# Near-infrared fluorescence image-guided surgery in esophageal and gastric cancer operations

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**Abstract**

Near-infrared fluorescence image-guided surgery helps surgeons to see beyond the classical eye vision. Over the last few years, we have witnessed a revolution which has begun in the field of image-guided surgery. Fluorescence technology using indocyanine green (ICG) has shown promising results in many organs, and in this review article, we wanted to discuss the 6 main domains where fluorescence image-guided surgery is currently used for esophageal and gastric cancer surgery. Visualization of lymphatic vessels, tumor localization, fluorescence angiography for anastomotic evaluation, thoracic duct visualization, tracheal blood flow analysis, and sentinel node biopsy are discussed. It seems that this technology has already found its place in surgery. However, new possibilities and research avenues in this area will probably make it even more important in the near future.

## Introduction

Over the last few years, near-infrared (NIR) fluorescence technology using indocyanine green (ICG) has shown promising results in image-guided surgery for many organs. Initially proposed by Kitai *et al.* in NIR fluorescence (NIRF) sentinel node biopsy (SNB) using ICG as a fluorophore, NIRF is currently used in various applications(1) worldwide. ICG is a water-soluble anionic amphiphilic tricarbocyanine probe(2). Its small 1.2nm diameter is accountable for the fast migration of this fluorophore in the lymphatic system. With the use of an NIR charge-coupled device, the excitation of this fluorophore is 778nm, and its emission is 830nm. This fluorescence tool has also found a place in upper gastrointestinal surgery. In this literature review, we describe 6 main domains, namely identification of lymphatic structures, tumor localization, angiography of blood supply of different organs, thoracic duct visualization, tracheal blood flow analysis, and sentinel lymph node biopsy navigation.

## Identification of lymphatic structures

A proper lymphadenectomy is a key issue associated with optimized gastric cancer outcomes since lymphadenectomy is recommended in advanced gastric cancer surgery(3), (4). Intraoperative lymphography may guide the surgeon in an appropriate lymph node (LN) dissection. The first fluorescence-guided lymphography using ICG for gastric cancer was performed by Herrera-Almario(5). It is clear that NIRF-guided lymphography has improved the visualization of LNs along gastric vessels. In a publication by Lan *et al.*,(6) more resected LNs were found in stations 4d and 6. In a randomized control trial by Chen *et al.*, it was clearly shown that a significantly higher number of LNs were dissected, and improved quality in optimized lymphadenectomy was achieved(7). Fluorescence lymphography may also be used for tailored lymphadenectomy, as presented by Baiocchi(8) where some nodes in station 11p would have been left in one patient, or in two patients. Additional potential LNs outside standard lymphadenectomy may have been stained with this fluorophore. In a study by Kim *et al.*, after complete lymphadenectomy, some ICG-stained tissue remained in 28% of patients. However, histologically confirmed LNs were only found in 4% of cases. In an article by Rho *et al.*, a mean of 2.1 non-fluorescent stations were found. This information, together with a 100% sensitivity in detecting metastatic LNs in fluorescent stations and a 100% negative predictive value in their study, may lead to the tailored extension of lymphadenectomy. However, further research is required, especially for obese patients considering the limited fluorescent penetration of ICG through adipose tissue(9). Some major limitations of this method need to be addressed. First, the problem of nodal involvement may limit the spread of ICG to

all required lymph node stations(10). Secondly, the effect of preoperative chemotherapy should be widely explored(11). Additionally, time, side, and depth of ICG injection should be standardized(12). Interestingly, Cianchi *et al.*(13) have shown that, in the case of linitis plastica, the occlusion of lymphatic vessels limits the spread of ICG. We must also recall preoperative endoscopic submucosal dissection (ESD), which may cause fibrosis and hamper proper lymphatic flow(9).

**Tumor localization**

Injection points for lymphography were used by Liu *et al.* as a landmark for early gastric cancer location during partial gastrectomy evaluation of the resection margin(14). Similar results of fluorescent marking with ICG were presented by Ushimaru *et al.*; in a group without ICG injection, a positive resection margin was found in 5% of cases, whereas in a group with ICG tumor position marking, it was found in 0% of cases(15). Tanaka *et al.* proposed a dosage of 0.1mL at a concentration of 0.5mg/mL for optimal visualization of injection sites(16). Diameters of ICG injection sites were much smaller (i.e. 21mm) than historical controls with India ink (52mm). Another valuable idea is the creation of a fluorescent rubber band generated from ICG mixed with a liquid rubber solution and placed endoscopically on the porcine stomach and colon. The localization of these clips was easily achieved, and the authors differentiated separate clips during observation. Additionally, the resection margins were sufficient after specimen extraction(17). Waiting for targeted fluorophores to become widely clinically available, this easy method may be used as a position of safe transection line during gastrectomy. Initial results of intraoperative imaging of colorectal cancer using a carcinoembryonic antigen (CEA)-targeting agent, namely SGM-101, were recently published, and a potential extension of these results to gastric cancer is anticipated(18).

**Angiography of blood supply of different organs**

After esophageal and gastric resection surgery, failure of anastomotic blood supply represents one of the main problems associated with complications. Intraoperative evaluation of blood perfusion using ICG is a new method which helps to predict anastomotic side leakage(19). Graft perfusion is an important factor of anastomotic integrity. It is a major clinical problem, with leakages in the range of 5 to 20% after esophagectomy(20–24), 1.2 to 6.7% after gastrectomy(25–29), and 0.5 to 6% after sleeve gastrectomy in bariatric surgery(30–33). In daily practice, tissue perfusion is evaluated using tissue color and vessel pulsation. Both are surgeon-dependent, and more reproducible objective methods for evaluation of graft viability

are necessary. In the literature review by Jansen *et al.*, several methods were examined, such as laser speckle contrast imaging, gastric tonometry, Doppler flowmetry, spectroscopy, infrared thermographic imaging, optical coherence tomography, and angiography(34–37). None of these approaches have been widely accepted in routine practice, mainly because of low reproducibility. NIR angiography using ICG has recently been adopted in many centers. Data from available studies are listed in Table 1 (38,39,48–57,40,58,41–47).

In a meta-analysis by Slooter *et al.*, a change in management based on ICG guidance was found in 24.55% of cases(59). The researchers also showed that less anastomotic leakage and graft necrosis were found in the ICG group, with an odds ratio (OR) of 0.30. The method of fluorescence angiography in the case of esophagectomy with gastric conduit anastomosis also revealed some important factors, which are discussed below.

- Time of visualization:

Conduit perfusion fluorescence angiography takes a median of – 37.5s(60). Shimada *et al.* described good visualization of the gastric cancer vasculature at the greater curvature after 1 min and visibility of the mucosal arterial network after 2 min(61). Karampiris *et al.*(46) presented that ICG angiography took 173s (± 74s), with no significant impact on operative time. In a publication by Mori *et al.* In gastric cancer patients, the time difference between ICG appearance on one or the other side of the anastomosis was an independent predictor of postoperative anastomotic leakage(62). in addition, different times of visualization for the gastric, jejunal, and duodenal sides were analyzed after total or subtotal gastrectomies(63).

- Complications:

The only temporal side effect of ICG intravenous injection and vascular angiography is a short drop in oxygenation immediately after injection. As presented by Murawa *et al.*(64), the saturation dropped to 90% without any further consequence. No other complications related to technical failures of different camera systems or other adverse events were reported.

- Quantification and validation:

Only a few studies have analyzed objective quantification of ICG angiography using an intensity and or time of fluorescence(44,45,49,52,54). The first description of different times of ICG fluorescence between the root of the right gastroepiploic artery and the tip of the conduit in patients with anastomotic leakage was described by Kumagai *et al.*(54). Inflow and outflow delays in perfusion analyzing two points of conduit vascularization was proposed by Yukaya *et al.*(52).

Koyanagi *et al.*(49) assessed fluorescence angiography flow speed by analyzing the length of the GC, the anatomical connection between the right and left gastroepiploic arteries, and the speed of NIR angiography. They found that flow speed was an independent prognostic factor for anastomotic leakage, with 1.76cm/s or less as a cut-off value. Interestingly, Noma *et al.* proposed a 30s rule as a cut-off time of demarcation for the optimal cervical anastomotic side. However, Kumagai *et al.*(44) prolonged this cut-off time up to 90 sec, obtaining promising results. In a publication by Nishikawa *et al.*, a quantitative analysis of blood flow using thermal imaging as compared to ICG angiography was presented to evaluate conduit viability(65). Both methods showed promising outcomes which need to be studied in the future.

- Intraoperative changes in surgical procedures:

In the systematic review by Van Daele *et al.* including 1,192 esophagectomy patients, ICGA was used perioperatively in 758 patients to guide esophageal reconstruction. A change in surgical strategy was found in 93 patients (12.4%). In 4 studies, the authors resected the tip of the conduit in the case of poor perfusion if sufficient length was obtained(66). Three authors changed the side of the anastomosis from end-to-side to end-to-end(43,47,64). Another 4 authors performed supercharge or super drainage arterial or venous anastomosis, increasing arterial perfusion or improving venous drainage of the cervical anastomosis(43,45,47,61). Modification in the surgical strategy led to an anastomotic leakage rate of 6.5%, which is much less than 20.5% without fluorescence angiography(66). This result is comparable to 6.3% of anastomotic leakage in the well-perfused group of patients.

- Dosage:

In the available literature, a wide range of ICG concentrations and volumes are used. In an animal model published by Diana *et al.*, a dose of 0.5mg/kg was found to be optimal using a virtual reality (VR) rendered software(67–69). Based on their studies, a dose of 0.2 to 0.5mg/kg is currently used in most studies. In the guidelines, it is proposed to use 2.5mg of ICG for colorectal and gastroesophageal anastomosis assessments(70).

Colon and small intestine conduits:

Although a gastric conduit is used after esophagectomy in some groups of patients, in most cases, other organ anastomoses with the remnant esophagus is also possible. In the case of free jejunal graft after pharyngoesophagectomy in a group of 26 patients, fluorescence angiography was performed(51). Five patients were diagnosed with venous anastomotic deficiency. In 3 cases, after fluorescence angiography, anastomosis was revised intraoperatively, and in 2 patients, an additional free jejunal graft transfer was required. The authors proposed that

T1/2max>9.6 sec might be a cutoff value to predict venous malperfusion in this group of patients.

A case report of a left colon supercharged with venous and arterial anastomoses in the neck conduit after esophagectomy has been presented(71). In a group of 23 patients, 1 patient required ileocolic graft reconstruction after esophagectomy in a report by Shimada *et al.*(61).

**Tracheal blood flow analysis**

Ischemia and necrosis of the tracheobronchial tree represent a severe complication which occurs after esophagectomy. This may originate from preoperative radiotherapy, trauma during surgery, or devascularization of the trachea and bronchus during esophageal resection. ICG fluorescence imaging can be used to assess tracheal blood perfusion during esophagectomy. Only one study published by Sugimura *et al.* focused on fluorescence imaging of the tracheal tree during this procedure(72). The researchers also considered the impact of preoperative treatment on the preservation of the right tracheobronchial artery. They visualized fluorescent tracheal blood flow in all included patients. Using a quantitative assessment, they found that lower trachea blood flow is linked with postoperative trachea ischemic changes in sputum discharge. Additionally, they revealed that resection of the right bronchial artery tended to be linked with a lower tracheal blood flow. In the case of resection of the right bronchial artery, preoperative neoadjuvant chemotherapy did not influence blood flow of the tracheobronchial tree.

Other methods to investigate tracheal blood flow changes during esophagectomy have been described. According to Fujita *et al.*, the hydrogen gas clearance method using electrochemically generated hydrogen in dogs showed that the ligation of the right bronchial artery is associated with 25% of tracheal blood flow. The same method used in 8 patients showed that esophagectomy decreased the tracheal blood flow by 43%, and by stopping the blood flow through the right bronchial artery, an additional 25% drop was found. Future studies are anticipated regarding this valuable topic.

**Thoracic duct visualization**

Chylothorax represents a major complication after esophagectomy, as reported in up to 43% of patients(73). Vecchiato *et al.* identified thoracic ducts in 19 patients undergoing minimally invasive esophageal resections(73). Percutaneous injection of IGC in the inguinal node area was performed, and the thoracic duct was visualized after 52.7 min. In 2 patients, due to oncologic radicality reasons, the successful ligation of the thoracic duct was performed under

fluorescence guidance. No postoperative chylothorax was noted. Some case reports have been published describing fluorescent thoracic duct fistula localization. In studies by Matsutani *et al.* and Kaburaki *et al.*, fluorescent node lymphography patients underwent reoperation on postoperative day 10, or in 2 patients, on postoperative day 28(74). ICG was injected into the bilateral inguinal node area subcutaneously, and the thoracic duct was visualized after 10 to 14 min(74,75). Another possibility of an injection site was proposed by Kaburaki *et al.* where 2ml of IGC were injected into the small bowel to identify the thoracic duct and to visualize the fistula in one patient.

**Sentinel lymph node biopsy (SNB) navigation**

Gastric cancer:

Gastrectomy with an appropriate lymphadenectomy, a procedure which has been standardized over many years, is the treatment of choice in gastric surgery(76,77). At early stages of gastric cancer, a less extensive resection and LN evaluation may be possible. Because of complex gastric lymphatic drainage, the concept of SNB is still under investigation. A systematic review by Cardoso *et al.* showed that the detection rate, sensitivity, and accuracy for the dye method and radioisotopes are similar(78). However, the negative rate was much higher for the dye method (34.7%) as compared to radioisotopes (18.5%). The meta-analysis by Wang *et al.* showed the diagnostic value of tracers, no matter what type was used(79). The dual tracer method seems to be most accurate. Looking for a new dye in 2004, for the first time, Nimura *et al.* proposed infrared electronic endoscopy for fluorescent ICG sentinel LN (SLN) visualization in GC(80). In a group of 84 patients with GC, fluorescent navigation detected all 11 patients with metastatic LNs, but four of the patients could not be visualized. The first SLN mapping with ICG which used NIR imaging was presented by Soltesz *et al.* in an animal model. Later on, mapping was reported in GC patients by Cusano *et al.*(81).

The method of ICG injection between the subserosa and submucosa represents another major issue(12). Some studies showed that a higher submucosal sensitivity could be found(12). The biggest concern about SLB in GC is that the tracer cannot come into metastatic LNs. In addition, the stomach lymphatic drainage is multidirectional and complex because cancer cell blockage of lymphatic lymph vessels and skip metastasis are possible in up to 11% of patients with LN metastasis. Another important issue associated with ICG LN biopsy is that it passes through higher tier LNs. An intraoperative injection shows a lower sensitivity as compared to a preoperative injection(82). It is an indication that we should wait about 20 min after intraoperative dye injection for optimal SLN mapping. In this study, false negative SNs and

metastatic non-SNs were found in the same group as SNs. Researchers have proposed to perform lymphatic basin dissection of LNs rather than using the pick-up method(83). An interesting possibility of CEA-targeted SLN detection in gastric cancer has been proposed by a Dutch group using SGM-101(84). The results of this study are awaited.


Esophageal cancer:

The concept of SLNs in esophageal cancer remains controversial as compared to other gastroesophageal cancers(43,85). Even in the case of T1 cancer, the rate of LN metastasis may reach up to 45%(86,87). Another challenge is a complicated lymphatic flow, which may vary from cervical to abdominal LN stations. To make it even more complicated, in about half of the patients with only one metastatic LN, skip metastasis may occur in distant lymphatic areas(88). This is even possible in the case of the negative involvement of the first regional LN compartment. The multidirectional lymphatic spread is a limitation of the usage of a blue dye. In addition, blue-stained LNs are often similar in color to antirachitic mediastinal nodes(89). In the case of the lower esophagus in the cardiac region, this is difficult to evaluate with preoperative lymphoscintigraphy with radiocolloids(90,91).

Lymphatic node mapping with radioactive tracers was first described by Kitagawa in 2000. Additionally, in their first pilot human trial, Krista *et al.* showed that ICG could be used to map LN drainage in esophageal cancer. Their study was performed in a group of 10 patients in whom a peritumoral injection of 2.5mL of ICG:HSA (indocyanine green:human serum albumin) was used to visualize the lymphatic pathway in esophageal cancer. In a study including a group of 9 patients with distal esophageal cancer, Schlottmann *et al.* presented intraoperative identification of LNs. The ICG was injected submucosally during endoscopy. Eight patients had metastatic LN along the left gastric artery, and one of them showed supradiaphragmatic LNs. In a group of 6 patients with distal esophageal cancer, Helminen *et al.* showed that intraoperative lymphatic mapping with NIR imaging could be useful to detect lymphatic stations which most likely present with metastatic disease and to guide the tailored extension of traditional lymphadenectomy. A Japanese study including 20 patients used the endoscopic submucosal injection of a dye called iopamidol with computed tomography (CT) to identify lymphatic drainage in SN(92). The comparison made in the group with ICG identification of SLN using CT lymphography was 100% and 95% in the ICG fluorescence group. One negative case of bulky metastasis was found. The authors pointed out that, during the long period between injection and LN dissection, the second and third lymph node stations were stained. The first usage of ICG LN mapping during minimally invasive esophagectomy was presented

by Hachey *et al.*(93). These authors used either ICG alone or IGC with HSA. Fluorescent LNs were not visualized in the case of three out of five patients with ICG usage without HSA. In the case of ICG with HSA, LN was fluorescent in all 4 patients. The visualization of fluorescent LN was difficult because of the shine-through effect.

A recent meta-analysis by Jimenez-Lillo *et al.* based on 6 studies revealed a high detection rate of ICG SNB in esophageal cancer of up to 89%(94). In addition, a trend towards a lower detection rate with a longer time between ICG injection and SLN biopsy was found. The authors also found a high rate of LN metastasis (84%). However, specificity was low (15%) because almost all nodes were stained with ICG. No difference was found in the type of esophageal cancer or the type of surgery performed.

**Conclusion**

New technology for NIR fluorescence image-guided surgery is used during gastroesophageal operations. In our review, we described 6 main domains in which research regarding the use of ICG fluorescence can be found. Although this technique is relatively new, many surgeons are looking for ways to implement such an approach in their daily practice. Surgery for gastric and esophageal diseases is complex, and it is sometimes associated with relatively significant complications. We have to look for and use all possible tools which will not only help to improve oncological results but also to decrease morbidity and mortality of such operations. Fluorescence image-guided surgery may be a good solution to improve surgical outcomes after gastroesophageal operations.

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