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Lymphatic flow mapping during colon cancer surgery using indocyanine green fluorescence imaging

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ABSTRACT

With the development of surgical technology, indocyanine green (ICG) fluorescence navigation systems may be useful in various areas of colorectal surgery, including tumor location confirmation, bowel perfusion, ureter identification, and lymph node mapping. This review provides an overview of the current status of ICG-based navigation surgery in colorectal surgery, emphasizing its role in lymphatic flow mapping. This state-of-the-art approach will allow for appropriate oncological surgeries in the field of colorectal cancer and improve the patient's prognosis.

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Colorectal cancer; laparoscopic surgery; navigation surgery; indocyanine green; lymphatic flow mapping

Introduction

Indocyanine green (ICG, DIAGNOGREEN INJ., 25 mg, Daiichi Sankyo, Tokyo, Japan) is a tricarbocyanine iodide dye molecule that is sterile, anionic, and water-soluble with a molecular weight of 774.96 Da. This agent was developed for near-infrared (NIR) photography by the Kodak Research Laboratories in 1955 [1]. ICG is the only safe NIR contrast agent approved by the U.S. Food and Drug Administration (FDA) for clinical application. It is used to determine cardiac output and assess or identify ophthalmic angiography, hepatic function, liver and bowel blood flow, and cholangiography. ICG binds to serum proteins when administered directly into veins or tissue. When serum protein-bound ICG is exposed to NIR light at 760–780 nm, it releases NIR at 800–850 nm [2]. Fluorescence imaging with ICG is under development, and the number of clinical uses for this fluorophore continues to increase. Recently, laparoscopic instruments capable of detecting NIR light have been developed and clinically applied.

In colorectal surgery, total mesorectal excision (TME), a secure resection of the tumor and its regional lymph nodes in the rectal mesentery [3], and complete mesocolic excision (CME) with central vessel ligation (CVL) [4–6], improve patient outcomes. Several recent reports have described techniques and results regarding the visualization of lymphatic vessels and nodes that may metastasize using ICG and NIR devices [7–9].

This review discusses the existing literature regarding ICG fluorescence imaging, including lymphatic flow mapping with ICG fluorescence imaging in colorectal surgery and other emerging clinical applications.

Equipment available for ICG detection

Various fluorescence NIR systems are available for laparoscopic and open surgery, including the 1588/1688 AIM Platform (Stryker, Portage, MI, USA), PINPOINT (Novadaq, Mississauga, ON, Canada), D-Light P NIR/ICG (Karl Storz GbmH & Co. KG, Tuttlingen, Germany), VISERA ELITE II System (Olympus, Tokyo, Japan), IC-View (Pulsion Medical Systems, Munich, Germany), PDE-neo System (Hamamatsu Photonics K.K., Hamamatsu, Japan), SPY Elite Kit (LifeCell Corporation, Bridgewater, NJ, USA), Artemis Spectrum (Quest Medical Imaging BV, Wieringerwerf, The Netherlands), EleVision™ IR Platform (Medtronic, Minneapolis, MN, USA), NIR-FI system (Schölly Fiberoptic GmbH, Denzlingen, Germany), and da Vinci Firefly robotic surgical system (Intuitive Surgical, Sunnyvale, CA, USA).

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These systems have the white light mode to be used throughout the procedure and NIR mode in which ICG is visualized as green fluorescence on a black background. Some latest laparoscopic systems allow NIR images to be overlaid on the white light mode. Therefore, the surgery can be conducted while ICG fluorescence is observed in real-time.

Current clinical applications using ICG fluorescence imaging for colorectal carcinoma

Colon cancer localization

Ponsky et al. first described endoscopic tattooing using India ink in 1975 [10]. However, this agent has been associated with complications and side effects such as colonic abscess formation, localized peritonitis, inflammatory pseudotumor, and adhesion ileus. The first clinical experience of ICG endoscopic tattooing was reported by Hammond et al. [11] who injected 1% ICG endoscopically and preoperatively and easily visualized it on the serosal surface of the colon during surgery. ICG remained visible 48 h after injection. The authors concluded that ICG is an excellent colonic tattooing agent to facilitate intraoperative localization of small colonic lesions without adverse events.

Miyoshi et al. also reported the effectiveness of non-fluorescent ICG tattooing during colorectal surgery [12] with no pre- or peri-operative adverse reactions and complications due to ICG injection. The median ICG-positive staining duration was four days (range: 1–73 days). Watanabe et al. reported the use of fluorescence imaging with light-emitting diode (LED)-activated ICG for colonic tattooing [13]. LED-activated ICG was visualized with the naked eye and accurately localized tumors. Satoyoshi et al. reported that a total of one milligram of ICG injection around the tumor site up to six days preoperatively can be detected during laparoscopic colorectal surgery [14].

Ahn et al. reported that the optimal ICG dosage of endoscopic submucosal injection for tumor localization ranged from 0.5–1 mg (from 0.2–0.4 ml of diluted ICG) for fluorescence-guided laparoscopic colorectal surgery [15].

Colonic perfusion

Several studies have reported that ICG fluorescence angiography is a safe and feasible tool for the intraoperative assessment of tissue perfusion during colonic resection [16–19]. A 0.2–0.5 mg/kg bolus of ICG followed by a flush of normal saline is injected intravenously by an anesthesiologist before anastomosis. After the intravenous injection of ICG, it is visualized using the NIR mode within 30–60 s. A fluorescent image can be obtained using the NIR camera. Bowel perfusion detected using ICG fluorescence angiography plays an important role in tissue repair after anastomosis, and the ability to visualize the image in real time is very useful compared to conventional, subjective evaluation methods. Non-fluorescence tissue or delayed perfusion indicates poor blood flow, suggesting that additional bowel resection may reduce the incidence of anastomotic leakage [20].

Multicenter randomized clinical trials (RCTs) of ICG fluorescence angiography have been conducted [21,22], and several RCTs are currently ongoing [23–25]. Published reports indicate that ICG angiography is a beneficial procedure that reduces anastomotic leakage [26–28]. However, the fluorescence intensity during ICG angiography is affected by several conditional factors including individual patient factors, such as vessel anatomy (Sudeck point and/or Griffith's point), cardiac ejection fraction, aortic sclerosis, and diabetes mellitus. Therefore, an optimal protocol and standardization of ICG angiography are necessary.

At our institution, ICG fluorescence angiography is conducted using the 1588 AIM Platform just prior to anastomosis during left-sided colorectal cancer surgery. The fluorescence is observed laparoscopically, under more physiologic-like conditions. NIR mode is used to observe the fluorescence 15–45 s after 5 ml of 2.5 mg/ml ICG and 20 ml of normal saline are intravenously injected. If fluorescence is observed in the anvil insertion site and the rectal staple line, the anastomosis is performed (Figure 1(a,b)). If a non-fluorescence area or delayed fluorescence area (>60 s) is observed, an additional resection is performed up to 1 cm on the oral side of the clear fluorescence area.

Lymph node mapping

Sentinel lymph node (SLN) mapping is used to identify the first draining lymph node of the primary tumor [29]. Common tracers used for SLN mapping include vital blue dye, technetium-99m-labeled colloids, and ICG [30–32]. These tracers have been used in patients with early-stage melanoma, breast cancer, and upper GI tract cancer to identify and harvest potentially metastatic lymph nodes.

In contrast, in patients with colorectal cancer, it is difficult to determine the dissection range due to the localization of the tumor and the variation of blood vessels. To determine a more accurate extent of lymph node dissection, lymph node mapping and dissection using ICG

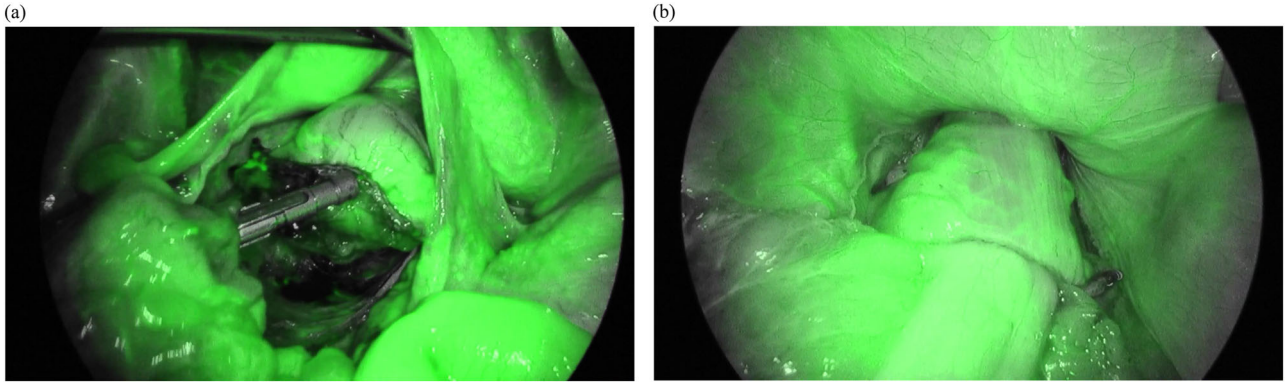

Figure 1. Bowel perfusion assessment. The fluorescent perfusion assessments using the near-infrared mode after injection of 5 ml (2.5 mg/ml) of indocyanine green and 20 ml of normal saline before (a) and after (b) anastomosis during anterior resection are shown.

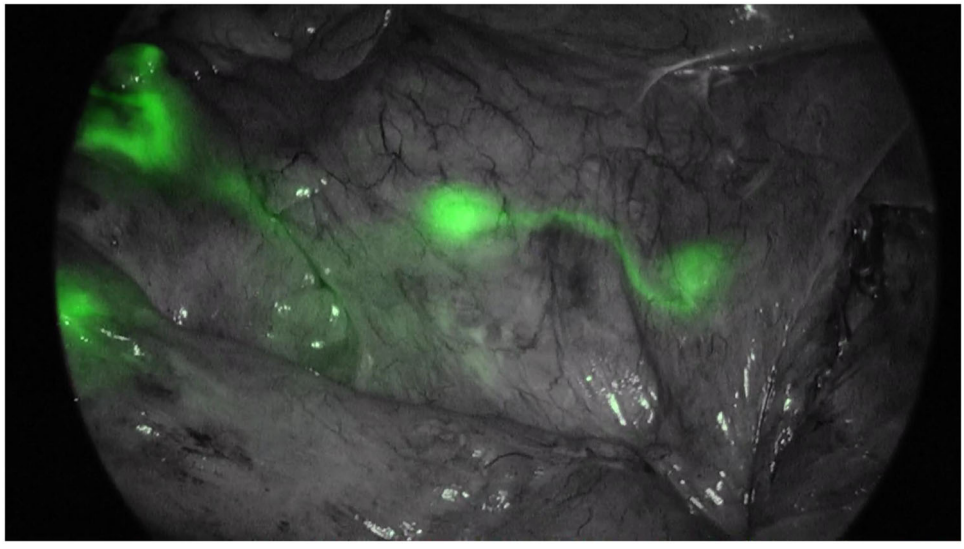

Figure 2. Lymphatic flow mapping. Lymphatic flow and the lymph nodes were identified alongside the right colic vessels in a patient with ascending colon cancer undergoing laparoscopic right colectomy.

fluorescence imaging with NIR light are used as well as blood perfusion assessment (Figure 2) [33–36].

ICG lymph node mapping in practice

Timing and dosage of ICG tattooing for lymph node mapping

When ICG is injected through the submucosal or subserosal layers around the tumor, the lymphatic vessels can be visualized using an NIR image system. The submucosal ICG injection around the tumor is performed preoperatively *via* colonoscopy, and the subserosal ICG injection is performed laparoscopically after intra-abdominal exploration. However, the reported timing and dosages of ICG injections vary and have yet to be standardized (Table 1) [7–9,31,37–42]. Preoperative, endoscopic ICG injection should be for lateral lymph node detection for patients with lower rectal cancer [38].

At our institution, endoscopic submucosal ICG injection was used when first introduced, though subserosal injections are currently used (Figure 3), as endoscopic submucosal ICG injections resulted in a low ICG lymph node detection rate and intraperitoneal leakage of ICG due to technical failure.

Usefulness of ICG lymphatic flow detection

ICG lymphatic flow mapping is useful to visualize the real-time lymphatic flow from the main tumor, which allows for a more reliable lymph node dissection than conventional lymphadenectomy that follows the vascular anatomy.

The splenic flexural colon receives blood flow from the left colic artery (LCA), the left branch of the

Table 1. The protocols of fluorescence lymph node mapping.

First Author [ref]	Year	Number of patients	Submucosal/ subserosal	ICG dosage at each point (diluted concentration, mg/ml)	Injection timing	Injection points	ICG detection rate (%)	NIR system
Caprioli et al. [37]	2022	32	Submucosal (14) /subserosal (18)	1 ml/2 ml (2.5 mg/ml)	7 days before–same day	4 points/ 1 point	100	IMAGE 1S (Karl Storz) 1588 AIM System (Stryker) PINPOINT system (Novadaq)
Ohya et al. [38]	2022	172 (NIR:84)	Submucosal	0.25 ml (2.5 mg/ml)	Just before surgery	4 points	–	D-light P (Karl Storz) 1588 AIM System (Stryker)
Ho et al. [39]	2022	21	Submucosal (7) /subserosal (14)	0.2–0.5 ml (2.5 mg/ml)	6 days before–same day	2–3 points	86	Firefly fluorescence imaging (Intuitive) VISERA ELITE II (Olympus) IMAGE 1S (Karl Storz)
Ribero et al. [40]	2022	70 (interim analysis)	Submucosal	1.5 ml (0.5 mg/ml)	1–3 days before	4 points	100	Firefly fluorescence imaging (Intuitive)
Sato et al. [7]	2021	155	Submucosal	0.1 ml (2.5 mg/ml)	–	2 points	–	1588/1688 AIM System (Stryker) Firefly fluorescence imaging (Intuitive)
Kakizoe et al. [8]	2021	72	Subserosal	1 ml (2.5 mg/ml)	Just before surgery	2 points	99	D-light P (Karl Storz) 1588 AIM System (Stryker)
Ushijima et al. [9]	2020	57	Submucosal	0.2–0.3 ml (2.5 mg/ml)	1–2 days before	1 point	75.4	PINPOINT system (Novadaq)
Park et al. [41]	2020	25	Submucosal	0.1–0.2 ml (2.5 mg/ml)	3–24 h before	1–2 points	100	D-light P (Karl Storz)
Currie et al. [42]	2017	30	Submucosal	1 ml (5 mg/ml)	Just before surgery	4 points	90	Prototype laparoscopic NIR system (Olympus)
Watanabe et al. [31]	2017	31	Subserosal	1ml (2.5 mg/ml)	Just before surgery	2 points	100	D-light P (Karl Storz)

ICG: indocyanine green.

middle colic artery (Lt-MCA), and the left accessory aberrant colic artery (LAACA), if present. Therefore, lymph node dissection for splenic flexural colon cancer may be required. In some patients, over-surgery may result in a strict CME with CVL. Watanabe et al. reported that the LAACA was the feeding artery in 38.7% of patients with splenic flexural colon cancer and was identified using laparoscopic real-time ICG fluorescence imaging [34]. No patients in the previous study exhibited lymph flow directed to the LCA and Lt-MCA. Therefore, an understanding of the lymphatic flow pattern *via* ICG lymphatic flow is useful in patients with splenic flexural colon cancer. Park et al. reported that the total number of harvested lymph nodes was significantly higher when ICG fluorescence-guided laparoscopic lymphatic flow mapping was used than when conventional lymph node dissection was used in patients with advanced right-sided colon cancer [41]. Ushijima et al. reported a low detection rate of lymphatic flow by ICG fluorescence imaging in patients with cStage III and IV, suggesting that ICG lymphatic flow mapping should be used in patients with early-stage colon cancers [9]. According to the interim analysis of a prospective observational study, the GREENLIGHT trial, ICG lymphatic flow mapping modifies the extension of the D3 lymphadenectomy in up to 50% of patients. This suggested the possibility of lymph node metastasis to sites not dissected by conventional D3 lymphadenectomy, such as metastasizing around the right gastroepiploic vessels in ascending colon cancer and around the right iliac artery in sigmoid colon cancer [40]. Therefore, a more accurate determination of the level of lymphadenectomy can be obtained using ICG lymphatic flow mapping. ICG lymphatic flow mapping is very important due to the complexity of lymphatic flow, especially in patients with hepatic or splenic flexural colon cancer.

Limitations of ICG lymph node mapping

There are several limitations of lymphatic flow observation using ICG fluorescence imaging in patients with colorectal cancer. This method evaluates lymphatic flow and lymph nodes in patients with normal lymphatic basins around the tumor. Therefore, in patients with bulky lymph node metastases, an accurate evaluation is not possible due to obstruction of the lymphatic vessels by tumor cells and altered lymphatic flow [7,8]. ICG fluorescence imaging also allows for the observation of normal lymphatic flow, which may metastasize from the tumor. Lymphatic

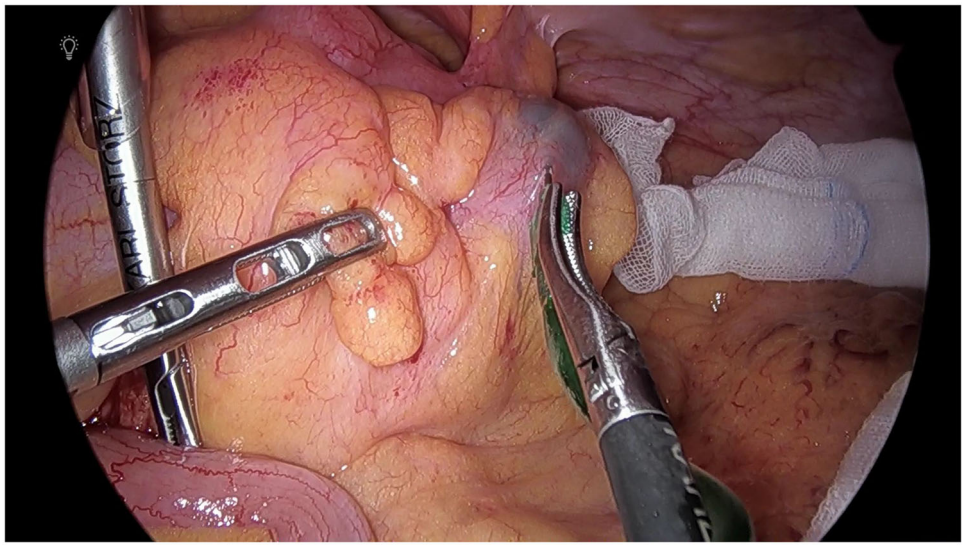

Figure 3. Subserosal ICG injection. A 23-gauge needle is used to inject 0.5 ml of 2,5mg/ml indocyanine green around the tumor.

flow from the tumor may flow in a central direction, such as to the paraaortic lymph nodes, resulting in an excessive dissection. In addition, when endoscopic ICG submucosal injections are used, the ICG must be injected at several points around the tumor for the accurate observation of lymphatic flow.

Although the local ICG injection method (submucosal or subserosal injections) and amount have not been clarified, ICG lymphatic flow mapping is beneficial for determining the extent of the lymph node dissection for patients with early-stage colon cancer in the hepatic and/or splenic flexures, where the dominant vessels differ [9].

Currently, the wavelength used during the NIR mode of ICG is <1,000 nm. In patients with thick visceral fat, false negatives of the lymphatic flow may occur. The development of NIR devices allowing for deeper observation at higher wavelengths is necessary.

Emerging technology using ICG fluorescence imaging

As described above, ICG is a useful agent and is only approved for clinical use for real-time observation of blood perfusion and lymphatic flow during colorectal cancer surgery. Research regarding blood perfusion suggests that ICG may be used with fewer adverse events and may be effective in preventing anastomotic leakage. However, ICG lacks specificity for tumor cells. A more specific agent is needed.

Kato et al. evaluated the effectiveness of fluorescence for the detection of lymph node metastasis from colon cancer in a mouse model using intraperitoneally-administered 5-aminolevulinic acid (5-ALA) [43]. This agent is metabolized into a fluorescent substance, protoporphyrin IX (PPIX), that accumulates in cancer cells. However, the penetration depth of red light (630 nm) ranges from 0.2 to 2 cm, and the depth of exciting blue light (380–449 nm) required to detect PPIX is less than that used in ICG fluorescence. Therefore, 5-ALA is useful for diagnosing metastases in resected lymph nodes, but not for diagnosing the intraoperative spread of metastases. In addition, the peak of PPIX accumulation and fluorescence expression in tumor cells after the oral administration of 5-ALA is approximately two to four hours, which is not suitable for clinical applications [44].

Recently, several tumor-specific ligands that recognize cancer-related molecular biomarkers have been developed for fluorescence image-guided surgery [45]. NIR fluorophore IRDye800CW with bevacizumab (bevacizumab-IRDye800CW) and a fluorescent anti-CEA monoclonal antibody (SGM-101) used with intraoperative fluorescence imaging are promising biomarkers that require more research [46,47].

Conclusions

Over the past two decades, the imaging technology used in the field of laparoscopic surgery has improved significantly, including high-resolution images, three-dimensional images, robotic surgery, and NIR fluorescence imaging. In addition, the observation of ICG that overlays white light with the NIR system has been developed, allowing for more appropriate surgeries.

ICG is the only safe agent with few adverse events that can be used clinically for fluorescence

observation, and its usefulness extends beyond the assessment of bowel perfusion and lymphatic flow in the field of colorectal cancer surgery. However, detailed studies regarding ICG fluorescence-guided surgery are needed to ensure a more reliable clinical application that leads to improved oncologic outcomes.

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No potential conflict of interest was reported by the author(s).

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