



A narrative review of intraoperative use of indocyanine green fluorescence imaging in gastrointestinal cancer: situation and future directions

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Background and Objective: As a surgical tool, indocyanine green (ICG) is increasingly used in surgery, especially in gastric and colorectal surgery. The use of ICG fluorescence imaging can improve the accuracy of tumor resection and potentially improve surgical outcomes for cancer patients. However, there are still different opinions or controversies on the application of ICG in the literature and the administration of ICG is still not uniform. In this review, we summarize the current status of its application and ICG administration methods in gastrointestinal cancer and discuss its existing limitations and future research directions.

Methods: Literature published in the PubMed database from 1969 to 2022 was searched for using the keywords “Indocyanine green or near-infrared imaging or ICG”, “gastric cancer”, “gastroesophageal junction cancer”, and “colorectal cancer” to summarize the main applications of ICG in gastrointestinal cancers.

Key Content and Findings: ICG guidance can rapidly determine tumor location and save operative time, and can also visualize lymph nodes (LNs) in real-time, helping surgeons to retrieve more LNs for better postoperative staging, but its use in identifying sentinel lymph node (SLN) in gastric cancer (GC) remains controversial due to false negatives. ICG fluorescent angiography has great potential in preventing colorectal anastomotic leakage, but there is a dearth of high-caliber research evidence. In addition, ICG has unique advantages in detecting colorectal liver micrometastasis. Notably, there is still no uniform administration method and dose of ICG.

Conclusions: In this review, we summarize the current status of ICG application in gastrointestinal cancer, and the current literature suggests that it is safe and effective and has the potential to change the clinical outcome of patients. Therefore, ICG should be routinely used in gastrointestinal cancers to improve the surgical outcomes of patients. In addition, this review summarizes the ICG administration in the literature, and we expect future guidelines to unitize and standardize the administration of ICG.

Keywords: Indocyanine green (ICG); gastrointestinal cancer; gastric cancer (GC); colorectal cancer (CRC); liver metastasis

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Introduction

Among gastrointestinal cancers, gastric cancer (GC) and colorectal cancer (CRC) are the fourth and second leading causes of cancer-related deaths in humans, respectively (1). At present, gastrointestinal cancers are treated by comprehensive treatment entailing surgery combined with radiotherapy, chemotherapy, immunotherapy, and targeted therapy, but surgery remains the cornerstone of treatment. In recent years, technological innovations have greatly reduced the complications of gastrointestinal cancer surgery, while improving the long-term prognosis of cancer patients (2,3). To improve patient survival, the principles of surgical oncology must be strictly adhered to, including complete resection of the tumor with negative margins and complete clearance of positive lymph nodes (LNs). However, numerous persistent issues in gastrointestinal cancer surgery remain poorly addressed, including intraoperative localization of the tumor, assessment of the extent of resection and anastomotic blood perfusion, and proper lymphadenectomy (4-6). In this context, the use of surgical tracers offers great convenience to the operator, such as classical carbon nanoparticles, methylene blue, recently emerging indocyanine green (ICG) dye, hyperspectral imaging, or multispectral imaging. Among them, ICG is generally favored by surgeons because of its easy accessibility, accuracy, and cost-effectiveness (7).

ICG is a fluorescent dye that can be excited by external light in the range of 750–810 nm and emits near-infrared (NIR) light at a wavelength of about 840 nm (8). The tissue penetration depth of its fluorescence ranges from 0.5 to 1.0 cm (9-11). Since the introduction of ICG angiography to assess choroidal circulation in clinical practice in 1989 (12), ICG fluorescence imaging (ICG-FI) has been widely used in a variety of cancer treatment options including GC (13), CRC (14), hepatobiliary cancer (15), breast cancer (16), and esophageal cancers (17). In particular, in the past few years, the use of ICG fluorescence in gastrointestinal cancer surgery has attracted great interest. Although several applications of ICG in gastrointestinal cancer have been described, they remain inadequate and non-specific. In particular, there are still no uniform standards for the timing of ICG injections, injection sites, and doses used.

This review aims to compare the different opinions or controversies about ICG application in the literature, as well as to analyze the prospects of ICG application in gastrointestinal cancer. In particular, we tried to define the

administration of ICG and its role in lymphatic visualization and anastomotic perfusion in gastrointestinal cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-230/rc>).

Methods

We reviewed the literature in the PubMed database from 1969 to December 2022. The search terms included “indocyanine green or near-infrared imaging or ICG”, “gastric cancer”, and “colorectal cancer”. The search strategy used for writing this paper is summarized in *Table 1*.

Discussion

Tumor localization

With the conduct of various clinical studies, minimally invasive laparoscopic or robotic-based treatment of GC and CRCs has been widely recognized as one of the standard procedures in the treatment of gastrointestinal cancers (18-20). Although minimally invasive treatment can shorten postoperative recovery time and improve patients' long-term postoperative quality of life (21,22), the lack of direct palpation of the hand during laparoscopic or robot treatment, especially in early stages when cancer has not yet invaded the gastrointestinal serosa, makes intraoperative localization of the tumor a challenge and makes a further determination of the line of tumor resection difficult. Several methods have been proposed, including preoperative submucosal injection of India ink or application of titanium clips and direct intraoperative endoscopic observation (23-25). However, these methods have increased the time and effort spent during intraoperative detection, and there is a risk of leakage of Indian ink affecting the surgical field. ICG is the best choice at this stage to overcome these problems because it is easier to visualize and is not visible in natural light, so it has no impact on the surgical field. Preoperatively or intraoperatively, the line of resection can be easily determined by injecting ICG at the appropriate location and using a fluorescent laparoscope or a da Vinci robot with a built-in ICG detection system to display the fluorescence to determine the location of the tumor (26), resulting in significant savings in operative time. In the surgical treatment of gastrointestinal cancer, obtaining negative tumor margins is of utmost importance, which is significantly associated with

Table 1 Search strategy summary

Items	Specification
Date of search	31 December 2022
Databases and other sources searched	PubMed
Search terms used	("colorectal cancer"[tiab] OR "Colorectal Neoplasms"[Mesh] OR "gastric cancer[tiab]" OR "Stomach Neoplasms"[Mesh] OR "gastroesophageal junction cancer"[tiab]) AND ("Indocyanine green"[tiab] OR near-infrared[tiab] OR "near-infrared imaging"[tiab] OR "near-infrared fluorescence imaging"[tiab] OR ICG[tiab])
Time frame	1969–2022
Inclusion and exclusion criteria	Only papers in English were included
Selection process	Two authors collected and assembled the data, and disagreements were resolved by all the authors through discussion

ICG, indocyanine green.

overall patient survival and long-term prognosis (27-30). Recent study has demonstrated that NIR-guided resection of the entire spread of ICG in the gastric wall can ensure 28 mm or greater resection margins (4). Likewise, the ICG-FI can easily and conveniently display the exact location of colorectal tumors (31-33). In radical surgery for GC and CRC, it is sometimes necessary to minimize the surgical margin distance to preserve normal tissues based on ensuring safe margin distance, and preserving more normal gastric bodies can significantly improve patients' postoperative quality of life (34). Ultra-low anastomosis for rectal cancer is undoubtedly a boon for patients with a strong desire to preserve the anus, and the key to its successful implementation is to accurately determine the location of the tumor to preserve a certain length of the lower rectum. It is easy to see the potential value of the successful application of ICG-FI in improving the long-term quality of life of patients after surgery. In addition, some studies have used preoperative endoscopically placed fluorescent clips to localize tumors intraoperatively by fluorescent signals from the clips (35-37). This is similar to ICG fluorescence, but its fluorescence signal and the ability to penetrate the tissue is weaker, and it is often necessary to change the camera angle or make the tissue thinner by stretching it in order to obtain the fluorescence signal in areas with abundant adipose tissue or thicker tissue (35).

In fact, in GC and CRC, the purpose of fluorescence imaging is not only to help the surgeon determine the location of the tumor more precisely but also to save time in detecting the tumor intraoperatively with other methods. In a retrospective comparative study of GC including a total of 93 patients, there was no significant difference in

proximal resection margin (PRM) in the ICG and non-ICG groups in the lower or middle section. However, there was a significant difference in operation time (OPT) between the 2 groups. The median OPT for the ICG group was 235 minutes, whereas the median OPT for the non-ICG group was 275 minutes, with a Kolmogorov-Smirnov (KS) P value of 0.006 (38), which significantly reduced OPT in the ICG group. Ushimaru *et al.* also showed that ICG-FI shortened the OPT of laparoscopic GC surgery (39). In an another study involving a total of 342 patients who had undergone laparoscopic colorectal resection after propensity score matching, 114 patients who received preoperative ICG tattoos had significantly lower OPT than non-tattooed patients (174.76±51.6 *vs.* 192.63±59.9) (40). There is published research showing that prolonged surgery time increases the risk of postoperative complications (41). Compared to other methods, the use of ICG not only saves surgical time but may be more meaningful because of its contribution to reducing the risk of postoperative complications. However, because ICG does not bind specifically to tumor cells, it is not available to further reduce the resection margin distance to preserve more normal tissue. The use of tumor-targeted fluorophores has increased dramatically in the last decade, and their facilitation of precise localization of tumors may be a potential solution for effective margin distance reduction. Several tumor-targeting fluorescent agents, such as SGM-101, have achieved good results in clinical study (42).

LN navigation

In GC, ICG was first used to detect sentinel lymph node

(SLN) (43,44). The SLN of the stomach is the first station of lymphatic drainage of GC, and the LN is most likely to metastasize (45). The application of SLN navigation surgery in gastrointestinal tumors is controversial (46,47), and there may be micrometastasis and skip metastasis in complex lymphatic drainage of GC (44,48-50). How to accurately identify the SLN remains the focus of gastrointestinal surgeons. A multicenter prospective trial in Japan used the endoscopic dual-tracer method with radiolabeled tin colloid and blue dye to detect SLN in clinical stage T1 primary GC of 4 cm or less and achieved a favorable outcome. The SLN detection rate determined by using the dual-tracer method was 97.5%, and the accuracy of metastatic status based on SLN evaluation was 99.0% (51). However, its clinical application has been hindered by the invasiveness of the dual tracer method, the restrictions on the use of radioactive colloid, and the high medical costs (52,53). ICG's advantages of innocence, convenience, low cost, and shorter learning curve (7) outweigh the drawbacks of radioactive tracers.

Many studies have confirmed the excellent performance of ICG in gastric SLN identification. Tajima *et al.* reported that ICG has achieved good results in identifying SLN in laparoscopy-assisted gastrectomy (LAG) and open gastrectomy (OG). The accuracy and false-negative rates were 97.2% and 25.0%, respectively, in LAG group patients, and 91.9% and 23.1%, respectively, in OG group patients (54). A meta-analysis showed that ICG or blue dye + radioactive tracer had a higher identification rate (99% and 98%, respectively) for gastric SLN than blue dye or radioactive colloid tracer alone. Moreover, as time went on, the identification rate and sensitivity of ICG to gastric SLN both increased (98% and 88% in 2001–2010 to 99% and 92% in 2011–2020). Using ICG for SLN biopsy is a worthwhile technique for experienced surgeons to consider (7,54–58). However, the JCOG0302 clinical trial conducted by Japanese researchers to evaluate the feasibility and accuracy of SLN biopsy in the diagnosis of T1 GC was finally forced to terminate because of the high false negative rate. Their team analyzed the reasons and found that it resulted from insufficient learning time and the histological evaluation of just 1 slice of green-stained nodes by frozen section (59). The intraoperative SLN biopsy technique was improved by Shoji *et al.* in a small sample prospective research. ICG was injected around the primary tumor during surgery, followed by a 1-step nucleic acid (OSNA) amplification assay to quickly determine the expression of epithelial protein CK19. The detection rate

of SLN was 85%, but the false negative rate was as low as 0%, indicating that it was accurate and feasible to use ICG-FI to detect SLN and OSNA detection to diagnose LN metastasis intraoperatively (60). Although the concept of SLN is technically feasible, more research is required to determine the best procedure and standard due to the causes of skip metastasis and false negative LNs brought on by complex drainage of GC. In addition, how to determine the resection scope when a SLN biopsy is positive should also be the direction of future research.

At present, standard gastrectomy and LN dissection based on laparoscopy or robotics is mainly used for GC treatment. Improved long-term survival for patients with GC results from maximal LN dissection with the standard scope of dissection (61–64). Comprehensive LN dissection is also strongly related to the appropriate clinical and pathological staging of patients with GC (62,63,65,66). Removal of a sufficient number of LNs during surgery becomes a basic requirement for the surgeon (27). ICG is also considered an effective visualization tool for LN dissection in standard gastrectomy.

In a prospective single-arm study, Kwon *et al.* used ICG-FI for lymphatic imaging to compare the number of LNs retrieved during robotic radical gastrectomy in stage I GC patients in the ICG group with the non-ICG group. More than 15 LNs were retrieved from each of the 40 patients in the ICG group, and more than 30 LNs were retrieved from 37 patients (92.5%). The mean (SD) number of LNs retrieved from each patient in the non-ICG group [35.2 (11.2)] was considerably lower than in the ICG group [48.9 (14.6)], and only 25 patients (62.5%) in the non-ICG group had a total of 30 or more LNs retrieved, as opposed to 37 patients (92.5%) in the ICG group. Noncompliance of lymph node dissection (LND) per station was defined as containing no LNs from the dissected station, and noncompliance per patient was defined as the absence of LNs from 2 or more LN stations that were supposed to be harvested. The rate of noncompliance per station in the non-ICG group (18.5%) was significantly higher than that in the ICG group (12.5%). Although this study clarified that ICG-guided LND can obtain more LNs and reduce the rate of noncompliance compared with traditional dissection, the patients included in this study were patients with stage I GC, and all metastatic LNs were fluorescent, but it was difficult to determine the specific sensitivity of metastatic LNs or the specificity of fluorescent LNs (67).

In a randomized clinical trial of GC, both the total number of LNs retrieved after distal and total gastrectomy

in the ICG group was considerably higher than that in the non-ICG group. The LN clearance rate was defined as the number of patients in whom a LN station was harvested divided by the total number of patients who required retrieval in the corresponding LN station. The LN dissection rates in the ICG group among patients who received distal gastrectomy were not substantially greater than those in the non-ICG group in each station. The LN dissection rates in the 4sa, 11d, and 12a stations of the ICG group were considerably greater than those in the non-ICG group for patients who received total gastrectomy. According to a comparison of LN noncompliance rates between the 2 groups, the ICG group's rate (31.8%) was lower than the non-ICG group's (57.4%) among all patients. This study indicated that ICG-guided LND was able to harvest more LNs and effectively reduce LN noncompliance compared to conventional surgery. However, regardless of the resection procedure, a comparison of the number of metastatic LNs between the 2 groups revealed that there were not substantially more in each station of the ICG group than in the non-ICG group. The ICG group's fluorescence and metastatic LNs had diagnostic sensitivity and specificity of 56.3 and 46.1, respectively (68). A shortcoming of ICG fluorescence is that it does not specifically identify metastatic LNs, so a significant number of normal LNs may also be removed during surgery. Therefore, prospective studies with large samples are needed to assess whether excessive LND is beneficial to the long-term prognosis of patients. In addition, it is worth noting that among patients in the ICG group, the LN metastasis rate of the 14v fluorescent station is as high as 30%.

In early GC, tumors often have not yet invaded and destroyed the perigastric lymphatic system, making ICG visualization of LNs and lymphatics appropriate, but the relatively low incidence of lymphatic metastasis in early GC has limitations in assessing the correlation between ICG-stained LNs and metastatic LNs. Park *et al.* innovatively used ICG to map the perigastric lymphatic network in advanced GC to assess its correlation with the correlation with metastatic LNs was assessed. A total of 687 LNs were retrieved from the 11 cases included, and only 260 (37.8%) LNs were stained by ICG. Among the total 75 metastatic LNs, only 40.0% were identified by ICG staining (69). This study does not have real-time ICG-FI, but rather fluorescence imaging of the specimen after gastrectomy and LNs clearance in a conventional manner, and it further demonstrates that we cannot rely on ICG imaging to

identify all metastatic LNs, much less to perform selective LN dissection to narrow resection of progressive GC by this technique. However, due to the large workload of this study, only 11 patients were included, and therefore this conclusion lacks confirmation by a large sample of clinical studies.

Many studies have demonstrated that ICG-guided LNs clearance is useful to improve the detection rate of LNs (67,68,70), but it remains unclear whether ICG-FI can detect all potentially metastatic LNs and accurately guide LNs clearance. In a study by Zhong *et al.*, the mean (SD) number of LNs that were ultimately retrieved in the ICG group was 49.9 (14.8), which was more than the number retrieved in the non-ICG group [42.0 (10.3)]. Stratified analysis showed that regardless of the resection method (distal or total gastrectomy), the number of recovered LNs in the ICG group was higher than that in the non-ICG group. Of the 385 patients, 221 had LN metastases. All metastatic LNs of 167 patients were in the fluorescence station, and ICG fluorescence tracing's sensitivity for identifying metastatic stations was 75.6% (167/221). Based on the pathological depth of invasion, the earlier the T-stage, the higher the sensitivity of the detection. According to the anatomical scope, the sensitivity of detecting metastatic LNs in D1+ and D2 stations was 100% for patients with cT1 and cT2 disease who underwent distal gastrectomy or total gastrectomy, except for D1 stations, and that the sensitivity of detecting metastatic LNs in D1+ stations and D2 stations was 100% regardless of distal or total gastrectomy for patients with pT1 and pT2 disease, except for D1 stations (71). This study showed that ICG fluorescence-guided GC LNs clearance was relatively more sensitive to metastatic LNs, especially in patients with early T-stage. Although ICG fluorescence could not specifically visualize metastatic LNs, it is still a valuable guide for surgeons to adopt different clearance strategies for patients with different stages. Notably, similar to the study by Chen *et al.* (68), the metastasis rates of LNs beyond the D2 scope (No.10 and 14v) in this study were 17.8% and 27.6%, respectively, with a diagnostic sensitivity of 87.5% in the No.14v fluorescent station. Further studies are needed to guide surgeons on whether to dissect LNs beyond the D2 scope but showing ICG fluorescence.

Currently, neoadjuvant chemotherapy (NAC) is an integral part of systemic therapy for patients with advanced gastric (AGC) cancer. It has been noted that for patients receiving NAC to accurately reflect their prognosis, more LN anatomy is required (72). Laparoscopic LND is made

more difficult by NAC-induced lymphoid tissue fibrosis and anatomical plane alterations (73,74). In addition, chemotherapy medications may alter the metabolism of tumor cells (75). As a result, the primary tumors and metastatic LNs will contract to owe to fibrosis, which may obstruct lymphatic drainage (76). Can ICG fluorescence be utilized in this situation to assist surgeons in more complete LN dissections? A multicenter study by Huang *et al.* showed that the total number of LNDs in laparoscopic radical gastrectomy is dramatically improved by use of ICG, and no matter how many LNs were in the D2, perigastric, or extragastric ranges, the overall number of LNs dissected in the ICG group was considerably higher than in the non-ICG group. Similarly, the ICG group's LN non-compliance rate was much lower than the non-ICG group's (77). However, in their study, patients with considerable tumor or LN regression following NAC did not see an increase in the number of LN dissections in the ICG group, and the LN non-compliance rate was comparable to that of the non-ICG group. This could be a result of the peripheral stomach's LNs fibrosis obstructing lymphatic channels. This demonstrates that ICG cannot significantly assist individuals who have achieved a strong remission after NAC.

It is not difficult to see that the application of ICG in GC is in full swing, but there are few studies on its use in gastroesophageal (GEJ) cancer. Recently Osterkamp *et al.* investigated whether ICG-FI is beneficial for LNs dissection in robotic-assisted resection of GEJ cancer (78). Additional fluorescent tissue was resected in 52% of patients after NIR examination. The 43 fluorescent tissues excised were pathologically confirmed to include 30 LNs, however, there were no positive metastatic LNs among them. The median number of LNs harvested per patient did not differ significantly from the control group, nor did the two groups differ significantly in terms of operative duration, intraoperative blood loss, and complications. Therefore, it remains uncertain whether ICG-FI will improve the oncological outcome of GEJ cancer.

In conclusion, preliminary evidence suggests that ICG-guided LNs dissection can help surgeons retrieve more LNs and assess the integrity of LN dissection. However, its application remains controversial due to the false negatives seen in detecting SLNs, not to mention its feasibility in reducing the extent of gastric LND. In addition, some studies have found a high rate of positive fluorescent LNs beyond the D2 scope (68,71), and high-quality research evidence is needed to guide surgeons on whether to

perform LND beyond D2 for such patients. Beyond that, it is inconclusive whether ICG helps LNs dissection in GEJ cancer.

Evaluation of anastomotic perfusion

Anastomotic leakage (AL) is one of the most serious complications of CRC surgery, the incidence and consequences of colorectal AL have not significantly decreased over the past few decades despite improvements in surgical methods. After colorectal surgery, AL still occurs 4–30% of the time (79–81). Poor bowel perfusion is considered the main cause of AL. Several methods have been described to assess anastomotic perfusion, including mesenteric vascular pulsation, active bleeding at the resection margins, and local tissue color changes (82). However, these are based on the subjective assessment of the surgeon and may not be reliable (83). ICG fluorescent angiography (ICG FA) can give surgeons immediate feedback on bowel perfusion, assisting them in deciding where to place the anastomosis. In the past few years, some studies have shown that ICG FA seems to be effective in preventing AL following CRC surgery. Chan *et al.* published a complete meta-analysis of colorectal anastomotic leakage, which included 5,498 patients from 20 studies (84). According to their summary analysis, the overall anastomotic leak rate for the 2,220 patients receiving ICG FA was 3.7%, whereas it was 8.6% for the 3,278 patients in the control group. The overall odds ratio (OR) for the study was 0.46 [95% confidence interval (CI): 0.34–0.62; $P < 0.00001$]. This demonstrates that ICG FA is associated with a significantly lower rate of patient AL. The meta-analysis of Safiejko *et al.* on ICG in CRC included 32 studies involving 11,047 patients, among which the AL rates of the ICG group and the non-ICG group were 3.7% and 7.6% respectively ($P < 0.001$) (14). The results indicate that ICG perfusion assessment is a valuable tool to reduce the incidence of AL after colorectal surgery.

A multicenter retrospective study utilizing ICG to assess the AL and reoperation rates followed stapled side-to-side anastomosis (SSSA) in colon cancer surgery (85). In the ICG group, 3.2% of the patients were judged as having poor perfusion and no perfusion, so the planned resection line was changed, and these patients did not have AL after surgery. The AL rate in the ICG group was 0.8%, whereas that in the non-ICG group was 3.5%. The AL and reoperation rate in the ICG group were significantly lower than those in the non-ICG group. The study showed

that ICG can significantly reduce the AL and reoperation rate following SSSA in colon cancer surgery. Another multicenter cohort study on the application of ICG in laparoscopic low anterior resection of rectal cancer revealed that 5.7% of patients in the ICG group experienced a change in the transverse line of the colon. In the non-ICG group, the AL rates for Clavien-Dindo (CD) grades II and III were 10.4% and 9.5%, respectively, whereas they were 4.7% and 2.8% in the ICG group. ICG-FI significantly reduced the AL rate of CD grade \geq II and \geq III, and reoperation rates were significantly reduced (86).

The majority of studies using ICG FA to assess the perfusion of colorectal anastomosis during surgery have been retrospective. In 2020, De Nardi *et al.* published the first randomized controlled trial (RCT) on ICG FA (87). Their study included 109 patients after low rectal resection and 131 patients after left colectomy. However, there were 6 patients (5%) in the ICG group and 11 patients (9%) in the non-ICG group among the 17 patients who had postoperative AL ($P=0.2$). No significant difference in AL rate was observed between the 2 groups. A single-center RCT was subsequently conducted to investigate the role of ICG FA in preventing AL in 377 patients with colorectal tumors. The incidence of AL in the ICG group was significantly lower than that in the non-ICG group (9.1% *vs.* 16.3%, $P=0.04$). Low colorectal anastomoses in their study were associated with a higher AL rate in both groups, but the AL rate was significantly lower in the ICG group versus the non-ICG groups (14.4% *vs.* 25.7%, $P=0.04$). According to the International Study Group of Rectal Cancer's grading of AL, Grade A is AL that does not require active treatment, and Grades B and C require active intervention. However, the difference in AL rates for the above low anastomoses is primarily the result of the non-ICG group having a higher incidence of AL grade A than the ICG group did. The rate of grades B and C AL (clinical AL) did not differ between the 2 groups (88): its clinical benefits are not significant, nor will it have a significant adverse impact on the prognosis of patients. In the later RCT to assess the perfusion outcomes of ICG in low anterior resection, no significant difference was observed in the AL rate between ICG and the standard group (9% *vs.* 9.6%, $P=0.37$) (89).

In addition to the use of ICG to assess colorectal anastomotic perfusion, there are other emerging fluorescent materials that can be used in colorectal surgery. For example, patients with retroperitoneally invading rectosigmoid

carcinoma who are at high risk of intraoperative ureteral injury may receive preoperative fluorescent ureteral insertion to ensure maximum resection without damaging the ureter (90-92).

In contrast to CRC, few studies have evaluated the utility of the ICG fluorescence system to assess anastomotic perfusion in GC surgery. A prospective study by Huh *et al.* evaluated the role of ICG FA in predicting AL during laparoscopic GC surgery (93). All patients studied had high clinical scores (pink tissue and pulsating blood vessels and no signs of ischemia) so the patients with lower fluorescence scores did not change their surgical plans. However, postoperatively one patient developed AL, and a video review revealed a focal perfusion defect in NIR mode. Although the study by Huh *et al.* included a relatively small number of patients (only 30), it showed the potential of ICG FA in assessing AL in laparoscopic GC surgery. Unfortunately, there it is not clear for determining the fluoroscopic predictive score that may lead to AL. Subsequently, Mori *et al.* studied anastomotic perfusion in 100 gastric cancer patients using ICG FA and found that the time difference between the appearance of fluorescence on both sides of the anastomosis was an independent predictor of the anastomotic leak by analysis of the time of appearance of ICG fluorescence (94). A meta-analysis evaluating the effectiveness of ICF FA in preventing AL after esophageal cancer surgery showed a 69% absolute risk reduction of AL with ICG (95). However, the literature included in this meta-analysis included a considerable number of patients with cervical anastomosis. The meta-analysis by Casas *et al.* aimed to analyze the use of ICF FA in patients undergoing intrathoracic anastomosis, however, the results showed that perfusion assessment using ICG FA did not seem to reduce AL rates in patients undergoing minimally invasive esophagectomy with intrathoracic anastomosis (96). This may suggest that perfusion assessment using ICG FA may be more relevant for patients undergoing cervical anastomosis.

In conclusion, ICG FA is secure and simple to apply. It has great potential in preventing postoperative AL in gastric and colorectal cancer. It can significantly reduce the AL and reoperation rate, according to some retrospective cohort studies and meta-analyses. There is a dearth of high-caliber research evidence, particularly its utility in preventing postoperative AL in esophageal cancer remains unclear, though, and more RCTs are anticipated to further demonstrate its efficacy.

Liver metastases

About 20–25% of patients diagnosed with CRC develop liver metastasis (CRLM) over the course of the disease, and up to 50% of patients will develop CRLM within 3 years of diagnosis (97–100). Radical resection is recommended as the only potential cure for patients with CRLM (101,102). Despite continual improvements in surgical techniques and chemotherapy regimens, 65–80% of patients relapse after resecting CRLM (103,104), suggesting that small metastases may have been missed during surgery. Nowadays, the preoperative detection of liver metastases mainly depends on computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US). The imaging results combined with intraoperative US (IOUS) enable surgeons to determine the approximate location of the tumor (105–107). Although intraoperative US has become the standard method to guide hepatectomy due to its advantages of real-time visualization, it also has undeniable shortcomings: it cannot detect lesions with a diameter of ≤ 3 mm, and there is a surface blind area of about 1 cm below the liver surface (108). In other words, it is difficult to detect small occult metastases on the surface of the liver (109,110). Intraoperative detection of small liver cancer is still insufficient, and 3–17% of CRLM can be detected only by microscopic examinations (111). As a tool that can be selected by surgeons, ICG-FI can detect small superficial metastasis (limit of depth ≤ 8 mm) (112). It may be that the bile excretion in the surrounding normal liver tissues compressed by the tumor is disordered after intravenous injection of ICG, and CRLM produces rim fluorescence (111).

The effectiveness of ICG-FI in CRLM has been widely reported. A systematic review by Liberale *et al.* (112) reported 11 studies on the application of ICG-FI to CRLM. Among them, 6 studies reported a sensitivity of more than 94%, of which 3 reported a sensitivity of 100%. In addition, ICG-FI detected additional micrometastasis in 0–43% of patients with CRLM (112). In a single-center study by van der Vorst *et al.*, 71 of 97 CRLM lesions were detected by ICG-FI, with 12.5% of patients having only superficial, occult CRLM detected by ICG-FI and none by conventional imaging. Some 27% of CRLM lesions were not detected by ICG-FI, and all of these metastases were greater than 8 mm in depth from the liver surface (113). ICG-FI may be a supplement to other detection methods. It can be used in combination with conventional IOUS, thus taking advantage of the benefits of each method.

Peloso *et al.* showed that the combined use of IOUS and ICG-FI significantly increased the number of metastases detected, especially for lesions ≤ 3 mm, and the sensitivity was significantly higher than that of preoperative CT and IOUS alone (108).

In addition to identifying micrometastases, ICG-FI can also be used to determine the resection margins of CRLM. In a multicenter study by Nierop *et al.*, 13% of patients had CRLM resection margins that were positive (114). This shows that it is particularly important to accurately determine the resection margin of CRLM to achieve R0 resection. All CRLM cases in the previously reported study achieved R0 resection using ICG-FI (115). However, false positives (e.g., nodular regenerative hyperplasia) were reported in this study, especially in patients with cirrhosis. Recently, Achterberg *et al.* used ICG-FI to identify the resection edge of CRLM, and all 16 lesions were successfully identified and fluorescent rims were displayed at the metastatic foci (116). If the microscopical distance from the resection plane to the tumor burden is less than 1 mm, the resection edge is considered margin-positive resection (R1). All resection specimens showing a protruding rim *in vivo* and *ex vivo* were reported as an R1 resection, and all other fluorescent negative lesions *in vivo* were reported as R0 resection, showing the sensitivity of ICG-FI to determine the resection margin. It is worth noting that this study reported a false negative lesion, which did not show a protruding fluorescent rim *in vivo*, but the pathological results showed that the resection margin was less than 1 mm from the tumor edge, that is, R1 resection.

Most studies of ICG-FI for CRLM have been conducted to verify its efficacy and sensitivity, and no long-term follow-up has been performed to examine its recurrence and survival rate. The first evaluation of long-term follow-up after fluorescence-guided resection of colorectal liver metastases has been published (117). The percentage of patients with additional lesions identified during surgery and the final R0 resection rate was significantly higher in the experimental cohort using the ICG-FI than in the control cohort (25% *vs.* 13%, 83% *vs.* 79%, respectively). At the 4-year follow-up, 47% of participants in the experimental cohort did not have a liver recurrence, compared with 39% of those in the control group ($P=0.40$). Overall survival (OS) at 4 years was 62% and 59%, respectively ($P=0.79$). At the 3-year follow-up of patients who solely underwent ICG-FI-guided CRLM resection, 52% had no recurrence in the liver and 48% had no recurrence at all. Unfortunately,

the substantial evidence of ICG-FI on clinical outcome measures including recurrence-free interval and OS was not demonstrated in this study. With most previous studies having been retrospective, He *et al.* published the first RCT of ICG-FI applied to CRLM (118). In the ICG group, there were significantly more intrahepatic CRLMs identified intraoperatively per patient than in the non-ICG group [mean (SD) 3.03 (1.58) vs. 2.28 (1.35); $P=0.045$]. Additionally, 25% of patients had subcapsular metastasis detected using ICG-FI only. However, 8% of the lesions detected by ICG-FI were confirmed as false positives by histological evaluation.

In conclusion, ICG-FI undoubtedly has great potential for detecting liver micrometastases, and its combination with IOUS can fully utilize the advantages of both: IOUS provides high sensitivity for the detection of intrahepatic lesions, whereas ICG-FI can detect superficial liver lesions with high resolution (108,113,118). Although deep CRLM cannot be detected using ICG-FI, it can be used to guide resection margins or determine the integrity of tumor resection in resected specimens (115,116,118). Therefore, ICG-FI is an effective complement to existing techniques for detecting CRLM, and considering its safety, effectiveness, and low cost, it can be considered for integration into existing routine surgical procedures. However, due to its non-specific identification of lesions, it also has the disadvantage of false positives and false negatives. Nishino *et al.* proposed that the concept of double-labeled fluorescence-guided surgery by labeling the metastatic liver tumors with SGM-101 and adjacent liver segments with ICG may provide a direction for future exploration (119). Future studies should yield substantial evidence that ICG-FI can detect CRLM that is not detected by other methods as well as help surgeons determine the resection margin, and further verify whether it can improve the postoperative survival of CRLM patients by large sample size follow-up and RCTs. Although the incidence is low, it is still worthwhile for future researchers to consider whether the problem of false positives and false negatives that occur when using ICG-FI to detect CRLM can be eliminated.

ICG administration

Although the technique of using ICG has been improved and refined since its application in surgery, there is no uniform standard for its use, injection methods and doses. Centers that have just started ICG-FI are particularly often

limited by their lack of experience. Thus, we summarized the ICG injection method and dosage in gastrointestinal cancer, hoping to help surgeons in surgery.

Localization and lymph node imaging of gastric cancer

In ICG fluorescence-guided radical gastrointestinal cancer surgery, the appropriate ICG injection dose, concentration, and injection site are essential for accurate intraoperative determination of the tumor site and clearance of an adequate number of LNs. In GC surgery, 20 mm is considered the ideal fluorescence signal size for tumor location to determine the appropriate transection line (120). In most studies, ICG has been injected by gastroscopy 1 day or 1–3 days before surgery, and most of them were injected in 4 quadrants around the tumor to clearly show the tumor localization. However, the injection concentration ranged from 0.05 to 1.25 mg/mL, and the injection dose per site ranged from 0.1 to 0.6 mL, with significant differences. For the identification of gastric SLN, ICG was injected at multiple sites around the tumor before the operation after anesthesia. In most studies, ICG was injected under an endoscope, with an injection concentration of 0.5–5 mg/mL and an injection dose of predominantly 0.5 mL per site. In terms of visualization of draining nodes to achieve LNs navigation, the ICG injection concentrations also varied, but most studies used an injection concentration of 1.25 mg/mL and an injection dose of 0.5 mL per site, and the injection method was mostly a 4-site injection around the tumor. A few studies have used intraoperative subserosal injections at 3 sites each in the lesser and greater curvatures of the stomach, mostly at a concentration of 0.5 mL per site and an injectable dose of 1.5 mL (Table 2). ICG injection methods in GC include endoscopic submucosal injection and intraoperative subserous injection (71,77,121). For early GC and advanced GC that has not invaded the serosa, it is difficult to identify the location from the outside of the stomach without preoperative or intraoperative tumor location (127). Subserosal injection often causes ICG leakage and blurring of the surgical field, and ICG fluorescence widely distributed in the surgical area makes further observation difficult (127–130). However, because ICG needs enough time to spread to LNs, endoscopic ICG injection during surgery will prolong the operation time (67), and not all operating rooms are routinely equipped with endoscopic equipment. To sum up, if it is not necessary to identify SLNs, it may be feasible to inject ICG at a concentration of 1.25 mg/mL and a dose of 0.5 mL at each site into the submucosa in the 4 quadrants around

Table 2 Summary of ICG administration in gastric cancer

Authors	Aim	Concentration	Dosage	Time of injection	Injection method	Injection location
Cho <i>et al.</i> (4)	Determine tumor location	0.625 mg/mL	0.6 mL per site	1 day before surgery	Endoscopic injection of submucosa	4 sites around the tumor
Miyashiro <i>et al.</i> (7)	Identifying the sentinel lymph nodes	0.5–2.5 mg/mL	2–4 mL in total	During surgery	Endoscopic injection	4–8 sites around the tumor
Nakanishi <i>et al.</i> (26)	Determine tumor location	1.0 mg/mL	0.1 mL per site	1–3 days before surgery	Endoscopic injection of submucosa	1 site around the tumor
Yoon <i>et al.</i> (38)	Determine tumor location	0.5 mg/mL	0.1 mL per site	1 day before surgery	Endoscopic injection of submucosa	4 sites around the tumor
Ushimaru <i>et al.</i> (39)	Determine tumor location	0.05 mg/mL	0.5 mL per site	1 day before surgery	Endoscopic injection of submucosa	4 sites around the tumor
Miyashiro <i>et al.</i> (59)	Identifying the sentinel lymph nodes	5 mg/mL	4–5 mL in total	During surgery	Subserosal injection	Multiple sites around the tumor
Kwon <i>et al.</i> (67)	Lymph node imaging	1.25 mg/mL	0.6 mL per site	1 day before surgery	Endoscopic submucosal injection	4 sites around the tumor
Chen <i>et al.</i> (68)	Lymph node imaging	1.25 mg/mL	0.5 mL per site	1 day before surgery	Endoscopic submucosal injection	4 sites around the tumor
Puccetti <i>et al.</i> (70)	Lymph node imaging	0.125 mg/mL	0.5 mL per site	12–24 h before surgery	Endoscopic submucosal injection	4 sites around the tumor
Zhong <i>et al.</i> (71)	Lymph node imaging	1.25 mg/mL	0.5 mL per site	1 day before surgery	Endoscopic submucosal injection	4 sites around the tumor
Zhong <i>et al.</i> (71)	Lymph node imaging	0.5 mg/mL	1.5 mL per site	20 min before lymph nodes dissection	Subserous injection under laparoscope	6 sites of the lesser and greater curvature
Huang <i>et al.</i> (77)	Lymph node imaging	0.5 mg/mL	1.5 mL per site	After preoperative exploration	Subserous injection under laparoscope	6 sites of the lesser and greater curvature
Tanaka <i>et al.</i> (120)	Determine tumor location	1 mg/mL	0.1 mL per site	1–3 days before surgery	Endoscopic injection of submucosa	1 site around the tumor
Lombardi <i>et al.</i> (121)	Lymph node imaging	0.125 mg/mL	0.5 mL per site	Within 20 hours before surgery	Endoscopic submucosal injection	4 sites around the tumor
Chen <i>et al.</i> (122)	Determine tumor location and lymph node imaging	1.25 mg/mL	0.5 mL per site	1 day before surgery	Endoscopic injection of submucosa	4 sites around the tumor
Yano <i>et al.</i> (123)	Identifying the sentinel lymph nodes	0.5 mg/mL	0.5 mL per site	During surgery	Endoscopic injection	4 sites around the tumor
Ohdaira <i>et al.</i> (124)	Identifying the sentinel lymph nodes	5 mg/mL	0.5 mL per site	During surgery	Endoscopic submucosal injection	4 sites around the tumor
Maruri <i>et al.</i> (125)	Lymph node imaging	1.25 mg/mL	0.6 mL per site	18–24 h before surgery	Endoscopic submucosal injection	4 sites around the tumor
Cianchi <i>et al.</i> (126)	Lymph node imaging	1.25 mg/mL	0.5 mL per site	1 day before surgery	Endoscopic submucosal injection	4 sites around the tumor

ICG, indocyanine green.

Table 3 Summary of ICG administration in colorectal cancer

Authors	Aim	Dosage	Injection time and method
Watanabe <i>et al.</i> (31)	Determine tumor location	0.5 mL of 2.5 mg/mL	Preoperative peritumoral injection
Ozawa <i>et al.</i> (32)	Determine tumor location	0.5 mL of 2.5 mg/mL	Peritumoral injection 1–2 days before surgery
Nagata <i>et al.</i> (33)	Determine tumor location	0.5 mL of 2.5 mg/mL	Peritumoral injection within 4 days before surgery
Park <i>et al.</i> (40)	Determine tumor location	0.5–1 mL of 12.5 mg/mL	4 sites injection around the tumor 1 day before surgery
Watanabe <i>et al.</i> (85)	Evaluation of anastomotic perfusion	0.25 mg/kg	Before intestinal anastomosis
Watanabe <i>et al.</i> (86)	Evaluation of anastomotic perfusion	0.25 mg/kg	Before the proximal colon transection
De Nardi <i>et al.</i> (87)	Evaluation of anastomotic perfusion	0.3 mg/kg	Before colon transection and after anastomosis
Alekseev <i>et al.</i> (88)	Evaluation of anastomotic perfusion	0.2 mg/kg	Before the proximal colon transection
Jafari <i>et al.</i> (89)	Evaluation of anastomotic perfusion	3.0±1.0 mL of 2.5 mg/mL	Before colectomy and after anastomosis
Miyoshi <i>et al.</i> (131)	Determine tumor location	1 mL of 12.5 mg/mL	2 sites injection around the tumor before surgery
Iwamoto <i>et al.</i> (132)	Evaluation of anastomotic perfusion	7.5 mg	Before intestinal anastomosis
Son <i>et al.</i> (133)	Evaluation of anastomotic perfusion	0.25 mg/kg	Before the proximal colon transection
Park <i>et al.</i> (134)	Evaluation of anastomotic perfusion	0.2 mg/kg	Before the proximal colon transection
Hasegawa <i>et al.</i> (135)	Evaluation of anastomotic perfusion	5 mg	Before the proximal colon transection
Kim <i>et al.</i> (136)	Evaluation of anastomotic perfusion	10 mg	Injection after colorectal mobilization, and repeat injections after anastomosis in patients with questionable perfusion
Ohya <i>et al.</i> (137)	Evaluation of anastomotic perfusion	0.25 mg/kg	Before intestine transection
van den Bos <i>et al.</i> (138)	Evaluation of anastomotic perfusion	0.2 mg/kg	(I) After devascularization of the segment; (II) before the actual transection; (III) after the anastomosis is made
Yanagita <i>et al.</i> (139)	Evaluation of anastomotic perfusion	0.1 mg/kg	Before the proximal colon transection
Otero-Piñeiro <i>et al.</i> (140)	Evaluation of anastomotic perfusion	0.25 mg/mL	Before proximal colon transection and after anastomosis
Benčurik <i>et al.</i> (141)	Evaluation of anastomotic perfusion	0.2 mg/kg	Before the proximal colon transection
Su <i>et al.</i> (142)	Evaluation of anastomotic perfusion	7.5 mg	Before the proximal colon transection
Ishii <i>et al.</i> (143)	Evaluation of anastomotic perfusion	5 mg	Before intestinal anastomosis
Hasegawa <i>et al.</i> (144)	Evaluation of anastomotic perfusion	5 mg	Before the proximal colon transection

ICG, indocyanine green.

the gastric tumor 1–3 days before surgery, which can give consideration to both localize the tumor and visualize the lymph nodes, and reduce the operative time compared with intraoperative subserosal injection, and prevent the unclear operative field caused by ICG leakage.

Localization and evaluation of anastomotic perfusion in CRC

In most studies, 0.5 mL of 2.5 mg/mL of ICG was injected

around the tumor to determine the localization of the colorectal tumor. For the assessment of anastomotic perfusion, ICG has been used in most studies at a dose of 0.2–0.25 mg/kg intravenously, which most clearly shows intestinal perfusion or ischemic lines (*Table 3*). To date, few studies have reported the use of ICG for CRC tattooing. Animal experiments have demonstrated that the green fluorescence gradually dissipates over time after local injection of ICG (145,146). In the study by Miyoshi *et al.*,

obvious fluorescence was seen in all patients who underwent surgery within 8 days after ICG marking at 12.5 mg/mL, with a significant decrease in positive ICG fluorescence after 9 days or more (131). However, in the study of Watanabe *et al.*, 2.5 mg/mL of ICG was used as the NIR fluorescent dye and significant fluorescence was still visible for 7 to days after colonic injection (31). The use of 0.5 mL of 2.5 mg/mL ICG has also been used with good results in other studies (Table 3). However, a higher sample size study is still needed for confirmation.

Although ICG FA can provide an initial assessment of anastomotic perfusion, its fluorescence intensity can only be based on the subjective visual judgment of the surgeon and there is still no standard method to quantify it, which is probably the biggest limitation of the current use of ICG FA for anastomotic evaluation. Some studies have explored this initially. Wada *et al.* published the first clinical study for quantitative evaluation of ICF-FI 5 years ago (147). The researchers created a time curve of fluorescence intensity using analysis software and retrospectively analyzed the differences in different fluorescence parameters between the AL group and the non-AL group and found that the F_{\max} (fluorescence difference between maximum and baseline) was less than 52.0 AU (arbitrary units) in all cases in the AL group (5/5), whereas only 8 cases in the non-AL group (8/107). If the F_{\max} cutoff value was 52.0 AU, the sensitivity and the specificity were 100% (5/107) and 92.5% (99/107), respectively. The slope of the AL group was less than 2.1 AU/sec in all cases (5/5) compared with 26 cases in the non-AL group (26/107), and if the slope cutoff was 2.1 AU/sec, the sensitivity and specificity of predicting AL were 100% (5 cases) and 75.7% (81 cases), respectively. It is worth noting that there is no correlation between the time from ICG injection to the first visible fluorescence signal and AL. Subsequently, in the study of Hayami *et al.*, the time from ICG injection to the beginning of fluorescence (T_0) in the AL group was significantly longer than that in the non-AL group (64.3 ± 27.6 and 18.2 ± 6.6 s, $P = 2.2 \times 10^{-3}$) and it was confirmed that all cases with $T_0 > 40$ s belonged to the AL group. In contrast, there was no difference in I_{\max} (same as the above F_{\max}) between the AL and non-AL groups. In addition, the authors asserted that I_{\max} is vulnerable to respiratory fluctuation, especially in laparoscopic surgery, which is an unreliable indicator for predicting AL. Therefore, they concluded that T_0 may be the most sensitive predictor of AL (148). The research of Iwamoto *et al.* also supports this conclusion (132). However, in a study by Son *et al.*, different conclusions were drawn: time from

first fluorescence increase to half of the maximum ($T_{1/2\max}$), and the time ratio ($TR = T_{1/2\max}/T_{\max}$) were considered sensitive predictors of anastomotic complications (133). Although these studies reached different conclusions, they provide an initial exploration of quantitative ICG-FI studies, but all were limited by too small sample sizes and other issues to identify clear factors and accurate cutoff values associated with AL, and future prospective multi-institutional large sample RCTs are needed to draw further conclusions.

Conclusions

ICF-FI is a valuable tool in gastrointestinal cancer, and the current literature demonstrates that its use in gastrointestinal cancer is safe and effective and has the potential to change clinical outcomes for patients; however, evidence from high-quality RCTs is still lacking. Although ICG-FI can significantly improve the number of surgical LNs retrieved for GC, there is still a lack of follow-up evidence to support the existence of a significant benefit on long-term survival and prognosis of patients with GC after surgery, and future studies of ICG applied to LN imaging in GC should pay attention to this point. Furthermore, although there is evidence supporting the effectiveness of ICG FA in preventing colorectal AL and potentially changing surgical decisions, further randomized studies are needed to validate this. In addition, an approach to quantify perfusion is necessary, quantification of the fluorescence signal is challenging; the selection of appropriate quantification parameters is a major issue, and the fluorescence intensity may be influenced by a variety of factors such as ambient light, the fluorescence emission source, and the distance between the camera and the colorectum (149,150). At present, there are only a few studies and very inconsistent results (132,133,147,148). An artificial intelligence-based microcirculation analysis system provides new ideas and can overcome the drawbacks of parameter-based assessment of microperfusion and may be one of the future research directions (134,151). There is still no uniform ICG administration applicable to all centers, which is an urgent problem to be solved. In addition, although ICG has powerful clinical benefits, it does not bind specifically to tumor tissue. Targeted fluorescent agents (e.g., SMG-101) are currently undergoing clinical trials and their future clinical benefits are expected. With the boom in NIR imaging, we also need to consider its cost. Whether the high price of fluorescence imaging devices will limit their

development in surgery is also an issue of concern.

In short, the use of ICG in gastrointestinal cancer is partially controversial and challenging, but it has been shown to be safe and effective and has the potential to improve clinical outcomes for patients. We recommend that ICG should be routinely used in gastrointestinal cancer surgery.

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Footnote

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