The evolving role of indocyanine green fluorescence in the treatment of low rectal cancer

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Abstract: The implementation of fluorescence imaging, specifically indocyanine green in rectal cancer surgery has been significantly evolving in the past few years. Its use for the prevention of anastomotic leaks (ALs) has been gaining popularity, with accumulating data about the lower leak rates with indocyanine green fluorescense (ICG). Additional promising applications of this technique in colorectal surgery are ureteral identification, lymphatic mapping and identification of metastatic implants.

Keywords: Anastomotic leak (AL); indocyanine green; rectal cancer

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Introduction

Indocyanine green fluorescense (ICG) has gained popularity in recent years in colorectal surgery in general with a special emphasis on low rectal resections. Moreover, in addition to perfusion assessment, other potential applications have been proposed.

The ICG compound was approved by the U.S Food and Drug Administration already in 1959 and has since that time has been used in various fields of surgery such as foregut and hepatobiliary. Its short half-life of less than 3 minutes and lack of hepatic metabolism has focused the interest of colorectal surgeons on its use in the assessment of bowel perfusion (1,2). The relevance of its application in modern colorectal surgery became pertinent after industry developed tools for the minimally invasive settings.

For decades, surgeons have acknowledged the paramount importance of adequate perfusion to the bowel as one of the basic surgical principles for a construction of healthy anastomosis.

The fear of the anastomotic leak (AL) is heightened in low rectal resections as reported leak rates are consistently above 10% (3,4). Thus, it is apparent that a method with a potential to discern acceptable perfusion, would carry a great promise to decrease the leak rate and improve outcomes.

Herein, we describe the technique of the ICG administration, the current available data on the potential benefits of ICG with regard to decreasing ALs. In addition, we also review other potential merits in Low rectal cancer surgery such as lymphatic mapping, peritoneal implants detection and avoiding ureteral injuries.

Avoiding anastomotic leakage

The much-dreaded complication of AL has a high prevalence in rectal resections, especially following low anterior resections (LAR) (4,5).

Several identified risk factors, such as the height of the anastomosis (<10 cm) and prior neoadjuvant radiation therapy enhance the patients' susceptibility to AL (6,7).

The ensuing morbidity, mortality and economic burden (8) have led to a continuing quest to try and improve anastomotic healing. Maintaining sufficient blood supply to the newly created anastomosis has been recognized as a crucial factor (9,10). Various methods have been implemented with variable success rates. The most common of which is the subjective evaluation performed by the surgeon during operation. The experienced surgeon looks at bowel color, palpates for pulse within supplying mesentery, and looks for bleeding in the transected edges. However, studies have shown that this evaluation is not very accurate at predicting AL (11). Several, more objective modalities have been proposed, including: spectroscopy, Doppler flowmetry, pH measuring and even on-table angiography (12-14).

They are all limited for different reasons: difficulty to use in the operating room, time consuming or costly. The standardization and reproducibility of these various technologies is yet another obstacle

Fluorescence angiography (FA) utilizing ICG allows for real-time intraoperative evaluation of bowel perfusion (15). The method of its application is appealing due to its ease of repetition, short time of implementation, and excellent visualization.

Technique

The anesthesiologist administers a bolus of 3.5 mL of ICG intravenously followed by a 10-mL flush of sterile normal saline (NS). Colonic perfusion is visualized and assessed via fluoroscopic angiography (FA) with a laparoscopic system. The line of demarcation between perfused and non-perfused tissue is noted and the colon is then divided within an area of well-perfused tissue.

After completion of the anastomosis, the anastomosis is assessed with FA. A second bolus of 3.5 mL of ICG is injected and followed by a 10-mL flush of sterile NS. In the first step the FA is performed via laparoscopy to assess the serosal aspects of both ends of the anastomosis. Afterwards, the endoscope is inserted into a custom designed rigid proctoscope, advanced towards the anastomosis with injection of a third bolus of 3.5 mL of ICG, followed by a 10-mL flush of NS. Then, the perfusion of both proximal and distal anastomotic mucosal surface is appreciated.

Several studies have been published which demonstrate the lower leak rates with ICG.

In the PILLAR II trial (16) it was found that in the high-risk group (<10 cm anastomosis and/or irradiated pelvis) the use of FA caused a revision of anastomosis in 1.8% and changed the planned resection margin during surgery in 7.5%. Both the radiologic and clinical AL rate in this high-risk group was as low as 1.9%. Kim *et al.* (17) has published a large series of patients who underwent robotic assisted rectal resection with AL of 0.8% in the study group, compared to 5.4% in the control group.

Ris *et al.* (18) published a large series with implementing FA in 504 patients, 90 of whom underwent LAR. The leak rate was 3.3% *vs.* 10.7% in the control group with only 4 minutes added time to surgery. In our recent study (19), the surgical plan was changed in 13.3% with no AL in the ICG group, whereas the leak rate in the control group was 6.7%. Implementing the FA for our TaTME group of patients we found AL in 2 patients, 4.5% with a change of surgical resection margins in about 22% (20).

The consensus conference of experts, held in UK concluded that fluorescence imaging is the most promising technology to try to reduce the burden of ALs (21).

Ris and his colleagues (18) reported that in 5 patients a planned stoma was omitted formation due to the FA findings.

Lymphatic mapping and peritoneal implants

The property of the ICG uptake in the lymphatic system has appealed surgeons to improve surgical decision making and oncological outcomes. Cahill *et al.* (22) found that 4 out of 18 patients had involved lymph nodes outside the planned resection margins, in the pelvic side walls or periaortic region.

A recent study by Chand and his colleagues from London demonstrated the feasibility of fluorescence for lymphatic mapping with 2 out of 10 patients having involved lymph nodes outside the planned resection margins, also confirmed in final pathology (23).

In a meta-analysis which included twelve studies looking at the detection of metastatic lymph nodes in colorectal cancer (24), the median sensitivity was found to be 73.7% and the specificity was as high as 100%.

The higher uptake of the ICG by colorectal peritoneal metastases was recently studied with an attempt to detect additional metastases during surgery that were otherwise overlooked. In cytoreductive surgery for peritoneal carcinomatosis from colorectal cancer with the use of ICG, 29% additional metastases were found (25). In their review, Liberale *et al.* found that though the data is scarce, the use of ICG might help in the detection of small hepatic, lymph nodes, and peritoneal metastatic deposits (26).

Ureter identification

Ureter identification is an integral part of any rectal resection surgery. The placement of ureteral stents to assist in the identification process during surgery is quite common, especially in pelvic reoperative surgery. However, the placement of stents is not without complications (27,28).

Thus, a non-invasive intra-operative method to recognize ureters during surgery is sought after. The novel technique to identify the ureters using FA was described in a rat model with sodium fluorescein (29) and then, in a latter study (30) with identification of ureters in 4 out of 11 patients, not otherwise identified. It was further described in a Yorkshire pig model with obtaining ureter visualization with near—infrared fluorescence, for over 2 hours in all of the pigs (31). This technique was also successfully utilized by gynecologic surgeons with an excellent safety profile, albeit in a small number of patients (32).

Conclusions

The use of ICG FA in the treatment of low rectal cancer is safe, cost-effective and carries a promise in reducing both intraoperative and post-operative complications. While there is already a pool of recent data for its role in lowering AL rates, studies are ongoing to establish its role as a cornerstone of modern colorectal surgery. The method's additional potential added value in identifying circulating tumor cell and metastases, such as in lymphatic mapping and also for clarification of anatomic structures such as the ureters is still evolving with further research required for its better implementation in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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