

# Feasibility and oncologic safety of low ligation of inferior mesenteric artery with D3 dissection in cT3N0M0 sigmoid colon cancer

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**Purpose:** There is no standard consensus for the ligation level of the inferior mesenteric artery during radical resection of sigmoid colon cancer. Especially, there is little research about low ligation combined with D3 dissection. The study was performed to compare feasibility and oncologic safety between low ligation with D3 dissection to high ligation in intermediately advanced sigmoid colon cancer.

**Methods:** From January 2008 to December 2013, 134 patients who underwent radical surgery for cT3N0M0 sigmoid colon cancer were evaluated retrospectively. Clinicopathologic factors and oncologic outcomes of high ligation (HL, n = 51) and low ligation (LL, n = 83) groups were compared.

**Results:** The mean operative time was significantly shorter in LL, and there was no difference in complications, distal margin or number of retrieved lymph node. The tumor size was significantly larger in HL, but there was no difference in number of metastatic lymph node, pT or pN stage. There was no difference in overall survival, disease-free survival, or local and systemic recurrence.

**Conclusion:** In cT3N0M0 sigmoid colon cancers, we suggest that low ligation with D3 dissection can be performed with feasibility and oncological safety.

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**Key Words:** Colon neoplasms, Inferior mesenteric artery, Lymph node excision, Feasibility studies, Survival

## INTRODUCTION

Contrary to standardization of complete mesocolic excision with central vascular ligation in right colon cancer, there is no standard consensus regarding the ligation level of the inferior mesenteric artery (IMA) during radical resection of sigmoid colon cancer. In spite of numerous studies on this subject, it remains unclear whether or not high ligation of the IMA improves oncologic outcomes compared to low ligation. There are many studies that suggest that central vessel ligation with D3 dissection, which means dissection of the central lymph node, is mandatory to improve node harvest, enable accurate

tumor staging, and perform maximizing radical resection [1-4]. However, other studies insist that low ligation, which means ligation below the origin of the left colic artery, does not result in inferior oncologic outcomes compared to high ligation [5-9]. If lymph node metastasis is definite or massive, or a primary tumor is far-advanced, i.e., beyond T4 stage, maximum extensive resection with high ligation for radical resection is considered to be essential to perform radical and *en bloc* resection [2,10]. On the contrary, for early cancer as intramucosal carcinoma or T1, extensive resection with high ligation is not considered to be mandatory. Sometimes, low ligation is often preferred because of surgical feasibility

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according to the patient's anatomy with benefits of superior preservation of circulation and autonomous innervation [11,12]. In those cases, low ligation with D3 dissection can be performed. There is little research reporting equality of surgical feasibility, postoperative complications, or oncologic outcomes of low ligation combined with D3 dissection comparing to high ligation. Although some studies reported its technical possibility and oncologic outcomes, they reported that it needed longer operation time and produced more genitourinary dysfunction [13,14]. To compare the feasibility and oncological safety of low ligation with D3 dissection to high ligation in intermediately advanced sigmoid colon cancers, we performed the present study.

## METHODS

### Patients

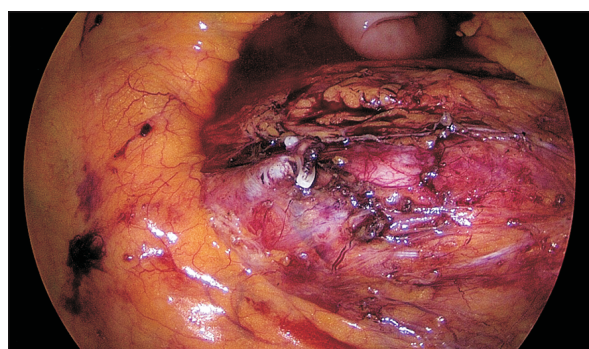
From January 2008 to December 2013, patients who underwent anterior resection or low anterior resection for sigmoid or recto-sigmoid colon cancer with curative intent were evaluated retrospectively. Preoperative evaluation consisted of history taking, physical examination, basic laboratory studies including serum CEA, colonoscopy or alternative flexible sigmoidoscopy when the scope could not pass through the obstructing tumor, abdominopelvic CT, and selective PET/CT. We included only clinically T3N0M0 cancers and excluded early (clinically TX, T1, or T2) and markedly advanced (definite lymph node metastasis or clinically T4) cancers to eliminate selection bias and to follow the principle that high ligation with extensive and *en bloc* resection is essential for far advanced lesion. Exclusion criteria were as follows: (1) tumor obstruction, perforation, or abscess which makes the operation more extensive due to nononcologic reasons, (2) dual colon cancers which makes the operation more extensive regardless of tumor stage, (3) left colic artery ligation of proximal sigmoid colon cancers, for standardization of surgical method. Total 134 patients including high ligation group (HL, n = 51) and low ligation group (LL, n = 83) were

evaluated.

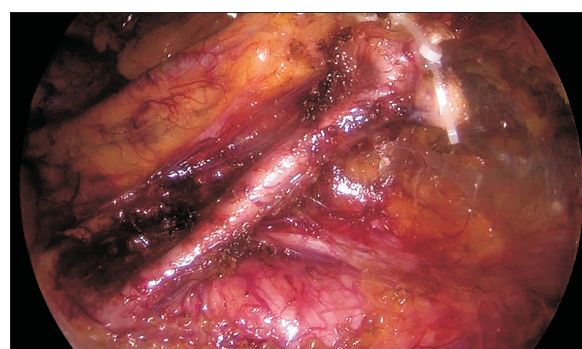
Patient baseline characteristics including age, sex, weight, height, and American Society of Anesthesiologists (ASA) physical status classification were evaluated and body mass indexes were calculated. Coexistence of atherosclerotic or microvascular diseases including hypertension, diabetes mellitus, ischemic heart disease, cerebral infarction, or chronic kidney disease and thromboembolic conditions including atrial fibrillation was evaluated, because they can influence postoperative complications as colonic or anastomotic ischemia and therefore it can be the factor that must be considered when selecting ligation level. Operation time, vessel ligation level, postoperative complications, and pathologic reports were evaluated.

### Surgical methods

All cases were performed laparoscopically. Ligation level was selected by surgeon's decision based on patient's status as comorbidity or anatomy. High ligation means ligation approximately 1 cm from the aortic origin of the artery with *en bloc* dissection of the inferior mesenteric lymph nodes as D3 dissection (Fig. 1). Low ligation means ligation below the origin of the left colic artery with preservation of the left colic artery and additional D3 dissection from the root of the IMA to the left colic artery, which is also called apical lymph node dissection [15] (Fig. 2). Ligation was generally performed at the origin of one sigmoidal artery. When more than 2 branches of the sigmoidal artery were found below the left colic artery and there was no space to ligate them at once, they were ligated separately. When another sigmoidal artery from the left colic artery was found, it was ligated if necessary. Dissection of the inferior mesenteric lymph nodes was performed simultaneously when skeletonization of the IMA and the left colic artery before ligation of the sigmoidal artery. If necessary, additional dissection was performed. The specimen of dissected lymph nodes was included or excluded with the main specimen.



**Fig. 1.** High ligation: ligation approximately 1 cm from the aortic origin of the artery with *en bloc* dissection of the inferior mesenteric lymph nodes as D3 dissection.



**Fig. 2.** Low ligation: ligation below the origin of the left colic artery with preservation of the left colic artery and additional D3 dissection from the root of the inferior mesenteric artery to the left colic artery.

## Statistical analyses

Univariate analyses were used to compare the baseline characteristics, surgical and pathologic outcomes of the 2 groups. The chi-square test, independent samples T test, and Fisher exact test were performed. Overall survival, disease-free survival, and local and systemic recurrence rates of 2 groups according to the ligation level were evaluated using Kaplan-Meier analyses. IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA) was used. The study was approved by the Institutional Review Board of Chungnam National University Hospital (approval number: 2016-10-014), and the statistician of the institute confirmed the analyses.

## RESULTS

There was no significant difference between patient baseline characteristics for both groups, including age, sex, BMI, ASA physical status classification, and comorbidity (Table 1). The mean operative time was significantly shorter in LL than HL (212.74 ± 59.92 minutes vs. 183.20 ± 53.91 minutes, P = 0.004). There was no significant difference between postoperative complications for both groups, including anastomotic leakage (2

vs. 0), pelvic abscess (0 vs. 2), ischemic colitis (1 vs.1), extrapelvic abscess (0 vs. 1), ileus (1 vs. 2), voiding problem (0 vs. 1), and pneumonia (0 vs. 1) (Table 2). Although the mean proximal margin was significantly shorter in LL than HL (129.33 ± 55.69 mm vs. 98.11 ± 48.44 mm, P = 0.001), the mean distal margins of both groups showed no significant difference (37.45 ± 23.40 mm vs. 44.31 ± 34.68 mm, P = 0.213). There was also no significant difference between both groups according to histologic grade, lymphatic invasion, and vascular invasion, however, the tumor size was significantly larger in HL in LL (4.60 ± 1.67 cm vs. 3.84 ± 1.33 cm, P = 0.005). For the numbers of retrieved and metastatic lymph nodes, both groups were equivalent. There was no significant difference between pT and pN stages for both groups (P = 0.088, P = 0.530) (Table 3). In the survival analyses, the mean follow up length was 53.76 months. There was no significant difference between 5-year overall survival, disease-free survival, local recurrence, and systemic recurrence of high and low ligation groups (84.1% vs. 87.5%, P = 0.906; 92.6% vs. 91.1%, P = 0.560; 0% vs. 1.3%, P = 0.440; 7.4% vs. 7.5%, P = 0.725) (Fig. 3A-D).

**Table 1.** Patient baseline characteristics

Characteristic	HL (n = 51)	LL (n = 83)	P-value
Age (yr)	66.09 ± 11.54	66.61 ± 10.73	0.792
Sex			0.590
Male	34	59	
Female	17	24	
Body mass index (kg/m <sup>2</sup> )	23.87 ± 3.15	24.03 ± 3.08	0.765
Comorbidity			0.602
No	30	45	
Yes	21	38	
ASA PS classification			0.262
I, II	42	74	
III, IV	9	9	

Values are presented as mean ± standard deviation or number.

HL, high ligation group; LL, low ligation group; ASA PS, American Society of Anesthesiologists physical status.

**Table 2.** Surgical outcomes

Variable	HL (n = 51)	LL (n = 83)	P-value
Operation time (min)	212.74 ± 59.92	183.20 ± 53.91	0.004
Anastomotic leakage	2	0	0.143
Pelvic abscess	0	2	0.525
Ischemic colitis	1	1	>0.999
Extrapelvic abscess	0	1	>0.999
Ileus or obstruction	1	2	>0.999
Voiding problem	0	1	>0.999
Pneumonia	0	1	>0.999

Values are presented as mean ± standard deviation or number.

HL, high ligation group; LL, low ligation group.

**Table 3.** Pathologic outcomes

Variable	HL (n = 51)	LL (n = 83)	P-value
Proximal margin (mm)	129.33 ± 55.69	98.11 ± 48.44	0.001
Distal margin (mm)	37.45 ± 23.40	44.31 ± 34.68	0.213
Tumor size (cm)	4.60 ± 1.67	3.84 ± 1.33	0.005
Histologic grade			>0.999
WD, MD	49	80	
PD, mucinous	2	3	
Lymphatic invasion			0.113
Negative	14	34	
Positive	37	49	
Vascular invasion			0.252
Negative	13	29	
Positive	38	54	
Retrieved lymph node	13.65 ± 7.33	14.40 ± 5.76	0.509
Metastatic lymph node	0.84 ± 1.73	0.61 ± 1.36	0.397
pT stage			0.088
T1	3	4	
T2	7	27	
T3	40	49	
T4	1	3	
pN stage			0.530
N0	33	61	
N1	14	18	
N2	4	4	

Values are presented as mean ± standard deviation or number.

HL, high ligation group; LL, low ligation group; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

## DISCUSSION

### Oncological features

According to the present study, LL obtained equivalent distal margin length and number of retrieved lymph nodes as HL. Based on these results, the arterial ligation level does not affect the distal resection margin. Although mean proximal margin of HL was significantly longer than in LL, that of LL was also considered to be oncologically appropriate. Based on the number of retrieved lymph nodes, we concluded that low ligation with D3 dissection around the root of the IMA can achieve the same quality as D3 dissection of high ligation. Some studies insist that we can achieve equivalent nodal harvest and tumor staging quality as high ligation if low ligation is combined with D3 dissection [13,14,16]. Titu et al. [17] reported that there was no clear evidence of survival improvement with high ligation in a systematic review with approximately 7,649 patients.

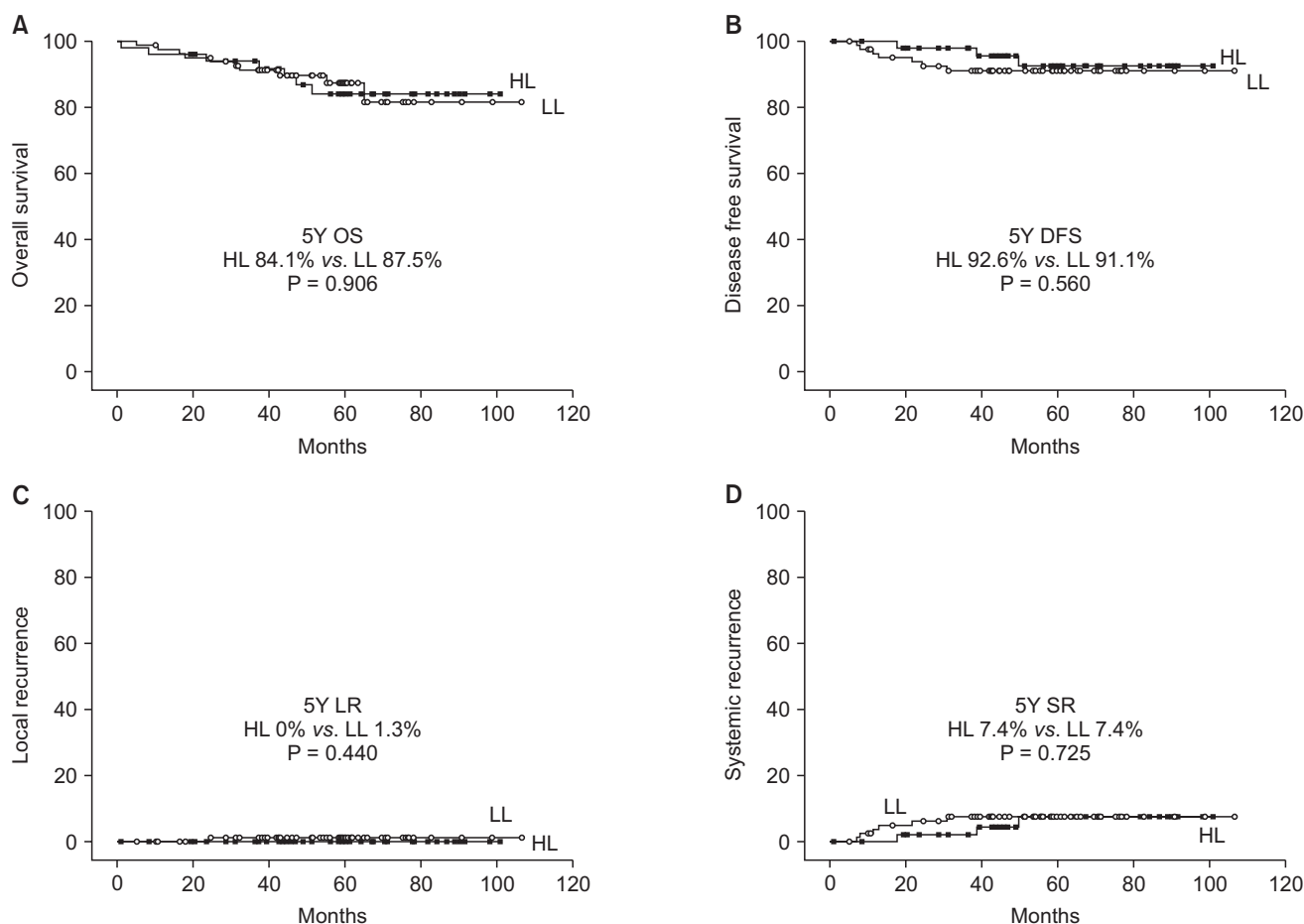
Notably, mean tumor size of HL was significantly larger than that of LL. This is supposed to be resulted from the selection bias. However, there was no significant difference of pT and pN stages.

As mentioned in the introduction, high ligation for most

radical and *en bloc* surgery is considered to be more appropriate for far advanced sigmoid colon cancer than low ligation. Also we can select the level of ligation more freely in early cancer. However, it would be more controversial in the intermediate cancer as cT3N0M0. In the present study, we confined the subject to cT3N0M0 patients to minimize the selection bias. Although pathologic stages of each group were heterogeneous despite to homogenous clinical stages, there was no significant difference between overall survival, disease free survival, local and systemic recurrence of both groups. It is considered to be oncologically safe based on that it could obtain equal pathologic and oncologic outcomes.

### Technical features

Occasionally, during surgery, low ligation was found to be more applicable or useful. For example, low ligation may be preferred in cases when the length of colon to be resected is expected to be excessively long if high ligation was performed, when the patient's anatomy is not appropriate for high ligation for any reasons, or when it is necessary to preserve the left colic artery to secure the circulation of the proximal colonic end and anastomosis due to underlying disease affecting the intestinal circulation. If the cancer is clinically advanced,



**Fig. 3.** (A) Five-year overall survival (OS) of high and low ligation groups. (B) Five-year disease-free survival (DFS) of high and low ligation groups. (C) Five-year local recurrence (LR) of high and low ligation groups. (D) Five-year systemic recurrence (SR) of high and low ligation groups. HL, high ligation group; LL, low ligation group.

it is oncologically proper to perform high ligation even if it is technically difficult. However, in the early stage, if high ligation might be less suitable, low ligation can be considered [18]. According to the present study, it could be also applied for intermediately advanced stage. Some studies reported that low ligation with D3 dissection demanded longer time than that spent for high ligation [13]. However, in this study, the mean operation time of LL was rather shorter than that for HL. As a result, preservation of the IMA with D3 dissection is considered to be not a time-consuming or less feasible procedure compared to ligation of the IMA root. On the contrary, high ligation demanded more time. We supposed that it is because the time for splenic flexure mobilization was required.

### Correlation with leakage

In the present study, there was no significant difference between groups in overall postoperative complications including anastomotic leakage, pelvic abscess, and ischemic colitis which could be influenced by intestinal circulation.

In most cases of sigmoid colon cancer surgery, the circulation

to the proximal colonic end can be maintained by preserving the marginal artery. However, blood flow to the proximal colonic limb and anastomosis is better when the left colic artery is preserved [12]. Especially for patients with microvascular disease or thromboembolic condition, a long marginal artery could be occluded even if it is preserved exteriorly. Accordingly, it is occasionally better to preserve the left colic artery to prevent ischemia and consequent anastomotic dehiscence, which results in necrosis of proximal colon or anastomotic leakage that is sometimes fatal.

Preservation of the proximal IMA, which results in fixation of the central mesentery, can decrease the mobility of the proximal colonic limb. When this situation occurs, forced anastomosis produces tension at the anastomosis. In this case, high ligation must be considered to prevent anastomotic leakage. Hall et al. [19] insisted that oxygenation was significantly affected by the location of the proximal resection site, not by the choice between high or low ligation, and that the sigmoid colon must be sacrificed and high ligation must be performed to create a tension-free anastomosis. Additionally,



Rutegård et al. [20] insisted that high ligation does not increase the risk of an anastomotic leakage. However, Buunen et al. [21] insisted that it was not necessary to perform a high ligation to create a tension-free anastomosis and that low ligation could be safely applied in 80% of cases. Furthermore, Bonnet et al. insisted that the additional gain in colonic length produced by high ligation was small [22].

However, many studies insist that there is no significant difference in postoperative complications between high and low ligation [4,14,16]. Although there are differences between the technical components and issues of the surgery required to prevent complications in each of these 2 procedures, we are of the opinion that there is no significant difference in complications if we observe basic surgical principles. If the proximal colonic mesentery is too short to create a tension free anastomosis, its maximal lengthening by high ligation of IMA and vein with full splenic mobilization could be mandatory to achieve successful and safe anastomosis and to prevent postoperative leakage consequently, even if the cancer is early.

### Postoperative function

Recently, preservation of the sympathetic plexus around the IMA has become easier with the support of fine visualization in laparoscopic surgery. The dissection territories of high and low ligations are equal if we perform D3 dissection. Nano et al. insisted that there was no risk of para-aortic nerve trunk damage during high ligation [23]. Therefore, there is no difference in the preservation of the nerve around the IMA root. However, some studies insist that low ligation can

preserve autonomous innervation along the proximal colonic limb and consequently preserve colonic function including motility [11]. Additionally, it was reported that colonic ischemia and reperfusion could decrease the number of ganglionic cells in the myenteric plexus, which did not recover in the late postoperative period in an animal model [24]. This result may explain newly developed constipation after anterior resection without mechanical abnormalities in imaging studies. If support with sufficient perfusion can preserve intestinal function, it can be considered that low ligation would have superiority in the functional aspect.

### Limitations

First, the present study was a retrospective study, which has the potential to include a selection bias. It was limited to investigate functional aspects as postoperative defecation or urination difficulty due to the lack of precise records or questionnaire, which was also due to the retrospective nature of the study. Second, the number of patients was small. Thus, a prospective randomized study with more patients would be helpful.

In conclusion, in cT3N0M0 sigmoid colon cancers, we suggest that low ligation with D3 dissection can be performed with feasibility and oncological safety.

### CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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