Review Article

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).

LNs 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 ≥ II and ≥ 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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (59)	Identifying the sentinel lymph nodes	5 mg/mL	4–5 mL in total	During surgery	Subserosal injection	Multiple sites around the tumor
Kwon *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (31)	Determine tumor location	0.5 mL of 2.5 mg/mL	Preoperative peritumoral injection
Ozawa *et al.* (32)	Determine tumor location	0.5 mL of 2.5 mg/mL	Peritumoral injection 1–2 days before surgery
Nagata *et al.* (33)	Determine tumor location	0.5 mL of 2.5 mg/mL	Peritumoral injection within 4 days before surgery
Park *et al.* (40)	Determine tumor location	0.5–1 mL of 12.5 mg/mL	4 sites injection around the tumor 1 day before surgery
Watanabe *et al.* (85)	Evaluation of anastomotic perfusion	0.25 mg/kg	Before intestinal anastomosis
Watanabe *et al.* (86)	Evaluation of anastomotic perfusion	0.25 mg/kg	Before the proximal colon transection
De Nardi *et al.* (87)	Evaluation of anastomotic perfusion	0.3 mg/kg	Before colon transection and after anastomosis
Alekseev *et al.* (88)	Evaluation of anastomotic perfusion	0.2 mg/kg	Before the proximal colon transection
Jafari *et al.* (89)	Evaluation of anastomotic perfusion	3.0±1.0 mL of 2.5 mg/mL	Before colectomy and after anastomosis
Miyoshi *et al.* (131)	Determine tumor location	1 mL of 12.5 mg/mL	2 sites injection around the tumor before surgery
Iwamoto *et al.* (132)	Evaluation of anastomotic perfusion	7.5 mg	Before intestinal anastomosis
Son *et al.* (133)	Evaluation of anastomotic perfusion	0.25 mg/kg	Before the proximal colon transection
Park *et al.* (134)	Evaluation of anastomotic perfusion	0.2 mg/kg	Before the proximal colon transection
Hasegawa *et al.* (135)	Evaluation of anastomotic perfusion	5 mg	Before the proximal colon transection
Kim *et al.* (136)	Evaluation of anastomotic perfusion	10 mg	Injection after colorectal mobilization, and repeat injections after anastomosis in patients with questionable perfusion
Ohya *et al.* (137)	Evaluation of anastomotic perfusion	0.25 mg/kg	Before intestine transection
van den Bos *et al.* (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 *et al.* (139)	Evaluation of anastomotic perfusion	0.1 mg/kg	Before the proximal colon transection
Otero-Piñeiro *et al.* (140)	Evaluation of anastomotic perfusion	0.25 mg/mL	Before proximal colon transection and after anastomosis
Benčurik *et al.* (141)	Evaluation of anastomotic perfusion	0.2 mg/kg	Before the proximal colon transection
Su *et al.* (142)	Evaluation of anastomotic perfusion	7.5 mg	Before the proximal colon transection
Ishii *et al.* (143)	Evaluation of anastomotic perfusion	5 mg	Before intestinal anastomosis
Hasegawa *et al.* (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, $P=2.2\times10^{-3}$) 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 ($T_{1/2MAX}$), and the time ratio ($TR = T_{1/2MAX}/T_{MAX}$) 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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References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Li GZ, Doherty GM, Wang J. Surgical Management of Gastric Cancer: A Review. JAMA Surg 2022;157:446-54.
3. Dekker E, Tanis PJ, Vleugels JLA, et al. Colorectal cancer. Lancet 2019;394:1467-80.
4. Cho M, Kim KY, Park SH, et al. Securing Resection Margin Using Indocyanine Green Diffusion Range on Gastric Wall during NIR Fluorescence-Guided Surgery in Early Gastric Cancer Patients. Cancers (Basel) 2022;14:5223.
5. Tang G, Pi F, Zhang DH, et al. Novel surgical procedure for preventing anastomotic leakage following colorectal cancer surgery: A propensity score matching study. Front Oncol 2022;12:1023529.
6. Ong CT, Schwarz JL, Roggin KK. Surgical considerations and outcomes of minimally invasive approaches for gastric cancer resection. Cancer 2022;128:3910-8.
7. Miyashiro I, Kishi K, Yano M, et al. Laparoscopic detection of sentinel node in gastric cancer surgery by indocyanine green fluorescence imaging. Surg Endosc 2011;25:1672-6.
8. Landsman ML, Kwant G, Mook GA, et al. Light-absorbing properties, stability, and spectral stabilization of indocyanine green. J Appl Physiol 1976;40:575-83.
9. Alander JT, Kaartinen I, Laakso A, et al. A review of indocyanine green fluorescent imaging in surgery. Int J Biomed Imaging 2012;2012:940585.
10. Schaafsma BE, Mieog JS, Hutteman M, et al. The clinical use of indocyanine green as a near-infrared fluorescent contrast agent for image-guided oncologic surgery. J Surg Oncol 2011;104:323-32.
11. Schols RM, Bouvy ND, van Dam RM, et al. Advanced intraoperative imaging methods for laparoscopic anatomy navigation: an overview. Surg Endosc 2013;27:1851-9.
12. Hayashi K, Hasegawa Y, Tazawa Y, et al. Clinical application of indocyanine green angiography to choroidal neovascularization. Jpn J Ophthalmol 1989;33:57-65.
13. Chen QY, Zhong Q, Li P, et al. Comparison of submucosal and subserosal approaches toward optimized indocyanine green tracer-guided laparoscopic lymphadenectomy for patients with gastric cancer (FUGES-019): a randomized controlled trial. BMC Med 2021;19:276.

14. Safiejko K, Tarkowski R, Kozlowski TP, et al. Safety and Efficacy of Indocyanine Green in Colorectal Cancer Surgery: A Systematic Review and Meta-Analysis of 11,047 Patients. Cancers (Basel) 2022;14:1036.
15. Dip F, LoMenzo E, Sarotto L, et al. Randomized Trial of Near-infrared Incisionless Fluorescent Cholangiography. Ann Surg 2019;270:992-9.
16. Bargon CA, Huibers A, Young-Afat DA, et al. Sentinel Lymph Node Mapping in Breast Cancer Patients Through Fluorescent Imaging Using Indocyanine Green: The INFLUENCE Trial. Ann Surg 2022;276:913-20.
17. Hong ZN, Huang L, Zhang W, et al. Indocyanine Green Fluorescence Using in Conduit Reconstruction for Patients With Esophageal Cancer to Improve Short-Term Clinical Outcome: A Meta-Analysis. Front Oncol 2022;12:847510.
18. Hyung WJ, Yang HK, Park YK, et al. Long-Term Outcomes of Laparoscopic Distal Gastrectomy for Locally Advanced Gastric Cancer: The KLASS-02-RCT Randomized Clinical Trial. J Clin Oncol 2020;38:3304-13.
19. Katai H, Sasako M, Fukuda H, et al. Safety and feasibility of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG 0703). Gastric Cancer 2010;13:238-44.
20. Tschann P, Weigl MP, Lechner D, et al. Is Robotic Assisted Colorectal Cancer Surgery Equivalent Compared to Laparoscopic Procedures during the Introduction of a Robotic Program? A Propensity-Score Matched Analysis. Cancers (Basel) 2022;14:3208.
21. Misawa K, Fujiwara M, Ando M, et al. Long-term quality of life after laparoscopic distal gastrectomy for early gastric cancer: results of a prospective multi-institutional comparative trial. Gastric Cancer 2015;18:417-25.
22. Kim YW, Baik YH, Yun YH, et al. Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial. Ann Surg 2008;248:721-7.
23. Yamazaki Y, Kanaji S, Takiguchi G, et al. Preoperative endoscopic tattooing using India ink to determine the resection margins during totally laparoscopic distal gastrectomy for gastric cancer. Surg Today 2021;51:111-7.
24. Kim HI, Hyung WJ, Lee CR, et al. Intraoperative portable abdominal radiograph for tumor localization: a simple and accurate method for laparoscopic gastrectomy. Surg Endosc 2011;25:958-63.
25. Xuan Y, Hur H, Byun CS, et al. Efficacy of intraoperative gastroscopy for tumor localization in totally laparoscopic distal gastrectomy for cancer in the middle third of the stomach. Surg Endosc 2013;27:4364-70.
26. Nakanishi K, Tanaka C, Kanda M, et al. Preoperative indocyanine green fluorescence injection to accurately determine a proximal margin during robotic distal gastrectomy. Asian J Endosc Surg 2023;16:152-6.
27. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017;20:1-19.
28. Davies J, Chew C, Bromham N, et al. NICE 2020 guideline for the management of colorectal cancer. Lancet Oncol 2022;23:e247.
29. Amri R, Bordeianou LG, Sylla P, et al. Association of Radial Margin Positivity With Colon Cancer. JAMA Surg 2015;150:890-8.
30. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol 2008;26:303-12.
31. Watanabe M, Murakami M, Ozawa Y, et al. Intraoperative Identification of Colonic Tumor Sites Using a Near-Infrared Fluorescence Endoscopic Imaging System and Indocyanine Green. Dig Surg 2017;34:495-501.
32. Ozawa Y, Murakami M, Watanabe M, et al. Preoperative colonic cancer tattooing using the near-infrared fluorescence laparoscopic imaging system. Asian J Endosc Surg 2016;9:340-3.
33. Nagata J, Fukunaga Y, Akiyoshi T, et al. Colonic Marking With Near-Infrared, Light-Emitting, Diode-Activated Indocyanine Green for Laparoscopic Colorectal Surgery. Dis Colon Rectum 2016;59:e14-8.
34. Gastrointestinal Surgery Group, Surgery Branch, Chinese Medical Association; Oncology Surgery Group, Surgical Branch, Chinese Medical Doctor Association; Upper Gastrointestinal Group, Surgical Branch, Chinese Medical Doctor Association, et al. Chinese expert consensus on function-preserving gastrectomy for gastric cancer (2021 edition). Zhonghua Wei Chang Wai Ke Za Zhi 2021;24:377-82.
35. Ryu S, Okamoto A, Nakashima K, et al. Usefulness of Preoperative Endoscopic Fluorescent Clip Marking in Laparoscopic Gastrointestinal Surgery. Anticancer Res 2020;40:6517-23.
36. Minoda Y, Hisamatsu Y, Ihara E. Usefulness of preoperative site marking with an indocyanine green fluorescent clip for gastrointestinal stromal tumor. Dig Endosc 2021;33:e95-6.
37. Choi Y, Kim KG, Kim JK, et al. A novel endoscopic fluorescent clip for the localization of gastrointestinal tumors. Surg Endosc 2011;25:2372-7.

38. Yoon BW, Lee WY. The oncologic safety and accuracy of indocyanine green fluorescent dye marking in securing the proximal resection margin during totally laparoscopic distal gastrectomy for gastric cancer: a retrospective comparative study. World J Surg Oncol 2022;20:26.
39. Ushimaru Y, Omori T, Fujiwara Y, et al. The Feasibility and Safety of Preoperative Fluorescence Marking with Indocyanine Green (ICG) in Laparoscopic Gastrectomy for Gastric Cancer. J Gastrointest Surg 2019;23:468-76.
40. Park JH, Moon HS, Kwon IS, et al. Usefulness of colonic tattooing using indocyanine green in patients with colorectal tumors. World J Clin Cases 2018;6:632-40.
41. Hyun DW, Kim KH, Lee SH, et al. Analysis of Postoperative Complications Following Laparoscopic Gastrectomy in 1332 Gastric Cancer Patients. J Minim Invasive Surg 2018;21:13-24.
42. Boogerd LSF, Hoogstins CES, Schaap DP, et al. Safety and effectiveness of SGM-101, a fluorescent antibody targeting carcinoembryonic antigen, for intraoperative detection of colorectal cancer: a dose-escalation pilot study. Lancet Gastroenterol Hepatol 2018;3:181-91.
43. Hiratsuka M, Miyashiro I, Ishikawa O, et al. Application of sentinel node biopsy to gastric cancer surgery. Surgery 2001;129:335-40.
44. Ichikura T, Morita D, Uchida T, et al. Sentinel node concept in gastric carcinoma. World J Surg 2002;26:318-22.
45. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992;127:392-9.
46. Joosten JJ, Strobbe LJ, Wauters CA, et al. Intraoperative lymphatic mapping and the sentinel node concept in colorectal carcinoma. Br J Surg 1999;86:482-6.
47. Chin PL, Medeiros J, Schwarz RE. Use of the sentinel lymph node to determine metastases of gastrointestinal malignancies: a word of caution. J Surg Oncol 1999;71:239-42.
48. Arai K, Iwasaki Y, Takahashi T. Clinicopathological analysis of early gastric cancer with solitary lymph node metastasis. Br J Surg 2002;89:1435-7.
49. Arigami T, Natsugoe S, Uenosono Y, et al. Evaluation of sentinel node concept in gastric cancer based on lymph node micrometastasis determined by reverse transcription-polymerase chain reaction. Ann Surg 2006;243:341-7.
50. Lee SE, Lee JH, Ryu KW, et al. Sentinel node mapping and skip metastases in patients with early gastric cancer. Ann Surg Oncol 2009;16:603-8.
51. Kitagawa Y, Takeuchi H, Takagi Y, et al. Sentinel node mapping for gastric cancer: a prospective multicenter trial in Japan. J Clin Oncol 2013;31:3704-10.
52. Bostick P, Essner R, Glass E, et al. Comparison of blue dye and probe-assisted intraoperative lymphatic mapping in melanoma to identify sentinel nodes in 100 lymphatic basins. Arch Surg 1999;134:43-9.
53. Giuliano AE, Jones RC, Brennan M, et al. Sentinel lymphadenectomy in breast cancer. J Clin Oncol 1997;15:2345-50.
54. Tajima Y, Murakami M, Yamazaki K, et al. Sentinel node mapping guided by indocyanine green fluorescence imaging during laparoscopic surgery in gastric cancer. Ann Surg Oncol 2010;17:1787-93.
55. Nimura H, Narimiya N, Mitsumori N, et al. Infrared ray electronic endoscopy combined with indocyanine green injection for detection of sentinel nodes of patients with gastric cancer. Br J Surg 2004;91:575-9.
56. Ishikawa K, Yasuda K, Shiromizu A, et al. Laparoscopic sentinel node navigation achieved by infrared ray electronic endoscopy system in patients with gastric cancer. Surg Endosc 2007;21:1131-4.
57. Kusano M, Tajima Y, Yamazaki K, et al. Sentinel node mapping guided by indocyanine green fluorescence imaging: a new method for sentinel node navigation surgery in gastrointestinal cancer. Dig Surg 2008;25:103-8.
58. Huang Y, Pan M, Chen B. A Systematic Review and Meta-Analysis of Sentinel Lymph Node Biopsy in Gastric Cancer, an Optimization of Imaging Protocol for Tracer Mapping. World J Surg 2021;45:1126-34.
59. Miyashiro I, Hiratsuka M, Sasako M, et al. High false-negative proportion of intraoperative histological examination as a serious problem for clinical application of sentinel node biopsy for early gastric cancer: final results of the Japan Clinical Oncology Group multicenter trial JCOG0302. Gastric Cancer 2014;17:316-23.
60. Shoji Y, Kumagai K, Kamiya S, et al. Prospective feasibility study for single-tracer sentinel node mapping by ICG (indocyanine green) fluorescence and OSNA (one-step nucleic acid amplification) assay in laparoscopic gastric cancer surgery. Gastric Cancer 2019;22:873-80.
61. Huang CM, Lin JX, Zheng CH, et al. Prognostic impact of dissected lymph node count on patients with node-negative gastric cancer. World J Gastroenterol 2009;15:3926-30.
62. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. J Clin Oncol 2005;23:7114-24.
63. Son T, Hyung WJ, Lee JH, et al. Clinical implication of an

insufficient number of examined lymph nodes after curative resection for gastric cancer. Cancer 2012;118:4687-93.
64. Seevaratnam R, Bocicariu A, Cardoso R, et al. A meta-analysis of D1 versus D2 lymph node dissection. Gastric Cancer 2012;15 Suppl 1:S60-9.
65. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439-49.
66. Liu YY, Fang WL, Wang F, et al. Does a Higher Cutoff Value of Lymph Node Retrieval Substantially Improve Survival in Patients With Advanced Gastric Cancer?-Time to Embrace a New Digit. Oncologist 2017;22:97-106.
67. Kwon IG, Son T, Kim HI, et al. Fluorescent Lymphography-Guided Lymphadenectomy During Robotic Radical Gastrectomy for Gastric Cancer. JAMA Surg 2019;154:150-8.
68. Chen QY, Xie JW, Zhong Q, et al. Safety and Efficacy of Indocyanine Green Tracer-Guided Lymph Node Dissection During Laparoscopic Radical Gastrectomy in Patients With Gastric Cancer: A Randomized Clinical Trial. JAMA Surg 2020;155:300-11.
69. Park JH, Berlth F, Wang C, et al. Mapping of the perigastric lymphatic network using indocyanine green fluorescence imaging and tissue marking dye in clinically advanced gastric cancer. Eur J Surg Oncol 2022;48:411-7.
70. Puccetti F, Cinelli L, Genova L, et al. Applicative Limitations of Indocyanine Green Fluorescence Assistance to Laparoscopic Lymph Node Dissection in Total Gastrectomy for Cancer. Ann Surg Oncol 2022;29:5875-82.
71. Zhong Q, Chen QY, Huang XB, et al. Clinical implications of Indocyanine Green Fluorescence Imaging-Guided laparoscopic lymphadenectomy for patients with gastric cancer: A cohort study from two randomized, controlled trials using individual patient data. Int J Surg 2021;94:106120.
72. Vahrmeijer AL, Hutteman M, van der Vorst JR, et al. Image-guided cancer surgery using near-infrared fluorescence. Nat Rev Clin Oncol 2013;10:507-18.
73. Li Z, Shan F, Ying X, et al. Assessment of Laparoscopic Distal Gastrectomy After Neoadjuvant Chemotherapy for Locally Advanced Gastric Cancer: A Randomized Clinical Trial. JAMA Surg 2019;154:1093-101.
74. An JY, Kim KM, Kim YM, et al. Surgical complications in gastric cancer patients preoperatively treated with chemotherapy: their risk factors and clinical relevance. Ann Surg Oncol 2012;19:2452-8.
75. Tan Y, Li J, Zhao G, et al. Metabolic reprogramming from glycolysis to fatty acid uptake and beta-oxidation in platinum-resistant cancer cells. Nat Commun 2022;13:4554.
76. Hu X. Timing of surgery after neoadjuvant chemotherapy for advanced gastric cancer. Zhonghua Wei Chang Wai Ke Za Zhi 2013;16:509-12.
77. Huang ZN, Su-Yan, Qiu WW, et al. Assessment of indocyanine green tracer-guided lymphadenectomy in laparoscopic gastrectomy after neoadjuvant chemotherapy for locally advanced gastric cancer: results from a multicenter analysis based on propensity matching. Gastric Cancer 2021;24:1355-64.
78. Osterkamp J, Strandby R, Nerup N, et al. Intraoperative near-infrared lymphography with indocyanine green may aid lymph node dissection during robot-assisted resection of gastroesophageal junction cancer. Surg Endosc 2023;37:1985-93.
79. Park JS, Choi GS, Kim SH, et al. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision: the Korean laparoscopic colorectal surgery study group. Ann Surg 2013;257:665-71.
80. Kang CY, Halabi WJ, Chaudhry OO, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg 2013;148:65-71.
81. Kingham TP, Pachter HL. Colonic anastomotic leak: risk factors, diagnosis, and treatment. J Am Coll Surg 2009;208:269-78.
82. Kudszus S, Roesel C, Schachtrupp A, et al. Intraoperative laser fluorescence angiography in colorectal surgery: a noninvasive analysis to reduce the rate of anastomotic leakage. Langenbecks Arch Surg 2010;395:1025-30.
83. Karliczek A, Harlaar NJ, Zeebregts CJ, et al. Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. Int J Colorectal Dis 2009;24:569-76.
84. Chan DKH, Lee SKF, Ang JJ. Indocyanine green fluorescence angiography decreases the risk of colorectal anastomotic leakage: Systematic review and meta-analysis. Surgery 2020;168:1128-37.
85. Watanabe J, Ishibe A, Ohya H, et al. Evaluating the Effect of Intraoperative Near-Infrared Observation on Anastomotic Leakage After Stapled Side-to-Side Anastomosis in Colon Cancer Surgery Using Propensity Score Matching. Dis Colon Rectum 2021;64:1542-50.
86. Watanabe J, Ishibe A, Suwa Y, et al. Indocyanine green fluorescence imaging to reduce the risk of anastomotic leakage in laparoscopic low anterior resection for rectal cancer: a propensity score-matched cohort study. Surg

Endosc 2020;34:202-8.
87. De Nardi P, Elmore U, Maggi G, et al. Intraoperative angiography with indocyanine green to assess anastomosis perfusion in patients undergoing laparoscopic colorectal resection: results of a multicenter randomized controlled trial. Surg Endosc 2020;34:53-60.
88. Alekseev M, Rybakov E, Shelygin Y, et al. A study investigating the perfusion of colorectal anastomoses using fluorescence angiography: results of the FLAG randomized trial. Colorectal Dis 2020;22:1147-53.
89. Jafari MD, Pigazzi A, McLemore EC, et al. Perfusion Assessment in Left-Sided/Low Anterior Resection (PILLAR III): A Randomized, Controlled, Parallel, Multicenter Study Assessing Perfusion Outcomes With PINPOINT Near-Infrared Fluorescence Imaging in Low Anterior Resection. Dis Colon Rectum 2021;64:995-1002.
90. Ushimaru Y, Ohigawa A, Yamashita K, et al. Real-time ureteral identification with novel, versatile, and inexpensive catheter. Surg Endosc 2020;34:3669-78.
91. Ryu S, Okamoto A, Nakashima K, et al. Ureteral navigation using a fluorescent ureteral catheter during laparoscopic colorectal surgery. Surg Endosc 2021;35:4882-9.
92. Ryu S, Ishida K, Okamoto A, et al. Laparoscopic fluorescence navigation for left-sided colon and rectal cancer: Blood flow evaluation, vessel and ureteral navigation, clip marking and trans-anal tube insertion. Surg Oncol 2020;35:434-40.
93. Huh YJ, Lee HJ, Kim TH, et al. Efficacy of Assessing Intraoperative Bowel Perfusion with Near-Infrared Camera in Laparoscopic Gastric Cancer Surgery. J Laparoendosc Adv Surg Tech A 2019;29:476-83.
94. Mori M, Shuto K, Hirano A, et al. A Novel Parameter Identified Using Indocyanine Green Fluorescence Angiography may Contribute to Predicting Anastomotic Leakage in Gastric Cancer Surgery. World J Surg 2020;44:2699-708.
95. Ladak F, Dang JT, Switzer N, et al. Indocyanine green for the prevention of anastomotic leaks following esophagectomy: a meta-analysis. Surg Endosc 2019;33:384-94.
96. Casas MA, Angeramo CA, Bras Harriott C, et al. Indocyanine green (ICG) fluorescence imaging for prevention of anastomotic leak in totally minimally invasive Ivor Lewis esophagectomy: a systematic review and meta-analysis. Dis Esophagus 2022;35:doab056.
97. Giannis D, Sideris G, Kakos CD, et al. The role of liver transplantation for colorectal liver metastases: A systematic review and pooled analysis. Transplant Rev (Orlando) 2020;34:100570.
98. Bengmark S, Hafström L. The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. Cancer 1969;23:198-202.
99. Shah SA, Bromberg R, Coates A, et al. Survival after liver resection for metastatic colorectal carcinoma in a large population. J Am Coll Surg 2007;205:676-83.
100. Wang K, Liu W, Yan XL, et al. Role of a liver-first approach for synchronous colorectal liver metastases. World J Gastroenterol 2016;22:2126-32.
101. Creasy JM, Sadot E, Koerkamp BG, et al. Actual 10-year survival after hepatic resection of colorectal liver metastases: what factors preclude cure? Surgery 2018;163:1238-44.
102. De Falco V, Napolitano S, Roselló S, et al. How we treat metastatic colorectal cancer. ESMO Open 2020;4:e000813.
103. Chiba N, Abe Y, Koganezawa I, et al. Efficacy of the Milan criteria as a prognostic factor in patients with colorectal liver metastases. Langenbecks Arch Surg 2021;406:1129-38.
104. Wong LH, Sutton TL, Walker BS, et al. Surgical and oncologic outcomes following repeat hepatic resection of colorectal liver metastasis: Who benefits? Am J Surg 2021;221:1114-8.
105. Elfrink AKE, Pool M, van der Werf LR, et al. Preoperative imaging for colorectal liver metastases: a nationwide population-based study. BJS Open 2020;4:605-21.
106. Renzulli M, Clemente A, Ierardi AM, et al. Imaging of Colorectal Liver Metastases: New Developments and Pending Issues. Cancers (Basel) 2020;12:151.
107. Stavrou GA, Stang A, Raptis DA, et al. Intraoperative (Contrast-Enhanced) Ultrasound Has the Highest Diagnostic Accuracy of Any Imaging Modality in Resection of Colorectal Liver Metastases. J Gastrointest Surg 2021;25:3160-9.
108. Peloso A, Franchi E, Canepa MC, et al. Combined use of intraoperative ultrasound and indocyanine green fluorescence imaging to detect liver metastases from colorectal cancer. HPB (Oxford) 2013;15:928-34.
109. Leen E, Ceccotti P, Moug SJ, et al. Potential value of contrast-enhanced intraoperative ultrasonography during partial hepatectomy for metastases: an essential investigation before resection? Ann Surg 2006;243:236-40.
110. Sahani DV, Kalva SP, Tanabe KK, et al. Intraoperative US in patients undergoing surgery for liver neoplasms:

comparison with MR imaging. Radiology 2004;232:810-4.
111. Ishizawa T, Fukushima N, Shibahara J, et al. Real-time identification of liver cancers by using indocyanine green fluorescent imaging. Cancer 2009;115:2491-504.
112. Liberale G, Bourgeois P, Larsimont D, et al. Indocyanine green fluorescence-guided surgery after IV injection in metastatic colorectal cancer: A systematic review. Eur J Surg Oncol 2017;43:1656-67.
113. van der Vorst JR, Schaafsma BE, Hutteman M, et al. Near-infrared fluorescence-guided resection of colorectal liver metastases. Cancer 2013;119:3411-8.
114. Nierop PMH, Höppener DJ, van der Stok EP, et al. Histopathological growth patterns and positive margins after resection of colorectal liver metastases. HPB (Oxford) 2020;22:911-9.
115. Aoki T, Murakami M, Koizumi T, et al. Determination of the surgical margin in laparoscopic liver resections using infrared indocyanine green fluorescence. Langenbecks Arch Surg 2018;403:671-80.
116. Achterberg FB, Sibinga Mulder BG, Meijer RPJ, et al. Real-time surgical margin assessment using ICG-fluorescence during laparoscopic and robot-assisted resections of colorectal liver metastases. Ann Transl Med 2020;8:1448.
117. Handgraaf HJM, Boogerd LSF, Höppener DJ, et al. Long-term follow-up after near-infrared fluorescence-guided resection of colorectal liver metastases: A retrospective multicenter analysis. Eur J Surg Oncol 2017;43:1463-71.
118. He K, Hong X, Chi C, et al. Efficacy of Near-Infrared Fluorescence-Guided Hepatectomy for the Detection of Colorectal Liver Metastases: A Randomized Controlled Trial. J Am Coll Surg 2022;234:130-7.
119. Nishino H, Turner MA, Amirfakhri S, et al. Proof of concept of improved fluorescence-guided surgery of colon cancer liver metastasis using color-coded imaging of a tumor-labeling fluorescent antibody and indocyanine green restricted to the adjacent liver segment. Surgery 2022;172:1156-63.
120. Tanaka C, Kanda M, Funasaka K, et al. Detection of indocyanine green fluorescence to determine tumor location during laparoscopic gastrectomy for gastric cancer: Results of a prospective study. Asian J Endosc Surg 2020;13:160-7.
121. Lombardi PM, Mazzola M, Nicastro V, et al. The iGreenGO Study: The Clinical Role of Indocyanine Green Imaging Fluorescence in Modifying the Surgeon's Conduct During the Surgical Treatment of Advanced Gastric Cancer-Study Protocol for an International Multicenter Prospective Study. Front Oncol 2022;12:854754.
122. Chen X, Zhang Z, Zhang F, et al. Analysis of safety and efficacy of laparoscopic radical gastrectomy combined with or without indocyanine green tracer fluorescence technique in treatment of gastric cancer: a retrospective cohort study. J Gastrointest Oncol 2022;13:1616-25.
123. Yano K, Nimura H, Mitsumori N, et al. The efficiency of micrometastasis by sentinel node navigation surgery using indocyanine green and infrared ray laparoscopy system for gastric cancer. Gastric Cancer 2012;15:287-91.
124. Ohdaira H, Nimura H, Takahashi N, et al. The possibility of performing a limited resection and a lymphadenectomy for proximal gastric carcinoma based on sentinel node navigation. Surg Today 2009;39:1026-31.
125. Maruri I, Pardellas MH, Cano-Valderrama O, et al. Retrospective cohort study of laparoscopic ICG-Guided Lymphadenectomy in gastric cancer from a Western country center. Surg Endosc 2022;36:8164-9.
126. Cianchi F, Indennitate G, Paoli B, et al. The Clinical Value of Fluorescent Lymphography with Indocyanine Green During Robotic Surgery for Gastric Cancer: a Matched Cohort Study. J Gastrointest Surg 2020;24:2197-203.
127. Lan YT, Huang KH, Chen PH, et al. A pilot study of lymph node mapping with indocyanine green in robotic gastrectomy for gastric cancer. SAGE Open Med 2017;5:2050312117727444.
128. Lu X, Liu S, Xia X, et al. The short-term and long-term outcomes of indocyanine green tracer-guided laparoscopic radical gastrectomy in patients with gastric cancer. World J Surg Oncol 2021;19:271.
129. Tajima Y, Yamazaki K, Masuda Y, et al. Sentinel node mapping guided by indocyanine green fluorescence imaging in gastric cancer. Ann Surg 2009;249:58-62.
130. Miyashiro I, Miyoshi N, Hiratsuka M, et al. Detection of sentinel node in gastric cancer surgery by indocyanine green fluorescence imaging: comparison with infrared imaging. Ann Surg Oncol 2008;15:1640-3.
131. Miyoshi N, Ohue M, Noura S, et al. Surgical usefulness of indocyanine green as an alternative to India ink for endoscopic marking. Surg Endosc 2009;23:347-51.
132. Iwamoto H, Matsuda K, Hayami S, et al. Quantitative Indocyanine Green Fluorescence Imaging Used to Predict Anastomotic Leakage Focused on Rectal Stump During Laparoscopic Anterior Resection. J Laparoendosc Adv Surg Tech A 2020;30:542-6.
133. Son GM, Kwon MS, Kim Y, et al. Quantitative analysis of colon perfusion pattern using indocyanine green (ICG) angiography in laparoscopic colorectal surgery. Surg

Endosc 2019;33:1640-9.
134. Park SH, Park HM, Baek KR, et al. Artificial intelligence based real-time microcirculation analysis system for laparoscopic colorectal surgery. World J Gastroenterol 2020;26:6945-62.
135. Hasegawa H, Tsukada Y, Wakabayashi M, et al. Impact of near-infrared fluorescence imaging with indocyanine green on structural sequelae of anastomotic leakage after laparoscopic intersphincteric resection of malignant rectal tumors. Tech Coloproctol 2022;26:561-70.
136. Kim JC, Lee JL, Park SH. Interpretative Guidelines and Possible Indications for Indocyanine Green Fluorescence Imaging in Robot-Assisted Sphincter-Saving Operations. Dis Colon Rectum 2017;60:376-84.
137. Ohya H, Watanabe J, Suwa H, et al. Incidence and risk factors for fluorescence abnormalities on near-infrared imaging using indocyanine green in stapled functional end-to-end anastomosis in laparoscopic colectomy. Int J Colorectal Dis 2020;35:2011-8.
138. van den Bos J, Jongen ACHM, Melenhorst J, et al. Near-infrared fluorescence image-guidance in anastomotic colorectal cancer surgery and its relation to serum markers of anastomotic leakage: a clinical pilot study. Surg Endosc 2019;33:3766-74.
139. Yanagita T, Hara M, Osaga S, et al. Efficacy of intraoperative ICG fluorescence imaging evaluation for preventing anastomotic leakage after left-sided colon or rectal cancer surgery: a propensity score-matched analysis. Surg Endosc 2021;35:2373-85.
140. Otero-Piñeiro AM, de Lacy FB, Van Laarhoven JJ, et al. The impact of fluorescence angiography on anastomotic leak rate following transanal total mesorectal excision for rectal cancer: a comparative study. Surg Endosc 2021;35:754-62.
141. Benčurik V, Škrovina M, Martínek L, et al. Intraoperative fluorescence angiography and risk factors of anastomotic leakage in mini-invasive low rectal resections. Surg Endosc 2021;35:5015-23.
142. Su H, Wu H, Bao M, et al. Indocyanine green fluorescence imaging to assess bowel perfusion during totally laparoscopic surgery for colon cancer. BMC Surg 2020;20:102.
143. Ishii M, Hamabe A, Okita K, et al. Efficacy of indocyanine green fluorescence angiography in preventing anastomotic leakage after laparoscopic colorectal cancer surgery. Int J Colorectal Dis 2020;35:269-75.
144. Hasegawa H, Tsukada Y, Wakabayashi M, et al. Impact of intraoperative indocyanine green fluorescence angiography on anastomotic leakage after laparoscopic sphincter-sparing surgery for malignant rectal tumors. Int J Colorectal Dis 2020;35:471-80.
145. Price N, Gottfried MR, Clary E, et al. Safety and efficacy of India ink and indocyanine green as colonic tattooing agents. Gastrointest Endosc 2000;51:438-42.
146. Lee JG, Low AH, Leung JW. Randomized comparative study of indocyanine green and India ink for colonic tattooing: an animal survival study. J Clin Gastroenterol 2000;31:233-6.
147. Wada T, Kawada K, Takahashi R, et al. ICG fluorescence imaging for quantitative evaluation of colonic perfusion in laparoscopic colorectal surgery. Surg Endosc 2017;31:4184-93.
148. Hayami S, Matsuda K, Iwamoto H, et al. Visualization and quantification of anastomotic perfusion in colorectal surgery using near-infrared fluorescence. Tech Coloproctol 2019;23:973-80.
149. Ahn HM, Son GM, Lee IY, et al. Optimization of indocyanine green angiography for colon perfusion during laparoscopic colorectal surgery. Colorectal Dis 2021;23:1848-59.
150. Kawada K, Hasegawa S, Wada T, et al. Evaluation of intestinal perfusion by ICG fluorescence imaging in laparoscopic colorectal surgery with DST anastomosis. Surg Endosc 2017;31:1061-9.
151. Cahill RA, O'Shea DF, Khan MF, et al. Artificial intelligence indocyanine green (ICG) perfusion for colorectal cancer intra-operative tissue classification. Br J Surg 2021;108:5-9.

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