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Factors Affecting Blood Flow at the Tip of the Reconstructed Gastric Tube During Esophagectomy: A Study Using Indocyanine Green Fluorescence Angiography

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The objective of this study was to clarify the factors affecting blood flow at the tip of the gastric tube during esophagectomy using indocyanine green (ICG) fluorescence angiography. The time until enhancement of the gastric tube tip determined using ICG fluorescence imaging is a useful indicator of blood flow, and has been shown not to differ significantly according to the connection status of the right or left gastroepiploic artery. Using ICG fluorescence imaging, the time until enhancement of the gastric tube tip was measured in 50 patients undergoing esophagectomy. Blood flow at the gastric tube tip was compared between 2 groups of patients: those in whom a connecting vessel from the left gastro-epiploic artery to the short gastric artery (l-s GA) was present and those in whom it was absent. The factors affecting blood flow to the gastric tube tip were also investigated using univariate and multivariate logistic regression analysis. The median time taken for the gastric tube tip to show enhancement with ICG was significantly shorter in the group with an l-s GA connection ($P = 0.02$). Multivariate analysis showed that the absence of an l-s GA connection ($P = 0.04$) and presence of arteriosclerosis-related disease ($P = 0.02$) were significant independent factors that delayed blood flow to the gastric tube. It is essential to preserve the whole vessel arcade of the greater curvature to achieve good perfusion of the gastric tube with blood. The

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presence of arteriosclerosis-related disease is a major factor affecting the safety of anastomosis during gastric tube reconstruction.

Key words: Esophageal cancer – Gastric tube reconstruction – Indocyanine green fluorescence – Blood flow – Angiography

Reconstruction after esophagostomy is one of the most important procedures during surgery for esophageal cancer. Anastomotic leakage is still considered the major complication and can sometimes become life threatening.[1–6] After esophagectomy, a gastric tube is most frequently used for reconstruction.[7] The most important factor for prevention of anastomotic leakage is to construct a gastric tube that is well perfused by blood. Several reported studies have assessed blood flow in the reconstructed gastric tube using laser Doppler flowmetry[8–11] or indocyanine green (ICG) fluorescence angiography.[12–16]

We previously investigated in detail the hemodynamics of the reconstructed gastric tube using ICG fluorescence angiography[12] and concluded that the time between initial ICG enhancement of the root of the right gastroepiploic artery and enhancement at the tip of the gastric tube was a useful parameter for assessment of blood flow to the gastric tube. In addition, we proposed that the gastric tube was divisible into 3 zones according to the dominant arteries present in the greater curvature: zone 1, the area dominated by the right gastro-epiploic vessels; zone 2, the area dominated by the left gastro-epiploic vessels (in all cases, the left gastro-epiploic artery being enhanced in a direction opposite to that of physiologic blood flow); and zone 3, the area initially perfused by short gastric vessels (we usually perform esophago-gastrostomy in this zone; Fig. 1). However, the factors affecting blood flow at the gastric tube tip (zone 3) are still unclear.

Here, based on analysis of pretreatment laboratory data, patient history, and surgical findings, we investigated factors that might affect blood flow to the gastric tube tip using ICG fluorescence angiography.

Materials and Methods

Patients

Sixty consecutive patients who underwent esophagectomy with gastric tube reconstruction for esophageal cancer at a single institution were prospectively enrolled. We excluded 10 patients because of insufficiency of laboratory data or incomplete assessment of blood flow from the recorded videos. There were 43 men and 7 women, with a median age of 69 years (range, 46–83 years). Four patients had cervical esophageal cancer, 43 had thoracic esophageal cancer, and 3 had abdominal esophageal cancer. We pulled up the reconstructed gastric tube via the retrosternal route in 41 cases, the mediastinal route in 7 cases, and the ante-thoracic route in 2 cases, considering the patients' individual conditions.

Procedures for gastric tube reconstruction

The procedures we used for gastric tube reconstruction were described in our previous paper.[12] In brief, the omentum was divided 2 cm distant from the right gastro-epiploic artery, and this vessel was preserved. In addition, we ligated and cut the root of the left gastro-epiploic artery, preserving the whole length of the vessel arcade of the greater curvature. At the lesser curvature, we preserved 2 or 3 branches of the right gastric artery. Finally, we constructed the gastric tube using a linear stapler (TLC75, Ethicon Endo Surgery, Inc, Hamilton County, Ohio).

After pulling up the tip of the gastric tube to the neck wound, we performed esophago-gastrostomy by hand-sewn anastomosis (layer-to-layer method). The cut end of the esophagus was end-to-side anastomosed to the posterior wall of the gastric tube. All esophago-gastrostomies were made at zone 3.

Equipment

Blood flow in the gastric tube was evaluated using ICG fluorescence imaging with a near-framed camera system (Photodynamic Eye, Hamamatsu Photonics K.K, Hamamatsu, Japan), and the video was recorded. In brief, images were obtained with a charge-coupled device (CCD) camera, using a light-emitting diode with a wavelength of 760 nm as the light source and a filter to eliminate light at a wavelength below 820 nm before detection. The fluorescence signals were sent to a digital video processor to be displayed on a television monitor in real time.

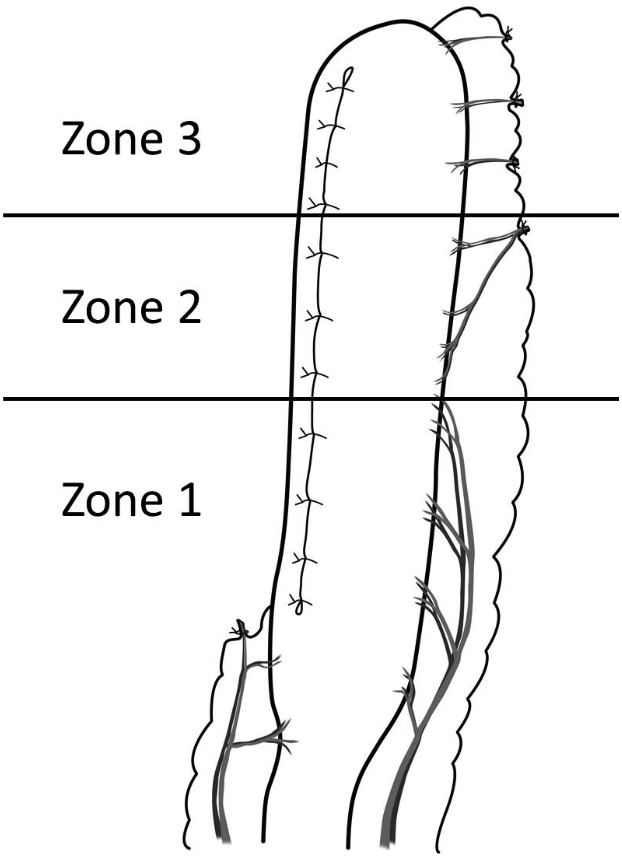

Fig. 1 Schema showing the gastric tube divided according to hemodynamic features (this figure is partially reprinted from ref. 12). Zone 1, area predominantly supplied by the right gastro-epiploic artery; zone 2, area predominantly supplied by the left gastro-epiploic artery; zone 3, area initially perfused by short gastric vessels.

ICG fluorescence angiography

Before pulling up the tip of the gastric tube to the neck, 2.5 mg of ICG dye (Diagnogreen, Dai-Ichi Pharm, Tokyo, Japan) was injected as a bolus from a peripheral vein. A few minutes after injection of the dye, blood flow was confirmed by ICG fluorescence imaging as passing through the right gastro-epiploic vessels. Simultaneously, the gastric tube was also enhanced with ICG. With regard to the blood flow at the tip of the gastric tube, we measured the time from initial ICG enhancement of the root of the right gastro-epiploic artery until enhancement of the gastric tube tip. All calculations were performed by 2 independent surgeons (YK and TI). The perfusion time was measured twice in each video, and the average of the values determined by the 2 surgeons was calculated.

We visually evaluated the relationship between the right and left gastro-epiploic vessels (r-l GV) and determined whether a connecting vessel between them was present or absent, with 34 and 16 cases being placed in these categories, respectively (Fig. 2).

From the recorded video obtained by ICG fluorescence angiography, we also assessed whether a connecting artery was present or absent between the left gastro-epiploic artery and the short gastric arteries (l-s GA), with 19 and 31 cases being placed in these categories, respectively (Fig. 3).

Statistical analysis

Continuous variables were expressed as median and range and compared using the Mann-Whitney U test. For logistic regression analysis, factors with $P <$ 0.1 determined by univariate analysis were subjected to multivariate analysis to yield the odds ratio (OR) and 95% confidence interval (95% CI). Intra- and interobserver variations were calculated using paired t test. Differences were considered to be significant at $P < 0.05$.

Written informed consent was obtained from all patients, and the study was performed under a protocol approved by our hospital ethics committee.

Results

With regard to the time taken for the gastric tube tip to become enhanced with ICG, intra- and interobserver variations were not significant and were considered to have little impact on the analysis ($P =$ 0.92 and $P = 0.77$, respectively).

Time taken for blood to flow to the gastric tube tip according to each type of vessel connection

When we divided patients according to whether a r-l GV connection was present or absent, the calculated median time from initial ICG enhancement of the right gastro-epiploic artery root until enhancement of the gastric tube tip was 30.8 seconds (range, 14.5–164 seconds) in the present group and 34.5 seconds (range, 23.0–59.5 seconds) in the absent group. The difference between the 2 groups was not significant ($P = 0.88$; Fig. 4).

When we divided patients according to whether a l-s GA connection was present or absent, the calculated median time from initial ICG enhancement of the right gastro-epiploic

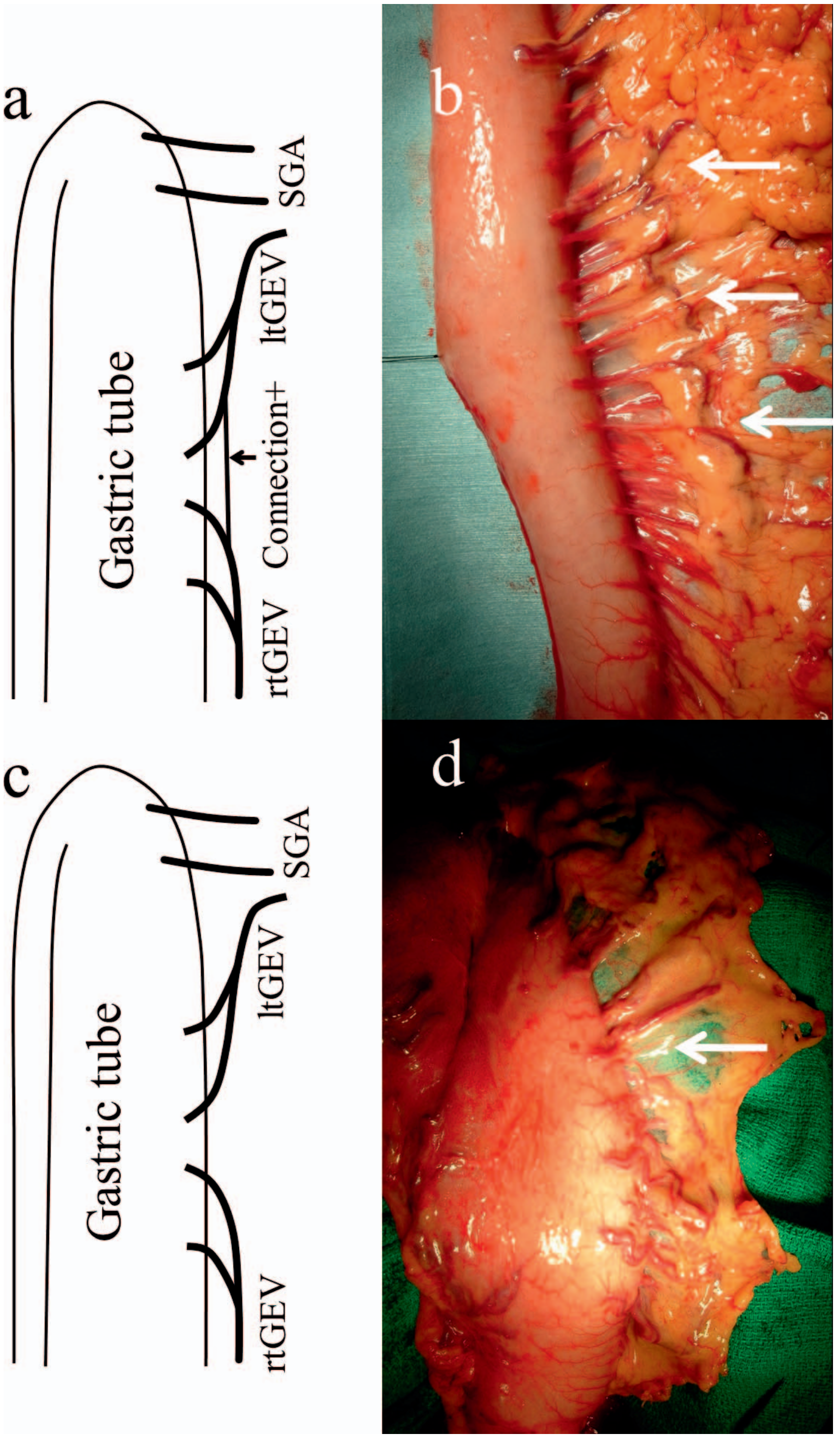

Fig. 2 Relationship between the right and left gastro-epiploic vessels. (a) Present case: schema showing a connecting vessel between the right and left gastro-epiploic vessels. (b) Macroscopic appearance of a present case, indicating a continuous connection between the right and left gastro-epiploic vessels, with no clear border between them (arrows). (c) Absent case: schema showing absence of a connecting vessel between the right and left gastro-epiploic vessels. (d) At the point of the arrow, no connection between the right and left gastroepiploic vessels is evident. rtGEA, right gastro-epiploic artery; ltGEA, left gastro-epiploic artery; SGA, short gastric artery.

artery root until enhancement of the gastric tube tip was 28.0 seconds (range, 18.0–59.0 seconds) in the present group and 49.5 seconds (range, 14.5–164 seconds) in the absent group. The difference between the 2 groups was significant ($P = 0.02$; Fig. 5).

Factors affecting blood flow to the gastric tube tip (Table 1)

As covariables, we evaluated age (<70 years: n = 26, ≥70 years: n = 24), sex (male: n = 43, female: n = 7), diabetes mellitus (present: n = 9, absent: n = 41), hypertension (present: n = 20, absent: n = 30), arteriosclerosis-related disease (cerebral infarction:

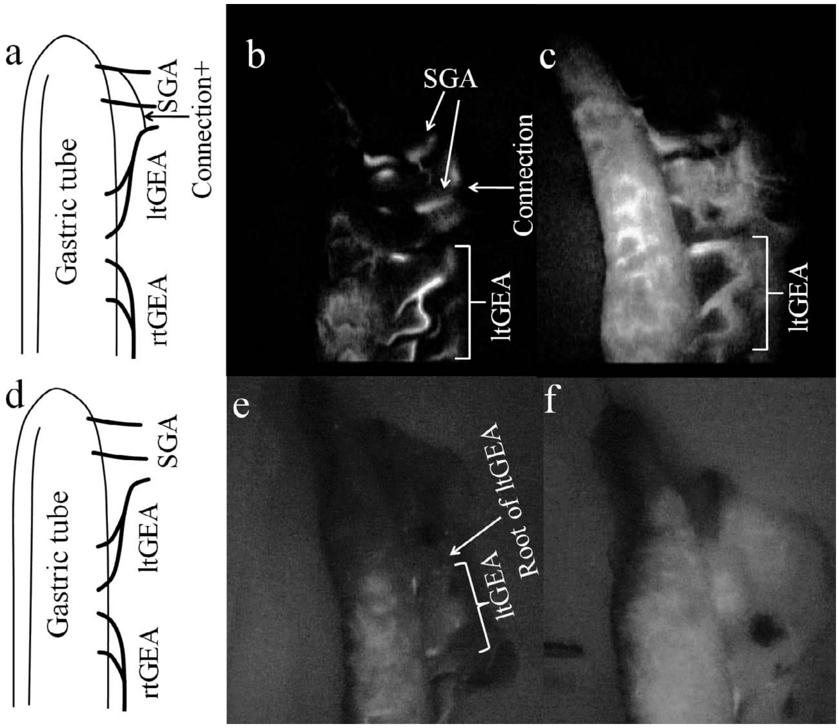

Fig. 3 Relationship between the left gastro-epiploic artery and short gastric artery. (a) Schema of a case in which a connecting vessel is present between the left gastro-epiploic artery and the short gastric artery. (b and c) A case with apparent connection between the left gastro-epiploic artery and short gastric artery. (b) Ten seconds after initial enhancement of the root of the right gastro-epiploic artery. Arterial blood flow from the left gastro-epiploic artery through the connecting artery enhanced the short gastric arteries. (c) Seventy seconds after initial enhancement of the root of the right gastro-epiploic artery. The gastric tube was completely enhanced. Blood flow through the short gastric artery preceded that inside the gastric wall. (d) Schema of a case in which any connection between the left gastro-epiploic artery and short gastric artery is absent. (e and f) A case in which the connection between the left gastro-epiploic artery and short gastric artery was absent. (e) Fourteen seconds after initial enhancement of the root of the right gastro-epiploic artery. At the greater curvature, the left gastro-epiploic artery was enhanced without enhancement of the short gastric arteries. (f) Ninety seconds after initial enhancement of the root of the right gastro-epiploic artery. The gastric tube was gradually enhanced by blood flow through the microcapillaries inside the gastric wall. The tip of the gastric tube was not enhanced because of the poor blood supply. rtGEA, right gastro-epiploic artery; ltGEA, left gastro-epiploic artery; SGA, short gastric artery.

n = 3, cardiac pectoris: n = 2, arteriosclerosis obliterans: n = 1; present: n = 6, absent: n = 44), ICG excretion rate at 15 minutes (<10%: n = 26, ≥10%: n = 24), serum albumin (<3.7 g/dL: n = 15, ≥3.7 g/dL: n = 35), estimated glomerular filtration rate (<70 mL/min: n = 24, ≥70 mL/min: n = 26), forced expiratory volume in 1 second (FEV 1.0%; <70%: n = 20, ≥70%: n = 30), neo-adjuvant chemotherapy (present: n = 4, absent: n = 46), irradiation of the proximal stomach (present: n = 3, absent: n = 47), r-l GV connection (present: n = 34, absent: n = 16), and l-s GA connection (present: n = 19, absent: n = 31). Using logistic regression analysis, we examined whether these factors affected the time taken for ICG enhancement to spread from the root of the gastroepiploic artery to the tip of the gastric tube (<50 seconds: n = 31, ≥50 seconds: n = 16).

Univariate analysis showed that lack of a l-s GA connection (P = 0.03, OR = 0.09) and presence of arteriosclerosis-related disease (P < 0.01, OR = 22.5) were significant independent factors that prolonged the time required for blood to perfuse the gastric tube. Multivariate analysis also identified lack of a l-s GA connection (P = 0.04, OR = 0.08) and presence of arteriosclerosis-related disease (P = 0.02, OR = 25.4) as significant factors that prolonged the time required for blood to perfuse the gastric tube.

Clinical outcome

We attempted to create an esophago-gastric anastomosis in an area showing good perfusion as

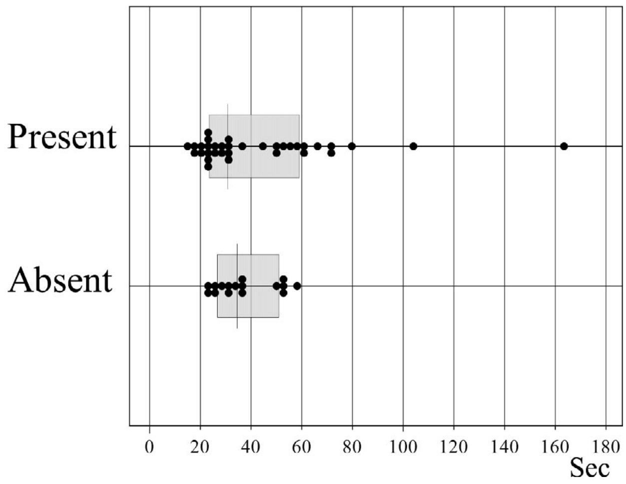

Fig. 4 The median time until perfusion of the tip of the gastric tube according to whether there was a connection between right gastro-epiploic vessel and left gastro-epiploic vessel. This was 30.8 seconds in the present group and 34.5 seconds in the absent group, the difference being nonsignificant ($P = 0.88$).

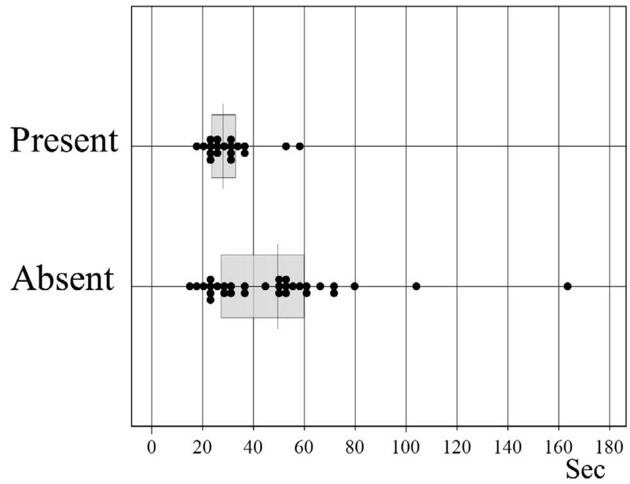

Fig. 5 The median time until perfusion of the tip of the gastric tube according to whether there was a connection between the left gastro-epiploic artery and short gastric artery. This was 28.0 seconds in the present group and 49.5 seconds in the absent group, the difference being significant ($P = 0.02$).

demonstrated by ICG enhancement (within 60 seconds) and resected any redundant area.

During the observation period, we experienced 1 case of gastric tube necrosis in an area that was enhanced within 103.50 seconds, which was clearly an excessive time interval. No l-s GA connection was evident in this patient, although an r-l GV connection was present. Minor leakage occurred in 2 patients. In 1 of these patients, enhancement occurred within 14.5 seconds, even though there was strong tension at the esophago-gastro anastomosis after resection of cervical esophageal cancer. An l-s GA connection was absent in this patient, whereas the r-l GV connection was present. In the other patient, 36.0 seconds was needed for enhancement, and examination showed that the l-s GA connection was present, whereas r-l GV connection was absent; this patient developed respiratory failure on the third postoperative day and required masked positive pressure ventilation.

Discussion

ICG fluorescence imaging has been applied for lymphography and sentinel node detection.[17–24] Recently, this technique has also been adopted for intraoperative assessment of the blood supply to various organs,[19–28] including the reconstructed gastric tube during esophagectomy.[12–16] The time required for enhancement and the intensity of ICG fluorescence have been reported as possible parameters for assessment of blood flow.[25–28] If the intensity of ICG fluorescence is used as a parameter for blood flow evaluation, the volume of injected ICG should be calculated for each patient according to individual physique. This necessitates some complex calculation by the surgeon during the operation. Furthermore, the intensity of ICG fluorescence shown on the monitor changes according to the distance between the surface of the organ and the CCD camera, due to the characteristics of the Photodynamic Eye. This is also considerably problematic because the CCD camera needs to be set at a fixed distance from the target organ in every case. Therefore, we used the time required for enhancement with ICG as a parameter for assessment of blood flow, because the difference in the time for enhancement due to the distance from the target organ and the dose of ICG would be negligible if the procedure is roughly the same in each examination. Based on their experience of patients with peripheral arterial disease, Igari *et al*[27,28] reported that this time was the most suitable parameter for assessment of blood perfusion using ICG fluorescence angiography. Therefore, we believe that the time taken for ICG enhancement is also the most appropriate parameter for this purpose in the present setting.

One limitation of ICG fluorescence angiography is that it does not allow assessment of venous return or speed of washout from tissues. Once vessels and tissues have become enhanced, obvious enhance-

Table 1 Factors affecting to the blood flow at the tip of gastric tube

Covariables	Univariate analysis OR (95% CI)	Univariate analysis *P* value	Multivariate analysis OR (95% CI)	Multivariate analysis *P* value
Age (>70 years)	0.90 (0.25–3.21)	0.87		
Sex (male, female)	—	0.45		
ICG 15 minutes (>10%)	1.37 (0.39–4.88)	0.62		
Serum albumin (>3.7 g/dL)	1.31 (0.27–4.915)	0.94		
eGFR (>70 mL/min)	2.10 (0.58–7.65)	0.26		
FEV 1.0% (>70%)	0.92 (0.25–3.35)	0.90		
DM	1.55 (0.33–7.36)	0.58		
Hypertension	1.40 (0.39–5.05)	0.60		
Arteriosclerosis-related disease	22.5 (2.30–219.8)	<0.01	25.4 (1.79–359.8)	0.02
Neoadjuvant chemotherapy	3.18 (0.40–25.31)	0.27		
Irradiation to proximal stomach	1.46 (0.12–17.56)	0.77		
Connection of l-s GV	0.09 (0.01–0.75)	0.03	0.08 (0.01–0.91)	0.04
Connection of r-l GA	3.34 (0.65–17.37)	0.15		

DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FEV, forced expiratory volume; ICG, indocyanine green excretion rate.

ment lasts about 15 minutes, until the liver secretes ICG into bile. However, ICG fluorescence allows clearer visualization of the demarcation line between ischemic and no-ischemic areas, because ICG enhances whole blood.

Several articles[1,4,5,15] have reported the risk factors for leakage at the esophago-gastro anastomosis after esophagectomy. Among them, Zehetner *et al*[15] reported that anastomosis in areas showing hypo-perfusion indicated by ICG fluorescence angiography were significantly associated with a high incidence of anastomotic leakage. In our previous study, we reported that the area of the gastric tube that was not perfused by ICG within 90 seconds after initial enhancement of the right gastro-epiploic artery tended to become necrotic. Since then, we have resected any area that is not perfused by ICG within 60 seconds and, as a consequence, have not experienced any anastomotic leakage in the last 48 consecutive patients. In some cases, we were unable to discriminate areas of hypo-perfusion macroscopically. Therefore, ICG fluorescence angiography is superior to conventional macroscopic observation for indicating blood flow. Zehetner *et al*[15] also reported that a history of hypertension was a significant risk factor for anastomotic leakage. Although our data did not suggest that a history of hypertension affected blood flow in the gastric tube, multivariate analysis indicated that a history of arteriosclerosis-related disease was a significant risk factor for delayed perfusion. The presence of arteriosclerosis would doubtless affect the blood supply to peripheral tissues.[26–28] The right gastro-epiploic artery is the main artery supplying blood to the reconstructed gastric tube and is also used as the graft for coronary artery bypass surgery.[29] It has been reported that 12.3% of patients with ischemic heart disease have stenosis of the right gastro-epiploic artery due to arteriosclerosis.[30] Patients with cerebrovascular disease or dyslipidemia are also known to have a high risk of cardiovascular disease.[31,32] Accordingly, it is necessary to pay careful attention to the presence of arteriosclerosis-related disease before surgery.

We previously reported that the median period from initial ICG enhancement of the root of the right gastro-epiploic artery until perfusion of the gastric tube tip did not differ significantly according to the connection between the right and left gastroepiploic vessels.[12] This observation was also confirmed in the present study. For construction of a well-perfused gastric tube, it is essential to cut the root of the left gastro-epiploic vessels and preserve the vessel arcade of the greater curvature, even if a connection between the right and left gastroepiploic vessels is absent.

We found that the presence of a l-s GA connection was a significant factor favoring a good supply of blood to the tip of the gastric tube. This route accounted for 38.0% (19/50) of the cases in our series. Connection between the left gastro-epiploic vessels and short gastric vessels was first introduced by Rino *et al*[16] as the "splenic hiatal route." We succeeded in observing the dynamic arterial blood flow along this route and clarified the importance of the l-s GA connection for better perfusion of the gastric tube. Gastric tubes with a l-s GA arterial connection showed rapid ICG enhancement via the short gastric artery, and in such cases, blood flow from the short gastric artery was faster than that inside the gastric wall. Therefore, it is necessary to cut the gastro-splenic ligament on the splenic side to preserve the l-s GA connection.

In conclusion, for good blood perfusion within the gastric tube, it is necessary to preserve the whole vessel arcade of the greater curvature to ensure a good connection between the right and left gastroepiploic arteries or the left gastroepiploic artery and the short gastric artery. The presence of arteriosclerosis-related disease is also a major factor affecting the safety of anastomosis during gastric tube reconstruction.

Acknowledgments

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