

# Ellen M. Cosgrove Research Competition

## Manuscript Competition

<b>Title of Submission</b>	Does Routine Use of Indocyanine Green Fluorescence Angiography Prevent Anastomotic Leaks? A Retrospective Cohort Analysis			
<b>Role</b> <i>Author, Mentor, Faculty, Other</i>	<b>Full First Name</b>	<b>Full Last Name</b>	<b>Degree</b>	<b>Institution</b>
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Author	William	Boyan	MD	MMC
Author	Bogdan	Protyniak	BS	SGU
Author	Abi	James	BS	SGU
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**Deadline for Submission is Thursday, May 4, 2017 NOON**  
**Award Ceremony Monday, June 5, 2017**

**Title:**

Does Routine Use of Indocyanine Green Fluorescence Angiography Prevent Anastomotic Leaks? A Retrospective Cohort Analysis

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## Abstract

**Background:** Insufficient perfusion to anastomoses in colorectal surgery is known to lead to complications including anastomotic leaks. The SPY Elite Imaging System has been introduced to assess tissue perfusion using indocyanine green fluorescence angiography. This tool provides objective, quantitative data when evaluating tissue perfusion prior to bowel anastomosis.

**Objective:** This study aims to evaluate whether routine use of fluorescence angiography alters the incidence of anastomotic leaks after colorectal surgery.

**Design:** This was a retrospective study of 597 colorectal resections with and without the use of intraoperative indocyanine green fluorescence angiography.

**Settings:** The study was conducted at a community teaching hospital.

**Patients:** Patients who underwent colorectal resections with an anastomosis.

**Interventions:** The absolute value from SPY Elite Imaging System using intraoperative indocyanine green fluorescence angiography was studied.

**Main Outcome Measures:** Anastomotic leak rates and whether angiography altered surgical management were the main outcomes measured.

**Results:** The 1.1% anastomotic leak rate prior to fluorescence angiography did not differ significantly from the 1.2% leak rate with the use of fluorescence angiography ( $p > 0.05$ ). Mortality was not statistically different before and after the use of fluorescence angiography, 0.9% and 0.4%, respectively ( $p > 0.05$ ). However, significantly more patients had alterations made to the planned anastomotic site in the fluorescence angiography group ( $n=13$ , 5.3%) as compared to the group prior to the use of fluorescence angiography who had no alterations made ( $p < 0.05$ ).

**Limitations:** Retrospective study design and small sample size.

**Conclusions:** No significant difference was found in anastomotic leak rates between the two groups studied. Routine use of fluorescence angiography significantly altered intra-operative decision-making without discernible change in clinical outcome. Randomized control trials are needed to establish the benefit of using fluorescence angiography in colorectal surgery before its routine use can be recommended.

## **Introduction**

An anastomotic leak is a devastating complication, leading to increased length of stay,<sup>1</sup> higher local recurrence,<sup>2</sup> greater cost and increased mortality.<sup>3</sup> Leak rates in colorectal surgery range from 1% to 30%.<sup>1</sup> Several tenets must be followed to prevent an anastomotic leak: aseptic technique with gentle and careful dissection, tension-free anastomosis, precise placement of sutures, appropriate staple height, and adequate blood flow to the bowel.<sup>4</sup> Proper blood supply is assured through various subjective measures, which include palpating mesenteric pulses, assessing cut edges for bleeding, and evaluating the color of the bowel. Other clinical adjuncts include Doppler signals, fluorescein injection, and indocyanine green fluorescence angiography.

Indocyanine green (ICG) fluorescence angiography (FA) has been used in numerous other fields, including ophthalmology, plastic and reconstructive surgery, as well as head and neck surgery to evaluate tissue perfusion.<sup>5</sup> Limited studies have only recently described its utilization in colon and rectal surgery.

The SPY Elite Intraoperative Perfusion Assessment System (Novadaq Technologies Inc., Bonita Springs, FL) is a tool that uses indocyanine green fluorescence angiography for visual assessment of blood flow. This system has been used in plastic, micro-, reconstructive, gastrointestinal and cardiovascular procedures to subjectively measure tissue perfusion. Unlike other systems using ICG-FA, the SPY-Q software provides an absolute numerical value, an objective measurement on a 0-256 gray scale. This number represents ICG fluorescence intensity and in theory perfusion, providing an objective measurement to what was once a subjective assessment.

This retrospective historical cohort aims to evaluate whether routine use of FA alters the incidence of anastomotic leaks after colorectal surgery.

### **Materials & Methods**

Over the period ranging from June 2013 to June 2016, all colorectal resections at a single institution performed with intra-operative ICG-FA were reviewed retrospectively. Prior to the anastomosis, intra-venous administration of 2mL of ICG was followed by FA using the SPY Elite Imaging System. Absolute fluorescence values on the 0-256 gray-scale were recorded using SPY-Q software 60 seconds after the initial fluorescence signal. Fluorescence values were recorded for both proximal and distal bowel segments except when performing low anterior resection (LAR) when it was not feasible to perform FA on a low-lying rectal stump *in vivo*. The splenic flexure was routinely mobilized during LAR to provide a tension-free anastomosis and the inferior mesenteric artery was ligated.

The decision to alter the anastomotic site based on FA results was also documented. Electronic medical records were reviewed to determine whether patients suffered clinically evident anastomotic leak post-operatively, defined as anastomotic disruption evidenced by post-operative imaging or endoscopy. A historical control group consisted of colorectal resections performed by the same two surgeons without the use of FA between January 2010 and July 2013. Multiple details of patient demographics for both groups were recorded with the primary endpoint being the rate of anastomotic leak. Confidence intervals with  $\alpha = 0.05$  were compared to determine statistical significance. Institutional review board approval was granted and no funding was obtained.

## Results

351 consecutive patients undergoing colorectal resection prior to the use of FA were compared to 246 consecutive patients where FA was utilized. The patients were matched for variables such as age, sex, BMI, type of disease process, diabetes, smoking, emergent cases, operative time and estimated blood loss. As demonstrated in Table 1, there was no significant difference in these demographics or variables. The 1.1% anastomotic leak rate prior to FA did not differ significantly from the 1.2% leak rate with the use of FA ( $p > 0.05$ ) as described in Table 2. Secondary endpoints evaluated mortality as well as alterations to the projected anastomotic site due to angiographic evaluation. Mortality was not statistically different before and after the use of FA, 0.9% and 0.4%, respectively ( $p > 0.05$ ). However, significantly more patients had alterations made to the planned anastomotic site in the FA group ( $n=13$ , 5.3%) as compared to the group prior to the use of FA who had no alterations made ( $p < 0.05$ ). Both of these findings are represented in Table 2. Of note, none of these 13 patients suffered any complications.

Table 1. Patient demographics

	Prior to FA (95% CI)	Using FA (95% CI)
<b>Age</b>	63.2 (34.9, 91.5)	61.9 (34.9, 88.8)
<b>BMI</b>	27.9 (10.0, 45.7)	28.2 (15.4, 40.9)
<b>ASA</b>	2.3 (1.2, 3.4)	2.3 (1.3, 3.2)
<b>%Female</b>	56.1% (50.9, 61.3)	54.5% (48.2, 60.7)
<b>%Malignant</b>	34.8% (29.8, 39.7)	35.0% (29.0, 40.9)
<b>%Diabetes</b>	17.7% (13.7, 21.7)	16.7% (12.0, 21.3)
<b>%Smokers</b>	15.4% (11.6%, 19.2%)	15.4% (10.9, 20.0)
<b>%Emergent</b>	2.3% (0.7%, 3.8)	2.0% (0.3%, 3.8%)
<b>OR Time (min)</b>	213.2 (105.8, 320.7)	233.8 (110.6, 356.9)
<b>Blood Loss (mL)</b>	133.5 (0, 530.3)	99.5 (0, 366.8)

ASA: American Society of Anesthesiologists; BMI: body mass index; FA: fluorescence angiography

Table 2. Endpoints before and after use of FA

	Pre-FA	FA
% Mortality	0.9% (0.0, 1.8)	0.4% (0.0, 1.2)
% Alteration	0.0% (0.0, 0.0)	5.3% (2.5, 8.1)
% Leak	1.1% (0.0, 2.3)	1.2% (0.0, 2.6)

## **Discussion**

Kingham and Pachter report a colorectal anastomotic leak rate between 1% to 30% with an acceptable leak rate ranging from 3% to 6% among experienced colorectal surgeons.<sup>1</sup> The ensuing morbidity and mortality has multiple implications, including longer length of stay, higher costs and adverse effects on cancer recurrence.<sup>1</sup> In a prospective study of patients who underwent colorectal resection between 1996-2004, 25 out of 1417 patients (1.8%) had an anastomotic leak.<sup>6</sup> Comparing patients with anastomotic leak versus those without, length of hospital stay was 28 days versus 10 days and mortality rate was 32% vs 4%, respectively.<sup>6</sup>

Clinical judgment is still considered the most important element utilized by surgeons to avoid anastomotic leak. However, prospective studies have shown that clinical assessment of bowel perfusion lacks predictive accuracy and clinical risk assessment by the surgeon has low predictive value for development of an anastomotic dehiscence.<sup>7</sup> Other adjuncts have been utilized including Doppler, fluorescein using UV Woods lamp and ICG-fluorescence. ICG is an ideal molecule to use intra-operatively as it binds strongly to plasma proteins causing it to remain in the intravascular space. Its short half-life of three to five minutes allows for rapid clearance and repeated usage in the same surgery. Furthermore, this molecule has an excellent safety profile with rare reported anaphylactic reactions.<sup>5</sup>

Spy Elite System utilizes ICG fluorescence to enable visualization of arterial inflow, venous return and tissue perfusion intra-operatively. As an adjunctive tool, the Spy System allows for visual assessment of blood flow in plastic, micro-, reconstructive and gastrointestinal and cardiovascular procedures.<sup>5</sup> In respect to colorectal surgery, there have been several studies examining the utility of ICG fluorescence angiography.

Kudszus et al. used IC View (Pulsion Medical Systems AG, Munich, Germany), an intraoperative laser fluorescence angiography (LFA) system to assess bowel perfusion at anastomotic site. The authors conducted a matched control retrospective study (n = 402) comparing patients who underwent colorectal resections without LFA to patients who underwent colectomies with LFA. The control group had an anastomotic leak rate of 7.5% compared to 3.5% in the LFA group. Moreover, the study revealed a significantly reduced hospital stay in the LFA group.<sup>8</sup>

Near-infrared fluorescence angiography (PinPoint System, Novadaq, Canada) is another system that uses ICG fluorescence during laparoscopic colorectal surgery and has been proven to be feasible and reproducible in several studies. Ris et al. analyzed 30 consecutive colorectal resections using this system; a diverting ostomy was avoided in three out of six patients in part because of the confidence imparted by the perfusion angiogram. There were no recorded anastomotic leaks.<sup>9</sup> The PILLAR II trial, a prospective, multi-centered clinical trial, evaluated the feasibility and utility of ICG FA using PinPoint system for intraoperative perfusion assessment as well. A total of 139 left colectomies and low anterior resections were analyzed with FA, changing surgical plans in 11 cases. The anastomotic leak rate was 1.4% (n=2). There were no leaks in the 11 cases that had alterations.<sup>10</sup>



In a case-matched retrospective study conducted by Kin et al., the authors sought to determine whether the use of intraoperative laser FA SPY Imaging System affected the anastomotic leak rate in colorectal resections. One hundred seventy three pairs were analyzed and the anastomotic leak rate was found to be comparable in those who utilized intra-operative FA (7.5%) versus those who did not (6.4%) with  $p=0.67$ . Eight patients (4.6%) underwent additional colon resection after angiographic evaluation. One anastomotic leak was recorded in this subset of patients. The authors concluded that the benefit of intraoperative fluorescence angiography is equivocal as their data revealed no association with decreased rates of leaks; however, it did alter surgical management in several cases.<sup>11</sup>

Lastly, Boni et al. used fluorescence angiography (KARL STORZ GmbH & Co. KG, Tuttlingen, Germany) intraoperatively to assess colonic perfusion prior to and after completion of the anastomosis in colorectal resections. A total of 107 patients were included in the study with 4 cases having alterations in the transection point based on fluorescence intensity. None of these patients suffered anastomotic leak.<sup>12</sup>

The abovementioned studies all interpreted ICG fluorescence in a qualitative manner and therefore remain a subjective adjunct to clinical judgment. The Spy Elite System software allows for quantification of perfusion by assigning numeric values of intensity of fluorescence. As stated in a previous study conducted at this institution, the utility of these values remains to be determined and studies are scarce.<sup>13</sup> In colorectal surgery, Foppa et al. conducted a prospective study to describe the impact of intraoperative ICG FA using Spy-Q evaluation for small bowel ischemia and left colon resections. ICG angiography played a role in decision making in four out of 160 cases.

The authors concluded that in cases of acute small bowel ischemia, resection is not warranted unless absolute values are below 19. In left colon resections, the recommended absolute unit for resection is less than 18.<sup>14</sup>

In this series, the authors utilized the absolute value to quantify bowel perfusion in 246 patients who underwent colorectal surgery. To the best of the authors' knowledge, this is the largest study to date to examine the absolute value of the Spy Elite System in colorectal surgery. These patients were compared to a historical group of similar patients (Table 1). The leak rate before the use of SPY was not significantly different when compared to the leak rate with the use of SPY ( $p > 0.05$ ). These results suggest that routine use of ICG fluorescence angiographic evaluation does not independently decrease the incidence of anastomotic leak when used by experienced colorectal surgeons. There were a total of thirteen operations that required additional proximal resections due to low ICG readings (5.3%). The mean absolute ICG value for all cases was greater than 51. The average absolute value when alteration was made was less than 40.

There are several limitations in this study. First, the sample size is small, albeit the largest available. Next, the study design is retrospective and is not a randomized control trial. Lastly, the low initial anastomotic leak rate may mask the benefit of ICF-FA in populations with higher rates of anastomotic leak.

### **Conclusion**

In this retrospective study, no significant difference was found in anastomotic leak rates between the group prior to the use of intraoperative angiography and the group utilizing fluorescence angiography. Routine use of ICG FA significantly altered intra-operative decision-making without discernible change

in clinical outcome. Randomized control trials are needed to establish the benefit of using fluorescence angiography in colorectal surgery before its routine use can be recommended. The clinical significance of absolute values in SPY-Q evaluation and their relationship to anastomotic leak requires further study.

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