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REVIEW

Lymph node yield, survival benefit, and safety of high and low ligation of the inferior mesenteric artery in colorectal cancer surgery: a systematic review and meta-analysis

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Abstract

Purpose The aim of this meta-analysis was to compare high inferior mesenteric artery (IMA) ligation (HL) with low IMA ligation (LL) for the treatment of colorectal cancer and to evaluate the lymph node yield, survival benefit, and safety of these surgeries.

Methods PubMed, Embase, Cochrane Library, Web of Science, and China Biomedical Literature Database (CBM) were systematically searched for relevant articles that compared HL and LL for sigmoid or rectal cancer. We calculated the odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous outcomes and the weighted mean difference (WMD) for continuous outcomes.

Results In total, 30 studies were included in this analysis. There were significantly higher odds of anastomotic leakage and urethral dysfunction in patients treated with HL compared to those treated with LL (OR = 1.29; 95% CI = 1.08 to 1.55; OR = 2.45; 95% CI = 1.39 to 4.33, respectively). There were no significant differences between the groups in terms of the total number of harvested lymph nodes, the number of harvested lymph nodes around root of the IMA, local recurrence rate, and operation time. Further, no statistically significant group differences in 5-year overall survival rates and 5-year disease-free survival rates were detected among all patients nor among subgroups of stage II patients and stage III patients, respectively.

Conclusions LL can achieve equivalent lymph node yield to HL, and both procedures have similar survival benefits. However, LL is associated with a lower incidence of leakage and urethral dysfunction. Thus, LL is recommended for colorectal cancer surgery.

Keywords High IMA ligation · Low IMA ligation · Colorectal cancer

Introduction

Colorectal cancer is the second leading cause of cancer-related death, with approximately 880,792 deaths and about 1,849,518 newly diagnosed cases in 2018 [1]. Both total mesorectal excision (TME) and complete mesocolic excision (CME) are reported to reduce local recurrence and improve survival rates in patients with rectal and colorectal cancer. Thus, these techniques have gradually became the standard techniques used in colorectal surgery [2, 3].

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In colorectal surgery, the inferior mesenteric artery (IMA) can be ligated at the origin of the aorta (high ligation) or distal to the origin of the left colic artery (low ligation) [4]. There is considerable controversy surrounding the use of these two techniques [5, 6]. Some researchers recommend high IMA ligation (HL), arguing that this technique results in more radical lymph node excision and improved node harvest [4]. However, it is also hypothesized that reducing blood flow to the distal colon may lead to increased risk of anastomotic leakage (AL) and may sacrifice the autonomic nerves around the origin of the IMA [7]. In contrast, the low IMA ligation (LL) technique maintains adequate blood supply to the colon proximal to the anastomotic stoma [8]. Further, there is little to no risk of injury to the autonomic nerve with this technique; however, it may result in slightly less radical clearance of nodes [9].

High-quality meta-analysis has been increasingly regarded as one of the key tools for obtaining evidence [10, 11]. Although there have been several meta-analyses examining which technique is better, it is important to note that the conclusions of these studies remain controversial and autonomic nerve damage has not been examined as an outcome [5, 6, 12–14]. Further, there have been several randomized controlled trials (RCTs) and retrospective cohort studies published in recent years examining the oncologic outcomes and safety of HL and LL; these have not been included in the published meta-analyses to date. Additionally, several studies have reported that HL may improve survival rate in patients at certain disease stages [15, 16]; the available meta-analyses have not addressed this finding. Thus, herein we performed a comprehensive meta-analysis including recently published studies to compare HL with LL. The current meta-analysis evaluated lymph node yield, survival benefit, and safety of each technique and further analyzed survival benefits in patients at different disease stages (stage II and stage III).

Methods

Search strategy

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [17].

PubMed, Embase, Web of Science, Cochrane Library, and the China Biomedical Literature Database (CBM) were comprehensively searched by two independent reviewers for relevant articles comparing HL and LL techniques in sigmoid or rectal cancer patients; the initial database searches encompassed studies published from the inception date of each database to November 2018. There were no language restrictions placed on these database searches. A final search was performed in March 2019, to check for any additional potentially eligible studies published since the initial database searches. Database-specific subject headings, known as Medical Subject Headings (MeSH) terms, and free texts terms were used to search for and identify potentially eligible studies; complete search algorithms for each database are available in Appendix 1. Reference lists of all retrieved articles were manually searched to identify additional studies. In order to ensure all relevant studies were identified, no restrictions were placed on the date of publication or regional state.

Study selection

Inclusion criteria

The inclusion criteria for our study were as follows: (1) patients definitely diagnosed with sigmoid or rectal cancer by enhanced computed tomography, colonoscopy, and pathological biopsy assessment; (2) study compares the initial therapy effects of HL and LL of the IMA for the treatment of sigmoid or rectal cancer, regardless of the etiology of colorectal cancer and differences in surgical approaches (open or laparoscopic); (3) no previous or simultaneous malignancies were detected in the patients before surgery; and (4) the study reports on at least one of the outcome measures mentioned below.

Exclusion criteria

The exclusion criteria for this study were as follows: (1) abstracts, letters, editorials and expert opinions, reviews without original data, case reports, and studies lacking control groups and (2) massive invasion of cancer into adjacent organs that could not be resected.

Data extraction

Data from each study reporting the outcomes of interest were extracted by two independent reviewers. The relevant data included first author, publication year, country, type of study, gender, age, cases of patients, patient recruitment period, BMI, follow-up duration, and patient clinical outcomes. Any discrepancies between the two reviewers were resolved by discussion to reach agreement; if an agreement between the two reviewers could not be reached, a third person was involved.

The patient clinical outcomes were categorized into one of the following three categories: lymph node yield, survival benefit, and safety. Lymph node yield outcomes included the total number of harvested lymph nodes and the number of harvested lymph nodes around the root of the IMA. Survival benefit outcomes included 5-year overall survival (OS) rates and 5-year disease-free survival (DFS) rates for all patients, as well as for stage II patients and stage III patients, respectively. The local recurrence rate was also included in this category.

The safety outcomes included anastomotic leakage, urethral dysfunction, and operation time.

Quality assessment

All studies were independently assessed by two investigators for quality and validity using two scales: the Cochrane Risk of Bias Tool for the six randomized controlled trials (RCTs) included in the review and the Newcastle-Ottawa Scale (NOS) for the remaining cohort studies and case-control studies [18, 19]. The results of this assessment are shown in Tables 1 and 2, respectively. Disagreements in the quality assessment were resolved by consensus.

Statistical analysis

All statistical analyses were performed using Stata 14 (StataCorp LP). We used random-effects models to analyze data because it thinks over the almost inevitable natural variation inherent between studies, especially in the field of surgical research [47]. We then calculated the odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous outcomes and the weighted mean difference (WMD) for continuous outcomes. Meanwhile, we explored statistical heterogeneity using the I^2 test statistic. A sensitive analysis was subsequently conducted by eliminating each study in the analysis at each turn. A potential publication bias was evaluated by visually inspecting the Begg's funnel plots in which the log OR is plotted against the standard error (SE). A P value of less than (<) 0.05 was considered statistically significant.

Subgroup analysis

Recently, a technique involving LL with apical lymph node dissection around the root of the IMA to achieve D3 lymph node dissection has been widely used in clinical settings, especially in Asian countries [48]. This approach is different from standard LL (i.e., LL procedure without lymph node dissection around the IMA) [37]. Our review identified studies of standard LL as well as LL with D3 lymph node dissection, which was defined for the purpose of this review as modified LL. Thus, we performed a subgroup analysis based on detailed data regarding the total number of lymph nodes harvested and the operative time in patients with these two LL techniques.

Results

Description of study selection

The initial search criteria captured 475 citations, and an additional 7 studies were identified by manually examining the reference lists of the identified studies. In total, 34 duplicate studies were removed. Then, the titles and abstracts of the remaining 448 records were screened for the inclusion criteria; this resulted in the exclusion of 410 studies. The full texts of the remaining 38 records were then read. Thirty of these studies were deemed to satisfy the inclusion criteria and were retained for analysis [4, 7, 9, 20–46]. The PRISMA flow diagram of this process is shown in Fig. 1 and the study characteristics are listed in Table 1.

Lymph node yield outcomes

Total number of harvested lymph nodes

The meta-analysis of 19 trials reporting this data indicated that there was no significant difference between the two groups (WMD = 0.64; 95% CI = − 0.65 to 1.93; P = 0.33), with certain heterogeneity (Fig. 2). The subgroup analysis did not reveal any significant difference between the group treated with modified LL and the group treated with HL (WMD = − 0.15; 95% CI = − 1.64 to 1.34; P = 0.84). However, the total number of harvested lymph nodes was significantly less than HL when standard LL was performed (WMD = 2.69; 95% CI = 0.53 to 4.85; P = 0.01) (Fig. 2).

The number of harvested lymph nodes around the root of the IMA

The meta-analysis of eight trials reporting this data showed no significant difference between the two groups (WMD = − 0.11; 95% CI = − 0.45 to 0.24; P = 0.54), with certain statistical heterogeneity (Fig. 3).

Survival benefit outcomes

Five-year OS

The meta-analysis showed no statistical difference between the HL group and LL group (OR = 1.07; 95% CI = 0.93 to 1.23; P = 0.34), with no evidence of significant heterogeneity. For stage II patients and stage III patients, the pooled results also showed no statistical difference between the two groups (OR = 2.29; 95% CI = 0.83 to 6.33; P = 0.11; OR = 0.81; 95% CI = 0.61 to 1.08; P = 0.15, respectively) (Fig. 4).

Five-year DFS

The meta-analysis showed no significant difference in 5-year DFS between the HL and LL groups (OR = 0.98; 95% CI = 0.69 to 1.40; P = 0.91), with no evidence of significant heterogeneity. There was also no significant difference between the two groups for stage II and stage III patients (OR = 1.23;

Table 1 General information and quality score of the included studies

Study	Year	Country	Sample Size		Male (%) HL/LL	Age (year) (Mean ± SD)		Patient recruitment period	BMI (kg/m^2) (Mean ± SD)		Study design	NOS score	Diagnosis
			HL	LL		HL	LL		HL	LL			
Pezim and Nicholls [20]	1984	Canada	784	586	NA	NA	NA	1953–1972	NA	NA	RC	7	Rectal cancer
Surtees et al. [21]	1990	UK	150	100	NA	56.0 ± 41.5	64.0 ± 39.3	1948–1983	NA	NA	RC	7	Sigmoid and rectal cancer
Corder et al. [9]	1992	UK	91	52	NA	NA	NA	NA	NA	NA	RC	7	Rectal cancer
Gao et al. [22]	1999	China	69	56	NA	64.9 ± 41.5	NA	1990–1998	NA	NA	RC	8	Rectal cancer
Chen et al. [23]	2000	China	158	211	62.0/62.0	56.0 ± 3.6	56.4 ± 3.7	1993–1998	NA	NA	RC	8	Rectal cancer
Kawamura et al. [24]	2000	Japan	132	379	65.9/64.1	62.0 ± 12.0	58.0 ± 12.0	1963–1995	NA	NA	RC	7	Descending and sigmoid and rectosigmoid cancer
Komen et al. [25]	2011	Netherlands	16	17	68.8/70.6	55.0 ± 17.0	61.0 ± 13.0	NA	25.0 ± 3.0	27.0 ± 7.0	RC	8	Rectal cancer
Sekimoto et al. [26]	2011	Japan	27	21	40.7/57.1	NA	NA	2007–2009	NA	NA	RC	7	Sigmoid and rectal cancer
Rutegard et al. [27]	2012	Sweden	818	1101	63.7/57.4	NA	NA	2007–2009	NA	NA	RC	8	Rectal cancer
Hinoi et al. [28]	2013	Japan	304	584	63.2/62.5	61.0 ± 8.9	63.0 ± 16.3	1994–2006	NA	NA	RC	8	Rectal cancer
Mihara et al. [29]	2014	Japan	117	745	62.4/64.6	60.0 ± 11.0	65.0 ± 13.6	1986–2011	NA	NA	RC	8	Sigmoid and rectal cancer
Yamamoto et al. [30]	2014	Japan	100	181	54.0/58.0	63.0 ± 35.6	64.0 ± 43.0	1998–2009	23.0 ± 10.4	23.0 ± 14.1	RC	8	Sigmoid or rectosigmoid colon cancer
Boström et al. [31]	2015	Sweden	334	388	72.2/67.0	NA	NA	2007–2010	NA	NA	RC	8	Rectal cancer
Charan et al. [32]	2015	India	44	16	72.7/75.0	NA	NA	2007–2008	NA	NA	RC	7	Descending and sigmoid and Rectal cancer
Guo et al. [33]	2015	China	29	28	NA	NA	NA	2013–2013	NA	NA	RCT	–	Rectal cancer
Matsuda et al. [7]	2015	Japan	51	49	64.7/69.4	69.0 ± 29.6	67.0 ± 32.6	2008–2011	NA	NA	RCT	–	Rectal cancer
Tanaka et al. [34]	2015	Japan	16	341	NA	NA	NA	2008–2013	NA	NA	CC	7	Rectal cancer
Wang et al. [35]	2015	China	63	65	60.3/64.6	56.8 ± 14.2	58.6 ± 13.7	2012–2013	21.7 ± 3.8	21.5 ± 4.0	RCT	–	Rectal cancer
Rutegard et al. [36]	2016	Sweden	5	18	80.0/66.7	67.8 ± 3.3	65.3 ± 9.0	2012–2013	27.3 ± 4.2	26.5 ± 3.7	PC	7	Rectal cancer
Yasuda et al. [37]	2016	Japan	43	147	61.9/62.6	64.5 ± 9.6	68.0 ± 9.1	1997–2007	NA	NA	RC	8	Sigmoid and rectal cancer
Zhang et al. [38]	2016	China	42	61	52.4/54.1	61.2 ± 12.5	60.5 ± 12.3	2015–2016	24.2 ± 7.5	23.5 ± 3.6	RC	8	Rectal cancer
Wu and Li [39]	2017	China	50	46	64.0/67.4	58.4 ± 9.3	59.1 ± 9.1	2014–2016	23.8 ± 1.6	22.5 ± 1.2	RCT	–	Rectal cancer
You et al. [40]	2017	China	72	64	58.3/56.3	58.1 ± 10.9	60.1 ± 10.8	2013–2016	NA	NA	RC	8	Rectal cancer
Dimitriou et al. [41]	2018	Greece	76	44	51.0/68.0	70.0 ± 11.9	72.0 ± 10.2	2009–2014	NA	NA	RC	8	Rectosigmoid and rectal cancer
Fujii et al. [4]	2018	Japan	164	160	62.8/60.6	65.9 ± 10.4	65.6 ± 11.5	2006–2012	23·0 ± 3·2	22·4 ± 3·5	RCT	–	Rectal cancer
Lee et al. [42]	2018	Korean	51	83	66.7/71.1	66.1 ± 11.5	66.6 ± 10.7	2008–2013	23.9 ± 3.2	24.0 ± 3.1	RC	8	Sigmoid or rectosigmoid colon cancer
Fen et al. [43]	2018	China	247	110	65.2/70.0	63.0 ± 11.0	66.0 ± 12.0	2015–2016	23.0 ± 3.2	22.5 ± 3.1	RC	8	Rectal cancer
Olofsson et al. [44]	2018	Sweden	239	760	56.9/56.3	NA	NA	2007–2009	NA	NA	RC	7	Sigmoid colon cancer
Xu and Hu [45]	2018	China	88	127	59.1/55.9	60.6 ± 11.8	60.4 ± 11.7	2013–2017	NA	NA	RC	8	Rectal cancer
Zhou et al. [46]	2018	China	52	52	59.6/61.5	52.7 ± 12.9	53.9 ± 14.5	2015–2016	25.4 ± 2.5	25.9 ± 2.0	RCT	–	Rectal cancer

HL high IMA ligation, *LL* low IMA ligation, *BMI* body mass index, *RC* retrospective cohort, *RCT* randomized controlled trial, *CC* case-control, *PC* prospective cohort, *NOS* Newcastle-Ottawa Scale, *NA* not available

95% CI = 0.58 to 2.58; $P = 0.59$; OR = 0.72; 95% CI = 0.36 to 1.42; $P = 0.34$, respectively) (Fig. 5).

Local recurrence rates

The meta-analysis of nine trials reporting this data showed no statistically significant difference between the HL and LL groups (OR = 0.95; 95% CI = 0.67 to 1.33; $P = 0.75$), with no evidence of significant heterogeneity (Fig. 6).

Safety outcomes

Anastomotic leakage

The meta-analysis of 22 trials reporting this data revealed a significant difference between the two groups (OR = 1.29; 95% CI = 1.08 to 1.55; $P = 0.005$), whereby LL-treated patients had a lower incidence of anastomotic leakage compared to HL-treated patients; there was no evidence of significant heterogeneity (Fig. 7).

Urinary dysfunction

The meta-analysis of five trials reporting this data indicated that the incidence of urinary dysfunction was significantly lower in the LL-treated group (OR = 2.45; 95% CI = 1.39 to 4.33; $P = 0.002$) compared to the HL group; there was no evidence of significant heterogeneity (Fig. 8).

Operation time

The meta-analysis of 13 trials reporting this data revealed no significant difference between the HL and LL groups (WMD = − 1.96; 95% CI = − 8.27 to − 4.34; $P = 0.54$), with certain heterogeneity (Fig. 9). The results of subgroup analysis showed no significant difference between standard low IMA ligation and HL (WMD = − 6.04; 95% CI = − 14.14 to − 26.23; $P = 0.56$) nor between modified low IMA ligation and HL (WMD = − 5.32; 95% CI = − 11.44 to 0.81; $P = 0.09$) (Fig. 9).

Sensitivity analysis

We performed a sensitivity analysis by investigating the influence of a single study on the overall pooled estimates; this was achieved by eliminating one study at a time and repeating the analyses. When we excluded the study of Zhou et al., the recalculated results showed that the total number of harvested lymph nodes in the HL group was greater than the LL group (WMD = 1.18; 95% CI = 0.11 to 2.25; $P = 0.03$; $I^2 = 82\%$); this is in contrast to the primary results including all studies (WMD = 0.64; 95% CI = − 0.65 to 1.93; $P = 0.33$; $I^2 = 89\%$). However, for the subgroup of patients who received modified LL, there remained no significant difference in the total number of harvested lymph nodes, compared to the HL group (WMD = 0.64; 95% CI = − 0.55 to 1.83; $P = 0.29$; $I^2 = 88\%$). It is clear that the heterogeneity did not change significantly when the study by Zhou et al. was excluded (total results $\triangle I^2 = 6\%$ and subgroup of modified LL results $\triangle I^2 = 5\%$). Therefore, the study by Zhou et al. is not the source of heterogeneity. Rather, wide inter-individual variations in both patients (anatomy) and surgeons (surgical technique) may have contributed to this heterogeneity. Thus, we did not exclude the study of Zhou et al. and conclude that there was no significant difference in the total number of harvested lymph nodes between the two groups.

Assessment of publication Bias

We only analyzed publication bias for outcomes included in 10 or more studies [18]. After viewing the funnel plots and Egger's tests, it was concluded that none of the four outcomes showed publication bias.

Discussion

Lymph node dissection is considered to be essential in oncological colorectal surgery [24], and several researchers have discussed the importance of radical lymph node dissection up to the root of the IMA [49]. One widely accepted advantage of HL is that it allows en bloc removal of additional nodes at and around the root of the IMA; thus, apical lymph nodes may be retrieved, possibly resulting in improved tumor staging and oncological outcomes [31]. However, in the current study, we did no observe any advantage of HL; the number of harvested lymph nodes, both in terms of the total number and the number around root of the IMA, was not statistically different from the LL group. We also conducted subgroup analysis to compare the different LL techniques. The total number of lymph nodes harvested in the standard LL group was significantly less than in the HL group, which appears to reflect an advantage of HL. However, there was no significant difference between the modified LL group and the HL group. This modified LL technique was initially used in clinical practice in Japan and was described by Japanese researchers [30, 37]. Since then, the number of published cases has increased rapidly. The feasibility and oncological safety of this technique have been confirmed in previous studies [37, 42]. However, it has been reported that this technique requires a longer operative time due to the increased difficulty of the surgery [26]. This is in contrast to the findings of the current study where no statistically significant difference in operation time was found between the modified LL group and the HL group. Recently, Sekimoto et al. reported an approach that can overcome the technical difficulties of the modified LL technique through emphasis of dissection of the layer between the vascular sheath and the artery; this is because there are only a few small

Table 2 Risk of bias of RCTs

Study	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Guo et al. [33]	2015	Low	Unclear	Low	Unclear	Low	Low	Low
Matsuda et al. [7]	2015	Low	Low	Unclear	High	Low	Low	Low
Wang et al. [35]	2015	Low	Unclear	Unclear	Unclear	Low	Low	Low
Wu and Li [39]	2017	Low	Unclear	Unclear	Unclear	Low	Low	Low
Fujii et al. [4]	2018	Low	Unclear	High	High	Low	Low	Low
Zhou et al. [46]	2018	Low	Unclear	Unclear	Unclear	Low	Low	Low

The level of bias was determined as follows: "High," indicating a risk of bias; "Unclear," indicating an uncertain risk of bias; and "Low," indicating no risk of bias

vessels in this region [26]. Although this study was only a single center study, it provides support for our pooled results.

According to a previous study, the 5-year OS rate in patients with IMA root nodal metastasis is poor compared with patients without metastasis [29]. Further, many studies have reported that HL does not improve survival benefit because steady rates of metastasis occur at the IMA root nodes with or without HL [29, 50]. Taken together, these findings

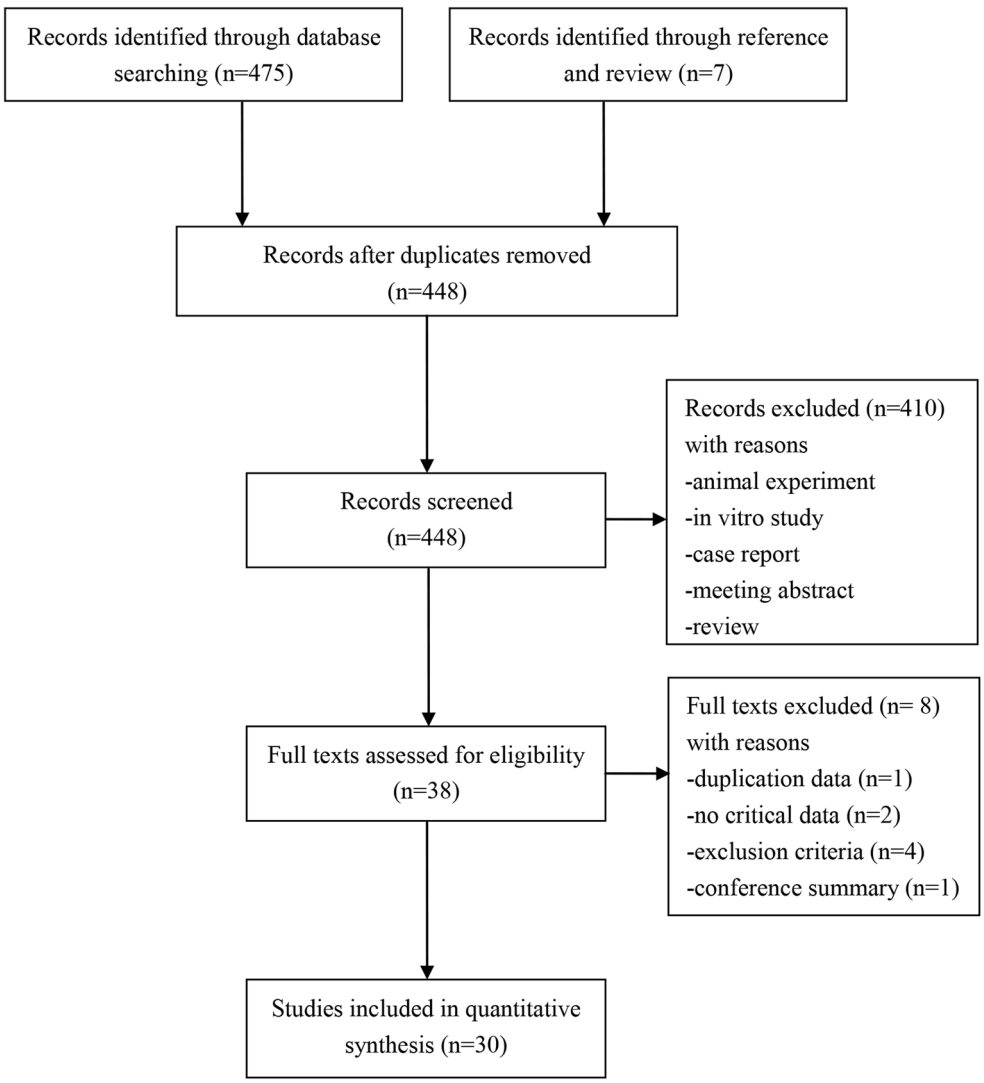

Fig. 1 The PRISMA flow diagram of literatures

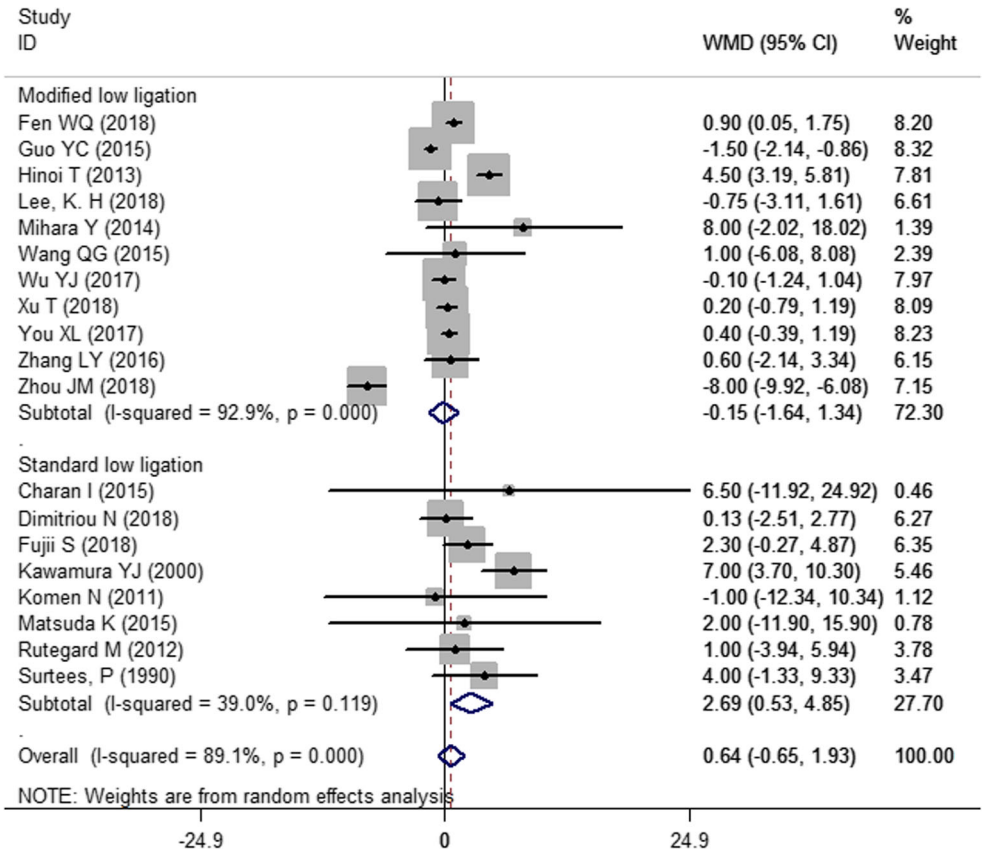

Fig. 2 The forest plot of subgroup and overall analysis of total number of harvested lymph nodes between HL group and LL group

demonstrate a relationship between the metastatic rate of the IMA root nodes and the survival rate, suggesting that any survival benefit relies on the scope of the lymphadenectomy and whether or not the IMA is ligated. Furthermore, Titu et al. argued that the status of the lymph nodes around the IMA root is the most important determinant of DFS [27]. Therefore, it is not surprising that we observed similar 5-year OS rates and 5-year DFS rate between the two groups because the total numbers of lymph nodes harvested and the number of harvested lymph nodes around the IMA root were not significantly different between the HL and LL groups. And, the metastasis rate of the IMA root nodes is stable and low [29].

While the results of the current study indicate that HL does not improve the 5-year survival of patients with rectal or sigmoid

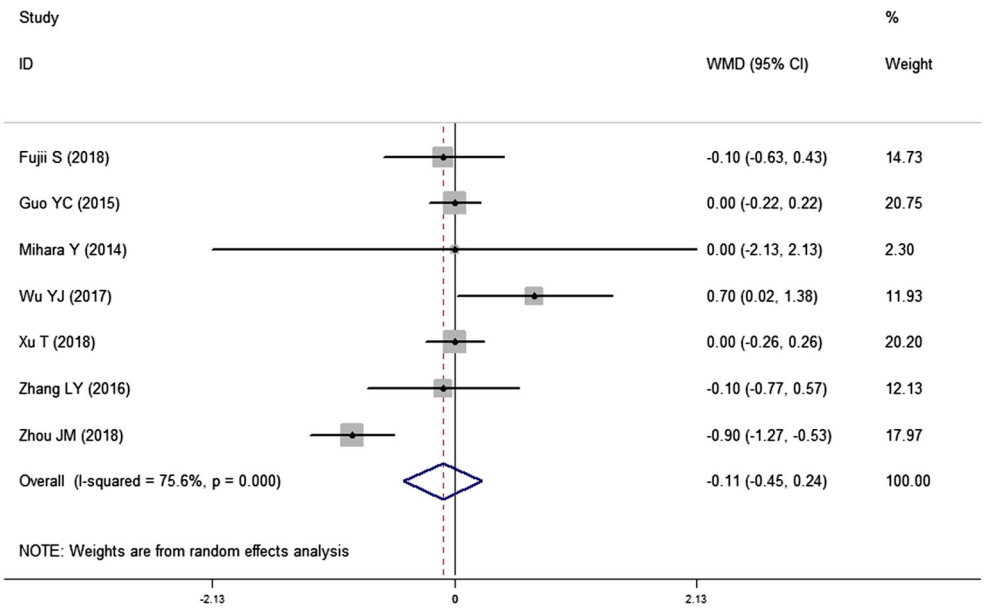

Fig. 3 The forest plot of the number of harvested lymph nodes around root of the IMA between HL group and LL group

cancer, specifically, as mentioned in the "Introduction," HL may provide survival benefit to patients at certain disease stages. Therefore, we further conducted analysis of the 5-year OS rate and DFS rate in patients with stage II and stage III disease, respectively. In performing this analysis, we also aimed to further explain our finding of no difference in survival between the HL group and LL group from another perspective besides lymph node yield. However, we found no difference in survival between the two IMA ligation techniques among stage II and stage III patients, respectively, though it should be noted that stage migration may confound these results [32]. These findings are inconsistent with the findings mentioned above and also contradict a recent meta-analysis which reported that HL should be recommended for suspected advanced stage patients or those at high risk of IMA-positive metastatic lymph nodes [13]. This recommendation was based on a pooled result showing that the 5-year OS rate was improved in stage III patients with HL relative to those with LL.

Stage II patients did not have any lymphatic metastasis [51]; thus, complete resection of the tumor could be accomplished as long as adequate circumferential and distal margins were ensured on the basis of TME or CME [27]. Leek et al. reported that LL can achieve equivalent distal margin length and oncologically appropriate mean proximal margin length compared to HL [42]; this finding could explain the similar survival rates observed in the current study.

Lymph node metastasis is an important factor affecting the prognosis of colorectal cancer patients. For stage III patients, there are a number of potential factors accounting for the similar survival rate observed between the HL and LL groups. Primarily, although lymphatic drainage of rectal and rectosigmoid cancers is still thought to occur predominantly along the IMA, other lymphatic pathways do exist and may confound the assessment of HL [20]. One typical example is the presence of lateral lymphatic drainage routes of tumors of the lower third of the rectum [20]. Secondly, lymph node dissection with ligation of drainage vessels is the standard procedure in colonic radical surgery [24]; all suspected positive lymph nodes beyond the origin of the feeding vessel should be biopsied or removed, or the scope of resection should be extended to include the suspicious lymph nodes. Nonetheless, skip metastases may still be present in 5% of cases [32]. Grinnell et al. reported that once neoplasms have invaded these high lymph nodes, it is likely that the cancer is widespread [52]. Kawamura et al. argued that extensive lymphadenectomy does not increase DFS in patients with lymph nodal involvement and it is likely that the unresected nodes will contain malignant cells [24].

Several recently published meta-analyses have compared HL and LL in terms of postoperative safety; however, the incidence of AL between the two groups remains controversial. Further, outcomes for the assessment of autonomic nerve function injury have not been reported in previous meta-analyses [5, 6, 12]. Therefore, in our study, we focused on the postoperative safety outcomes of AL and UD.

AL is a very serious postoperative complication that occurs in patients who have undergone radical surgery. The incidence of AL is reported to be approximately 10% [34]. Rutegard et al. argued that with the advent of the TME technique, complications such as AL have been increasing in frequency [36]. Further, AL is reported to be associated with subsequent local recurrence and distant metastasis as well as operative mortality rate [34]. Therefore, reducing the likelihood of AL is crucial for good surgical outcomes. It is well known that there are many risk factors for AL [36]; however, blood supply and anastomotic tension are most focused by surgeons due to an anastomosis free of tension with a good blood supply is of crucial importance in radical resection of colorectal cancer [9]. In our study, the pooled result showed that the incidence of AL was significantly lower in the LL group as compared with the HL group. This finding is consistent with two meta-analyses recently published by Fan et al. and Zeng et al. [5, 6]. However, our findings are in contrast to those of Yang et al. [12].

The colon below the root of the IMA is perfused by both the IMA and the marginal artery (MA) of Drummond emanating from the middle colic artery (MVA) [33]. Some studies suggest that the MA is adequate for providing blood supply to the proximal colon in patients who have undergone HL [33, 36]. However, because the left colic artery (LCA) and its ascending branch are ligated when HL is performed, there is no longer a second pathway for the perfusion of the colon proximal to anastomosis. Therefore, perfusion of the proximal loops is greatly affected [33]. Dworkin et al. and Allen Mersh et al. assessed the affection using Doppler flowmetry and found that HL significantly reduces perfusion of the proximal limb of the colon [53]. The decrease in proximal intestinal perfusion blood flow may lead to the incidence of anastomotic ischemia. If the affected proximal limb has evidence of ischemia, the surgeon usually chooses to perform an additional colectomy [31]. This would increase the risks associated with the surgery and the incidence of AL. From an anatomical point of view, the left branch of the MCA and the ascending branch of the LCA form anastomotic branches near the splenic flexure through the Riolan arc, but anastomosis in this area is usually thin and is absent in 5% of cases [38]; this undoubtedly increases the incidence of AL in HL-treated patients. On the other hand, several studies that have examined the area of the descending colon have reported that the quality of the MA between the final two branches of the LCA may be poor; thus, the final divisions must be carefully performed to support the MA in this region [21]. Further, given that laparoscopic techniques are widely used for surgery, bipolar electrosurgery instruments or high-power ultrasonic dissection devices might cause damage to the MA leading to a lack of blood supply to the anastomosis [28]. This would also increase the risk of AL in patients with HL. While our study did not include an outcome reflecting anastomosis tension, many researchers argue

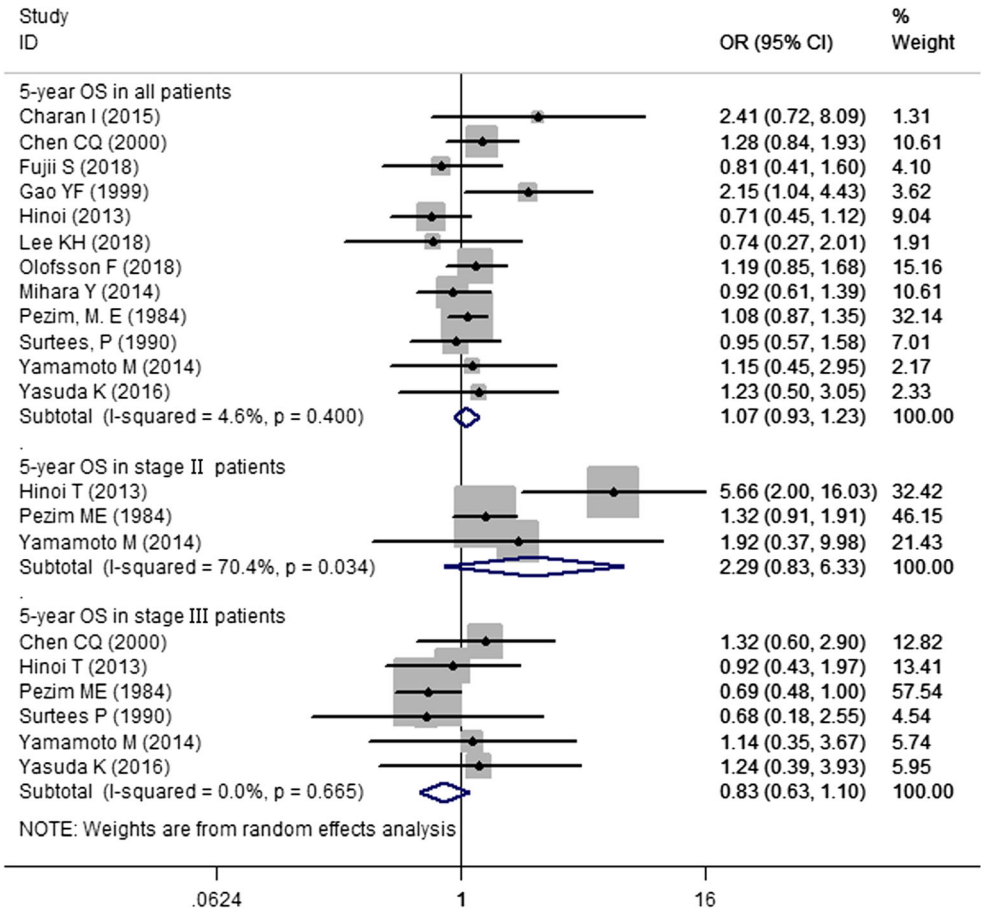

Fig. 4 The forest plot of 5-year OS between HL group and LL group

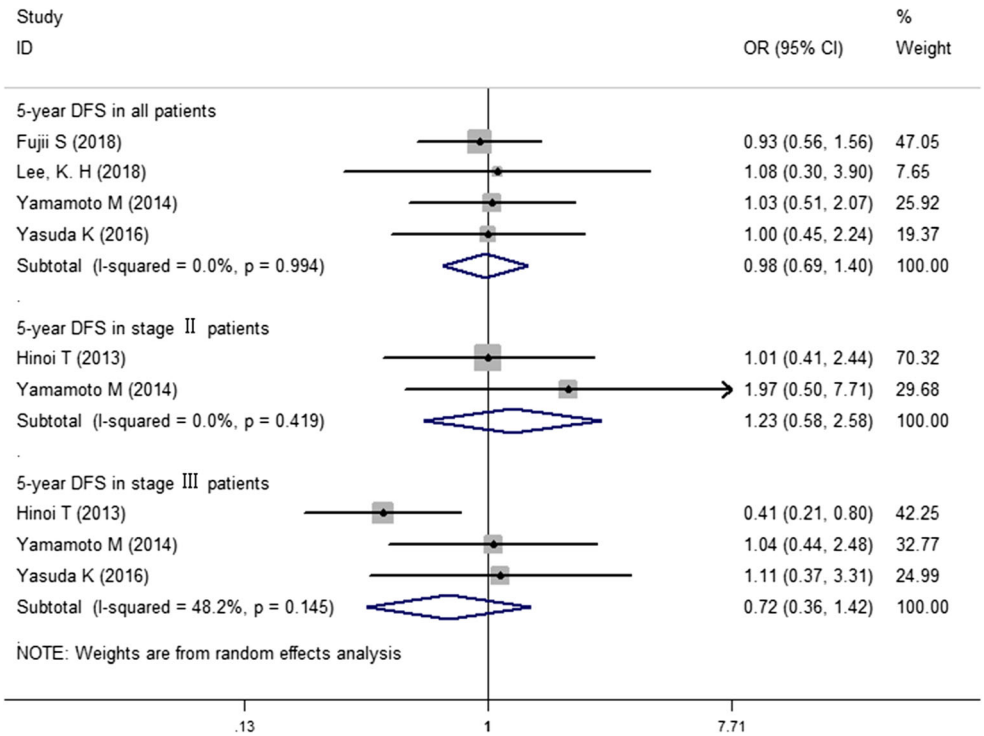

Fig. 5 The forest plot of 5-year DFS between HL group and LL group

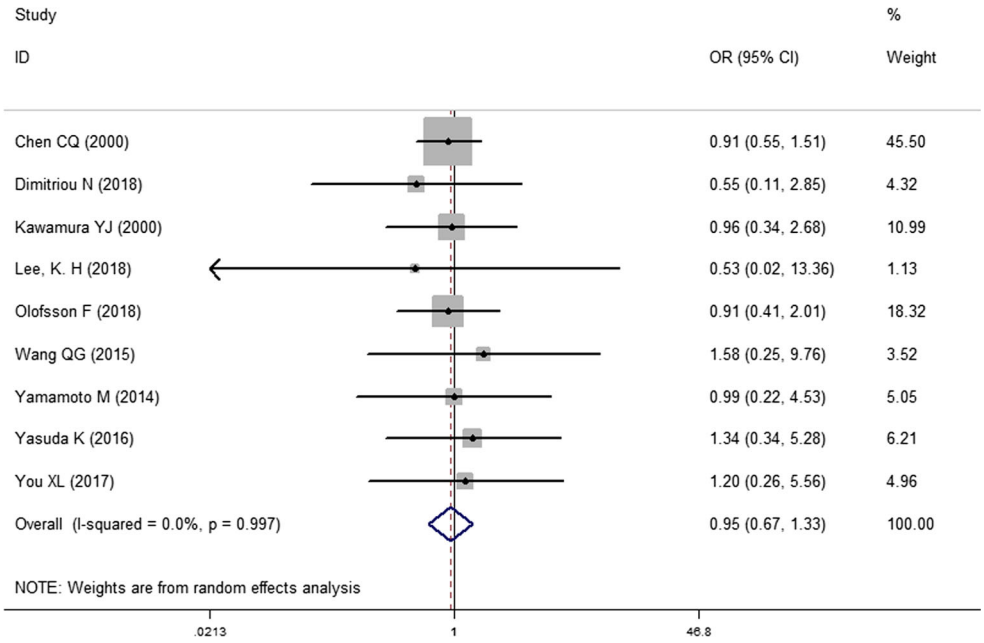

Fig. 6 The forest plot of local recurrence rates between HL group and LL group

that LL offers sufficient length to create tension-free anastomosis [36] and Bonnet et al. insisted that the additional gain in colonic length produced by HL is only small [42].

Autonomic nerve injury is another common postoperative complication of colon cancer surgery. Based on the primary studies evaluated in the current meta-analysis, we can only analyze postoperative UD. The pooled result indicated that the incidence of UD was significantly lower in the LL group. Anatomically, the lumbar splanchnic nerves associated with bladder function are distributed at the origin of the IMA [29]. Therefore, the reduced occurrence of UD in the LL group may be due to the protection of autonomic nerves from injury.

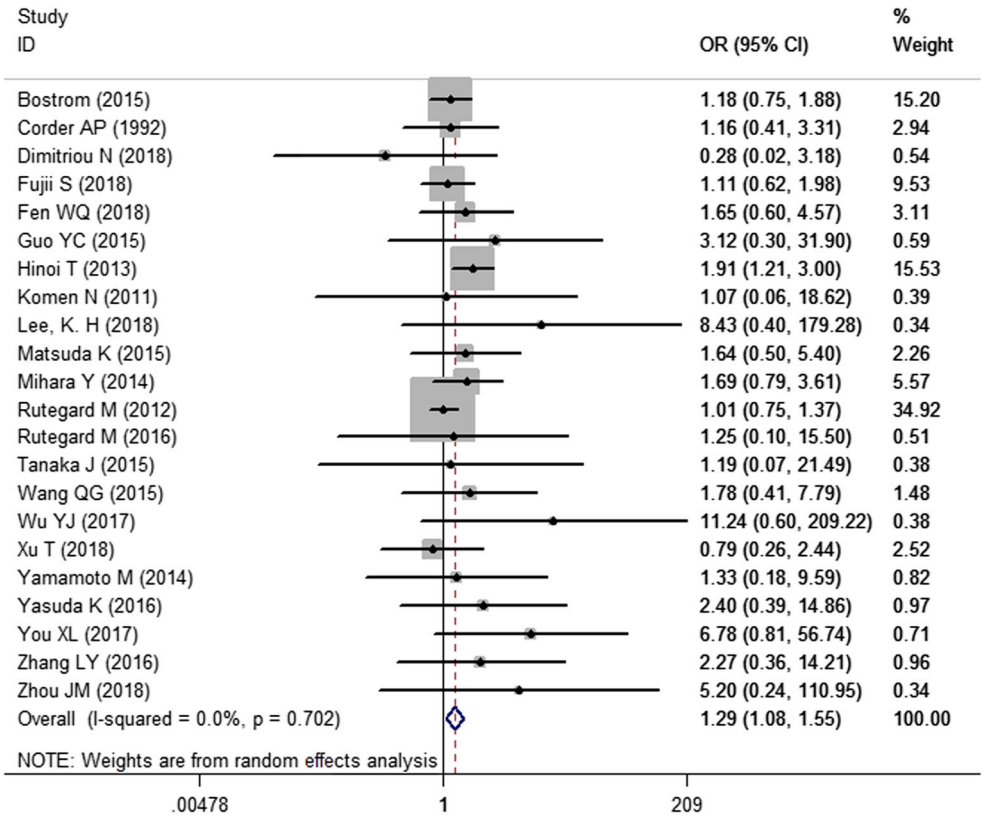

Fig. 7 The forest plot of incidence of anastomotic leakage between HL group and LL group

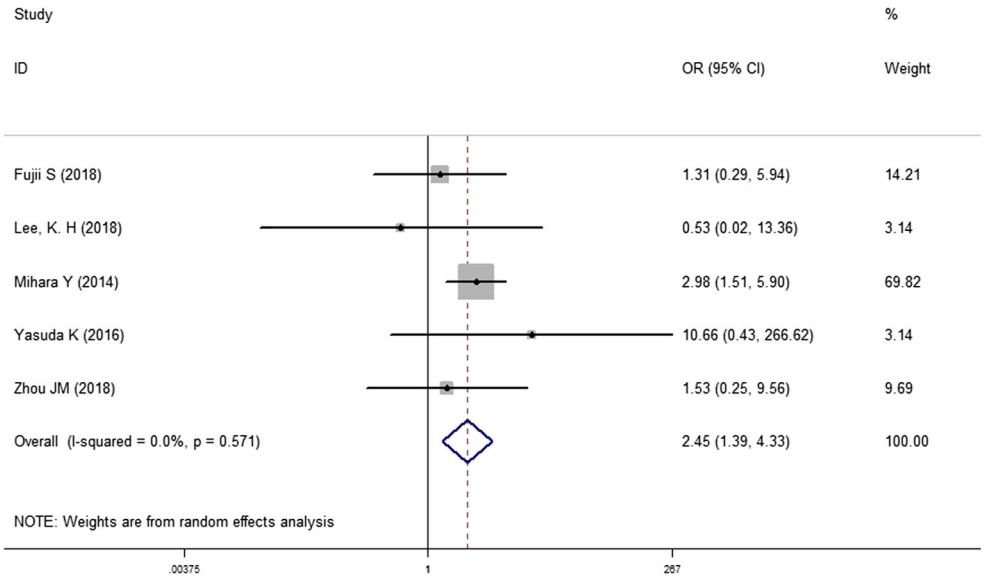

Fig. 8 The forest plot of incidence of urinary dysfunction between HL group and LL group

Our meta-analysis has several advantages over the available published meta-analyses. First, we included a large number of studies. In particular, we included several RCTs and retrospective cohort studies that have been recently published and were not captured by previous meta-analyses. Second, our meta-analysis included more than 11,000 patients from nine different countries, allowing us to obtain results that are broader in scope and richer in meaning. Finally, we further performed analysis of 5-year OS rate and DFS rate in stage II and stage III patients in order to assess whether there is a difference between the two techniques in patients at different disease stages.

Despite these advantages, the pooled results of this meta-analysis should be interpreted with caution for several reasons. First, the literature review retrieved 30 eligible studies; six of these were RCTs and the remaining 24 studies were retrospective observational studies. The observational studies that may lead to the overall level of clinical evidence obtained here are relatively low [54]. Second, the lack of a formal definition of

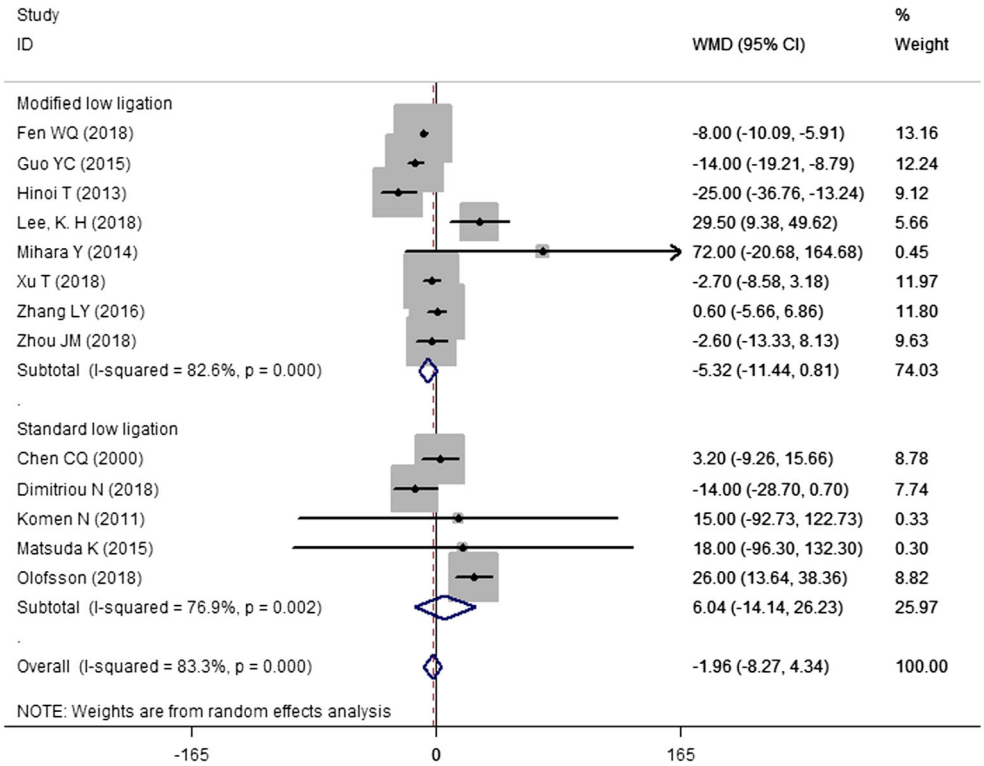

Fig. 9 The forest plot of subgroup and overall analysis of operation time between HL group and LL group

anastomotic leakage may attenuate associations between level of ligation and leakage [31]. Third, we analyzed the total number of harvested lymph nodes and the operative time based on the two different LL techniques; however, the two LL techniques could not be analyzed separately with respect to the other outcomes examined in our study due to a lack of available data. Finally, as Betrand et al. [55] and Murono et al. [48] showed in their respective study, there is inter-individual variation in the anatomy of the division of the branches of the IMA. Due to individual differences between patients (anatomy) and surgeons (surgical techniques), it is difficult, if not impossible, to identically reproduce a surgical procedure. Therefore, some outcomes of our meta-analysis exhibited high heterogeneity, which may affect the quality of evidence to some extent.

Conclusion

In conclusion, LL can achieve equivalent lymph node yield and survival benefit as compared to HL and is associated with a lower incidence of AL and UD. Another advantage of LL is that surgery on the residual colon can be performed since the LCA is preserved. For patients with recurrent ascending or transverse colon tumors after surgery for rectal or sigmoid cancer, the left transverse colon is more likely to be able to be retained because there is blood flow to the LCA [37]. Thus, based on the current available evidence, LL is recommended for colorectal cancer surgery regardless of the stage of the tumor. High-quality RCTs that investigate the efficiency and safety of the two techniques, especially with respect to modified LL, are needed to provide more reliable evidence and validate these recommendations.

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Authors' contributions TKG, KHY, and MBS carried out the concepts, design, definition of literature search, data acquisition, data analysis, and manuscript preparation. MBS, PJY, and ZYD provided assistance for data acquisition, data analysis, and statistical analysis. LYL, HWT, and WJJ fulfilled literature search, data acquisition, and quality assessment. WTJ, JY, and CWH accomplished data analysis and statistical analysis. MBS and ZYD wrote the manuscript. Finally, TKG, KHY, and XES reviewed and revised the paper. All authors have read and approve the content of the manuscript.

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Compliance with ethical standards

Conflict of interest Mou-Bo Si, Pei-Jing Yan, Zhen-Ying Du, Lai-Yuan Li, Hong-Wei Tian, Jia Yang, Cai-Wen Han, Xiu-E Shi, Ke-Hu Yang, and Tian-Kang Guo have declared no conflict of interest or financial ties to disclose.

Ethical approval This study is a systematic review and meta-analysis therefore Institutional Review Board (IRB) approval was not needed.

Appendix 1

Table 3 Search algorithms for each database

Database	Search strategy
PubMed	(("Rectal Neoplasms" [Mesh]) OR "Sigmoid Neoplasms" [Mesh]) OR ((((((((((((((((((((((((Neoplasm*, Rectal [Title/Abstract]) OR Rectal Neoplasm* [Title/Abstract]) OR Rectal Tumor* [Title/Abstract]) OR Rectal Cancer* [Title/Abstract]) OR Rectum Cancer* [Title/Abstract]) OR Neoplasm, Rectum [Title/Abstract]) OR Rectum Neoplasm [Title/Abstract]) OR Tumor, Rectal [Title/Abstract]) OR Cancer of Rectum [Title/Abstract]) OR Cancer, Rectal [Title/Abstract]) OR Cancer, Rectum [Title/Abstract]) OR Cancer of the Rectum [Title/Abstract]) OR Neoplasm*, Sigmoid [Title/Abstract]) OR Neoplasm*, Sigmoid Colon [Title/Abstract]) OR Sigmoid Neoplasm* [Title/Abstract]) OR Sigmoid Colon Neoplasm* [Title/Abstract]) OR Colon Neoplasm*, Sigmoid [Title/Abstract]) OR Sigmoid Cancer [Title/Abstract]) OR Cancer, Sigmoid [Title/Abstract]) OR Sigmoidal Cancer [Title/Abstract]) OR Sigmoid Colon Cancer [Title/Abstract]) OR Cancer, Sigmoid Colon [Title/Abstract]) OR Colon Cancer, Sigmoid [Title/Abstract]) OR Cancer of Sigmoid [Title/Abstract]) AND (((((high ligation [Title/Abstract]) OR high tie [Title/Abstract]) OR Left colic artery ligation [Title/Abstract]) OR LCAL [Title/Abstract])) AND ((((low ligation [Title/Abstract]) OR low tie [Title/Abstract]) OR left colic artery preservation [Title/Abstract]) OR LCAP [Title/Abstract]).
Embase	#1 rectum tumor'/exp. #2 mass, rectum':ab,ti OR 'neoplasma recti':ab,ti OR 'pararectal tumor':ab,ti OR 'pararectal tumor':ab,ti OR 'rectal mass':ab,ti OR 'rectal neoplasm*':ab,ti OR 'rectal tumor':ab,ti OR 'rectal tumor':ab,ti OR 'rectum mass':ab,ti OR

Table 3 (continued)

Database	Search strategy
	'rectum neoplasm':ab,ti OR 'rectum tumor':ab,ti OR 'retrorectal tumor':ab,ti OR 'retrorectal tumor':ab,ti OR 'tumor recti':ab,ti OR 'tumor recti':ab,ti
	#3: #1 OR #2
	#4 'colon tumor'/exp.
	#5 'colon neoplasm':ab,ti OR 'colon sigmoid tumor':ab,ti OR 'colon sigmoid tumor':ab,ti OR 'colon tumor':ab,ti OR 'colon villous tumor':ab,ti OR 'colon villous tumor':ab,ti OR 'colonic neoplasms':ab,ti OR 'colonic tumor':ab,ti OR 'colonic tumor':ab,ti OR 'mesocolon tumor':ab,ti OR 'mesocolon tumor':ab,ti OR 'sigmoid colon tumor':ab,ti OR 'sigmoid colon tumor':ab,ti OR 'sigmoid neoplasms':ab,ti OR 'sigmoid tumor':ab,ti OR 'sigmoid tumor':ab,ti
	#6: #4 OR #5
	#7: #3 OR #6
	#8 'high ligation*':ab,ti OR 'high ligature*':ab,ti OR 'high tie*':ab,ti OR 'left colic artery ligation':ab,ti OR 'lcal':ab,ti
	#9 'low ligation*':ab,ti OR 'low ligature*':ab,ti OR 'low tie*':ab,ti OR 'left colic artery preservation':ab,ti OR 'lcap':ab,ti
	#10: #7 AND #8 AND #9
The Cochrane Library	#1 MeSH descriptor: [Rectal Neoplasms] explode all trees
	#2 MeSH descriptor: [Sigmoid Neoplasms] explode all trees
	#3 Rectal Cancer*
	#4 Rectum Cancer*
	#5 Rectum Neoplasm*
	#6 Rectal Tumor*
	#7 Neoplasm*, Rectal
	#8 Cancer, Rectal
	#9 Cancer of Rectum
	#10 Tumor, Rectal
Database	search strategy
The Cochrane Library	#11 Rectal Neoplasm
	#12 Neoplasm, Rectum
	#13 Sigmoid Colon Neoplasm*
	#14 Neoplasm*, Sigmoid Colon
	#15 Neoplasm*, Sigmoid
	#16 Sigmoid Neoplasm
	#17 Colon Neoplasms, Sigmoid
	#18 Cancer of Sigmoid
	#19 Colon Cancer, Sigmoid
	#20 Sigmoid Cancer
	#21 Sigmoidal Cancer
	#22 Cancer, Sigmoid
	#23 Cancer of the Sigmoid
	#24 Sigmoid Colon Cancer
	#25 Cancer, Sigmoid Colon
	#26 Sigmoid Colon Neoplasm
	#27 Neoplasm, Sigmoid Colon
	#28 Sigmoid Colon Neoplasms
	#29 Neoplasms, Sigmoid Colon
	#30 Neoplasm*, Sigmoid
	#31 Sigmoid Neoplasm
	#32 Colon Neoplasms, Sigmoid
	#33 Cancer of Sigmoid
	#34 Colon Cancer, Sigmoid
	#35 Sigmoid Cancer
	#36 Sigmoidal Cancer
	#37 Cancer, Sigmoid
	#38 Cancer of the Sigmoid
	#39 Sigmoid Colon Cancer
	#40 Cancer, Sigmoid Colon
	#41: #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40
	#42 high ligation*
	#43 high ligature*
	#44 high tie*
	#45 Left colic artery ligation

Table 3 (continued)

Database	Search strategy
	#46 LCAL #47 #42 or #43 or #44 or #45 or #46 #48 low ligation* #49 low ligature* #50 low tie* #51 left colic artery preservation #52 LCAP #53 #48 or #49 or #50 or #51 or #52 #54: #41 and #47 and #53
Web of science	#1 Topic: (Rectal Neoplasms) OR Topic: (Sigmoid Neoplasms) OR Topic: (Rectal Cancer*) OR Topic: (Rectum Cancer*) OR Topic: (Rectum Neoplasm*) OR Topic: (Rectal Tumor*) OR Topic: (Neoplasm*, Rectal) OR Topic: (Cancer, Rectal) OR Topic: (Cancer, Rectum) OR Topic: (Cancer of Rectum) OR Topic: (Tumor, Rectal) OR Topic: (Rectal Neoplasm) OR Topic: (Neoplasm, Rectum) OR Topic: (Sigmoid Colon Neoplasm*) OR Topic: (Neoplasm*, Sigmoid Colon) OR Topic: (Neoplasm*, Sigmoid) OR Topic:
Database	search strategy
Web of science	(Sigmoid Neoplasm) OR Topic: (Colon Neoplasms, Sigmoid) OR Topic: (Cancer of Sigmoid) OR Topic: (Colon Cancer, Sigmoid) OR Topic: (Sigmoid Cancer) OR Topic: (Sigmoidal Cancer) OR Topic: (Cancer, Sigmoid) OR Topic: (Cancer of the Sigmoid) OR Topic: (Sigmoid Colon Cancer) #2 Topic: (Cancer, Sigmoid Colon) OR Topic: (Sigmoid Colon Neoplasm) OR Topic: (Neoplasm, Sigmoid Colon) OR Topic: (Sigmoid Colon Neoplasms) OR Topic: (Neoplasms, Sigmoid Colon) OR Topic: (Neoplasm*, Sigmoid) OR Topic: (Sigmoid Neoplasm) OR Topic: (Colon Neoplasms, Sigmoid) OR Topic: (Cancer of Sigmoid) OR Topic: (Colon Cancer, Sigmoid) OR Topic: (Sigmoid Cancer) OR Topic: (Sigmoidal Cancer) OR Topic: (Cancer, Sigmoid) OR Topic: (Cancer of the Sigmoid) OR Topic: (Sigmoid Colon Cancer) OR Topic: (Cancer, Sigmoid Colon) #3:#2 OR #1 #4Topic: (high ligation*) OR Topic: (high ligature*) OR Topic: (high tie*) OR Topic: (Left colic artery ligation) OR Topic: (LCAL) #5Topic: (low ligation*) OR Topic: (low ligature*) OR Topic: (low tie*) OR Topic: (left colic artery preservation) OR Topic: (LCAP) #6: #5 AND #4 AND #3
CBM	1 “结直肠肿瘤”[不加权:扩展] 2 ((((“结直肠癌”[常用字段:智能]) OR “结直肠腺癌”[常用字段:智能]) OR “直肠癌”[常用字段:智能]) OR “结肠癌”[常用字段:智能]) OR “乙状结肠癌”[常用字段:智能] 3 (#2) OR (#1) 4 (“高位结扎”[常用字段:智能]) OR “保留左结肠动脉”[常用字段:智能] 5 (“低位结扎”[常用字段:智能]) OR “不保留左结肠动脉”[常用字段:智能] 6 (#5) AND (#4) AND (#3)

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