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Visualization of Anorectal Lymphatic Flow Using Indocyanine Green Fluorescence Imaging: An Observational Study

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Abstract. *Background/Aim: Currently, only a small part of functional lymphatic flow around the anorectal region has been anatomically analyzed. Despite the fact that local recurrence is often experienced in the pelvic floor, the functional lymphatic network in this region has rarely been studied due to difficulties in observation. This prospective observational study aimed to observe anorectal lymphatic flow around the pelvic floor using intraoperative indocyanine green fluorescence imaging during laparoscopic or robot-assisted rectal surgery. Patients and Methods: Fourteen patients who underwent laparoscopic (n=7) or robot-assisted (n=7) surgery without any preoperative therapy between April and December 2022 were enrolled. Indocyanine green solution (0.25 mg) was injected into the submucosa at the dentate line of the anterior, posterior, and bilateral walls prior to surgery. During and after total mesorectal excision, lymphatic flow was observed using a near-infrared camera system. Results: Lymphatic flow visualized by indocyanine green was detected not only in the already-known route from the low rectum to the lateral pelvic lymph nodes via the lateral ligament, but also in the novel route from the low rectum to the surface of the levator ani muscle and hiatal ligament. Fluorescence was widely spread in the pelvic floor between the longitudinal muscle of the low rectum and the surface of the levator ani muscle. Conclusion: Even though the results are preliminary since histological analyses were not performed, a novel widespread lymphatic network on the surface of the levator ani muscle originating from the longitudinal muscle fibers of the low rectum was revealed.*

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Few studies have analyzed the functional lymphatic flow in the anorectal region. In particular, the flow around the pelvic floor has rarely been studied owing to difficulties in observing this region. Examining the lymphatic flow in this complex region may provide important information for choosing therapeutic strategies for patients with low rectal cancer (RC). Recently, intraoperative indocyanine green (ICG) fluorescence imaging (FI) has been used for the detection of lateral pelvic lymph nodes (LPLNs) (1, 2). Moreover, the authors used ICG-FI for the analysis of lymphatic flow in the pelvic floor (3). ICG fluorescence was widely spread from the low rectum to the surface of the levator ani muscle (LAM). To our knowledge, this study was the first to visualize widespread lymphovascular flow around the pelvic floor. Even though the visualization of lymphatic flow using intraoperative ICG-FI is considered preliminary, since histological analyses are difficult, this method can be the basis of future research. However, the study population comprised patients with RC who underwent preoperative chemotherapy, which poses a critical limitation because preoperative chemotherapy induces fibrillation (4) and, consequently, changes lymphatic flow. To resolve this limitation, the present study observed lymphatic flow around the pelvic floor in patients with RC who did not undergo preoperative therapy using intraoperative ICG-FI during laparoscopic or robot-assisted rectal surgery.

Patients and Methods

Study design and patient selection. This prospective observational study was approved by the Human Research Ethics Committee of the Hakodate Municipal Hospital (Hokkaido, Japan; reference

number 220-1) and is in accordance with the tenets of the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all participants, and this study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies. The study population comprised patients with RC who underwent laparoscopic or robot-assisted radical surgery, including cases in which trans-anal total mesorectal excision (TaTME) was used in combination, without any preoperative therapy at the Hakodate Municipal Hospital between April and December 2022. Patients who had iodine hypersensitivity and those who did not consent to participate in the study were excluded. Patients who were scheduled to undergo lateral pelvic lymph node dissection were also excluded because a previous study reported that ICG-FI may affect the number of harvested LPLNs (2). Staging was performed according to the third English edition of the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinomas (5).

ICG-FI and image analyses. ICG solution was prepared as previously described (3). ICG powder (25 mg; Diagnogreen; Daiichi Pharmaceuticals, Tokyo, Japan) was dissolved in 10 ml of distilled water. After general anesthesia was administered general anesthesia, 0.1 ml (0.25 mg) of the ICG solution was injected into the submucosa at the dentate line 3 cm orally from the anal verge at the anterior, posterior, and bilateral walls prior to the operation. Tumor-occupied regions were injected with the ICG solution. During and after total mesorectal excision (TME), lymph flow was observed using a laparoscopic near-infrared camera system (VISERA ELITE II; OLYMPUS, Tokyo, Japan) or the Da Vinci Xi® surgical system (Intuitive Surgical, Inc., Sunnyvale, CA, USA). During TME, we first observed ICG fluorescence in the lateral ligament as a control of lymphatic flow from the low rectum to the lateral pelvic lymph nodes, as reported in a previous study (2). After completing TME, we observed ICG fluorescence in the pelvic floor, especially on the surface of LAM.

Results

Patient characteristics. Table I presents the characteristics and clinicopathological findings of patients. Seven patients (50%) underwent laparoscopic surgery, with two patients undergoing TaTME in combination. Seven other patients (50%) underwent robot-assisted surgery, with one patients undergoing TaTME in combination. Six patients (42.9%) had lymph node metastases, and 10 (71.4%) had lymphatic invasion. No adverse events related to the ICG injections were observed.

Observation of the lymphatic flow using ICG-FI. Under normal light, the lateral ligament was identified as a structure comprising a broad band of connective tissue that spanned from the lateral walls of the low rectum to the lateral pelvic region (Figure 1A). The middle rectal artery was observed to have passed through the lateral ligament. During observation using ICG-FI, ICG fluorescence was identified along the middle rectal artery (Figure 1B) and in the LPLNs (Figure 2A and B).

In the normal light view of the pelvic floor after completing TME, the muscular layer of the low rectum was attached to the LAM, and the surface of the LAM was covered with thin band-like tissue continuing from the longitudinal muscle of the low rectum (Figure 3A). During observation using ICG-FI, ICG fluorescence was observed on the surface of LAM and was found to have widely spread between the longitudinal muscle of the low rectum and LAM surface (Figure 3B). In the posterior portion, the hiatal ligament (HL) was identified as a thick white bundle connected to the low rectal wall (Figure 4A). ICG fluorescence was observed in the HL during observation using ICG-FI (Figure 4B).

Discussion

In the present study, lymphatic flow around the pelvic floor was visualized using intraoperative ICG-FI in patients with RC. To our knowledge, only one study observed lymphatic flow in this region using ICG-FI under the same setting (3), and our study is the first to comprise subjects who did not undergo preoperative therapy. Therefore, the visualized lymphatic flow in the present study eliminated the critical limitation of our previous study and may reflect a flow more precise than that observed in previous studies. The results of the present study showed that participants who did not undergo preoperative therapy had anatomical features similar to those of patients in the authors' previous study. Furthermore, this study is the first to use a robot-assisted surgical system (Da Vinci Xi® Surgical System) to observe the lymph flow of the pelvic floor. This study demonstrates the potential of robot-assisted surgical systems for future research on lymph flow analyses.

According to our observation, the lymphatic flow visualized by ICG was detected not only in the already-known route from the low rectum to the LPLNs via the lateral ligament (6), but also in the novel route from the surface of LAM and to the HL (Figure 5). Currently, the interpretation of anatomical structures on the surface of LAM is complicated. Generally, the endopelvic fascia (EF) is considered a sheet of fascia lining the pelvic walls and floor, covering the obturator internus, piriformis, LAM, and coccygeus muscles (7). Colorectal surgeons usually recognize EF intraoperatively as the fascia on the surface of LAM. However, histological findings have demonstrated that the original EF seems to comprise collagen and elastic fibers, not smooth muscle fibers (8). Tsukada *et al*. reported that smooth muscle fibers continued from the longitudinal muscle and were directly attached to the LAM as an indentation (9). Accordingly, smooth muscle fibers from the rectal longitudinal muscle and EF seem to attach relatively extensively to the surface of LAM, and the border between them is unclear. HL, also known as the "ventral layer of the anococcygeal ligament" and "anococcygeal raphe", is an

Table I. *Patient characteristics and clinicopathological findings*.

Case	Age (years)	Sex	BMI (kg/m^2)	Tumor location	Approach	Operation	Operative time (min)	Bleeding (ml)	ICG-related adverse events	Postoperative complications (Clavien-Dindo grade)	Postoperative hospital stay (days)	pT	pN	pM	pStage	Lymphatic invasion
1	53	Male	26.2	Middle rectum	Laparoscopic	LAR	290	20	None	None	7	1a	0	0	I	+
2	84	Female	27.5	Middle rectum	Laparoscopic	LAR	147	50	None	None	8	3	0	0	IIa	–
3	80	Female	18.9	Low rectum	Laparoscopic	APR	231	250	None	None	18	3	0	0	IIa	–
4	75	Female	21.8	Middle rectum	Laparoscopic	LAR	100	5	None	Surgical site infection (I)	13	4a	2a	0	IIIc	+
5	74	Male	20	Middle rectum	Laparoscopic	LAR	188	20	None	None	15	3	2a	0	IIIc	+
6	72	Male	20.3	Middle rectum	Robot	LAR	290	5	None	None	7	3	1b	0	IIIb	+
7	64	Male	24.2	Middle rectum	Robot	LAR	367	70	None	None	7	1b	0	0	I	–
8	42	Female	28.5	Low rectum	Robot	APR	386	180	None	None	9	2	0	0	I	–
9	64	Male	21.9	Low rectum	Robot	LAR	247	5	None	None	10	2	0	0	I	+
10	79	Male	24.7	Upper rectum	Robot	LAR	244	20	None	None	7	2	0	0	I	+
11	71	Male	26.2	Upper rectum	Robot	LAR	234	10	None	None	6	4a	2a	1c	IVc	+
12	87	Male	16.8	Low rectum	Laparoscopic (TaTME in combination)	APR	209	100	None	None	28	3	2a	0	IIIb	+
13	74	Female	25.1	Anal canal	Robot (TaTME in combination)	APR	286	100	None	None	9	4b	0	0	IIc	+
14	78	Female	25.9	Low rectum	Laparoscopic (TaTME in combination)	APR	302	50	None	Intraabdominal bleeding (IIIa)	20	3	2b	0	IIIc	+

BMI, Body mass index; ICG, indocyanine green; TaTME, trans-anal total mesorectal excision; LAR, low anterior resection; APR, abdominoperineal resection.

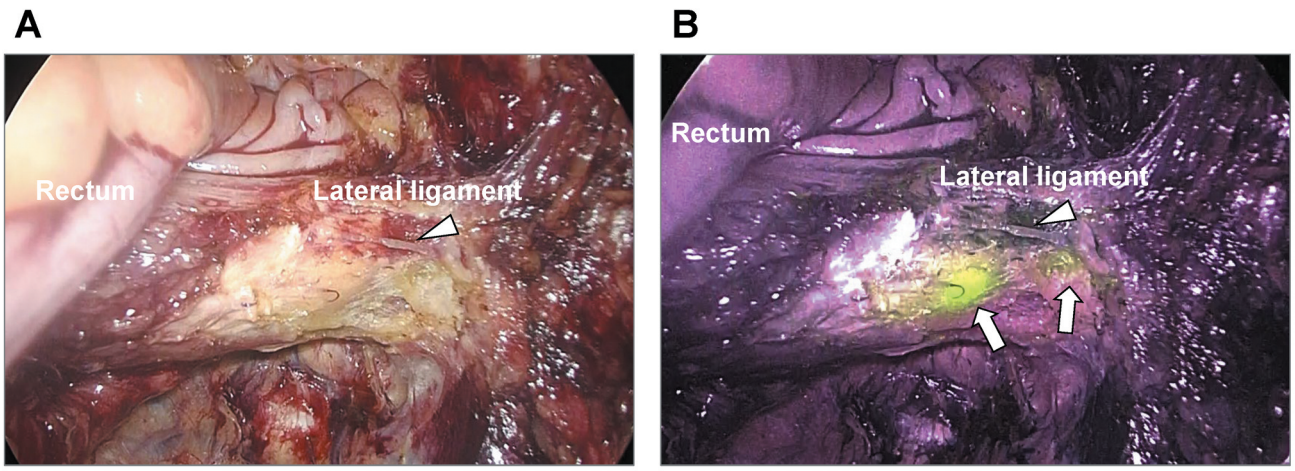

Figure 1. *ICG-FI findings of the lateral ligament during laparoscopic surgery in a 53-year-old man with low RC (Case 1 in Table I). (A) Image of the normal light view. (B) Image of the ICG-FI. The middle rectal artery run in the lateral ligament (arrowhead). ICG fluorescence was identified along with the middle rectal artery (arrows). RC, Rectal cancer; ICG-FI, intraoperative indocyanine green fluorescence imaging.*

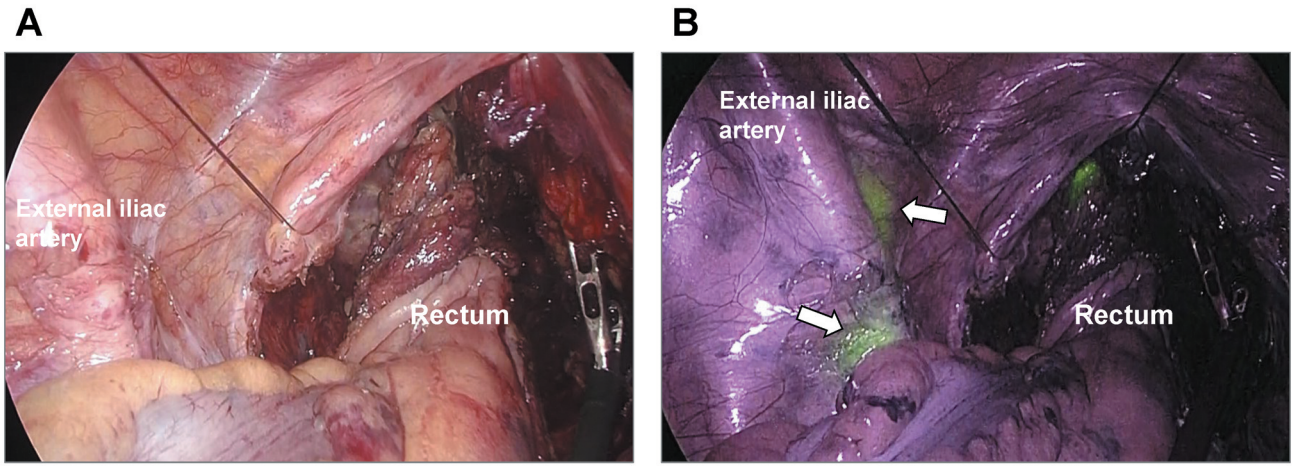

Figure 2. *ICG-FI findings of the LPLNs during laparoscopic surgery in a 53-year-old man with low RC (Case 1 in Table I). (A) Image in normal light view of the left lateral pelvic region. (B) Image of the ICG-FI. ICG fluorescence was reached to the LPLNs along with the iliac artery (arrows). RC, Rectal cancer; ICG-FI, intraoperative indocyanine green fluorescence imaging; LPLNs, lateral pelvic lymph nodes.*

important structure during low rectal surgery. According to previous studies, the HL is recognized as a thick white bundle that comprises abundant smooth muscle and elastic fibers and connects the anal canal and coccyx (9, 10). Tsukada *et al*. suggested that the smooth muscle in the HL is connected to the longitudinal muscle of the posterior wall of the anal canal (9). Based on these previous anatomical findings and the findings of our present study, ICG flow on the surface of LAM and in the HL seems to have spread via the smooth muscle fibers continued from the longitudinal muscle of the low rectum.

The results of this study possibly suggest the limitations of surgery-only therapy and the importance of multidisciplinary therapy for low RC. For example, local excision (LE) has been introduced for early low RC owing to the corresponding postoperative quality of life of patients (11). However, the recurrence rate has been reported to be higher among patients who underwent LE than among those who underwent TME (12), and lymphovascular invasion has been reported to be a risk factor for recurrence (13). Currently, adjuvant chemoradiotherapy (CRT) following LE may be a safe and effective alternative in patients who refuse

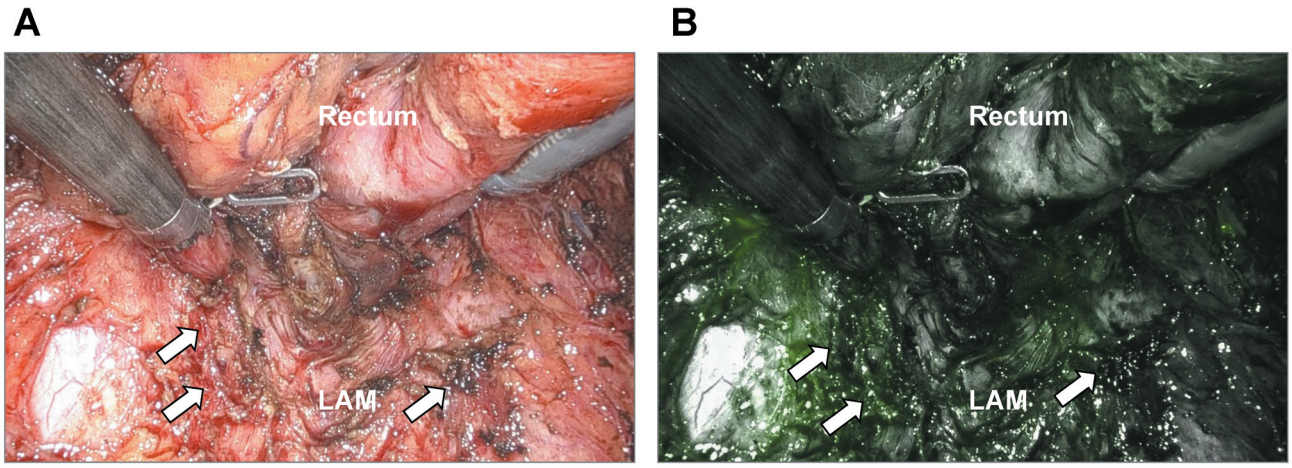

Figure 3. *ICG-FI findings on the surface of LAM during robot-assisted surgery in a 42-year-old woman with low RC (Case 8 in Table I). (A) Image in normal light view around the posterior portion of the low rectum after completing TME. (B) Image of the ICG-FI. The surface of LAM was covered with a thin band-like tissue originating from the longitudinal muscle of the low rectum (arrows). ICG fluorescence was observed on the surface of LAM and was widely spread between the longitudinal muscle of the low rectum and surface of LAM (green fluorescence in B). RC, Rectal cancer; ICG-FI, intraoperative indocyanine green fluorescence imaging; LAM, levator ani muscle; TME, total mesorectal excision.*

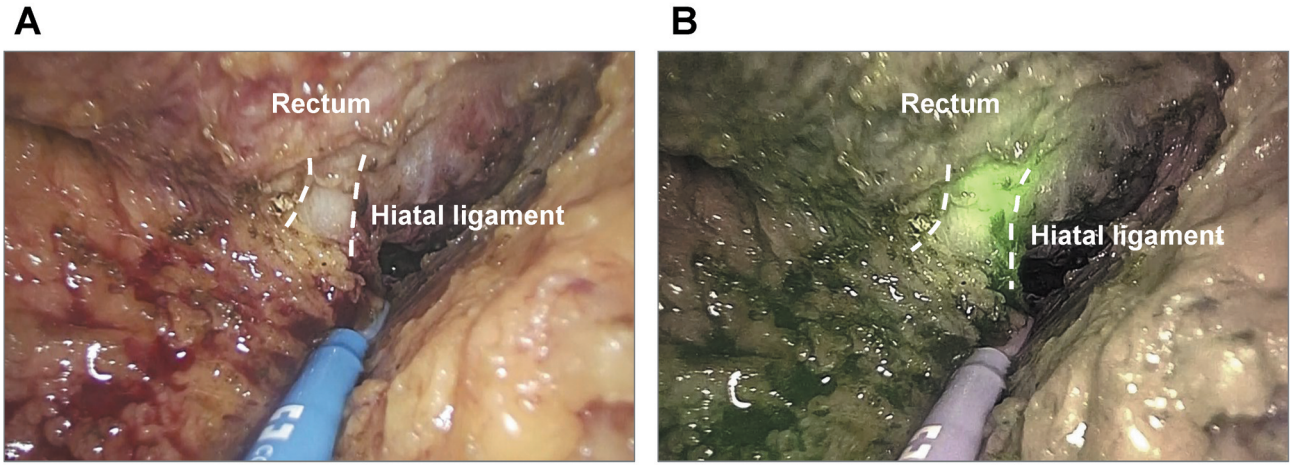

Figure 4. *ICG-FI findings of the hiatal ligament during TaTME in a 87-year-old man with low RC (Case 12 in Table I). (A) Image in normal light view of the posterior portion during TaTME. (B) Image of the ICG-FI. The hiatal ligament was identified as a structure comprising a thick white bundle connecting to the low rectal wall surrounded by dotted lines. During observation using ICG-FI, ICG fluorescence was observed in the hiatal ligament (B). RC, Rectal cancer; ICG-FI, intraoperative indocyanine green fluorescence imaging; TaTME, trans-anal total mesorectal excision.*

or are unfit for transabdominal resection according to the National Comprehensive Cancer Network (NCCN) guidelines (14). The results of our present study seemingly support this therapeutic strategy since CRT may control widespread tumor invasion on the surface of LAM and via the HL. A previous study observed changes in lymphatic function following radiation in mice and evaluated lymphatic degeneration and remodeling after radiation (15). Sakuyama *et al*. also reported that fibrosis extended to deeper layers in neoadjuvant CRT (NACRT) than in neoadjuvant chemotherapy in patients with RC (4). These studies, which evaluated the histological effects of radiation and CRT, also support the indication for CRT following LE with lymphatic invasion.

Our study may also help consider therapeutic strategies for advanced low RC from an anatomical perspective. Although

lymphovascular invasion has been reported to be associated with poor prognosis in patients with advanced low RC (16), anatomical and functional lymphovascular networks in anorectal lesions have not been studied because of difficulties in observation. Laparoscopic and robotic (including TaTME) intraoperative ICG-FI enable the observation of this lesion, especially on the pelvic floor. Considering the results of our study, the reason that lymphovascular invasion is associated with poor prognosis may be the incomplete resection of the widespread lymphatic network on the surface of LAM and via the HL. Standard surgery-only therapy seems insufficient for patients with advanced low RC, especially in cases with lymphatic invasion. The resection lines of low anterior resection, intersphincteric resection, and standard abdominoperineal resection (APR) may not cover the area of widespread lymphatic flow on the surface of LAM. In fact, APR demonstrates poor prognosis, and extralevator abdominoperineal excision (ELAPE) has been introduced as an adequate alternative (17). Previous studies have reported that, compared to APR, ELAPE reduced local recurrence rates and improved overall and disease-free survival (18). In contrast, a previous study has reported that ELAPE yielded higher recurrence rates compared to other methods (18). Similarly, the outcomes of ELAPE remain controversial. Although ELAPE may allow for the resection of the lymphatic network on the surface of LAM, its higher invasiveness and complication rate may affect the recurrence (19).

Considering the results of our study, NACRT also seems to be beneficial since ELAPE may not promise total resection of the widespread lymphatic network on the surface of LAM. Currently, according to the NCCN guidelines, NACRT is standard therapy for advanced low RC (14). Considering the histological effects of radiation and CRT (4, 15), NACRT may contribute to reducing the local recurrence of the pelvic floor. In fact, NACRT has been reported to reduce the recurrence rates in patients with low RC. Thus, considering therapeutic strategies from the aspects of the anatomical evaluation of lymphatic flow, as well as clinicopathological data, may resolve these controversies.

This study had certain limitations. First, we only stated the lymphatic flow on the surfaces of LAM and HL. Interpretations of lymphatic flow in the anterior and anterolateral portions, including Denonvillier's fascia and neurovascular bundle, were difficult only during observation using ICG-FI because of the complex relationship between the low rectum and urogenital organs. To analyze these regions, a combination of ICG-FI and histological analyses seems to be beneficial. Second, the participants in this study were patients with RC, and some patients had lymph node metastases. The presence of cancer induces lymphangiogenesis in both the primary tumor and lymph nodes (20), and this might cause anatomical differences. An observation using a fresh cadaver without rectal cancer seems beneficial. Third, we did not histologically analyze whether ICG fluorescence truly reflected lymphatic flow. In this study, we only resected the area of the standard procedures, and the tissues on the surface of LAM were not resected. Therefore, we were unable to perform a histological analysis. To resolve this controversy, histological analysis using fluorescence staining should be performed. However, ICG was injected preoperatively, and ICG imaging analyses of the anorectal lesions were performed at least several hours after injection. Therefore, the possibility that ICG fluorescence reflects vascular flow seems low. To resolve the above-mentioned limitations, observation using ICG-FI and histological analysis using fluorescence staining in fresh cadavers seem to be beneficial for future research.

In conclusion, the present study suggests a widespread lymphatic network on the surface of the LAM and in the HL

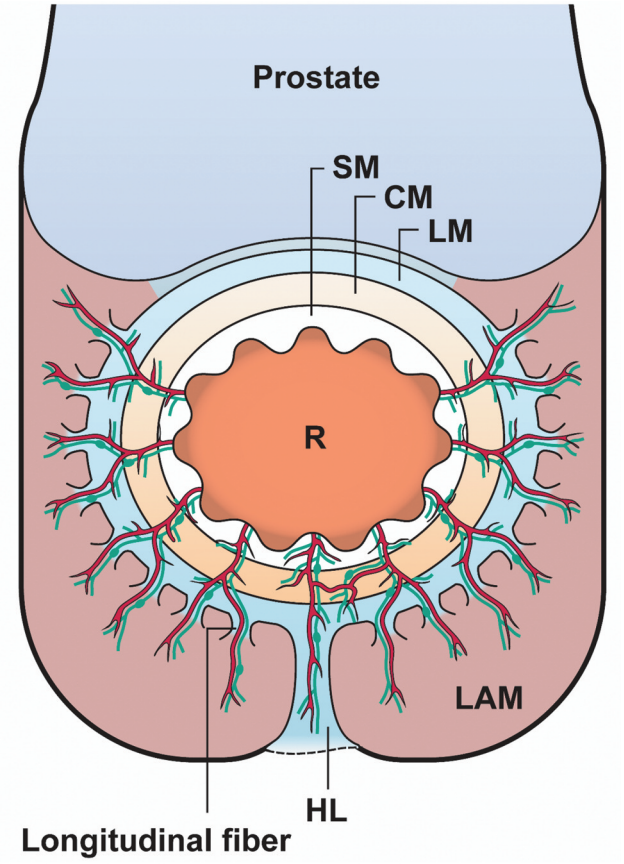

Figure 5. *A schema of lymphatic flow around the low rectum. Male axial section around the low rectum and LAM. Communications of lymphatic ducts (green solid lines) between the LM of the low rectum and hiatal ligament and longitudinal fibers on the surface of LAM are demonstrated. CM, Circular muscle; HL, hiatal ligament; LAM, levator ani muscle; LM, longitudinal muscle; R, rectum; SM, submucosa. The figure was obtained from reference (3).*

originating from the longitudinal muscle fibers of the low rectum. Data on functional lymphatic flow in this complex area may help choose therapeutic strategies for patients with low RC.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

All Authors contributed to the study. Kentaro Sato, Hiroyuki Kasajima, and Ken Imaizumi conducted this study. Kentaro Sato wrote the manuscript and prepared its original draft. Kentaro Sato, Hiroyuki Kasajima, Ken Imaizumi, Michihiro Kurushima, Minoru Umehara, Yosuke Tsuruga, Daisuke Yamana, Aya Sato, Kentaro Ichimura, Takumu Fukasawa, Keiichiro Ito, and Marina Isokawa performed the operations and managed the postoperative course. Kazuaki Nakanishi supervised the study. All Authors have read and approved the final manuscript.

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