Review Paper

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Indocyanine Green Fluorescence-Guided Surgery for Gastrointestinal Tumors: A Systematic Review

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Objective: To conduct a systematic review of the currently available literature on the use of ICG to guide surgical dissection in gastrointestinal (GI) cancer surgery.

Background: Real-time indocyanine green (ICG) fluorescence-guided surgery has the potential to enhance surgical outcomes by increasing patient-tailored oncological precision.

Methods: MEDLINE, PubMed, EMBASE, and Google Scholar were searched for publications on the use of ICG as a contrast agent in GI cancer surgery until December 2020. Perfusion studies were excluded. Quality of the studies was assessed with the Methodological Index for nonrandomized Studies or Jadad scale for randomized controlled trials. A narrative synthesis of the results was provided, with descriptive statistics when appropriate.

Results: Seventy-eight studies were included. ICG was used for primary tumor and metastases localization, for sentinel lymph node detection, and for lymph flow mapping. The detection rate for primary colorectal and gastric tumors was 100% after preoperative ICG endoscopic injection. For liver lesions, the detection rate after intravenous ICG infusion was 80% and up to 100% for lesions less than 8 mm from the liver surface. The detection rate for sentinel lymph nodes was 89.8% for esophageal, 98.6% for gastric, 87.4% for colorectal, and 83.3% for anal tumors, respectively. In comparative studies, ICG significantly increases the quality of D2 lymphadenectomy in oncological gastrectomy.

Conclusion: The use of ICG as a guiding tool for dissection in GI surgery is promising. Further evidence from high-quality studies on larger sample sizes is needed to assess whether ICG-guided surgery may become standard of care.

Keywords: colorectal surgery, fluorescence-guided surgery, GI surgery, HPB surgery, ICG-guided surgery, image-guided surgery, indocyanine green, near-infrared visualization, surgical oncology, upper GI surgery

Gastrointestinal (GI) surgical oncology strives to balance oncological radicality with tissue and functional preservation. Many technological advances have been adopted in the last decades to enhance surgical outcomes, with the increasing implementation of real-time fluorescence-guided surgery, with indocyanine green (ICG) being the most widely used fluorophore.

Indocyanine green (ICG) is a nontoxic dye that emits fluorescence when illuminated by near-infrared light.[1,2] Its physical properties make it suitable for the intraoperative visualization of several anatomical structures. A recent consensus statement[3] has identified ICG-fluorescence imaging (ICG-FI) guided surgery as both safe and effective, with the potential to simplify a wide range of procedures and significantly improve patient outcomes. However, the routine use of ICG is far from being established.

ICG-guided gastrointestinal surgery has been extensively studied, but most studies are characterized by a weak methodology and a great variability in the technical aspects of ICG administration and visualization. For these reasons, a systematic review was deemed the most appropriate method to summarize what is currently known, focusing both on clinical results and on technical aspects of ICG use. A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted: while some systematic reviews focusing on one singular use of ICG are underway, no systematic reviews on the entire field of ICG use for gastrointestinal surgical oncology were identified. The objective of this systematic review is to give a comprehensive overview of the currently available literature on the use of ICG to guide dissection in gastrointestinal surgical oncology. It also aims to serve as a basis for future studies, providing both conceptual and methodological tools for their design.

METHODS

This study was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension.[4]

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Search Strategy and Information Sources

The literature search was carried out until December 31, 2020. The studies were searched for via the most relevant medical databases for systematic reviewing including Medline (PubMed), Embase, Google Scholar. Medical Subject Headings (MeSH) terms and text words from the MEDLINE search strategy are reported in Supplemental Digital Content—Search terms http://links.lww.com/AOSO/A155. The research field for all these terms was "Title/Abstract," and the research was restricted to "Humans." Duplicate records were removed using their clinical trial registry number or other approaches to identify matching studies. To ensure that all pertinent articles were included, the reference lists of the studies selected from the databases were manually reviewed.

Inclusion/exclusion Criteria

Human randomized controlled trials, quasi-experimental, cohort, case-control, and review studies concerning the use of Indocyanine green as a contrast agent in GI cancer surgery were included, with no restrictions in terms of publication dates. Studies were excluded according to the following criteria: (a) articles that involved only animals; (b) articles that were not about surgery nor oncology; (c) articles that were not focused on the gastrointestinal system; (d) articles focused on ICG used as contrast agent for fluorescent angiography (perfusion studies); (e) articles that were reviews, guidelines, journal indexes, book chapters, or editorials; (f) nonpertinent articles (ie, those articles where the acronym "ICG" does not stand for "Indocyanine green"); (g) articles where full text was not available; and (e) articles not in English.

Study Selection and Data Collection Process

The identified studies were independently screened by three reviewers (PB, NS, and MA). Whenever the title and abstract clearly indicated that the study failed to meet the selection criteria, it was immediately excluded. For the remaining studies, the full text was analyzed to decide for its inclusion: in case of disagreement between the reviewers, the final decision was taken together with the senior Authors (CS and VM). Finally, studies including less than 10 (esophagogastric surgery) and less than 5 (liver and gallbladder) patients and studies with no information on the dosage of ICG used were excluded.

The following information was collected from the selected studies: authors' name; publication year; journal of publication; study's design (prospective/retrospective, comparative/single-arm); study's aims; organ and type of tumor studied; surgical procedure performed; ICG's timing, dose and route of administration; fluorescent imaging (FI) used; type of control; number of patients enrolled; results.

Data Analysis, Quality Assessment, and Evidence Synthesis

The articles were evaluated for relevance, sample numbers, the underlying disease process, statistical power, analytical validity, quality of evidence, and conclusions. The Methodological Index for Nonrandomized Studies (MINORS)[5] was used to assess the methodological quality of the included nonrandomized studies: it was deemed the most appropriate method since almost all the included studies were nonrandomized, comparative, or noncomparative. The quality of the included randomized controlled studies was assessed through the Jadad scale.[6]

Results were summarized in a narrative synthesis, with descriptive statistics when appropriate. For noncomparative studies, pooled detection rates were assessed, while weighted means were used for continuous outcomes.

Finally, for comparative studies, the weighted mean difference with the corresponding 95% confidence interval (CI) was calculated as the effect size for continuous variables, while relative risks (RR) with 95% CIs were used for dichotomous variables. Heterogeneity between studies was determined with the chi-square test and I^2 test. In case of significant heterogeneity ($P < 0.1$ and $I^2 > 50\%$), a random effects model was used to calculate the pooled weighted mean difference or RR. A fixed effects model was used if $P > 0.1$ and $I^2 < 50\%$.

RESULTS

As shown in Figure 1, the initial search yielded 1770 publications. After screening, 1610 articles were excluded as they did not meet the selection criteria. The full text of the remaining 160 studies was assessed for eligibility, and 78 studies were finally included for the qualitative synthesis. Most of these studies were published after the year 2006, with a significant increase in the last decade. After qualitative review of the papers, the following main areas of application of ICG in oncological gastrointestinal surgery were identified: esophagus-stomach, liver and gallbladder, colon-rectum. The results of the systematic review were therefore summarized according to these areas of application.

Assessment of Methodological Quality and Risk of Bias

Detailed evaluation of the risk of bias assessment is reported in Table S1 (http://links.lww.com/AOSO/A147). Among the 77 observational studies evaluated, the median MINORS score was 12 out of 16 for the 57 noncomparative studies and 17.5 out of 24 for the 20 comparative studies. In particular, it was 11 and 15.5 for the 21 noncomparative and 4 comparative studies concerning esophageal and gastric cancer, 12 and 18 studies for the 20 noncomparative and 9 comparative studies concerning HPB tumors, and 12.5 and 17.5 for the 17 noncomparative and 6 comparative studies concerning colorectal tumors, respectively. The items carrying the highest risk of bias were unbiased assessment of the study endpoint and prospective calculation of the study size. The only RCT included, assessed with the Jadad scale, exhibited a low risk of bias as shown in Table S2 (http://links.lww.com/AOSO/A148).

Gastric and Esophageal Cancer Surgery. Forty-two eligible studies regarding gastric and esophageal cancer surgery were retrieved: after assessing the full text for eligibility, 26 studies were finally included. One study evaluated the intraoperative detection of gastric tumors, 18 studies evaluated the identification of sentinel lymph nodes (SLN, of which 2 in esophageal and 15 in gastric tumors) and 8 studies evaluated the visualization of lymph nodal stations draining the primary tumor to improve the accuracy of lymphadenectomy (LND). The results are presented in Table 1.

Primary Tumor Localization

One study by Tanaka et al[7] evaluated the use of ICG as a marking method for T1 gastric tumors during laparoscopic gastrectomy in 29 patients. They determined that the optimal amount of ICG to inject was 0.1 mL at a concentration of 0.5 mg/mL in the peritumoral submucosa 1–3 days before surgery. The detection rate was 100%, and all cases achieved negative resection margins at pathology.

SLN in Esophageal Cancer

Two studies[8,9] evaluated the application of ICG injection for the identification of SLN in esophageal cancer. In the first study,

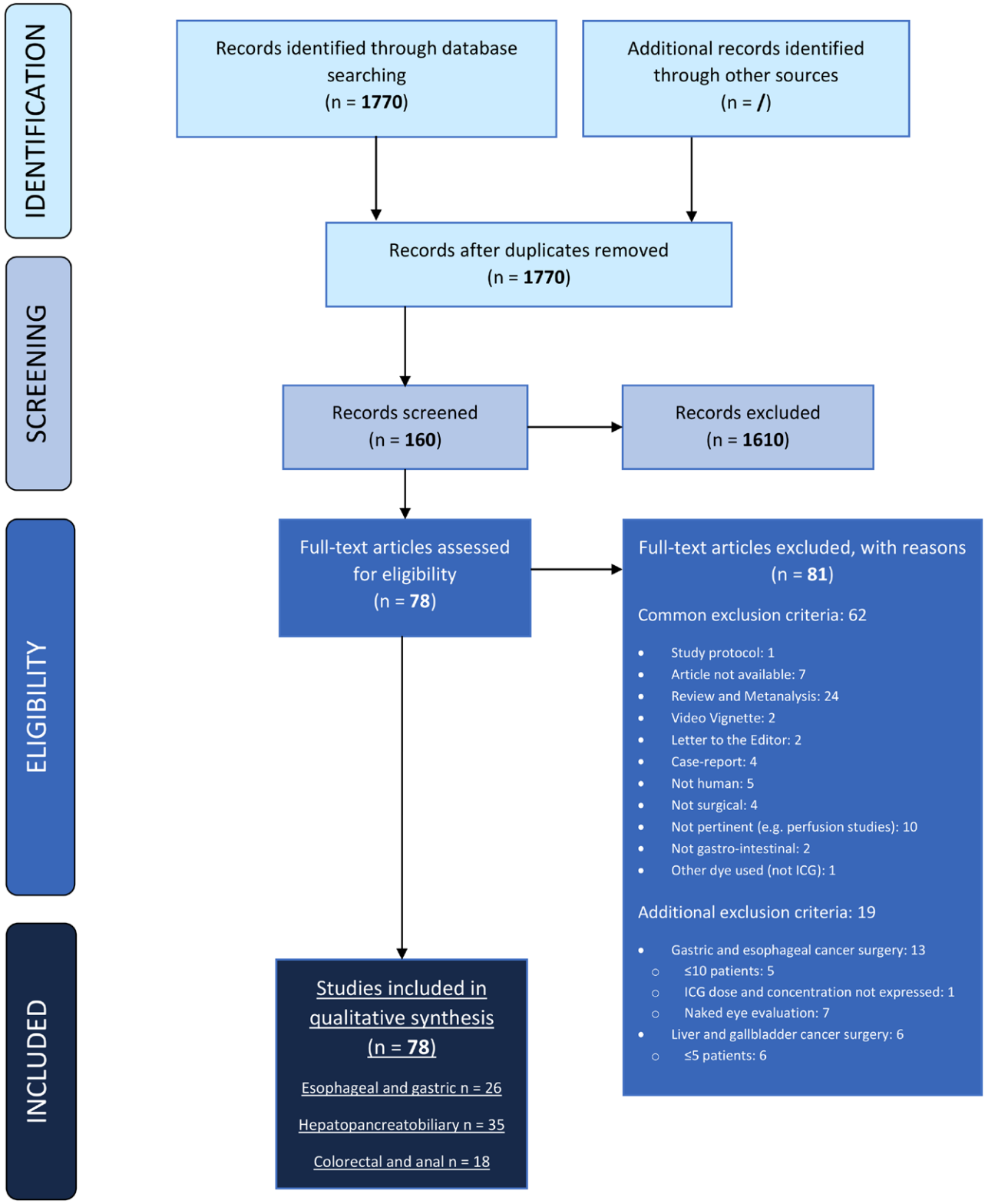

FIGURE 1. PRISMA flow chart illustrating the selection of sources of evidence for the systematic review.

Yuasa et al[8] compared intraoperative submucosal injection of ICG plus NIR identification of SLN to preoperative peritumoral injection of Iopamidol plus CT-scan identification of SLN. In the 20 patients enrolled, SLN detection rate with ICG was 95%, but a high false-negative rate of 25% was found (one over 4 metastatic SLN was not detected). In case of advanced tumors, disruption or obstruction of the lymph flow due to tumor occupation may impede LN staining. A more recent study[9] prospectively evaluated the feasibility of NIR-guided lymphatic mapping of bilateral recurrent laryngeal nerve nodes in 29 patients who underwent esophagectomy for squamous-cell carcinoma. ICG-stained basins could be identified in 25 patients (86.2%): 6 of them (24.0%) had nodal metastasis at frozen sections and therefore underwent extended LND. With a negative predictive value

Table 1.

ICG Use in Esophageal and Gastric Cancer

			Localization of Primary Tumor	
Site	**N. Studies**	**N. Patients**	**Detection Rate**	**ICG Injection**
Stomach	1	29 (all laparoscopic)	29/29 (100%)	Peritumoral submucosal injection of 0.1 mL at 0.5 mg/mL 1–3 days before surgery
			SNL Mapping	
Site	**N. Studies**	**N. Patients**	**SNL per Patient***	**ICG Injection**
Esophagus	2	49 (all mini-invasive)	n.e.	Peritumoral submucosal injection
Stomach	16	962 (347 laparoscopic, 324 open, 291 n.a.)	6.7	Endoscopic injection of 2 mL of ICG (at a concentration of 5 mg/mL) in the submucosa of the stomach at 4 points around the tumor
			Description of Lymph Flow Patterns	
Site	**N. Studies**	**N. Patients**	**Detection Rate**	**ICG Injection**
Stomach	8	334 (213 laparoscopic, 121 robotic)	89.8% (44/49) 98.6% (759/770)	
			Total Number of RLNs per Patient†	**LNs Noncompliance per Patient**
Stomach	8	334 (213 laparoscopic, 121 robotic)	ICG vs NE 7.02 LN (95% CI 1.37–12.67, $P = 0.015$)	RR 0.57 (95% CI 0.44–0.73, $P < 0.001$)

Endoscopic submucosal injection 24 h before surgery around tumor (at a concentration of 1.25 mg/mL; dose 2 mL); intraoperative endoscopic submucosal injection

*Pooled mean.
†Weighted mean difference.

of 100%, the authors conclude that the real-time assessment of bilateral recurrent laryngeal nerve nodes was technically feasible and safe, and it would help to determine the optimal extent of LND. Details of the included studies are shown in Table S3 (http://links.lww.com/AOSO/A149).

SNL in Gastric Cancer

Sixteen studies assessing the performance of NIR visualization of the SLN after ICG injection in 962 patients were found.[10–24] The main characteristics of the studies are resumed in Table S4 (http://links.lww.com/AOSO/A150): all are Eastern series, consisting mostly of prospective single-arm cohort trials with no RCT available, and the level of evidence is middle-low grade. Most studies are focused on early gastric cancer (EGC, 12 studies, 75%) and aim at reducing unnecessary extended lymphadenectomies.[10] NIR fluorescence in the setting of SLN identification is studied both in laparoscopic and open approach, but its usefulness for the isolation and dissection of SLNs in comparison to naked eye is more frequently reported in the mini-invasive settings.[11,25] Most studies report endoscopic injection of 2 mL of ICG (at a concentration of 5 mg/mL) in the submucosa of the stomach at 4 points around the primary tumor.[17,19,22] Timing of injection is heterogeneous, mainly reported either before skin incision or the day before surgery. Tajima et al[17] recently demonstrated a significantly higher mean number of retrieved SNs, better accuracy rate and lower false-negative rate when ICG was injected preoperatively in comparison to intraoperative injection. The adsorption of ICG to a nanocolloid (ICG: Nanocoll) increases its hydrodynamic diameter and may result in better retention of the lymphatic tracer in the SLN, as recently demonstrated by Tummers et al.[13,26] The quantification of ICG-fluorescence intensity, and its clinical meaning, is still an unmet need. Okubo et al[10] evaluated the correlation between radioisotope (RI) uptake and ICG-fluorescence intensity studied with a ICG intensity imaging software (Mizuho Corporation, Ltd., Tokyo, Japan). In 17 patients with EGC, they found a significant correlation between RI uptake and fluorescence intensity in each lymph node ($P = 0.0002$, $\gamma = 0.347$), and demonstrated that dissecting fluorescent nodes with intensity levels of 1–6 resulted in 92.1% dissection of hot-nodes by RI. Overall, the accuracy of ICG-guided surgery in identify and detect basin and SLNs is high with a mean overall detection rate of 98.6% (759/770 evaluated patients), as shown in Table 1. Details of the included studies are shown in Table S4 (http://links.lww.com/AOSO/A150).

Improving Performance of D2 Lymphadenectomy in Gastric Cancer

Eight studies[14,27–33] assessed the impact of NIR visualization on the performance of D2 LND in 334 patients with gastric cancer. Five studies[27–30,32] evaluated the performance of ICG use on the total number of LN retrieved, comparing 240 cases with 331 controls (Figure S1, http://links.lww.com/AOSO/A145). The number of LN retrieved was higher with ICG (mean difference 7.02 LN, 95% CI 1.37–12.67, $P = 0.015$). The studies showed a high heterogeneity ($I^2 = 81\%$, $P < 0.001$).

Five studies[27–31] evaluated the number of retrieved LN per station. Two studies[28,30] found a higher number of retrieved LNs at station 4 and station 6 when ICG was used. In contrast, Park et al[29] found no difference regarding the number of LNs retrieved from the infrapyloric area ($P = 0.434$) and overall stations ($P = 0.333$). Kim et al[31] evaluated the completeness of naked eye LND with ICG-FI: 15 additional fluorescent tissues were found in the D2 LND area in 14 out of 50 patients (28%); 2 of them were confirmed as nonmetastatic LNs at pathology.

Two studies[27,28] evaluated LN noncompliance per patient, defined as LN absence from more than one dissected station. The LN noncompliance was 31.8% in the ICG group versus 57.4% in the control group ($P < 0.001$) in the RCT on

Table 2.

ICG Use in HPB Tumors

Detection of Hepatic Lesions				
N. Studies	**N. Patients**	**Type of Lesion/Approach**	**Tumor Detectability†**	**Newly Detected Lesions**
26	1090	HCC 538 (49%) CRLM 466 (43%)* ICC 28 (3%) Other 58 (5%) Open 19 (845 pts) Laparoscopic 9 (216 pts) Robotic 3 (29 pts)	79.7% (range 43–100%) on liver surfaces (all studies) 98.1% (range 88–100%) < 6–8 mm (9 studies, 317 pts) 98.2% (range 93–100%) on specimen (6 studies, 242 pts)	18/26 studies 122/1807 (6.75%) lesions were newly detected tumors

Detection of Liver Micrometastases			
N. Studies	**N. Patients**	**Type of Lesion**	**Main Findings**
3	231	Pancreatic cancer	Micrometastases detected in 31/207 patients (15%) PPV 80%, NPV 95%
1	24 (micrometastases evaluated in 15)	cT2 gallbladder cancer	Micrometastases detected in 3/15 patients (20%) Liver resection smaller with ICG than S4a/S5 segmentectomy ($P < 0.0001$)

Detection of Peritoneal Metastases of HPB				
N. Studies	**N. Patients**	**Type of Lesion**	**Main Findings**	
4	82‡	50 HCC 2 ICC 22 CRLM 7 others 72 open 8 laparoscopic 2 robotic	**HCC** Metastases detected in 15/15 (100%) 3/3 studies reporting detection of unknown metastases§ 8/15 (53.3%) lesion were newly detected	**Non-HCC** Metastases detected in 0/1
1	25	17 pancreas 3 duodenum 3 ampulla of Vater 2 distal common bile duct All laparoscopic	Metastases detected in 0/1	

*One study comprised both laparoscopic and open procedures. Liu et al.[52] was excluded because of missing data and non-comparable methodology. Zhang et al was excluded because of intraoperative ICG administration. For Takahashi et al.[45] only cases with preoperative ICG administration were included. For Kobayashi et al.[61], the 4 patients of the 0.25 mg group were excluded.

†Tumor detectability on liver surfaces was calculated pooling data from all the included studies. Tumor detectability on the specimen and for tumors < 8 mm reports the weighted mean of the included studies.

‡Satou et al.[67] also included patients undergoing thoracotomy for lung metastases.

§Not suspected preoperatively, nor visible at inspection.

258 patients by Chen et al, while it was 35% versus 57.5% ($P = 0.04$) in the prospective cohort study by Kwon et al on 40 ICG patients matched with 40 patients from an historical cohort. The pooled relative risk for LN noncompliance per patient with ICG was 0.57 (95% CI 0.44–0.73, $P < 0.001$), as shown in Figure S2 (http://links.lww.com/AOSO/A146). The studies showed low heterogeneity ($I^2 = 0\%$, $P = 0.750$). Details of the included studies are shown in Table S5 (http://links.lww.com/AOSO/A151).

Hepatopancreatobiliary Cancer Surgery. A total of 35 studies were included: 29 studies on the intraoperative staging of hepatic lesions, 4 studies on the detection of unknown liver micrometastases (3 from pancreatic tumors, 1 from gallbladder cancer), 5 studies on the detection of extrahepatic metastases from HPB tumors, 1 study on the visualization of the lymphatic flow in hepatobiliary tumors. The results are presented in Table 2.

Intraoperative Staging of Hepatic Lesions

The most studied and prominent use of ICG in HPB surgery is the detection of hepatic lesions after preoperative intravenous injection of ICG: this was the focus of 29 studies.[34–62]

ICG intraoperative fluorescence allows the identification of approximately 80% of all tumors present in the liver by studying the surface directly (average value in 1090 patients, with a range from 43% to 100% as seen in Table 2). The sensitivity considerably increases if only superficial lesions are considered, reaching as high as 98% for tumors <8 mm deep.[36,39,42,44,45,51,57,62] Indeed, the subsequently removed tumors show fluorescence in almost all cases when studied by placing the probe very close to the specimens.[34,36,39,41,49,51,54,57] The positive predictive value, which can be as high as 100% in noncirrhotic livers, is reduced in case of cirrhosis (with reports ranging between 5.4% and 71.1% in cirrhotic livers).[7,48,50,51,53,54,57,59]

The largest study on HCC was published by Ishizawa et al[50] in 2014 on 276 HCC in 170 patients: ICG-fluorescence imaging identified 273 HCCs (99%) on the resected specimens. Thirty-five HCCs were visualized that had not been diagnosed preoperatively: 14 were detected during liver resection and 21 were found by macroscopic examination of the resected specimen via ex vivo fluorescence imaging.

The largest study on colorectal liver metastases was published by Handgraaf et al[41] in 2017: 86 patients underwent resection with FI and 87 without. In significantly more patients of the FI cohort additional metastases were identified during surgery (25% vs 13%, $P = 0.04$). Tumors identified solely by FI were significantly smaller compared to additional metastases identified also by inspection, palpation, or intraoperative ultrasound (3.2 ± 1.8 mm vs 7.4 ± 2.6 mm, $P < 0.001$). Liver-specific recurrence-free survival at 4 years was 47% with FI imaging and 39% without (hazard ratio at multivariate analysis 0.73, 95% CI 0.42–1.28, $P = 0.28$). Overall survival at 4 years was 62% and 59%, respectively ($P = 0.79$).

Fluorescence findings need to be integrated with those obtained by inspection, liver palpation, and ultrasound. A study

Table 3.

ICG Use in Colorectal Cancer

Localization of Primary Tumor

Site	N. Studies	N. Patients	Detection Rate	ICG Administration
Colon	2	24	24/24 (100%)	Preoperative injection (time range: after general anesthesia—6 days) in the peritumoral submucosa (1–4 points) of either 0.5 mL at 2.5 mg/mL (36, 66), 1.6 mL at 31.25 μg/mL ICG + 62.5 mg/mL colloid [40], or 0.1 mL at 5 mg/mL (Satoyoshi)
Rectum	3*	14†	14/14 (100%)	
Any	1	141§	141/141 (100%)	
Total	4	179 (177 laparoscopic, 2 open)	179/179 (100%)	

SNL Mapping

Site	N. Studies	N. Patients	Detection Rate	SNL per Patient (Mean)	ICG Administration
Colon	5	115 (91 laparoscopic, 24 open)	85.2% (98/115)	1.7 (range 0–5)	
Rectum	3	33 (5 laparoscopic, 3 transanal, 25 open)	93.9% (31/33)	2.4 (range 1–4)	Preoperative injection in the peritumoral submucosa of either 1 mL (128) or 4 mL (109) at 5 mg/mL 1.6 mL at 31.25 μg/mL ICG + 62.5 mg/mL colloid (40)
Any	1	26 (10 laparoscopic, 16 open)	88.5 (23/26)	2.6 ± 2.4 (mean, SD)	Intraoperative injection of 2 mL ICG at 5 mg/mL in the peritumoral subserosa
Total	9	174 (106 laparoscopic, 3 transanal, 65 open)	87.4% (152/174)	-	

Description of Lymph Flow Patterns

Site	N. Studies	N. Patients	Detection Rate
Colon	3	41 (all laparoscopic)	95%‡ (57/60)
Rectum	1	12 (all laparoscopic)	100% (12/12)
Total	4	53 (all laparoscopic)	95.8% (69/72)

Fluorescence in Metastatic LN

Site	N. Studies	N. Patients	Detection Rate	ICG Administration
Flexural cancer	1	72 (13 with metastatic LN, all laparoscopic)	0% (0/15) in occupied LN 80% (8/10) in nonoccupied LN	IO injection of 1 mL ICG at 2.5 mg/mL in the peritumoral subserosa/submucosa

*Two studies evaluated both colon and rectal cancers.

†One patient from Handgraaf et al.[41] was excluded, as NIR was not visualised during the procedure due to an operator mistake.

‡For Satoyoshi et al.[85], only patients marked within 6 days before surgery were included.

§For Chand et al.[74], only patients with complete lymphatic visualization were included (7/10). For Jun et al., one patient was excluded, as NIR was not visualised due to a technical mistake.

by Boogerd et al[44] in 2017 showed that the association between FI and intraoperative ultrasound (IOUS) can achieve 100% sensitivity, while the sensitivity of the individual methods were 92% and 86%, respectively. Kose et al compared ICG with preoperative imaging, IOUS and diagnostic laparoscopy: the detection rate was 74%, 92%, 43%, and 43%, respectively.[62]

The optimal dose and timing of ICG injection for liver cancer imaging have not been clearly determined yet. Most authors administer ICG intravenously at a dose of 0.5 mg/kg of the patient's body weight within 2 weeks before surgery, the same dosage as the ICG retention test. If the ICG retention test has been performed more than 2 week before surgery, Kobayashi et al[61] recommend the administration of 2.5 mg of ICG the day before surgery. Details of the included studies are shown in Table S6 (http://links.lww.com/AOSO/A152).

Detection of Unknown Liver Micrometastases

Thanks to its high sensitivity, ICG can be used to identify small lesions that are difficult to detect with preoperative studies, for example, liver micrometastases in patients with pancreatic cancer[63–65] and hepatic metastases from gallbladder cancer.[66] Table 2 shows the results from three studies[63–65]: a total of 207 patients with no preoperative evidence of liver metastases from pancreatic cancer underwent staging laparoscopy with FI. Micrometastases were found in 31 patients (later histologically confirmed), thus futile laparotomies were avoided. Patients in whom micrometastases were identified developed metastases in 12/15 cases (positive predictive value of 80%), while negative patients developed metastases in only 2 cases with a negative predictive value of 95%. Details of the included studies are shown in Table S7 (http://links.lww.com/AOSO/A153).

Extrahepatic Metastases and Lymphatic Drainage of Primary HPB Tumors

Because of the capacity of HCC cells to uptake the ICG from the bloodstream, NIR imaging after ICG injection has been studied to improve the detection of extrahepatic metastases: 3 studies[46,67,68] involving 50 patients confirmed this assumption reporting a 100% overall detection rate. In particular, Satou et al[67] conducted a study on 17 patients with suspected HCC metastases in the lung, adrenal gland, lymph nodes, and peritoneum. Out of the 28 suspected lesions, 24 exhibited intraoperative fluorescence and all were confirmed as HCC metastases at histology. An additional 5 metastases in 2 cases were newly identified by ICG. The positive predictive value of in vivo and ex vivo ICG FI were both 100%, while the negative predictive value of those methods were 50% and 86%, respectively. Conversely, when ICG was used to detect extrahepatic metastases in non-HCC tumors, the tumor detection rate was 0%.[45,63]

Finally, Noji et al[69] investigated the use of ICG for the visualization of the lymphatic flow by injecting ICG into the subserous membrane of Calot's triangle in 42 patients with HPB tumors. They detected lymph nodal fluorescence in 26 patients in both regional and para-aortic lymph nodes, in 3 patients only in para-aortic nodes and in 3 patients only in regional nodes. The detection rate for both regional and para-aortic lymph nodes was 69% (29/42).

Colorectal Cancer Surgery. A total of 18 studies[21,70–86] including 578 patients were found. Four studies evaluated primary tumor localization, 11 studies evaluated SNL mapping, 4 studies evaluated lymph flow patterns, and one study evaluated ICG-fluorescence in metastatic LN. Their results are summarized in Table 3. The studies presented great heterogeneity concerning doses (range: 0.5–4 mL), concentrations (range: 31.25 μg/mL–5 mg/mL), site (submucosal, subserosal, or intramural), number (1–4), and timing (preoperative, intraoperative, ex vivo) of peritumoral ICG injections, as well as timing and interval of visualization. Details of the included studies are shown in Table S8 (http://links.lww.com/AOSO/A154).

ICG Use in Primary Tumor Localization

Four studies[70–72,85] evaluated ICG use in primary tumor localization, and all reported a high success rate by preoperative endoscopic tattooing with ICG. In particular, Satoyoshi et al[85] reported a detection rate of 100% (141/141) for tumors marked within 6 preoperative days, of 60% (6/10) for those marked between 7 and 9 days before surgery, and of 0% (0/4) for those marked more than 10 days before surgery. Visibility scores of ICG-FI proved significantly higher than those obtained by naked eye visualization; the observed fluorescent areas coincided with tumor localization according to histological examination.[72] When compared with India ink, ICG-FI was able to indicate tumor localization in all patients (24/24; 100%), while India ink staining was found positive in only 14 of the 24 patients (58%).[70]

ICG Use in SLN Mapping

Eleven studies[21,71,74–76,78,80,81,83] evaluated SNL mapping after ICG injection. One prospective study[82] investigated the feasibility of lymphatic mapping and SLN biopsy by ICG-FI in 12 patients with anal squamous-cell carcinoma, and reported a SLN detection rate of 83.3% (10/12 patients). One study[84] evaluated the identification of lateral pelvic region sentinel nodes by naked eye observation after ICG injection, with a detectability of 28% (7/25 patients), suggesting that a near-infrared camera system is necessary for adequate visualization. The remaining 9 studies,[21,71,74–76,78,80,81,83] including 174 CRC patients, reported a SLN detection rate of 87.4%.

Two studies compared ICG-FI to standard blue dye techniques in SLN mapping.[76,78] Liberale et al[78] found no significant differences in the mean number of SNLs identified by the two techniques ex vivo, with a sensitivity of 43% and 57%, respectively. Andersen et al[76] compared in vivo ICG-FI with ex vivo methylene blue: the detection rate and sensitivity were 65.5% and 20%, respectively, for in vivo ICG, and 37.9% and 10%, respectively, for ex vivo methylene blue. Liberale et al and Currie et al[75,78] reported a higher rate of false negatives in pT3/pT4 tumors.

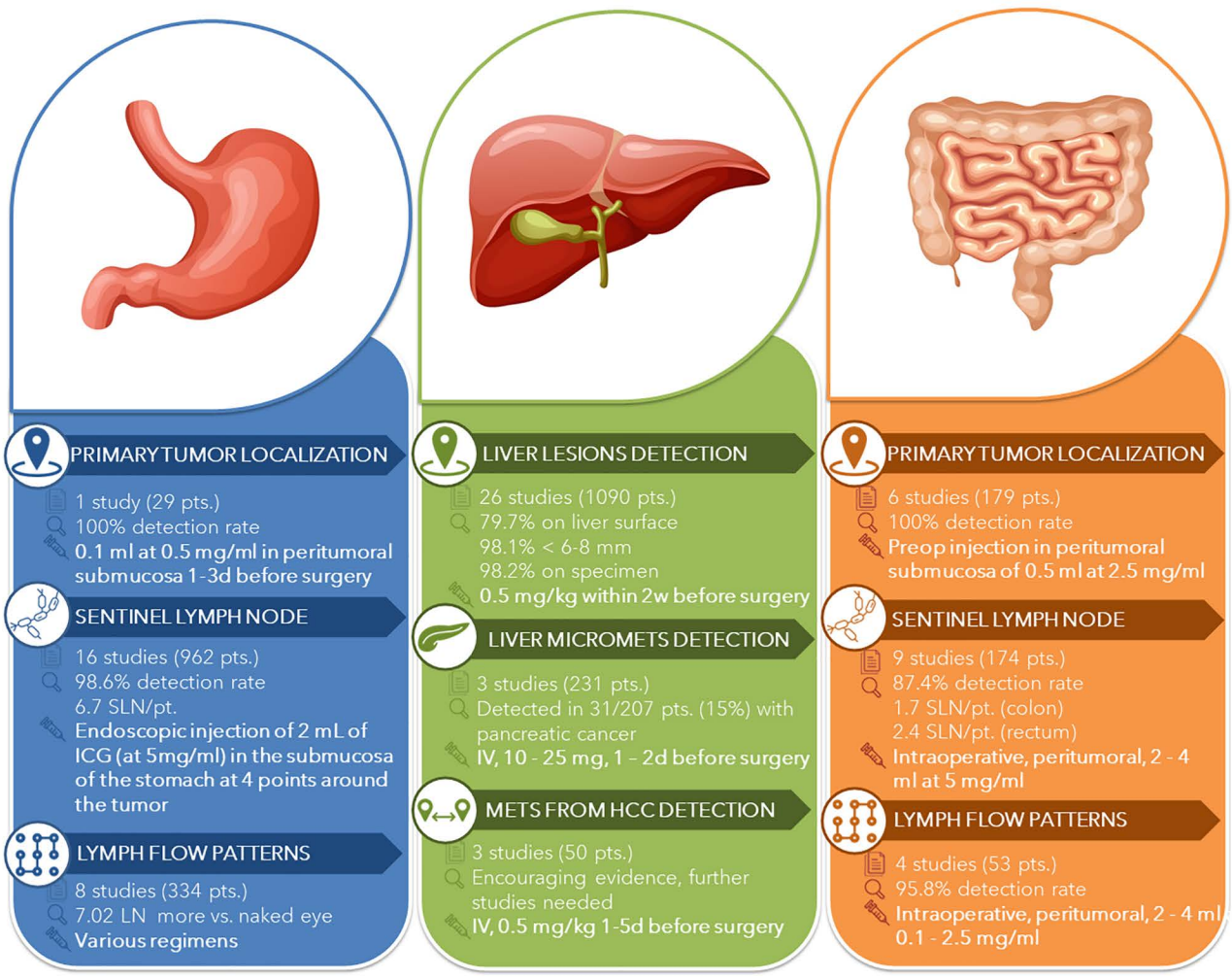

FIGURE 2. Clinical uses of ICG-FI in surgical oncology of the GI tract.

Table 4.

Summary of the Clinical Applications of ICG-FI in Surgical Oncology of the GI Tract

Primary Tumor Detection				
Site	**N. Studies**	**N. Patients**	**Main Findings**	**Most Common Schedule, Dose, and Route of Injection**
Upper GI	1 (stomach)	29	100% detection rate, all with negative resection margins at pathology	1–3 days before surgery 0.1 mL at 0.5 mg/mL endoscopic injection in the peritumoral submucosa
Liver*	21†	624	80% detection (higher if <8 mm in depth). Positive predictive value reduced in case of cirrhosis.	Within 2 weeks before surgery 0.5 mg/kg IV administration
CRC	4	203	100% detection rate if marked within 6 preoperative days	Before surgery 0.5 mL at 2.5 mg/mL endoscopic injection in the peritumoral submucosa
Sentinel Lymph Node Detection				
Site	**N. Studies**	**N. Patients**	**Main Findings**	**Most Common Schedule, Dose, and Route of Injection**
Upper GI	18 (2 esophagus, 16 stomach)	1011	Detection rate 89.8% in esophageal, 98.6% in gastric. In gastric, mean of 6.7 SNL per patient.	Intraoperative 2 mL at 5 mg/mL endoscopic injection in the peritumoral submucosa
CR + anal	9 + 1	174 + 12	Detection rate 87.4% in CR, 83.3% in anal.	Intraoperative 2–4 mL at 5 mg/mL endoscopic injection in the peritumoral submucosa
Lymph Flow Mapping				
Site	**N. Studies**	**N. Patients**	**Main Findings**	**Most Common Schedule, Dose, and Route of Injection**
Upper GI	8	334	Increase of 7.02 retrieved LNs with ICG (95% CI 1.37–12.67, $P < 0.015$). RR for LN noncompliance with ICG 0.57 (95% CI 0.44–0.73, $P < 0.001$).	1 day before surgery 2 mL at 1.25 mg/mL endoscopic injection in the peritumoral submucosa
CR	4	53	95.8% detection rate ICG may be useful to guide lymphadenectomy	Intraoperative 2–4 mL at 0.1–2.5 mg/mL endoscopic injection in the peritumoral submucosa
HPB	1	42	69% detection rate of regional and paraortic nodes	Intraoperative 0.5 mL at 5 mg/mL into Calot's triangle
Detection of Metastases				
Site	**N. Studies**	**N. Patients**	**Main Findings**	**Most Common Schedule, Dose, and Route of Injection**
Liver mtx of PB	4 (3 on pancreatic cancer 1 on gallbladder cancer)	231 (207 pancreatic, 24 gallbladder)	Possibility to individualize liver resection in gallbladder cancer. For pancreatic micrometastases, PPV 80% and NPV 95%‡	1–2 days before surgery 10–25 mg IV administration
CRLM*	21†	466	80% detection (higher if < 8 mm in depth)	Within 2 weeks before surgery 0.5 mg/kg IV administration
Extrahepatic mtx of HPB	1	17	PPV 100%, NPV 50% in vivo, 86% ex vivo	1–5 days before surgery 0.5 mg/kg IV administration
Peritoneal mtx of HPB, CR	5 (4 liver, including CRLM, 1 pancreatic)	107 (83 liver, 25 pancreatic)	ICG may show peritoneal metastases of liver tumors. No evidence for other GI tumors.	1–14 days before surgery 0.5 mg/kg IV administration

*Results include both primary liver tumors and CRLM, as individual results could not be extrapolated.

†Studies excluded from Table 2 were not included.

‡Results calculated only on patients in which micrometastases were identified (n = 31).

Noura et al[83] studied the feasibility and usefulness of lateral pelvic region sentinel node (LPSN) identification during open surgery. LPSNs were visualized in 23 of 25 patients, of whom 6 had positive LPSN and received lateral pelvic LN dissection. Concordance between the LPSNs and the dissected lateral LN status by HE was 100%.

ICG Use in the Description of Lymph Flow Patterns

The use ICG-FI to evaluate lymphatic drainage in colon cancer was the focus of three studies.[74,77,79] Chand et al,[74] in a prospective dose-escalation feasibility trial, established that optimal visualization of lymphatic drainage in colon cancer occurred 10 minutes after subserosal injection of 4 mL of a 0.5 mg/mL ICG solution. In Watanabe et al,[79] 5 cases of 20 required modification of the extent of CME because the area of lymph flow observed during surgery differed from that of the preoperative diagnosis. All metastatic lymph nodes occurred in lymph flow areas determined by the fluorescence lymphatic flow evaluation.[79] Zhou et al[73] compared the use of ICG-enhanced NIR-FI in guiding laparoscopic lateral pelvic lymph node dissection (LPLD) with standard LPLD in patients with rectal cancer (12 in the ICG group vs 30 controls). The ICG group had lower intraoperative blood loss (55.8 ± 37.5 mL vs 108.0 ± 52.7 mL, P = 0.003), and a higher number of nodes harvested (11.5 ± 5.9 vs 7.1 ± 4.8, P = 0.017). Finally, Kakizoe et al,[86] in their study on 72 patients undergoing ICG injection at the tumor site during laparoscopic surgery for cancer of the splenic flexure, evaluated the fluorescence of paraffin-embedded metastatic LNs. They found that, out of 25 metastatic LNs from 13 patients, no occupied LN (ie, metastatic LN with complete loss of normal LN structure) showed fluorescence (0/15), while 80% (8/10) nonoccupied LN exhibited fluorescence. The 2 nonoccupied LN that did not show fluorescence had 90% and 95% occupation, respectively, while the fluorescent nodes all had lower rates of occupation.

DISCUSSION

We conducted a systematic review that included 78 studies on ICG-guided GI cancer surgery. Our study shows that ICG-FI may find several applications in the field of GI cancer surgery, and has the potential to increase precision and accuracy in patient-tailored oncological surgery.

The majority of the included studies was observational, with moderate to high quality: the median MINORS score was 12 out of 16 for the 57 noncomparative studies and 17.5 out of 24 for the 20 comparative studies. For most of the topics analyzed, strong conclusions were impeded by a high interstudy heterogeneity in dosages of ICG, timing, and routes of administration. Nonetheless, we sought to provide the readers a key message on the best (or most commonly used in literature) dosage and timing of ICG injection for each of the topic and organs analyzed, as shown in Figure 2. A summary of findings is provided in Table 4.

ICG does not seem to exhibit a specific tropism for metastatic tissues with the exception of hepatocellular carcinoma: ICG-FI have shown high sensibility in the identification of lesions during surgery for adrenal gland or lung metastases.[23,35] In liver surgery, most studies have reported good results for the intraoperative identification of tumors by injecting the dose of 0.5 mg/kg—normally used for the ICG retention test—within two weeks before surgery.[36] Metastatic lesions usually exhibit rim-enhancement, while primary tumors present heterogeneous patterns of enhancement because the exposure to the dye is solely linked to the hypo- or hypervascularization of the lesions. ICG removal from noncancerous tissue might be insufficient in patients with an impaired liver function, resulting in false-positive nodules.[20] ICG-FI has low specificity for determining the nature of liver lesions, but it can help achieve an R0 resection by direct visualization of the cut surface, particularly in the mini-invasive setting[36]. However, no studies comparing radicality in liver surgery with ICG-FI versus direct visualization have been published to date.

NIR visualization after ICG "tattooing" has been studied as a guidance during surgery for colon and gastric cancers, and might be particularly useful in laparoscopic surgery where tactile sensation is lost. Most studies compare the sensitivity of ICG with respect to India ink tattooing: ICG provides a higher detection rate than India ink, has no impact on the intraoperative visualization by naked eye when blurring occurs and has no impact on peritumoral inflammation at histology.[26,37] The main drawback of the use of ICG as a tattooing agent is the limited window of visualization after the endoscopic procedure (1 to 3 days).

Regarding the identification of the sentinel lymph node, ICG has been primarily studied in the setting of gastrectomy for early stage gastric cancer, to avoid unnecessary LND.[38] Several studies reported a high effectiveness of technetium 99 m-labeled tin colloid[39] for the identification of SLN, but its use is limited by costs and limited access to radioisotopes.[40] The overall accuracy of ICG in the identification of the SLN is high (mean overall detection rate of 98.6%, mean number of 6.7 SLNs per patient), and in the future it might replace radioisotopes given its inferior costs and ease of use. Differently from radioisotopes, the quantification of ICG-fluorescence intensity is still an unmet need, and only few pilot studies have addressed this issue.

In colorectal cancer, where systematic mesenteric LND is always performed, it is unlikely that the identification of SLN will become extensively used. However, ICG-guided detection of SLNs might improve the sensitivity of pathological analysis for metastatic LNs in very early tumors or after endoscopic resection. On 9 evaluated studies (174 patients), we found a SLN detection rate of 87.4% (85.2–93.9%), higher than that of the standard of care blue dye,[41] probably because of a higher penetrance of ICG through adipose tissue. Currently, in vivo SLN mapping and analysis cannot be used to decide on the extension of mesenteric LND due to the potential presence of skip nodal metastases or micrometastase. However, the identification of lateral pelvic SLN after ICG has proved to be feasible and safe[29] in lower rectal cancer, and in the future it might become a useful tool to decide on lateral pelvic lymph nodes dissection (LPLD).

Radical LND can significantly improve long-term survival and accuracy of tumor staging in patients with gastric cancer.[42] Even when LND is performed along the correct anatomic boundaries, some LN stations might be incompletely sampled: in comparative studies ICG-FI guided LND allows for a higher number of retrieved LNs[15–18,43] and a lower LN noncompliance[16,18] than standard LND, potentially translating into a survival advantage.[44] Given these findings, and since ICG-FI facilitates reproducibility and feasibility of LND during gastrectomy, it is likely that the technique will become extensively used in the near future. On the contrary, ICG-FI has limited application in LND during colorectal cancer surgery, probably due to different and clearer anatomical boundaries: even if most studies report a high rate of correct visualization of the lymph flow pattern, its application seems limited to didactic purposes. Finally, ICG-FI for SLN identification or to improve effectiveness of LND in primary tumors of the liver has been studied only in preclinical models. Further studies on the topic are warranted, but given the heterogeneity of liver tumors in terms of dimensions, vascularization, and lymphatic drainage, it is unlikely for the technique to become extensively used in the future.

Our systematic review has some limitations related to the broadness of the selected topic, the observational nature of most studies and the great heterogeneity in aims, dose, timing, and site of ICG administration between studies. Despite these limitations, the use of ICG as a guiding tool for dissection in GI cancer surgery seems extremely promising. Further evidence from high-quality studies on larger sample sizes is needed for ICG-guided surgery to be included in standard practice.

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