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ORIGINAL ARTICLE

Colonic perfusion assessment with indocyanine-green fluorescence imaging in anterior resections: a propensity score-matched analysis

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Abstract

Background Colonic perfusion is crucial for anastomotic healing and this could be evaluated intraoperatively using indocyanine-green fluorescence imaging (ICG FI). The aim of this study was to ascertain whether the use of ICG FI resulted in the reduction of anastomotic complications, i.e. AL and anastomotic stricture.

Methods Consecutive patients who underwent anterior resections or low anterior resections at our institution in the period from January 1st 2013 to December 31st 2018 were retrospectively reviewed. Surgery performed during the period from January 1st 2013 to December 31st 2015 did not involve the use of ICG FI (ICG−) while surgery during the period from January 1st 2016 to December 31st 2018 was performed with the use of ICG FI (ICG+). The anastomotic leakage rates of the two groups were compared after propensity score matching, taking into account the height of the anastomosis and any history of pelvic irradiation.

Results There was a total of 258 and 317 patients who had surgery with and without ICG FI, respectively. There were 253 patients in each group after propensity score matching. The overall anastomotic leakage rate was 3.6% and 7.9% for ICG+ and ICG−, respectively, ($p=0.035$). Subgroup analysis showed that the use of ICG FI was significantly associated with a lower anastomotic leakage rate in total mesorectal excision (TME), 4.7% versus 11.6%, $p=0.043$, but not in non-TME resections, 3.5% versus 2.4%, ($p=0.612$). ICG FI, together with sex and anastomotic height, were independent predictors of anastomotic leakage.

Conclusions The routine use of ICG FI was associated with a lower anastomotic leakage rate in anterior resections. The reduction in anastomotic leakage rate was mainly seen in TME.

Keywords Indocyanine-green · Anterior resection · Anastomotic leakage · Total mesorectal excision

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Introduction

Anastomotic leakage (AL) after colorectal resection results in significant morbidity and increases the chance of mortality [1]. The risk of local recurrence and cancer-specific survival after cancer surgery are adversely affected and the surge in health costs is a burden to the health care provider [2–4]. Despite advances in surgical techniques, AL remains a significant problem with the highest incidence in left-sided colorectal resection [3]. The rate of AL after low rectal resections varies from 2 to 39% in the literature [5]. The cause of AL is multifactorial. Male sex, low rectal anastomosis, and history of pelvic irradiation are some of the known risk factors for AL [6]. Hypoperfusion to the anastomosis is one of the potentially modifiable risk factors for AL [7]. There is a recent interest in using indocyanine-green fluorescence imaging (ICG FI) for real-time intraoperative assessment of colonic perfusion. Multiple observational studies have reported favorable outcomes with this technique [8–11]. Nevertheless, one of the multicenter randomized studies was hampered by slow recruitment and was terminated prematurely [12]. The aim of our study was to evaluate whether the use of ICG FI resulted in the reduction of anastomotic complications, i.e. AL and anastomotic stricture.

Materials and methods

This was a retrospective study carried out in a single academic institution with approval from the institutional review board. Consecutive patients undergoing elective left-sided colorectal resections during the period from January 1st 2013 to December 31st 2018 were included. Only colorectal resections that involved the ligation of the inferior mesenteric artery IMA), i.e. anterior resections and low anterior resections, were included. Cases that did not involve the ligation of the IMA, i.e. sigmoidectomies or left hemicolectomies, and cases in which primary anastomosis were not performed were excluded. Multi-visceral resections, pelvic exenterations and total proctocolectomy with ileal pouch- anal anastomosis were also excluded.

The operations that were carried out during the period from January 1st 2013 to December 31st 2015 did not involve the use of ICG FI and were labeled as group ICG−. Routine use of ICG FI in elective left-sided resections was started in 2016 and those patients who were operated on between January 1st 2016 and December 31st 2018 were labeled as ICG+. The clinical outcomes of the two groups were compared and the primary outcome was the rate of AL within 60 days from the index operation.

The preoperative workup of patients with sigmoid or rectal cancer followed a standardized protocol that was described in a previous publication [13]. All rectal cancer cases were discussed in the multi-disciplinary team meeting for the need for neoadjuvant treatment. The chemoradiation regimen generally consisted of long-course radiation with 4500–5400 cGy in 5–6 weeks with synchronous chemotherapy. The typical interval between completion of neoadjuvant treatment and surgery was 8 weeks. Patients were routinely given mechanical bowel preparation using polyethylene glycol preoperatively. Non-absorbable oral antibiotics were not routinely given. Antibiotic prophylaxis with 1.5 gm cefuroxime and 500 mg metronidazole was given on induction of general anesthesia unless contraindicated. The operative technique adopted in the unit was standardized with minor variations between different surgeons. For anterior resections, the IMA was ligated close to its origin. The inferior mesenteric vein was generally ligated close to the level of IMA ligation. Splenic flexure mobilization was generally performed to achieve a tension-free anastomosis. The rectum was transected with a linear stapler and intestinal continuity was restored by fashioning an end-to-end colorectal anastomosis with a circular stapler. For low rectal tumors requiring intersphincteric resections, coloanal anastomoses were fashioned manually. Colonoscopy was used to check the integrity of the anastomosis. Drains were placed at the surgeon's discretion. Diversion stoma was generally performed after total mesorectal excision (TME) or when there was prior pelvic irradiation. Intraoperative colonic perfusion assessment was performed with one of the following: the SPY Elite System (Stryker, USA), Pinpoint System (Stryker, USA) and the Da Vinci Xi (Firefly, Intuitive Surgical, Sunnyvale, CA, USA). The technique was described previously [14]. The assessment was performed prior to the proximal transection of the left colon. A bolus of 5 mg ICG was injected intravenously followed by 10 ml of saline flush for the SPY Elite System. For the Pinpoint and the Da Vinci Xi Firefly system, the dosage of ICG was 7.5 mg. Fluorescence should be evident in less than 1 min and the proximal transection site was selected accordingly. In cases where the intended transection site had suboptimal perfusion, the surgeon would attempt to mobilize and anastomose with, in the order of preference, the descending colon, the transverse colon or even the ascending colon (the Deloyers procedure) to achieve a well-perfused anastomosis. Perfusion assessment after the fashioning of the anastomosis was not repeated routinely except in rare circumstances when the color of the colon looked dubious in the later part of the surgery. This could be done via the Pinpoint System intracorporeally or transanally.

Clinical and operative parameters were prospectively maintained. Besides, all cases were retrospectively reviewed

and searched for clinical evidence that might suggest AL. When there was clinical suspicion of AL during the postoperative period, as evidenced by postoperative fever, leukocytosis, peritonitis, prolonged paralytic ileus, pus or feces discharge from drains, pustular discharge from the anus or gapping of anastomosis noted on digital rectal examinations, or other factors the usual practice would be an assessment by either contrast computed tomography (CT) scan or endoscopy. CT scans that were performed within the first 3 months after the operation were reviewed for any intra-abdominal or pelvic collections. All postoperative sigmoidoscopies or colonoscopies, up to September 2019, were reviewed for any evidence of anastomotic dehiscence, sinuses, fistula or stricture. Any records of reoperation at our institution or other public hospitals within the territory were reviewed. Patients with diversion stoma routinely undergo water-soluble contrast enema before reversal. These were reviewed for any extravasation of contrast at the level of the anastomosis.

The International Study Group of Rectal Cancer definition of AL was adopted [15]. Grade A (asymptomatic leakage) was defined as leakage detected on imaging, without any clinical symptoms or abnormal laboratory findings. Grade B was defined as anastomotic leakage that required active therapeutic intervention without the need for reoperation. Grade C was defined as AL that required reoperation. The secondary outcome was anastomotic stricture. Strictures were defined as narrowing of anastomosis that required digital, bougie or endoscopic dilatation.

Patients in the two groups were matched according to the history of pelvic irradiation and anastomotic height, using propensity scores. The matching was one to one, using the nearest neighbor method and tolerance of 0.05. The incidence of AL and anastomotic stricture were compared between the two groups. Categorical variables were compared with the χ^2 test or Fisher's exact test when appropriate. Continuous variables were compared with the independent sample T test. A p value of <0.05 was considered statistically significant. Univariate analysis was performed for the association between various clinicopathological parameters and AL. Multivariate analysis was performed by logistic regression using the stepwise forward likelihood ratio method, with AL being the dependent variable and clinicopathological parameters with $p<0.1$ in the univariate analysis as the independent variables. Statistical analysis was performed using IBM SPSS version 25 (IBM, USA).

Results

There were 317 and 258 patients that fulfilled the inclusion criteria in the group ICG− and ICG+, respectively. There were 253 patients in each group after propensity score matching. The two groups were comparable in terms of age, sex, indications, history of pelvic irradiation, American Society of Anaesthesiologists (ASA) grade, Charlson co-morbidity index [16], preoperative serum creatinine and albumin level, the proportion of TME, T4 disease, estimated blood loss, operating time, anastomotic height and anastomotic method (Table 1). There was a higher percentage of current smokers in the ICG+ group.

For the ICG+ group, perfusion assessment was accomplished by the SPY Elite System, the Pinpoint System and the Da Vinci Xi Firefly system in 49.4%, 48.2%, and 2.4%, respectively. A revision of the transection site was seen in 20.9% of the patients. The overall AL rate was 3.8% in those who had a revision of the transection site. It was similar to the rate in the rest who did not, 3.5%, ($p=0.596$).

The ICG+ group had a significantly lower overall AL rate, 3.6%, as compared to 7.9% in the ICG− group, ($p=0.035$) (Table 2). The percentages of grades A, B and C AL were 0.8%, 1.2%, and 1.6%, respectively, in the ICG+ group. The percentages of grades A, B and C AL were 2.0%, 4.0%, and 2.0%, respectively, for those in the ICG− group. 2.4% in the ICG− group and 2.0% in the ICG+ group had anastomotic stricture ($p=0.760$).

Subgroup analysis was performed for non-TME and TME patients. For non-TME patients, the overall AL rate was 3.5% and 2.4% for ICG− and ICG+, respectively, ($p=0.612$). The incidences of anastomotic stricture were 0.9% and 0.8% for the ICG− and ICG+ group, respectively ($p=0.948$).

For patients who had TME, there was significantly less AL, 4.7%, in the ICG+ group, compared to 11.6% in the ICG− group, ($p=0.043$). The percentages of grades A, B and C AL were 3.6%, 7.2%, and 0.7%, respectively, for the ICG− group. The percentages of grades A, B and C AL were 1.6%, 1.6%, and 1.6%, respectively, for the ICG+ group. The incidence of anastomotic stricture was 3.6% and 3.1% for ICG− and ICG+, respectively ($p=0.832$).

Univariate analysis showed that male sex, longer operation duration, more distal anastomosis, TME, hand-sewn anastomosis, coloanal anastomosis and the lack of ICG FI were associated with an increased risk of AL (Table 3). In addition to the above variables, a history of pelvic irradiation was also included in the multivariate analysis model. The model showed that the use of ICG FI ($p=0.032$, OR 0.408, 95% CI 0.179–0.926), gender ($p=0.021$, OR 3.573, 95% CI 1.210–10,549) and anastomotic height ($p=0.006$, OR 0.860, 95% CI 0.773–0.958) were independent predictors of AL.

Discussion

The incidence of AL is generally higher in left-sided colorectal resections [3]. In anterior resections, after the division of the IMA, the blood supply to the remaining left colon relies on the marginal artery of Drummond which can be

Table 1 Clinicopathological characteristics of patients in the ICG− and ICG+ group

	ICG− $n=253$	ICG+ $n=253$	p
Age (years, mean ± SD)	67.2 ± 11.0	66.6 ± 10.6	0.528
Sex			
Male (%)	64.4	65.6	0.780
Female (%)	35.6	34.4	
History of smoking			
Non-smoker (%)	71.5	59.3	0.003
Current smoker (%)	7.1	15.4	
Ex-smoker (%)	21.3	25.3	
ASA class			
1 (%)	11.8	7.5	0.300
2 (%)	58.1	59.5	
3 (%)	30.1	32.9	
Charlson co-morbidity index (mean ± SD)	5.0 ± 1.7	5.1 ± 2.0	0.361
Preoperative blood test			
Albumin (g/L, mean ± SD)	40.9 ± 4.8	40.8 ± 5.0	0.842
Creatinine (μmol/L, mean ± SD)	80.8 ± 35.1	81.3 ± 29.9	0.867
T4 tumor (%)	10.3	7.5	0.274
Tumor height (cm, mean ± SD)	17.8 ± 44.2	12.6 ± 7.9	0.120
History of pelvic irradiation (%)	23.7	19.4	0.234
Indication			
Benign (%)	2.8	4.3	0.337
Malignancy (%)	97.2	95.7	
Operation duration (min, mean ± SD)	227.0 ± 80.6	218.2 ± 90.6	0.247
Estimated blood loss (ml, mean ± SD)	157.0 ± 265.4	182.7 ± 455.2	0.467
Anastomotic height (cm, mean ± SD)	7.6 ± 4.2	7.8 ± 4.5	0.560
Surgical approach			
Open (%)	11.1	6.3	0.165
Laparoscopic or robotic assisted (%)	85.4	89.7	
Laparoscopic converted to open (%)	3.6	4.0	
Surgery			
Non-TME (%)	45.4	49.8	0.363
TME (%)	54.5	50.2	
Method of anastomosis			
Stapled (%)	94.1	96.0	0.305
Hand-sewn (%)	5.9	4.0	
Type of anastomosis			
Colorectal (%)	90.1	87.7	0.395
Coloanal (%)	9.9	12.3	
Diversion stoma (%)	50.6	51.8	0.790

ASA American Society of Anaesthesiologist grade, *TME* total mesorectal excision, *ICG* Indocyanine green

unpredictable [17]. Conventional means of determining colonic perfusion include observing the color, bleeding, peristalsis, and pulsations. However, this was proven to be of low reliability [18].

ICG FI is a simple, safe and relatively inexpensive way to assess colonic perfusion and reduce hypoperfusion-related anastomotic complications. The PILLAR II study, which was a prospective multicenter observational trial, reported an encouragingly low AL rate of 1.4% after left colectomy and anterior resections [19]. Jafari et al. reported a lower AL rate after low anterior resections with the use of ICG FI, 6% compared to 18% in the control group [9]. Two similar studies also reported a lower AL rate of 0.8% and 3% using ICG FI, in which the AL rate in the control group was 5.4% and 10.7%, respectively [10, 11].

Table 2 A comparison of the rate of anastomotic leakage and stricture between the two groups

	ICG−	ICG+	*p*
All patients	*n* = 253	*n* = 253	
Anastomotic leakage (%)	7.9	3.6	0.035
Leakage grade			
A (%)	2.0	0.8	
B (%)	4.0	1.2	
C (%)	2.0	1.6	
Stricture (%)	2.4	2.0	0.760
TME cases	*n* = 138	*n* = 127	
Anastomotic leakage (%)	11.6	4.7	0.043
Leakage grade			
A (%)	3.6	1.6	
B (%)	7.2	1.6	
C (%)	0.7	1.6	
Stricture (%)	3.6	3.1	0.832
Non-TME cases	*n* = 115	*n* = 126	
Anastomotic leakage (%)	3.5%	2.4%	0.612
Leakage grade (%)			
A (%)	0	0	
B (%)	0	0.8	
C (%)	3.5	1.6	
Stricture (%)	0.9	0.8	0.948

TME total mesorectal excision

Nevertheless, not all authors arrived at the same conclusion. Kin et al. showed, in a case-matched comparison study with a much lower percentage of low rectal anastomosis, that the rate of AL was similar between those with and without ICG FI [20]. Likewise, Kawada et al. found that the rate of AL after low anterior resections was 12% with ICG FI and was similar to their historical cohort [21]. A meta-analysis of five observational studies showed that ICG FI only significantly reduced the AL rate in those who had colorectal cancer as the operative indication [22]. This effect was more pronounced in rectal cancer resections.

De Nardi et al. conducted a multicenter randomized controlled trial on left-sided resections [23]. The AL rate in the arm with ICG FI was lower, 9% versus 5%. However, with a sample size of 240 patients, the difference did not reach statistical significance. Unfortunately, another multicenter randomized controlled trial evaluating the use of ICG FI, the PILLAR III study, was terminated due to slow recruitment [12]. There are other ongoing randomized controlled trials, e.g. the IntAct trial which aimed to recruit 880 patients and will hopefully produce valuable evidence in the future [24]. Given the significant clinical implications from AL, whether the use of ICG FI reduces its incidence remained an important question.

This study showed that the use of ICG FI reduced the AL rate and the effect was more obvious in TME cases. This finding and the reported AL rate were similar to with the results of some of the studies in the literature [11, 23]. The main limitation of our study was the selection bias associated with retrospective studies. To minimize this, consecutive cases were included and the two groups were matched. After matching, the clinicopathological characteristics of the two groups were comparable. Nevertheless, the ICG+ group had a significantly higher proportion of current smokers. This should have an adverse effect on the AL rate as smoking is considered one of the risk factors for AL [3]. The result, however, was in favor of ICG FI. The difference in AL rate was not significant in the non-TME group, i.e. those who had high rectal anastomosis. Whether ICG FI truly had no effect on this group, or that a smaller difference, given a lower AL rate in high rectal anastomosis, was not detected with this sample size remains a question. Likewise, for anastomotic stricture, a small difference might not be detected by the current sample size. The follow-up period of the ICG− group, given that it was the historical cohort, was longer than that of the ICG+ group. The study was conducted 9 months after the last ICG+ case. AL should be evident within this time interval so the difference in follow-up period should have had only a minimal effect on the rate of AL. However, there remains a possibility that the long-term stricture rate was underreported in the ICG+ group.

Another limitation of our retrospective study was the underreporting of AL [25]. AL was prone to be underreported due to its variable clinical presentation and definitions. The use of diversion stoma and the lack of routine investigations to check the anastomotic integrity before closure render some of the asymptomatic AL undetected. In this study, the records were thoroughly reviewed and searched for clinical evidence of anastomotic complications. Also, a routine water-soluble contrast study was performed before the reversal of stoma. There remains a chance that minor asymptomatic AL healed before these examinations. Studies have shown that the usual time-frame for the healing of asymptomatic leaks was about 4–5 months [26, 27]. As the water-soluble contrast study was generally performed within this period, the chance of underreporting should have been minimized.

Conclusions

The use of ICG FI was associated with a significantly lower AL rate. The difference was mainly seen in patients who had TME. The difference in the rate of AL in non-TME cases was not significant. The rate of anastomotic stricture was similar in those with and without ICG FI. This study supports the routine use of ICG FI in TME cases.

Table 3 The association between clinicopathological parameters and anastomotic leakage

	AL+ $n=477$	AL− $n=29$	*P*
Age (years, mean ± SD)	66.0 ± 11.3	66.9 ± 10.7	0.638
Sex			
Male (%)	86.2	63.7	0.014
Female (%)	13.8	36.3	
History of smoking			
Non-smoker (%)	48.3	66.5	0.101
Current smoker (%)	20.7	10.7	
Ex-smoker (%)	31.0	22.9	
ASA class			
1 (%)	14.8	9.0	0.554
2 (%)	51.9	59.4	
3 (%)	33.3	31.6	
Charlson co-morbidity index (mean ± SD)	4.8 ± 1.7	5.1 ± 1.9	0.472
Preoperative blood test			
Albumin (g/L, mean ± SD)	40.7 ± 6.0	40.8 ± 4.8	0.898
Creatinine (μmol/L, mean ± SD)	87.5 ± 29.3	80.7 ± 32.6	0.274
T4 tumor (%)	6.9	9.0	0.697
Tumor height (cm, mean ± SD)	6.7 ± 3.6	15.4 ± 30.7	0.166
History of pelvic irradiation (%)	34.5	20.8	0.081
Indication			
Benign (%)	0.0	96.2	0.287
Malignancy (%)	100.0	3.8	
Operation duration (min, mean ± SD)	262.5 ± 105.4	220.1 ± 84.0	0.010
Estimated blood loss (ml, mean ± SD)	163.1 ± 323.6	169.1 ± 367.2	0.935
Anastomotic height (cm, mean ± SD)	5.4 ± 4.2	7.8 ± 4.4	0.003
Surgical approach			
Open (%)	3.4	9.0	0.299
Laparoscopic or robotic assisted (%)	96.6	87.0	
Laparoscopic converted to open (%)	0.0	4.0	
Surgery			
Non-TME (%)	24.1	48.8	0.010
TME (%)	75.9	51.2	
Method of anastomosis			
Stapled (%)	82.8	95.8	0.002
Hand-sewn (%)	17.2	4.2	
Type of anastomosis			
Colorectal (%)	72.4	89.9	0.003
Coloanal (%)	27.6	10.1	
Diversion stoma (%)	65.5	50.3	0.112
ICG FI (%)	31.0	51.2	0.035

AL anastomotic leakage, *ASA* American Society of Anaesthesiologists, *TME* total mesorectal excision, *ICG FI* indocyanine-green fluorescence imaging

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interests.

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster approved this study.

Informed consent For this type of study formal consent is not required.

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