Key clinical applications for indocyanine green fluorescence imaging in minimally invasive colorectal surgery

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Abstract

Near-infrared indocyanine green (ICG) fluorescence imaging has gained solid acceptance over the last years, and rightly so, as this technology has so much to offer, especially in the field of minimally invasive surgery. Firm evidence from ongoing and future studies will hopefully transform many of the applications of ICG fluorescence into the standard of care for our patients. This review examines the current status of ICG fluorescence for assessment of bowel perfusion, lymphatic mapping as well as intraoperative localisation of ureter in light of the published academic literature in English.

Keywords: Bowel perfusion, fluorescence imaging, indocyanine green, lymphatic mapping, ureter localisation

INTRODUCTION

Because indocyanine green (ICG) is cheap, readily available and safe, it is the most employed fluorophore in the clinical setting of general surgery. ICG is a water-soluble, tricarbocyanine compound dye that absorbs near-infrared (NIR) light at 800–810 nm and emits it at slightly longer wavelengths, 830 nm. It has been approved by the Food and Drug Administration and the European Medicines Agency for both intravascular and interstitial application. After intravenous injection, it binds to plasma proteins with a half-life of 3–5 min and is eliminated by the liver in 15–20 min, thus, it is ideal for repeated applications. The fluorophore remains confined in the intravascular compartment until elimination, in due time after excitation, it provides information about tissue perfusion. When injected into tissues, the ICG migrates through lymphatic vessels into lymph nodes (LNs), where it deposits in macrophages, thereby providing information about lymphatic drainage basin.[1]

Special NIR imaging system, which is able to both excite and detect the fluorophore, is needed. Many are available on the market: Stryker 1588 AIM Platform (Portage, USA), PINPOINT (Novadaq, Canada), D-Light NIR/ICG (Karl Storz, Germany), SPY Elite Kit (LifeCell Corporation, USA) and others. At our institution, we use the D-Light imaging system from Karl Storz for laparoscopic surgery and Firefly da Vinci system for robotic surgery (Intuitive Surgical, USA). All of these systems have a conventional white light working mode but are then activated into NIR mode after ICG is applied.[2]

This review examines the current status of ICG fluorescence for the assessment of bowel perfusion, lymphatic mapping as well as ureter localisation in light of the published academic literature in English.
of the published academic literature in English. PubMed and Scopus databases were searched in a systematic way to retrieve the relevant studies included in our review.

**Bowel perfusion**

Causes of anastomotic leaks (AL) are multifactorial, however, perfusion of the bowel segments to be joined plays a key role; inadequate blood flow results in the failure of anastomotic healing and subsequent leakage. AL increases not only the morbidity and mortality but was also found to increase the risk of local cancer recurrence.

There is a particular risk for AL when anastomoses are performed in the most proximal and the most distal parts of the gastrointestinal tract. However, large retrospective cohort studies show, that approximately 20% of the colorectal anastomoses leak.

Surgeons evaluate bowel perfusion intraoperatively on the basis of the colour of the bowel wall, the presence of bowel peristalsis, bleeding from the edges of the bowel as well as by trying to palpate pulsations of mesenteric arteries. The sensitivity of approximately 60% and a specificity of nearly 90% of such macroscopic assessment show, however, that predicting the AL is a difficult task even for experienced surgeons, as was shown by Karliczek et al. Moreover, in minimally invasive surgery intestinal colour is more difficult to assess and direct palpation of blood vessels to the anastomosis is not possible. Many studies have shown that ICG fluorescence angiography can effectively demonstrate bowel perfusion when injected intravenously, both before and after the anastomosis is performed. The true impact of such «in real time» demonstration of perfusion is, however, not yet truly known.

van Manen et al. reviewed 21 studies that used ICG for the evaluation of colorectal anastomoses. There was a wide variation in the reported change of surgical plan (3.7%–40%), while the rate of AL with using ICG was evaluated by some authors only. The rate of AL was thoroughly analysed by Degett and others in their work, in which they screened almost 800 papers and then reviewed 14 of them. Ten studies (n = 916) included patients with colorectal anastomoses, and ICG assessment of perfusion was associated with a significantly reduced rate of AL (3.3% vs. 8.5%). Nevertheless, due to heterogeneity of the studies, the comparison between them was limited, and no firm conclusion could be made. The case-matched retrospective study, done by Kin et al., did not confirm aforementioned results. Their case matching produced comparable 173 pairs, patients with and without the intraoperative angiography. There was no statistically significant difference between the groups in the rate of developed AL, despite the fact that the intraoperative ICG angiography did change surgical management in several patients by changing the proximal point of transection. However, the retrospective nature of this study and matching the patients to a historical control group are limitations of this study and that could also be a reason for the disparity of its results to those of other studies.

Despite the fact that more and more published reports support the concept that intraoperative assessment of perfusion affects the surgical management and patient outcomes, including the incidence of AL, there is still a lack of randomised controlled trials powered to have big enough samples, that will hopefully confirm the positive impact on AL rate and define the standard of use of this technology. Some such studies are on-going, one of them is IntAct, which is a multicentre randomised controlled trial comparing surgery with intraoperative fluorescence angiography against standard care (surgery with no IFA) for patients with rectal cancer. Over 3 years, this study wants to recruit as many as 880 patients from 25 European centres that will be followed up for 90 days. The primary end-point of the study is the rate of clinical AL at 90 days following the surgery.

Besides reducing the AL rate, ICG angiography could also be an important adjunct in the concept of highly selective diversion of anastomosis after total mesorectal excision for rectal cancer, done either by «traditional» laparoscopic total mesorectal excision (TME) or transanal TME [Figure 1]. Routine diversion is being more and more debated as the benefits often do not outweigh the disadvantages. Data from a comparative cohort study, albeit single institutional, published by Blok et al., show that such «on-demand» diversion did
ICG NIR fluorescent angiography was proven for directly visualizing perfusion in the gastrointestinal tract. However, due to heterogeneous studies and lack of high level of evidence, the real clinical impact of this technique is so far still inconclusive.

The other disadvantages of ICG FA are that the evaluation of fluorescence is still mainly subjective as objective cut-off levels for sufficient perfusion are still not established. There are some published reports, where authors tried to establish a method to quantify perfusion in ICG fluorescence angiography in animal models. Results confirmed a strong correlation between regional blood flow and the slope of the fluorescence curves, with acceptable correlation to developed algorithms. The clinical application of this interesting concept is still pending. Some studies evaluated the possibility to quantify the assessment of intestinal perfusion by reviewing recorded video images and creating a time-fluorescence intensity curve at the point of bowel transection. The difference in fluorescence between maximum and baseline had a sensitivity of 100% and specificity of 92.5% for predicting the AL. Another study was done by Son et al. They tried to quantitatively evaluate perfusion patterns using ICG by measuring the fluorescence intensity of colonic flow sequentially, thereby producing perfusion graphs using a video analysis and modelling tool. Using the fluorescence slope and time ratio, such perfusion patterns could potentially be applied to detect segments of poor colonic perfusion.

Despite the fact, that these studies are promising, at present, the perfusion assessment remains subjective, until the quantitative models will be validated by controlled trials.

**Lymphatic mapping**

The concept of fluorescence lymphatic mapping was established for sentinel node (SN) detection in breast, melanoma, penile, vulvar and other cancers.

The sentinel lymph node (SLN) identification and biopsy represented a big shift from extensive resections, possibly plagued with high morbidity rates, to more individualised care. Unfortunately, to date, the concept works best for patients with melanoma and breast cancer. Its clinical application for other solid tumours is still limited, and the prognostic value of SLN in colon cancer is still under debate and remains controversial, as the methods, materials and patient selection vary by institution and surgeon. Van der Zaag and others in their systematic review of all published studies of SN in colorectal cancer analysed the diagnostic accuracy of the procedure. Their study is a very thorough assessment of the test performance characteristics of the SN procedure reported in the literature. Out of 98 potentially eligible studies they finally analysed 57, including 3934 patients. Identification rate was an overall acceptable (92%), with higher identification rates for colon cancers than rectal cancers. Their results show that SN procedure in colorectal cancer has an overall sensitivity of 70%, with increased sensitivity and refined staging in early-stage colon cancer. The opposite is true for advanced cancers, arguably because tumour cells block lymphatic system changing the lymphatic drainage. Such altered lymphatic flow is also seen due to radiotherapy-induced fibrosis in rectal cancer. An accompanying false negative rate of approximately 30% means that the pathological examination of only the SLN cannot replace the routine examination of complete excised mesentery. However, in contrast to breast cancers and melanomas, SN mapping in colorectal cancer patients does not have therapeutic implications, but rather its purpose is to refine staging. Emile et al. reviewed the use of ICG NIR fluorescence SLN mapping in patients with colorectal cancer. Twelve studies including 248 patients were analysed, where authors used different devices for generation of NIR fluorescence and the time of its application for SLN detection varied from intraoperative, *ex vivo*, to both intraoperative and *ex vivo*. As far as technical aspects of ICG injection were concerned, the studies used different concentrations and doses of the dye as well as different injections sites. The results of their systematic review with meta-analysis showed that the median sensitivity, specificity and accuracy rate were 73.7, 100 and 75.7. The pooled sensitivity and specificity rates were 71% and 84.6%.

Surgical resection is the mainstay treatment of the colon cancer. Radical resection confers the greatest chance for patients’ long-time survival; thus, primary tumour with associated LN basin should be resected. When excising the tumour, all the resection margins must be free of disease (R0 resection). This is relatively consistently achieved; however, the extent of mesenteric lymphadenectomy is variable. *En bloc* resection of lymphatic basin that drains the tumour is a pillar in achieving local control of the disease, but it is also a basis for cancer staging that drives the decision for appropriate adjuvant treatment planning. Hence, it affects overall survival. The AJCC recommends that at least 12 LNs are to be harvested if the final staging is to be accurate.

Following the same sound principles of rectal surgery (TME), a complete mesocolic excision (CME) with
central vascular ligation (CVL) assures resection of colon carcinoma using embryological tissue planes along with the entire regional mesocolon in an intact peritoneal and fascial line package. Proponents of CME concept argue that such technique brings along a significantly better overall survival due to a greater number of LNs harvested and oncologically superior specimen. Therefore, and based on results of some cohort studies, CME concept became a standard in many centres and is also included in the German guidelines for treatment of colorectal cancer.

True consensus for CME is, however, lacking, as there are concerns over increased morbidity after such extended resections. Lymphatic mapping could therefore, potentially identify the drainage LN basin with its true status and possible aberrant drainage roots. Hence, a so-called »tailored« instead of »radical« lymphadenectomy could be done, avoiding the need for CME with the associated risks for post-operative morbidity.

Lymphatic mapping philosophically differs from SLN identification in terms of selective removal of the mesocolon draining a tumour. The technology could lead to a more precise minimally invasive surgery, guiding to an optimal oncologic resections without the need for risk-associated CME. Regardless of CME, ICG fluorescent lymphangiography could elucidate the correct mesocolic resection margin, resulting in better lymphadenectomy as well as influencing the recommendations for adjuvant therapy. Second, aberrant LNs, not seen on pre-operative imaging or acknowledged during the operation, could be appreciated and removed. This was clearly shown by Chand et al. in their prospective pilot study of colon cancer patients undergoing curative laparoscopic resection. They evaluated ICG fluorescent lymphangiography in ten consecutive patients. In all of them, lymphatic channels were seen at least to some extent, and moreover, eight had drainage to SLN. In two cases, the resection was extended due to the discovery of additional LN, in both cases, these were positive on the final pathology.

Cahill et al. found that four out of 18 analysed patients had fluorescein SLN outside the previously planned resection area. Similar results were reported by Nishigori et al. They performed ICG fluorescent visualisations in 21 patients, of blood and lymph flow as well. Their surgical plan of the lymphadenectomy had to be changed in 23.5%. According to their results, metastatic rate of ICG-positive nodes was 10%, and the metastatic rate of ICG-negative nodes was 5.3%.

Even if we accept CME with CVL as a state-of-the-art colon cancer treatment, thereby neglecting voices of concern over post-operative morbidity, ICG fluorescent lymphatic mapping could be very useful in laparoscopic surgery for colon cancer located in the hepatic or splenic flexure. Lymphatic drainage at these sites can vary, and the precise site of lymphatic dissection is uncertain.

Cancer in the splenic flexure has several lymphatic drainage roots. These can be the left branch of the middle colic artery and left colic artery (LCA) areas in addition to the left accessory aberrant colic artery when present. Moreover, drainage pathways to the intraparenchymal node region and the splenic hilum are also possible.

These kinds of lymph flow patterns were evaluated by Watanabe et al. in their study, in which they included 31 patients with non-metastatic splenic flexural cancer with a pre-operative diagnosis of N0. According to their results, the LN dissection at the root of the inferior mesenteric vein (IMV) is important; however, both the middle colic artery and the LCA may not necessarily need to be ligated. Based on their findings, they also recommended specific CME types for different tumour localisations: For cancers in the first part of the descending colon, a CME with LN dissection of the LCA and the root of the IMC areas is to be undertaken; distal third of the transverse colon cancer requires CME with lymphadenectomy of the MCA and the root of the IMV areas. Colon cancer, located in splenic flexure, can have lymphatic drainage in different directions. Results of their study did not show lymphatic drainage to both the LCA and MCA; hence, they believe that ligation of both vessels is not absolutely needed.

Surgery in rectal cancer surgery is much more straightforward. Mesorectum must be excised, either partially or in total. The latter technique (TME) involves en bloc removal of the entire mesorectum, including associated vascular and lymphatic structure, fatty tissue and mesorectal fascia as a »tumour package« through sharp dissection. Dissection must be precise (along the embryiological avascular areolar plane, between the mesorectal fascia propria and the fascia of the pelvic sidewall) and done in a sharp, not blunt, manner.

ICG fluorescent guidance could, therefore, help mainly in therapeutic lateral pelvic node dissection, with the purpose of visualising LNs in real time.

According to systematic review by Emile et al., best outcomes are to be expected if ICG is given preoperatively via colonoscopy submucosally, in a concentration, dependent on the body weight (0.25 mg/kg). When applied intraoperatively, it can be done so completely
intracorporeally like described by Watanabe or Nishigori. The alternative is the technique reported by Chand et al. When operating on their patients, they laparoscopically ligated the main vascular pedicle (the ileocolic artery or inferior mesenteric/ascending ICA) and mobilised the colon. Subsequently, they extracorporeally percutaneously used a transport system with a wound retractor and administered subserosal injection of ICG in four sites around the tumour. This is also the technique employed at the moment at our institution [Figure 2].

**Intraoperative ureter localisation**

The iatrogenic ureteric injury is a complication most often seen in gynaecologic surgery, with reported incidence from 0.2%–2.5% to as high as 10%–30% for routine gynaecologic pelvic operations and radical procedures for malignant conditions, respectively. Fortunately, the injuries to the ureter are much more rare in colorectal surgery. However, the morbidity associated with it remains significant, even more so, as the majority of cases are unrecognised during the index operation. Moreover, the reported incidence looks to be much higher for minimally invasive colorectal resection as opposed to open surgery, being 0.66% and 0.15%, respectively.

To reduce the incidence of ureteral injury, it is essential to accurately identify the ureters (primary prevention), as well as to recognise such injury as early as possible, which allows for a rapid repair (secondary prevention). Several risk factors predispose ureters to the iatrogenic injury during colorectal surgery. Some of them distort the normal anatomy, such as endometriosis, pelvic masses and congenital anomalies. Others cause correct identification and dissection of the ureters difficult like radiotherapy, previous pelvic operations or pelvic inflammatory disease. Nevertheless, most ureteral injuries, in fact, occur in patients lacking these risk factors. During minimally invasive surgery, the surgeon lacks tactile feedback and must rely primarily on visual cues. Therefore, techniques that emphasise such cues to primarily and secondarily prevent ureteral injuries should be employed.

Lee et al. reviewed the major techniques used to prevent iatrogenic ureteral injuries and assessed their efficacy during robotic surgery. On top of this, they also examined the use of ICG and subsequent visualisation using NIR fluorescence to prevent iatrogenic ureteral injuries. By cystoscopical insertion of ureteral catheter into one or both ureters prepared ICG is subsequently injected into the lumen of ureter, thereby allowing for the ureter to be greenly illuminated under NIR. Clamping of the ureteral catheters minimises leakage of ICG that binds proteins on the urothelial layer of the ureter, reversibly staining the inner lining of the ureter. The fluorescence can be visualised after approximately 5 min following the injection, lasting over 3 h. Because ICG fluorescence penetrates tissue, the entire course of the ureters can be precisely localised, even when the ureters are embedded in surrounding adipose or fibrotic tissue or are anatomically distorted. There are two clinically relevant features for intraureteral ICG application, that must be taken into account. First of all, it is not yet approved by the FDA, so the surgeons must disclose that intraureteral ICG is an off-label use. Second, it still brings along at least some invasiveness, because it requires instrumentation of the bladder and the ureters, or at least ureteric orifice. Although insertion of ureteral stents is generally considered to be safe, causing only transient haematuria, occasionally it may lead to more serious complications such as reflux anuria. This is why other dyes for the use with NIR fluorescence that can be intravenously administered and is cleared through the kidneys are being tested. Methylene blue is a dye that has long been used in humans with a good safety profile. The first successful use for ureter delineation was reported by Verbeek et al. in 2013.

Subsequently, only a handful of other reports were published with somewhat conflicting results. There are also some disadvantages for the use of methylene blue. First of all, the dye cannot be used in patients with reduced renal function and has some safety issues. Among these is the impairment of the saturation readings intraoperatively, as well as induction of serotonin syndrome and methemoglobinemia in some patients. Most of these issues can be significantly avoided with dose reduction. Nevertheless, methylene blue has low ability to penetrate
tissue and has a low quantum yield which means it is not a very efficient fluorophore with a low brightness.\cite{40}

Consequently, fluorophores that are renally excreted but have similar emission wavelengths to ICG at the same time are in development work is currently done preclinically in animal models.\cite{41}

**CONCLUSIONS**

ICG NIR fluorescence imaging is a promising tool for intraoperative decision-making during different minimally invasive surgical procedures. Primarily, it was used for perioperative blood flow assessment and identification of SLN in heart revascularisation surgery and melanoma and breast cancer surgery.

*Lymphatic mapping and assessment of blood flow* are probably key clinical applications in minimally invasive colorectal surgery, with proven feasibility and safety as well as potential major benefits for the patients.

**Intraureteral ICG** and subsequent visualisation under NIR fluorescence seem a very promising technique for primary and secondary prevention against iatrogenic ureteral injury. However, shortage of reports and current off-label use with yet to be clearly defined adverse effect profile limits its use for the time being.

Ongoing and future studies will hopefully give firm evidence regarding clinical and cost-effectiveness of ICG technology that has so many different clinical applications in surgery. Some of them will, undoubtedly, be transformed into the standard of care in the near future.\cite{42‑44}

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**Conflicts of interest**

There are no conflicts of interest.

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