
ORIGINAL RESEARCH ARTICLE

Microanatomy of inferior mesenteric artery sheath in colorectal cancer surgery

Wataru Sakamoto¹⁾, Leo Yamada¹⁾, Osamu Suzuki²⁾, Tomohiro Kikuchi¹⁾, Hirokazu Okayama¹⁾, Hisahito Endo¹⁾, Shotaro Fujita¹⁾, Motonobu Saito¹⁾, Tomoyuki Momma¹⁾, Zenichiro Saze¹⁾, Shinji Ohki¹⁾ and Koji Kono¹⁾

1) *Department of Gastrointestinal Tract Surgery, School of Medicine, Fukushima Medical University, Fukushima, Japan*

2) *Department of Diagnostic Pathology, School of Medicine, Fukushima Medical University, Fukushima, Japan*

Abstract:

Objectives: Left colic artery preserving lymph node dissection around the inferior mesenteric artery (IMA) is a standard procedure for rectal cancer surgery. Although the IMA sheath is a well-known structure, to our knowledge, there are no reports describing its microanatomy from an oncological point of view; therefore, there is no consensus on how to handle the sheath for accurate lymph node dissection around IMA. We aimed to investigate the components of the IMA sheath pathologically, focusing particularly on the presence of lymph nodes (LNs) and lymphatic ducts (LDs). **Methods:** We evaluated rectal and sigmoid cancer specimens resected with high-tie technique in our institute in April 2017–April 2018. The specimens were collected consecutively, without any selection. In the resected specimens, the entire anatomical structure of IMA was investigated. We defined the IMA sheath as the tissues located between the surface of the IMA adventitia and collagenous layers connecting the outermost nerve fibers. The microanatomy around the IMA was examined using H&E staining, and LDs were identified using D2-40 immunohistochemistry. **Results:** Twenty patients were enrolled. No LNs were observed within the sheath in any of the cases. However, there were a significant number of LDs (11.08 ± 3.35) within the sheath. **Conclusions:** Our anatomical definition of IMA sheath was feasible and objectively possible. These microanatomical results partially support the surgical concept of left colic artery preserving lymph node dissection around the IMA. It may be difficult to remove all lymphatic ducts without removing the IMA itself.

Keywords:

inferior mesenteric artery, low-tie with lymph node dissection, left colic artery, colorectal cancer, lymph node dissection

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Introduction

Colorectal cancer (CRC) is one of the most common cancers and the fourth leading cause of cancer-related death worldwide¹⁾. Laparoscopic surgery for CRC has been widely-developed and has become one of the standard surgical procedures for CRC. It is generally accepted that the advantages of laparoscopic surgery include visual magnification, which improves the surgeon's microanatomical understanding of the operative field for rectal cancer²⁾, including

the rectal fascia propria, prehypogastric nerve fascia, hypogastric nerve, and bilateral lumbar splanchnic nerve, which branches off and forms a part of the inferior mesenteric artery (IMA) sheath.

Theoretically, in cases of anterior resection for rectal cancer, IMA ligation at its origin (high-tie) reduces blood flow to the anastomosis, resulting in an increased leakage rate³⁾. Previous studies have reported a significant reduction of blood flow in the proximal limb after ligation of the IMA at its origin^{4,5)}. Therefore, many surgeons employ left colic ar-

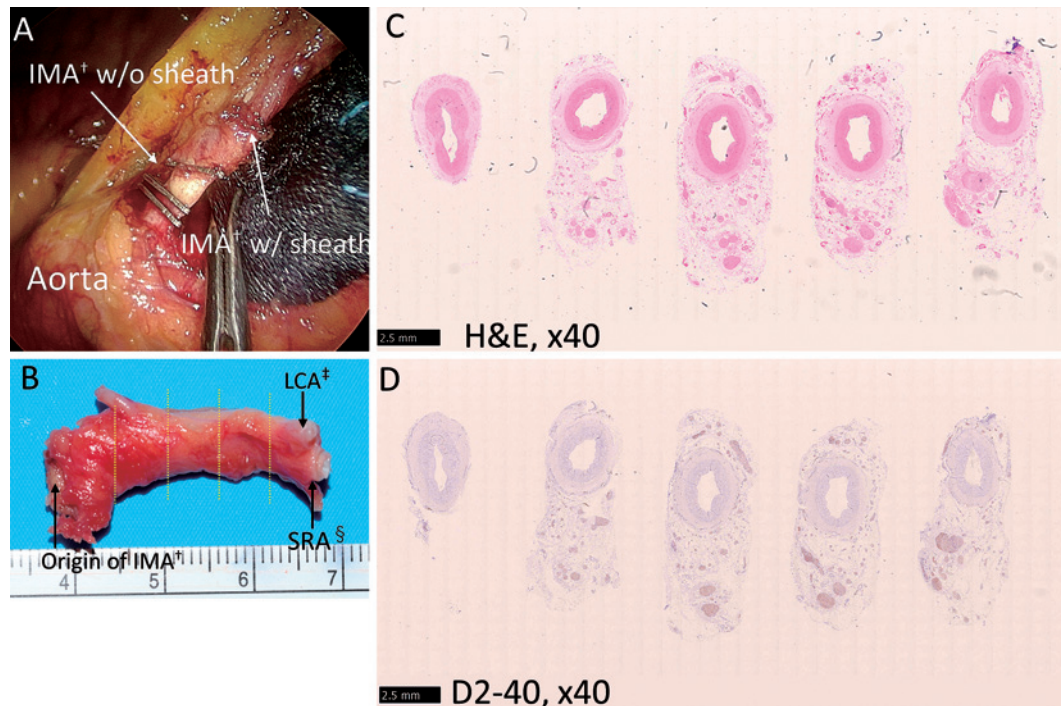


Figure 1.

A representative specimen of the inferior mesenteric artery (IMA) (Case 3). A: intraoperative photo of the root of the IMA just before high-tie. The sheath of the IMA was peeled off partially for IMA transection. B: An IMA specimen before formalin fixation. The IMAs from its origin to the left colic artery branch without peeling off the sheath were used for the analysis. IMA specimens were formalin-fixed, cut into 5 mm sections and paraffin embedded for histological analysis. C: H&E staining. D: D2-40 immunohistochemistry staining.

†: inferior mesenteric artery, ‡: left colic artery, §: superior rectal artery

tery (LCA) preserving lymph node dissection around the IMA (low-tie with LND) as one of the standard surgical methods for rectal cancer^{6,7)} in order to reduce the anastomotic leakage rate and to preserve a chance for next left colic surgery in case of the second carcinogenesis⁸⁾. On the other hand, the Japanese Society for Cancer of the Colon and Rectum reported the rate of positive lymph node metastasis around the IMA of 5.1% in patients with pathological T3/T4 (pT3/T4, TNM classification, UICC 7th) rectal cancer⁹⁾, which is not negligible from an oncological point of view. Therefore, an optional surgical procedure for CRC, low-tie with LND, has been developed. In fact, a previous report demonstrated that low-tie with LND showed the same overall survival and relapse-free survival in cases of rectal cancer when compared to high-tie in Japan⁸⁾.

Although low-tie with LND may theoretically preserve blood flow, the oncological radicality of the low-tie with LND may be spoiled due to the possibility that lymph nodes or lymphatic ducts may be present within the IMA sheath. To the best of our knowledge, there are no reports pathologically describing the strict anatomical definition of the IMA sheath and the microanatomy of lymph nodes and lym-

phatic ducts within the IMA sheath. Therefore, the aim of the present study was to investigate the components of the IMA sheath pathologically, especially focusing on the distribution of lymph node and lymphatic duct around IMA and its sheath.

Methods

Samples

We evaluated rectal and sigmoid cancer specimens resected with high-tie technique in the Department of Gastrointestinal Tract Surgery, Fukushima Medical University, Japan, between April 2017 and April 2018. We collected the specimens consecutively, without any selection. For our investigation, we used the entire anatomical IMA structure from its origin to the LCA branch without peeling off the sheath, by using surgically resected specimens (Figure 1A& B). The IMA specimens were formalin-fixed, cut into 5 mm sections, and paraffin embedded for histological analysis. The IMA sheath and lymph nodes were observed by hematoxylin/eosin staining (Figure 1C), and the lymphatic ducts

Table 1. Clinicopathological Characteristics of the Cases Enrolled in this Study.

case	tumor location	age	sex	type	histological type	pT [†]	pN [†]	M [†]	pStage [†]	ly [‡] :	v [§]	NAC [¶]
1	RS	76	M	2	tub2	4a	0 (251:0/3, 252:0/2, 253:0/1)	1a	IVa	0	3	
2	Ra	56	M	2	tub2	4a	2b (251:6/11, 252:0/1 253:1/2)	0	IVa	3	3	
3	Rb	36	F	2	tub2>por2	3	0 (251:0/12, 252:0/8, 253:0/1)	0	IIA	0	0	
4	S	67	M	2	tub2	4a	0 (241:0/6, 252:0/5, 253:0/1)	1a	IVa	1	0	CAPOX*
5	Rb+P	57	M	2	tub2	3	2b (251:11/14, 252:4/5, 253:0/9, 263Prt:1/1)	1a	IVa	1	1	
6	S	66	M	2	tub2	4a	0 (241:0/7, 252:0/4, 253:0/7)	0	IIB	1	2	
7	RS	70	F	2	tub2	2	1a (251:1/7, 252:0/2, 253:0/4)	0	IIIA	2	2	
8	Rb	59	F	3	tub1	3	0 (251:0/2, 252:0/1, 253:0/1)	0	IIA	1	3	
9	RS	76	M	3	tub1	2	1b (251:2/18, 252:0/2, 253:0/4)	0	IIIA	0	1	
10	RaRS	67	M	2	tub1	3	0 (251:0/18, 252:0/2, 253:0/4)	0	IIA	0	2	
11	S	74	M	5	tub2	4a	0 (241:0/5, 252:0/2, 253:0/1)	1a	IVa	0	1	
12	Rb	81	M	2	tub1>tub2	4b (muscle)	2b (251:6/14, 252:0/5, 253:2/5)	0	IIIC	1	2	
13	S	88	M	3	tub2>tub1	3	0 (241:0/10, 252:0/5, 253:0/12)	0	IIA	0	0	
14	S	69	M	2	tub2	2	1b (241:2/10, 252:0/4, 253:0/0)	0	IIIA	1	2	
15	S	69	M	1	tub2	3	0 (241:0/5, 252:0/3, 253:0/8)	0	IIA	1	2	
16	RSRa	84	M	2	tub1>tub2	3	0 (251:0/15, 252:0/4, 253:0/6)	0	IIA	0	1	
17	Ra	69	M	3	tub2	3	0 (251:0/12, 252:0/8, 253:0/13)	0	IIA	0	3	CAPOX
18	Ra	64	M	2	tub2	3	1a (251:1/8, 252:0/10, 253:0/12)	0	IIIA	1	3	
19	RaRb	78	M	2	tub2>tub1	4a	2b (251:5/24, 252:0/5, 253:0/3, 263lt:3/5, 283lt:4/6)	0	IIIC	1	3	CAPOX
20	S	67	M	1	tub2	1	0 (241:0/10, 252:0/3, 253:0/3)	0	I	0	1	

[†]: TNM classification (UICC 7th), [‡]: pathological lymphatic invasion, [§]: pathological vascular invasion, [¶]: neoadjuvant chemotherapy,

*: capecitabine+oxaliplatin

and lymph nodes were identified by D2-40 immunohistochemistry (Figure 1D).

Definition of the IMA sheath

According to the definition of the superior mesenteric artery (SMA) sheath by Kovanov et al.¹⁰⁾ and referring Jin et al.¹¹⁾, we defined the IMA sheath as the tissues located between the surface of IMA adventitia and collagenous layers connecting the outermost nerve fibers, which include the layer of autonomic nerve plexus, adipose tissue, collagenous fibers, and micro-vessels. We then investigated the existence of lymph nodes and lymphatic ducts within the sheath and measured the distance from the IMA adventitia to the nearest lymphatic duct. We also measured the maximum and minimum thickness of the sheath and the diameter of the IMA per section and presented the data with the averages. For each parameter, the measurement was objectively performed by the Nanozoomer system and its application (Hamamatsu Photonics, Hamamatsu City, Japan). This study protocol was approved by the Ethics Committee of Fukushima Medical University, Approval No. 29102. All participants provided written informed consent form prior to participation.

Results

Patient characteristics

Twenty IMA specimens from sigmoid colon/rectal cancer patients were used in the study. Patient backgrounds and pathological diagnoses are provided in Table 1. The mean age of enrolled patients was 68.7 ± 11.4 years old with a male/female ratio of 17:3. The 20 specimens were from the sigmoid colon (n = 7), rectosigmoid (RS) (n = 4), the upper rectum (Ra, the rectum located between lower border of second sacral vertebra and the peritoneal reflection) (n = 5), and the lower rectum (Rb, the rectum located between the peritoneal reflection and upper border of the anal canal) (n = 4) cancers. The pathological diagnosis indicated one patient in stage I, seven in IIA, one in IIB, four in IIIA, two in IIIB, and five in IVa (UICC 7th), indicating that most of the enrolled patients had advanced CRC. Among them, three patients received neoadjuvant chemotherapy with capecitabine and oxaliplatin.

IMA sheath structure

In all cases, objective pathological identification of the IMA sheath was possible. The representative section of the IMA sheath is shown in Figure 2 and the measurement of

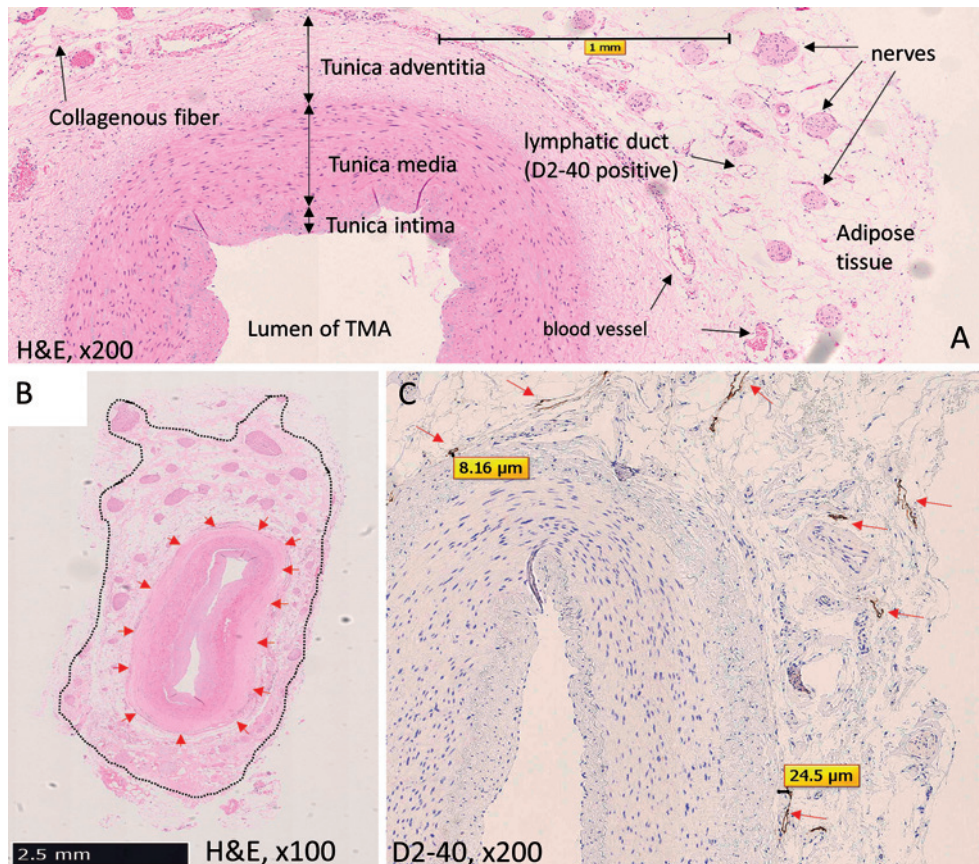


Figure 2.

Components of the inferior mesenteric artery (IMA) sheath and the way of measuring.

A: The IMA and its surrounding tissue. The IMA is surrounded by micro-vessels, adipose tissue, nerves and collagenous fibers.

B: We defined the IMA sheath as the tissues located between the surface of IMA adventitia (red arrows) and collagenous layers connecting the outermost nerve fibers (dotted black line), which include the layer of autonomic nerve plexus, adipose tissue, collagenous fibers and micro-vessels in the current study. We measured the minimum and maximum thickness of the sheath and diameter of the IMA and calculated each average.

C: Lymphatic ducts were identified immunohistochemically as D2-40 positive ducts (red arrows). The distance from the adventitia of the IMA to the nearest lymphatic duct was measured, and the average was calculated.

each parameter is shown in Table 2. The average IMA diameter was 2.67 ± 0.52 mm, the average thickness of the IMA sheath was 1.64 ± 0.57 mm, the average distance from the IMA to the nearest lymphatic duct was 73.55 ± 23.43 μ m, and the average ratio of sheath thickness/IMA diameter was 0.64 ± 0.23 .

Lymph nodes and lymphatic ducts within the IMA sheath

Notably, in all cases, no lymph nodes were detected within the IMA sheath pathologically. Regarding the lymphatic ducts, we could identify 11.08 ± 3.35 D2-40 positive ducts within the IMA sheath. Cancer cells were not pathologically observed in the lymphatic ducts in the IMA sheath sections, even in cases of the pathologically positive

lymph node metastasis (N+) group.

Discussion

The present study provided a novel and important finding that the anatomical definition of the IMA sheath is feasible and there were no lymph nodes within the IMA sheath, although there were lymphatic ducts within the IMA sheath.

The ligation level of the IMA in the radical operations for rectal cancer, whether high-tie¹²⁾ or low-tie¹³⁾, has been discussed worldwide for a long time; however, the consensus remains undetermined¹⁴⁾. In Japan, since the rate of positive lymph node metastasis around the IMA is 5.1% in pT3/T4 rectal cancer⁹⁾, LND around the IMA for advanced rectal

Table 2. Result of Number of Lymph Nodes in the Sheath, Sheath Thickness, IMA Diameter, Number of Lymph Ducts in the Sheath, Distance to the Nearest Lymphatic Duct from Adventitia and the Ratio of Sheath Thickness to IMA Diameter of Each Case. There Were No Lymph Nodes in the Sheath of Our 20 IMA Specimens.

Case	number of LNs [†]	Sheath thickness (mm)	IMA [‡] diameter (mm)	Number of LD [§] s in the Sheath	Nearest LD from Ad [¶] (μm)	Sheath thickness / IMA diameter
1	0	1.08	1.97	7.20	126.09	0.55
2	0	1.79	2.78	10.33	64.23	0.66
3	0	2.24	2.92	7.60	66.58	0.81
4	0	2.27	2.67	10.00	87.98	0.85
5	0	1.84	2.58	13.25	86.22	0.72
6	0	1.56	2.80	13.60	53.68	0.56
7	0	1.05	1.95	17.33	60.65	0.52
8	0	1.38	2.42	12.20	29.52	0.58
9	0	1.86	2.16	12.67	62.10	0.90
10	0	0.52	2.57	4.40	84.16	0.21
11	0	0.38	3.42	5.00	107.25	0.13
12	0	1.05	2.13	13.60	51.14	0.50
13	0	2.14	3.73	11.67	70.40	0.57
14	0	2.14	2.97	15.80	61.20	0.73
15	0	2.02	3.57	13.33	44.17	0.56
16	0	1.86	2.31	10.67	109.67	0.80
17	0	1.79	2.70	12.00	86.54	0.66
18	0	2.29	2.31	13.00	86.82	1.05
19	0	1.44	3.21	9.67	65.00	0.46
20	0	2.05	2.14	8.20	67.52	0.99
Ave±SD	0	1.64±0.57	2.67±0.52	11.08±3.35	73.55±23.43	0.64±0.23

[†]: lymph node, [‡]: inferior mesenteric artery, [§]: lymphatic duct, [¶]: adventitia of IMA

cancer is considered to be necessary as a standard treatment. In addition, low-tie without LND around the IMA is permitted only for patients whose tumor invasion depth is within the muscular layer and who clinically do not have lymph node metastases¹⁵. The low-tie with LND has been currently established as one of the standard surgical procedures in Japan^{7,8}) and has gradually been accepted globally^{16,17}). In addition, although the technique is not widely accepted, in low-tie with LND, at least two techniques are available; one is IMA-sheath preserving low-tie with LND^{6,18}), while another is IMA-sheath non-preserving low-tie with LND, which is a peel-away sheath technique⁷) (Figure 3). In such situations, it is extremely important to understand the microanatomy around the IMA. However, there have been no previous reports describing the microanatomy with a particular focus on lymph nodes and lymphatic ducts around the IMA. In the present study, we were able to show the microanatomy of the IMA sheath (Figure 2A&B), including the layer of autonomic nerve plexus, adipose tissue and collagenous fibers that surround the adventitia of the IMA.

In the field of pancreatic cancer, discussions around whether peri-superior mesenteric artery SMA plexuses

(SMA sheath) dissection should be included in the lymph node dissection or not have developed the anatomical studies for lymph nodes and lymphatic ducts around SMA by using D2-40 and LYVE-1 immunohistochemistry specific for lymphatic duct in the cadavers^{11,19,20}). Therefore, we employed D2-40 as the marker of lymphatic ducts in freshly resected specimen from colorectal surgery. These studies of SMA sheath mainly used cadavers as materials because SMA is essential artery for surviving. On the other hand, IMA is resectable artery in sigmoid and rectal cancer surgery, which is why we could conduct this anatomical study using sigmoid and rectal cancer specimens without using cadavers.

In all cases in the present study, our pathological identification of the IMA sheath was objectively possible and no lymph nodes were observed within the IMA sheath, but existed only outside of the nerve layer (Figure 4), indicating that lymph node dissection with preserving IMA sheath may be reasonable from oncological viewpoints. On the other hand, a significant number of lymphatic ducts existed within the IMA sheath in the present study (Figure 1C). It has been believed for a long time that an ideal LND would include

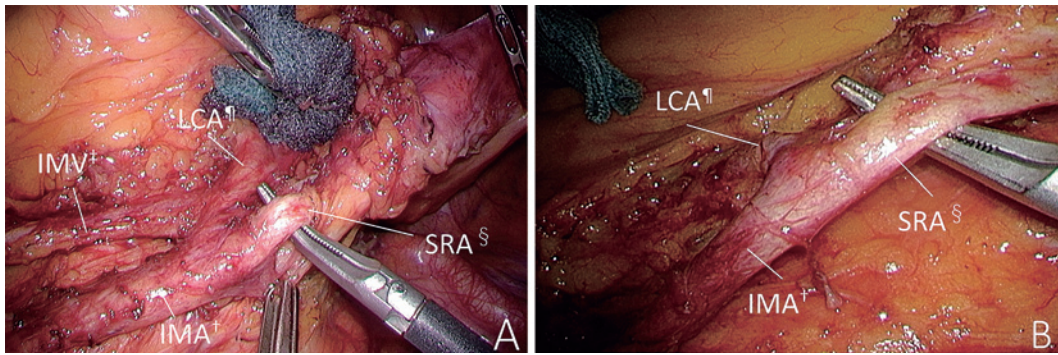


Figure 3.

Representative examples of two methods of low-tie with lymph node dissection.

A: Sheath preserving low-tie. The inferior mesenteric artery (IMA) sheath is preserved.

The sheath is peeled off partially at the origin of the superior rectal artery for clipping.

B: Non-sheath preserving low-tie. The IMA sheath is peeled off, and no connective tissue is around the IMA.

‡: inferior mesenteric artery, †: inferior mesenteric vein, §: superior rectal artery, ¶: left colic artery.

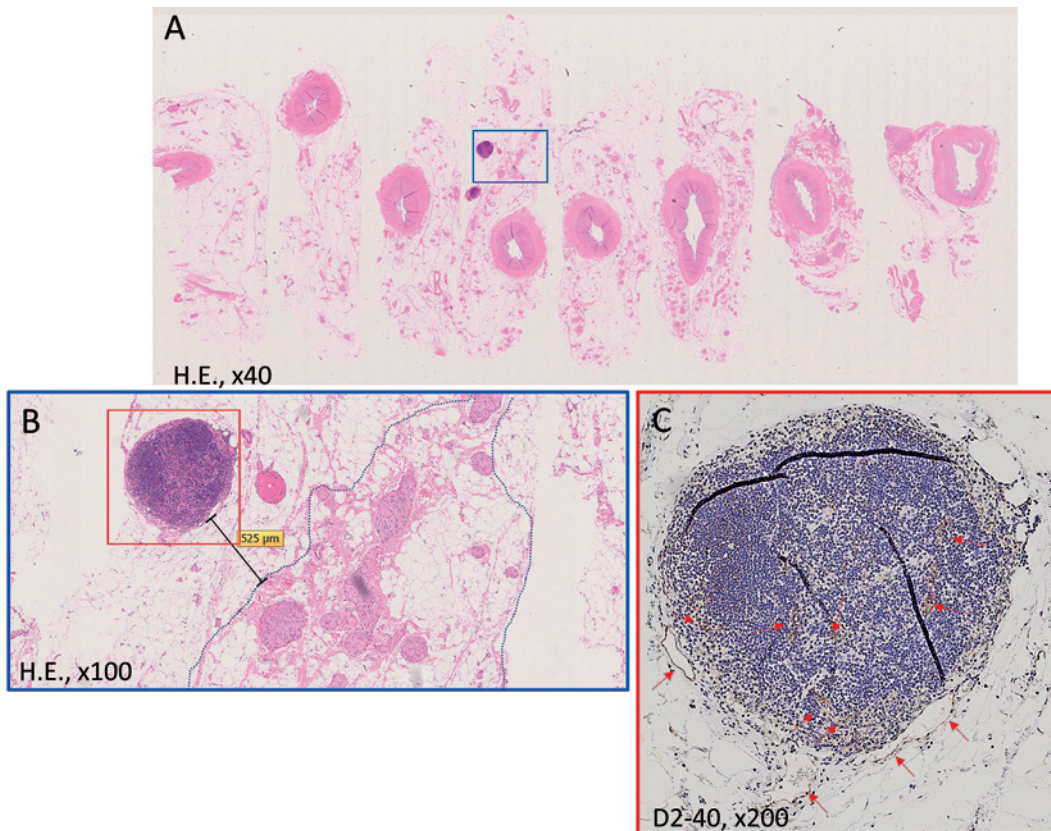


Figure 4.

Lymph node located only outside of the inferior mesenteric artery (IMA) sheath.

A: In all cases, only one case (case7) has lymph node around IMA sheath

B: Lymph node was located outside of IMA sheath. The distance from the sheath was about 0.5 mm.

C: D2-40 stain showed that many lymphatic ducts (red arrows) flowed into the lymph node.

the removal of lymph nodes with lymphatic ducts as en-bloc, since the lymphatic duct might contain isolated cancer cells^{21,22}). In this regard, oncological radicality with preserv-

ing IMA sheath is debatable. Interestingly, several reports from retrospective studies have shown that the low-tie with the LND procedure does not affect relapse-free survival or

overall survival of the CRC patients in comparison to the patients receiving the high-tie procedure^{8,17,23}. Therefore, removing lymphatic ducts within the IMA sheath may not affect the patient's oncological outcome and the low-tie procedure with LND may be acceptable. Furthermore, there is, to our knowledge, no previous report describing long-term oncological outcomes in the peel-away sheath technique (IMA-sheath non-preserving low-tie with LND), although the short-term result including surgical complications was acceptable⁷. Needless to say, in order to confirm the clinical significance of lymphatic duct removal within the IMA sheath, we need to perform a prospective randomized clinical trial to compare the clinical outcome between high-tie and low-tie with LND.

The present study clearly showed that there were no lymph nodes within the IMA sheaths, but lymphatic ducts were observed in the IMA sheath close to the surface of the IMA adventitia. Since the current study is based on a relatively small number of samples, a conclusive study with larger number of cohorts needs to be performed. The present microanatomical results may partially support the surgical concept of the low-tie procedure with LND around the IMA, although the clinical significance for removing of lymphatic ducts within the IMA sheath remains unclear.

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Conflicts of Interest

There are no conflicts of interest.

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