported the number of lymph nodes harvested around the root of IMA (Fig. 2). There was no significant difference between the 2 groups (MD -0.01, 95% CI -0.18 to 0.16, P=.89) (I²=37%).

6.6. Meta-analysis for anastomotic leakage

Anastomotic leakage after anterior resection of the rectum is defined as a defect of the integrity of the intestinal wall at the anastomotic site which leads to a communication between the intra and extraluminal compartments. Patients included in our meta-analysis were with symptomatic anastomotic leakage, which requires active therapeutic intervention. The anastomotic leakage rate obtained from 16 studies, which reported this outcome, was 9.92% (269/2712) and 7.68% (239/3114) respectively in LCA non-preservation group and LCA preservation group and the statistical analysis showed significant difference between the 2 groups (OR 1.23, 95% CI 1.02–1.48, P=.03) with low heterogeneity (I²=4%) (Fig. 3). Due to the lack of sufficient data on the fashioning of a covering stoma, thus a subgroup analysis was not performed.

6.7. Meta-analysis for urogenital and defaecatory dysfunction

The sexual dysfunction rate of 3 studies reporting this outcome was 11.88% (57/480) in LCA non-preservation group and 10.62% (44/415) in LCA preservation group and the analysis did not evidence a statistically significant difference (OR 0.98, 95% CI 0.64–1.50, P=.93) (I²=0%) (Fig. 4). Urinary retention is defined as patients is unable to completely empty the bladder after the operation. The urinary retention rate of 6 studies in LCA non-preservation and LCA preservation group was 9.59% (61/636), 6.80% (46/676), respectively. The statistical analysis also did not

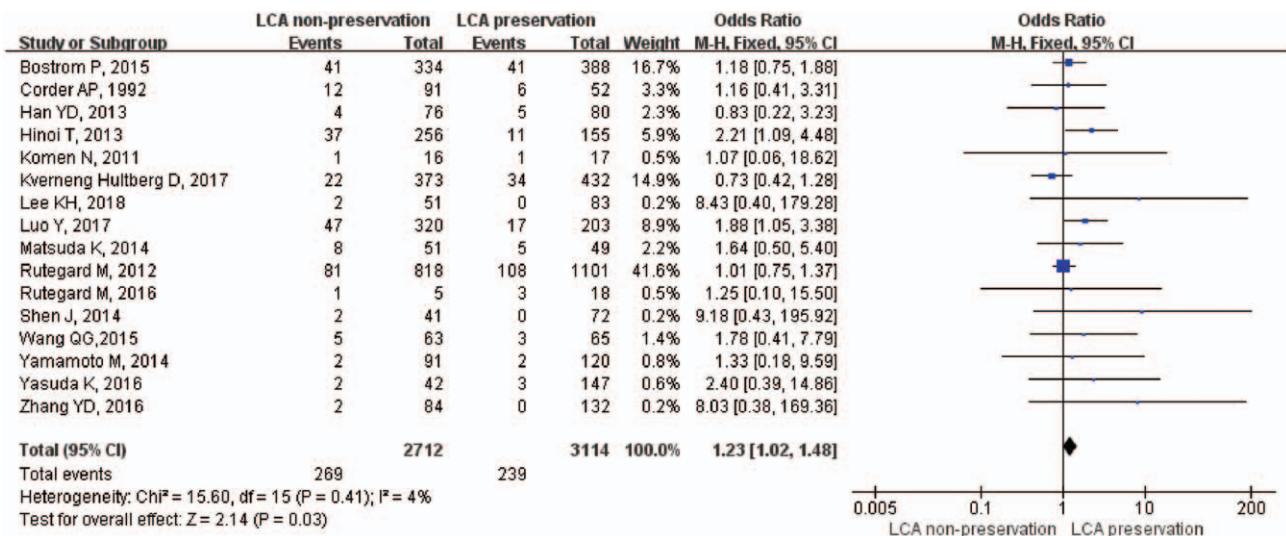


Figure 3. Forest plot of the anastomotic leakage.

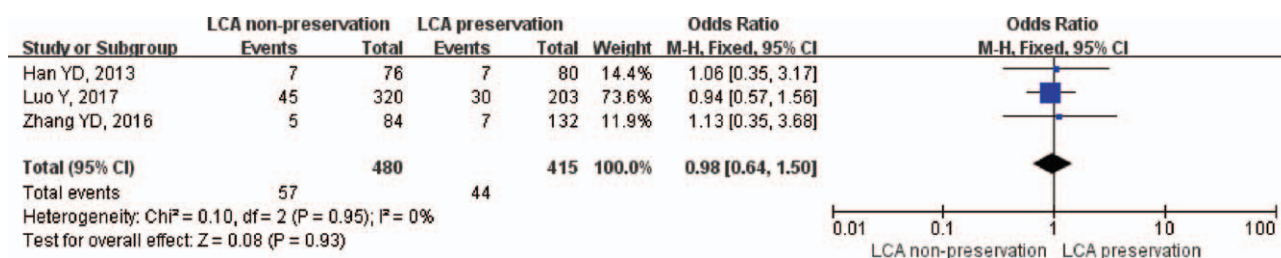


Figure 4. Forest plot of the sexual dysfunction.

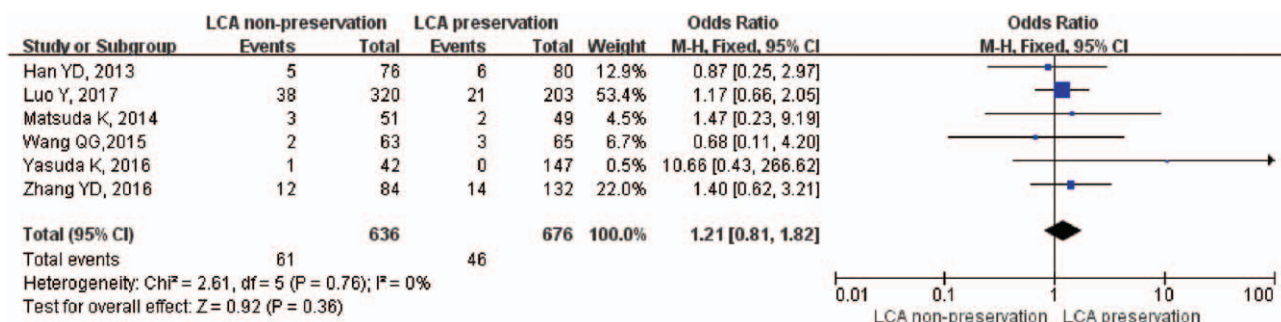


Figure 5. Forest plot of the urinary retention.

show a significant difference (OR 1.21, 95% CI 0.81–1.82) ($I^2 = 0\%$) (Fig. 5).

There were only 2 studies concerned defaecatory function after operation (Table 5). Matsuda et al and Wang et al reported the Wexner score in patients underwent rectal resection 3 months and 12 months after the operation.^[30,39] There was no significant difference between the 2 groups.

6.8. Meta-analysis for oncologic outcomes

Table 6 listed the studies reported the oncologic outcomes. Eight studies reported the overall survival (OS) outcomes, 5 of them were included in quantitative synthesis and the statistical analysis did not show significant difference between the 2 groups (HR 0.84, 95% CI 0.46–1.52, $P = .56$) ($I^2 = 0\%$) (Fig. 6). With regard to DFS, 4 of 5 studies reported 5-year DFS were included in quantitative analysis and there was no significant difference between 2 groups (HR 1.34, 95% CI 0.78–2.28, $P = .29$) ($I^2 = 0\%$) (Fig. 7). Meta-analysis for overall recurrence showed that

there was also no significant difference between 2 groups (OR 1.06, 95% CI 0.80–1.42, $P = .68$) ($I^2 = 0\%$) (Fig. 8).

7. Heterogeneity analysis

Although subgroup analysis was performed based on the study design, there still existed highly significant heterogeneity among studies concerned operation time, blood loss, the first postoperative exhaust time. This may be caused by different surgical proficiency and outcomes measured by different methods.

8. Publication bias

A funnel plot of the studies used in the meta-analysis reporting on overall recurrence after colorectal resection with LCA non-preservation and LCA preservation was shown in Figure 9. None of the studies lay outside the limits of the 95% CI, and there was no evidence of obvious publication bias or heterogeneity among the studies.

Table 5

Studies reporting defaecatory function in patients underwent LCA non-preservation or LCA preservation surgery.

First author, yr	Design	No. patients		Procedure	Tumor location	Outcomes		
		LCA non-preservation	LCA preservation			LCA non-preservation	LCA preservation	
Matsuda, ^[30] 2015	RCT	51	49	Laparoscopy or open	Rectum	Wexner score: 4.4* 3 mo after operation; 2.2* 1 yr after operation	Wexner score: 4.2* 3 mo after operation; 3.8* 1 yr after operation	No significant difference
Wang, ^[39] 2015	RCT	63	65	Laparoscopy or open	Rectum	Wexner score: 4.5±1.5 3 mo after operation; 3.0±0.9 1 yr after operation	Wexner score: 4.3±1.8 3 mo after operation; 3.2±1.3 1 yr after operation	No significant difference

* = mean value, LCA=left colic artery, RCT=randomized controlled trial.

Table 6

Studies reporting oncologic outcomes in patients underwent LCA non-preservation or LCA preservation surgery.

First author, yr	No. patients		Overall survival (OS)		Disease-free survival (DFS)		Overall recurrence	
	LCA non-preservation	LCA preservation	LCA non-preservation	LCA preservation	LCA non-preservation	LCA preservation	LCA non-preservation	LCA preservation
Charan, ^[20] 2014	44	16	Median OS 62 mo	Median OS 42 mo	NS	—	—	—
Han, ^[24] 2013	76	80	Mean OS 61.93 mo	Mean OS 61.97 mo	NS	—	—	18.8%
Hinoi, ^[25] 2013	256	155	—	—	NS	—	NS	—
Lee, ^[28] 2018	51	83	5-yr OS rate 84.1%	5-yr OS rate 87.5%	NS	5-yr DFS rate 92.6%	5-yr DFS rate 91.1%	7.4%
Matsuda, ^[31] 2017	51	49	5-yr OS rate 79.3%	5-yr OS rate 83%	NS	5-yr DFS rate 74.9%	5-yr DFS rate 80.7%	23.5%
Pezini, ^[32] 1984	586	784	Dukes A: 5-yr OS rate 94.5%	Dukes A: 5-yr OS rate 80.5%	NS	—	—	—
			Dukes B: 5-yr OS rate 70.9%	Dukes B: 5-yr OS rate 64.9%	NS	—	—	—
			Dukes C: 5-yr OS rate 40.4%	Dukes C: 5-yr OS rate 55%	NS	—	—	—
Shen, ^[35] 2014	41	72	—	—	—	—	—	7.3%
Shen, ^[36] 2017	154	168	5-yr OS rate 70.1%	5-yr OS rate 69.5%	NS	5-yr DFS rate 59.7%	5-yr DFS rate 57.2%	39.6%
Surtrees, ^[37] 1990	150	100	Dukes C1: 5-yr OS rate 64%	Dukes C1: 5-yr OS rate 54%	NS	—	—	NA
Wang, ^[39] 2015	63	65	—	—	—	—	—	4.8%
Yamamoto, ^[40] 2014	91	120	Stage II: 5-yr OS rate 94.8%	Stage II: 5-yr OS rate 91.8%	NS	Stage II: 5-yr DFS rate 93.0%	Stage II: 5-yr DFS rate 87.6%	Stage II: 4.7%
			Stage III: 5-yr OS rate 88.3%	Stage III: 5-yr OS rate 86.9%	NS	Stage III: 5-yr DFS rate 71.4%	Stage III: 5-yr DFS rate 69.8%	Stage III: 27.1%
Yasuda, ^[41] 2016	42	147	5-yr OS rate 84.2%	5-yr OS rate 80.3%	NS	5-yr DFS rate 75.6%	5-yr DFS rate 76.2%	38.10%

Overall recurrence including local recurrence and systematic recurrence. — = data not available, DFS = disease free-survival, LCA = left colic artery, NS = no significant, OS = overall survival.

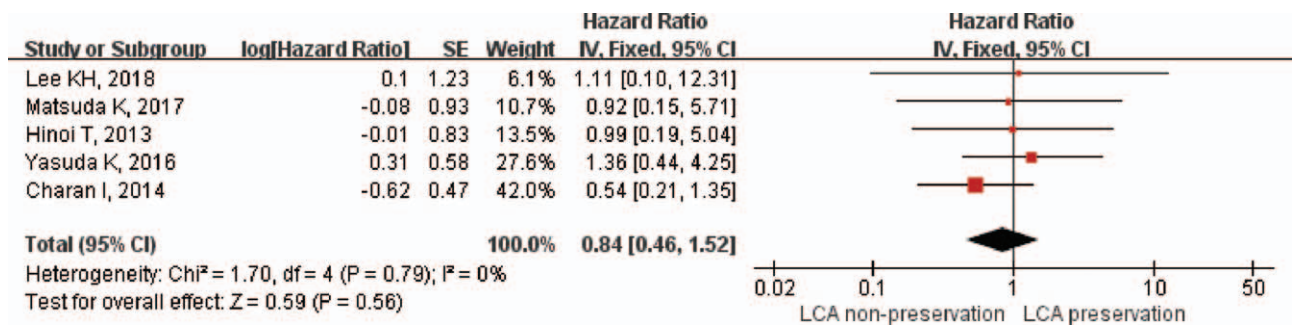


Figure 6. Forest plot of the 5-yr overall survival.

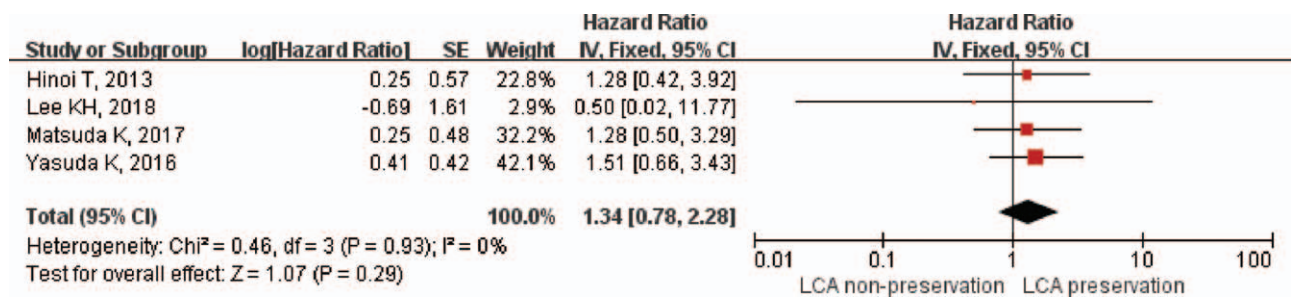


Figure 7. Forest plot of the 5-yr disease-free survival.

9. Sensitivity analysis

Highly significant heterogeneity was detected for operation time ($I^2=85\%$, $P<.01$), blood loss ($I^2=99\%$, $P<.01$), the first postoperative exhaust time ($I^2=93\%$, $P<.01$). We evaluated the effect of each study on the pooled results by omitting single study sequentially, and there was no significant change (data not shown). Additionally, a sensitivity analysis was undertaken by using high-quality studies, studies published in or after 2000, and studies with more than 20 patients in each group. However, compared with primary results, the outcomes still did not change (data not shown).

10. Discussion

There is still no consensus on the preservation of LCA when performing left colon and rectal cancer surgery. Our goal of this systemic review and meta-analysis was to compare the short-term and long-term results of the LCA non-preservation and LCA

preservation for colorectal resection. Our results renew the latest meta-analysis on this hot topic which was limited by inadequately pooled data.

With regard to operation time, 2 studies had shown that longer operation time in LCA preservation group than that of LCA non-preservation group.^[25,29] However, with respect to blood loss, no significant difference was found in the 2 groups.^[22,26,30,35,40,42] Actually, with the dissemination of laparoscopy in colorectal surgery, it is more easier to perform the non-preservation of LCA under laparoscopy.^[43] This is because preservation of LCA with apical lymph nodes dissection is technically demanding and requires a long time to complete. Additionally, 3 studied showed that the first postoperative exhaust time in LCA preservation group shorter than that of LCA non-preservation group.^[24,29,42] Bowel movement might be influenced by the decreased blood supply in the LCA non-preservation group.^[44] Given that there was heterogeneity in measurement criteria among included studies, it was hard to draw a definitive conclusion. Therefore, in

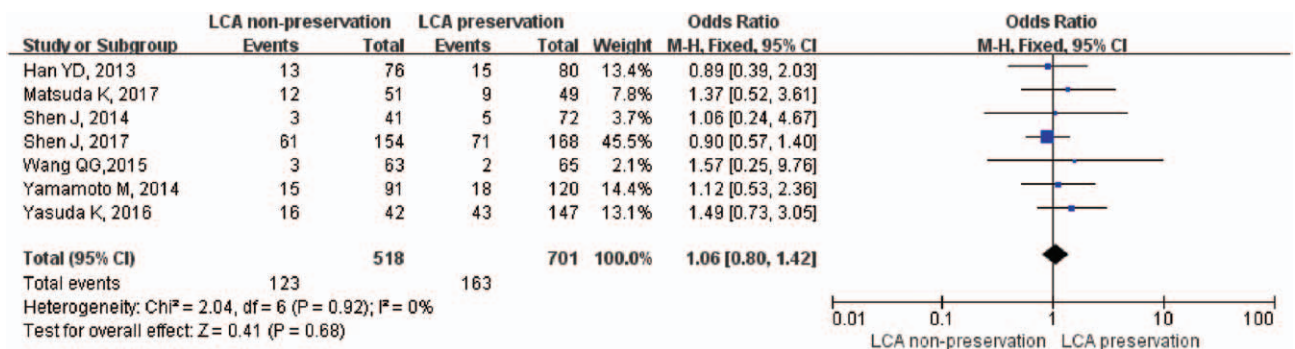


Figure 8. Forest plot of the overall recurrence.

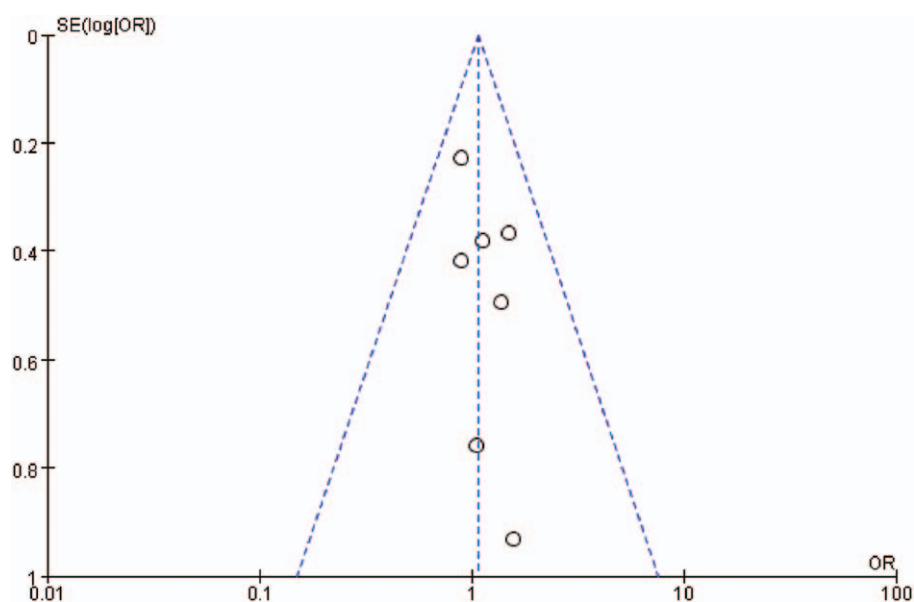


Figure 9. Funnel plot of the overall recurrence.

term of operation time, blood loss, and the first postoperative exhaust time, future high powered and well-designed RCTs are still needed to investigate these issues.

Noticeably, our meta-analysis found a statistically significant difference between the LCA non-preservation and LCA preservation group in the anastomotic leakage and non-preservation of LCA caused more anastomotic leakage. The incidence of anastomotic leakage is ranged from 2.2% to 12%.^[8] Anastomosis blood transfusion is the most crucial risk factor influencing anastomotic leakage.^[10] The surgical technique of LCA non-preservation includes the section of the IMA at its aortic origin to obtain extra length to fashion low pelvic anastomosis without tension. However, after the high IMA tie, the distal colon completely depends on the marginal artery arising from the middle colic artery. Although some studies had shown that the marginal artery provided adequate blood supply to the remaining colon.^[23,34,45,46] From prospective intraoperative measurement, Komen et al and Guo et al argued that non-preservation of LCA significantly reduced blood perfusion of the proximal limb.^[22,26]

Additionally, Dworkin et al found that 41% to 86% blood flow reduction after non-preservation of LCA and no increase in perianastomotic colonic perfusion during the first 5 postoperative days. Furthermore, for elderly patients with atherosclerotic arteries, non-preservation of LCA might result in hypoperfusion of the proximal limb.^[47] On the contrary, the preservation of LCA and mobilization of the splenic flexure provides adequate blood supply to the proximal anastomosis and reduces the anastomotic tension.^[48] Therefore, based on our pooled results and previous studies, we believed that the preservation of LCA had the important advantage of providing adequate perfusion of the proximal anastomosis and reducing postoperative anastomotic leakage.

As common complication after anterior rectal resection, urogenital and anorectal dysfunction had a significant impact on patients' postoperative quality of life. The preservation of pelvic autonomic nerves plays a crucial role in preventing urogenital and anorectal dysfunction.^[49] Some authors thought that non-preservation of LCA was associated with a worse postoperative urogenital dysfunction compared to LCA preservation for superior

hypogastric plexus lesion caused by high IMA tie.^[50] However, our meta-analysis confirmed that there was no significant difference in sexual dysfunction and urinary retention between the LCA non-preservation group and the LCA preservation group. Due to the development of the meticulous laparoscopy-assisted surgery, the preaortic and inferior mesenteric nerves could be identified and protected when performing high IMA tie. On the other hand, high IMA tie disrupts the descending autonomic fibers and causes a long denervated colon segment which leads to defaecatory function.^[51,52] This complication could be improved along with the past of time after the operation, which was suggested by Matsuda et al and Wang et al.^[30,39]

The number and status of lymph nodes is a key prognosis factor in colorectal disease. The rate of lymph nodes metastasis around the root of the IMA was reported 3.6% in pT3/T4 sigmoid colon cancer and 5.1% in rectal cancer.^[53] Our meta-analysis suggested that there was no significant difference in the number of apical lymph nodes harvested around the root of the IMA between the 2 groups. The result was contrary to previous studies which had shown that the LCA non-preservation surgery was expected to increase lymph nodes yield and thus improve the accuracy of tumor staging.^[2] This might be due to the preservation of LCA performed in those studies without apical lymph nodes dissection.

This meta-analysis confirmed that the non-preservation of LCA was not associated with a significantly better long-term oncologic outcomes compared with LCA preservation in patients with colorectal cancer curative resection, in accordance with previous systematic reviews.^[5,9,10] Although the last meta-analysis conducted by Singh showed significant OS benefit of LCA non-preservation than LCA preservation in IMA positive lymph nodes group, there was no significant difference in the all case group.^[6] Chen et al found that non-preservation of LCA had better 5-year OS, which may be limited by the included studies published before 2000.^[12]

There were some limitations in our meta-analysis. First, most included studies in this meta-analysis were retrospective, except for 4 RCTs with small sample sizes. Second, in order to avoid

potential language bias, the language of studies was not limited to English. Thus, some included studies in our systematic review were published in Chinese. However, according to the sensitivity analysis, these studies did not influence the whole results. Third, when estimating the operation time, blood loss, the first postoperative exhaust time, perfusion of the proximal limb of anastomosis, and defaecatory function, there was highly significant heterogeneity among studies. Thus, qualitative synthesis was adopted which may decrease the power of our outcomes.

11. Conclusion

Our study suggested that the LCA preservation preferred over LCA non-preservation in term of anastomotic leakage. With regard to sexual dysfunction, urinary retention, the number of apical lymph nodes and long-term oncologic outcomes, there was no significant difference between the LCA non-preservation and LCA preservation. It was hard to make a conclusion on other outcomes including operation time, blood loss, the first postoperative exhaust time, and perioperative morbidity and mortality for insufficient data and highly significant heterogeneity among studies. Therefore, despite our rigorous methodology, the inherent limitations of included studies prevented us from reaching definitive conclusions on the preferred vascular ligation level in colorectal cancer surgery. Future more large-volume, well-designed RCTs with extensive follow-up are warranted to confirm and update the findings of this analysis.

Author contributions

Xuyang Yang, Pingfan Ma, and Xubing Zhang contributed equally to this work. Ziqiang Wang, and Xiangbing Deng conceive this meta-analysis. Xuyang Yang, Pingfan Ma and Xubing Zhang perform the research, collect and analyze the data, draft the article. Mingtian Wei, Yazhou He and Chaoyang Gu analyze the data and revise critical intellectual content. All authors read and approve the final manuscript and agree to be accountable for all aspects of work to ensure that questions regarding accuracy and integrity investigated and resolved.

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