EVALUATION OF GASTRIC CONDUIT PERFUSION RESULTS BASED ON REAL-TIME INDOCYANINE GREEN FLOW SIGNAL IN THORACOSCOPIC SURGERY FOR ESOPHAGEAL CANCER

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Abstract

Objectives*:** To evaluate gastric conduit perfusion (GCP) images based on indocyanine green (ICG) flow signal timing in thoracoscopic surgery for esophageal cancer (EsC). ***Methods: A cross-sectional descriptive study was conducted on 70 patients who were applied ICG to evaluate GCP during thoracoscopic surgery to treat EsC at 108 Military Central Hospital and Military Hospital 103 from June 2022 to June 2024. ***Results:*** The mean age was 59.0 ± 7.9 (32 - 71) years old; 100% were male. The anastomotic leak rate was 7.1%, with a mean gastric conduit (GC) width of 5.1 ± 0.2cm. Through ICG imaging, 17 patients with missing GC were detected. The average ischemic GC length was 2.7 ± 0.6cm. The time of appearance of the ICG signal in segments (B-C) and segments (A-D) of the anastomotic leak group was longer than that of the group without anastomotic leak ($p < 0.05$). Multivariable logistic regression analysis found that the greater the rate of ischemic GC, the higher the anastomotic leak rate (OR = 59.27; 95%CI= 1.25 - 2802.03; p = 0.04). ***Conclusion:*** Evaluation of GCP images based on ICG flow signal timing is feasible, safe, and objective. ICG current signal timing helps detect the location of the poorly perfused GC and select the appropriate location to create the anastomosis with a low anastomotic leak rate.

Keywords: Esophageal cancer; Gastric conduit; Indocyanine green.

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INTRODUCTION

Anastomotic leak is a common complication after esophagectomy for EsC, with a rate of about 5 - 25% [1, 2]. Factors related to anastomotic leak include patients' nutritional status, the tunnel where the GC is placed, the location or technique of anastomosis, and the tension of the anastomosis. Among them, ischemia of the GC is an important factor causing anastomotic leak and anastomotic stenosis [3]. Around the world, the near-infrared fluorescence method using ICG has been applied as a valuable, objective tool in surveying and evaluating the perfusion status of the GC. To evaluate GCP, the authors used one of the following three methods: ICG signal duration, flow rate, and ICG current intensity in the GC. Many authors rely on ICG flow signal duration as an objective index to evaluate GCP. Noma et al. reported that if the GC blood supply is enhanced with ICG within 20 seconds, the GC is said to be well perfused at that location, and anastomosis performed in this area will ensure good [4]. Kumagai et al. proposed the "90-second rule" to confirm good perfusion of the GC. All anastomoses performed in the area of the ICG-enhanced GC within 90 seconds of the ICG signal appearing at the origin of the right gastric omental artery [5]. EM de Groot demonstrated that in patients with anastomotic leakage, the mean time to reach maximum ICG intensity at the tip of the GC was 56 seconds (ranging from 30 - 83 seconds) compared with 34 seconds (ranging from 12 - 66 seconds) in patients without anastomotic leakage [6]. In Vietnam, thoracoscopic esophagectomy is performed routinely in many central hospitals, but there has not been any work or research reported on the use of ICG to evaluate GCP. Therefore, we conducted this study to: *Evaluate the results of GC blood supply based on ICG flow signal timing in thoracoscopic surgery for EsC.*

MATERIALS AND METHODS

1. Subjects

Including 70 EsC patients who underwent thoracoscopic esophagectomy and ICG imaging to evaluate the blood supply of the replacement GC for EsC from June 2022 to June 2024.

* *Inclusion criteria:* Diagnosis of carcinoma in the thoracic esophagus and undergoing thoracoscopic radical esophagectomy for the preoperative stage: cT1b-cT2, N0 or cT1b-cT3, N+ after preoperative chemotherapy; undergoing ICG imaging for evaluation of the blood supply of the replacement GC; ASA-PS ≤ 3.

Exclusion criteria: Patients undergoing thoracoscopic esophagectomy for non-cancerous causes or those with tumor invasion at the T4b level, according to the American Joint Committee on Cancer classification.

2. Methods

Study design: A cross-sectional descriptive study.

Surgical procedure using ICG to assess GCP:

Thoracoscopic radical esophagectomy and 2-region lymph node dissection were applied to all patients.

Thoracic step: Thoracoscopic surgery.

Abdominal surgery: Laparoscopic or open surgery was possible in cases with a history of previous abdominal surgery.

Technique to create a large GC:

The reconstructed GC was approximately 5cm wide, retaining the right and left gastroepiploic arteries, some of the first branches of the right gastric artery, and the arcade between the right and left gastroepiploic arteries.

The GC was created using an open stapler with open surgery, assisted laparoscopic surgery, and an endoscopic stapler with laparoscopic surgery.

Fluoroscopy uses ICG to evaluate GCP:

Measure the dimensions of the GC with a tape measure:

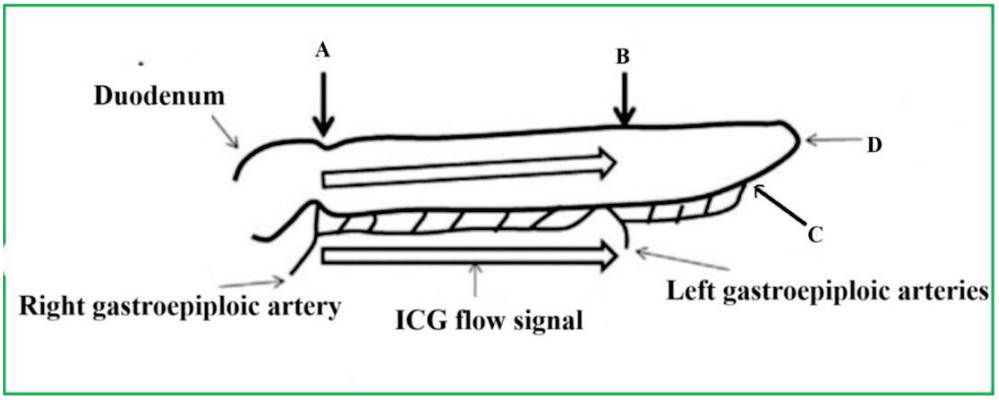

Figure 1. Image of marking positions to measure GC dimensions.
Source: According to Kazuo Koyanagi in 2016 [7].

Point (A) is the pylorus;

Point (B) is the location of the connection between the right and left gastroepiploic arteries;

Point (C) is the last point of the pulsatile GC to the final tip of the stomach;

Point (D) is the final point of the GC.

The camera had a near-infrared light source placed in front of the GC at a 3 - 5cm distance to ensure clear recorded images.

The injection technique in the study was applied according to author Rao-Jun Luo (2020) [5] as follows:

Injection dose: 2.5mg ICG injection/ 1 time.

Injection site: Can be injected into a central vein (right external jugular vein) or peripheral vein (right cephalic vein).

Injection time: Rapid bolus injection of ICG in about 3 - 5 seconds.

Number of injections: 1st ICG injection: After completing the shaping of the GC.

The purpose is to evaluate the GCP status when the shaping is completed. Second ICG injection: Recheck GCP after the GC is inserted through the posterior mediastinal tunnel to the neck.

The time to appear ICG was calculated when the blue signal begins to appear at point a (origin of the right gastroepiploic artery).

Based on the time of ICG appearance calculated from point a to the distal end of the GC in the arterial phase at the 1st injection.

The GC segment was considered to be well perfused when the time to appear ICG is < 60 seconds from point A. The GC segment was considered poorly perfused when the time to appear ICG is ≥ 60 seconds from point A.

* *Data analysis:* All statistical analyses were performed using SPSS software (version 26.0, 64-bit from IBM Corporation, NY, USA).

3. Ethics

This study was conducted in accordance with the declaration of Helsinki, approved by the Ethics Council of Military Hospital 103, on December 9th, 2022, approval number 193/CNChT - HĐĐĐ. Participants fully agreed and voluntarily participated in the study. Written informed consents were obtained with full signatures. Military Hospital 103 granted permission for the use and publication of the research data. The authors declare to have no conflicts of interest in the study.

RESULTS

70 patients participated in the study from June 2022 to June 2024. The average age was 59.0 ± 7.9 (32 - 71) years old; 100% were male. ASA = 2, accounted for 64.3%. ASA = 3, accounted for 35.7%. Patients received preoperative chemotherapy and radiotherapy, accounting for 77.1%. The anastomotic leak rate was 7.1% (5 patients)

* *Characteristics of GC esophageal replacement used in research:*

GC width: 5.1 ± 0.2cm; GC length (AD): 31.4 ± 1.3cm; length of GC segment (AB): 18.9 ± 1.3cm; length of GC segment (AC): 29.1 ± 1.2cm; length of GC segment (BC): 10.2 ± 1.0cm.

Table 1. Real-time ICG flow signals in the GC (arterial phase).

Real-time ICG flow signals in the GC (arterial phase)	N^0 of patients	Min	Max	Mean ± SD/ Median (Q1-Q3)
First injection				
Segment (A-B) (sec)	70	3	14	6.2 ± 2.0
Segment (A-C) (sec)	70	9	32	18.4 ± 5.1
Segment (A-D) (sec)	70	14	120	24.0 (21.0 - 59.3)
Segment (B-C) (sec)	70	5	24	12.2 ± 4.2
Segment (C-D) (sec)	70	2	105	6.0 (4.0 - 40.3)
Second injection				
Segment (A-C) (sec)	70	12	32	18.9 ± 4.6
Segment (A-D) (sec)	70	17	120	25.0 (22.0 - 48.0)
Segment (C-D) (sec)	70	1	105	7.0 (5.0 - 31.3)

When injecting ICG for the first time, the GC immediately after shaping, the time to appear ICG in the entire GC (A-D) was 24.0 (21.0 - 59.3) seconds. The appearance time of ICG segments (A-C) and (B-C) were 18.4 ± 5.1 seconds and 12.2 ± 4.2 seconds, respectively. When the GC was placed in the posterior mediastinal tunnel, the ICG appearance time of the entire GC (A-D) and segment (A-C) was 25.0 (22.0 - 48.0) seconds and 18.9 ± 4.6 seconds, respectively.

Table 2. Comparison of determining the GC with poor blood supply between visual observation and ICG fluorescence imaging.

Perfusion of the GC		ICG imaging		Total
		No	Yes	n (%)
Visual observation	No	53	8	61 (87.1)
(The first observation)	Yes	0	9	9 (12.9)
Visual observation	No	53	8	61 (87.1)
(The second observation)	Yes	0	9	9 (12.9)
Total		53	17	70 (100)
Management of the ischemic portion of the GC observed by ICG imaging				
Excision of the ischemic portion of GC				17 (24.3)
Suture burying the ischemic part of GC				0
The average length of the GC that was removed (cm): 2.7 ± 0.6 (2 - 4)				

Clinical observation by 2 experienced surgeons found 9 patients with poorly perfused GCs. Re-examination with ICG imaging detected 17 patients with poorly perfused GCs, including 9 patients who were visually observed and the remaining 8 patients who were not visually observed. All poorly perfused GCs had the ischemic part removed; the average conduit length of the ischemic GC was 2.7 ± 0.6cm.

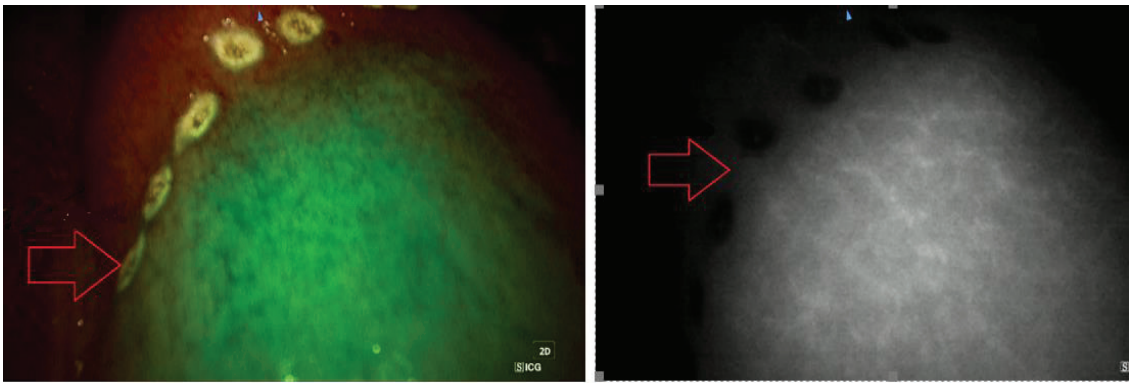

Figure 2. Boundary ICG image identifies an ischemic GC.
Source: Patient Le K, file number 22836724.

Table 3. The relationship between ICG imaging characteristics and injection.

ICG images	Central vein	Peripheral veins	p
First injection			
ICG appearance time of segment (A-B) (sec)	6.1 ± 2.0	6.4 ± 1.9	0.61
ICG appearance time of segment (A-C) (sec)	17.9 ± 4.9	18.9 ± 5.3	0.45
ICG appearance time of segment (A-D) (sec)	24 (21 - 54)	24 (20.8 - 63.5)	0.81
ICG appearance time of segment (B-C) (sec)	11.8 ± 4.1	12.5 ± 4.3	0.49
Second injection			
ICG appearance time of segment (A-C) (sec)	18.6 ± 4.3	19.3 ± 5.0	0.58
ICG appearance time of segment (A-D) (sec)	26 (22 - 42.3)	25 (21 - 63.3)	0.54

There was no relationship between ICG imaging characteristics and the injection route.

Table 4. The relation of ICG flow signal time to the vascular connection between the right and left gastroepiploic arteries.

ICG images	The arcade between the right and left gastroepiploic arteries		p
	No	Yes	
First injection			
ICG appearance time of segment (A-B) (sec)	6.5 ± 2.4	6.1 ± 1.6	0.39
ICG appearance time of segment (A-C) (sec)	18.9 ± 4.6	18.1 ± 5.4	0.56
ICG appearance time of segment (A-D) (sec)	25 (22 - 71)	24 (21 - 37)	0.13
ICG appearance time of segment (B-C) (sec)	12.4 ± 3.3	12.1 ± 4.7	0.76
Second injection			
ICG appearance time of segment (A-C) (sec)	19.1 ± 4.4	18.8 ± 4.8	0.81
ICG appearance time of segment (A-D) (sec)	26 (22 - 72)	25 (22 - 39)	0.36

The real-time appearance of ICG flow signals in the GC at marked locations was not related to the vascular connection between the right and left gastroepiploic arteries.

Table 5. Real-time correlation of ICG flow signal appearance with anastomotic leakage.

ICG image	Anastomotic leakage		p
	No (n = 65)	Yes (n = 5)	
First injection			
ICG appearance time of segment (A-B) (sec)	6.3 ± 2.0	5.6 ± 0.9	0.46
ICG appearance time of segment (A-C) (sec)	18.1 ± 5.1	22.0 ± 2.7	0.10
ICG appearance time of segment (A-D) (sec)	24 (21 - 41.5)	65 (43.5 - 73.5)	0.04
ICG appearance time of segment (B-C) (sec)	11.9 ± 4.1	16.4 ± 2.5	0.02
Second injection			
ICG appearance time of segment (A-C) (sec)	18.7 ± 4.7	22.4 ± 2.5	0.08
ICG appearance time of segment (A-D) (sec)	24 (21.5 - 39.5)	65 (45.5 - 73.5)	0.02

The real-time appearance of ICG flow signals in segments (B-C) and segments (A-D) at the 1st injection of the anastomotic leak group was longer than that of the group without an anastomotic leak. This difference was statistically significant,

with p = 0.02 and p = 0.04. The above results were similar in the second injection when comparing the ICG flow signal time in segments (A-D) in the 2 groups of anastomotic leak and without an anastomotic leak.

Table 6. Multivariable logistic regression for factors predicting anastomotic leak.

Variables	OR	95%CI	p
Age	0.83	0.66 - 1.05	0.12
Smoke	4.19	0.16 - 113.41	0.40
BMI	1.02	0.55 - 1.89	0.94
Protein	1.10	0.82 - 1.46	0.53
Albumin	0.69	0.35 - 1.36	0.29
Surgery time	1.03	0.98 - 1.07	0.28
Blood loss during surgery (mL)	1.00	0.99 - 1.01	0.95
GC shaping technique	0.53	0.02 - 11.75	0.69
The connection between the right and left gastroepiploic vessels	1.15	0.07 - 19.09	0.92
Poor blood supply of distal GC after the 1st injection	59.27	1.25 - 2802.03	0.04

When analyzing multivariable logistic regression, it was found that the more significant the proportion of GCs with poor perfusion, the higher the rate of anastomotic leakage (OR = 59.27; 95%CI = 1.25 - 2802.03; p = 0.04). Other factors such as age, protein, BMI, and the amount of blood loss are not related to anastomotic leak.

DISCUSSION

Based on real-time ICG flow signals in the GC to investigate the perfusion of the GC, it shows that the shorter the real-time, the better the perfusion of the GC. Normally, the ICG flow signal time will appear early in the pyloric region of the GC. This location of the GC is better perfused than other locations. Some authors have chosen short real-time ICG flow signals. This choice aims to ensure better perfusion of the GC and enough conditions to create an anastomosis. However, if we choose a short time for the ICG signal to appear, the GC's length is often not enough to reach the neck area. This means that the GC will be longer. Choosing locations where the ICG signal image will appear longer is necessary.

When injecting the first time, the GC was placed in front of the chest, the ICG appearance time of the entire GC (A-D) was 24 (21 - 59.3) seconds, segment (A-C) was 18.4 ± 5.1 seconds, and segment (B-C) was 12.17 ± 4.2 seconds. Evaluation of GCP revealed 17 patients with ICG signal time appearing in GC ≥ 60 seconds, a sign of poor blood supply in GC. Table 3 demonstrates that the central and peripheral intravenous routes are unrelated to the time the ICG flow signal takes in GC. When injecting the second time, the GC was placed in the posterior mediastinal tunnel, the time of total ICG appearance of the GC segment (A-D) was 25 (22 - 48) seconds, and segment (A-C) was 18, 9 ± 4.6 seconds (*Table 1*).

Table 5 shows that when comparing the ICG appearance time between different positions of the GC, we get the result that the ICG appearance time of the GC segment (B-C) in the anastomotic leak group is longer than the no-leak group. Anastomosis during the 1st injection, the difference between these 2 groups was statistically significant with p = 0.02. It is important to know that segment (B-C) is the location of GC that often has anemia and is also the area that needs to be investigated before GC shaping. The time to appear ICG signal of the entire GC (A-D) in the anastomotic leak group was longer than the group without anastomotic leak, 65 (43.5 - 73.5) seconds compared to 24 (21 - 41.5) seconds in the first injection and 65 (45.5 - 73.5) seconds in the no anastomotic leak group compared to 24 (21.5 - 39.5) seconds in the anastomotic leak group in the second injection.

Kumagai et al. proposed a 90-second rule to confirm a well-perfused GC position. The anastomosis was performed in the area of the GC with an enhanced IG flow signal less than 90 seconds from the appearance of the initial ICG signal at the origin of the right gastroepiploic artery. Based on this rule, poor perfusion GC had poor perfusion fecal resection in 50% (35/70), and the planned site of anastomosis was changed in 18 of those 35 cases. No patient underwent anastomosis creation at the site with ICG enhancement slower than 90 seconds. One case out of 70 cases (1.4%) showed anastomotic leakage when the anastomotic site where ICG appeared after 77 seconds [5].

Noma reported that if the GCP is enhanced by ICG within 20 seconds at that location of the GC that is considered well perfused, an anastomosis performed in this area will ensure good perfusion. The study showed that the anastomotic leak rate in patients using ICG was significantly lower than in patients who did not use ICG (8.8% vs. 22%, p = 0.03) [4].

In Rao-Jun Luo's study, with a total of 192 patients, 86 patients were in the ICG injection group, and 106 patients were in the non-ICG injection group. All patients in the ICG group underwent fluorescein angiography successfully. As a result, 32 patients out of 86 patients who received ICG injections found that GCs were judged to be well perfused within 60 seconds, meaning that these GCs did not have areas of poor perfusion. For the remaining 54 patients, there was an area of GC with poor perfusion with varying lengths of the GC following the 60-second rule. In the ICG group, the anastomosis was performed at the site where green fluorescent GC was observed for less than 60 seconds. ICG imaging confirmed blood flow, and perfusion was clearly visualized within 60 seconds. After 60 seconds, the fluorescence image of the GC was jagged and uneven, which was an inappropriate location for selecting the anastomotic area. Therefore, Rao-Jun Luo hypothesized that the risk of anastomotic leakage is minimized if the anastomosis is created in an area where the ICG is enhanced within 60 seconds. The poorly perfused GC area was excised before performing the anastomosis. The anastomotic leak rate in esophagectomy for EsC was 10.4% in the non-ICG group and was significantly higher than 1.2% in the ICG group. This suggests that the anastomotic leak rate can be reduced by approximately 9% by using ICG. This evidence strongly suggests that adequate perfusion of the GC is important for complete tissue healing at the anastomotic site [8].

Table 5 shows that the time to appear ICG signal in the segment (B-C) of the 1st injection of the anastomotic leak group was longer than the group without an anastomotic leak. This difference is statistically significant ($p = 0.02$).

EM de Groot demonstrated that in patients with anastomotic leakage, the median time to reach maximum ICG intensity at the tip of the GC was 56 seconds (30 - 83) compared with 34 seconds (12 - 66) in patients without anastomotic leakage. Based on the time of ICG appearance, the initial location chosen to perform the anastomosis had to be changed to another location in 14% of patients. The mean time to peak intensity was shorter at the base of the GC (25 seconds, ranging from 13 - 49) than at the distal tip (34 seconds, ranging from 12 - 83) [6].

Kazuya Yamaguchi uses the "90 to 60-second rule", meaning that the esophageal-gastric anastomosis will be performed where the ICG signal increases within 90 seconds (preferably within 60 seconds). The authors have demonstrated that using the 90 to

60-second ICG imaging rule reduces the anastomotic leakage rate. When performing the anastomosis in the enhanced ICG position within 90 seconds, anastomotic leakage occurred in 4 cases (3.1%) out of 129 cases, of which 3 cases (2.4%) out of 126 cases had junction sites where the ICG current signal enhanced within 60 seconds and 1 case (33.3%) out of 3 cases with time ICG enhancement exceeded 60 seconds (p = 0.09) [9].

According to table 6, multivariable logistic regression analysis shows that the higher the rate of poorly perfused GC (ICG appearance time ≥ 60 seconds), the higher the rate of anastomotic leak (OR = 59.27; 95%CI = 1.25 - 2802.03; p = 0.04) at the 1st injection. Other factors, such as age, protein, BMI, and blood loss, were unrelated to anastomotic leak. This further demonstrates the importance of ICG imaging in detecting GC perfusion.

CONCLUSION

Assessment of GC perfusion based on ICG flow signal timing is feasible, safe, and objective. The ICG flow signal time is an objective index that helps choose the appropriate GC location to create the anastomosis, and the anastomotic leak rate is low (7.1%). By ICG, 17 patients with GC were detected with poor perfusion. The time to appear ICG signal in segments (B-C) and segments (A-D) of GC in the anastomotic leak group was longer than that in the group without anastomotic leak (p < 0.05). Multivariable logistic regression analysis found that the higher the rate of anemic GC, the higher the anastomotic leak rate (OR = 59.27; 95%CI= 1.25 - 2802.03; p = 0.04).

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