Real-time fluorescence image-guided gastrointestinal oncologic surgery: Towards a new era

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Abstract

Technological improvements are crucial in the evolution of surgery. Real-time fluorescence-guided surgery (FGS) has spread worldwide, mainly because of its usefulness during the intraoperative decision-making processes. The success of any gastrointestinal oncologic resection is based on the anatomical identification of the primary tumor and its regional lymph nodes. FGS allows also to evaluate the blood perfusion at the gastrointestinal stumps after colorectal or esophageal resections. Therefore, a reduction on the anastomotic leak rates has been postulated as one of the foreseeable benefits provided by the use of FGS in these procedures. Although the use of fluorescence in lymph node detection was initially described in breast cancer surgery, the technique is currently applied in gastric or splenic flexure cancers, as they both present complex and variable lymphatic drainages. FGS allows also to perform intraoperative lymphograms or sentinel lymph node biopsies. New applications of FGS are being developed to assist in the detection of peritoneal metastases or in the evaluation of the tumor resection margins. The present review aims to provide a general overview of the current status of real-time FGS in gastrointestinal oncologic surgery. We put a special focus on the different applications of FGS, discussing the main findings and limitations found in the contemporary literature and also the promising near
INTRODUCTION

Fluorescence-guided surgery (FGS) was first developed in 1947 with the introduction of fluorescein, a near-infrared (NIR) fluorescent dye, in brain tumor resections[1]. During the last decades, several authors have investigated the different applications of NIR as an intraoperative imaging tool in many gastrointestinal oncologic procedures. FGS is today considered a useful tool to complement the preoperative standard explorations and to assist in the intraoperative decision-making processes, contributing to improvements in both clinical and oncologic outcomes. Indocyanine green (ICG) is a NIR contrast agent that becomes fluorescent when excited by 800–900 nm wavelength light. In recent years, the intraoperative use of fluorescence with angiographic purposes has been expanded by surgeons and within centers worldwide. The objective is to assess the bowel’s perfusion before and after the anastomosis confection to reduce the risk of anastomatic leakage[2]. This complication is the most dreadful after both upper and lower gastrointestinal resections and often relates to an inadequate blood supply in the intestinal stumps. Additionally, NIR imaging is currently used or under investigation in a growing number of applications in the field: To identify peritoneal implants or sentinel lymph nodes, to perform lymph mapping, to guide an oncologic tumor resection, or to visualize biliary and urinary structures preventing iatrogenic harms. Then, real-time NIR is becoming an important tool in the surgeon’s armamentarium to perform safe and successful cancer resections, with the greatest future expectancies favored by the continuous technological improvements. We aimed to provide a complete and critical overview of the current evidence focusing on the different applications of FGS in gastrointestinal oncologic surgery.

ASSESSMENT OF THE ANASTOMOSIS PERFUSION AFTER COLORECTAL RESECTIONS

Colorectal cancer (CRC) is the third most common malignant tumor worldwide and the second cause of cancer-related death. CRC is responsible for 9.2% of the cancer deaths in the world[3]. Anastomotic leakage (AL) is the most feared complication after any colorectal resection[4]. AL is associated with increased mortality and poorer long-term oncological outcomes[5,6], especially in rectal cancer patients[7]. High rates of AL are still reported despite the successive improvements in the stapler devices and minimally-invasive techniques during the last years[8]. Several risk factors for AL

Key Words: Surgery; Colorectal cancer; Esophageal cancer; Fluorescence; Image-guided surgery; Anastomotic leak; Lymph node

Core Tip: The continuous improvements on the postoperative and the oncological outcomes of patients undergoing gastrointestinal cancer surgery has focused the efforts of the whole surgical community during the last decades. Fluorescence-guided surgery is currently being developed and implemented in many countries and centers with promising expectancies. Fluorescence-guided surgery has the potential to reduce anastomotic leak rates of colorectal or esophagogastrectomy surgery. Moreover, this new technology provides intraoperative real-time lymph node mapping and detection of sentinel lymph nodes or occult peritoneal metastases.

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have been described. They include male gender, age, comorbidities, malnutrition, obesity, smoking, alcoholism, immunosuppression, neoadjuvant treatments, etc.[9,10]. The individual surgeon performance, which was systematically obviated in the literature, has been shown also to be an independent risk factor for AL[11,12]. However, there is a general agreement in considering the ischemia of the anastomotic stumps as a key factor in the development of the majority of AL[9,13,14].

AL can be defined as the separation between two bowel segments that were previously attached. The definition includes a wide spectrum of situations, from small leaks without systemic consequences, to severe peritonitis causing septic shock or death. The high clinical variability in such terms and its definition highly jeopardizes the comparisons within the multiple studies on the subject. To overcome those biases, research teams have attempted to unify the criteria to define and grade AL through the elaboration of different systems. The Colon and the Dutch leakage scores were created for this purpose[15-17]. In 2010, the International Study Group of Rectal Cancer (ISGRC) presented an extensive literature review and proposed a new definition and grading system for AL in rectal resections. AL was defined as any defect of the intestinal wall integrity at the colorectal or coloanal anastomotic site leading to a communication between the intra- and extra-luminal compartments[18]. This definition included leaks from suture and the staple lines of neo-rectal reservoirs or pelvic abscess close to the anastomosis. The ISGRC graded AL in a three-tiered system: Grade A reflects no need for therapeutic intervention; grade B if the AL requires therapeutic intervention but is manageable without re-laparotomy; and grade C when it requires re-laparotomy[18].

The assessment of the anastomosis perfusion is a crucial step during colorectal resections. Multiple methods have been described to assess the viability of the intestinal stumps, mainly implying different degrees of subjectivity[19]. The air leak test was proposed by Lazorthes et al[20] in the 1980s. Conventional inspection by the surgical team is based on the bowel appearance and coloration, bleeding on the edges of the intestinal stumps, or in the detection of the arterial pulse[6,21]. In the last years, the use of ICG fluorescence angiography (ICG-FA) has become widespread, especially within colorectal surgeons (Table 1). The first large clinical experience with ICG-FA was reported by Kudszus et al[22] in 2010. They used laser fluorescence angiography by injecting ICG to assess the bowel perfusion. They compared the study group with a matched historical cohort, 201 patients in each group. Overall, 3.5% of the patients in the laser fluorescence angiography group developed Grade C AL compared to 7.5% of the controls. The use of ICG reduced the risk of AL by 60% in elective surgery and changed the surgical plan in the 16% of the operations[22]. The safety and feasibility of ICG-FA were further confirmed in two phase-2 prospective clinical trials[23,24]. Moreover, in 2020 two randomized controlled trials (RCT) assessed the effectiveness of the new technique when compared with the conventional surgeon’s judgment. The first was a multi-centric Italian superiority RCT. Two hundred fifty-two patients were referred for laparoscopic anterior rectal resection or left colectomy with a colorectal anastomosis, which was expected to be located between 2 and 15 cm from the anal verge. The primary outcome was the rate of AL defined by the ISGRC criteria within 30 d from surgery. In 13 patients, extended resections were performed according to the ICG-FA findings (11%). AL were developed in 6 (5%) patients in the ICG-FA group and in 11 patients (9%) in the control group (P = not significant)[25]. The second RCT enrolled 380 patients who underwent sigmoid or rectal resections between 2018 and 2019 in a single Russian institution. They observed that ICG-FA did not decrease the rate of AL in high (i.e. 9-15 cm from the anal verge) anastomoses: 1.3% vs 4.6% in the control group (P = not significant). In low colorectal anastomoses (i.e. 4–8 cm), the AL rate was significantly lower in ICG FA group: 14.4% vs 25.7%, respectively (P = 0.04). However, the difference was caused by the higher rate of Grade A leaks in the control group. The rates of clinically relevant AL (Grades B and C) were found to be similar between the two arms[26]. Arezzo et al[27] recently published an individual patient data meta-analysis including the two previous RCT and seven non-randomized studies. Pooled data from 1330 patients were analyzed, 862 in the ICG-FA group and 468 in the control group. The main outcome was the rate of AL during the first 30 d after surgery. The site of the anastomosis was modified after ICG-FA in 11.3% of the patients, whereas a new anastomosis was performed in 2% of the cases. ICG-FA reduced the odds of AL by 89.7%; indeed, the incidence of AL was significantly lower in the ICG-FA group than in the control group (4.2% vs 11.3%, respectively)[27].
Table 1 Summary of the outcomes of indocyanine green-fluorescence angiography to prevent anastomotic leakage after colorectal and esophageal resections

| Ref.          | Study design       | Total n | ICG group | Non-ICG group | Anastomosis leak n (%) | P value | Surgical plan change (%) |
|---------------|--------------------|---------|-----------|---------------|-------------------------|---------|--------------------------|
| Colorectal    |                    |         |           |               |                         |         |                          |
| Kudszus et al [22], 2010 | Retrospective-matched | 402     | 201       | 201           | ICG: 7 (3.5%); NICG: 15 (7.5%) | 0.04    | 16%                      |
| Jafari et al [23], 2013 | Case-control       | 38      | 16        | 22            | ICG: 1 (6%); NICG: 4 (18%) | NS      | 19% cases 4.5% controls  |
| Kim et al [24], 2015 | Case-control       | 436     | 123       | 313           | ICG: 1 (0.8%); NICG: 17 (5.4%) | NS      | Not reported             |
| De Nardi et al [25], 2020 | Randomized controlled trial | 240     | 118       | 122           | ICG: 6 (5%); NICG: 11 (9%) | NS      | 11%                      |
| Alekseev et al [26], 2020 | Randomized controlled trial | 377     | 187       | 190           | ICG: 17 (9.1%); NICG: 31 (16.3%) | 0.04    | Not reported             |
| Arezzo et al [27], 2020 | Meta-analysis       | 1330    | 862       | 468           | ICG: 36 (4.2%); NICG: 53 (11.3%) | < 0.001 | 11.3%                    |
| Esophageal    |                    |         |           |               |                         |         |                          |
| Zehetner et al [43], 2015 | Prospective        | 150     | 150       | N/A           | 4.6%                    | N/A     | 66%                      |
| Kumagai et al [47], 2018 | Cohort series      | 70      | 70        | N/A           | 1.4%                    | N/A     | 50%                      |
| Ladak et al [45], 2019 | Meta-analysis       | 1067    | 631       | 436           | Overall: 10.8%; ICG: 5.7%; NICG: 22.9% | NR      | Not reported             |
| Slooter et al [48], 2020 | Cohort series      | 84      | 84        | N/A           | 14.3%                   | N/A     | 2.4%                     |

ICG: Indocyanine green; N/A: Not applicable; NICG: Non-indocyanine green; NR: Not reported; NS: Not significant.

**ASSESSMENT OF GASTRIC TUBE PERFUSION FOLLOWING ESOPHAGECTOMY**

The surgical resection of esophageal cancers is associated with high rates of postoperative morbidity and mortality. AL and respiratory complications are the most frequent severe adverse events following an esophagectomy [28,29]. The incidence of AL in the literature ranges between 5% and 20% and has been associated with mortality rates of 18% to 40% [30,31]. Remarkably, up to 40% of the long-term survivors after an AL will develop an anastomotic stricture and therefore may require additional interventions or permanent nutritional support [32,33]. The most frequent methods for intestinal reconstruction after an esophageal resection include the performance of a stapled gastric tube by using the greater curvature of the stomach. The gastroplasty is then anastomosed with the cervical or the thoracic esophagus. The ischemia of the gastric tube is known to be the main predisposing factor for AL at esophageogastric anastomosis [34-36]. The tip of the gastric tube is the poorest perfused area [37]. Many other predictors for AL following esophagectomy have been described and include male gender, tobacco or alcohol abuse, obesity, the severity of comorbidities, corticoid therapy, emergency setting, and blood transfusions [30,35,36]. The conventional intraoperative methods to evaluate the perfusion of the gastric conduit are mainly based on the human visual inspection and therefore offer low accuracy. In recent years, different teams have experienced with ICG-IF intending to mitigate the burden of this deleterious complication, with variable results (Table 1). Some of them showed no effect of the ICG-IF to prevent an AL [28,38], while others did not [29]. Other authors showed lower severity of AL but not a decrease in the AL rates [39-42].

Zehetner et al [43] presented in 2015 one of the earliest prospective studies using laser-assisted angiography with ICG. They enrolled 150 patients who underwent esophagectomy with a cervical reconstruction. Two-thirds of all anastomosis sites were changed due to the angiographic findings. There was one postoperative death, and 22% of the participants developed major complications. AL occurred in 16.7% of the cases, but most of them were successfully managed without a surgical reoperation.
The placement of the anastomosis and the precedent of arterial hypertension were significantly associated with AL. Later, Koyanagi et al. evaluated 40 prospective patients with esophageal cancer to receive ICG-FA. They established four points in the gastric tube and determined the flow by calculating the time spent by the ICG to move between them. After they divided the flow into simultaneously or delayed. Morbidity was greater in the delayed group (60% vs 32%; \( P = 0.055 \)). AL was observed in 7 patients, all belonging to the latest group. The same researchers designed an ancillary study recruiting 109 additional patients to confirm the findings of their first work. They also evaluated the calcifications in the aorta, celiac trunk, and superior mesenteric artery with computerized tomography scan. AL rate was 13.7% in the study. The blood flow at the gastric conduit and the calcifications in the superior mesenteric artery were significantly correlated with AL development. Ladak et al. recently published a systematic review including 17 studies and 1067 patients. The pooled anastomotic leak rate was found to be 10% when ICG was used. They performed a meta-analysis including six non-RCTs that resulted in a risk reduction of 69% for ICG compared with the control group (odds ratio 0.31, 95% confidence interval: 0.15–0.63). However, there was high heterogeneity between the few studies published to date, and there is no prospective study comparing ICG and no-ICG for this indication. Therefore, the quality of the evidence regarding the real effectiveness of ICG-FA in esophagogastric anastomosis is still poor.

Recently, the quantification of the time-dependent change in the fluorescence signal has been postulated as a promising method to assess the future viability of the gastric conduit. New studies appeared recently with the aim to establish a standardized quantitative method for evaluation. One of the first was conducted by Kumagai et al. presenting the 90-s rule to find the best place to perform the anastomosis as the one enhancing within 90 s of the injection. They conducted a further prospective study including 70 patients. In 50% of the cases, the tip of the gastric tube was excised. Only a minor AL was diagnosed and developed into one of the 3 cases in which the enhancement time exceeded 60 s. Slooter et al. recently presented a prospective study aiming to evaluate the time until the fluorescent enhancement of the gastric conduit as a quantitative fluorescent value for ICG-FA. They determined a threshold to predict anastomotic complications in 84 patients. The anastomosis site was changed in 2.4% of the cases as a result of ICG-FA. AL was observed in 14.3% of the included patients. When using the 90-s threshold, the time before ICG injection and the enhancement of the gastric conduit tip was a predictor for AL with a specificity of 98% but a sensitivity of 17% in the study.

**LYMPH NODE DETECTION AND MAPPING**

In 1992, Morton et al. introduced the sentinel lymph node (SLN) concept by injecting technetium-labeled dextran to 223 patients with non-advanced melanoma. Shortly after, Giuliano et al. applied this technique by using blue dye in 172 women with breast cancer. Both groups obtained excellent results, the SLN procedure expanded, and it is currently being implemented in the treatment of a growing number of cancers. The use of ICG for SLN was first reported in 2005, also in breast cancer. Nowadays, the knowledge gained regarding SLN biopsy (SLNB) in breast cancer and melanoma has been extrapolated to gastrointestinal cancers, especially gastric and colorectal ones. The metastatic involvement of the lymph nodes is a major prognostic factor in those tumors. There is a permanent controversy regarding whether more extensive lymphadenectomies provide survival benefits in gastrointestinal malignancies. It is noteworthy that greater lymphadenectomies are associated with higher morbidity and mortality rates.

The available preoperative radiologic examinations do not achieve enough accuracy to identify adequately the lymph node metastases. In this scenario, ICG emerged as a promising tool, allowing the performance of real-time intraoperative lymphograms. Similar to the above mentioned applications of ICG in oncologic digestive surgery, the timing, dose, and technique presented high heterogeneity within the existing literature on the subject. The latency time from the injection to the measurement was 40 min (range 3 to 152), which represents a non-despicable increase in the duration of the anesthesia. Most authors prefer the intraoperative injection to perform LN mapping (LNM), while others the day before surgery looking for a more complete LNM in gastric cancers. Peritumoral and subserosal seem to be the most widespread injection sites. However, some authors have reported a series of submucosal injections obtaining favorable results.
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| Ref. | Patients | Detection rate | Sensitivity | Specificity | Considerations |
|------|----------|----------------|-------------|-------------|----------------|
| Kusano et al [57], 2008 | 26 CRC, 22 GC | CRC: 90.9%, GC: 88% | CRC: S: 25%, GS: 40%<sup>1</sup> | Sp: 100%<sup>1</sup>, Sp: 100%<sup>1</sup> | CRC: PPV: 100%, NPV: 81%, GC: PPV: 100%, NPV: 62.5% |
| Cahill et al [78], 2009 | 891 | NR | 81% | 93.2%<sup>1</sup> | PPV: 62%, NPV: 95%. Lower FN if tumor size is less than 35 mm. IHC analysis increases sensitivity |
| Noura et al [58], 2010 | 25 | 92% | 100% | 100% | FN: 0%. NPV: 100% Performed lateral pelvic dissection in order to increase SN detection accuracy |
| Kitagawa et al [80], 2013 | 397 | 97.5% | 93.44%<sup>1</sup> | 98.99%<sup>1</sup> | Uses dual technique (blue dye and ICG) |
| Kinami et al [82], 2015 | 72 | 90% | 98%<sup>2</sup> | FN: 1.3% |
| Tummers et al [79], 2016 | 26 | 95% | 75% | 88.9% | Reduces second-tier nodes using nanocolloids |
| Lee et al [83], 2016 | 20 | 95% | 100% | 94.4% | FN: 0% |
| Villegas-Tovar et al [57], 2020 | 281 | 91% | 64.3% | 65% | AUC: 66.5% |

<sup>1</sup>Calculated using the data provided at the papers. AUC: Area under the curve; CRC: Colorectal cancer; FN: False negatives; FNR: False negative rate; GC: Gastric cancer; ICH: Immunohistochemistry; NPV: Negative predictive value; NR: Non reported; PPV: Positive predictive value; SN: Sentinel node.

69]. Xiong et al [70] showed that concentrations < 5 mg/mL and volumes injected ≥ 2 mL presented higher sensitivity and detection rates.

With the injection of ICG and a subsequent LNM, extra-anatomical routes of lymphatic spread can be evidenced in real-time. This is especially useful in gastric[71] or splenic flexure colonic cancers[65], both presenting complex lymphatic drainages. Likewise, ICG has demonstrated its usefulness to detect the lateral SLN in mid-low rectal cancer and to decrease the rate of complications[72]. Noura et al [58] reported a 92% detection rate of lateral SN in low rectal cancer in a pilot study with 25 patients. Moreover, ICG combined with NIR allows a deeper visualization of the lymphatic structures than the classical contrasts under conventional light[63,72]. This would increase the lymph node harvest and mitigate the risk for tumor downstaging and then suboptimal indications of adjuvant treatments[73-75]. This can be of particular interest in Western countries because of the high prevalence of obesity[63].

Kusano et al [76] reported the first experience of SLNB in gastrointestinal tumors with SLN detection rates of 90.9% in CRC and 88% in gastric cancer. Following them, many teams repeated the experience, and the detection rates ranged between 80% and 99%[57]. Those rates, as the accuracy of SLNB, are influenced by the tumor size, the T-stage, the body mass index, the tracer used, and the surgeon’s experience[77]. Cahill et al [78] suggested that ICG-guided SLNB in CRC is more sensitive and has a lower tumor false negative (FN) rate if the tumor size is less than 35 mm. The SLNB could be useful in selected patients presenting cT1-2 gastric tumors where a routine D2 lymphadenectomy could lead to unacceptable morbidity. However, the main issue that limits the applicability of ICG to SLNB is caused by its diffusion towards the second-tier nodes. Tummers et al [79] addressed this problem by adding nanocolloids to the ICG. However, 9% of the patients were FN (i.e. macrometastatic nodes not stained), likely due to a tumoral blockage of the lymph flow. In a recent meta-analysis, the detection rate of SLN with ICG in CRC was 91%. Nevertheless, the accuracy in the prediction of nodal involvement was poor with an area under the curve of 66.5% and a sensitivity of 65%[57]. Other authors used dual-tracer techniques (i.e. blue dye + radiotracers) and reported an accuracy close to 99% in gastric cancer patients with stages cT1 and cT2 smaller than 4 cm but still with a high FN rate in the T2-stages[80]. The high FN rate is the most critical limitation in ICG-guided SLNB. The Japan Clinical Oncology Group multicenter trial (JCOG0302) was suspended due to a high proportion of FN in ICG-guided SLNB[81]. Although Kinami et al [82] and Lee et al [83] reported a 1.3% and 0% rate of FN, respectively, the majority of the studies have FN rates of approximately 20%, with small variations among them[60,65,79,84].

Last, by applying molecular biology techniques such as immunohistochemistry or one-step nucleic acid amplification it is possible to detect micrometastases and isolated...
tumor cells in the lymph nodes. The meta-analysis by Ankersmit et al.\textsuperscript{[73]} reported an upstaging rate of 15% after immunohistochemistry analysis due to the detection of micrometastasis. Even higher upstaging rates have been reported with the combination of ICG and intraoperative one-step nucleic acid amplification analysis of the fluorescence nodes\textsuperscript{[85-87]}. Although there is currently no recommendation to indicate adjuvant treatments in colorectal or esophageal cancers based on the presence of isolated tumor cells, in the foreseeable future the ICG-guided SLNB may contribute to offer more personalized and optimized options to treat the patients.

**PERITONEAL METASTASIS DETECTION AND TUMOR RESECTION**

Peritoneal metastases (PM) are a common evolution of gastrointestinal cancer, and they are strongly associated with a poor prognosis. Around 8%-25% of CRC patients will develop PM\textsuperscript{[88,89]}. In the 1990s, the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy was proposed by Sugarbaker et al.\textsuperscript{[90]}, showing a marked improvement in the patient’s overall survival. Those aggressive procedures are associated with non-despicable rates of postoperative morbidity (16%-64%) and mortality (5%)\textsuperscript{[91]}. Moreover, the completeness of tumor removal is still the most critical prognostic factor in patients with CRC and PM, as patients undergoing incomplete resections may expect only few oncologic benefits from the surgery. Thus, a careful patient selection in these complex scenarios is mandatory. Unfortunately, the available preoperative diagnostic imaging systems, as the intraoperative visual inspection, have shown a low sensitivity to detect PM nodules smaller than 5 mm\textsuperscript{[92,93]}. The use of fluorescence via ICG for these purposes is based on an effect named “enhanced permeability and retention” (EPR). The EPR illustrates the affinity of ICG towards the tumoral and near-tumoral tissue due to neovascularization and impaired lymphatic drainage. ICG detection in PM nodules was described by Kosaka et al.\textsuperscript{[94]} in animal models. To date, only four groups have evaluated the role of ICG in the detection of PM from CRC. Liberale et al.\textsuperscript{[95]} published the proof-of-concept in 2016. They included 14 patients (63 evaluable nodules) after excluding patients with peritoneal carcinomatosis index (PCI) > 17. In the first procedure, 0.25 mg/kg of free ICG were injected intravenously 24 h before surgery, but no fluorescence was detected during the surgery. Thereafter, ICG was injected intraoperatively after a complete abdominal exposition. Nodules were classified in vivo as hyperfluorescent, moderately hyperfluorescent, or hypofluorescent. ICG detected additional PM in 3 patients (21.4%). All these PM were found in the abdominal flank regions and paracolic gutters. Sensitivity and specificity in patients with non-mucinous adenocarcinoma were 87.5% and 100%, respectively. In patients with mucinous tumors, ICG was poorly sensitive (0%). The authors attributed these findings to the correlation between the presence of mucinous material and the absence of vascularized tissue within tumor nodules\textsuperscript{[95]}.

Barabino et al.\textsuperscript{[96]} presented the same year a prospective study aiming to evaluate the detection of PM nodules ex vivo using NIR and ICG injected 24 h before surgery in 10 patients and 88 Lesions. During the surgery, only the tissues macroscopically suspicious were resected. The group presented their results in three different publications. In the first report, they showed that the overall sensitivity and specificity for CRC-PM detection were 72.4% and 77.3%, respectively, which were lower than initially expected. They also found a high false-positive rate of 40%\textsuperscript{[96]}. The same team published an ancillary report over the same 10 patients to assess the impact of bevacizumab, an anti-angiogenic agent, on the extravasation of ICG. It was hypothesized that it may reduce the EPR effect and increase the FN rates. All the patients in the study received preoperative chemotherapy, 4 treated with bevacizumab and 6 without (4 cetuximab/2 no biotherapy) who were included as controls. Sensitivity and specificity were similar within groups\textsuperscript{[97]}. In a further correspondence letter, the authors provided the data of 2 patients (22 nodules) presenting mucinous adenocarcinomas\textsuperscript{[96,99]}. The analysis showed a sensitivity of 72.2% and specificity of 75%, which was similar than the whole population, and contrasted with the findings of the earlier study on the subject. In 2018, Lieto et al.\textsuperscript{[100]} reported 4 patients in which ICG was injected intraoperatively and then detected by the INR camera system. Sixty-nine specimens were analyzed in vivo and ex vivo with complete correspondence. The use of ICG added 25% of diagnostic improvement, as detected 16 nodules missed by conventional procedures. Sensitivity was 96.9% and specificity 75%, with a false positive rate of 25% and a FN rate of 3%\textsuperscript{[100]}.

There are currently alternative imaging systems to detect PM. Narrow-band imaging (NBI) appeared in 2005 and has been routinely used in gastrointestinal
**Table 3 Summary of the studies evaluating the role of indocyanine green to detect peritoneal carcinomatosis**

| Ref.       | Yr   | Patients | Nodules | Additional nodules | Sensitivity | Specificity | Considerations                                                                 |
|------------|------|----------|---------|--------------------|-------------|------------|--------------------------------------------------------------------------------|
| Liberale et al [95], 2020 | 2016 | 14       | 63      | 21.4%              | 87.5%       | 100%       |                                                                                |
| Barabino et al [96], 2020 | 2016 | 10       | 88      |                    | 72.4%       | 77.3%      |                                                                                |
| Filippello et al [97], 2020 | 2016 | 10       | 29      |                    | 65%         | 57.1%      | Same patients than Barabino et al[96], but comparing the use of bevacizumab or not |
| Lieto et al[100], 2020 | 2018 | 4        | 69      | 16                 | 96.9%       | 75%        | ICG adds 25% of diagnostic improvement                                          |
| Sluiter et al [104], 2020 | 2019 | 28       | 169     |                    | 80%         | 74.8%      | NBI increases sensitivity from 80% to 96% when compared with white light, with the same specificity |

ICG: Indocyanine green; NBI: Narrow band imaging.

The use of fluorescence imaging in gastrointestinal oncologic surgery has expanded in the last years. The technology has demonstrated to be safe and has the potential to improve both the clinical and the oncologic outcomes. Preliminary studies showed that ICG-FA may reduce the risk to develop ALs after esophageal or colorectal resections. ICG has been found to be successful to perform lymphographies or to detect sentinel nodes, with acceptable accuracy rates. Few studies recently addressed endoscopy [101]. The system consists of a camera filter that allows the identification of 415-540 nm wavelength light. They match with the two absorption peaks of the hemoglobin, then highlighting the microvascular architecture [102].

Previous studies have shown promising results during staging laparoscopy in advanced gastric cancer when compared with the standard white light imaging [103]. Recently, Sluiter et al [104] published the results from a prospective clinical trial over 28 patients comparing three advanced imaging techniques with the conventional white-light to detect PM from CRC: (1) NBI; (2) NIR-ICG administrated 3-12 h before surgery; and (3) Spray-dye chromoendoscopy. The use of the two latest was discontinued after 10 patients because the lesions were not fluorescent using NIR-ICG, and the spray-dye chromoendoscopy did not allow the entire visualization of the peritoneal cavity. The main finding of the study was that NBI increased the sensitivity in detecting PM to 96% when compared with the white light (Table 3).

We can consider that NIR-ICG imaging is a feasible tool to assist in the detection of the PM of CRC. The main advantages of ICG are its safety and its commercial availability. However, ICG is a non-specific molecule to detect the neoplastic tissue, therefore its specificity is limited. The standard dosage or timing of ICG injection are still to be determined. Moreover, its effectiveness may be limited in patients with mucinous neoplasms or already treated with antiangiogenics. The next step may be the detection of tumor tissue by molecular-FGS. The first clinical study evaluating the safety and feasibility of molecular-FGS using bevacizumab-800CW to detect PM from CRC reported a sensitivity of 100% and a specificity of 54%. The study involved 7 patients; in 2 of them additional tumor deposits were detected. There were no serious adverse events related to the administration of the tracer [105]. A multicenter pilot study has been recently published including 14 patients diagnosed with PM from colorectal origin in which SGM-101, a carcinoembryonic antigen-specific tumor-targeted fluorescent agent, was administrated to identify peritoneal malignant tissue. There was no adverse effect. Sensitivity was 98.5% and specificity 62.2%. The positive predictive value was 82.3% and the negative predictive value was 95.8% [106].

The bevacizumab-800CW fluorescent tracer has been also recently used for backtable evaluation of the circumferential resection margin in eight fresh surgical resection specimens of locally-advanced rectal cancer [107]. The future development of these techniques towards its intraoperative application could drive surgical decision-making in the case of positive circumferential resection margin to extend resections or to indicate concomitant intraoperative radiation therapy.

**CONCLUSION**

The use of fluorescence imaging in gastrointestinal oncologic surgery has expanded in the last years. The technology has demonstrated to be safe and has the potential to improve both the clinical and the oncologic outcomes. Preliminary studies showed that ICG-FA may reduce the risk to develop ALs after esophageal or colorectal resections. ICG has been found to be successful to perform lymphographies or to detect sentinel nodes, with acceptable accuracy rates. Few studies recently addressed...
the applicability of fluorescence to identify occult peritoneal disease, also with promising returns. However, there is a notorious heterogeneity regarding the dosage, timing, and imaging systems used in the different studies. This heterogeneity is also noted in the outcomes they have evaluated. Future standardization is mandatory to elucidate the real role of FGS in these scenarios.

REFERENCES

1. Moore GE. Fluoresentin as an Agent in the Differentiation of Normal and Malignant Tissues. Science 1947; 106: 130-131 [PMID: 17750790 DOI: 10.1126/science.106.2745.130-a]

2. de'Angeis N, Moroni P, Brunetti F, Martínez-Pérez A. Indocyanine green fluorescence guided robotic right colectomy with intra-corporeal anastomosis - a video vignette. Colorectal Dis 2019; 21: 1459-1460 [PMID: 31402537 DOI: 10.1111/codi.14820]

3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

4. Frouws MA, Snijders HS, Malm SH, Liefers GJ, Van de Velde CJH, Neijenhuis PA, Kroon HM. Clinical Relevance of a Grading System for Anastomotic Leakage After Low Anterior Resection: Analysis From a National Cohort Database. Dis Colon Rectum 2017; 60: 706-713 [PMID: 28594720 DOI: 10.1097/DCR.0000000000000800]

5. Ha GW, Kim JH, Lee MR. Oncologic Impact of Anastomotic Leakage Following Colorectal Cancer Surgery: A Systematic Review and Meta-Analysis. Ann Surg Oncol 2017; 24: 3289-3299 [PMID: 28608118 DOI: 10.1245/s10434-017-5881-9]

6. Nachiappan S, Faiz O. Anastomotic Leak Increases Distant Recurrence and Long-term Mortality After Curative Resection for Colon Cancer. Ann Surg 2015; 262: e111 [PMID: 24950267 DOI: 10.1097/SLA.0b013e31827b8ed9]

7. Park JS, Choi GS, Kim SH, Kim HR, Kim NK, Lee KY, Kang SB, Kim JY, Kim BC, Bae BN, Son GM, Lee SI, Kang H. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision: the Korean laparoscopic colorectal surgery study group. Ann Surg 2013; 257: 665-671 [PMID: 23333881 DOI: 10.1097/SLA.0b013e318278e6d0]

8. Rausa E, Zappa MA, Kelly ME, Turati L, Russo A, Aiolfi A, Bonitá G, Ugol I. A standardized use of intraoperative anastomotic testing in colorectal surgery in the new millennium: is technology taking over? Tech Coloproctol 2019; 23: 625-631 [PMID: 31302816 DOI: 10.1007/s10151-019-02034-6]

9. McDermott FD, Heaney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg 2015; 102: 462-479 [PMID: 25703524 DOI: 10.1002/bjs.9697]

10. Frasson M, Flor-Lorente B, Rodríguez JL, Granero-Castro P, Hervás D, Álvarez Rico MA, Bravo MJ, Sánchez González JM, García-Granero E; ANACO Study Group. Risk Factors for Anastomotic Leak After Colon Resection for Cancer: Multivariate Analysis and Nomogram From a Multicentric, Prospective, National Study With 3193 Patients. Ann Surg 2015; 262: 321-330 [PMID: 25361221 DOI: 10.1097/SLA.0000000000000973]

11. Marinello FG, Baguena G, Lucas E, Frasson M, Hervás D, Flor-Lorente B, Esclapez P, Espli A, García-Granero E. Anastomotic leakage after colon cancer resection: does the individual surgeon matter? Colorectal Dis 2016; 18: 562-569 [PMID: 26558741 DOI: 10.1111/codi.13121]

12. García-Granero E, Navarro F, Cerdán Santacruz C, Frasson M, García-Granero A, Marinello F, Flor-Lorente B, Espi A. Individual surgeon is an independent risk factor for leak after double-stapled colorectal anastomosis: An institutional analysis of 800 patients. Surgery 2017; 162: 1006-1016 [PMID: 28739093 DOI: 10.1016/j.surg.2017.05.023]

13. Vignali A, Ghiotta L, Braga M, Radaelli G, Malvezzi I, Di Carlo V. Altered microperfusion at the rectal stump is predictive for rectal anastomotic leak. Dis Colon Rectum 2000; 43: 76-82 [PMID: 10813128 DOI: 10.1007/BF02237248]

14. Morse BC, Simpson JP, Jones YR, Johnson BL, Knott BM, Kotrady JA. Determination of independent predictive factors for anastomotic leak: analysis of 682 intestinal anastomoses. Am J Surg 2013; 206: 950-955; discussion 955-956 [PMID: 24070663 DOI: 10.1016/j.amjsurg.2013.07.017]

15. Dekker JW, Liefers GJ, de Mol van Otterloo JC, Putter H, Tollenaar RA. Predicting the risk of anastomotic leakage in left-sided colorectal surgery using a colon leakage score. J Surg Res 2011; 166: e27-e34 [PMID: 21195424 DOI: 10.1016/j.jss.2010.11.004]

16. den Dulk M, Noter SL, Hendriks ER, Brouwers MA, van der Vlies CH, Oostenbroek RJ, Menon AG, Steup WH, van de Velde CJ. Improved diagnosis and treatment of anastomotic leakage after colorectal surgery. Eur J Surg Oncol 2009; 35: 420-426 [PMID: 18585889 DOI: 10.1016/j.ejso.2008.04.009]

17. den Dulk M, Witvliet MJ, Kortram K, Neijenhuis PA, de Hingh IH, Engel AF, van de Velde CJ, de Brauw LM, Putter H, Brouwers MA, Steup WH. The DULK (Dutch leakage) and modified DULK score compared: actively seek the leak. Colorectal Dis 2013; 15: e528-e533 [PMID: 24199233 DOI: 10.1111/codi.12379]
Martínez-López E et al. Fluorescence image-guided gastrointestinal oncologic surgery

18 Rahbarni NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, Holm T, Wong WD, Tietz E, Moriya Y, Lauerberg S, den Dulk M, van de Velde C, Büchler MW. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010; 147: 339-351 [PMID: 20004450 DOI: 10.1016/j.surg.2009.10.012]

19 Hirst NA, Tiernan JP, Millner PA, Jayne DG. Systematic review of methods to predict and detect anastomotic leakage in colorectal surgery. Colorectal Dis 2014; 16: 95-109 [PMID: 23992607 DOI: 10.1111/ced.12411]

20 Lazorthes F, Chiotassol P. Stapled colorectal anastomoses: peroperative integrity of the anastomosis and risk of postoperative leakage. Int J Colorectal Dis 1986; 1: 96-98 [PMID: 3611941 DOI: 10.1007/BF01648414]

21 Urbanavičius L, Pattyn P, de Putte DV, Venskutonis D. How to assess intestinal viability during surgery: A review of techniques. World J Gastrointest Surg 2011; 3: 59-69 [PMID: 21666808 DOI: 10.4240/wjgs.v3.i5.59]

22 Kudszus S, Roesel C, Schachtrupp A, Hёer JJ. Intraoperative laser fluorescence angiography in colorectal surgery: a noninvasive analysis to reduce the rate of anastomotic leakage. Langenbecks Arch Surg 2010; 395: 1025-1030 [PMID: 20700603 DOI: 10.1007/s00423-010-0699-x]

23 Jafari MD, Wexner SD, Mertz JE, McEmore EC, Margolin DA, Sherwinta DA, Lee SW, Senagore AJ, Phelan MJ, Stanos MJ. Perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II): a multi-institutional study. J Am Coll Surg 2015; 220: 82-92.e1 [PMID: 25451666 DOI: 10.1016/j.jamcollsurg.2014.09.015]

24 Ris F, Liot E, Buchs NC, Kraus R, Ismael G, Belfontai V, Douissard J, Cunningham C, Lindsey I, Guy R, Jones O, George B, Morel P, Mortensen NJ, Humphes R, Cahill RA; Near-Infrared Anastomotic Perfusion Assessment Network VOIR. Multicentre phase II trial of near-infrared imaging in elective colorectal surgery. Br J Surg 2018; 105: 1359-1367 [PMID: 29663330 DOI: 10.1002/bjs.10844]

25 De Nardi P, Elmore U, Maggi G, Maggiore R, Boni L, Cassinoti E, Fumagalli U, Gardani M, De Pascale S, Parise P, Vignali A, Rosati R. 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 [PMID: 30030276 DOI: 10.1007/s00464-019-08730-0]

26 Alekseev M, Rybakov E, Shefygin Y, Chernyshov S, Zarodnyuk I. A study investigating the perfusion of colorectal anastomoses using fluorescence angiography: results of the FLAG randomized trial. Colorectal Dis 2020; 22: 1147-1153 [PMID: 32189424 DOI: 10.1111/codi.15037]

27 Areszo A, Bonino MA, Ris F, Boni L, Cassinoti E, Foo DCC, Shum NF, Brolese A, Ciarelleglio F, Keller DS, Rosati R, De Nardi P, Elmore U, Fumagalli Romario U, Jafari MD, Pigazzi A, Rybakov E, Alekseev M, Watanabe J, Vettoretto N, Cirocchi R, Passera R, Forcigniano E, Morino M. Intraoperative use of fluorescence with indocyanine green reduces anastomotic leak rates in rectal cancer surgery: an individual participant data analysis. Surg Endosc 2020; 34: 4281-4290 [PMID: 32556609 DOI: 10.1007/s00464-020-07735-w]

28 Dalton BGA, Ali AA, Crandall M, Awad ZT. Near infrared perfusion assessment of gastric conduit during minimally invasive Ivor Lewis esophagectomy. Am J Surg 2018; 216: 524-527 [PMID: 29203037 DOI: 10.1016/j.amjsurg.2017.11.026]

29 Karampinis I, Ronellentitsch U, Mertens C, Gerken A, Hetjens S, Post S, Kienle P, Nowak K. Indocyanine green tissue angiography affects anastomotic leakage after esophagectomy. A retrospective, case-control study. Int J Surg 2017; 48: 210-214 [PMID: 29146267 DOI: 10.1016/j.ijsu.2017.11.001]

30 Van Dalee E, Van de Putte D, Ceelen W, Van Nieuwenhove Y, Pattyn P. Risk factors and consequences of anastomotic leakage after Ivor Lewis oesophagectomy. Interact Cardiovasc Thorac Surg 2016; 22: 32-37 [PMID: 26433973 DOI: 10.1093/icvts/ivw276]

31 Biere SS, Maas KW, Cuesta MA, van der Feest DL. Cervical or thoracic anastomosis after esophagectomy for cancer: a systematic review and meta-analysis. Dig Surg 2011; 28: 29-35 [PMID: 21293129 DOI: 10.1159/000322014]

32 Helminen O, Kyto V, Kauppila JJ, Gunn J, Lagergren J, Silvio E. Population-based study of anastomotic stricture rates after minimally invasive and open oesophagectomy for cancer. BJNS Open 2019; 3: 634-640 [PMID: 31592081 DOI: 10.1002/bjs5.50176]

33 van Heijl M, Gooszen JA, Fockens P, Busch OR, van Lanschot JJ, van Berge Henegouwen MI. Risk factors for development of benign cervical strictures after esophagectomy. Ann Surg 2010; 251: 1064-1069 [PMID: 20485137 DOI: 10.1097/SLA.0b013e3181de4b87]

34 Ryan CE, Panzica A, Meguid RA, McCarter MD. Transhiatal Anastomotic Leak After Esophagectomy: Current Trends. Ann Surg Oncol 2017; 24: 281-290 [PMID: 27406098 DOI: 10.1245/s10434-016-5417-7]

35 Markar SR, Arya S, Karthikesalingam A, Hanna GB. Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. Ann Surg Oncol 2013; 20: 4274-4281 [PMID: 23943035 DOI: 10.1245/s10434-013-3189-x]

36 Junemann-Ramirez M, Awad MI, Khan ZM, Rahamim JS. Anastomotic leakage post-esophagectomy for esophageal carcinoma: retrospective analysis of predictive factors, management and influence on long-term survival in a high volume centre. Eur J Cardiothorac Surg 2005; 27: 3-7 [PMID: 15621463 DOI: 10.1016/j.ejcts.2004.09.018]
Akiyama H, Miyazono H, Tsurumaru M, Hashimoto C, Kawamura T. Use of the stomach as an esophageal substitute. *Ann Surg* 1978; **188**: 606-610 [PMID: 718285 DOI: 10.1097/00000658-197810000-00004]

Di Furia M, Romano L, Salvatorelli A, Brandolin D, Lomanto D, Cianca G, Schietroma M, Carlei F, Giuliani A. Indocyanine Green Fluorescent Angiography During Laparoscopic Sleeve Gastrectomy: Preliminary Results. *Obes Surg* 2019; **29**: 3786-3790 [PMID: 3121110 DOI: 10.1007/s11695-019-04085-7]

Noma K, Shirakawa Y, Kanaya N, Okada T, Maeda N, Ninomiya T, Tanabe S, Sakurama K, Fujiwara T. Visualized Evaluation of Blood Flow to the Gastric Conduit and Complications in Esophageal Reconstruction. *J Am Coll Surg* 2018; **226**: 241-251 [PMID: 29174858 DOI: 10.1016/j.jamcollsurg.2017.11.007]

Kitagawa H, Namikawa T, Iwabu J, Fujisawa K, Uemura S, Tsuda S, Hanazaki K. Assessment of the blood supply using the indocyanine green fluorescence method and postoperative endoscopic evaluation of anastomosis of the gastric tube during esophagectomy. *Surg Endosc* 2018; **32**: 1749-1754 [PMID: 28916466 DOI: 10.1007/s00464-017-5857-6]

Kitagawa H, Namikawa T, Iwabu J, Yokota K, Uemura S, Munekage M, Hanazaki K. Correlation between indocyanine green visualization time in the gastric tube and postoperative endoscopic assessment of the anastomosis after esophageal surgery. *Surg Today* 2020; **50**: 1375-1382 [PMID: 32445048 DOI: 10.1007/s10595-020-02025-3]

Koyanagi K, Ozawa S, Oguma J, Kazuno A, Yamazaki Y, Ninomiya Y, Ochiai H, Tachimori Y. Blood flow speed of the gastric conduit assessed by indocyanine green fluorescence: New predictive evaluation of anastomotic leakage after esophagectomy. *Medicine (Baltimore)* 2016; **95**: e4386 [PMID: 27472732 DOI: 10.1097/MD.0000000000004386]

Zehetner J, DeMeester SR, Alicuben ET, Oh DS, Lipham JC, Hagen JA, DeMeester TR. Intraoperative Assessment of Perfusion of the Gastric Graft and Correlation With Anastomotic Leaks After Esophagectomy. *Ann Surg* 2015; **262**: 74-78 [PMID: 25029436 DOI: 10.1097/SLA.0000000000000811]

Koyanagi K, Ozawa S, Ninomiya Y, Oguma J, Kazuno A, Yatabe K, Higuchi T, Yamamoto M. Association between indocyanine green fluorescence blood flow speed in the gastric conduit wall and superior mesenteric artery calcification: predictive significance for anastomotic leakage after esophagectomy. *Esophagus* 2021; **18**: 248-257 [PMID: 33165752 DOI: 10.1007/s10388-020-00797-8]

Ladak F, Dang JT, Switzer N, Mocanu V, Tian C, Birch D, Turner SR, Karmali S. Indocyanine green for the prevention of anastomotic leaks following esophagectomy: a meta-analysis. *Surg Endosc* 2019; **33**: 384-394 [PMID: 30386993 DOI: 10.1007/s00464-018-6503-7]

Kumagai Y, Ishiguro T, Haga N, Kusumoto K, Kawanoto T, Ishida H. Hemodynamics of the reconstructed gastric tube during esophagectomy: assessment of outcomes with indocyanine green fluorescence. *World J Surg* 2014; **38**: 138-143 [PMID: 24196170 DOI: 10.1007/s00268-013-2237-9]

Kumagai Y, Hatanos S, Sobajima J, Ishiguro T, Fukuchi M, Iishihasi KI, Mochiki E, Nakajima Y, Ishida H. Indocyanine green fluorescence angiography of the reconstructed gastric tube during esophagectomy: efficacy of the 90-second rule. *Dis Esophagus* 2018; **31**: 29897432 DOI: 10.1093/dote/doy052

Slooter MD, de Bruin DM, Eshuis WJ, Veelo DP, van Dieren S, Gisbertz SS, van Berge Henegouwen MI. Quantitative fluorescence-guided perfusion assessment of the gastric conduit to predict anastomotic complications after esophagectomy. *Dis Esophagus* 2021; **34**: [PMID: 33016305 DOI: 10.1093/dote/dua100]

Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, Foshag LJ, Cochran AJ. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; **127**: 392-399 [PMID: 1558490 DOI: 10.1001/archsurg.1992.01420040034005]

Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994; **220**: 391-398; discussion 398-401 [PMID: 8092905 DOI: 10.1097/00000658-199409000-00015]

Kiti T, Inomoto T, Miwa M, Shikayama T. Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. *Breast Cancer* 2005; **12**: 211-215 [PMID: 16110291 DOI: 10.2232/jbca.12.211]

Yu P, Du Y, Xu Z, Huang L, Cheng X. Comparison of D2 and D2 plus radical surgery for advanced distal gastric cancer: a randomized controlled study. *World J Surg Oncol* 2019; **17**: 28 [PMID: 30728027 DOI: 10.1186/s12957-019-1572-1]

Athanasios CD, Markides GA, Koth A, Jia X, Gonsalves S, Miskovic D. Open compared with laparoscopic complete mesocolic excision with central lymphadenectomy for colon cancer: a systematic review and meta-analysis. *Colorectal Dis* 2016; **18**: O224-O235 [PMID: 27187520 DOI: 10.1111/codi.13385]

Koh FH, Tan KK. Complete mesocolic excision for colon cancer: is it worth it? *J Gastrointest Oncol* 2019; **10**: 1215-1221 [PMID: 31949942 DOI: 10.21037/jgo.2019.05.01]

Kim H, Lee SK, Kim YM, Lee EH, Lim SJ, Kim SH, Yang J, Lim JS, Hyung WJ. Fluorescent iodized emulsion for pre- and intraoperative sentinel lymph node imaging: validation in a preclinical model. *Radiology* 2015; **275**: 196-204 [PMID: 25747180 DOI: 10.1148/radiol.14114159]

Tajima Y, Yamazaki K, Masuda Y, Kato M, Yasuda D, Aoki T, Kato T, Murakami M, Miwa M, Kusano M. Sentinel node mapping guided by indocyanine green fluorescence imaging in gastric...
Martínez-López E et al. Fluorescence image-guided gastrointestinal oncologic surgery

cancer. *Ann Surg 2009; 249*: 58-62 [PMID: 19106676 DOI: 10.1097/SLA.0b013e3181927267]

Villegas-Tovar E, Jimenez-Lillo J, Jimenez-Valerio V, Diaz-Giron-Gidi A, Faes-Petersen R, Otero-Piñero A, De Lacy FB, Martinez-Portilla RJ, Lacy AM. Performance of Indocyanine green for sentinel lymph node mapping and lymph node metastasis in colorectal cancer: a diagnostic test accuracy meta-analysis. *Surg Endosc 2020; 34*: 1035-1047 [PMID: 31754853 DOI: 10.1007/s00464-019-07274-2]

Noura S, Ohue M, Seki Y, Tanaka K, Motoori M, Kissi K, Miyashiro I, Ohigashi H, Yano M, Ishikawa O, Miyamoto Y. Feasibility of a lateral region sentinel node biopsy of lower rectal cancer guided by indocyanine green using a near-infrared camera system. *Ann Surg Oncol 2010; 17*: 144-151 [PMID: 19774415 DOI: 10.1245/s10434-009-0711-2]

Noura S, Ohue M, Seki Y, Yamamoto T, Idota A, Fujii J, Yasamaki T, Nakajima H, Murata K, Kameyama M, Yamada T, Miyashiro I, Ohigashi H, Yano M, Ishikawa O, Imaka S. Evaluation of the lateral sentinel node by indocyanine green for rectal cancer based on micrometastasis determined by reverse transcriptase-polymerase chain reaction. *Oncol Rep 2008; 20*: 745-750 [PMID: 18813813]

Hirche C, Mohr Z, Kneif S, Doniga S, Murawa D, Strik M, Hünemeir B. Ultrasound-guided colon cancer by sentinel node biopsy using fluorescence navigation with indocyanine green. *Int J Colorectal Dis 2012; 27*: 319-324 [PMID: 21912878 DOI: 10.1007/s00384-011-1106-5]

Liberalie G, Galdon MG, Moreau M, Vankerckhove S, El Nakadi I, Larsimont D, Donckev V, Bourgeois F. Ex vivo detection of tumor lymph nodes of colorectal origin with fluorescence imaging after intraoperative intravenous injection of indocyanine green. *J Surg Oncol 2016; 114*: 348-353 [PMID: 27224200 DOI: 10.1002/jso.24381]

Chen QY, Xie JW, Zhong Q, Wang JB, Lin JX, Lu J, Cao LL, Lin M, Tu RH, Huang ZN, Lin JL, Zheng HL, Li P, Zheng CH, Huang CM. Safety and Efficacy of Indocyanine Green Targeted Lymph Node Dissection During Laparoscopic Radical Gastrorectomy in Patients With Gastric Cancer: A Randomized Clinical Trial. *JAMA Surg 2020; 155*: 300-311 [PMID: 32101269 DOI: 10.1001/jamasurg.2019.6033]

Kwon IG, Son T, Kim H, Hyung WJ. Fluorescent Lymphography-Guided Lymphadenectomy During Robotic Radical Gastrorectomy for Gastric Cancer. *JAMA Surg 2019; 154*: 150-158 [PMID: 30427990 DOI: 10.1001/jamasurg.2018.4267]

Andersen HS, Bennedsen ALB, Burgdorf SK, Eriksen JR, Eiholm S, Toxværd A, Riis LB, Rosenberg J, Gögenur İ. In vivo and ex vivo sentinel node mapping does not identify the same lymph nodes in colon cancer. *Int J Colorectal Dis 2017; 32*: 983-990 [PMID: 28210851 DOI: 10.1007/s00384-017-2779-9]

Watanabe J, Ota M, Suwa Y, Ishibe A, Masui H, Nagahori K. Real-Time Indocyanine Green Fluorescence Imaging-Guided Complete Mesocolic Excision in Laparoscopic Flexural Colon Cancer Surgery. *Dis Colon Rectum 2016; 59*: 701-705 [PMID: 27270525 DOI: 10.1097/DCR.0000000000000608]

Chand M, Keller DS, Josh MI, Devoto L, Rodríguez-Justo M, Cohen R. Feasibility of fluorescence lymph node imaging in colon cancer: FLICC. *Tech Coloproctol 2018; 22*: 271-277 [PMID: 29551004 DOI: 10.1007/s10151-018-1773-6]

Currie AC, Briggie A, Thomas-Gibson S, Suzuki N, Moorghen M, Jenkins JT, Faiz OD, Kennedy RH. A pilot study to assess near infrared laparoscopy with indocyanine green (ICG) for intraoperative sentinel lymph node mapping in early colon cancer. *Eur J Surg Oncol 2017; 43*: 2044-2051 [PMID: 28919031 DOI: 10.1016/j.ejso.2017.05.026]

Schaafsma BE, Verbeek FP, van der Vorst JR, Hutteman M, Kuppen PJ, Frangioni JV, van de Velde CJ, Vahrmeir AE. Ex vivo sentinel node mapping in colon cancer combining blue dye staining and fluorescence imaging. *J Surg Res 2013; 183*: 253-257 [PMID: 23391167 DOI: 10.1016/j.jss.2013.01.003]

Hutteman M, Choi HS, Micog JS, van der Vorst JR, Ashitate Y, Kuppen PJ, van Groningen MC, Löwik CW, Smit VT, van de Velde CJ, Frangioni JV, Vahrmeir AE. Clinical translation of in vivo sentinel lymph node mapping for colorectal cancer using invisible near-infrared fluorescence light. *Ann Surg Oncol 2011; 18*: 1006-1014 [PMID: 21080086 DOI: 10.1245/s10434-010-1426-0]

Xiong L, Gazyakan E, Yang W, Engel H, Hünemeir M, Knuers U, Hirche C. Indocyanine green fluorescence-guided sentinel node biopsy: a meta-analysis on detection rate and diagnostic performance. *Eur J Surg Oncol 2014; 40*: 843-849 [PMID: 24613744 DOI: 10.1016/j.ejso.2014.02.228]

Tokunaga M, Ohyama S, Hiki N, Fukunaga T, Yamada K, Sano T, Yamaguchi T. Investigation of the lymphatic stream of the stomach in gastric cancer with solitary lymph node metastasis. *World J Surg 2009; 33*: 1235-1239 [PMID: 1928280 DOI: 10.1007/s00268-009-9985-6]

Zhou SC, Tian YT, Wang XW, Zhao CD, Ma S, Jiang J, Li EN, Zhou HT, Liu Q, Liang JW, Zhou XZ, Wang XS. Application of indocyanine green-enhanced near-infrared fluorescence-guided imaging in laparoscopic lateral pelvic lymph node dissection for middle-low rectal cancer. *World J Gastroenterol 2019; 25*: 4502-4511 [PMID: 31496628 DOI: 10.3748/wjg.v25.i31.4502]

Ankersmit M, Bonjer HJ, Hamnik G, Schoonmade LJ, van der Pas MHGM, Meijerink WJHJ. Near-infrared fluorescence imaging for sentinel lymph node identification in colon cancer: a prospective single-center study and systematic review with meta-analysis. *Tech Coloproctol 2019; 23*: 1113-1126 [PMID: 31741099 DOI: 10.1007/s10151-019-02107-0]

Cianchi F, Indentinitate G, Paoli B, Ortolani M, Lami G, Manetti N, Tarantino O, Messeri S, Foppa...
C, Badis B, Novelli L, Skalamera I, Nelli T, Coratti F, Perigil G, Staderini F. The Clinical Value of Fluorescent Lymphography with Indocyanine Green During Robotic Surgery for Gastric Cancer: a Matched Cohort Study. J Gastrointest Surg 2020; 24: 2197-2203 [PMID: 31485904 DOI: 10.1007/s11605-019-04382-y]

Gooy JJ, Ryu DG, Kim HW, Park SB, Kang DH, Choi CW, Kim SJ, Nam HS, Kim HS, Son GM, Park BS. Efficacy of preoperative colonoscopic tattooing with indocyanine green on lymph node harvest and factors associated with inadequate lymph node harvest in colorectal cancer. Scand J Gastroenterol 2019; 54: 666-672 [PMID: 31071272 DOI: 10.1080/03055542.2019.1612940]

Kusano M, Tajima Y, Yamazaki K, Kato M, Watanabe M, Miwa M. Sentinel node mapping guided by indocyanine green fluorescence imaging: a new method for sentinel node navigation in gastrointestinal cancer. Dig Surg 2008; 25: 103-108 [PMID: 18379188 DOI: 10.1159/000121905]

Bembeneck AE, Rosenberg B, Wagler E, Gretschen S, Sendler A, Siewert JR, Nährig J, Witzigmann H, Hauss J, Knorr C, Dimmler A, Gröne J, Buhr HJ, Hatzer H, Herbst H, Tepel J, Siphos B, Kleespie A, Koensigraenner A, Stoecklein NH, Horstmann O, Grützmann R, Imdahl A, Svoboda D, Wittekind C, Schneider W, Wehmecke KD, Schlag PM. Sentinel lymph node biopsy in colon cancer: a prospective multicenter trial. Ann Surg 2007; 245: 858-863 [PMID: 17522509 DOI: 10.1097/01.sla.0000250428.46565.7c]

Cahill RA, Bembeneck A, Sirop S, Waterhouse DF, Schneider W, Leroy J, Wiese D, Beufter T, Bilichk A, Saha S, Schlag PM. Sentinel node biopsy for the individualization of surgical strategy for cure of early-stage colon cancer. Ann Surg Oncol 2009; 16: 2170-2180 [PMID: 19492012 DOI: 10.1245/s10434-009-0510-9]

Tummers QR, Boogerd LS, de Steur WO, Verbeek FP, Boonstra MC, Hartgink HH, Frangioni JV, van de Velde CJ, Hartgrink HH, Vahrmeijer AL. Near-infrared fluorescence sentinel lymph node detection in gastric cancer: A pilot study. World J Gastroenterol 2016; 22: 3644-3651 [PMID: 27053856 DOI: 10.3748/wjg.v22.i13.3644]

Kitagawa Y, Takeuchi H, Takagi Y, Natsugoe S, Terashima M, Murakami N, Fujimura T, Tsujimoto H, Hayashi H, Yoshimizu N, Takagane A, Mohri Y, Nabeshima K, Uenoosono Y, Kinami S, Sakamoto J, Morita S, Aikou T, Miwa K, Kitajima M. Sentinel node mapping for gastric cancer: a prospective multicenter trial in Japan. J Clin Oncol 2013; 31: 3704-3710 [PMID: 24019550 DOI: 10.1200/JCO.2013.50.3789]

Miyashiro I, Hiratsuka M, Sasaki M, Sano T, Mizusawa J, Nakamura K, Nishimoto A, Tsuburaya A, Fukushima N, Gastric Cancer Surgical Study Group (GCSSG) in the Japan Clinical Oncology Group (JCOG). 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: 316-322 [PMID: 23933782 DOI: 10.1007/s10120-013-0285-3]

Kinami S, Oonishi T, Fujita I, Tomita Y, Funaki H, Fujita H, Nakano Y, Ueda N, Kosaka T. Optimal settings and accuracy of indocyanine green fluorescence imaging for sentinel node biopsy in early gastric cancer. Oncol Lett 2016; 11: 4055-4062 [PMID: 27313740 DOI: 10.3892/ol.2016.4492]

Lee CM, Park S, Park SH, Jung SW, Choe JW, Sul JY, Jang YJ, Mok YJ, Kim JH. Sentinel Node Mapping Using a Fluorescent Dye and Visible Light During Laparoscopic Gastrectomy for Early Gastric Cancer: Result of a Prospective Study From a Single Institute. Ann Surg 2017; 265: 766-773 [PMID: 27058946 DOI: 10.1097/SLA.0000000000001739]

Weixler B, Rickenbacher A, Raptis DA, Viehl CT, Güller U, Rueff J, Zettl A, Zuber M. Sentinel Lymph Node Mapping with Isosulfan Blue or Indocyanine Green in Colon Cancer Shows Comparable Results and Identifies Patients with Decreased Survival: A Prospective Single-Center Trial. World J Surg 2017; 41: 2378-2386 [PMID: 28508233 DOI: 10.1007/s00268-017-4051-2]

Güller U, Zettl A, Worni M, Langer I, Cabalzar-Wondberg D, Viehl CT, Demartines N, Zuber M. Molecular investigation of lymph nodes in colon cancer patients using one-step nucleic acid amplification (OSNA): a new road to better staging? Cancer 2012; 118: 6039-6045 [PMID: 22684906 DOI: 10.1002/cncr.27667]

Vogelaar PJ, Reimers MS, van der Linden RL, van der Linden JC, Smit VT, Lips DJ, van de Velde CJ, Bosscha K. The diagnostic value of one-step nucleic acid amplification (OSNA) for sentinel lymph nodes in colon cancer patients. Ann Surg Oncol 2014; 21: 3924-3930 [PMID: 24912612 DOI: 10.1245/s10434-014-3820-5]

Croner RS, Geppert CI, Bader FG, Nitsche U, Späth C, Rosenberg R, Zettl A, Matias-Guiu X, Tsuburaya M, Güller U, Stürzl M, Zuber M. Molecular staging of lymph node-negative colon carcinomas by one-step nucleic acid amplification (OSNA) results in upstaging of a quarter of patients in a prospective, European, multicentre study. Br J Cancer 2014; 110: 2544-2550 [PMID: 24722182 DOI: 10.1038/bjc.2014.170]

Hompes D, D’hoore A, Van Cutsen E, Fieuws S, Ceelen W, Peeters M, Van der Speeten K, Bertrand C, Legendre H, Kerger J. The treatment of peritoneal carcinomatosis of colorectal cancer with complete cytoreductive surgery and hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) with oxaliplatin: a Belgian multicentre prospective phase II clinical study. Ann Surg Oncol 2012; 19: 2186-2194 [PMID: 22395983 DOI: 10.1245/s10434-012-2264-z]

Flood M, Narasimhan V, Waters P, Ramsay R, Michael M, Warrier S, Heriot A. Survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastases: A systematic review and discussion of latest controversies. Surgery 2020 [PMID: 33023847 DOI: 10.1016/j.surge.2020.08.016]
Using Bevacizumab-800CW in Patients with Locally Advanced Rectal Cancer. WB. Back-Table Fluorescence-Guided Imaging for Circumferential Resection Margin Evaluation JH, Hospers GAP, Havenga K, Mansfield P, Ajani JA, Badgwell BD. Yield of Staging Laparoscopy and Lavage Cytology for Radiologically Occult Peritoneal Carcinomatosis of Gastric Cancer. Ann Surg Oncol 2016; 23: 4332-4337 [PMID: 27384751 DOI: 10.1245/s10434-016-5409-7]

Kosaka N, Mitsuamga M, Longmire MR, Choyke PL, Kobayashi H. Near infrared fluorescence-guided real-time endoscopic detection of peritoneal ovarian cancer nodules using intravenously injected indocyanine green. Int J Cancer 2011; 129: 1671-1677 [PMID: 21469142 DOI: 10.1002/ijc.26113]

Liberal G, Vankerekhove S, Caldon MG, Ahmed B, Moreau M, Nakadi IE, Larsimont D, Donckier V, Bourgeois P; Group R&D for the Clinical Application of Fluorescence Imaging of the Jules Bordet’s Institute. Fluorescence Imaging After Indocyanine Green Injection for Detection of Peritoneal Metastases in Patients Undergoing Cytoreductive Surgery for Peritoneal Carcinomatosis From Colorectal Cancer: A Pilot Study. Ann Surg 2016; 264: 1110-1115 [PMID: 27828822 DOI: 10.1097/SLA.0000000000001615]

Barabino G, Klein JP, Porcheron J, Grichine A, Coll JL, Cottier M. Intraoperative Near-Infrared Fluorescence Imaging using indocyanine green in colorectal carcinomatosis surgery: Proof of concept. Eur J Surg Oncol 2016; 42: 1931-1937 [PMID: 27378159 DOI: 10.1016/j.ejso.2016.06.389]

Filippello A, Porcheron J, Klein JP, Cottier M, Barabino G. Affinity of Indocyanine Green in the Detection of Colorectal Peritoneal Carcinomatosis. Surg Innov 2017; 24: 103-108 [PMID: 27909239 DOI: 10.1177/1553350616681897]

Liberal G, Bourgeois P, Donckier V; R&D Clinical Applications Fluorescence Imagings (GCAFI). Comments on “intraoperative near-infrared fluorescence imaging using indocyanine green in colorectal carcinomatosis surgery: proof of concept”. Eur J Surg Oncol 2017; 43: 240-241 [PMID: 27720565 DOI: 10.1016/j.ejso.2016.08.025]

Barabino G, Klein JP, Porcheron J, Grichine A, Coll JL, Cottier M. Reply to: Comments on ‘Intraoperative near-infrared fluorescence imaging using indocyanine green in colorectal carcinomatosis surgery: Proof of concept’. Eur J Surg Oncol 2017; 43: 242-243 [PMID: 27780676 DOI: 10.1016/j.ejso.2016.10.001]

Lieto E, Auricchio A, Cardella F, Mabilia A, Basile N, Castellano P, Orditura M, Galizia G. Fluorescence-Guided Surgery in the Combined Treatment of Peritoneal Carcinomatosis from Colorectal Cancer: Preliminary Results and Considerations. World J Surg 2018; 42: 1154-1160 [PMID: 28929277 DOI: 10.1007/s00268-017-4237-7]

Muto M, Horimatsu T, Ezeo Y, Hori K, Yukawa Y, Morita S, Miyamoto S, Chiba T. Narrow-band imaging of the gastrointestinal tract. J Gastroenterol 2009; 44: 13-25 [PMID: 19159070 DOI: 10.1007/s00535-008-2291-5]

Gono K. Narrow Band Imaging: Technology Basis and Research and Development History. Clin Endosc 2015; 48: 476-480 [PMID: 26668792 DOI: 10.5946/ce.2015.48.6.476]

Kikuchi H, Endosc Gono K. Narrow Band Imaging and Peritoneal Metastases in Patients Undergoing Cytoreductive Surgery for Peritoneal Carcinomatosis. J Gastroenterol 2014; 49: 3954-3962 [PMID: 24859934 DOI: 10.1007/s00268-014-3781-8]

Sluiter NR, Vlek SL, Wisjumuller AR, Brandsma HT, de Vet HCW, van Grieken NCT, Kazemier G, Tuyman JB. Narrow-Band Imaging Improves Detection of Colorectal Peritoneal Metastases: A Clinical Study Comparing Advanced Imaging Techniques. Ann Surg Oncol 2019; 26: 156-164 [PMID: 30421052 DOI: 10.1245/s10434-018-7905-5]

Harlaar NJ, Koller M, de Jongh SJ, van Leeuwen BL, Hemmer PH, Kuiffijt S, van Ginkel RJ, Been LB, de Jong JS, Kats-Ugurlu G, Linssen MD, Jorritsma-Smit A, van Oosten M, Nagengast WB, Nizichristos V, van Dam GM. Molecular fluorescence-guided surgery of peritoneal carcinomatosis of colorectal origin: a single-centre feasibility study. Lancet Gastroenterol Hepatol 2016; 1: 283-290 [PMID: 28404198 DOI: 10.1016/S2468-1253(16)30082-6]

Schaap DP, de Valk KS, Deken MM, Meijer RJP, Burggraaf J, Vahrmeijer AL, Kusters M; SGM-101 study group. Carcinobromyic antigen-specific, fluorescent image-guided cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for metastatic colorectal cancer. Br J Surg 2020; 107: 334-337 [PMID: 31960953 DOI: 10.1002/bjs.11523]

de Jongh SJ, Tjasma JJJ, Koller M, Linssen MD, Vonk J, Dobosz M, Jorritsma-Smit A, Kleinbeuker JH, Hopsers GAP, Havenga K, Hemmer PHJ, Karrenbeld A, van Dam GM, van Etten B, Nagengast WB. Back-Table Fluorescence-Guided Imaging for Circaumferential Resection Margin Evaluation Using Bevacizumab-800CW in Patients with Locally Advanced Rectal Cancer. J Nucl Med 2020; 61: 655-661 [PMID: 31628218 DOI: 10.2967/jnumed.119.23355]
