Possibilities Of Fluorescence Imaging In Laparoscopic Surgery

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Abstract

Fluorescent imaging is increasingly being used to assist surgeons in making intraoperative decisions, which requires the use of fluorescent dyes that accumulate in anatomical or pathological structures, and their radiation is recorded by a laparoscope, with the function of detecting fluorescence. This review focuses on the use of fluorescent imaging in gastrointestinal surgery. The advantage of using fluorescent dyes is that they are highly selective for the target of interest. When using the indocyanine green, the intensity of the fluorescence signal detected in the tissue can be used as a marker of tissue perfusion, to assess the state of intestinal perfusion, intestinal anastomoses, anastomotic leaks, and the presence of affected lymph nodes. According to our data, the introduction of ICG into the mucosa around the tumor at the beginning of the operation makes it possible to clearly define the boundaries of the tumor lesion, which excludes the intersection of the intestine near the tumor. In addition, it is possible to visualize all the lymph nodes and lymphatic vessels through which the outflow of lymph from the tumor occurs. This makes it possible to determine the primary "sentinel" lymph node, the defeat of which requires an extended lymph node dissection, and in patients in whom the "sentinel" lymph node is not affected, you can limit yourself to a smaller volume of surgery. There is now increasing evidence that the use of fluorescence imaging during laparoscopic surgery can help the surgeon make intraoperative decisions in a wide range of situations, especially in assessing tissue perfusion, tumor pathology, lymphatic drainage, and identification of the urinary tract.

Keywords: fluorescence imaging, indocyanine green, sentinel lymph node, gastric cancer, rectal cancer

Introduction

Fluorescence imaging is increasingly being used to assist surgeons in the intraoperative decisions making, which requires the use of fluorescent stains that accumulate in anatomical or pathological structures, and their radiation is recorded by a laparoscope with the fluorescence detecting function [3, 21, 25]. This review focuses on the use of the fluorescence imaging in the gastrointestinal surgery, which can be roughly divided into four categories: (1) assessment of the tissue perfusion and vasculature; (2) the tumor evaluation; (3) lymphatic drainage; and (4) the ureters identification.

All the fluorescent stains used in surgery can be divided into specific and non-specific ones [1, 6, 15, 21]. The specific stains are those having a specific affinity for the target of interest, such as the fluorescent-labeled antibodies or nanoparticles. The preference of using certain stains is that they are highly selective for the target of interest. However, they are more expensive than non-specific stains, their total fluorescence is weaker as a rule. They are novel agents and for the clinical use the approval from the national regulatory authorities is required (e.g. FDA/MHRA).

The non-specific stains are those having no specific targets, but when administered *in vivo*, they have an ability to accumulate in tissues and anatomical structures [2, 5, 17, 25]. Examples of the non-specific stains include indocyanine green (ICG) and methylene blue (MB). Both of these stains have been used *in vivo* for many years with excellent safety profiles, and the inherent fluorescent properties have made them very popular as stains in fluorescence imaging [4, 8, 18]. In particular, ICG emits in the near infrared (NIR) range, and this wavelength gives the best signal-to-noise ratio and penetrates deep through the tissues [9, 20, 25].

Different companies have developed commercially available fluorescent laparoscopes including PINPOINT (Novadaq/Stryker), Firefly (built into the Da Vinci robotic platform), and OPAL1 (Karl Storz). All of them are adjusted to detect radiation in the spectra of the near-IR range [21, 25].

Tissue Perfusion Assessment

ICG can be administered intravenously and the intensity of the fluorescence signal found in the tissue can be used as a perfusion marker. It was used to assess the state of intestinal perfusion [1, 2], intestinal anastomoses [3], anastomotic leakage after anterior resection is a serious complication, the frequency of which according to literature data is from 10 to 15% [4–6].

The prospective multicentre clinical investigation PILLAR II allowed to determine the effectiveness of fluorescence imaging for assessing intraoperative perfusion during the left-sided hemicolectomy and the anterior rectal resection [7]. 139 patients were analyzed at 11 US centers. The fluorescence angiography changed surgical plans in 11 (8%) patients, mainly due to changes in the level of proximal intestinal transection (7%). The total incidence of anastomotic leakage was in 2 patients (1.4%). Whereas, in patients where the anastomotic perfusion status was assessed, there was no leakage.

So, in 29 (5.8%) patients, due to the fluorescence assessment of intestinal tissue perfusion, the level of crossing the proximal intestine was changed, and there was no anastomotic leakage in this group [8].

In the retrospective examination of 347 patients undergoing colectomy with primary anastomosis, the patients were divided into groups: 238 patients were used the fluorescent tissue perfusion imaging and 109 patients were not. In the first group, only two patients (0.84%) had anastomotic

leakage. There were six (5.5%) anastomotic leakages in the second group. Besides, according to the results of the tissue perfusion assessment in group 1, the level of crossing the proximal intestine was changed in 11 (4.6%) patients, and anastomotic leakage developed in none of them [9].

Watanabe et al. reported the 3-centre retrospective investigation focusing on the laparoscopic resections with the rectal cancer [10]. In 211 patients, the intestinal perfusion fluorescence assessment technique was used, and in 211 patients (control group) this technique was not used. In the control group, the anastomotic leakage rate was 9.5%, and in the main group — 2.8%.

De Nardi P. et al. conducted a multicenter randomized controlled investigation in 240 patients who underwent laparoscopic resections of the sigmoid and rectum [11]. Anastomotic leakage occurred in 11 patients (9%) of the control group and in 6 patients (5%) of the experimental group.

Four other investigations (Impellizzeri et al. [12], Yanagita et al. [13], Marquardt et al. [14], and Hasegawa et al. [15]) dealt with results of the laparoscopic colon surgery with and without ICG imaging. According to the authors, the incidence of anastomotic leakage decreased from 6% to 0% with sigmoid resection and with low anterior rectum resection — from 13.6% to 2.8–4.5%.

The INTACT randomized study is currently underway, which should give a clear answer to the question: can fluorescence angiography significantly reduce the incidence of colonic anastomotic leakage [16].

It still remains a problem what level of fluorescence can be considered sufficient for normal healing of anastomoses [17–19].

The ICG fluorescence has also been used to assess small intestine perfusion in patients with acute mesenteric ischemia in order to preserve the small intestine length as much as possible [20]. Among 52 patients, the use of ICG resulted in a significant change in operative management in 6 patients (11%), resulting in a significant clinical effect.

Fluorescence imaging of tumors and metastatic lymph nodes

When the ICG is administered intravenously, it is metabolized by hepatocytes and excreted through the biliary system. In the presence of colorectal metastases, the ICG fluorescence was noted at the edge of metastases [22]. The normal hepatocytes showed fluorescence, while tumor cells did not, due to a defect in bile clearance [23]. The ICG fluorescence can identify small lesions that were not identified before the operation and therefore may be a useful tool to provide R0 boundaries when removing colorectal liver metastases [23, 24].

Data from our study conducted in the period from 2009 to 2021, included 184 patients with rectal cancer, operated on at the Odessa Regional Clinical Hospital using transanal endoscopic resections (TEM). The age of the patients ranged from 42 to 86 years. All 184 patients were divided into 2 groups. In group I, 90 patients were diagnosed stage I rectal cancer (T1-2N0M0), while the age of those patients ranged from 42 to 86 years. In group II, 94 patients were diagnosed stage II rectal cancer (T3N0M0) before surgery. 172 patients after diagnosing rectal cancer, according to the preoperative biopsy results were required to undergo neoadjuvant chemoradiation therapy. This complex preoperative treatment made it possible to significantly reduce the size of the tumor, its invasion into the wall of the rectum, and minimize the risk of metastasis to regional “sentinel” lymph nodes. To perform this operation, the surgical equipment “Karl Storz TEO” was used. In group I, a standard TEM procedure was performed. A special port for electrosurgical instruments was inserted into the rectum. After carbon dioxide insufflation, the tumor resection zones were marked with an electrocoagulation hook, at least 10 mm away from the tumor edge. The resection was performed in layers, using a hook, as well as a “LigaSure” coagulator, Covidien. After resection of the tumor within intact tissues, the rectum was sanitized with Betadine solution, after which the defect of the rectum was sutured using a self-tightening thread “V-Lock”, Covidien.

In group II, taking into account the presence of stage II RC in patients, and the high possibility of recurrence and metastasis, after performing local excision of tumors using the TEM method, we improved this method. Performing the operation according to the standard TEM method, 1–2 ml of ICG stain was injected into the submucosal layer of the tumor. In 15 minutes laparoscopy was performed with the regional lymph nodes staining. For a clearer visualization of the “sentinel” lymph vessels and regional lymph nodes, the ultraviolet illumination mode was used on a video laparoscopic rack, “Karl Storz”. After a laparoscopic removal of “sentinel” LN, their urgent histological examination was performed. If there were no cancer micrometastases in the LN, the tumor was resected using the TEM technique. In the presence of metastatic involvement of “sentinel” lymph nodes, laparoscopic or laparoscopically assisted low anterior resection of the rectum was performed, with an obligatory removal of the mesorectum and periampullary tissue – a total mesorectectomy (TME). In group II, no cancer metastases were found in the “sentinel” LN in 58 patients; these patients underwent radical resection of the rectal tumor using the standard TEM technique. In 36 patients in this group, rectal cancer metastases were found in regional LN, these patients underwent low anterior resection of the rectum with TME.

All 184 patients had no purulent-septic, thromboembolic and urological complications. There were no severe intraoperative complications, and none of the patients died. The average time of the hospital stay was (3.4±1.7) days (from 2 to 6 days). The lower edge of the tumor was at the average height of (7.5±4.2) cm from the anal canal (from 5 to 16 cm), the average size of the tumor was from (2.8±1.7) cm (from 1.5 to 4 cm). The histological study of the removed preparations in all cases revealed that the tumor was removed within intact tissues.

At the early postoperative period, acute bleeding occurred in 8 patients of group I, which required the second surgical intervention using the TEM method; during the operation bleeding vessels were visualized, carefully coagulated and sutured. These patients were discharged from the hospital on the 7th day.

Intraoperative perforation into the abdominal cavity was in 6 (6.6%) patients when the tumor was located at a height

of 13 and 15 cm from the anal canal. In these patients, the defect of the intestine was sutured laparoscopically from the side of the abdominal cavity without the protective stomy. The tightness of the sutures was checked intraoperatively by the appearance of air bubbles when gas was injected into the rectum. These patients were discharged from the hospital 8–10 days after surgery. When monitoring these patients in the late postoperative period, it was found that defects in the rectum healed satisfactorily.

The average follow-up period ranged from 12 to 60 months. Recurrence of rectal cancer was found in 12 (13.3%) patients, group I. Cancer recurrence occurred in those patients who refused chemotherapy and radiotherapy. Patients with recurrences were operated on again by way of classical Low anterior resections of the rectum with total mesorectumectomy.

When monitoring patients of group II at the period from 12 to 40 months, tumor recurrence and distant metastases were not detected. The method of studying the "sentinel" LN in patients with RC has a high diagnostic value for the detection of lymphogenic metastases.

According to our data, the indocyanine green introduction into the mucosa around the tumor at the beginning of the operation makes it possible to clearly define the boundaries of the tumor lesion, which excludes the transection of the intestine near the tumor [21, 25]. Besides, it is possible to visualize all the lymph nodes and lymph vessels through which the lymph outflows from the tumor. It gives an opportunity to detect the primary "sentinel" lymph node, in case of its involvement the extended lymph node dissection is required, and in patients with an intact "sentinel" lymph node, it is possible to use a smaller volume of surgery [21, 25].

The lymphatic drainage from colorectal cancer can be detected by administering the ICG around the tumor in the submucosal plane either before surgery or during the procedure [26, 27]. It may reveal the degree of mesocolectomy required and therefore determine the margin of the dissection, for example, in a tumor of the flexure of the liver [27]. During investigation of 21 patients, the ICG changed the surgical plan of the lymphadenectomy level in 23.5% of cases [26]. In another study of 42 patients with moderate to low rectal cancer, the use of the ICG fluorescence resulted in significantly more extracted lateral pelvic lymph nodes and reduced intraoperative blood loss compared to the white light imaging alone [28].

Some studies detected whether the ICG fluorescence in lymph nodes correlates with the presence of colorectal metastases. Liberale et al. report that the affected lymph nodes are hyperfluorescent as compared to unaffected lymph nodes [29]. Nishigori et al. reported that the metastasis rate of the ICG-positive nodes was 10%, while the metastasis rate of the ICG-negative nodes was 5.3% [26]. They also demonstrated the absence of metastatic nodes that would be ICG negative at a distance of more than 5 cm from the tumor.

The ICG has also been used to evaluate peritoneal disease in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy [29, 30]. In 9 patients with the non-mucinous adenocarcinoma 42 nodes were analyzed. It turned out that the average ratio of tumor fluorescence to the background was 1.92 in malignant disease as compared to 1.02 in benign nodes ($p = 0.0099$). The use of fluorescence made it possible to detect tumor nodes in 4 of 14 patients (29%), which were not detected under normal light [29].

Identification of the ureters

Identification of the ureters during colorectal surgery is often a difficult task, especially in cases of intra-abdominal obesity, the diverticular disease, previous pelvic radiotherapy, or retroperitoneal fibrosis. When administered intravenously, methylene blue is excreted through the renal system and fluoresces at a wavelength of 660 nm. Evidence of the principal studies demonstrates that methylene blue administration is safe, has no side effects, and can reveal the location of the ureters on fluorescence [31, 32].

The average time of the ureter identification was 14 minutes after the methylene blue injection, and ureters could be visualized up to 75 minutes after the stain injection [31]. In addition to this study, 40 patients more were examined and 69 ureters were assessed, of which 64 ones were visible under fluorescence. Of them, 14 were not visible in white light. 50 ureters were visible under fluorescence and white light, with 14 of them were previously visible under fluorescence. In 10 cases, fluorescence showed that the ureter was in a different location than initially expected [33].

We conducted a retrospective study of the analysis of the results of laparoscopic left-sided colectomy in patients with sigmoid and rectal cancer, as well as in patients with a complicated sigmoid diverticulosis. From 2017 to 2021, 62 patients undergoing laparoscopic left-sided hemicolectomies. Sigmoid colon cancer was in 26 patients, rectal cancer in 19 patients, and a complicated sigmoid diverticulosis in 17 patients. In the first period from 2017 to 2019, operations were performed according to standard methods. During the second period from July 2019 to December 2021, ICG-imagination was used in patients with complicated diverticular disease and colon cancer to visualize the left ureter. The technique consisted in the following: before the operation, patients undergoing the left ureter catheterization. A 5-6 Fr open-ended ureteral catheter was insert up to 20-25 cm; during the operation, 15 mg of ICG was injected through the ureteral catheter to feeding vessels and mobilization of the large intestine. In this case, the left ureter was visualized in bright green and it was easy to differentiate it from vessels and other tissues. In the first period, laparoscopic left-sided colectomy was performed in 34 patients, while damage to the left ureter was detected in 7 patients (20.5%): in 3 patients with cancer of the sigmoid colon and upper-ampullar rectum during tumor invasion into the anterior abdominal wall and the left ureter; in 4 patients with diverticular disease of the colon complicated by perforation of diverticula. At the same time, in 5 patients, the ureteral injury was repaired intraoperatively, and 2 patients with ureteral strictures were re-operated by urologists. In the second period, a total of 28 patients were operated on: 19 patients with sigmoid and rectal cancer, and 9 patients with a complicated form of diverticular disease. In difficult cases, when it was difficult to visualize the left ureter, the ICG-imagination technique was performed. Damage of the left ureter during this period was

detected only in 1 patient (3.5%) with advanced cancer of sigmoid colon.

Nowadays all the commercial fluorescent laparoscopes are adjusted to a near-IR range that does not catch the methylene blue signal. So, the widespread use of methylene blue in fluorescence will require the commercial development of adjustable fluorescent laparoscopes. Santi et al. describe the ICG use to identify ureters during surgery by injection through a urinary catheter [34].

Conclusion

There is increasing evidence that the use of fluorescence imaging during the colorectal surgery can help the surgeon in making intraoperative decisions of a wide range of situations, especially in assessing the tissue perfusion, tumor pathology, lymphatic drainage, and ureters identification. There is a great need in randomized controlled trials in order to demonstrate the efficacy and benefits of routine use of fluorescence imaging.

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