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RESEARCH

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Blood flow assessment of gastric tube with indocyanine green fluorescence angiography and postoperative endoscopy during esophagectomy: indocyanine green enhancement time indicated congestion

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Abstract

Background During esophagectomy, evaluation of blood supply to the gastric tube is critically important to estimate and avoid anastomotic complications. This retrospective study investigated the relationship between indocyanine green (ICG) fluorescence angiography during esophagectomy and postoperative endoscopy findings, especially mucosal color change.

Methods This study retrospectively collected data from 86 patients who underwent subtotal esophagectomy and reconstruction using a gastric tube for esophageal cancer at the Tokyo Medical and Dental University between 2017 and 2020. The flow speed of ICG fluorescence in the gastric tube was evaluated during the operation. Additionally, the main root of ICG enhancement and pattern of ICG distribution in the gastric tube were evaluated. On postoperative day 1 (POD1), the change in the mucosal color to white, thought to reflect ischemia, or black, thought to reflect congestion of the proximal gastric tube, was evaluated. The correlations between these factors, clinical parameters, and surgical outcomes were evaluated. Univariate and multivariate analyses used logistic regression to identify the risk factors affecting mucosal color change.

Results Multivariate analyses revealed that the only independent significant predictor of mucosal congestion on POD1 was the ICG enhancement time of the right gastric tube tip (odds ratio, 14.49; 95% confidential interval, 2.41–87.24; $P = 0.004$).

Conclusions This study indicated that the ICG enhancement time is related to venous malperfusion and congestion rather than arterial malperfusion and ischemia.

Keywords Esophagectomy, Indocyanine green fluorescence, Gastric tube reconstruction, Mucosal color change

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Background

Anastomotic leakage is one of the most significant and fatal postoperative complications of esophagectomy. A recent systematic review showed that the incidence of anastomotic leakage during esophagectomy was 0–35% [1].

The stomach is widely used for reconstruction, and to play the role of a reconstructed conduit, the blood flow in the gastric tube is a very important factor. Inadequate blood flow can lead to ischemic or congestive necrosis of the gastric tube. Assessing blood flow in the gastric tube is critical to estimate and avoid complications, especially anastomotic leakage.

Indocyanine green (ICG) fluorescence angiography during esophagectomy has been used to assess blood flow in the gastric tube, primarily the arterial blood flow [2–6]. ICG fluorescence angiography was performed during an esophagectomy in 2017 at our institute. We previously reported the feasibility, applicability, and appropriate use of ICG fluorescence in a gastric tube as a reconstructed conduit [7]. ICG can visualize intraoperative blood flow, primarily the arterial blood flow. Several previous studies have shown a strong correlation between ICG administration during esophagectomy and gastric tube tip necrosis, which results in anastomotic leakage and poor ICG distribution [8, 9]. However, a previous study using ICG fluorescence angiography could not detect venous congestion in the graft because the ICG fluorescence signal was detected as a result of arterial perfusion rather than venous perfusion [10].

Postoperative endoscopy enables direct observation of the anastomosis and inner lining of the reconstructed gastric tube. In 2008, we began endoscopic examinations on postoperative day 1 (POD1) to assess the reconstructed gastric tube and anastomotic site. We previously reported that POD1 endoscopy helps predict poor healing of esophagogastric anastomosis on POD7 by identifying the findings of mucosal color change in the gastric tube [11]. We also observed gastric tube mucosal color change, particularly around the anastomotic site, which may indicate poor circulation from ischemia, arterial malperfusion to congestion, venous malperfusion and subsequent mucosal necrosis. Although performing postoperative endoscopy may help confirm the cause of anastomotic complications and provide important information for the postoperative management of patients, all endoscopic assessments can only be performed postoperatively compared with ICG fluorescence, which can be performed during surgery. Therefore, there is a gap in the literature regarding the correlation between ICG fluorescence angiography findings during esophagectomy and postoperative endoscopy results.

This retrospective study investigated the correlation between the findings of ICG fluorescence angiography during esophagectomy and postoperative endoscopy, especially mucosal color change.

Methods

This study included 122 patients who underwent subtotal esophagectomy and reconstruction for esophageal cancer using gastric tubes between August 2017 and December 2020. Patients who did not undergo cervical esophagogastric anastomosis or those who underwent additional surgeries were excluded. Additionally, patients who did not undergo postoperative endoscopy were excluded. Therefore, this study included 86 patients.

Surgical procedure

Details of the surgical procedure for esophagectomy at our institution have been previously reported [12]. After the esophagectomy, a gastric tube was created as the reconstructed conduit. In order to create the gastric tube, the omentum was cut approximately 2 cm from the right gastroepiploic artery area, and the vessel was completely preserved. The root of the left gastroepiploic artery was excised, and the entire vessel arcade in the greater curvature was preserved. We preserved the first and second branches of the right gastric artery and cut the antrum from the lesser curvature using linear staplers to create a gastric tube. The flexible gastric tube was pulled up to the neck, and an esophagogastric anastomosis was performed with a circular stapler near the final branch of the left gastroepiploic artery. We used a 25 (21–29) mm circular stapler. This surgical procedure is standardized at our institution, and board-certified surgeons (Japan Esophageal Society) always perform these operations [12, 13].

Evaluation of the gastric tube with ICG fluorescence angiography

Before pulling the gastric tube up to the neck, 2.5 mg of ICG dye (Diagnogreen, Dai-Ichi Pharm, Tokyo, Japan) was injected intravenously. Blood flow was assessed by ICG fluorescence angiography using a near-infrared camera system (Photodynamic Eye [PDE]; Hamamatsu Photonics K. K, Hamamatsu, Japan), and a video was recorded simultaneously. We measured the time from the initial ICG enhancement of the right gastroepiploic artery until the ICG enhancement of the gastric tube tip. In addition to the enhancement time, we evaluated whether the main root of ICG enhanced the gastric tube from the greater curvature or lesser curvature (Fig. 1A and B). We also evaluated the pattern of ICG distribution in the gastric tube. Especially at the tip of the gastric tube, blood distribution was mainly intramural. There were generally two patterns of ICG distribution: wall-dominant or vessel-dominant (Fig. 1C and D). Two independent surgeons (JS and AH) performed all measurements,

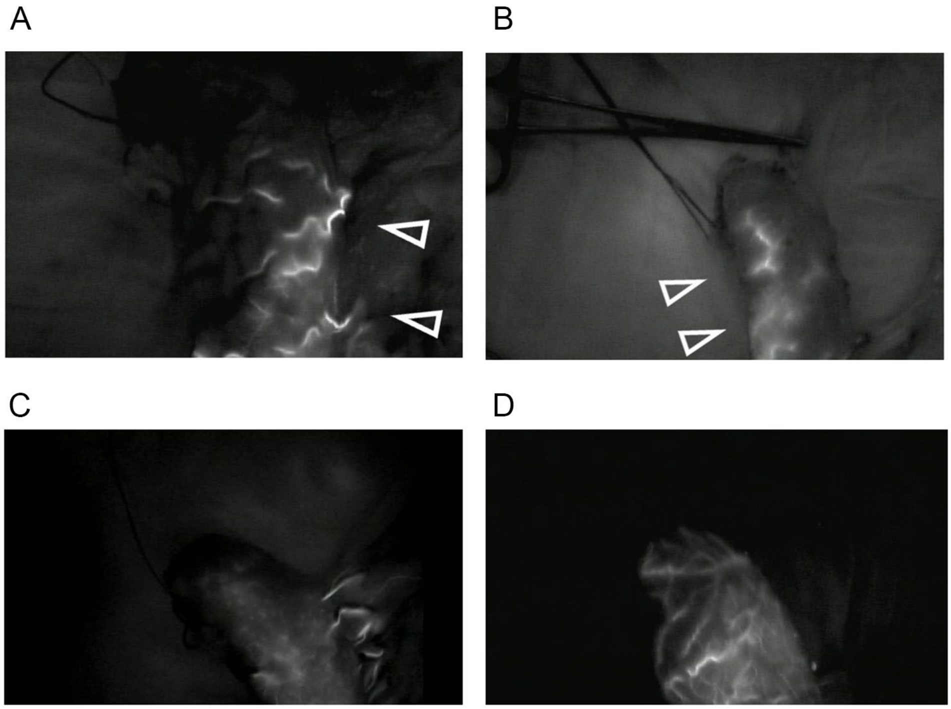

Fig. 1 The ICG findings during operation. (**A**). The main root of ICG enhancement in the gastric tube enhanced from the greater curvature, which is located in the right side of the gastric tube (left side of the body). (**B**). The main root of ICG enhancement in the gastric tube, enhanced from the lesser curvature, which is located in the left side of the gastric tube (right side of the body). (**C**). The pattern of ICG distribution to the gastric tube, wall-dominant. In the wall-dominant pattern, vessel enhancement is relatively obscure. (**D**). The pattern of ICG distribution to the gastric tube, vessel-dominant. In the vessel-dominant pattern, vessel enhancement is relatively clear

and the average values were used. After ICG fluorescence imaging, the gastric tube was pulled up to the neck and anastomosed.

Evaluation of gastric tube with postoperative endoscopic examination

We performed a trans-nasal endoscopy on postoperative day 1 (POD1) (EG-530N2 or EG-530NW; Fuji, Japan). Endoscopic examinations were performed by physicians at our institute, and two or more physicians assessed the findings. We first observed the site of the anastomosis and the mucosal color in the gastric tube. In addition, we checked for vocal cord paralysis, which indicated recurrent laryngeal nerve palsy.

Among the findings of POD1 endoscopic examination, we particularly identified a mucosal color change to white or black around the anastomotic site (Fig. 2). We speculated that such findings of mucosal color change may indicate impairment of the gastric tube blood flow. In mucosal color change, white is thought to reflect ischemia, and black is thought to reflect congestion. A predominant finding was considered in cases of mixed findings of ischemia and congestion [11].

We also performed the same endoscopic examination on POD8 to identify abnormalities of leakage and ulcers compared with the findings on POD1.

Relationship between the findings of ICG fluorescence angiography and those of postoperative endoscopy

The primary endpoint of this study was mucosal congestion or ischemia in the proximal gastric tube, as indicated by the mucosal color change following the endoscopic examination on POD1. The relationship between ICG fluorescence angiography findings and mucosal congestion or ischemia on POD1 was investigated retrospectively.

Statistical analysis

The Chi-square test was used to analyze the qualitative data. Univariate analyses were performed to distinguish relevant factors entered into the multivariate analysis if the univariate analyses yielded a P-value <0.1. Logistic regression was used to perform univariate and multivariate analyses to determine the risk factors for mucosal color change. Differences were considered statistically significant at $P<0.05$. All analyses were performed using EZR version 1.52 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

The characteristics of the 86 patients are summarized in Table 1. The study group comprised 75 males and 11 females with a median age of 70 years. We identified mucosal color change in 44 (51.2%) patients. There were

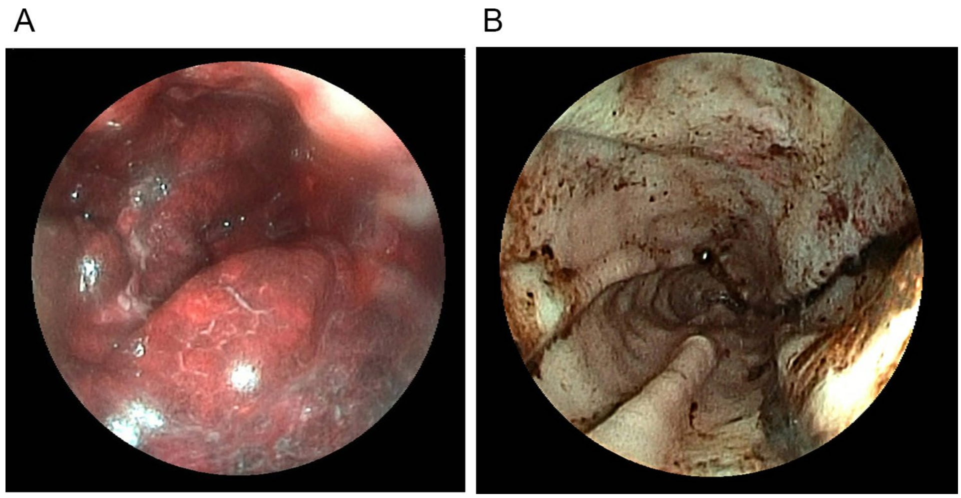

Fig. 2 The endoscopic findings on postoperative day 1. (**A**). Mucosal color change to black. (**B**). Mucosal color change to white

Table 1 Patient characteristics and perioperative outcomes

Characteristics of the study population ($n=86$)		Number
Variables		
Age (years)	≤ 70	46(53.4%)
Sex	Male	75(87.2%)
BMI (kg/m^2)	≥ 22	40(46.5%)
Hypertension	presence	22(25.6%)
Diabetes	presence	15(17.4%)
Arteriosclerosis	presence	8(9.3%)
Chronic Kidney Failure	presence	5(5.8%)
COPD	presence	7(8.1%)
Multiple Cancers	presence	19(22.1%)
Location	Ce/Ut	27(31.4%)
	Mt/Lt/Ae	59(68.6%)
pStage	0/I/II	50(58.1%)
	III/IV	36(41.9%)
Preoperative therapy	None	51(59.3%)
	Chemo/Chemoradiotherapy	35(40.7%)
Method of esophagectomy	Open	30(34.9%)
	MIE	56(65.1%)
Anastomotic leakage (Clavien-Dindo grade ≥ 2)	presence	4(4.7%)

BMI: body mass index; COPD: chronic obstructive pulmonary disease; MIE: minimally invasive esophagectomy

25 (29.1%) patients with congestive conditions (black) and 19 (22.1%) with ischemic conditions (white).

We measured the time from the initial ICG enhancement of the right gastroepiploic artery until the ICG enhancement of the gastric tube tip. The median time until enhancement of the gastric tube tip was 30 (12–165) s. We previously reported that gastric tube necrosis can be avoided if the area showing an enhancement time exceeding 90 s is excised (within the 90-s rule) [14]. Thus, all anastomoses were made in the gastric tube area requiring < 90 s for ICG enhancement. We generated a receiver operating characteristics (ROC) curve of the time until ICG enhancement of the gastric tube tip to predict mucosal color change, especially the congestive change on POD1 endoscopic examination. We determined that the time cutoff value until ICG enhancement of the gastric tube tip was 55 s, and the area under the ROC curve was 0.61. The ICG enhancement time was significantly correlated with mucosal congestion on POD1 ($P=0.006$).

In addition to the time of enhancement, we evaluated whether the main root of the ICG enhanced the gastric tube and the pattern of ICG distribution in the gastric tube. However, neither the type of ICG main root nor the pattern of ICG distribution correlated with the endoscopic mucosal color change (Table 2).

Table 3 shows the relationship between the clinical parameters and the occurrence of mucosal congestion on POD1. Neither preoperative nor surgical factors correlated with mucosal congestion. Only the ICG enhancement time of the right gastric tube tip correlated with mucosal congestion ($P=0.007$). Based on the results of the univariate analysis, we selected the ICG enhancement time of the right gastric tube tip and hypertension, which are considered risk factors for mucosal congestion on POD1 for multivariate analyses. Of these, logistic regression analysis determined that the only independent significant predictor of mucosal congestion on POD1 was the ICG enhancement time of the right gastric tube tip (odds ratio, 14.49; 95% confidential interval, 2.41–87.24; $P=0.004$).

Discussion

This study investigated the relationship between ICG fluorescence angiography findings in gastric tube reconstruction during esophagectomy and postoperative endoscopy, especially mucosal color change. Several

Table 2 The relationships between the findings of ICG during esophagectomy and the postoperative endoscopy (mucosal color change)

	Congestion		*p* value	Ischemia		*p* value
	(+)	(-)		(+)	(-)	
	n = 25	*n* = 61		*n* = 19	*n* = 67	
ICG contrast pattern						
Greater curvature	4 (33.3%)	8 (66.7%)	0.077	3 (25.0%)	9 (75.0%)	0.948
Lesser curvature	14 (41.2%)	20 (58.8%)		7 (20.6%)	27 (79.4%)	
Diffuse	7 (17.5%)	33 (82.5%)		9 (22.5%)	31 (77.5%)	
Blood flow distribution pattern						
Superior gastric wall	6 (17.6%)	28 (82.4%)	0.088	7 (20.6%)	27 (79.4%)	1.000
Superior intramural blood vessel	19 (36.5%)	33 (63.5%)		12 (23.1%)	40 (76.1%)	
ICG enhancement time (second)						
≤ 55	18 (23.7%)	58 (76.3%)	0.006	18 (23.7%)	58 (76.3%)	0.447
> 55	7 (70.0%)	3 (30.0%)		1 (10.0%)	9 (90.0%)	

ICG: indocyanine green; ICG enhancement time: enhancement time from the root of the right gastroepiploic artery and the gastric tube tip

Table 3 Univariate and multivariate analyses of factors related to mucosal congestion on postoperative day 1

Variables		Number of Patients	Univariate	*p* value	Multivariate	*p* value
			OR (0.95%CI)		OR (95%CI)	
Age	≤ 70	46	0.16 (-1.26-7.09)	0.16	2.04 (0.69–6.02)	0.19
Sex	Male	75	1.99 (0.40–9.95)	0.32	1.57 (0.29–8.51)	0.6
BMI	≥ 22	40	1.71 (0.67–4.38)	0.26		
Hypertension	Presence	22	0.30 (0.08–1.13)	0.07	0.16 (0.03–0.84)	0.07
Diabetes	Presence	15	1.83 (0.57–5.81)	0.23		
Arteriosclerosis	Presence	8	0.32 (0.04–2.76)	0.26		
Chronic Kidney Failure	Presence	5	4.02 (0.63–25.71)	0.15		
COPD	Presence	7	3.68 (0.76–17.84)	0.11		
Multiple Cancers	Presence	19	1.17 (0.39–3.52)	0.5		
Location	Ce/Ut	27	1.04 (0.38–2.87)	0.93		
	Mt/Lt/Ae	59				
pStage	0/I/II	50	0.44 (0.17–1.14)	0.27		
	III/IV	36				
Preoperative therapy	None	51	1.92 (0.75–4.93)	0.17		
	Chemo/Chemoradiotherapy	35				
Method of Esophagectomy	Open	30	0.73 (0.28–1.92)	0.52		
	MIE	56				
The time from initial ICG enhancement(seconds)	≥ 55	10	7.52 (1.76–32.12)	0.007	14.49 (2.41–87.24)	0.004
Anastomotic leakage (C-D ≥ grade2)	Presence	4	0.81(0.08–8.14)	0.67		

OR: odds ratio; CI: confidential interval; BMI: body mass index; COPD: chronic obstructive pulmonary disease; MIE: minimally invasive esophagectomy; C-D: Clavien–Dindo classification; ICG enhancement time: enhancement time from the root of the right gastroepiploic artery and the gastric tube tip

previous studies have reported that ICG fluorescence angiography in the reconstructed gastric tube, especially regarding the blood flow time≥90 s between the root of the right gastroepiploic artery and the gastric tube tip, has a high possibility of gastric tube necrosis [14]. Additionally, several previous studies have reported the relationship between the findings of postoperative endoscopy after esophagectomy and anastomosis-related complications [10, 11, 15]. Although this study is not an appropriate predictive assessment of anastomotic leakage, to the best of our knowledge, this is the first report to evaluate the relationship between ICG fluorescence angiography findings during esophagectomy and postoperative endoscopy findings, especially mucosal color change.

Traditionally, ICG enhancement time has been thought to be correlated with poor tissue blood perfusion, especially arterial perfusion. Arterial malperfusion tends to result in subsequent mucosal necrosis of the gastric tube. According to our previous study and the "within the 90-s rule," an esophagogastric anastomosis should be created at the gastric tube area, where the ICG enhancement time between the root of the right gastroepiploic artery and gastric tube tip is within 90 s [14]. Following this, there was no correlation between the ICG enhancement time and mucosal ischemia of the gastric tube. This study revealed that ICG enhancement time is correlated with venous malperfusion and congestion, which suggests that congestion, in other words, elevated tissue pressure, has a possible relationship with slow ICG fluorescence signals. Suppose venous malperfusion could be observed with ICG fluorescence angiography intraoperatively. In that case, performing additional surgery, such as a superdrainage operation, might be helpful to avoid congestion of the distal end of the reconstructed gastric tube [16, 17].

A previous study showed the relationship between slow ICG fluorescence signals and graft malperfusion in head and neck surgery [18]. Radical surgery for hypopharyngeal and cervical esophageal cancers involves reconstruction after pharyngolaryngoesophagectomy using free jejunal grafts. This study showed that unusually slow fluorescence signals in the free jejunal graft predicted venous malperfusion of the graft. Our study showed that the tendency observed in the case of a free jejunal graft can also be observed in the case of a pedicled gastric tube.

This study had some limitations. First, this observational study was conducted through a single-institute medical record review. Second, the study population was relatively small. In addition, the ICG findings and mucosal color changes are sometimes objective, and recognizing these findings can be difficult in some cases universally. We used an institution-specific system to classify the endoscopic findings [11], which were rather subjective.

Conclusions

This study investigated the relationship between ICG fluorescence angiography findings in gastric tube reconstruction during esophagectomy and those of postoperative endoscopy, especially mucosal color change. This study indicated that the ICG enhancement time was related to venous malperfusion and congestion rather than arterial malperfusion and ischemia.

Abbreviations

ICG indocyanine green
POD postoperative day

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Author contributions

JS wrote the paper. AH and HF collected the data and contributed to writing the paper. KK, KO, TT, SH, MT and YK reviewed the paper and surgical technique. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Tokyo Medical and Dental University Institutional Review Board approved this study (M2020-051), and written informed consent was obtained from each patient, including for postoperative endoscopy.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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