

Meta-Analysis

The difference between preserving and non-preserving left colonic artery for low rectal cancer: a meta-analysis

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ABSTRACT

The aim of this study is to compare the superiority and safety of preserving and non-preserving left colonic artery. PubMed, Google scholar and Medline were searched for eligible studies from 1965 to 2018. Operative time, blood loss, number of resected lymph nodes, anastomotic leakage, and ileus, and morbidity, hospital length of stay, wound infection and mortality were the main outcome study. 23 studies involving 10,644 patients were included in the analyses. Compared with the preserving approach, the non-preserving approach had less operative time (weighted mean difference (WMD)=9.37 min, 95% confidence interval (CI) (8.92,9.81), $p<0.01$), less blood loss (WMD=8.28, 95% CI (7.43, 9.13), $p<0.01$), and preserving approach had shorter duration of hospital stay (WMD=-2.84 days, 95% CI (-5.49, -0.19), $p<0.06$) and also anastomotic leakage (WMD=0.79, 95% CI (0.67, 0.95), $p<0.54$). No other significant differences were observed. Preserving left colonic artery proves to be safer and more feasible as compared to the non-preserving left colonic artery in terms of reducing the incidence of anastomotic leakage and hospital length of stay. Non-preserving left colonic artery proved to have less operative time and blood loss, because most of the surgery was done laparoscopically.

Keywords: Preservation, Non-preservation, Low tie, High tie, Colorectal cancer, Neoplasm, Inferior mesenteric artery

INTRODUCTION

Remarkably, colorectal cancers (CRC) are accountable for about ten percent of all cancers worldwide, which hugely measures to hundreds of millions of people that are now affected. Moreover, it is the third most predominant cancer in men and second most in women.¹ Left colonic and rectal cancers represent just under two thirds of all colorectal malignancies.² Resection of the tumor with sufficient margins and related mesentery, including the lymph nodes, remains the main modality of treatment of colorectal cancer.

Excision of the apical lymph node at the root of the inferior mesenteric artery (IMA) is understood to be obligatory for radical resection of rectal cancer since apical lymph node resection contributes to improve lymph node retrieval rates and the accuracy of tumor staging.³ Presently, most surgeons perform a high ligation of the IMA in rectal cancer patients to attain apical lymph node resection, a procedure in which the IMA is ligated at its origin and the blood supply to the distal colon depends entirely on the marginal artery that arises from the middle colic artery. Notwithstanding it being accepted, that the marginal artery is satisfactory for supporting the viability of the remaining colon.^{4,5} Several studies have actually shown that a high

tie of the IMA suggestively reduces perfusion of the proximal limb.⁶⁻⁹ Nevertheless, the resulting insufficient collateral circulation has the potential risk of leading to severe colonic ischemia in some patients.¹⁰ It has been suggested that low ligation, which is defined as ligation below the origin of the left colic artery (LCA) might resolve this difference.⁹ Still, this alternative procedure may end in a diminished number of harvested lymph nodes while distorting lymph node staging, thereby negatively affecting post-operative treatment. Also, avoided metastases may occur in some patients. With the viewpoint of these concerns, it was recently recommended that lymph node dissection nearby the IMA with preservation of the LCA would yield superior results.^{11,12} Supposedly, this surgical method would offer a better anastomotic blood supply also guarantee adequate lymph node retrieval rates. Studies trying this hypothesis in practice are obviously lacking but are immediately needed in order to advance the research and progress of the technique.

The goal of this study is to reveal the difference between preserving and non-preserving left colonic artery in low rectal cancer in terms of dominance and safety.

Left colic artery

The left colic artery is a subdivision of the inferior mesenteric artery that runs to the left behind the peritoneum and in front of the psoas major muscle, and after a short, but variable, course divides into an ascending and a descending branch; the stem of the artery or its branches cross the left ureter and left internal spermatic vessels. The branches of the left colic artery anastomose with branches of the middle colic and sigmoid arteries and contribute to the formation of the marginal artery of Drummond, an arterial channel that supplies the large intestine. After completing its course, the left colic artery divides into its terminal branches; the ascending and descending branch.

Ascending branch

Courses superiorly, anterior to the left kidney and then enters the transverse mesocolon. In the area of the splenic flexure, the ascending branch of the left colic artery anastomoses with the left branch of the middle colic artery, which arises from the superior mesenteric artery. This anastomosis is called the arcade of Riolan, which signifies a direct communication between the superior and inferior mesenteric arteries. This communication is significant to provide collateral blood flow in the event of a stenosis and occlusion.

Descending branch

Courses laterally in the retroperitoneum towards the descending colon, where it anastomoses with one of the sigmoid arteries, thereby contributing to the formation of the marginal artery of Drummond. (Figure 9)

METHODS

Search strategy

Studies published in English between the years of 1962 to 2018, were searched in the databases of PubMed, Google scholar and Medline using the main search terms “preservation”, “non-preservation”, “low tie”, “high tie”, “colorectal cancer”, “neoplasm”, “inferior mesenteric artery”. The search strategy differed per database by their different requirements. Additionally, relevant studies in the references of related articles were also screened.

Inclusion and exclusion criteria

Studies with the following criteria were included

The article language was restricted to English. Full text was available, and the compared outcomes contained at least one of the items mentioned below. If the same research team participated in multiple studies, only the study with the most comprehensive data was included. Patients underwent preserving or low tie and non-preserving or high tie approach for reasons other than rectal cancer (example- colorectal cancer. sigmoid cancer). Preservation or non-preservation of the LCA as the only difference between the experimental group and the control group.

Studies were excluded for the following reasons

Data on the main outcomes were unavailable. Case report reviews, comment, non-English articles, meta-analysis, animal study.

Data extraction and study quality assessment

Data extraction was performed by using specially designed data extraction sheets. After we collected 23 full papers, which included the author, year, country, design and number of patients. The primary research outcomes of this meta-analysis were operation time, blood loss, number of resected lymph nodes, morbidity, anastomotic leakage, hospital stay, wound infection and mortality were all considered.

Statistical analysis

The meta-analysis was performed using the review manager software 5.3 that was provided by the Cochrane Collaboration. Continuous variables were pooled using the mean difference (MD) with a 95% confidence interval (95% CI), and dichotomous variables were pooled using the odds ratio (OR) with a 95% CI. Studies that reported only the median, range, and size of the trial, the means and standard deviations were calculated according to Hozo et al.¹³ Statistical heterogeneity was evaluated by I^2 , and it was considered to be high if the I^2 statistic was greater than 50%. The fixed effects model was used for studies with low or moderate statistical heterogeneity, and the random

effects model was used for studies with high statistical heterogeneity.

RESULTS

Selected studies

Four hundred twenty studies were identified by the search strategy previously described (Figure 1). Thirty pertinent studies were found after reading the abstracts. Finally, twenty-three studies were considered eligible after they were found to fit the inclusion criteria upon reading the full text. Studies were made up of 18 retrospective cohorts, 2 prospective studies and 3 randomized control trial studies. The studies were from UK, Canada, New York, Sweden, Japan, China, and Korea. In total, 3116 patients underwent preserving approach (n=3116) and non-preserving approach (n=7528) (Table 1).

Operation time

Nine studies 14-22 reported a significant difference of operative time between the NPLCA group compared to the PLCA (WMD=9.37 min, 95% CI (8.92, 9.81), $p<0.01$). Less operative time was observed in the NPLCA group. A fixed effect model was used due to significant heterogeneity ($p<0.0001$, $I^2=78\%$) Heterogeneity:

$\text{Chi}^2=35.86$, $\text{df}=8$ ($p<0.0001$); $I^2=78\%$. Test for overall effect: $Z=41.26$ ($p<0.00001$). (Figure 2)

Blood loss

Six studies reported a significant difference of blood loss between the NPLCA group compared to the PLCA (WMD=8.28, 95% CI (7.43, 9.13), $p<0.01$).^{15,18-22} Less blood loss was observed in the NPLCA group. A fixed effect model was used due to significant heterogeneity ($p=0.25$, $I^2=24\%$). Heterogeneity: $\text{Chi}^2=6.59$, $\text{df}=5$ ($p=0.25$); $I^2=24\%$. Test for overall effect: $Z=19.10$ ($p<0.00001$). (Figure 3)

Two studies reported a significant difference of hospital length of stay between the NPLCA group compared to the PLCA (WMD=-2.84, 95% CI (-5.49, -0.19), $p=0.04$).^{15,20} Less duration was observed in the PLCA group. A fixed effect model was used due to significant heterogeneity ($p=0.04$, $I^2=72\%$). Heterogeneity: $\text{Chi}^2=3.61$, $\text{df}=1$ ($p=0.06$); $I^2=72\%$. Test for overall effect: $Z=2.10$ ($p=0.04$). However, according to this analysis the PLCA having less hospital length of stay has nothing to with a laparoscopic or open technique. Therefore, preservation of the LCA during a laparoscopic or open rectal cancer resection does not affect the postoperative hospital stay.

Table 1: The basic characteristics of studies included in the meta-analysis.

Authors	Year	Country	Design	No. of patient PLCA/NPLCA
Rosi et al ³⁶	1962	-	Retrospective cohort	154/137
Grinnel et al ³⁵	1965	-	Retrospective cohort	181/179
Corder et al ⁶	1992	UK	Retrospective cohort	52/91
Pezim et al ²³	1994	Canada	Retrospective cohort	784/586
Slanetz et al ³⁰	1997	Ny	Retrospective cohort	1154/1107
Adachi et al ³⁴	1998	Japan	Retrospective cohort	38/134
Komen et al ¹⁶	2011	Netherland	Prospective cohort	17/16
Hinoi et al ¹⁵	2013	Japan	Retrospective cohort	155/256
Han et al ²⁶	2013	China	Retrospective cohort	80/76
Rutegard et al ²⁹	2012	Sweden	Retrospective cohort	1101/818
Shen et al ¹⁹	2014	China	Retrospective cohort	72/41
Yamamoto et al ²⁰	2014	Japan	Retrospective cohort	70/43
Matsuda et al ¹⁸	2015	Japan	RCT	49/51
Bostrom et al ²⁵	2015	Sweden	Retrospective cohort	388/334
Zhang et al ²¹	2016	China	Retrospective cohort	132/84
Rutegard et al ²⁸	2016	Sweden	Prospective cohort	18/5
Yasuda et al ²⁴	2016	Japan	Retrospective cohort	147/42
Zedan et al ³³	2016		Retrospective studies	76/38
Wang et al ³²	2015	China	RCT	65/63
Guo et al ⁴⁸	2017	China	RCT	28/29
Luo et al ²²	2017	China	Retrospective cohort	203/320
Kverneng et al ²⁷	2017	Sweden	Retrospective cohort	432/373
Lee et al ¹⁷	2018	Korea	Retrospective cohort	83/51

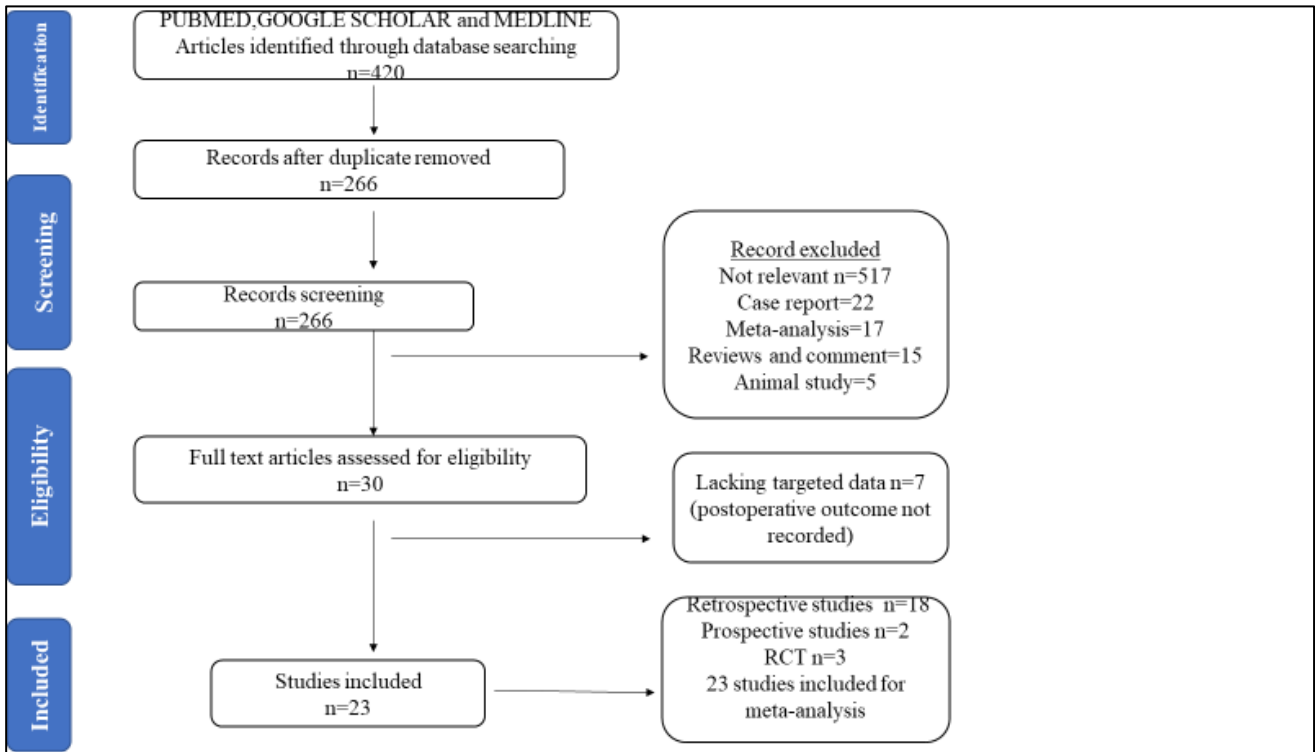


Figure 1: Flow chart showing the process for selecting the included studies.

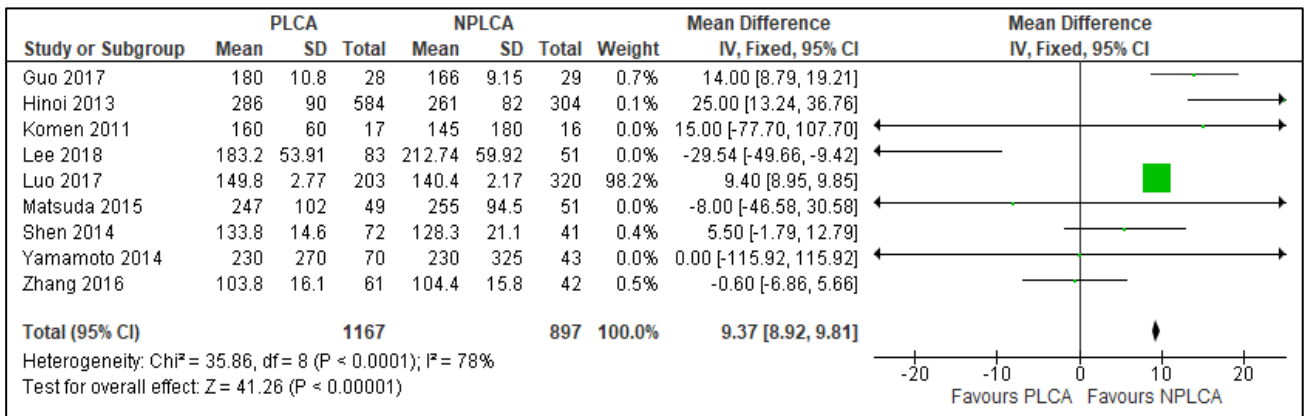


Figure 2: Preserved left colonic artery group versus non preserved left colonic artery, outcome. Operation time (min).

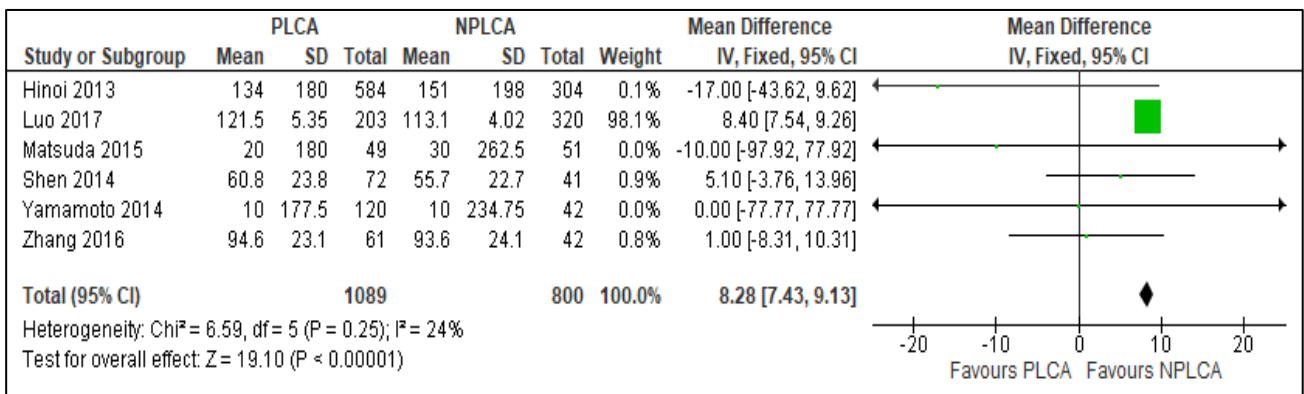


Figure 3: Preserved left colonic artery group versus non preserved left colonic artery, outcome: Blood loss (mL).

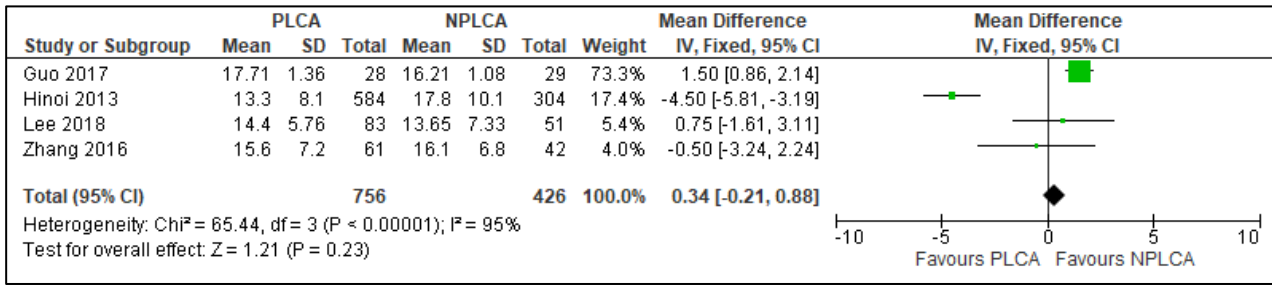


Figure 4: Preserved left colonic artery group versus non-preserved left colonic artery, outcome: lymph node Harvested.

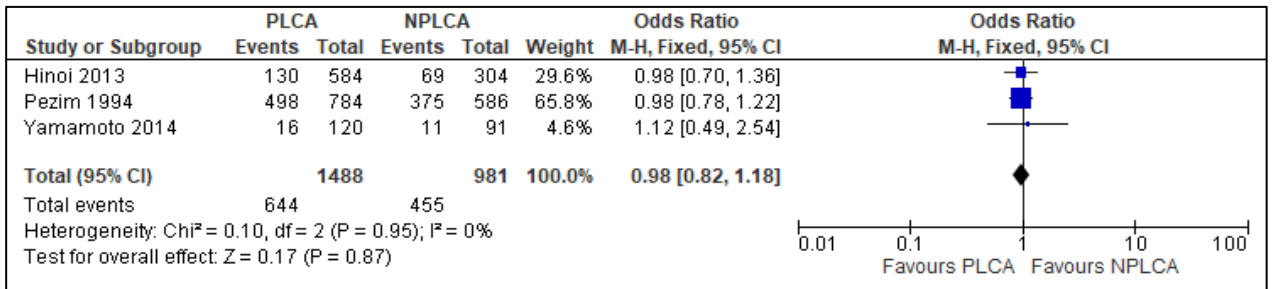


Figure 5: Preserved left colonic artery group versus non preserved left colonic artery, outcome: morbidity.

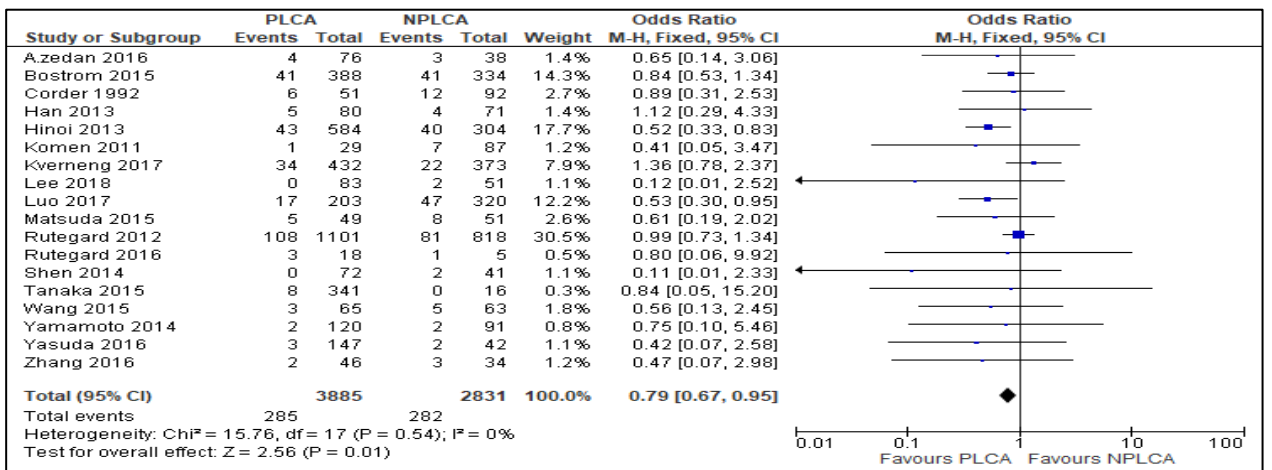


Figure 6: Preserved left colonic artery group versus non preserved left colonic artery, outcome: Anastomotic leakage.

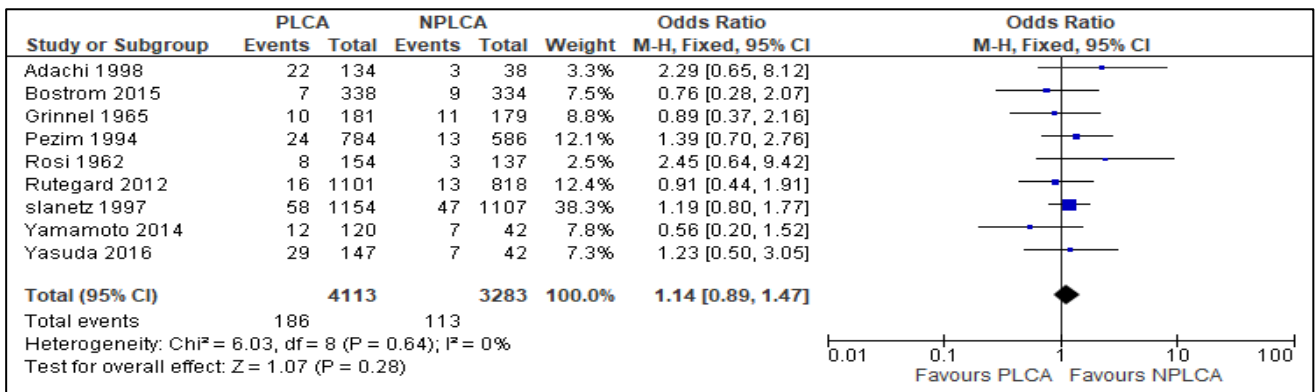


Figure 7: Preserved left colonic artery group versus non preserved left colonic artery, outcome: Mortality.

Lymph node harvested

Four studies reported the number of harvested lymph nodes. After pooling the results, we found no significant difference between the two groups (WMD=0.34, 95% CI -0.21, 0.88, p=0.23).^{14,15,17,21} No statistical significance was noted. Heterogeneity: $\text{Chi}^2=65.44$, $\text{df}=3$ ($p<0.00001$); $I^2=95\%$. Test for overall effect: $Z=1.21$ ($p=0.23$). (Figure 4)

Morbidity

Three studies reported morbidity and there was no significant difference found between the two groups for morbidity (OR= 0.94, 95% CI (0.82, 1.18), $p=0.87$).^{15,20,23} No significant heterogeneity was noted; thus, the fixed-effect model was used. Heterogeneity: $\text{Chi}^2=0.10$, $\text{df}=2$ ($p=0.95$); $I^2=0\%$. Test for overall effect: $Z=0.17$ ($p=0.87$). (Figure 5)

Three studies reported wound infection and there was no significant difference found between the two groups for wound infection (OR=0.84, 95% CI (0.47, 1.51), $p=0.55$).^{15,20,24} No significant heterogeneity was noted; thus, the fixed-effect model was used. Heterogeneity: $\text{Chi}^2=3.62$, $\text{df}=2$ ($p=0.16$); $I^2=45\%$. Test for overall effect: $Z=0.59$ ($p=0.55$).

Anastomotic leakage

Eighteen studies reported anastomotic leakage.^{6,15-22,25-23} There was a significant difference between the two groups for anastomotic leakage (OR=0.79, 95% CI (0.67, 0.95), $p=0.01$). The PLCA group observed less anastomotic leakage compared to NPLCA group. Significant heterogeneity was noted; thus, the fixed-effect model was used Heterogeneity: $\text{Chi}^2=15.78$, $\text{df}=18$ ($p=0.61$); $I^2=0\%$. Test for overall effect: $Z=2.55$ ($p=0.01$). (Figure 6)

Mortality

Nine studies were collected for mortality and there was no significant difference found between the two groups for mortality (OR=1.14, 95% CI (0.89, 1.47), $p=0.28$).^{20,23-25,29,30,34-36} No significant heterogeneity was noted; thus, the fixed-effect model was used. Heterogeneity: $\text{Chi}^2=6.03$, $\text{df}=8$ ($p=0.64$); $I^2=0\%$. Test for overall effect: $Z = 1.07$ ($p=0.28$) (Figure 7).

Publication bias

The funnel plot on the anastomotic leakage is shown in figure below. Because all studies laid inside the 95% CI limits, no evidence of publications bias was noted. Egger test was performed to provide statistical evidence regarding funnel plot symmetry. Result still did not reveal any evidence of publication bias in anastomotic leakage (Heterogeneity: $\text{Chi}^2=15.78$, $\text{df}=18$ ($p=0.61$); $I^2=0$. (Figure 8)

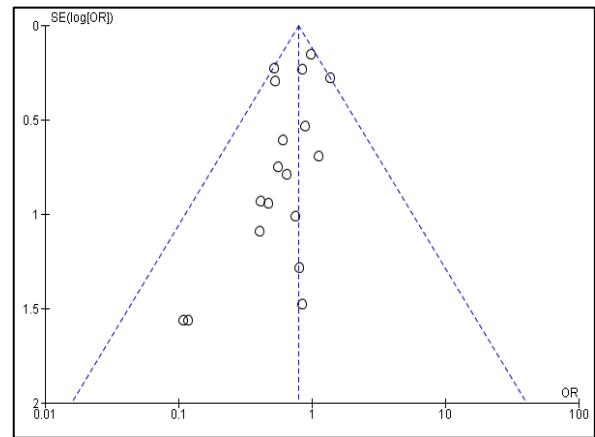


Figure 8: Funnel comparison: preserve versus non preserve left colonic artery: anastomotic leakage.

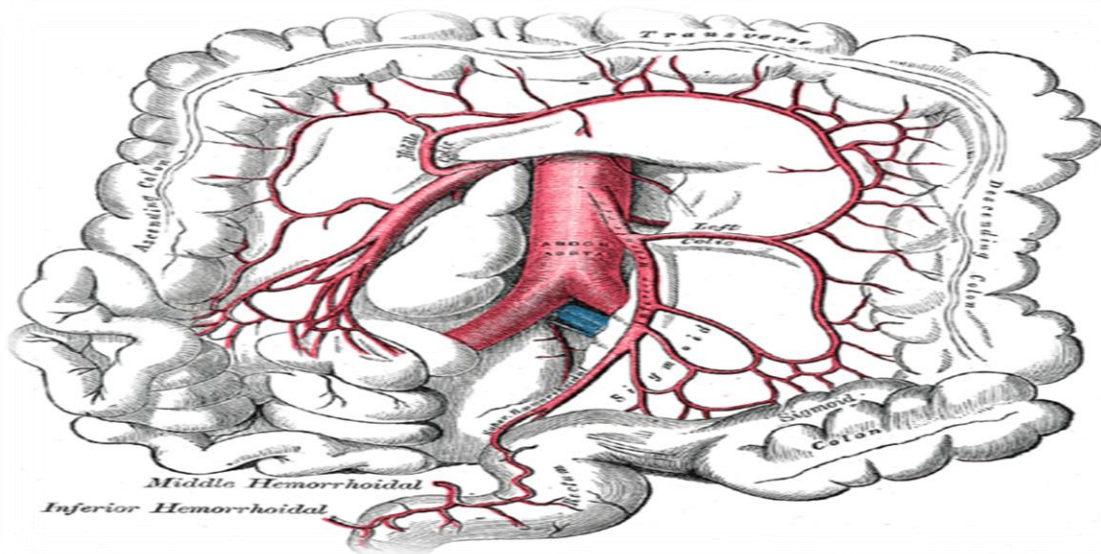


Figure 9: The inferior mesenteric artery and its branches. (Left colic artery visible at center right).

DISCUSSION

To date, the discussion of PLCA versus NPLCA persists. This study focuses on the safety and feasibility after PLCA compared to NPLCA. In rectal cancer surgery, the level of IMA ligation has always been debated.^{6,37-40} Although dividing the IMA is a small issue for rectal cancer surgery, there is still no consensus. The optimal ligation level should be demonstrated in light of several considerations, especially in light of oncological outcomes.

Surgical intervention plays a vital role in the survival of patients inflicted with colorectal cancer. But there is not a consensus to the question whether to preserve the LCA or not. According to Lowry et al, preservation of the LCA means low ligation of the IMA, while ligating the LCA means high ligation of the IMA.⁴¹ Arguments about preserving versus ligating the LCA have existed for at least the last 100 years. The first explanation of this argument was made by Moynihan in 1908 and he argued that ligation and division of the IMA should be flushed with the aorta, which signifies his agreement to ligate the LCA.⁴² Ligating the LCA was thought of to be easy and could decrease the tension of the anastomosis. Collectively, entire pieces of the IMA lymph nodes were removed, assisting in the determination of the stage and prognosis of the cancer.⁴³ Kanemitsu et al demonstrated that ligation of the LCA aided in the curative resection and long-term survival in patients with cancer of sigmoid or rectum colon, as well as, nodal metastases at the origin of the IMA.³⁸

Our goal of this meta-analysis was to differentiate the preservation of the left colonic artery compared to the non-preservation left colonic artery related to operative time, blood loss, and lymph node harvest, hospital length of stay, anastomotic leakage, wound infection, morbidity and mortality. Within the studies, anastomotic leakage was the most common occurrence. Taking into account operation time, nine of the included studies had exhibited a much longer operation time in PLCA group than that of NPLCA group (weighted mean difference (WMD)=9.37 min, 95% CI (8.92, 9.81), $p<0.01$) and six studies also recorded a significant difference in blood loss, whereby NPLCA observed the least blood loss (weighted mean difference (WMD)=8.28, 95% CI (7.43,9.13), $p<0.01$)^{14,16,19-21}. Yet to come high powered and well-designed random control trials will still be required to examine these issues. However, in regards to lymph node harvest, no significant difference was found in the 2 groups (WMD=0.34, 95% CI-0.21, 0.88, $p=0.23$). Recent studies have demonstrated that patients with metastatic lymph nodes above the left colic artery had a poor 5-year disease free survival rate, 31.9% versus 69.4% subsequently, in the metastatic and negative IMA lymph nodes groups.^{44,45} The preserved left colonic artery also reported a decreased length in hospital stay over the non-preserved group (WMD=-2.84, 95% CI (-5.49, -0.19), $p=0.04$) in two studies. Noticeably, our studies found a statistically significant difference between the PLCA and NPLCA group in the anastomotic leakage

and non-preservation of LCA instead caused more anastomotic leakage.⁴⁶ Anastomosis blood transfusion is the most critical risk factor that influences the anastomotic leakage.⁴⁷ The surgical technique of LCA non-preservation includes the section of the IMA at its aortic origin to obtain extra length to perform 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, there was not any difference in wound infection and morbidity between the two groups. Nine studies also collected mortality rate and there was no significant difference between the two groups (OR= 1.14, 95% CI (0.89, 1.47), $p=0.28$) but, explanations of those outcomes may be associated with several factors. Firstly, the extent of lymph node dissection of two groups was equivalent, which indicates that patients in both groups could receive the same radical range of tumor. Secondly, the number of positive lymph nodes was not significantly different between the two groups. The invasion depth of tumor in surgeries can be accurately evaluated during surgeries, combined with postoperative pathological situation, the accuracy in tumor staging will be no different and additional treatment will be the same. Thirdly, previous studies, including this meta-analysis, showed no significant difference in the long-term complications and recurrence rate between the two groups. Hence, we had unequivocal evidence that preservation of the LCA could have the same effect as non-preservation.

It is acknowledged that several limitations and imperfections were encountered throughout this study. First, most studies were retrospective cohort, with few randomized control and prospective studies were available in this field, which may reduce each result's reliability. Second, the limited number of applicable studies may influence the statistical power. Third, the experience and skill of each surgeon likely differed between studies, which would produce certain bias.

CONCLUSION

In summary, our meta-analysis suggested that preserving the left colonic artery was preferred over not preserving the left colonic artery in terms lower risk of anastomotic leakage and hospital stay duration. The PLCA proves to be safe, feasible and an efficacious technique for patients with colorectal cancer. There was found to be compelling differences between PLCA and NPLCA, NPLCA had less operative time and less blood loss when the operation was done by laparoscopic method unlike PLCA. Nevertheless, in regards to the number of lymph node harvest, wound infection, morbidity and mortality, there was no significant difference between PLCA and NPLCA. However, as there are limitations of this meta-analysis, conclusions should be regarded with some scepticism.

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