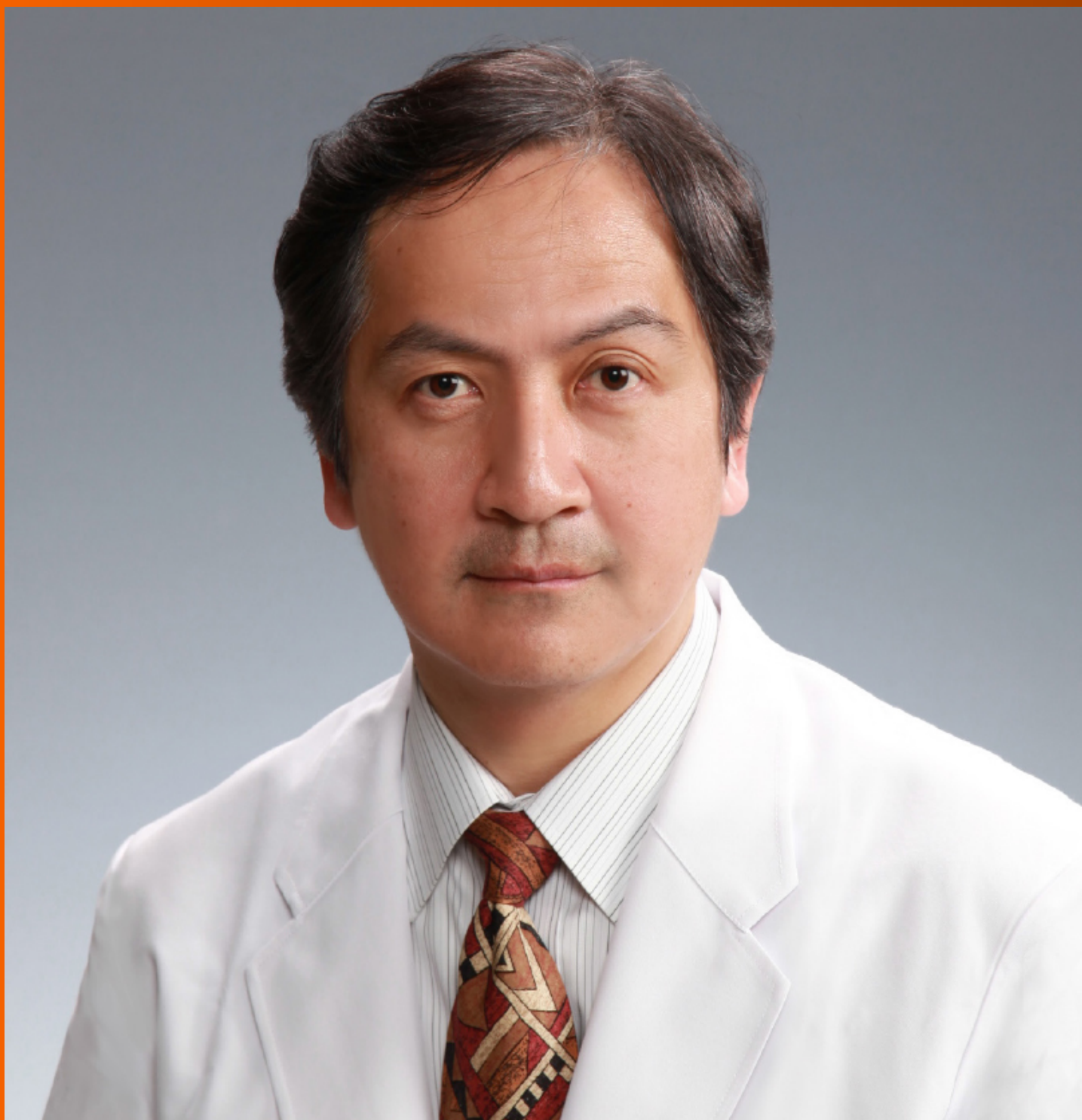


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Editorial Board Member of *World Journal of Gastroenterology*, Shunji Fujimori, MD, PhD, AGAF, Director, Professor, Department of Gastroenterology, Chiba Hokusoh Hospital, Nippon Medical School, 1715, Kamagari, Inzai-City, Chiba 270-1694, Japan. s-fujimori@nms.ac.jp

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Role of near-infrared fluorescence in colorectal surgery

Elodie Zocola, Jeremy Meyer, Niki Christou, Emilie Liot, Christian Toso, Nicolas Christian Buchs, Frédéric Ris

ORCID number: Elodie Zocola 0000-0003-1338-4915; Jeremy Meyer 0000-0003-3381-9146; Niki Christou 0000-0003-2125-0503; Emilie Liot 0000-0002-2856-5260; Christian Toso 0000-0003-1652-4522; Nicolas Christian Buchs 0000-0001-9255-3929; Frédéric Ris 0000-0001-7421-6101.

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Elodie Zocola, Medical School, University of Geneva, Genève 1205, Switzerland

Jeremy Meyer, Emilie Liot, Christian Toso, Nicolas Christian Buchs, Frédéric Ris, Division of Digestive Surgery, University Hospitals of Geneva, Genève 1205, Switzerland

Niki Christou, Service de Chirurgie Digestive, Endocrinienne et Générale, CHU de Limoges, Limoges Cedex 87025, France

Corresponding author: Jeremy Meyer, MD, PhD, Surgeon, Division of Digestive Surgery, University Hospitals of Geneva, Rue Gabrielle-Perret-Gentil 4, Genève 1205, Switzerland. jeremy.meyer@hcuge.ch

Abstract

Near-infrared fluorescence (NIRF) is a technique of augmented reality that, when applied in the operating theatre, allows the colorectal surgeon to visualize and assess bowel vascularization, to identify lymph nodes draining a cancer site and to identify ureters. Herein, we review the literature regarding NIRF in colorectal surgery.

Key Words: Fluorescence; Enhanced reality; Anastomotic leak; Ureter; Anastomosis

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Core Tip: Near-infrared fluorescence appears to be a useful tool that assists surgeons performing colorectal surgery by identifying poorly vascularized areas of the bowel and therefore decreasing the incidence of anastomotic leak, visualizing lymphatic drainage and identifying the ureters during difficult surgery.

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INTRODUCTION

Augmented reality (AR) is increasingly used in the operating room to help surgeons in

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their work. AR is created by overlaying digital information on an image being viewed through a device in real time, allowing us to extend our perception of reality.

Fluorescence is the property of absorbing light of short wavelengths and emitting light of longer wavelengths. In near-infrared (NIR) fluorescence (NIRF) imaging, a fluorescent dye, namely a fluorochrome emitting in the NIR spectrum, is injected intravenously or directly into the tissue. The AR acquisition system functions as a laparoscope but uses two cameras at the same time: A white light camera acquiring real-world images and a second infrared camera for acquiring the fluorescence images emitted by the dye. On the fluorescent images, the rays emitted by the fluorochromes are visualized by white pixels on a black background. The AR image is then constructed by superposition of the real-world image and the recoloured NIR image.

Radiation, like light, penetrates biological tissue while becoming increasingly depleted in energy up to the depth at which all energy transported has been absorbed. Biological tissues absorb and scatter shorter wavelength light, and NIR light can penetrate biological tissues (such as skin and blood) more efficiently than visible light. Therefore, it creates a "transparency" effect of the tissues and allows the acquisition of fluorescent images through several millimetres of depth.

Indocyanine green (ICG) is the most commonly used fluorophore in NIRF imaging and has been approved by the Food and Drug Administration for clinical and research use in humans since 1956. Its fluorescent capabilities have been used increasingly since the 2000s in various specialties, such as neurosurgery, plastic surgery, gynaecology or general surgery. ICG is an iodine dye[1] that can be injected intravenously. The compound is 98% bound to plasma proteins and has a hepatic clearance rate of 18% to 24% *per minute* into the bile. This leads to a half-life of generally 3 to 4 min depending on the vascularization of the organ of interest, with no known metabolites. Its quick clearance rate allows the dye to be used for multiple injections during a procedure. ICG is excited between 750 and 800 nm, and fluorescence is viewed at approximately 830 nm[2]. This fluorochrome is well-tolerated in patients. However, there have been few described cases of hypotension, tachycardia, dyspnoea, urticarial and anaphylactic shock[3]. In colorectal surgery, NIRF imaging uses not only ICG but also other fluorochromes and is employed for three main functions: Estimation of the blood supply, oncological applications and highlighting of anatomical elements such as the ureters.

PREVENTION OF ANASTOMOTIC LEAKS

In colorectal surgery involving intestinal resection, the most feared complication is anastomotic leak (AL), which occurs in 8.1% of procedures according to the European Society of Coloproctology snapshot audit for right hemicolectomies[4] and in up to 17.5% of low colorectal anastomoses. AL causes devastating morbidity and mortality [5,6]. Complete anastomosis healing requires adequate perfusion; therefore, one of the most important risk factors for AL is poor perfusion of the anastomosis[7,8]. Intraoperatively, the selection of an optimal site for anastomosis depends on subjective clinical indicators of good perfusion, such as the colour of the bowel wall, palpable pulsations of the mesenteric arteries, or bleeding of the resection margins[9,10]. Nonetheless, two studies[11,12] showed that the surgeon's subjective AL prediction based on perfusion underestimated the risks of AL. Numerous objective quantitative techniques of intraoperative bowel viability assessment exist, such as measurement of tissue oxygen levels, laser Doppler flowmetry, pulse oximetry, pH measurement and NIR fluorescence angiography[13], but only a few are applicable in colorectal surgery, especially in laparoscopic surgery.

NIR fluorescence angiography using ICG as a fluorochrome is an ever-increasing technique used in the operating room. The first clinical study reporting this method in colorectal surgery was performed by Kudsus *et al*[14] in 2010. ICG was injected intravenously to highlight the microvasculature and enabled surgeons to detect poorly perfused areas more precisely[3]. Indeed, ischaemic demarcation of the intestine is visible with normal light more than 10 min after vessel division, whereas NIRF nearly immediately distinguishes vascularized from ischaemic tissue areas[15]. Fluorescence is visible within 30 to 60 s after fluorochrome injection[16,17], which is performed after the division of the mesenteric vessels when the operator has chosen the resection margins and/or after the anastomosis in order to verify good perfusion of the surrounding tissues.

Thereafter, in a meta-analysis of 10 studies from 2010 to 2017 (894 patients), van den Bos *et al*[18] reported a change in the initial surgical plan in 10.8% of patients. In most articles, the resection was extended to better perfused tissues or the anastomosis was

redone if the perfusion was unsatisfactory[16]. The use of ICG also helped to invalidate the clinical impression of poor perfusion and thus indicated that the resection margins did not need to be extended further. For instance, Kudsus *et al*[14] described a non-extended resection in 2.5% of patients (5/201) despite a clinical impression of poor perfusion. In the study by Kim *et al*[17], the use of ICG determined competent perfusion of the bowel at the anastomosis in 13 patients (10.6%) at risk of ischaemia due to restrictive mesocolon, malrotation, marginal vessel deficiency, accidental left colic artery excision, and oedema due to irradiation.

The effect of NIRF angiography on intraoperative decision-making seems to allow a reduction in the risk of AL (Table 1). However, due to the small sample sizes, only 4 out of 11 studies reported a statistically significant ($P < 0.05$) reduction in AL[16–20]. In other investigations, subgroup analysis showed significant reductions in AL for colorectal cancer (CRC) surgery[14,21], rectal surgery[22], elective resection and hand-sewn anastomosis[14]. However, in two larger studies[23,24], the use of fluorescence angiography did change the decision-making, but there was no discernible change in AL outcome.

The first randomized controlled trials in the field were released in 2019 and 2020 by De Nardi *et al*[25] and Jafari *et al*[26], respectively. In these prospective, single-blinded trials, the authors did not find a significant difference in the AL rate between the NIRF group and the control group (De Nardi *et al*[25]: Incidence of AL = 5% in the NIR group *versus* 9% in the control group; $P = 0.2$; Jafari *et al*[26]: Incidence of AL = 9.0% in the NIR group *vs* 9.6% in the control group; $P = 0.37$). However, these studies might be underpowered. Of note, Jafari *et al*[26] stopped the trial before including the minimum number of 450 patients, as mentioned in their research protocol. Nevertheless, Alekseev *et al*[27] randomized controlled trial including 380 patients showed significant results, with an incidence of AL of 9.1% in the NIR group *vs* 16.3% in the control group ($P = 0.04$). This might be explained by the marked incidence of AL in the included population. Indeed, the authors pro-actively searched for leaks *via* contrast exams performed on every patient 30 d after surgery if the post-operative period was entirely uneventful.

Based on these randomized controlled trials, it can be concluded that the effect of fluorescence probably exists but that this effect is most likely modest and more pronounced in patients with a high risk for AL. New randomized studies are ongoing and will allow us to reach a conclusion on the subject (notably: Armstrong *et al*[28], NCT03602677, NCT03390517).

Regarding economic aspects, AL leads to extended hospitalization. Therefore, the use of NIRs may reduce the length of hospital stay[14] and reduce costs by preventing the occurrence of AL. The initial outlay for the material of the NIR fluorescence system was 70.000€ for Kim *et al*[17], then 13€ *per* patient for the dye; the corresponding cost was 110.000€ (purchase and 5-year maintenance) for Ris *et al*[16], and then 130€ *per* patient for 3 injections. AL increases the treatment costs by €12600[29] to €21500[30]. Therefore, the NIRF technique seems to be cost effective[31], and the acquisition costs of a NIRF-ICG system could be covered in a year if it prevents two ALs *per* year. All the studies do not share this point of view, as Jafari *et al*[32] reported an initial cost of \$167500 to \$223750 and a cost *per* case of \$999 to \$1099. Consequently, a randomized controlled trial assessing the effect of NIRF on AL, including a cost-benefit analysis, is needed.

In addition to being used to reduce the rate of AL in elective surgery, NIRF can be used during emergency surgery, *e.g.*, in acute ischaemic disease, to identify bowel segments to be resected. However, only a few studies have applied NIRF to emergency surgery, and these studies included only small numbers of patients ($n = 4$ to 56)[33–35].

In the Liot *et al*[34]'s study, NIR fluorescence led to a change of plan in 32% of the cases: 67% were slated for a less aggressive approach, while only 33% were scheduled for larger resection. None of those patients underwent reoperation for ischaemia. Nevertheless, another study reported two false positive cases where the ICG injection showed good perfusion, while the pathological report finally revealed signs of necrosis.

IDENTIFICATION OF METASTATIC LYMPH NODES

CRC is the third most common cancer worldwide, accounting for approximately 10% of all new cases, and is the fourth most common cause of death from cancer[36]. The 5-year survival of CRC is determined by the stage of the disease at diagnosis and ranges from 90% in early-stage localized tumours to 14% in distant metastatic disease[37].

Table 1 Retrospective cohort studies

| Ref. | Indication for resection | Sample size | ICG injection time | Change of plan (%) | AL rate (%) |
|----------------------------------|---|---------------------------|----------------------------|--------------------|--|
| Kudszus <i>et al</i> [14], 2010 | Colorectal cancer | ICG: 201. Control: 201 | Before anastomosis | 16.4 | ICG: 3.5. Control: 7.5 |
| Kin <i>et al</i> [23], 2015 | Colorectal cancer, Diverticulitis, IBD, other | ICG: 173. Control: 173 | Before anastomosis | 4.6 | ICG: 7.5. Control: 6.4 |
| Jafari <i>et al</i> [3], 2013 | Rectal cancer | ICG: 16. Control: 22 | Before anastomosis | 19 | ICG: 6. Control: 18 |
| Kim <i>et al</i> [17], 2016 | Rectal cancer | ICG: 123. Control: 313 | Before ± after anastomosis | 0 ² | ICG: 0.8 ^a . Control: 5.4 |
| Boni <i>et al</i> [15], 2015 | Colorectal cancer | ICG: 42. Control: 38 | Before + after Anastomosis | 4.7 | ICG: 0. Control: 5.2 |
| Wada <i>et al</i> [87], 2019 | Rectal cancer ¹ | ICG: 34. Control: 34 | Before anastomosis | 27.1 ¹ | ICG: 8.8. Control: 14.7 |
| Dinallo <i>et al</i> [24], 2019 | ND | ICG: 234. Control: 320 | Before anastomosis | 5.6 ^a | ICG: 1.3. Control: 1.3 |
| Mizrahi <i>et al</i> [88], 2018 | Rectal cancer | ICG: 30. Control: 30 | Before + after anastomosis | 13.3 | ICG: 0. Control: 6.7 |
| Kim <i>et al</i> [19], 2017 | Rectal cancer | ICG: 310. Control: 347 | Before anastomosis | ND | ICG: 0.6 ^a . Control: 5.2 |
| Ris <i>et al</i> [16], 2018 | Colorectal cancer (65.5%), diverticular disease (18.8%), Crohn's disease, ulcerative colitis, other | ICG: 504 Control: 1173 | Before + after anastomosis | 5.8 | ICG: 2.4 ^a . Control: 5.8 |
| Watanabe <i>et al</i> [20], 2020 | Rectal cancer | ICG: 211. Control: 211 | Before anastomosis | ND | ICG: 4.7 ^a . Control: 10.4 |

¹149 (48:101).²Fluorescent imaging correctly determined competent perfusion of the bowel adjacent to the anastomosis in 10.6% who were possibly susceptible to anastomotic site ischemia.^aP < 0.05. ND: No data available; IBD: Inflammatory bowel disease; AL: Anastomotic leak; ICG: Indocyanine green.

Lymph node status is a prognostic factor and a determinant for adjuvant therapeutic intervention. The sentinel lymph node (SLN) concept is based upon the observation that tumour cells migrating from a primary tumour metastasize to one or a few lymph nodes before involving other lymph nodes. This concept was first described in 1960[38], and its application contributed to the identification of lymph nodes with the highest probability of malignant infiltration for the staging of a tumour.

There are various methods for intraoperative mapping of SLNs. Currently, surgeons use direct visualization identification after the injection of dyes such as isosulfan blue [39], patent blue[40], methylene blue[41], or scintigraphy after the injection of radiocolloids around the tumour[42], and for over ten years, the use of NIRF after the injection of ICG.

The capability of ICG NIRF to identify metastatic LNs in various types of malignancies was extensively investigated. The sensitivity of ICG NIRF varied according to the site of the primary malignancy: 50% to 100% for endometrial and cervical carcinoma[43], 50%-100% for gastric cancer[44], and up to 95% to 100% for breast cancer[44]. Lymph nodes and lymph vessels draining the injection site and thus containing ICG can be visualized by NIR without ionizing radiation or radioactivity involvement. In the meta-analysis performed by Emile *et al*[45] in 2017 regarding SLN in CRC, the pooled sensitivity and specificity rates were 71 and 84.6, respectively. On the other hand, when the proportion of patients with early-stage tumours was > 50% of the sample size[46-48], the median sensitivity and specificity increased to 100%. This difference has also been found in the meta-analysis of Burghgraef *et al*[49], where the T1-T2 group had a 1.25 higher accuracy rate than the T3-T4 group (CI: 1.05-1.47). The hypothesis was that the flow through nodes with obvious nodal metastases could be obstructed by the tumour, leading to lymph drainage through alternative pathways (aberrant drainage concept). According to these results, sentinel node mapping with ICG is feasible for early-stage cancer/radiologically localized colorectal neoplasia[50]. Additionally, preoperative T staging should be performed before SLN mapping[46].

The ability of ICG NIRF to detect metastatic LN was compared with patent blue dye in two studies[51,52], which respectively examined both techniques in 20 and in 50 patients with colon cancer and reported that both methods had the same detection rates (95%, 99.5%) for SLN, but higher sensitivity in favour of ICG was observed by Liberale *et al*[51], especially in patients with higher BMIs (> 25 kg/m²).

Regional lymphadenectomy directly influences the risk of distant failure, provides prognostic information and guides postoperative management, such as chemotherapy administration. The number of nodes retrieved from the surgical specimen improves the accuracy of prognosis and influences survival outcomes in patients with colon cancer. NIR lymph node mapping can modify the surgical procedure when ICG shows additional lymph nodes outside of the proposed resection margins to achieve radical lymph resection for curative surgery[48,53-55]. For that purpose, ICG injection is usually performed between 1 and 3 d before surgery[55]. This technique may serve to optimize and individualize the excision of patient specificities rather than theoretical anatomic generalization.

Another way to use ICG in metastatic lymph node mapping is as an intravenous injection. In tumour tissue, neoangiogenesis is responsible for the presence of immature and permeable vessels allowing ICG-bound molecules to pass into the extravascular space. As the half-life of ICG in blood circulation is approximately 5 min, ICG is rapidly cleared from the vascular space, but extravascular ICG accumulation will be responsible for the observed hyperfluorescence of tumour tissue in contrast to surrounding normal tissue[56]. This phenomenon is known as the enhanced permeability and retention effect. In one study (Liberale *et al*[57], 15 min after intraoperative intravenous injection of ICG, no lymph nodes other than those containing cancer cells were fluorescent, suggesting that fluorescence was directly related to the presence of tumoural tissue inside LNs.

This method also enables us to highlight peritoneal metastasis (PM). The first application of ICG-based fluorescence imaging in patients with PM of colorectal origin was demonstrated in 2016[58]. According to the last study by Lieto *et al*[59], the diagnostic performance of ICG NIRF was significantly better than preoperative and intraoperative conventional procedures. In this study, intraoperative ICG identified additional hyperfluorescent metastatic nodules and then confirmed them by histopathology (16/17). The sensitivity increased from 76.9% to 96.9% with NIRF.

PREVENTION OF IATROGENIC URETERAL INJURY

Iatrogenic ureteral injury is a complication occurring in 0.15% to 1.9%[60,61] of patients undergoing colorectal surgery. These lesions include ureteral sections, ligations, crushing, coagulation or indirect injuries, such as burn and ischaemic lesions, and may require secondary/subsequent surgery in a later stage. Even if it is a rare event, the consequences of such injuries are important and lead to increased postoperative mortality, morbidity, hospital stay and health costs[62].

Preoperative ureter stent placement is a technique used in surgery to help identify the ureters. These stents can be palpated during open surgery, but in laparoscopic surgery, in which tactile feedback is limited, this technique loses its interest[63]. In an effort to enhance visualization of ureters throughout laparoscopic dissection, lighted ureteral stents were devised[64,65]. However, preoperative ureteral stent placement is an invasive procedure that harbours increased risks of complications, such as ureteral perforation and urinary tract infection[66]. New techniques have been or are being developed for ureter visualization with AR assistance (Table 2).

Because of the hepatic clearance of ICG, its use in ureter visualization requires the placement of a ureteral catheter for retrograde injection of the dye directly into the lumen of the ureter. This technique allows identification of the entire course of the ureters from the surrounding tissue in laparoscopic and open surgery and enables the location of a lesion made during the surgery in real time by leakage of the dye in the intraperitoneal space[67]. A small cohort study including 10 patients showed 100% visualization of ureters directly after injection[68]. The importance of this method was confirmed by two case studies[69,70]. Considering the potential complications of ureteral catheters, new dyes were investigated to offer non-invasive alternatives to improve preoperative ureteral identification.

Methylene blue is a dye that has long been used in humans with a good safety profile. Its NIR fluorescent properties were discovered at micromolar concentrations only ten years ago[71]. When used at the typical clinical concentration of 1% (*i.e.*, 31.3 mmol/L), methylene blue is bright blue but has virtually no NIRF because of

Table 2 Ureteral visualization studies using intravenous dye

| Ref. | Model | Surgery | Dye | n (%) | Visible ureters | Visible time after injection | Visibility duration |
|-------------------------------------|-------|--------------------------|----------------|-------|-----------------|------------------------------|---------------------|
| Matsui <i>et al</i> [71], 2010 | Pig | Open ¹ | Methylene blue | 20 | 100% (40/40) | 10 min | 65 min |
| | | Laparoscopy ¹ | | 2 | 50% (2/4) | 10 min | 20 min |
| Verbeek <i>et al</i> [89], 2013 | Human | Open ¹ | Methylene blue | 12 | 100% (20/20) | 10 min | ≥ 50 min |
| Al-Taher <i>et al</i> [90], 2016 | Human | Laparoscopy | Methylene blue | 10 | 62,5% (5/8) | ND | ND |
| Barnes <i>et al</i> [72], 2018 | Human | Laparoscopy | Methylene blue | 34 | 93.6% (59/63) | 0 min | 2 h |
| | | Open | | 6 | 66.6% (4/6) | | |
| Tanaka <i>et al</i> [67], 2007 | Rat | Open | IRDye 800CW | 12 | 100% | 3-5 min | ND |
| | Pig | Open | IRDye 800CW | 6 | 100% | 10 min | > 20 min |
| Schols <i>et al</i> [74], 2014 | Pig | Laparoscopy | IRDye 800cw | 2 | 50% (1/2) | 10 min | ND |
| Korb <i>et al</i> [75], 2015 | Pig | Laparoscopy | IRDye 800CW | 6 | 100% | 10 min | ≥ 50 min |
| Van den Bos <i>et al</i> [18], 2018 | Pig | Laparoscopy | IRDye 800 BK | 1 | 100% (2/2) | 35 min | 3 h |
| | | | IRDye 800NOS | 1 | 100% (2/2) | 45 min | ND |
| | | | IRDye 800CW | 1 | 100% (2/2) | 10 min | ≥ 15 min |
| Al-Taher <i>et al</i> [77], 2018 | Pig | Laparoscopy | IRDye 800BK | 3 | 100% (6/6) | 1-20 min | ≥ 100 min |

¹With dissection to highlight ureters.

ND: No data available.

quenching. However, when diluted to 20 mmol/L (quenching threshold) or below, methylene blue displays moderate NIRF[71], with absorption occurring at 668 nm and excitation emission at 688 nm[72]. When the emission wavelength is shorter than that of ICG, the fluorescence of methylene blue is visible less deeply. Because a major route of excretion of methylene blue is through the kidneys, the urinary excretion rate amounts to 28.6% ($\pm 3.0/24$ h)[73], and urine becomes NIR fluorescent after a single intravenous dose, which permits real-time identification of the ureters. As the urine flow in the ureter is not continuous but pulsatile and the fluorescence signal is related to urine flow, the fluorescence signal in ureters varies over time. However, a preclinical study using this technique showed that a diuretic, which increased the flux of urine through the ureters, did not increase NIRF[71].

Barnes *et al*[72] showed that 93% of the ureters were seen with NIR techniques. The ureteric fluorescence was bright enough to assure the surgeon that the ureter was positively identified; therefore, no additional dissection was required to identify the ureter under white light. Moreover, 20% of all ureters were visible only under fluorescence and not seen with white light. In laparoscopy, fluorescence was deemed useful; in 10 cases, fluorescence revealed the ureter to be in a place different from the one that the surgeon predicted, and in 2 cases, the surgical plan was subsequently modified. Fluorescence was not deemed useful in open surgery, as tactile feedback is sufficient to detect ureters. The ureters can be seen directly after the injection of methylene blue for more than two hours. According to various studies, the fluorescence time and the visualization quality seemed to depend on the dose and concentration of dye administered.

There were no adverse events observed after the administration of the dye in these studies. However, methylene blue is known to cause severe adverse reactions, such as anaphylaxis, methemoglobinemia or severe haemolysis, in subjects with known glucose-6-phosphate dehydrogenase deficiency[71]. It is important to note that intravenous injection of methylene blue causes an artificial drop in oxygen saturation measured *via* pulse oximetry that lasts up to several minutes. This phenomenon is caused by the principle of pulse oximetry, which is based on the red and infrared light absorption characteristics of oxygenated and deoxygenated haemoglobin.

Recently, experimental dyes have been studied for intraoperative visualisation of ureters using NIRF imaging in laparoscopic surgery. First, IRDye 800CW (LI-COR Biosciences, Lincoln, Nebraska, United States) is a tetrasulfonated heptamethine indocyanine dye that, after intravenous injection, is cleared by the kidneys and excreted into urine. Its maximum absorption occurs at 775 nm, and its maximum

excitation emission occurs at 796 nm, which enables a visualization depth equivalent to ICG. Animal studies[67,74,75] have successfully demonstrated the potential of this dye for the identification of ureters. However, a major disadvantage of IRDye 800CW is its cost, which is almost tenfold that of ICG. In 2018, a new preclinical dye, IRDye 800BK (LI-COR Biosciences), with a maximum absorption of 774 nm and a maximum emission of 790 nm, was developed for NIRF visualization, and its price should be similar to that of ICG. Because of its hydrophilic nature, IRDye 800BK is primarily cleared by the kidneys and enables visualization of the ureters in pigs[76,77].

A comparison of IRDye 800BK *vs* 800CW by Van den Bos *et al*[76] showed that IRDye 800BK successfully identified the course of the ureter in living pig models but also resulted in the highest contrast between the ureter and background. This new dye would allow ureter visualization from 20 min to ≥ 120 min post intravenous injection [77], and the duration and quality of the visualization would be influenced by the concentration of dye. The first study in humans is currently underway (NCT03387410 Thomas Barnes, Oxford University Hospitals NHS Trust).

DISCUSSION

This review of the literature presents the role of NIRF imaging in colorectal surgery. The literature in the field suggests that NIRF imaging is safe and feasible. Furthermore, NIRF imaging seems to be useful for helping the surgeon make decisions during surgical procedures.

NIRF imaging is suitable for all types of surgery but is of particular interest in laparoscopy, where surgeons do not have tactile feedback. Indeed, this modality seems helpful for the detection of ureters to reduce the risk of iatrogenic ureteral lesions. Various dyes have been tested, and a new fluorochrome is under investigation to improve NIR brightness compared to that of methylene blue.

Even if several meta-analyses have been performed for the estimation of intestinal vascularization, very few randomized trials have validated the technique in its different indications. Despite the increase in the number of clinical studies, the interpretation of fluorescence is based on the subjective evaluation of the surgeon, and only a few published studies[19,78] have attempted to determine an objective threshold of fluorescence quantification to normalize the technique on a larger scale. Although some notions of the costs of the methods can be found in the articles read, these data come from heterogeneous studies with small sample sizes and are therefore not comparable. Thus, cost-effectiveness studies would be interesting in the future.

In oncology, the NIRF imaging system is currently used in operating rooms using non-specific fluorescent probes, such as ICG, to visualize SLNs. In recent years, many studies have focused on developing targeted fluorescent probes. Targeted fluorochromes are composed of a carrier molecule that specifically binds to a certain target (*i.e.*, monoclonal antibodies, peptides, small molecules), conjugated to a fluorescent dye. Studies should focus on tumour markers that could provide surgeons real-time feedback about the location and extent of tumours. Seven potential targets for imaging CRC have been identified: CXCR4, EpCAM, EGFR, CEA, Muc1, MMP, and VEGF-A [79], and some have been investigated in other types of cancers. To date, in CRC, two phase I feasibility studies have been performed in humans[80,81], and more molecules have been tested in mice with human CRC xenografts[82-84].

Cancer detection is not the only indication of these new targeted dyes. Neumann *et al*[85] described using an enzymatic marker made by a dye becoming fluorescent only in response to MMP for early identification of AL by targeted fluorescence endoscopy during the healing process. Hingorani *et al*[86] demonstrated in *ex vivo* human nerves and in *vivo* mouse models that the fluorescent FAM-HNP401 peptide, when injected intravenously, localized to the connective tissue surrounding peripheral nerves and highlighted these nerves.

CONCLUSION

NIRF imaging appears to be a useful tool to assist surgeons in colorectal surgery. This technique has been tested for three main indications: (1) In the estimation of intestinal vascularization to detect areas of poor perfusion and therefore prevent AL, or in the assessment of the extent of ischaemic segments during acute intestinal ischaemia; (2) In the visualization of lymphatic drainage and (especially in oncological contexts) SLNs and lymphatic and peritoneal metastases in order to prevent recurrence and

adapt further adjuvant treatment; and (3) In the detection of ureters in order to reduce the risk of iatrogenic ureteral lesions, particularly during laparoscopic surgery. Randomized controlled trials and prospective studies with larger sample sizes are needed to validate the methods. Additional studies are underway for the first use of new fluorescent molecules in humans.

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