

# A Short-Term Outcome on Ligating the Different Levels of the Inferior Mesenteric Artery (IMA). A Prospective Cohort Study.

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## Research

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# Abstract

**Background:** This study is to analyze the impact on the level of Inferior mesenteric artery (IMA) ligation of Colorectal cancer surgery. The retrieval of lymph nodes (LNs) and anastomotic leakage was the main concern of this study.

**Methods:** In this prospective study, the high and low ligation cases were selected. The retrieved LNs from roots of the inferior mesenteric artery (IMA) and left colic artery (LCA) was sent for histopathological examination (HPE), irrespective of the method of ligation. The observation of HPE results and Anastomosis leakage were analyzed.

**Result:** In the total numbers of 369 cases, 12 cases were cancer positive LNs at the root of IMA despite 349 harvested LNs. On another hand, just one case showed LCA positive LNs obviously because just 12 cases were had harvested LNs at the root of LCA. where Two cases of leakage were seen in both groups over a three-month follow-up.

**Conclusions:** This result signifies the importance of IMA root LNs clearance and concern of high ligation. However, the small number of cases demand further well-designed RCTs to make an evidence-based decision.

## Introduction

Colorectal cancer is a major public health issue, and it is the third-most commonly diagnosed with cancer and also the fourth cause of cancer death throughout the world.<sup>[1]</sup> The increasing worldwide burden of colorectal cancer (CRC) is anticipated to increase by 60% to over 2.2 million new cases and 1.1 million deaths by 2030.<sup>[2]</sup> The early pioneer of colorectal cancer surgeons has experienced that cancer of the rectum can be only cured by the surgeon and it is still the mainstream of colorectal cancer treatment.<sup>[3]</sup> In the first technique of Miles, he proposed ligation of arterial supply was below the left colic artery. However, Moynihan claimed that by applying low ligation, the atypical groups of lymph nodes near to the inferior mesenteric artery could be the source of metastases sooner or later. In his opinion, the high ligation should be done near to the aorta. But with time leakage became an issue. Since the controversy started and yet to be resolved.<sup>[4]</sup>

Japanese doctors working with the concept of lateral lymph node dissection. However, this technique is abandoned in Europe even though the article from Japan showed local cancer control and survival improvement. The ongoing open debate is “do we need high ligation and maximum lymph node retrieval for long-term survival or shall we need to abandon it for anastomosis leakage? Does really, high ligation cause anastomotic leakage? Unfortunately, the disagreement on it may also compromise complete lymph node retrieval which leads to the harbor of cancer cells at the root of IMA. Which somehow may cause vulnerability to cancer reoccurrence to some extent.

In this study, we aim to explore the possible short-term outcome of high and low ligation to elucidate the prognostic impact on distal colorectal cancer. The main concern was to know the possibility of lymph nodes at the root of IMA and the Number of leakages after high ligation.

## **Materials And Methods**

### **Inclusion and exclusion criteria**

The data of 369 consecutive patients who underwent colorectal cancer surgery from July 2017 to July 2019 in the Department of Gastrointestinal Surgery, West China Hospital were prospectively collected and analyzed. The inclusion criteria were - Histologically proven and primary colorectal cancer cases, the case of the distal descending colon with less than 45 cm from the anal verge, sigmoid or rectal cancer, High and low ligation (defined by surgeons), all cases underwent through colorectal surgery with primarily end to end anastomosis, Tension-free anastomosis continuity, Histo-pathological (HP) margin free cancer at the end-to-end anastomosis. The exclusion criteria were – Noncancer colorectal surgery. Age above 80 years old. Colorectal cancer surgery with a permanent colostomy, Have secondaries metastasis (liver), and previously operated colorectal cancer cases.

### **Surgical Method And Follow-up**

The high ligation was done at the root of the aorta while low ligation just at the distal root of the LCA. Our choice of high and low ligation depends on the surgeon. It is based on the gross intraoperative evaluation of cancer extension and observation of LNs Metastasis at the root of IMA. We have undergone either open laparotomy or laparoscopic operative procedures depending upon the surgeon's choice after fulfilled all eligible criteria of exclusion and inclusion.

The retrieval of LNs was irrespective of the level of IMA ligation. we cleared IMA root lymph nodes even in low ligation cases. Patients with advanced cancer received extensive excision, With tumor-specific mesorectal excision. All patients' anastomoses were reconstructed by end-to-end anastomosis. Lateral pelvic LN dissection was done for low rectal cancer patients. The potential lymph nodes were retrieved intraoperatively in obtainable instances. Further LNs were harvested by pathologists from the resected specimens of IMA or LCA. We had divided these LNs into two groups according to anatomical location, namely IMA and LCA lymph nodes. Where another analysis of high and low ligation patient group categorized for leakage analysis. We analyzed lymph node's status basis on the HPE report and leakage over three months of potential follows up period. We considered leakage-free anastomosis after initiation of liquid to solid diet after or before hospital discharge with the passage of stool. We found just a total of two complaints of leakage in each group of high and low ligation procedures in the three months of the follow-up study.

### **Clinicopathologic Characteristics-**

The clinicopathological characteristics were followed from the colorectal cancer Database of West China Hospital, Sichuan University, with regards to each patient's age, sex, tumor size, tumor location, histopathological examination report of T, N, M staging based on resected lymph nodes patterns of high ligation and low ligation. However, the retrieved LNs numbers (< 12) don't meet the "N"-staging criteria of NCCN guidelines<sup>[5]</sup>. Probably it's one of the disadvantages of our research and it possibly due to no routine use of any dye for the LNs mapping. Thus, our study has a major limitation to the establishment of precise TNM staging level of prospective follow-up at the root of IMA. However, histopathological examination (HPE) acquired its own level of sensitivity and specificity with detecting LN from resected samples. Which is helpful to the approximate idea of LNs metastatic level.

## Statistical Analyses –

The statistical analysis is presented in tables and percentages.

## The Results Of Prospective Research

Table-B1

Procedure	No. of patients	No. of complications	No. of leakage
High ligation	239(64.8%)	18(7.5%)	2(0.83%)
Low ligation	130(35.3%)	14(10.7%)	2(1.5%)
Total Number	369	32(8.7%)	4(1.08%)

Table-B1 Showing number of leakages

Table-B2

Nature of LNs	IMA LNs	LCA LNs
Harvested lymph nodes	349(94.6%) cases	12(3.25%) cases
Cancer positive lymph nodes	12(3.25%) cases	1(0.27%) cases

Table -B2 Showing harvested and oncological positive lymph nodes at different levels

Table B-1, For mainly about leakage where Table B-2 presenting the Number of metastatic and oncological positive Lymph nodes at LCA and IMA.

HP-histopathological, +VE = Positive, LCA-Left colic artery, IMA- Inferior mesenteric artery.

This analysis is among 369 cases where 239 cases went under high ligation and 130 of low ligation. All cases were staged as T<sub>2-4</sub> by HPE reports. The entire case's retrieved LNs of the whole specimens, at IMA, and at LCA was harvested manually and then by a histopathologist. The presence of lymph nodes at IMA root was seen in 349(94.6%) cases where at LCA root was only in 12(20.6%) cases. The IMA cancer-

positive lymph nodes were in 12(3.25%) cases and they do not have necessarily LCA positive lymph nodes. The LCA cancer positive LNs was just 1 (0.27%) among all harvest lymph nodes. It indicates somehow skipping of sentinel LNs or it may display a comparative picture of Sentinel Lymph nodes which less likely present at proximal or at LCA root. Besides these, there are some other peramesenteric retrieved LNs which has shown a maximum number of malignant LNs near the IMA root. This may support the concept of possible total mesocolon-resection with possible-IMA-root-LNs-retrieval. Further analysis of leakage relation in between High and low ligation. It shows both groups have two cases of leakage which is 0.83 and 1.5 in the percentage of total high and low ligation respectively. It demonstrates no much incidence of leakage in highlighting. However, this cannot be judged by such a small number of patients. On another hand, IMA showed a greater number of lymphatic metastasis and positive malignant nodes, despite IMA comes after LCA in the path of the Lymphatic spread. Which may have a direct relationship with prognosis evaluation.

## Discussion

This prospective study aimed to evaluate the different levels of inferior mesenteric artery ligation (high-low) and its impact on leakage and LNs retrieval. Anastomotic leakage is one of the short-term complications of high ligation, which is debated most dominantly for a long. Despite the benefits of high ligation and IMA root LNs resection which has distinct long-term oncological survival importance.

In our prospective study among 369 cases, 239 went under high ligation and 130 in the low ligation group. The presence of lymph nodes at IMA root was seen in 349(94.6%) cases where at LCA root was only in 12(20.6%) cases. The IMA cancer positive lymph nodes were in 12(3.25%) cases where LCA cancer positive LNs was just one (0.27%) case among all harvest lymph nodes. IMA root has shown a greater number of harvested lymph nodes and positive malignant lodging than the LCA deposits. Interestingly IMA root positive LNs do not have necessarily LCA root positive lymph nodes, despite all these cases were staged as T3 or greater. Additionally, the LCA, lymphatic station comes first then IMA along the path from cancer origin and metastasis. This phenomenon may indicate somehow skipping sentinel LNs in the case of colorectal surgery. In another sense, it may display a comparative picture of potent Sentinel Lymph nodes station at IMA, irrespective of the location of cancer origin colorectal surgery. Possibly it may have a direct relationship with prognosis. Besides these results of IMA and LCA, there is some other malignant para mesenteric deposition of LNs which has shown a maximum number of malignant LNs deposition among all harvested LNS. This may support the concept of possible total mesocolon-resection or TME.

Further Analysis of the relation of leakage between High and low ligation hasn't shown any significant difference in our prospective study. In total 239(64.8%) cases of high ligations, 18(7.5%) cases were seen with complications where just 2(0.83%) with leakage. On the other hand, 130(35.3%) cases of low ligation had 14(10.7%) cases of complication and 2(1.5%) cases of leakage which is statically higher than high ligation. This analysis demonstrates the controversial relation of leakage with high ligation and contrary to the condemned opinion of high ligation just because of leakage. However, it's hard to conclude in this

small number of cases. Thus, in our short-term prospective research, the analysis attempted to rethink our procedure from a different future approach rather than making a current judgmental decision.

In our previous meta-analysis, we found high ligation and IMA root LNs clearance carries a beneficial oncological outcome whenever it has lymphatic metastasis.<sup>[6]</sup> Collectively, these outcomes support high ligation with IMA LNs resection and should be preferably suitable for the prognostic dilemma of the oncological patient instead of low ligation concerning anastomotic leakage.

Currently, In the early stage of cancer with low risk of IMA positive or in the advanced stage with a high risk of IMA lymphatic metastasis, and application of high or low ligation solely depends upon the practitioner. In both cases, the surgeon's opinion varies. The controversy over the choice of high or low ligation of IMA has focused on the anastomotic leakage and oncological outcomes, these two have their own aspects.<sup>[7]</sup> High ligation ensures the IMA lymphatic clearance even though debated for increasing the risk of anastomotic leakage as it jeopardized the blood supply of LCA.<sup>[8, 9]</sup> Low ligation preserves the LCA and ensured blood supply of the marginal artery while leading to incomplete lymphatic resection of IMA.<sup>[10]</sup> As far concerning anastomosis leakage, A basic study recommends sigmoid colon is only not suitable for anastomosis due to its natural course of insufficient vascular supply but the marginal artery delivers sufficient vascular supply to the transverse and descending colon. Thus, the sigmoid colon is sacrificed and there should be no uncertainty in performing a high ligation.<sup>[2]</sup> Therefore, the prognostic significance of IMA lymphatic clearance dominates the choice of surgeons over the risk of anastomotic leakage which is a short-term outcome.

The origin of IMA is the third station of lymphatic drainage from the sigmoid and rectum. The incidence of IMA lymph node metastasis has been reported in fewer studies. It is associated predominantly with histopathological tumor staging along the course of IMA. Chen et al<sup>[11]</sup> reported, the IMA lymph node metastases were 0% (pT1 ), 1.0 % (pT2), 2.6% (pT3) and 4.3% (pT4) by of TNM staging. Korematsu et al<sup>[12]</sup> study showed the 8.3 percent (99 of 1188) incidence of metastasis to the origin of LCA. Nodal metastasis occurred more commonly in patients with pT3 and pT4 lower rectal cancer. The incidences of metastasis are at the root of IMA about 1.7 percent (20 of 1188). This represented how residual metastatic nodes could usually have been forgotten in low ligation if the IMA root not been cleared. Some surgeons still claim no evidence that high ligation may increase the prognosis and prefer to apply low ligation even in advanced cancer cases. However, our findings do not support low ligation without clearing IMA root LNs in advanced or suspicious cases metastasis cases.

Reviewing articles on anastomosis leakage, Some studies have concluded, high ligation has no indisputable proof of increased survival, Although the usage of IMA high ligation plays an important role in the improvement of lymph node retrieval, the precision of tumor staging, and to avoid tension in low pelvic anastomoses.<sup>[2, 7, 10]</sup> Dworkin et al<sup>[13]</sup> reported the high ligation results 41%-86% decrease in sigmoid blood supply around Five days. The sacrifice of LCA leads to Poor blood supply and it is one of the most important risk factors for anastomotic leakage. However, an RCT has shown the level of IMA

ligation in patients with rectal cancer didn't show any difference in anastomotic leakage.<sup>[14]</sup> In an addition, The local recurrence of cancer, hand-sewn versus stapled anastomoses, age, Intraoperative blood pressure, nutritional status of the patient including other factors subsequently leads to anastomotic leakage and can reduce survival<sup>[15-17]</sup>. Therefore, the accessible studies on the anatomical concern of leakage are controversial and somehow favor the high ligation from the oncological perspective. In fact, the supply of blood could be satisfied once if the colonic marginal arch was well maintained. Furthermore, a meta-analysis showed high ligation reduced 13% of 5-year OS compared to low ligation.<sup>[11]</sup>

Regardless of the above major related issues, available research for the anatomical consideration preferred the high ligation. A significant benefit of the high ligation is definitely by the resection of the IMA at its origin, which allows it to gain extra length and facilitate tension-free anastomosis.<sup>[18]</sup> Ghavami et al<sup>[19]</sup> reported, the precise mobilization of the splenic flexure significantly reduces, the anastomotic tension and in most cases allows the preservation of LCA. However, practically it's very difficult to achieve the additional length in low Colo-anal anastomosis or even in colonic J-pouch surgery unless high ligation of IMA. LCA is comparatively shorter and less feasible to the low Colo-anal anastomosis. The advantages of additional length usually support anastomosis using the descending colon rather than the sigmoid when performing an anastomosis. Not just the sigmoid colon generates fairly high pressure but additionally because it could consequently lead to relatively poor function and more importantly, the marginal artery may be minimal or absent in the sigmoid which is prone to ischemia if used for anastomosis. Hence in colonic implant anastomosis will almost always need a high ligation. However, this is for technical rather than cancer-specific reasons which also does support high ligation. <sup>[20]</sup>

The modern aspect of surgical evolution to visualize real-time lymphatic channels and vasculatures plays a great role in the prevention of anastomotic leakage as well as a high volume of LNs retrieval. The technology as the ICG Imaging System provides a real-time intraoperative evaluation of vascular perfusion. It's the best tool for Intraoperative evaluation of bowel anastomosis perfusion. Hypoperfusion can be well-recognized which is the main reason behind anastomotic leakage. It is normally subjectively approximated throughout the surgery by the surgeon based on the color or pulsation of the bowel in addition to a visible assessment of pulsatile bleeding from the edge of the bowel for use for anastomosis.<sup>[21-23]</sup> In another hand, ICG can also ensure an imaging approach for the discovery of tiny LNS, its channels, precise hepatic Mets, and peritoneal metastatic deposits.it may enable much better staging plus more comprehensive surgical resection of lymph nodes across the major artery and division of vessels which may potentially help to prevent compromise blood vessels and consequently ischemia. This is having a potential prognostic benefit for patients.<sup>[24-26]</sup> This technique may help even for clearing IMA root without compromising the left colic artery with complete mesocolon resection.

## Limitations Of This Prospective Study

This a non-randomized ongoing prospective research that has still a small number of patients. The bowel function has followed only for 3 months that is just based on vascular supply instead of oncological reoccurrence. The outcome of the patient's survival yet to be evaluated in the oncological aspect. The entire LNs retrieval was not precisely contrast-based. Even the use of the ICG system has a short duration of visualization for the lymphatics/vasculature supply, thus it does not guide throughout the surgical course of action. More importantly, it can not be applied routinely. we are still not very sure about the specificity and sensitivity of HPE results on the detection of cancer LNs. It is also because the advancing new techniques of detecting cancer LNs by polymerase chain reaction (PCR) may change the concept of LNs retrieval.

## **Conclusion**

This prospective study has attempted to rethink our future approach to the IMA ligation procedure at different levels. It might have an impact on the lymph nodes retrieval to avoid future harboring and spread of malignant LNs for better survival. It does not show much difference in leakage in either group. An unambiguous consensus remains to be achieved for the routine evidence-based level of high ligation practice.

## **Abbreviations**

CI = confidence interval, HR = hazard ratio, IMA = inferior mesenteric artery, LCA = left colic artery, LN =lymph node, OS = overall survival, RCT = randomized control trial, SLN = sentinel lymph node.

## **Declarations**

### **Ethical Approval and Consent to participate-**

The work was authorized by the department from the gastrointestinal surgery ethics committee.

### **Consent for publication**

All participants were kept informed about the intention of the research, and written well-informed consent was obtained from all participant's patients who underwent the potentially curative surgical procedure.

### **Availability of data and materials**

The Department of Gastrointestinal Surgery, West China Hospital. Data prospectively collected and analyzed.

### **Competing interests**

There are no Competing interests.

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**Authors' information and contributions:** -

**Dujanand Singh:** - Study design, Lymph node retrieval, Acquisition of data; interpretation of data, drafting of the manuscript (clinical investigators).

**He Long:** Lymph node retrieval, Database access, and collection, statistical analysis, interpretation of data. (participating investigators)

**Lie Yang\*** Critical revision of the manuscript for important intellectual content, scientific advisors.

**Cun Wang:** Lymph node retrieval and cared for study patients.

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