Original Article

Application of Intraoperative Indocyanine Green Fluorescence for Patients with Sigmoid Colon and Rectal Cancer

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Key Words
Intraoperative indocyanine green fluorescence angiography;
Anterior resection;
Low anterior resection;
Anastomotic leakage

Purpose. To analyze the outcomes and anastomotic leakage rate of patients undergoing sigmoid colon and rectal resections with indocyanine green (ICG) fluorescence angiography.
Method. We retrospectively analyzed patients who underwent minimally invasive surgery with ICG-enhanced fluorescence-assisted imaging, performed by a single surgeon at National Cheng Kung University Hospital between July 2018 and June 2019. Clinical parameters, perioperative characteristics, and pathologic outcomes were analyzed.
Results. A total of 22 patients were included. Two patients (9.1%) underwent preoperative radiotherapy. Three patients (13.6%) presented with near total obstruction before surgery. Anterior resection was noted in 10 patients (45.5%). The anastomotic level was between 6 and 8 cm AAV in four patients, and between 0 and 5 cm AAV in eight patients. High ligation of the inferior mesenteric artery was performed in 21 patients, and proximal stoma diversion was performed in 6 patients (27.3%). ICG fluorescence indicated a change in resection level in one patient. No patients experienced anastomotic complications.
Conclusion. ICG fluorescence angiography could identify the patients for poor perfusion to anastmosis area, which may help to reduce the anastomotic leakage in sigmoid colon and rectal resections.
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Advancements in modern surgical tools and techniques and the development of the neoadjuvant chemoradiation therapy regimen have improved the outcomes of patients with resectable sigmoid and rectal cancers. Despite these advancements, studies have reported that the prevalence of anastomotic leakage remains at approximately 10%-30%.[1-3] The outcomes for such patients, including morbidity, mortality, and local recurrence rate, were markedly worse than for those with no complications.[4,5]

Risk factors were examined, and the following were reported to increase anastomosis-related complications: obesity, level of anastomosis, tobacco usage, preoperative radiation, male sex, adverse intraoperative events, and anastomotic techniques.[6-11] Inadequate vascular perfusion over the anastomotic area was considered to be a major factor associated with anastomotic outcomes.[12,13]

Indocyanine green (ICG) fluorescence angiography has been proposed as an effective assessment tool

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for the evaluation of anastomotic perfusion.[14,15] The use of a near-infrared camera following ICG injection could provide real-time information on patients' intraoperative perfusion condition. We hereby present our research on the application of ICG in sigmoid and rectal cancer resections.

Methods

We retrospectively analyzed patients who underwent minimally invasive surgery with an ICG-enhanced fluorescence imaging system performed by a single surgeon at National Cheng Kung University Hospital (NCKUH) between July 2018 and June 2019. Patients were included if they were older than 18 years, had sigmoid or rectal adenocarcinoma, and underwent laparoscopic or robotic anterior resection and low anterior resection. The decision for using traditional minimal invasive surgery or ICG enhanced equipments were decided by both the surgeon and patient mutually before surgery. Patients who had unstable hemodynamic status, were pregnant, or underwent emergency surgery were excluded. Patients with a history of allergic or adverse reactions to ICG or iodine were also excluded.

The perioperative characteristics of patients, including age, sex, body mass index (BMI), medical comorbidities, whether they received preoperative radiation therapy, and whether they presented with near total obstruction were recorded.

During anterior and low anterior resections, the inferior mesenteric artery (IMA) was identified, and the operating surgeon decided the ligation level during operation. High ligation was defined as ligation at the origin of the IMA, just above the aorta. Low ligation was defined as ligation above the IMA branch, below the origin of the left colic artery.

Intraoperative ICG-enhanced fluorescence was used for the evaluation of bowel perfusion before and after anastomosis. ICG (25 mg) was diluted in 10 mL of sterile water. The anesthesiologist injected a bolus of 12.5 mg of ICG by using a central venous catheter, before the extracorporeal resection of the proximal tumor margin was performed. Another bolus of 12.5 mg of ICG was directly administered before the intracorporeal colorectal anastomosis. Bowel perfusion was assessed by the surgical team including the primary surgeon, surgical assistant, surgical resident, and a colorectal department fellow. Surgery proceeded upon agreement that perfusion was adequate. If perfusion was deemed inadequate, then the resection level was changed appropriately. Pictures and surgical videos were recorded and stored in the database of the Colorectal Surgery Department.

Following anastomosis, an air leak test was performed to check for potential anastomosis defects. In the event that a defect was detected, direct repair or reanastomosis was performed by the surgeon and subsequently assessed again. The integrity of anastomotic double donuts was also recorded. If the resection level was too low and the double stapling technique was too difficult to perform, then anal pull-through handsewn anastomosis was performed.

Anastomotic leakage was defined as leakage which required surgical intervention or drainage. The anastomotic leakage rate of all patients who underwent minimal invasive anterior resection and low anterior resection for malignant tumors at NCKUH from July 2018 to June 2019 was calculated for comparison.

Pathological features, including pathological (pT) stage, lymph node status, diameter of the largest tumor, and sizes of the distal and proximal margins, were recorded and analyzed. Short-term outcomes, including one-year local recurrence and one-year distant metastasis were collected.

The PINPOINT Endoscopic Fluorescence Imaging System, manufactured by Novadaq Technologies Inc., was used in all cases. It provides imaging in both high-definition white light and near-infrared fluorescence modes and allows for the simultaneous display of both images. Real-time fluorescence images can be viewed in the following two modes: PINPOINT image, in which the ICG displays a bright pseudo-green color superimposed on a white light image, and SPY image, in which a black and white near-infrared fluorescence image is displayed.

Continuous variables were expressed as the mean and standard deviation and nominal variables were expressed as numbers and percentages.

Results

A total of 22 patients were included in this study. Their baseline characteristics are presented in Table 1. Their mean age was 61.86 years, and male patients accounted for 63.6%. The mean BMI was 24.17. Two patients (9.1%) underwent preoperative radiotherapy, and three patients (13.6%) presented with near total obstruction before surgery. The medical comorbidities that could affect anastomotic healing were also documented.

Perioperative parameters are presented in Table 2. Anterior resection was noted in 10 patients (45.5%). The anastomotic level was between 6 and 8 cm AAV in four patients, and between 0 and 5 cm AAV in eight patients. High IMA ligation was performed in 21 patients. Intraoperative air leak tests yielded positive results in three patients, and all three underwent direct repair followed by a negative air leak test. Complete donuts were observed in all patients after anastomosis. Proximal stoma diversion was performed in six patients (27.3%). Among the diverted patients, two underwent preoperative radiation therapy, two patients had medical comorbidity which could affect anastomotic healing, and two had low anastomosis level over 0-5 cm AAV. A necessary change in resection level through ICG was noted in one patient. The patient underwent low anterior resection with poor perfusion noted while resection of proximal stump. The resection level was shift to 2 cm proximal to initial resection margin. None of the patients experienced anastomotic leakage. In the one-year follow up period, no local recurrence was identified, distant metastasis were observed in 4 patients (18.18%).

Between July 2018 and June 2019, a total of 101 patients in NCKUH underwent minimal invasive anterior resection or low anterior resection for malignant tumors. There were 6 patients who had anastomotic leakage requiring further surgical intervention or drainage. The overall anastomotic leakage rate in NCKUH for minimal invasive anterior resection or low anterior resection patients for malignant tumors between July 2018 and June 2019 was approximately 5.94%.

The patients' pathological features are listed in Table 3. There were two T1 patients, three T2 patients, fourteen T3 patients and three T4 patients. The mean lymph node status yielded a total mean of 16.32 lymph nodes, with a positive mean of 2.09 lymph nodes. The mean tumor length of the largest tumor was 4.73 cm, the mean distal margin was 4.71 cm, and the mean proximal margin was 12.40 cm.

Table 1. Patient characteristics, n = 22. Numbers (%) or mean (standard deviation)

Age	61.86 (11.67)
Sex	
Male	14 (63.6)
Female	8 (36.4)
BMI	24.17 (3.79)
Preoperative radiotherapy	2 (9.1)
Near total obstruction	3 (13.6)
Medical comorbidity	
Diabetes mellitus	5
Chronic kidney disease	2
Cardiovascular related	2*
Other malignant neoplasm	3**
Asthma	1
Inflammtory bowel disease	1
Cirrhosis	1

* One patient with cardiovascular disease, one patient with atrial septal defect.

** Bladder cancer, gastric adenocarcinoma, breast ductal carcinoma in situ.

Discussion

No anastomotic leakage was detected in our study

Table 2. Peri-operative characteristics, n = 22. Numbers (%)

Anastmosis level	
Sigmoid	10 (45.45)
6-8 cm AAV	4 (18.18)
0-5 cm AAV	8 (36.36)
IMA level	
High	21 (97.8)
Low	1 (2.1)
Intraoperative air leak test positive	3 (13.6)
Double donuts after stapling	22 (100)
Proximal stoma diversion	6 (27.3)
Change of resection level by ICG	1 (2.1)
Anastomosis leakage	0

AAV, above anal verge; IMA, inferior mesenteric artery.

Table 3. Pathologic characteristics, n = 22. Numbers (%) or mean (SD)

pT stage	
T1	2 (9.09)
T2	3 (13.64)
T3	14 (63.64)
T4	3 (13.64)
pN	
N0	13 (59.09)
N1	4 (18.18)
N2	5 (22.73)
LN status	
Positive	2.09 (4.77)
Total	16.32 (5.27)
Tumor size	4.73 (2.09)
Distal margin	4.71 (3.37)
Proximal margin	12.40 (12.41)

LN, lymph node.

group. One patient (4.5%) showed insufficient perfusion during ICG angiography evaluation leading to change of resection level. Although the initial perfusion during direct visual evaluation seemed normal, the anastomotic area was rather in a suboptimal perfusion status. The possibility that lead to delayed leakage, anastomosis stenosis or stricture in the future is high. ICG angiography could be used for real-time assessment of the vascularization of the colic stump during operation, which may be beneficial for the prevention of immediate or delayed anastomotic complications.

In an average of 10% of all published cases, insufficient perfusion across the initial resection area was detected through ICG angiography, leading to a change of resection level, ranging from 2.5%-20%.[16-19] A recent systemic review, which included 516 patients, reported 10.9% of cases had such results.[16] In a case-control study consisting 346 patients, although no difference in anastomotic leakage rate in patients with or without intraoperative angiography were detected, 5% of the patients who underwent intraoperative angiography showed poor perfusion of the proximal colon which led to additional colon resection.[20] Another multicenter randomized controlled trial showed 11% of cases had insufficient perfusion over rectal stump leading to a more extended bowel resection. None of the further resected patients subsequently developed anastomosis leakage. In the author's opinion, this could be interpreted as an advantage of the intraoperative angiography over the control group.[21] We also consider that the value of ICG enhanced technique lies in these patients. ICG angiography has the potential to detect the high risk group of patients with anastomotic poor perfusion, and to prevent further reoperation or intervention.

Vascular insufficiency is a major cause of perfusion abnormalities in sigmoid and rectal cancer resections.[6,13] The descending or remaining sigmoid colon is pulled down for anastomosis after resection. Perfusion in these portions of the colon depends on the patency of the IMA, left colic artery, middle colic artery, marginal artery of Drummond, and Riolan arcade.[22,23] Anatomic variations, such as the absence of the middle colic artery or a prominent left colic artery, were observed in 10%-25% of cases.[24] After high ligation of the IMA, perfusion in the proximal colon may be compromised, leading to vascular insufficiency.[25]

Many assessment methods have been proposed for evaluating anastomotic perfusion. The most widely used is the direct intraoperative visual appraisal of bowel or mucosal color, the bleeding edge of the resection margin, or pulsation.[1,17] However, many factors can interfere with the evaluation quality and potentially lead to an underestimation of regional perfusion. Factors such as the time interval for assessment, visceral obesity, and experience level of the surgeon have been identified as possible risk factors.[26]

Other assessment methods could assist in the evaluation of vascular perfusion in colon anastomosis, such as a transabdominal Doppler ultrasound, transabdominal laser Doppler flowmetry, and oxygen spectroscopy.[1,21,27-30] However, these methods are not widely adopted for operations because of technical difficulties, equipment cost, and a lack of reproducibility. Preoperative computed tomography angiography (CTA) was proposed as an alternative noninvasive tool for the evaluation of colonic vasculature, but small colonic mesenteric arteries are difficult to identify using such a method.[19,26]

ICG fluorescence has been proposed as an alternative for such evaluations. ICG is a sterile, water-solu-

ble, tricarboncyanine component that is injected intravenously, binding firmly to plasma proteins and remaining confined to the intravascular space. When exposed to near-infrared light, it becomes fluorescent and assists in the real-time display of vessel alignment and the condition of regional perfusion during operation. This technique has been applied in plastic surgery, neurosurgery, and other gastrointestinal surgeries.[31-33]

Several studies have been conducted on the usage of ICG angiography in minimally invasive surgery for sigmoid colon and rectal cancers. Most were retrospective cohort studies, and some used propensity score matching during analysis.[21,34] Two prospective cohort studies and two randomized controlled trials were evaluated.[21,35-37] The anastomotic leakage rate exhibited a minor decrease in the ICG angiography group, though not all members of this group demonstrated clinically significant differences. Among the two randomized controlled trials, one reported a significant reduction of anastomotic leakage for low (4-8 cm) colorectal anastomosis (25.7% in the non-ICG group compared with 14.4% in the ICG group, $p = 0.04$[35]), and the other showed no significant difference.[21] In the presenting study, there were no anastomosis leakage detected, comparing with an overall leakage rate of 5.94% during the same study period.

Despite there were no obvious difference in anastomotic leakage rate, published results had stated about 10% of patients had changed of resection level due to poor perfusion detected by ICG angiography. It would be difficult and unethical to observe whether these patients will further develop anastomosis complication if no change of resection level were decided initially. In most of the reported cases, patients who had changed resection level according to ICG results did not develop further anastomosis complications. ICG fluorescence angiography had the potential to detect possible candidates who were high risk for immediate or delayed anastomotic complications.

Limitation

This was a single-armed, single-doctor, non-randomized, retrospective observational study. Selection bias cannot be ruled out. Additional cases, more participating surgeons, and a prospective randomized trial are essential for further deciphering the usefulness of ICG fluorescence angiography.

Conclusion

With the assistance of ICG fluorescence angiography, the real-time evaluation of anastomosis perfusion can be assessed, which may help to identify patients with suboptimal perfusion over resection area and further prevent anastomotic complications.

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原　著

乙狀結腸癌及直腸癌切除手術中使用 ICG 螢光血管攝影的結果分析

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目的　分析於乙狀結腸癌及直腸癌手術中使用 ICG 的結果與吻合處滲漏率。

結果　共 22 位病人。其中有二位病人 (9.1%) 進行術前放射線治療，三位病人 (13.6%) 在手術前有阻塞的情形。十位病人進行前位切除手術，四位病人吻合處位於 6~8 cm AAV，八位病人位於 0~5cm AAV。21 位病人進行 IMA 高位結紮。六位病人 (27.3%) 進行近端造口。有一位病人因 ICG 的結果而改變切除位置。所有的病人都沒有發生吻合處滲漏。

結論　在前位切除及低前位切除手術中，ICG 螢光血管攝影可偵測到吻合處血液循環不好的病人，可進一步預防後續吻合處滲漏的產生。

關鍵詞　ICG 螢光血管攝影、前位切除手術、低前位切除手術、吻合處滲漏。