**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript No:** 65266

**Manuscript Type:** MINIREVIEWS

**Role of near-infrared fluorescence in colorectal surgery**

Zocola E *et al*. Fluorescence in colorectal surgery

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

**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

**Author contributions:** Ris F conceived the manuscript; Zocola E, Meyer J and Ris F wrote the draft of the manuscript; all authors reviewed and accepted the manuscript.

**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

**Received:** March 3, 2021

**Revised:** April 27, 2021

**Accepted:** July 30, 2021

**Published online:** August 21, 2021

**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

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Zocola E, Meyer J, Christou N, Liot E, Toso C, Buchs NC, Ris F. Role of near-infrared fluorescence in colorectal surgery. *World J Gastroenterol* 2021; 27(31): 5189-5200 URL: https://www.wjgnet.com/1007-9327/full/v27/i31/5189.htm

DOI: https://dx.doi.org/10.3748/wjg.v27.i31.5189

**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.

**INTRODUCTION**

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

Fluorescenceis 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 hepaticclearance 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 Kudszus *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, Kudszus *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] reportedan 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]’sstudy, 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].

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 techniqueused 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 lumenof 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 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% (± 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 that93% 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 qualityseemed 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 tocause 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.

**REFERENCES**

1 **Reinhart MB**, Huntington CR, Blair LJ, Heniford BT, Augenstein VA. Indocyanine Green: Historical Context, Current Applications, and Future Considerations. *Surg Innov* 2016; **23**: 166-175 [PMID: 26359355 DOI: 10.1177/1553350615604053]

2 **Benson RC**, Kues HA. Fluorescence properties of indocyanine green as related to angiography. *Phys Med Biol* 1978; **23**: 159-163 [PMID: 635011 DOI: 10.1088/0031-9155/23/1/017]

3 **Jafari MD**, Lee KH, Halabi WJ, Mills SD, Carmichael JC, Stamos MJ, Pigazzi A. The use of indocyanine green fluorescence to assess anastomotic perfusion during robotic assisted laparoscopic rectal surgery. *Surg Endosc* 2013; **27**: 3003-3008 [PMID: 23404152 DOI: 10.1007/s00464-013-2832-8]

4 **2015 European Society of Coloproctology collaborating group.**. The relationship between method of anastomosis and anastomotic failure after right hemicolectomy and ileo-caecal resection: an international snapshot audit. *Colorectal Dis* 2017 [PMID: 28263043 DOI: 10.1111/codi.13646]

5 **Vallance A**, Wexner S, Berho M, Cahill R, Coleman M, Haboubi N, Heald RJ, Kennedy RH, Moran B, Mortensen N, Motson RW, Novell R, O'Connell PR, Ris F, Rockall T, Senapati A, Windsor A, Jayne DG. A collaborative review of the current concepts and challenges of anastomotic leaks in colorectal surgery. *Colorectal Dis* 2017; **19**: O1-O12 [PMID: 27671222 DOI: 10.1111/codi.13534]

6 **Turrentine FE**, Denlinger CE, Simpson VB, Garwood RA, Guerlain S, Agrawal A, Friel CM, LaPar DJ, Stukenborg GJ, Jones RS. Morbidity, mortality, cost, and survival estimates of gastrointestinal anastomotic leaks. *J Am Coll Surg* 2015; **220**: 195-206 [PMID: 25592468 DOI: 10.1016/j.jamcollsurg.2014.11.002]

7 **Trencheva K**, Morrissey KP, Wells M, Mancuso CA, Lee SW, Sonoda T, Michelassi F, Charlson ME, Milsom JW. Identifying important predictors for anastomotic leak after colon and rectal resection: prospective study on 616 patients. *Ann Surg* 2013; **257**: 108-113 [PMID: 22968068 DOI: 10.1097/SLA.0b013e318262a6cd]

8 **Sheridan WG**, Lowndes RH, Young HL. Tissue oxygen tension as a predictor of colonic anastomotic healing. *Dis Colon Rectum* 1987; **30**: 867-871 [PMID: 3677962 DOI: 10.1007/BF02555426]

9 **Nachiappan S**, Askari A, Currie A, Kennedy RH, Faiz O. Intraoperative assessment of colorectal anastomotic integrity: a systematic review. *Surg Endosc* 2014; **28**: 2513-2530 [PMID: 24718665 DOI: 10.1007/s00464-014-3520-z]

10 **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: 23992097 DOI: 10.1111/codi.12411]

11 **Karliczek A**, Harlaar NJ, Zeebregts CJ, Wiggers T, Baas PC, van Dam GM. Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. *Int J Colorectal Dis* 2009; **24**: 569-576 [PMID: 19221768 DOI: 10.1007/s00384-009-0658-6]

12 **Markus PM**, Martell J, Leister I, Horstmann O, Brinker J, Becker H. Predicting postoperative morbidity by clinical assessment. *Br J Surg* 2005; **92**: 101-106 [PMID: 15635697 DOI: 10.1002/bjs.4608]

13 **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]

14 **Kudszus S**, Roesel C, Schachtrupp A, Höer 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]

15 **Boni L**, David G, Mangano A, Dionigi G, Rausei S, Spampatti S, Cassinotti E, Fingerhut A. Clinical applications of indocyanine green (ICG) enhanced fluorescence in laparoscopic surgery. *Surg Endosc* 2015; **29**: 2046-2055 [PMID: 25303914 DOI: 10.1007/s00464-014-3895-x]

16 **Ris F**, Liot E, Buchs NC, Kraus R, Ismael G, Belfontali V, Douissard J, Cunningham C, Lindsey I, Guy R, Jones O, George B, Morel P, Mortensen NJ, Hompes 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]

17 **Kim JC**, Lee JL, Yoon YS, Alotaibi AM, Kim J. Utility of indocyanine-green fluorescent imaging during robot-assisted sphincter-saving surgery on rectal cancer patients. *Int J Med Robot* 2016; **12**: 710-717 [PMID: 26486376 DOI: 10.1002/rcs.1710]

18 **van den Bos J**, Al-Taher M, Schols RM, van Kuijk S, Bouvy ND, Stassen LPS. Near-Infrared Fluorescence Imaging for Real-Time Intraoperative Guidance in Anastomotic Colorectal Surgery: A Systematic Review of Literature. *J Laparoendosc Adv Surg Tech A* 2018; **28**: 157-167 [PMID: 29106320 DOI: 10.1089/lap.2017.0231]

19 **Kim JC**, Lee JL, Park SH. Interpretative Guidelines and Possible Indications for Indocyanine Green Fluorescence Imaging in Robot-Assisted Sphincter-Saving Operations. *Dis Colon Rectum* 2017; **60**: 376-384 [PMID: 28267004 DOI: 10.1097/DCR.0000000000000782]

20 **Watanabe J**, Ishibe A, Suwa Y, Suwa H, Ota M, Kunisaki C, Endo I. Indocyanine green fluorescence imaging to reduce the risk of anastomotic leakage in laparoscopic low anterior resection for rectal cancer: a propensity score-matched cohort study. *Surg Endosc* 2020; **34**: 202-208 [PMID: 30877565 DOI: 10.1007/s00464-019-06751-9]

21 **Shen R**, Zhang Y, Wang T. Indocyanine Green Fluorescence Angiography and the Incidence of Anastomotic Leak After Colorectal Resection for Colorectal Cancer: A Meta-analysis. *Dis Colon Rectum* 2018; **61**: 1228-1234 [PMID: 30192332 DOI: 10.1097/DCR.0000000000001123]

22 **Blanco-Colino R**, Espin-Basany E. Intraoperative use of ICG fluorescence imaging to reduce the risk of anastomotic leakage in colorectal surgery: a systematic review and meta-analysis. *Tech Coloproctol* 2018; **22**: 15-23 [PMID: 29230591 DOI: 10.1007/s10151-017-1731-8]

23 **Kin C**, Vo H, Welton L, Welton M. Equivocal effect of intraoperative fluorescence angiography on colorectal anastomotic leaks. *Dis Colon Rectum* 2015; **58**: 582-587 [PMID: 25944430 DOI: 10.1097/DCR.0000000000000320]

24 **Dinallo AM**, Kolarsick P, Boyan WP, Protyniak B, James A, Dressner RM, Arvanitis ML. Does routine use of indocyanine green fluorescence angiography prevent anastomotic leaks? A retrospective cohort analysis. *Am J Surg* 2019; **218**: 136-139 [PMID: 30360896 DOI: 10.1016/j.amjsurg.2018.10.027]

25 **De Nardi P**, Elmore U, Maggi G, Maggiore R, Boni L, Cassinotti 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: 30903276 DOI: 10.1007/s00464-019-06730-0]

26 **Jafari MD**, Pigazzi A, McLemore EC, Mutch MG, Haas E, Rasheid S, Wait AD, Paquette IM, Bardakcioglu O, Safar B, Landmann RG, Varma M, Maron DJ, Martz J, Bauer J, George VV, Fleshman JW, Steele SR, Stamos MJ. Perfusion Assessment in Left-Sided/Low Anterior Resection (PILLAR III): A Randomized, Controlled, Parallel, Multicenter Study Assessing Perfusion Outcomes with PINPOINT Near-Infrared Fluorescence Imaging in Low Anterior Resection. *Dis Colon Rectum* 2021 [PMID: 33872284 DOI: 10.1097/DCR.0000000000002007]

27 **Alekseev M**, Rybakov E, Shelygin 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]

28 **Armstrong G**, Croft J, Corrigan N, Brown JM, Goh V, Quirke P, Hulme C, Tolan D, Kirby A, Cahill R, O'Connell PR, Miskovic D, Coleman M, Jayne D. IntAct: intra-operative fluorescence angiography to prevent anastomotic leak in rectal cancer surgery: a randomized controlled trial. *Colorectal Dis* 2018; **20**: O226-O234 [PMID: 29751360 DOI: 10.1111/codi.14257]

29 **Ashraf SQ**, Burns EM, Jani A, Altman S, Young JD, Cunningham C, Faiz O, Mortensen NJ. The economic impact of anastomotic leakage after anterior resections in English NHS hospitals: are we adequately remunerating them? *Colorectal Dis* 2013; **15**: e190-e198 [PMID: 23331871 DOI: 10.1111/codi.12125]

30 **Hammond J**, Lim S, Wan Y, Gao X, Patkar A. The burden of gastrointestinal anastomotic leaks: an evaluation of clinical and economic outcomes. *J Gastrointest Surg* 2014; **18**: 1176-1185 [PMID: 24671472 DOI: 10.1007/s11605-014-2506-4]

31 **Boni L**, David G, Dionigi G, Rausei S, Cassinotti E, Fingerhut A. Indocyanine green-enhanced fluorescence to assess bowel perfusion during laparoscopic colorectal resection. *Surg Endosc* 2016; **30**: 2736-2742 [PMID: 26487209 DOI: 10.1007/s00464-015-4540-z]

32 **Jafari MD**, Wexner SD, Martz JE, McLemore EC, Margolin DA, Sherwinter DA, Lee SW, Senagore AJ, Phelan MJ, Stamos 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]

33 **Nowak K**, Sandra-Petrescu F, Post S, Horisberger K. Ischemic and injured bowel evaluation by Fluorescence imaging. *Colorectal Dis* 2015; **17 Suppl 3**: 12-15 [PMID: 26394737 DOI: 10.1111/codi.13032]

34 **Liot E**, Assalino M, Buchs NC, Schiltz B, Douissard J, Morel P, Ris F. Does near-infrared (NIR) fluorescence angiography modify operative strategy during emergency procedures? *Surg Endosc* 2018; **32**: 4351-4356 [PMID: 29770885 DOI: 10.1007/s00464-018-6226-9]

35 **Karampinis I**, Keese M, Jakob J, Stasiunaitis V, Gerken A, Attenberger U, Post S, Kienle P, Nowak K. Indocyanine Green Tissue Angiography Can Reduce Extended Bowel Resections in Acute Mesenteric Ischemia. *J Gastrointest Surg* 2018; **22**: 2117-2124 [PMID: 29992520 DOI: 10.1007/s11605-018-3855-1]

36 **World Health Organisation, Intenational Angency Research on Cancer.** 2020. All cancers fact sheet [Internet].[cited 10 January 2021]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf

37 **Howlader N,** Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review 1975-2017 [Internet]. National Cancer Institute. 2020. [cited 10 January 2021]. Available from: https://seer.cancer.gov/csr/1975\_2017/results\_merged/sect\_06\_colon\_rectum.pdf

38 **Gould EA**, Winship T, Philbin PH, Kerr HH. Observations on a "sentinel node" in cancer of the parotid. *Cancer* 1960; **13**: 77-78 [PMID: 13828575 DOI: 10.1002/1097-0142(196001/02)13:1<77::aid-cncr2820130114>3.0.co;2-d]

39 **Albayrak Y**, Oren D, Gündoğdu C, Kurt A. Intraoperative sentinel lymph node mapping in patients with colon cancer: study of 38 cases. *Turk J Gastroenterol* 2011; **22**: 286-292 [PMID: 21805419 DOI: 10.4318/tjg.2011.0214]

40 **Wakeman C**, Yu V, Chandra R, Staples M, Wale R, McLean C, Bell S. Lymph node yield following injection of patent blue V dye into colorectal cancer specimens. *Colorectal Dis* 2011; **13**: e266-e269 [PMID: 21689343 DOI: 10.1111/j.1463-1318.2011.02673.x]

41 **Vasala A**, Nair HG, Rao ST, Tagore KR, Murthy SS, Fonseca D. Impact of methylene blue staining in the retrieval of lymph nodes in resected colorectal cancer specimens. *Indian J Pathol Microbiol* 2016; **59**: 504-506 [PMID: 27721282 DOI: 10.4103/0377-4929.191804]

42 **de Haas RJ**, Wicherts DA, Hobbelink MG, van Diest PJ, Vleggaar FP, Borel Rinkes IH, van Hillegersberg R. Sentinel lymph node mapping in colon cancer using radiocolloid as a single tracer: a feasibility study. *Nucl Med Commun* 2012; **33**: 832-837 [PMID: 22743586 DOI: 10.1097/MNM.0b013e328353bc0c]

43 **Rocha A**, Domínguez AM, Lécuru F, Bourdel N. Indocyanine green and infrared fluorescence in detection of sentinel lymph nodes in endometrial and cervical cancer staging - a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2016; **206**: 213-219 [PMID: 27750179 DOI: 10.1016/j.ejogrb.2016.09.027]

44 **Xiong L**, Gazyakan E, Yang W, Engel H, Hünerbein M, Kneser 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]

45 **Emile SH**, Elfeki H, Shalaby M, Sakr A, Sileri P, Laurberg S, Wexner SD. Sensitivity and specificity of indocyanine green near-infrared fluorescence imaging in detection of metastatic lymph nodes in colorectal cancer: Systematic review and meta-analysis. *J Surg Oncol* 2017; **116**: 730-740 [PMID: 28570748 DOI: 10.1002/jso.24701]

46 **Nagata K**, Endo S, Hidaka E, Tanaka J, Kudo SE, Shiokawa A. Laparoscopic sentinel node mapping for colorectal cancer using infrared ray laparoscopy. *Anticancer Res* 2006; **26**: 2307-2311 [PMID: 16821607]

47 **Watanabe J**, Ota M, Suwa Y, Ishibe A, Masui H, Nagahori K. Evaluation of lymph flow patterns in splenic flexural colon cancers using laparoscopic real-time indocyanine green fluorescence imaging. *Int J Colorectal Dis* 2017; **32**: 201-207 [PMID: 27695977 DOI: 10.1007/s00384-016-2669-4]

48 **Cahill RA**, Anderson M, Wang LM, Lindsey I, Cunningham C, Mortensen NJ. Near-infrared (NIR) laparoscopy for intraoperative lymphatic road-mapping and sentinel node identification during definitive surgical resection of early-stage colorectal neoplasia. *Surg Endosc* 2012; **26**: 197-204 [PMID: 21853392 DOI: 10.1007/s00464-011-1854-3]

49 **Burghgraef TA**, Zweep AL, Sikkenk DJ, van der Pas MHGM, Verheijen PM, Consten ECJ. In vivo sentinel lymph node identification using fluorescent tracer imaging in colon cancer: A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2021; **158**: 103149 [PMID: 33450679 DOI: 10.1016/j.critrevonc.2020.103149]

50 **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 surgery in gastrointestinal cancer. *Dig Surg* 2008; **25**: 103-108 [PMID: 18379188 DOI: 10.1159/000121905]

51 **Liberale G**, Vankerckhove S, Galdon MG, Larsimont D, Ahmed B, Bouazza F, Moreau M, El Nakadi I, Donckier V, Bourgeois P; R&D Group for the Clinical Application of Fluorescence Imaging at the Jules Bordet Institute. Sentinel Lymph Node Detection by Blue Dye Versus Indocyanine Green Fluorescence Imaging in Colon Cancer. *Anticancer Res* 2016; **36**: 4853-4858 [PMID: 27630340 DOI: 10.21873/anticanres.11048]

52 **Weixler B**, Rickenbacher A, Raptis DA, Viehl CT, Guller 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]

53 **Tuech JJ**, Pessaux P, Regenet N, Bergamaschi R, Colson A. Sentinel lymph node mapping in colon cancer. *Surg Endosc* 2004; **18**: 1721-1729 [PMID: 15643527 DOI: 10.1007/s00464-004-9031-6]

54 **Chand M**, Keller DS, Joshi HM, Devoto L, Rodriguez-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]

55 **Nishigori N**, Koyama F, Nakagawa T, Nakamura S, Ueda T, Inoue T, Kawasaki K, Obara S, Nakamoto T, Fujii H, Nakajima Y. Visualization of Lymph/Blood Flow in Laparoscopic Colorectal Cancer Surgery by ICG Fluorescence Imaging (Lap-IGFI). *Ann Surg Oncol* 2016; **23 Suppl 2**: S266-S274 [PMID: 25801355 DOI: 10.1245/s10434-015-4509-0]

56 **Liberale G**, Bourgeois P, Larsimont D, Moreau M, Donckier V, Ishizawa T. Indocyanine green fluorescence-guided surgery after IV injection in metastatic colorectal cancer: A systematic review. *Eur J Surg Oncol* 2017; **43**: 1656-1667 [PMID: 28579357 DOI: 10.1016/j.ejso.2017.04.015]

57 **Liberale G**, Vankerckhove S, Galdon MG, Donckier V, Larsimont D, Bourgeois P. Fluorescence imaging after intraoperative intravenous injection of indocyanine green for detection of lymph node metastases in colorectal cancer. *Eur J Surg Oncol* 2015; **41**: 1256-1260 [PMID: 26081552 DOI: 10.1016/j.ejso.2015.05.011]

58 **Liberale G**, Vankerckhove 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 Bordetʼs 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.0000000000001618]

59 **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]

60 **Palaniappa NC**, Telem DA, Ranasinghe NE, Divino CM. Incidence of iatrogenic ureteral injury after laparoscopic colectomy. *Arch Surg* 2012; **147**: 267-271 [PMID: 22430909 DOI: 10.1001/archsurg.2011.2029]

61 **Kutiyanawala**, Scott, Jameson. Ureteric injuries during colorectal surgery: strategies for prevention. *Colorectal Dis* 1999; **1**: 334-337 [PMID: 23574597 DOI: 10.1046/j.1463-1318.1999.00087.x]

62 **Halabi WJ**, Jafari MD, Nguyen VQ, Carmichael JC, Mills S, Pigazzi A, Stamos MJ. Ureteral injuries in colorectal surgery: an analysis of trends, outcomes, and risk factors over a 10-year period in the United States. *Dis Colon Rectum* 2014; **57**: 179-186 [PMID: 24401879 DOI: 10.1097/DCR.0000000000000033]

63 **da Silva G**, Boutros M, Wexner SD. Role of prophylactic ureteric stents in colorectal surgery. *Asian J Endosc Surg* 2012; **5**: 105-110 [PMID: 22776608 DOI: 10.1111/j.1758-5910.2012.00134.x]

64 **Marcelissen TA**, Den Hollander PP, Tuytten TR, Sosef MN. Incidence of Iatrogenic Ureteral Injury During Open and Laparoscopic Colorectal Surgery: A Single Center Experience and Review of the Literature. *Surg Laparosc Endosc Percutan Tech* 2016; **26**: 513-515 [PMID: 27846171 DOI: 10.1097/SLE.0000000000000335]

65 **Boyan WP Jr**, Lavy D, Dinallo A, Otero J, Roding A, Hanos D, Dressner R, Arvanitis M. Lighted ureteral stents in laparoscopic colorectal surgery; a five-year experience. *Ann Transl Med* 2017; **5**: 44 [PMID: 28251123 DOI: 10.21037/atm.2017.02.01]

66 **Chahin F**, Dwivedi AJ, Paramesh A, Chau W, Agrawal S, Chahin C, Kumar A, Tootla A, Tootla F, Silva YJ. The implications of lighted ureteral stenting in laparoscopic colectomy. *JSLS* 2002; **6**: 49-52 [PMID: 12002296]

67 **Tanaka E**, Ohnishi S, Laurence RG, Choi HS, Humblet V, Frangioni JV. Real-time intraoperative ureteral guidance using invisible near-infrared fluorescence. *J Urol* 2007; **178**: 2197-2202 [PMID: 17870110 DOI: 10.1016/j.juro.2007.06.049]

68 **Siddighi S**, Yune JJ, Hardesty J. Indocyanine green for intraoperative localization of ureter. *Am J Obstet Gynecol* 2014; **211**: 436.e1-436.e2 [PMID: 24835212 DOI: 10.1016/j.ajog.2014.05.017]

69 **Foppa C**, Spinelli A. Ureteric identification with indocyanine green fluorescence in laparoscopic redo pouch surgery. *Tech Coloproctol* 2018; **22**: 627-628 [PMID: 30167911 DOI: 10.1007/s10151-018-1838-6]

70 **Gila-Bohórquez A**, Gómez-Menchero J, García-Moreno JL, Suárez-Grau JM, Guadalajara-Jurado JF. Utility of indocyanine green for intra-operative localization of ureter in complex colo-rectal surgery. *Cir Esp* 2019; **97**: 233-234 [PMID: 30241671 DOI: 10.1016/j.ciresp.2018.07.006]

71 **Matsui A**, Tanaka E, Choi HS, Kianzad V, Gioux S, Lomnes SJ, Frangioni JV. Real-time, near-infrared, fluorescence-guided identification of the ureters using methylene blue. *Surgery* 2010; **148**: 78-86 [PMID: 20117811 DOI: 10.1016/j.surg.2009.12.003]

72 **Barnes TG**, Hompes R, Birks J, Mortensen NJ, Jones O, Lindsey I, Guy R, George B, Cunningham C, Yeung TM. Methylene blue fluorescence of the ureter during colorectal surgery. *Surg Endosc* 2018; **32**: 4036-4043 [PMID: 29785456 DOI: 10.1007/s00464-018-6219-8]

73 **Peter C**, Hongwan D, Küpfer A, Lauterburg BH. Pharmacokinetics and organ distribution of intravenous and oral methylene blue. *Eur J Clin Pharmacol* 2000; **56**: 247-250 [PMID: 10952480 DOI: 10.1007/s002280000124]

74 **Schols RM**, Lodewick TM, Bouvy ND, van Dam GM, Dejong CH, Stassen LP. Application of a new dye for near-infrared fluorescence laparoscopy of the ureters: demonstration in a pig model. *Dis Colon Rectum* 2014; **57**: 407-411 [PMID: 24509470 DOI: 10.1097/DCR.0000000000000055]

75 **Korb ML**, Huh WK, Boone JD, Warram JM, Chung TK, de Boer E, Bland KI, Rosenthal EL. Laparoscopic Fluorescent Visualization of the Ureter With Intravenous IRDye800CW. *J Minim Invasive Gynecol* 2015; **22**: 799-806 [PMID: 25796218 DOI: 10.1016/j.jmig.2015.03.008]

76 **van den Bos J**, Al-Taher M, Bouvy ND, Stassen LPS. Near-infrared fluorescence laparoscopy of the ureter with three preclinical dyes in a pig model. *Surg Endosc* 2019; **33**: 986-991 [PMID: 30478696 DOI: 10.1007/s00464-018-6596-z]

77 **Al-Taher M**, van den Bos J, Schols RM, Kubat B, Bouvy ND, Stassen LPS. Evaluation of a novel dye for near-infrared fluorescence delineation of the ureters during laparoscopy. *BJS Open* 2018; **2**: 254-261 [PMID: 30079395 DOI: 10.1002/bjs5.59]

78 **Son GM**, Kwon MS, Kim Y, Kim J, Kim SH, Lee JW. Quantitative analysis of colon perfusion pattern using indocyanine green (ICG) angiography in laparoscopic colorectal surgery. *Surg Endosc* 2019; **33**: 1640-1649 [PMID: 30203201 DOI: 10.1007/s00464-018-6439-y]

79 **van Oosten M**, Crane LM, Bart J, van Leeuwen FW, van Dam GM. Selecting Potential Targetable Biomarkers for Imaging Purposes in Colorectal Cancer Using TArget Selection Criteria (TASC): A Novel Target Identification Tool. *Transl Oncol* 2011; **4**: 71-82 [PMID: 21461170 DOI: 10.1593/tlo.10220]

80 **Harlaar NJ**, Koller M, de Jongh SJ, van Leeuwen BL, Hemmer PH, Kruijff S, van Ginkel RJ, Been LB, de Jong JS, Kats-Ugurlu G, Linssen MD, Jorritsma-Smit A, van Oosten M, Nagengast WB, Ntziachristos 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]

81 **Boogerd LSF**, Hoogstins CES, Schaap DP, Kusters M, Handgraaf HJM, van der Valk MJM, Hilling DE, Holman FA, Peeters KCMJ, Mieog JSD, van de Velde CJH, Farina-Sarasqueta A, van Lijnschoten I, Framery B, Pèlegrin A, Gutowski M, Nienhuijs SW, de Hingh IHJT, Nieuwenhuijzen GAP, Rutten HJT, Cailler F, Burggraaf J, Vahrmeijer AL. Safety and effectiveness of SGM-101, a fluorescent antibody targeting carcinoembryonic antigen, for intraoperative detection of colorectal cancer: a dose-escalation pilot study. *Lancet Gastroenterol Hepatol* 2018; **3**: 181-191 [PMID: 29361435 DOI: 10.1016/S2468-1253(17)30395-3]

82 **Boogerd LSF**, Boonstra MC, Prevoo HAJM, Handgraaf HJM, Kuppen PJK, van de Velde CJH, Fish A, Cordfunke RA, Valentijn ARPM, Terwisscha van Scheltinga AG, MacDonald GC, Cizeau J, Premsukh A, Vinkenburg van Slooten ML, Burggraaf J, Sier CFM, Vahrmeijer AL. Fluorescence-guided tumor detection with a novel anti-EpCAM targeted antibody fragment: Preclinical validation. *Surg Oncol* 2019; **28**: 1-8 [PMID: 30851880 DOI: 10.1016/j.suronc.2018.10.004]

83 **Marston JC**, Kennedy GD, Lapi SE, Hartman YE, Richardson MT, Modi HM, Warram JM. Panitumumab-IRDye800CW for Fluorescence-Guided Surgical Resection of Colorectal Cancer. *J Surg Res* 2019; **239**: 44-51 [PMID: 30798171 DOI: 10.1016/j.jss.2019.01.065]

84 **Cho HJ**, Lee S, Park SJ, Lee YD, Jeong K, Park JH, Lee YS, Kim B, Jeong HS, Kim S. Tumor microenvironment-responsive fluorogenic nanoprobe for ratiometric dual-channel imaging of lymph node metastasis. *Colloids Surf B Biointerfaces* 2019; **179**: 9-16 [PMID: 30928802 DOI: 10.1016/j.colsurfb.2019.03.047]

85 **Neumann PA**, Twardy V, Becker F, Geyer C, Schwegmann K, Mohr A, Faust A, Lenz P, Rijcken E. Assessment of MMP-2/-9 expression by fluorescence endoscopy for evaluation of anastomotic healing in a murine model of anastomotic leakage. *PLoS One* 2018; **13**: e0194249 [PMID: 29566031 DOI: 10.1371/journal.pone.0194249]

86 **Hingorani DV**, Whitney MA, Friedman B, Kwon JK, Crisp JL, Xiong Q, Gross L, Kane CJ, Tsien RY, Nguyen QT. Nerve-targeted probes for fluorescence-guided intraoperative imaging. *Theranostics* 2018; **8**: 4226-4237 [PMID: 30128049 DOI: 10.7150/thno.23084]

87 **Wada K,** Oba S, Tsuji M, Goto Y, Mizuta F, Koda S, Uji T, Hori A, Tanabashi S, Matsushita S, Tokimitsu N, Nagata C. Green tea intake and colorectal cancer risk in Japan: the Takayama study. *Jpn J Clin Oncol* 2019; **49:** 515-520 [PMID: 30855678 DOI: 10.1093/jjco/hyz030]

88 **Mizrahi I,** de Lacy FB, Abu-Gazala M, Fernandez LM, Otero A, Sands DR, Lacy AM, Wexner SD. Transanal total mesorectal excision for rectal cancer with indocyanine green fluorescence angiography. *Tech Coloproctol* 2018; **22:** 785-791 [PMID: 30430309 DOI: 10.1007/s10151-018-1869-z]

89 **Verbeek FP,** van der Vorst JR, Schaafsma BE, Swijnenburg RJ, Gaarenstroom KN, Elzevier HW, van de Velde CJ, Frangioni JV, Vahrmeijer AL. Intraoperative near infrared fluorescence guided identification of the ureters using low dose methylene blue: a first in human experience. *J Urol* 2013; **190:** 574-579 [PMID: 23466242 DOI: 10.1016/j.juro.2013.02.3187]

90 **Al-Taher M,** van den Bos J, Schols RM, Bouvy ND, Stassen LP. Fluorescence Ureteral Visualization in Human Laparoscopic Colorectal Surgery Using Methylene Blue. *J Laparoendosc Adv Surg Tech A* 2016; **26:** 870-875 [PMID: 27575463 DOI: 10.1089/lap.2016.0264]

**Footnotes**

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) licence, which permits others to distribute, remix, adapt, build upon this work non-commercially, and licence their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licences/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** March 3, 2021

**First decision:** April 17, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Switzerland

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Bencurik V **S-Editor:** Fan JR **L-Editor: P-Editor:**

**Table 1 Retrospective cohort studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Ref. | Indication for resection | Sample size | ICG injection time | Change of plan (%) | AL rate (%) |
| Kudszus *et al*[14], 2010 | Colorectal cancer | ICG: 201. Control: 201 | Before anastomosis | 16.4 | ICG: 3.5. Control: 7.5 |
| Kin *et al*[23], 2015 | Colorectal cancer, Diverticulitis, IBD, other | ICG: 173. Control: 173 | Before anastomosis | 4.6 | ICG: 7.5. Control: 6.4 |
| Jafari *et al*[3], 2013 | Rectal cancer | ICG: 16. Control: 22 | Before anastomosis | 19 | ICG: 6. Control: 18 |
| Kim *et al*[17], 2016 | Rectal cancer | ICG: 123. Control: 313 | Before ± after anastomosis | 02 | ICG: 0.8a. Control: 5.4 |
| Boni *et al*[15], 2015 | Colorectal cancer | ICG: 42. Control: 38 | Before + after Anastomosis | 4.7 | ICG: 0. Control: 5.2 |
| Wada *et al*[87], 2019 | Rectal cancer1 | ICG: 34. Control: 34 | Before anastomosis | 27.11 | ICG: 8.8. Control: 14.7 |
| Dinallo *et al*[24], 2019 | ND | ICG: 234. Control: 320 | Before anastomosis | 5.6a | ICG: 1.3. Control: 1.3 |
| Mizrahi *et al*[88], 2018 | Rectal cancer | ICG: 30. Control: 30 | Before + after anastomosis | 13.3 | ICG: 0. Control: 6.7 |
| Kim *et al*[19], 2017 | Rectal cancer | ICG: 310. Control: 347 | Before anastomosis | ND | ICG: 0.6a. Control: 5.2 |
| Ris *et al*[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: 2.4a. Control: 5.8 |
| Watanabe *et al*[20], 2020 | Rectal cancer | ICG: 211. Control: 211 | Before anastomosis | ND | ICG: 4.7a. 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.

a*P* < 0.05. ND: No data available; IBD: Inflammatory bowel disease; AL: Anastomotic leak; ICG: Indocyanine green.

**Table 2 Ureteral visualization studies using intravenous dye**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Ref. | Model | Surgery | Dye | *n* (%) | Visible ureters | Visible time after injection | Visibility duration |
| Matsui *et al*[71], 2010 | Pig | Open1 | Methylene blue | 20 | 100% (40/40) | 10 min | 65 min |
| Laparoscopy1 | 2 | 50% (2/4) | 10 min | 20 min |
| Verbeek *et al*[89], 2013 | Human | Open1 | Methylene blue | 12 | 100% (20/20) | 10 min | ≥ 50 min |
| Al-Taher *et al*[90], 2016 | Human | Laparoscopy | Methylene blue | 10 | 62,5% (5/8) | ND | ND |
| Barnes *et al*[72], 2018 | Human | Laparoscopy | Methylene blue | 34 | 93.6% (59/63) | 0 min | 2 h |
| Open | 6 | 66.6% (4/6) |
| Tanaka *et al*[67], 2007 | Rat | Open | IRDye 800CW | 12 | 100% | 3-5 min | ND |
| Pig | Open | IRDye 800CW | 6 | 100% | 10 min | > 20 min |
| Schols *et al*[74], 2014 | Pig | Laparoscopy | IRDye 800cw | 2 | 50% (1/2) | 10 min | ND |
| Korb *et al*[75], 2015 | Pig | Laparoscopy | IRDye 800CW | 6 | 100 % | 10 min | ≥ 50 min |
| Van den Bos *et al*[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 *et al*[77], 2018 | Pig | Laparoscopy | IRDye 800BK | 3 | 100% (6/6) | 1-20 min | ≥ 100 min |

1With dissection to highlight ureters.

ND: No data available.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**