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## **Review Article**

### **Advances in laparoscopic surgery for colorectal cancer: fluorescence- guided surgery**

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#### **Abstract**

Laparoscopic surgery for colorectal cancer (CRC) has been thoroughly investigated in a multitude of studies and has proved to have equivalent oncologic outcomes to open surgery, yet with the advantages of minimal tissue trauma, shorter hospital stay and quicker recovery. Recent advances in laparoscopic surgical treatment of CRC have been introduced in attempt to enhance the technique and improve the clinical outcome. One of such advances was the fluorescence-guided surgery (FGS) which has already been examined in other surgical specialties. Fluorescence- guided laparoscopic surgery for CRC appeared to be a promising tool to improve the outcome of laparoscopic colorectal surgery on the technical and oncologic levels. On the technical level, FGS can help prevent major complications such as anastomotic leakage and ureteral injury through real-time assessment of bowel perfusion and clear identification of the ureter along its entire course. On the oncologic aspect, FGS can help detect metastatic tumor deposits in the draining lymph nodes, peritoneum, or the liver. Detection of metastatic disease contributes to more accurate staging and enables fluorescence-guided resection of any metastatic lesions which can help increase the overall and disease-free survival rates. The present article aimed to review the current literature for the clinical utility of FGS in the laparoscopic management of colon and rectal cancer, illustrating how FGS can become the next frontier in laparoscopic colorectal surgery.

**Keywords:** fluorescence; guided surgery; laparoscopic; colorectal cancer; advances

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## **Background**

Colorectal cancer (CRC) is one of the most common human cancers ranking as the second most common cancer in females and the third most common in males. Treatment of CRC is dependent on the stage of the disease. Surgery is the only curative option for stage I-III disease and is potentially curative for stage IV CRC with limited metastatic disease [1]. Surgery for CRC can be undertaken via conventional laparotomy or minimally invasive surgery including the laparoscopic and robotic-assisted platforms.

Surgical treatment of CRC has been revolutionized by the introduction of laparoscopy. Several trials [2-4] concluded that the laparoscopic approach to CRC is comparable to laparotomy in regards complication, recurrence, mortality, and readmission rates. In addition, both approaches had also similar oncologic outcomes. Laparoscopy has been increasingly used for the treatment of CRC owing to its inherent advantages such as minimal trauma to the tissues, smaller incisions, lower incidence of wound-related complications, quicker recovery, and shorter hospital stay.

With the increasing use of laparoscopy in management of CRC, advances in the laparoscopic platform have been made in order to optimize the technique and improve the outcome, one of the recent advances was the introduction of fluorescence-guided laparoscopic surgery.

Fluorescence-guided surgery (FGS) is an imaging technique used to detect fluorescently labelled structures during surgery. The first description of FGS was by Moore and colleagues [5] when they used fluorescein to enhance the imaging of brain tumors, cysts, and edema.

Indocyanine green (ICG) a cyanine dye commonly used in FGS. It binds tightly to plasma proteins and has a

half-life of 150-180 seconds. The fluorescence spectrum of ICG is in the near infrared (NIR) region, hence the fluorescence system is called ICG-NIR fluorescence imaging [6]. The present review sheds light on the role of fluorescence-guided laparoscopic surgical treatment of CRC with emphasis on the role of ICG-NIR fluorescence imaging in FGS.

## **Search strategy**

The electronic databases of PubMed/Medline were searched for studies discussing the role of FGS using ICG-NIR in the laparoscopic treatment of CRC from inception through July 2017. Keywords used in the search process included “indocyanine green”, “ICG”, “Fluorescence”, “near-infrared”, “fluorescence-guided surgery”, “colorectal cancer, “colon cancer”, “rectal cancer”, “laparoscopy”, and “laparoscopic”. The references section of the retrieved articles was manually screened to identify relevant articles.

Only articles in the English language were included. Duplicate reports and conference abstracts were excluded. Articles were systematically screened by title, then by abstract screening as an initial step, and subsequently by full-text screening.

## **Clinical applications of FGS in the laparoscopic treatment of CRC**

After organized search of the published literature, five clinical applications of FGS in the laparoscopic treatment of CRC were identified. The applications comprised: 1) perfusion assessment prior to bowel anastomosis; 2) mapping of metastatic or sentinel lymph nodes (SLN); 3) visualization of the ureter; 4) detection of peritoneal

carcinomatosis; 5) fluorescence-guided resection of colorectal liver metastasis. Perfusion assessment before bowel anastomosis

Anastomotic leakage (AL) is a dreaded complication after any gastrointestinal, particularly colorectal, anastomosis. Although a number of patient-related and technical factors were suggested to contribute to the development of AL, deficient perfusion or ischemia of the bowel ends is considered the most important predisposing factor for AL [7].

Assessment of perfusion of bowel ends before performing an anastomosis is crucial. Traditional methods for perfusion assessment such as evaluation of tissue color, mesenteric pulsations, and degree of bleeding from the resection margins are merely subjective and could not prevent or reduce the incidence of AL [8]. With the establishment of ICG-NIR FGS, assessment of bowel perfusion became more reliable and accurate.

A number of prospective and retrospective studies evaluated the role of ICG-NIR fluorescence imaging in the assessment of bowel perfusion and its impact on the rate of AL. Mizrahi and Wexner [9] reviewed the outcome of studies that employed ICG-NIR fluorescence imaging for perfusion assessment in different types of laparoscopic resection of CRC. Kudzus et al. [10] published a case-control study involving patients with right and left colectomies and low anterior resection and noted that the group in which ICG-NIR fluorescence imaging was used had a lower incidence of AL (3.5% Vs 7.5%) and lower rate of operative reintervention (3.1% Vs 7.7%)

compared to the control group. Surgical plan was altered and the level of anastomosis was changed in around 16% of patients as ICG-NIR fluorescence implied insufficient tissue perfusion of the resection margins.

In another case control study involving patients with laparoscopic and open left colectomy and low anterior resection Kin et al. [11] found comparable rates of AL among patients in ICG-NIR group and those in the control group (7.5% Vs 6.4%). The use of ICG-NIR caused a change in the operative plan in 5% of patients. In contrast, Boni and associates [12] studied 80 patients who underwent laparoscopic low anterior resection and reported no AL in the ICG-NIR group versus a rate of 5% in the control group with change in the surgical plan in 4.7% of patients.

Ris and colleagues [13] performed a case series study on 30 patients who underwent either laparoscopic right or left colectomy or low anterior resection and reported no AL, a technical success of 97% and change in the level of anastomosis in half of the patients. In a larger case series study, The PILLAR II trial [14], AL occurred in 1.4% of patients with technical success of more than 98%. The level of anastomosis had to be revised in around 8% of patients.

Grone and affiliates [15] examined the utility of ICG-NIR in 18 patients with rectal cancer who were treated with laparoscopic low anterior resection. The authors reported technical success in all patients with an AL rate of 6% and change in surgical plan in 28% of patients. On the other hand, Kawada et al [16] used ICG-NIR to assess intestinal perfusion in 68 patients with CRC who

underwent laparoscopic left colectomy or low anterior resection with double stapled anastomosis. AL developed in 4.5% of patients and surgical plan was altered as result of ICG-NIR examination in around 31% of patients. Watanabe et al. [17] studied the intestinal blood flow near the rectosigmoid junction in 119 patients and recognized four different patterns of blood flow with no difference in the incidence of AL among them. The overall AL rate was 5.9% and none of the patients required a change in the level of anastomosis based on the findings of ICG-NIR fluorescence examination.

Overall, the rates of AL after laparoscopic resection of CRC from 0 to 10% and change in the surgical plan ranged between 0 and 100% after perfusion assessment with ICG-NIR [9]. The largest multicenter randomized trial evaluating the role of ICG-NIR fluorescence imaging (PILLAR III trial) is still underway with an estimated sample size of 550 patients.

#### Mapping of metastatic lymph nodes

Detection and removal of metastatic lymph nodes is an integral part of the radical treatment of CRC. Mapping of SLN can be achieved preoperatively via various imaging modalities or intraoperatively. SLN detection can lead to better staging of CRC and warrant the indication for adjuvant chemotherapy in some cases. Furthermore, SLN mapping helps recognize aberrant lymphatic patterns which may change the extent of radical lymphadenectomy [18].

A recent meta-analysis [19] reported the results of 12 trials which assessed the diagnostic accuracy of ICG-NIR in SLN detection in patients with CRC.

Several investigators used different methods for injection of ICG, including intravenous injection and peritumor injection either subserosal during surgery or submucosal using endoscopy. Similarly, different concentrations and dosage of ICG have been used. The timing of ICG injection also varied as some authors injected ICG intraoperatively while others injected the dye before the start of surgery.

The median sensitivity and specificity of ICG-NIR technique in detection of metastatic LNs were 73.7% and 100%. However, the pooled sensitivity was 71% and the pooled specificity was 84.6% [19]. Subgroup analysis revealed significant heterogeneity in sensitivity, specificity, and accuracy of ICG-NIR fluorescence imaging in SLN detection when different techniques of injection were compared. This wide variability in the outcome parameters calls for further trials to determine which technique of injection and fluorescence confers the highest sensitivity and specificity rates, hence help standardizing the technique.

Some can argue that SLN mapping in CRC can be achieved by other, well recognized, methods such as the injection of patent blue dye. Librale et al [20] compared the diagnostic accuracy of patent blue dye and ICG-NIR in patients with CRC. Although ICG-NIR had higher sensitivity rate, both techniques had the same accuracy rates with an overall correlation of more than 80%. Since ICG-NIR provides an additional advantage to patent blue dye that is perfusion assessment before colorectal anastomosis, the application of ICG-NIR as a tool for SLN mapping can be justified.

ICG-NIR fluorescence imaging was also used in the assessment of lymphatic drainage of splenic flexure carcinoma. Watanabe and colleagues [21] used laparoscopic real-time ICG-NIR fluorescence and found no lymphatic flow to the left colic and left branch of middle colic arteries, therefore routine ligation of both arteries was deemed unnecessary in contrast to the current practice. Moreover, the authors concluded that distal pancreatectomy and splenectomy are also not necessary in management of splenic flexure carcinoma since no lymphatic flow was directed towards splenic hilum and pancreas. The findings of this particular study can cause a paradigm shift in the surgical management of splenic flexure carcinoma by avoiding some steps which may reduce the overall morbidity rates and improve postoperative recovery.

Cahill and colleagues [22] believed that the clinical utility of ICG-NIR extends beyond its use for pathological staging as it can become a reliable tool for defining lymphatic drainage of the colon intraoperatively which may help define the ultimate draining lymphatic basin for various tumors. The authors thought that LN mapping using ICG-NIR fluorescence would enable the surgeon to follow a tailored surgical approach specified to each patient instead of simply following the general text-book anatomy.

Nishigori et al. [23] used ICG-NIR fluorescence for visualization of blood and lymphatic flow during laparoscopic surgery for CRC. Advantages of ICG-NIR according to the authors was having high sensitivity, fast feedback, and absence of radiation. ICG-NIR

fluorescence helped the surgeons to perform complete D3 lymphadenectomy which ensured removal of the highest draining LN that may harbor occult metastasis. This explains why the surgical plan of lymphadenectomy was changed in 23.5% of patients in the study after performing ICG-NIR test.

#### Visualization of the ureter

Although ureteral injuries in colorectal surgery are not frequent with an incidence of less than 0.5% according to Halabi et al. [24], such injuries can have serious consequences. In order to avoid such injuries, proper identification of the ureters intraoperatively is imperative. Placement of ureteral stents can help identify the ureters in laparoscopic surgery; however according to a recent study [25] less than 5% of patients undergoing laparoscopic colorectal surgery had a ureteral stent. Patients with diverticular disease, need for radical resection, and recent radiotherapy were the predictors for stent placement. Using ureteral stents in laparoscopic colorectal surgery can be associated with complications such as mucosal edema, reflex anuria, ureteral perforation, and ureteral obstruction as Pathak and colleagues reported [26]. Using different fluorescent agents, the ureters can be clearly delineated in pelvic, including colorectal, surgery and hence avoid insertion of ureteral stents.

ICG-NIR fluorescence imaging can be a safe and accurate method for identification of the ureters in pelvic surgery. Siddighi et al. [27] injected 25 mg of ICG dissolved in 10 mL of water through a 6-F ureteral catheter that was inserted into the ureteral orifice. ICG binds to proteins on the urothelial layer of the ureter staining its inside lining.

On application of NIR, the ureter fluoresces in green color allowing tracing it along its entire course which serves to prevent inadvertent injury of the ureter during surgery.

Yeung et al. [28] published a preliminary report on in-situ identification of the ureters in open and laparoscopic colorectal surgery. The report compared identification of the ureter in situ under white light illumination and after intravenous injection of methylene blue under fluorescence illumination. Eight patients aging between 27 and 76 years were included to the study. Of 11 ureters examined, 10 were successfully visualized under fluorescence. The strongest signal was obtained after using a concentration of 1 mg/kg and the maximum fluorescence was detected between 9 and 20 minutes after intravenous administration. The authors came to a conclusion that intravenous injection of methylene blue is a safe and simple method for localizing the ureter during colorectal surgery, yet larger clinical studies are required.

Another study [29] used intravenous injection of methylene blue for visualization of the ureters during laparoscopic colorectal surgery. Out of 10 patients included to the study, the ureter was successfully detected in five with no recorded adverse effects related to the administration of methylene blue indicating that ureteral fluorescence imaging using methylene blue is a safe and feasible option. However, methylene blue injection did not provide a practical advantage over conventional laparoscopic imaging for identification of the ureter.

Korb and associates [30] conducted

an animal study on adult female pigs using systemic injection of IRDye800CW-CA and FDA approved NIR system. Images of the ureters were captured every 10 minutes for one hour. The ureter was identified in all pigs and the peak intensity was at 30 minutes after injection and remained elevated throughout the duration of imaging. The conclusion of the study was that systemic administration of IRDye800CW-CA is a promising tool for ureteral identification during laparoscopic surgery that has the advantages of low dose and rapid time to visualization without any invasive ureteral instrumentation.

#### Detection of colorectal peritoneal carcinomatosis

Similar to its role in the detection of metastatic LNs in CRC, ICG-NIR can be valuable in the detection of peritoneal carcinomatosis and hepatic secondaries of primary CRC [31]. The preoperative detection of peritoneal carcinomatosis is currently being done using conventional or metabolic imaging modalities. However, such imaging modalities have low sensitivity in detection of peritoneal carcinomatosis reaching up to 47% for computed tomography scan (CT) and up to 57% for PET/CT scan [32]. Intraoperatively, peritoneal carcinomatosis is recognized by direct visual inspection and palpation which are subjective methods for assessment [31].

ICG-NIR fluorescence imaging can be considered a promising tool for detection of colorectal peritoneal carcinomatosis. Detection of peritoneal carcinomatosis can help to achieve more accurate staging and more radical surgical treatment of CRC which may

improve the prognosis ultimately.

Librale et al. [33] first evaluated the role of ICG-NIR in the detection of peritoneal metastases in patients undergoing cytoreductive surgery for colorectal peritoneal carcinomatosis. 0.25 mg/kg of free ICG was injected intravenously in 14 patients with CRC admitted for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). Among 63 peritoneal nodule evaluated for fluorescence, 53 were malignant and 10 were benign. The surgical plan was altered in 29% of patients after ICG-NIR fluorescence imaging detected additional peritoneal metastases that were not detected by direct visualization and palpation.

Barabino et al. [34] performed a pilot study involving 10 patients with colorectal peritoneal carcinomatosis scheduled for cytoreductive surgery. Each patient received 0.25mg/kg of ICG intravenously 24 hours preoperatively. Blind analysis of each specimen was followed. Of 88 lesions analyzed, 58 were malignant by pathologic examination, of which 42 were correctly identified by NIR camera as malignant lesions. The overall sensitivity and specificity of ICG-NIR fluorescence imaging in detection of peritoneal carcinomatosis was 72.4% and 60%, respectively. The study came to a conclusion that FGS using ICG-NIR “could help the surgeon to determine resection margins and reduce the risk of locoregional recurrence”.

Filippello and colleagues [35] conducted a clinical trial to demonstrate the mode of diffusion of ICG in peritoneal carcinomatosis secondary to CRC based on the effect of bevacizumab.

The trial included 10 patients with colorectal peritoneal carcinomatosis who all received preoperative chemotherapy. The patients were divided into two groups; a group that received bevacizumab (n=4) and a control group that did not receive bevacizumab (n=6). Twenty-nine peritoneal nodules were obtained from the bevacizumab group and 59 from the control group. In the bevacizumab group, 13 of the 20 peritoneal nodules were fluorescent, and 6 of the 9 non tumoral nodules were not fluorescent. The overall sensitivity and specificity rates were 65% and 66.7%, respectively. On the other hand, in the control group, 29 of the 38 peritoneal nodules were fluorescent and 12 of the 21 non-tumoral nodules were not fluorescent, with overall sensitivity and specificity rates of 76.3% and 57.1%, respectively.

Harlaar and coworkers [36] examined the utility of molecular FGS using the fluorescent tracer bevacizumab-IRDye800CW in seven patient with colorectal peritoneal carcinomatosis scheduled for cytoreductive surgery and HIPEC. 4.5 mg of bevacizumab-IRDye800CW were administered intravenously 48 hours before surgery. One mortality was recorded at the 4th day postoperatively due to asystole and one patient developed abdominal sepsis at the 5th day. Both adverse effects were related to the cytoreductive surgery and HIPEC, and not to bevacizumab-IRDye800CW itself. Fluorescent signals were detected in all patients during surgery and molecular FGS was able to detect tumor tissues that were missed initially in two patients. All of the non-fluorescent areas were found to be benign, and 53% of the

fluorescent areas were diagnosed as malignant tissues by pathologic examination. Although the study concluded that molecular FGS using bevacizumab-IRDye800CW is safe and feasible method, phase 2 trial is needed to substantiate this conclusion and to determine the true impact of FGS on clinical decision making in colorectal peritoneal carcinomatosis.

#### Fluorescence-guided resection of colorectal liver metastasis

ICG-NIR fluorescence has been recognized to have various clinical applications in hepatic surgery. ICG can be injected into the biliary tract, known as fluorescence cholangiography, or intravenously. After injecting ICG preoperatively the intraoperative fluorescence imaging can be helpful in identifying subcapsular primary or secondary hepatic tumors. This utility is particularly useful in laparoscopic surgery where the role of visual inspection and palpation of hepatic tumors is limited in comparison with open surgery [37].

Ishizawa et al [38] demonstrated the real time identification of liver cancer by ICG-NIR fluorescence imaging. The study included 63 patients with hepatocellular carcinoma and 28 with colorectal liver metastasis. Well differentiated hepatocellular carcinomas appeared as uniformly fluorescing lesions whereas colorectal liver secondaries appeared as rim-fluorescing lesions. 51% of hepatocellular carcinomas and all colorectal liver secondaries were identified by ICG-NIR examination before resection.

van der Vorst et al. [39] exploited the utility of ICG-NIR fluorescence in 40 patients with colorectal liver metastasis.

Seventy-one subcapsular colorectal liver metastases were detected and resected with guidance by ICG-NIR imaging. Liver metastases were visualized as non-fluorescent lesions surrounded by a rim of fluorescence representing entrapment of dye around CK7-positive hepatocytes compressed by the tumor. In 12.5% of patients, ICG-NIR was able to detect additional small subcapsular lesions that were not detected by preoperative CT scanning, intraoperative ultrasound, or visual inspection and palpation. However, 26 colorectal liver metastases identified by conventional imaging were not detectable by ICG-NIR imaging, all were deeper than 8 mm from the liver surface. Sensitivity of ICG-NIR in detection of colorectal liver metastasis was 73% compared to 75% for preoperative CT scanning.

Uchiyama and associates [40] used fluorescence navigation system in conjunction with contrast-enhanced intraoperative ultrasound for identifying colorectal liver metastasis in 32 patients. ICG was injected within two weeks of hepatic resection. The liver was examined by intraoperative ultrasound enhanced by sonazoid and by ICG-NIR imaging. Fifty-six lesions were resected, 52 of which were proven to be malignant lesions by histopathologic examination. The combined application of sonazoid-enhanced ultrasound and ICG-NIR was able to detect 51 metastatic lesions where preoperative CT/MRI detected 46 lesions. Moreover, the sensitivity of this combined imaging technique was 98.1%, higher than the sensitivity of preoperative multidetector CT and MRI (88.5%)

In agreement with the previous study, Peloso and colleagues [41] used



ICG-NIR in combination with intraoperative ultrasound for detection of colorectal liver metastasis in 25 consecutive patients. Patients received a bolus dose of ICG (0.5 mg/kg) 24 hours before surgery. Liver secondaries were identified by the surrounding rim of ICG fluorescence under NIR light. The accumulation of ICG around hepatic lesions is mostly due to defective biliary clearance. ICG-NIR combined with ultrasound detected 77 metastatic liver nodules compared to 55 detected by intraoperative ultrasound alone and 45 detected by CT scanning. It was obvious that the combined use of ICG-NIR and intraoperative ultrasound was superior to other techniques, especially in detection of small (<3mm) hepatic lesions.

Although ICG-NIR fluorescence imaging appears to be a promising tool for detection of colorectal liver metastasis, either alone or combined with intraoperative ultrasound, a few shortcomings of the technique should be addressed. Firstly, in order to detect hepatic lesions by ICG-NIR, the lesion has to be located on the liver surface as lesions located at a depth of > 8 mm from the liver surface are likely to be missed. Secondly, after portal vein embolization, ICG-NIR cannot assess any suspected lesion at the embolized hepatic area. Thirdly, it is difficult to differentiate any suspected liver lesions from the surrounding parenchyma in patients with underlying liver disease or if ICG was injected within 8 hours of surgery due to high signal intensity of the surrounding hepatic parenchyma [42].

In addition to fluorescence-guided resection of colorectal liver metastasis, ICG clearance test was also used in the

evaluation of chemotherapy associated liver injuries in patients with liver metastasis. Wakiya et al. [43] reviewed the outcome of 94 patients who underwent liver resection for colorectal liver metastasis after chemotherapy. The degree of histopathologic injury of the liver parenchyma away from the tumor was recorded and the correlation between the pathologic score and the ICG retention rate at 15 min (ICG-R15) was analyzed. Sinusoidal injury and steatohepatitis were observed in 33% and 42.5% of patients, respectively. There were no strong correlations between the preoperative ICG-R15 value and the sinusoidal pathological score or nonalcoholic fatty liver disease activity score rendering the prediction of chemotherapy associated liver injury by preoperative ICG clearance test difficult.

### **Summary and conclusion**

FGS can be considered the next frontier in the laparoscopic surgical treatment of colon and rectal cancer. Different fluorescent agents are used in fluorescence-guided colorectal surgery, among which ICG is the most commonly described in the literature. FGS can facilitate laparoscopic surgery for CRC and serve to achieve better outcome.

The clinical utility of FGS can be recognized on both technical and oncologic aspects. On the technical aspect, FGS helps reduce the rates of AL by accurate, real-time assessment of perfusion of the bowel ends prior to anastomosis. Additionally, using fluorescence imaging in visual identification of the ureters helps to avoid accidental ureteral injury and can be a practical alternative to the

placement of ureteral stents.

FGS also can have a positive impact on the oncologic outcome of CRC by detection of metastatic disease including metastatic LNs, peritoneal nodules, and hepatic metastasis. Detection of these metastatic lesions aids in performing navigation-guided resection of all tumor tissues, achieving the principles of tailored resection and precision surgery.

Although the initial trials have disclosed promising results of using FGS in the laparoscopic treatment of CRC, further trials are needed to ascertain these preliminary findings and to help in standardizing and optimizing the technique.

#### **Conflict of interest**

The authors have no potential conflicts of interest to disclose.

#### **References**

1. Dragovich T. Colon Cancer. Medscape. <http://emedicine.medscape.com/article/277496-overview#a6>. Accessed online on July 29, 2017.
2. Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW Jr, Hellinger M, Flanagan R Jr, Peters W, Nelson H; Clinical Outcomes of Surgical Therapy Study Group. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. *Ann Surg* 2007; 246:655-662; discussion 662-664.
3. Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, Heath RM, Brown JM; UK MRC CLASICC Trial Group. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *J Clin Oncol* 2007; 25(21):3061-3068.
4. Kuhry E, Schwenk WF, Gaupset R, Romild U, Bonjer HJ. Long-term results of laparoscopic colorectal cancer resection. *Cochrane Database Syst Rev* 2008; CD003432.
5. Moore, George; Peyton, William T; French, Lyle A.; Walkter, Walter W. The clinical use of fluorescein in neurosurgery; the localization of brain tumors. *J Neurosurg* 1948; 5:392-398.
6. Sabapathy V, Mentam J, Jacob PM, Kumar S. Noninvasive Optical Imaging and In Vivo Cell Tracking of Indocyanine Green Labeled Human Stem Cells Transplanted at Superficial or In-Depth Tissue of SCID Mice. *Stem Cells Int* 2015; 2015:606415.
7. Chadi SA, Fingerhut A, Berho M, DeMeester SR, Fleshman JW, Hyman NH, Margolin DA, Martz JE, McLemore EC, Molena D, Newman MI, Rafferty JF, Safar B, Senagore AJ, Zmora O, Wexner SD. Emerging Trends in the Etiology, Prevention, and Treatment of Gastrointestinal Anastomotic Leakage. *J Gastrointest Surg* 2016; 20:2035-2051.
8. 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.
9. Mizrahi I, Wexner SD. Clinical role of fluorescence imaging in colorectal surgery - a review. *Expert Rev Med Devices* 2017; 14:75-82.
10. Kudzus S, Roesel C, Schachtrupp A, Hoer JJ. Intraoperative laser fluorescence angiography in colorectal surgery: a noninvasive analysis to reduce the rate of anastomotic leakage. *Langenbecks Arch Surg* 2010; 395:1025-4130.
11. 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.
12. Boni L, Fingerhut A, Marzorati A, Rauseri S, Dionigi G, Cassinotti E. Indocyanine green fluorescence angiography during laparoscopic low anterior resection: results of a case-matched study. *Surg Endosc* 2017; 31:1836-1840.
  13. Ris F, Hompes R, Cunningham C, Lindsey I, Guy R, Jones O, George B, Cahill RA, Mortensen NJ. Near-infrared (NIR) perfusion angiography in minimally invasive colorectal surgery. *Surg Endosc* 2014; 28:2221-2226.
  14. 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.
  15. Gröne J, Koch D, Kreis ME. Impact of intraoperative microperfusion assessment with Pinpoint Perfusion Imaging on surgical management of laparoscopic low rectal and anorectal anastomoses. *Colorectal Dis* 2015; 17:22-28.
  16. Kawada K, Hasegawa S, Wada T, Takahashi R, Hisamori S, Hida K, Sakai Y. Evaluation of intestinal perfusion by ICG fluorescence imaging in laparoscopic colorectal surgery with DST anastomosis. *Surg Endosc* 2017; 31:1061-1069.
  17. Watanabe J, Ota M, Suwa Y, Suzuki S, Suwa H, Momiyama M, Ishibe A, Watanabe K, Masui H, Nagahori K, Ichikawa Y, Endo I. Evaluation of the intestinal blood flow near the rectosigmoid junction using the indocyanine green fluorescence method in a colorectal cancer surgery. *Int J Colorectal Dis* 2015; 30:329-335.
  18. Tuech JJ, Pessaux P, Regenet N, Bergamaschi R, Colson A. Sentinel lymph node mapping in colon cancer. *Surg Endosc* 2004; 18: 1721-1729.
  19. 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 Jun 1.
  20. 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.
  21. 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.
  22. 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.
  23. 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:S266-S274.
  24. 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.

25. Speicher PJ, Goldsmith ZG, Nussbaum DP, Turley RS, Peterson AC, Mantyh CR. Ureteral stenting in laparoscopic colorectal surgery. *J Surg Res* 2014; 190:98-103.
26. Pathak RA, Taylor AS, Alford S, Broderick GA, Igel TC, Petrou SP, Wehle MJ, Young PR, Thiel DD. Urologic-Induced Complications of Prophylactic Ureteral Localization Stent Placement for Colorectal Surgery Cases. *J Laparoendosc Adv Surg Tech A* 2015; 25:966-970.
27. Siddighi S, Yune JJ, Hardesty J. Indocyanine green for intraoperative localization of ureter. *Am J Obstet Gynecol* 2014; 211:436.e1-e2.
28. Yeung TM, Volpi D, Tullis ID, Nicholson GA, Buchs N, Cunningham C, Guy R, Lindsey I, George B, Jones O, Wang LM, Hompes R, Vojnovic B, Hamdy F, Mortensen NJ. Identifying Ureters In Situ Under Fluorescence During Laparoscopic and Open Colorectal Surgery. *Ann Surg* 2016; 263:e1-e2.
29. 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.
30. 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.
31. 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.
32. Dromain C, Leboulleux S, Auperin A, Goere D, Malka D, Lumbroso J, Schumberger M, Sigal R, Elias D. Staging of peritoneal carcinomatosis: enhanced CT vs. PET/CT. *Abdom Imaging* 2008;33:87-93.
33. 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 Bordet's Institute. Fluorescence Imaging After Indocyanine Green Injection for Detection of Peritoneal Metastases in Patients Undergoing Cytoreductive Surgery for Peritoneal Carcinomatosis From Colorectal Cancer: A Pilot Study. *Ann Surg* 2016; 264:1110-1115.
34. Barabino G, Klein JP, Porcheron J, Grichine A, Coll JL, Cottier M. Intraoperative Near-Infrared Fluorescence Imaging using indocyanine green in colorectal carcinomatosis surgery: Proof of concept. *Eur J Surg Oncol* 2016; 42:1931-1937.
35. Filippello A, Porcheron J, Klein JP, Cottier M, Barabino G. Affinity of Indocyanine Green in the Detection of Colorectal Peritoneal Carcinomatosis. *Surg Innov* 2017; 24:103-108.
36. 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.
37. Ishizawa T, Saiura A, Kokudo N. Clinical application of indocyanine green-fluorescence imaging during hepatectomy. *Hepatobiliary Surg Nutr* 2016; 5:322-328.
38. Ishizawa T, Fukushima N, Shibahara J, Masuda K, Tamura S, Aoki T, Hasegawa K, Beck Y, Fukayama M, Kokudo N. Real-time identification of liver cancers by using indocyanine green fluorescent imaging. *Cancer* 2009;

115:2491-504.

39. van der Vorst JR, Schaafsma BE, Hutteman M, Verbeek FP, Liefers GJ, Hartgrink HH, Smit VT, Löwik CW, van de Velde CJ, Frangioni JV, Vahrmeijer AL. Near-infrared fluorescence-guided resection of colorectal liver metastases. *Cancer* 2013; 119:3411-3418.

40. Uchiyama K, Ueno M, Ozawa S, Kiriya S, Shigekawa Y, Yamaue H. Combined use of contrast-enhanced intraoperative ultrasonography and a fluorescence navigation system for identifying hepatic metastases. *World J Surg* 2010; 34:2953-2959.

41. Peloso A, Franchi E, Canepa MC, Barbieri L, Briani L, Ferrario J, Bianco C, Quaretti P, Brugnattelli S, Dionigi P, Maestri M. Combined use of intraoperative ultrasound and indocyanine green fluorescence imaging to detect liver metastases from colorectal cancer. *HPB (Oxford)* 2013; 15:928-934.

42. Kokudo N, Ishizawa T (eds). *Fluorescent Imaging: Treatment of Hepatobiliary and Pancreatic Diseases*. *Front Gastrointest Res*. Basel, Karger, 2013, vol 31, pp. 18-24.

43. Wakiya T, Kudo D, Toyoki Y, Ishido K, Kimura N, Narumi S, Kijima H, Hakamada K. Evaluation of the usefulness of the indocyanine green clearance test for chemotherapy-associated liver injury in patients with colorectal cancer liver metastasis. *Ann Surg Oncol* 2014; 21:167-172.