Langenbeck's Archives of Surgery (2024) 409:90
https://doi.org/10.1007/s00423-024-03284-1

RESEARCH

Blood flow evaluation of reconstructed gastric tube in esophageal surgery using near-infrared imaging and retrospective time-intensity curve analysis

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Received: 5 January 2024 / Accepted: 7 March 2024

Abstract

Purpose Near-infrared fluorescence imaging using indocyanine green (ICG-NIFI) can visualize a blood flow in reconstructed gastric tube; however, it depends on surgeon's visual assessment. The aim of this study was to re-analyze the ICG-NIFI data by an evaluator independent from the surgeon and feasibility of creating the time-intensity curve (TIC).

Methods We retrospectively reviewed 97 patients who underwent esophageal surgery with gastric tube reconstruction between January 2017 and November 2022. From the stored ICG videos, fluorescence intensity was examined in the four regions of interest (ROIs), which was set around the planned anastomosis site on the elevated gastric tube. After creation the TICs using the OpenCV library, we measured the intensity starting point and time constant and assessed the correlation between the anastomotic leakage.

Results Postoperative leakage occurred for 12 patients. The leakage group had significantly lack of blood flow continuity between the right and left gastroepiploic arteries (75.0% vs. 22.4%; $P < 0.001$) and tended to have slower ICG visualization time assessed by the surgeon's eyes (40 vs. 32 s; $P = 0.066$). TIC could create in 65 cases. Intensity starting point at all ROIs was faster than the surgeon's assessment. The leakage group tended to have slower intensity starting point at ROI 3 compared to those in the non-leakage group (22.5 vs. 19.0 s; $P = 0.087$).

Conclusion A TIC analysis of ICG-NIFI by an independent evaluator was able to quantify the fluorescence intensity changes that the surgeon had visually determined.

Keywords Near-infrared fluorescence · Indocyanine green · Time-intensity curve · Gastric tube · Esophagus

Introduction

Surgical treatment for esophageal cancer includes esophagectomy and esophageal bypass surgery [1], in both cases, gastric tube (GT) reconstruction is commonly performed because of its technical simplicity and sufficient blood flow via intra-wall arterial networks [2]. However, an incidence of anastomotic insufficiency is not low in esophageal surgery as compared with other gastrointestinal surgeries [3], probably because there are cases where communication between right to left gastroepiploic artery (GEA) is not sufficient. In such cases, blood supply at the tip of GT is dependent solely on the intra-wall arterial networks [4], which can be affected when the GT is elevated to the neck due to compression by the clavicle or sternum at the thoracic inlet [5]. Although perfusion in the GT tip has been conventionally assessed by surgeon's inspection of GT such as color as well as palpation of nearby arteries, they are subjective [6]. For accurate assessment, near-infrared fluorescence imaging (NIFI) using indocyanine green (ICG) has been introduced [7] and has proved to be effective in reducing anastomotic leakage in esophageal surgery [8]. Thus, we introduced it in 2011 [9] and have found that (1) better ICG-NIFI evaluation of reconstructed GT is related to the postoperative endoscopic analysis of the anastomosis [10];

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(2) delayed ICG visualization of GT tip elevated to the neck was a risk factor for anastomotic leakage [11].

However, assessment remains subjective and may lead to misinterpretation because it is assessed by the surgeon's eyes after they have been exposed to the intense light for hours [12]. While analysis on the time-intensity curve (TIC) [13] appears to be promising as a potential solution for this clinical problem, hopefully by building a program for creating TIC directly from ICG-NIFI data at real time, it is necessary as a prerequisite to clarify: (1) the way of data collection which is suitable for this purpose; and (2) the parameters which predict anastomotic leakage. Thus, this study was aimed: (1) to re-analyze the ICG-NIFI data retrospectively in a frame-by-frame manner by a rater independent from the surgeon and without an influence of exposure to intense light before assessment and correlate it with an occurrence of leakage; and (2) to examine the feasibility of creating the TIC from the stored data and clarify the requirements for future data collection.

Methods

Subjects and the protocol of ICG-NIFI

We retrospectively reviewed 97 patients who underwent thoracic esophagectomy or esophageal bypass and GT reconstruction via a retro-sternum or posterior-mediastinum route with a circular stapler anastomosis between January 2017 and November 2022. Thoracic esophagectomy and mediastinal lymph node dissection were performed thoracoscopically, and GT creation was performed under direct view through a small incision laparotomy. The initial ICG-NIFI was done prior to the GT creation using LIGHT VISION (Shimadzu corporation, Kyoto, Japan). After ICG of 5 mg in 2 mL solution was injected via a central venous catheter, followed by 20 mL of saline for flushing, to examine the presence of blood flow continuity between the left and right GEAs and to measure the time duration from injection to the beginning of visualization of GT tip (first visualization time). Based on this assessment, the GT was created using a linear stapler (Fig. 1). After the GT was elevated to the neck, the second ICG-NIFI was done in the same manner for determining the optimal anastomosis site and measuring the second visualization time. The anastomosis site was selected at least 60 s after ICG injection, near the border of visualization on the greater curvature and marked on the GT using a surgical pen, and cervical esophagus-GT anastomosis was performed using a circular stapler, while the region in the GT tip without visualization was resected and closed using a linear stapler.

Measurement of ICG visualization time and determination of the blood flow continuity between the right and left GEA were performed by the same surgeon. When blood

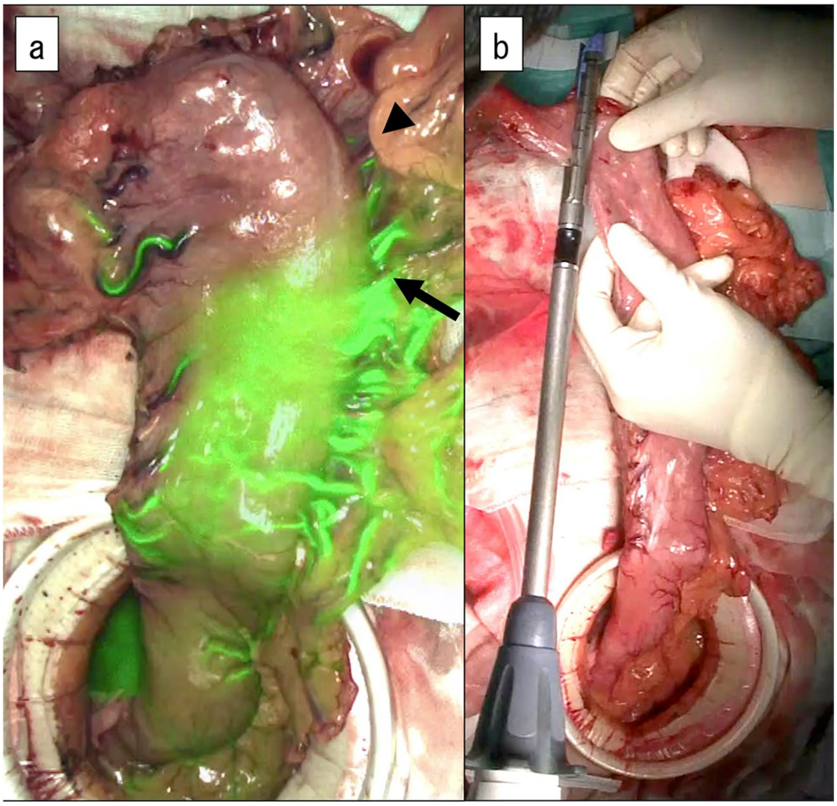

Fig. 1 Gastric tube creation and ICG blood flow visualization. **a** ICG evaluation before creation of the gastric tube. The ICG visualization time, from the injection of 5 mg ICG and flushing with 20 mL saline to the blood flow reaching the tip of the gastric tube, was measured. The presence or absence of blood flow continuity in the right (arrow) and left (arrowhead) gastroepiploic arteries was checked. **b** A gastric tube was created using a linear stapler. ICG, indocyanine green

flowed directly from the RGEA to the LGEA or through a nearby vessel, it was defined as “Yes.” When blood flow entered the GT wall from the RGEA and then ascended into the stomach wall toward the tip of the GT without flowing to the LGEA, it was defined as “No.” If it was difficult to determine which of the two was the case, it was considered as “Unclear.” Correlation between these data and the parameters of patient profile as well as postoperative leakage was analyzed.

Retrospective re-analyses from stored ICG-NIFI video data and creation of TIC

The data of second ICG-NIFI were used for investigations. Intensity of brightness was examined in the four regions of interest (ROIs) of 0.5 cm by 0.5 cm, which was set based on the mark drawn on the GT: two on the proximal side and two on the distal side, that is ROI 1, 2, 3, and 4 from the distal side (Fig. 2). The ROIs were set to be equally spaced, starting from the apical side of the GT, based on the markings. The distance between each ROI was 1 cm. From the video data (mpeg4 format, 1920 × 1080 pixels, 30.0 frame per second), still images of 0.5-s interval were extracted and converted to gray-scale images (brightness level, 0–255), then saved in each specific folder. These data were processed in two ways. First, the visualization time in each ROI was assessed by an independent rater (KO) at offline using these frame images. Second, the average brightness in each ROI was measured in each frame image. In this analysis, a specific program was created using the OpenCV library in Python 3.9.12, the imported images were processed, and intensity data (0–255) were exported to Excel (Microsoft Corp., Redmond, WA, USA). Then TIC graphs were created to measure three parameters: (1) intensity starting point; time from ICG administration until the luminance curve began to rise; and (2) time constant, the time from the starting point until 63.2% of the intensity peak value, known as indicator of the time to reach the peak plateau (Fig. 3).

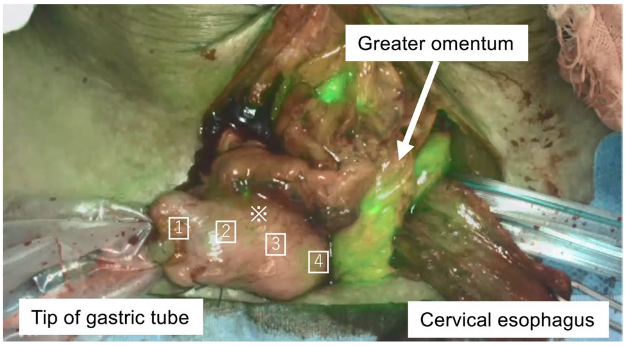

Fig. 2 Four ROIs, two on the proximal and two on the distal side of the anastomosis site (※) were defined. The ROIs were 0.5 cm in size and were designated ROI 1, 2, 3, and 4 from the distal side. ROI, region of interest

Statistical analysis

Statistical analyses were performed using the JMP® software version 13.0.0 (SAS Institute, Cary, NC, USA). Groups were compared using the Mann–Whitney *U* test for groups with no correspondence and the Wilcoxon signed-rank test for groups with correspondence; categorical data were compared using the χ^2 test (Yates correction). Statistical significance was set at $P < 0.05$.

Results

Table 1 presents the characteristics of all 97 patients, of whom 94 had esophageal cancer, 2 were trachea-esophageal fistula due to other cancer and 1 had an aorto-esophageal fistula. Esophagectomy was performed in 92 patients and esophageal bypass in 5. The ICG visualization times were 18 s before GT creation and 33 s after GT elevation to the neck, with a median difference of 15 s (delay). The continuity of blood flow between the right and left GEA could not be confirmed in 28 patients (28.9%). Anastomotic leakage occurred in 12 patients (12.4%). Comparing an occurrence of anastomotic leakage, more patients in the anastomotic leakage group lacked blood flow continuity between the right and left GEA (22.4% vs. 75.0%; $P < 0.001$) than those

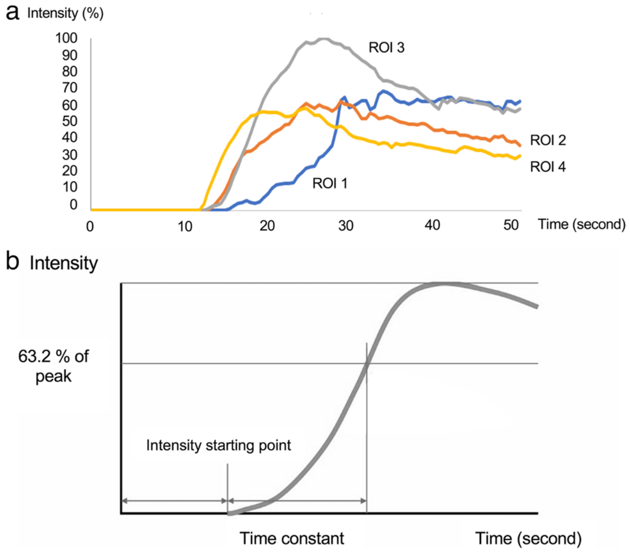

Fig. 3 **a** Time-intensity curves on 4 ROIs in the elevated gastric tube created from the indocyanine green video. Intensity starting point, time from ICG administration until the luminance curve began to rise. **b** Time constant, the time from the starting point until 63.2% of the intensity peak value, known as indicator of the time to reach the peak plateau

Table 1 Patient characteristics of 97 cases analyzed for perfusion in the gastric tube and with/without anastomotic leakage following surgery

Characteristic	All (*n* = 97)	Without leakage (*n* = 85)	Leakage (*n* = 12)	*P* value
Age, years	70 (46–91)	71 (46–91)	69 (57–77)	0.591
Sex, male, *n* (%)	81 (83.5)	69 (81.2)	12 (100)	0.100
Body weight, kg	54.9 (33.7–82.6)	54.7 (33.7–82.6)	62.5 (38.0–81.4)	0.090
Body mass index, kg/m^2	22.0 (14.0–33.1)	21.3 (14.1–33.1)	22.9 (14.0–30.4)	0.418
Preoperative albumin level (g/dL)	3.9 (2.6–4.9)	3.9 (2.6–4.9)	4.0 (3.3–4.6)	0.995
Disease, *n* (%)				0.025
Esophageal cancer	94 (96.9)	83 (97.7)	11 (91.7)	
Trachea-esophageal fistula	2 (2.1)	2 (2.4)	0	
Aorta-esophageal fistula	1 (1.0)	0	1 (8.3)	
Tumor location, *n* (%)				0.059
Ce/Ut	23 (23.7)	20 (22.5)	3 (25.0)	
Mt/Lt/Jz	71 (73.2)	63 (74.1)	8 (66.7)	
Clinical stage, *n* (%)				0.187
I	36 (37.1)	31 (36.5)	5 (41.7)	
II	9 (9.3)	9 (10.6)	0	
III	23 (23.7)	20 (23.5)	3 (25.0)	
IV	26 (26.8)	23 (27.1)	3 (25.0)	
Comorbidities				
Diabetes mellites, *n* (%)	15 (15.5)	14 (16.5)	1 (8.3)	0.685
Cardiovascular disease, *n* (%)	24 (24.7)	20 (23.5)	4 (33.3)	0.484
History of radiation therapy, *n* (%)	11 (11.3)	10 (11.8)	1 (8.3)	1
Sternum-vertebral distance, mm (range)	47 (23–66)	47 (23–66)	45 (30–52)	0.102
Surgery				1
Esophagectomy, *n* (%)	92 (94.8)	80 (94.1)	12 (100)	
Esophageal bypass, *n* (%)	5 (5.2)	5 (5.9)	0	
Reconstruction route				0.684
Retro-sternum, *n* (%)	16 (16.5)	15 (17.7)	1 (8.3)	
Posterior-mediastinum, *n* (%)	81 (83.5)	70 (82.4)	11 (91.7)	
Operation time, min	595 (239–772)	595 (239–772)	589 (320–693)	0.848
Blood loss, mL	130 (10–380)	130 (10–380)	135 (40–320)	0.860
ICG visualization time assessed by the surgeon's eyes				
① Before GT creation, seconds	18 (6–39)	18 (6–37)	15 (9–39)	0.763
② After GT pull-up, seconds	33 (14–104)	32 (14–78)	40 (21–104)	0.066
Delay ②–①, seconds	15 (0–91)	15 (0–50)	26 (2–91)	0.069
Blood flow continuity between the right and left GEA				<0.001
Yes, *n* (%)	68 (70.1)	65 (76.5)	3 (25.0)	
No, *n* (%)	28 (28.9)	19 (22.4)	9 (75.0)	
Unclear, *n* (%)	1 (1.0)	1 (1.1)	0	
Time-intensity curve analysis				
Intensity starting point				
ROI 1, seconds	22.5 (5.0–66.5)	22.0 (5.0–45.5)	27.0 (13.0–66.5)	0.126
ROI 2, seconds	21.0 (7.5–56.0)	21.0 (8.0–56.0)	20.3 (7.5–50.0)	0.971
ROI 3, seconds	19.0 (3.5–40.5)	19.0 (3.5–36.5)	22.5 (15.5–40.5)	0.087
ROI 4, seconds	17.5 (8.5–37.5)	17.5 (8.5–37.5)	21.8 (15.5–32.0)	0.123
Time constant				
ROI 1, seconds	17.0 (3.0–50.0)	18.0 (3.0–50.0)	17.0 (17.0–17.0)	1
ROI 2, seconds	14.0 (3.0–46.5)	14.0 (3.0–46.5)	10.0 (4.5–15.5)	0.431
ROI 3, seconds	14.0 (3.0–41.5)	13.5 (3.5–41.5)	14.5 (3.0–18.0)	0.504
ROI 4, seconds	13.5 (3.5–47.0)	14.0 (3.5–47.0)	6.0 (6.0–6.0)	0.205

Data are presented as median (range). *ICG* indocyanine green, *GT* gastric tube, *GEA* gastroepiploic artery, *ROI* region of interest

Table 2 Association with blood flow continuity between the right and left GEA and ICG fluorescence time of the gastric tube

Characteristic	Blood flow continuity between the right and left GEA		*P* value
	Yes (*n* = 68)	No (*n* = 28)	
Reconstruction route			0.227
Post-sternum, *n* (%)	9 (13.2)	7 (25.0)	
Post-mediastinum, *n* (%)	59 (86.8)	21 (75.0)	
ICG visualization time assessed by the surgeon's eyes			
① Before GT creation, seconds	16 (6–37)	20 (10–39)	0.013
② After GT pull-up, seconds	31 (14–104)	40 (18–94)	0.017
Delay ②–①, seconds	15 (0–91)	21 (0–55)	0.017
Anastomotic leakage, *n* (%)	3 (4.4)	9 (32.1)	< 0.001
Time-intensity curve analysis			
Intensity starting point			
ROI 1, seconds	22.0 (5.0–45.5)	24.0 (13.0–66.5)	0.338
ROI 2, seconds	21.0 (8.0–56.0)	22.0 (7.5–50.0)	0.755
ROI 3, seconds	18.5 (4.0–36.5)	19.5 (3.5–40.5)	0.601
ROI 4, seconds	18.0 (8.5–37.5)	17.5 (8.5–32.0)	0.955
Time constant			
ROI 1, seconds	13.0 (3.0–50.0)	19.5 (17.0–44.0)	0.136
ROI 2, seconds	12.0 (3.0–46.5)	18.5 (4.5–27.5)	0.517
ROI 3, seconds	13.0 (3.5–41.5)	16.0 (3.0–24.5)	0.874
ROI 4, seconds	13.0 (3.5–47.0)	18.0 (6.0–28.5)	0.584

Data are presented as median (range). *ICG* indocyanine green, *GT* gastric tube, *GEA* gastroepiploic artery, *ROI* region of interest

in the non-leakage group. The patient with aorta-esophageal fistula developed leakage, while patients with tracheoesophageal fistula did not. The ICG visualization time on elevated GT to neck assessed by the surgeon's eyes was tended to be slower in the leakage group than those in the non-leakage group (32 s vs. 40 s; $P = 0.066$).

TIC could create in 65 cases (67.0%). The reason of TIC creation failure in 32 cases was as follows: moving the GT ($n = 19$) or change the intensity setting during recording ($n = 2$), low intensity of the elevated GT ($n = 9$), and video record error ($n = 2$). In some cases, the fluorescence intensity of the initial injection of ICG was still present, but the intensity was set to zero and the rise from that point was measured. In the TIC analysis, intensity starting point at all ROIs (ROI 1, 2, 3, and 4 were 22.5 s, 21.0 s, 19.0 s, 17.5 s, respectively) was faster than the surgeon's assessment (33 s). The time constant could be measured for only 40 cases because the intensity did not reach the peak and plateau, or we moved the GT or camera before reaching it during ICG-NIFI recording. In the TIC analysis, patients in the leakage group tended to have slower intensity starting point at ROI 1, ROI 3, and ROI 4, and faster time constant at ROI 2 and ROI 4 compared to those in non-leakage group. Logistic analysis showed that lack of blood flow continuity between the right and left GEA (odds ratio 7.835; 95% confidence interval, 1.187–51.740; $P = 0.033$) was an independent risk factor of anastomotic leakage.

Comparing with and without blood flow continuity between the right and left GEA for 96 patients excluded "unclear" case, patients in the without group had significantly slower ICG visualization time assessed by the surgeon's eyes and anastomotic leakage than those in the with group; however, there was no difference in the intensity starting point and time constant of the TIC analysis (Table 2).

Discussion

This study demonstrated that lack of blood flow continuity between the right and left GEA was correlated with anastomotic leakage, and a TIC analysis of ICG-NIFI by an independent evaluator was able to quantify the fluorescence intensity changes that the surgeon had visually determined.

Previous studies have reported that the use of ICG-NIFI reduced anastomotic leakage after esophageal surgery, but most of these observations were made in the abdomen prior to the elevation of the GT to the neck. Koyanagi et al. [14] reported a relationship between arterial calcification and delayed blood flow velocity, with a higher risk of anastomotic leakage in these cases. However, in our study, there was no significant difference between ICG visualization time before GT creation and the occurrence of anastomotic leakage, although there was a significant difference after GT elevation. This is because when the GT is elevated to the neck, its intra-wall vascular network is surrounded by the sternum, clavicle, and vertebral body at the thoracic inlet and compressed, delaying blood flow to the GT tip. When there is blood flow continuity between the right and left GEA, the blood flow from the right GEA is delivered directly to the tip of the stomach tube through the left GEA; when there is insufficient blood flow continuity between the right and left GEA, the blood flow from the right GEA must reach the tip of the stomach tube through the intra-wall vascular network [15], and compression can cause ischemia in the tip of the GT, increasing the risk of anastomotic leakage. Therefore, when blood flow continuity between the right and left GEA is deficient, it is necessary to carefully determine, via ICG-NIFI, whether blood flow reaches the GT tip. The earlier the ICG fluorescence appears, the better the blood flow and the lower the risk of anastomotic leakage [16, 17]; however, it is difficult to evaluate fluorescence objectively and quantitatively because it depends on the surgeon's vision and the surrounding environment.

Ishige et al. [18] used the ROIs software (Hamamatsu Photonics K.K., Hamamatsu, Japan) to plot TIC in 20 cases. They measured one arbitrary ROI and classified into two types: normal pattern, in which the fluorescence intensity rapidly decreased to a plateau following a sharp, high peak, and gradual pattern, in which the intensity gradually increased. They could not show the clinical significance of this classification because no anastomotic leakage occurred. In contrast, our method established four ROIs in the GT elevated to the neck, with fluorescence expected to appear sequentially from the center to the periphery. The results were in accordance with this, as ROIs 3 and 4 had the fastest intensity starting points and ROI 1 had the slowest. This is because the fluorescence changes occurred from the proximal side of the GT, where blood flow reaches most quickly, toward the tip. These results might use to establish appropriate anastomotic and apical dissection sites for side-to-end anastomosis procedures. When the intensity at the ROI 1 or 2 was low, conversion to the end-to end anastomosis at the ROI 3 or 4 might contribute to avoid leakage at the tip of the GT.

In this study, the intensity starting point determined by TIC analysis was faster than the surgeon's assessment, with a difference of more than 10 s. When the elevated GT was compressed at the thoracic inlet, it may be difficult to visualize the blood flow fluorescence of the vascular network in the GT wall, which might delay the determination of blood flow arrival. In addition, reflections from operating room monitors and goggles worn by surgeons to protect against infection might make it difficult to see fluorescence, and individual differences in light perception might influence the fluorescent arrival determination by the opinion of an experienced surgeon. In contrast, mechanical determination by TIC may be objective, reproducible, and useful in bridging the experience gap between surgeons. Time constant tended to be shorter in the leakage group. This was not because the fluorescence intensity quickly rose to its peak, but rather because the increase in fluorescence intensity was insufficient. Thus, it was thought that perfusion of the intramural vascular network of the elevated GT was weak and fluorescence intensity did not increase.

The limitations of this study were that it was a retrospective, observational study with a small number of cases, and only 40 cases could be converted to TIC. The advantage of ICG-NIFI is that blood flow can be evaluated intraoperatively in real time, including observation of the posterior wall of the GT, however, to perform TIC analysis retrospectively, it is necessary to wait until the peak and plateau of the fluorescence change are reached without moving the GT or camera, with only anterior wall observation.

Another drawback of retrospective TIC analysis was that the fluorescence intensity of TIC is a relative value, so it was not possible to compare absolute values between cases with different imaging conditions.

To solve these problems, the brightness of the operating room, the distance between the camera and the GT, the angle of view, the ROI settings should be kept as identical as possible. The presence or absence of blood flow continuity between the right and left GEA should be also considered to the length of ICG-NIFI recording time. And the major limitation of this study was that the intensity starting point and time constant obtained in the TIC analysis did not show a significant correlation with the incidence of anastomotic leakage. We thought that leakage might occur at the GT apical transection (ROI 1 or ROI 2) in end-to-side anastomosis, even though the intensity starting point at ROI 3, which corresponds to the anastomotic site, tended to be slower in cases of leakage. Although it is difficult to differentiate leakage at the anastomosis and at the apical transection of GT, we need to consider it when setting the ROI location.

In conclusion, the programming TIC analysis of ICG-NIFI measured by an independent inspector might be useful as an objective and supplemental method to surgeon's visual assessment. Based on this study, further research will be conducted to establish a TIC assessment of the ICG-NIFI on the GT for esophageal surgery and expected to be used for artificial intelligence technology.

Acknowledgements We would like to express my sincere gratitude to Dr. Hiroyuki Nishimoto for his exceptional guidance and support in conducting this study.

Author's contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by NY, HK, KY, TN, KO, and SS. NY wrote the main manuscript and all authors reviewed the manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval This study was conducted in accordance with the Declaration of Helsinki, Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects, and other relevant guidelines and considered the human rights and safety of the research participants, and written informed consent was obtained. The study protocol was approved by the Ethics Committee of Kochi Medical School (ERB-107532).

Competing interests The authors declare no competing interests.

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