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Indocyanine Green (ICG) fluorescence angiography of gastric conduit after transhiatal thoracic esophagectomy with proximal gastrectomy for esophagogastric junction adenocarcinoma: A case report and initial experience at a tertiary government hospital in the Philippines

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ABSTRACT

INTRODUCTION AND IMPORTANCE: We documented the initial experience in our institution where we used indocyanine green (ICG) fluorescence angiography as adjunct in the evaluation of the vascular supply of a reconstructed gastric conduit for esophageal replacement for esophagogastric junction (EGJ) cancer surgery.

CASE PRESENTATION: A 62-year-old patient consulted with a two-month history of melena and weight loss and unremarkable chest and abdominal physical examinations.

CLINICAL FINDINGS AND INVESTIGATIONS: Upper endoscopy and contrast-enhanced computed tomography scans of the chest and abdomen demonstrated an EGJ tumor with no nodal and distant metastases, which revealed adenocarcinoma on biopsy.

INTERVENTION AND OUTCOME: The patient underwent combined thoracoscopic-assisted and transhiatal thoracic esophagectomy with proximal gastrectomy. Esophageal reconstruction was done via a retrosternal gastric pull-up. The perfusion and viability of the gastric conduit were confirmed as per usual methods of inspection and palpation. ICG fluorescence angiography further demonstrated and confirmed the vascular perfusion of the gastric conduit and the optimal site of anastomosis. The patient had an unremarkable postoperative course with no reported anastomotic leakage and stricture formation at 12 months follow-up.

RELEVANCE AND IMPACT: ICG fluorescence angiography represents a feasible and promising tool in assessing viability of esophageal replacement and choosing the optimal site for anastomosis with the proximal esophagus. It can aid in choosing the most appropriate site of anastomosis to prevent ischemia-related complications such as leakage or stricture. This particular case can serve as an initial learning experience to guide surgeons in our institution in the use of ICG fluorescence angiography for esophageal replacements after esophagectomy.

1. Introduction

Esophageal cancer, including cancer of the esophagogastric junction (EGJ), represents a significant health burden particularly for low and middle-income countries [1]. In 2018, it ranked 7th and 6th in cancer incidence and mortality, respectively, worldwide [2]. However, in the Philippines, esophageal cancer is uncommon, ranking 21st and 17th in incidence and mortality during the same period [3].

Surgical management of esophageal cancer is complex, not only from the standpoint of extirpation of the primary tumor and the regional lymph nodes, but also in regards to esophageal replacement to re-establish intestinal continuity. Following thoracic esophagectomy, common methods of esophageal replacement include gastric pull-up, colonic interposition, and jejunal interposition. With any of these techniques, vascularity of the gastric conduit must be ensured to avoid ischemia-related complications such as conduit necrosis and anastomotic leakages and/or stricture.

In a government hospital like ours, this is the first time we have undertaken an innovative means of evaluation of the vas-

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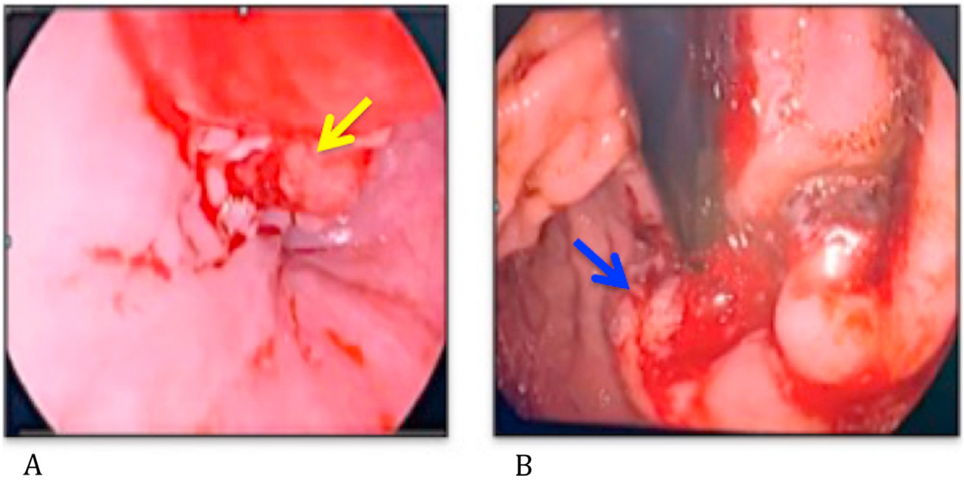

Fig. 1. Endoscopic images of the EGJ tumor. A: Proximal extent of the EGJ tumor in the esophagus *(yellow arrow)*. B: Distal extent of the EGJ tumor in the cardia of the stomach in retroflexion view *(blue arrow)*.

cular supply of a reconstructed gastric conduit. This report shares an interesting experience in our institution, where we utilized ICG fluorescence angiography for the first time and can help us guide future esophageal replacements not just in surgeries for esophageal cancer, but in strictures as well. However, there is a need to further standardize methods of its use and clearly define objective parameters and thresholds to assess perfusion using this technique. This case report has been reported in line with the SCARE 2020 criteria [4].

2. Presentation of case

A 62-year-old patient, of good functional capacity, consulted at the outpatient clinic for a two-month history of melena and weight loss. He was managed previously in another hospital for anemia secondary to melena, for which he was given blood transfusions and was subsequently discharged with improvement.

He had well-controlled diabetes and a 20-pack-year smoking history. He had no history of alcoholism or recreational drug use, no previous surgeries, allergies, and no family history of cancer. He's been married, retired from work, and lives with his family in the province.

Review of systems, chest and abdominal physical examination findings were unremarkable. He had optimal nutritional parameters with a body mass index of 21 kg/m^2 and serum albumin of 42 g/L. Upper gastrointestinal (GI) endoscopy demonstrated a non-circumferential nodular friable tumor at the EGJ, 40–50 cm from the incisors (Fig. 1A) and within 5 cm from the junction distally (Fig. 1B). Our primary impression was a malignancy of the esophagogastric junction based on the clinical presentation and findings on upper GI endoscopy; however, lower GI bleeding could also present with anemia from tumors and diverticulosis of the lower GI tract but were ruled out by the unremarkable colonoscopy and abdominal computed tomography (CT) findings.

Endoscopic biopsy was adenocarcinoma. Contrast-enhanced CT scan of the chest, abdomen, and pelvis showed an EGJ soft tissue density without nodal or distant metastasis (Fig. 2A, B). Pulmonary function test showed a restrictive ventilatory pattern with a low forced expiratory volume in 1 s (FEV1−53.3% predicted), which was deemed intermediate risk of complications for thoracic surgery. Overall, he was assessed to have an intermediate clinical risk for surgery. Preoperatively, the patient took oral nutritional supplementation for the reported weight loss, performed deep breathing exercises via incentive spirometry, and was advised smoking cessation.

The EGJ adenocarcinoma was classified as Siewert type II and staged clinically as stage III – cT3cN0cM0 (American Joint Committee on Cancer, 8th edition, 2017) [1]. A combined thoracoscopic-assisted and transhiatal thoracic esophagectomy with proximal gastrectomy and gastric pull-up under general endotracheal anesthesia was performed. Initial thoracic esophageal mobilization was performed thoracoscopically through the right chest with the patient in modified left lateral decubitus position. The patient was then repositioned supine for the laparotomy. The stomach was mobilized on the greater curvature side with identification and preservation of the right gastroepiploic vessels and division of the gastrocolic ligament at least 3 cm from the gastroepiploic vascular arcade to ensure its preservation. The left gastroepiploic vessels and short gastric vessels were ligated as mobilization proceeded proximally towards the esophageal hiatus. Good communication between the right and left gastroepiploic vessels was confirmed visually. On the lesser curvature side, the right gastric artery was preserved. Division of the gastrohepatic omentum was done close to the liver going proximally towards the esophageal hiatus. Dissection of the nodes along the common hepatic artery, splenic artery, celiac axis, and left gastric artery along with ligation of the left gastric vein and artery were done. The phrenoesophageal ligament was opened and additional mobilization of the distal esophagus was done transhiatally under direct visualization.

Left transverse cervical incision was then performed to access the distal cervical esophagus and further mobilize the proximal thoracic esophagus. The esophagus was transected proximally at the distal cervical esophagus. The thoracic esophagus was then pulled out transhiatally into the abdomen. Distal transection at the stomach coincided with creation of the narrow gastric conduit (Fig. 3A). A 4-cm-wide gastric conduit was created using linear stapler (Johnson&Johnson Ethicon Linear Cutters, 55 mm Selectable Linear Cutter with 3D Staples) starting proximal to the incisura angularis in the lesser curvature, preserving initial branches of the right gastric artery into the stomach. Sequential stapling was performed on the lesser curvature side of the stomach towards the fundus while maintaining an adequate margin of at least 5 cm from the tumor border. The created gastric conduit appeared viable based on assessment of color and visible pulsations of the most cranial vessels along the greater curvature (Fig. 3B). The

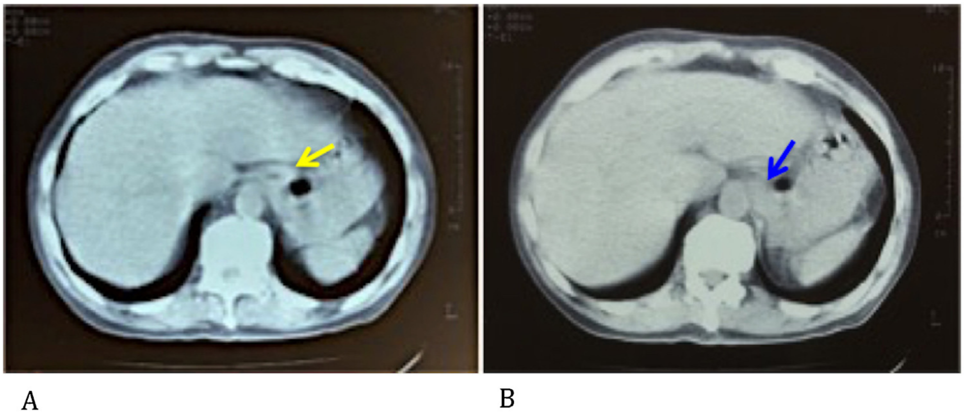

Fig. 2. Contrast-enhanced CT scan images demonstrating A: EGJ wall thickening *(yellow arrow)* and B: EGJ wall thickening extending to proximal gastric portion *(blue arrow)* with no enlarged lymph nodes and no liver metastases.

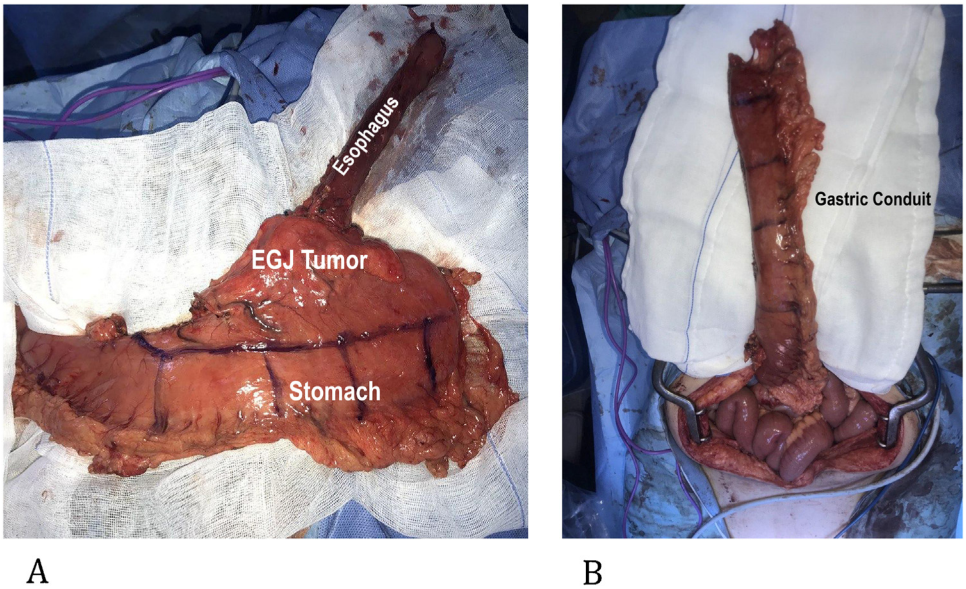

Fig. 3. A. Gross appearance of the esophagus (pulled transhiatally) and stomach showing the EGJ tumor and planned distal resection coinciding with creation of gastric conduit. B. Created gastric conduit before retrosternal pull-up and anastomosis with the cervical esophagus.

most suitable area of the conduit for later anastomosis with the esophagus as judged based on clinical assessment was marked. Pyloroplasty was done to complete the preparation of the gastric conduit.

ICG fluorescence angiography of the gastric conduit was then performed by injecting 2.5 mg of ICG [5–7] (Diagnogreen; Dai-Ichi Pharm Sankyo Co., Ltd.) as a bolus into the peripheral vein. The HyperEye Medical System (HEMS; Mizuho Ikaogyo Co., Ltd., Tokyo, Japan) [5] was used to detect fluorescence using near-infrared camera system. The charge-coupled camera device was held over the gastric conduit after dye injection and fluorescence signals were sent to digital video processor and displayed on a monitor. The right gastroepiploic artery (RGEA) enhanced 52 s after injection after which there was rapid and intense enhancement of the area served by the RGEA (Fig. 4A–C). This was followed by slower, less intense enhancement of the area supposedly served by the left gastroepiploic artery (LGEA) through the gastroepiploic arcade. The most cranial vessel from the gastroepiploic arcade going into the greater curvature enhanced at 68 s. The most proximal part of the conduit devoid of visible blood vessels on the greater curvature side enhanced at 100 s (Fig. 4D). This area enhanced much less intensely and more slowly. Based on the ICG enhancement of the proximal part of the conduit, chosen area for anastomosis was revised and noted to be more caudal to the site chosen pre-fluorescence.

Retrosternal tunnel was created by blunt dissection and the gastric conduit was pulled towards the neck through this route. After pull-up of the gastric conduit retrosternally, conduit perfusion was reassessed by re-injecting 2.5 mg bolus of ICG [5–7] peripherally and positioning the camera over the part of the gastric conduit in the neck. Perfusion of the tip of the conduit and chosen anastomotic site on the stomach was reconfirmed (Fig. 4E, F). There was good bleeding upon incision at the site of anastomosis on the gastric conduit. Cervical esophagogastric anastomosis was performed handsewn, end-to-side in 2 layers. Nasogastric tube was passed through the anastomosis. The entire operation was completed in 480 min with 800 mL intraoperative blood loss. Patient remained hemodynamically stable throughout the operation without any hypotensive episode. There was no adverse reaction to ICG.

The surgery was performed in a tertiary government hospital in the Philippines – the Philippine General Hospital of the University of the Philippines Manila. The operating team was composed of a surgical oncology fellow-trainee, who was the primary sur-

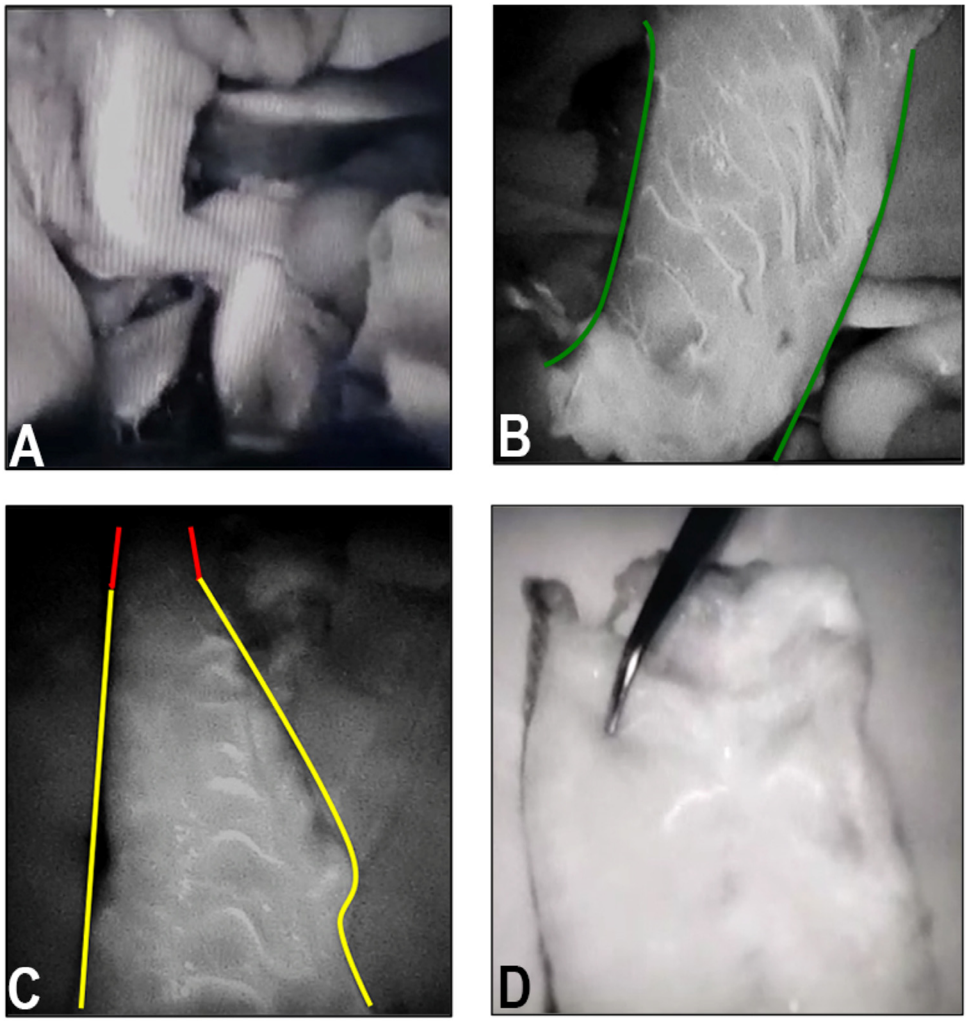

Fig. 4. Images of ICG enhancement of the reconstructed gastric conduit. A: Enhancement of the right gastroepiploic artery, B: Enhancement of the caudal half of the gastric conduit *(green outline)*, C: Area of intermediate intensity enhancement (*yellow outline*) of the area served by the left gastroepiploic artery (LGEA). Least intense enhancement at the tip of the gastric conduit devoid of vascular branches from the gastroepiploic arcade (*red outline*), and D: Site of anastomosis chosen based on ICG enhancement of conduit tip.

geon of this case with 5 years training in general surgery at the same institution, assisted by her two surgical oncology consultants.

The patient had an unremarkable postoperative course. He did not develop fever and the wound remained dry, flat, and non-erythematous. Liquid sips were initiated 5 days after surgery and diet gradually progressed. No cervical anastomotic leakage was noted clinically. He was discharged on full diet with remarkable improvement in his condition, 11 days postoperatively. No surgical site infection in the neck was noted within the 7-day and 30-day outpatient clinic follow-up (Fig. 5).

Histopathology of the resected specimen showed a 5-cm moderately differentiated adenocarcinoma at the EGJ, infiltrating the full thickness of the esophageal wall with two nodes positive for tumor and negative surgical margins (Fig. 6). At 3-monthly interval and at 12 months follow-up, there was no noted clinical evidence of anastomotic stricture as he was able to tolerate solid diet without difficulty. The patient had completed adjuvant chemotherapy without complications or adverse outcomes. Surveillance contrast-enhanced CT scan of the chest and abdomen showed no evidence of disease.

3. Discussion

This case illustrates the initial experience of our institution with the use of ICG fluorescence angiography as an adjunct to clinical gastric conduit viability assessment and choice of optimal anastomotic site.

Optimal perfusion of the esophageal replacement, whether stomach, colon or jejunum, is an important determinant of esophageal surgery outcomes. Ischemia-related complications of the conduit can range from subclinical to ischemia-related anastomotic leakage to frank necrosis [8]. The impact of anastomotic leakages on long-term recurrence and survival of esophageal cancer patients following surgery remains debatable [9,10]. However, anastomotic leakages are associated with postoperative mortality, reoperations, prolonged hospital and critical care unit stay, delayed or non-administration of adjuvant therapy, and stricture formation that may require subsequent endoscopic or surgical treatment [9–13]. There are several patient, disease, and technical factors that contribute to anastomotic leakage but adequacy of perfusion at the anastomotic site, a surgically modifiable factor, is considered one of the most crucial [11–17].

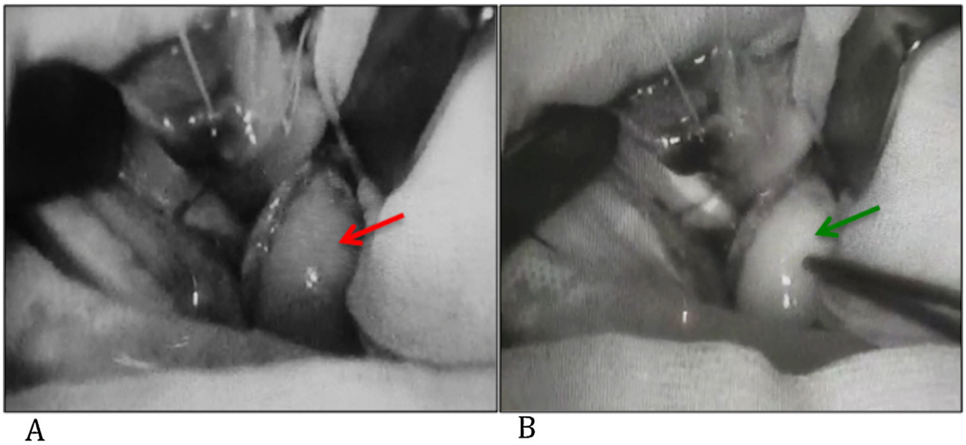

Fig. 5. Images of pulled up gastric conduit in the neck before and after ICG administration. A: Tip of the gastric conduit after pull-up into the neck prior to ICG administration (*red arrow*), and B: Tip of the gastric conduit in the neck showing enhancement after re-injecting 2.5 mg of ICG dye (*green arrow*).

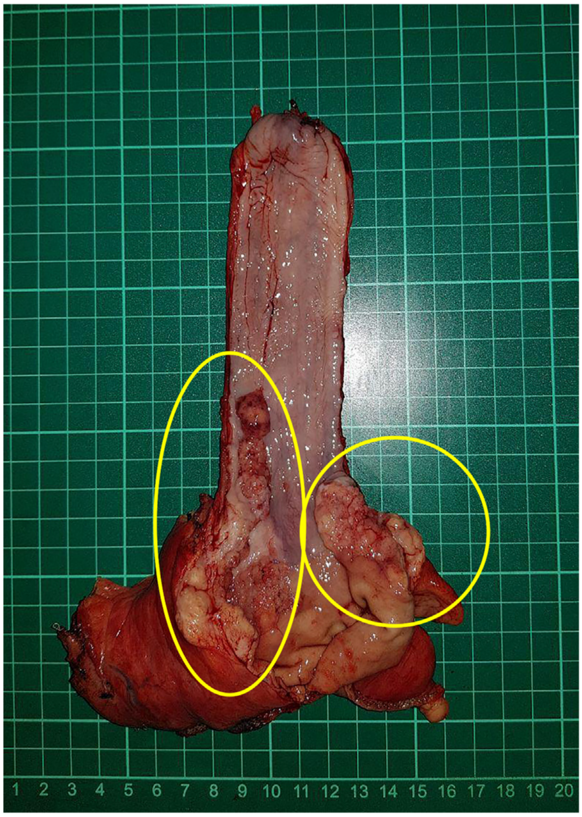

Fig. 6. Cut section of the esophagus and cardia of the stomach containing the EGJ tumor.

The stomach is a frequent choice for esophageal reconstruction due to its robust blood supply. When creating the gastric conduit, the right gastroepiploic artery (RGEA) and, when possible, the right gastric artery (RGA) are preserved along with their corresponding veins [18,19]. However, blood supply of the gastric conduit is mainly through the RGEA [6–8,15,20,21]. The gastric conduit remains viable even with just single arterial supply and drainage due to its extensive intramural arterial and venous vascular network [18]. As demonstrated by the fluorescence imaging in this case, even if preserved, the contribution of the RGA is minimal [20]. According to an anatomic study, 60 % of the gastric conduit is supplied by the RGEA and its branches, represented here by the fast and intense enhancement of the caudal half of the conduit [20,21]. Twenty (20 %) of the conduit towards the cranial end is supplied through the connections of RGEA with the LGEA [20,21]. Hence, it is essential to preserve the gastroepiploic arcade during gastric conduit creation. In up to 30 % of cases, there is no connection between RGEA and LGEA, in which case, supply to the proximal part of the gastric conduit relies on the intramural vascular network [21]. The tip of the gastric conduit corresponds to the area of the fundus previously supplied by the short gastric arteries [20]. With these arteries ligated, the supply to this area is through intramural microscopic network of capillaries and arterioles, hence the slower and less intense enhancement in this case [20]. This is the area where anastomosis is done, hence the importance of assessing perfusion in the gastric conduit tip.

Intraoperative assessment of the viability and perfusion of the gastric conduit that depends on the pulsations of vessels, color of the gastric serosa, peristalsis, bleeding from the cut edge, visualized connection of the right and left gastroepiploic vessels, and temperature are subjective and dependent on surgeon experience. [5,8,13,16] These parameters may also be affected by several factors such as tissue damage, cardiopulmonary instability, and inotropic support [5,16].For this case, potential site of anastomosis was initially identified and marked using traditional intraoperative assessment by the surgeon.

Recognizing the limitations of clinical judgment, various technical modalities have been introduced to assist in the intraoperative assessment of the gastric conduit viability and perfusion, one of which is the ICG fluorescence angiography. The technology is based on the ability of protein-bound ICG to emit near-infrared fluorescence with peak wavelength of 800–850 nm when illuminated with near-infrared light of 760–780 nm wavelength. [5,22] A color camera system with charged-coupled device (CCD) captures the ICG fluorescence illuminated with light-emitting diodes (LED) [5]. The camera captures visible and near-infrared rays hence its ability to generate natural images [5]. The signals are sent to the digital video processor and displayed on a monitor in real time [12]. ICG fluorescence angiography allows real-time assessment of vascular structures, both macro- and microvascular, and organ perfusion that can be repeated due to the short half-life of ICG at 150–180 seconds [5,23]. Complete washout of the ICG occurs within 20 min of injection [23]. The technology is informative, easy to use, and not linked to any major complication [14,15,19].

Studies have investigated several applications of ICG in gastric conduit construction including evaluation of blood supply, choice of appropriate site of anastomosis, prediction of anastomotic leakage risk, and as adjunct during gastric mobilization particularly during minimally-invasive esophagectomy [5,7,11–17,19,23,24].

ICG fluorescence angiography is able to distinguish ischemic and non-ischemic areas more objectively than the usual macroscopic evaluation [12,16]. Hence, it can theoretically enable more precise identification of the best site for anastomosis. An early study by Shimada, et al. failed to demonstrate reduction in incidence of anastomotic leakage with the use of ICG fluorescence angiography despite its ability to evaluate the blood supply and detect microvasculature of the gastric conduit [17]. However, majority of the succeeding studies have demonstrated its usefulness in predicting the risk of anastomotic leakage [8]. Visualized evaluation of blood flow to the conduit by ICG fluorescence angiography significantly reduced risk of anastomotic complications compared to when it is not used [11,16]. Blood flow speed by ICG fluorescence was also found to predict risk of anastomotic leakage [13]. A reduction in anastomotic leakage was seen when anastomosis was performed in the zone of optimal perfusion defined by ICG fluorescence compared to historical controls where site selection was based on macroscopic visual assessment alone [19]. A recent meta-analysis of 22 observational studies revealed less incidence of anastomotic leakages and graft necrosis when ICG fluorescence angiography was used (OR 0.3, 95 % CI: 0.14−0.63) with pooled incidence of 11.1 % [14].

Use of ICG fluorescence angiography can lead to modifications in intraoperative decisions such as resection of ischemic areas at the tip of the gastric conduit [15], choice of different area for anastomosis in the conduit [8,19], use of alternative conduits such as the colon or jejunum, and additional procedures such as supercharging or superdrainage whereby additional microvascular anastomoses between the conduit vessels and vessels in the neck in case of cervical anastomosis are performed [11,17,25]. In one study, 23 % of cases deviated from the anastomosis site chosen by usual visual assessment [19]. In this case, the initial choice of the site of anastomosis in the gastric conduit was altered by the findings on ICG fluorescence angiography. In a meta-analysis, pooled change in the management rate consisting of either resection of poorly perfused part of the conduit or change in anastomosis site following ICG fluorescence angiography was 24.6 % (95 % CI: 19.2–30.9 %) [10]. Interestingly, after change in the management, pooled incidence of anastomotic leakages and necrosis was higher at 14.1 % (95 % CI: 6.55–27.7 %), which could be due to the ensuing anastomosis being under tension due to the resection or selection bias with patients having poor vascularization to begin with [14].

Use of ICG fluorescence angiography has several limitations including absence of standardized protocols and methods for its application, subjectivity of some parameters being evaluated, lack of definite quantitative threshold to define adequate perfusion, and limitation in evaluating venous drainage. Notably, the ICG studies on gastric conduit have utilized various doses ranging from 1.25 to 25 mg with fluorescence detected within a minute of ICG administration as in this case. [7] Majority of the studies used 2.5 mg of ICG [5–7,11,13]. Different parameters relating to speed and/or intensity of blood flow were evaluated in the studies [16]. Some of the studies assessed blood flow and perfusion by visual, subjective evaluation of fluorescence images [12,24]. Yukaya, et al. proposed a more objective approach by quantifying luminance using the analytical software LumiView [22]. Several studies looked at the speed of fluorescence at certain observation areas in the conduit to judge perfusion and choice of anastomotic site. In one study, an ICG flow speed in the conduit wall of 1.76 cm/s or less as determined by receiver operating characteristic (ROC) curve significantly predicted anastomotic leakage with an odds ratio of 36.5 (95 % CI 4.02–905.7) [13]. In that study, enhancement of the root of RGEA occurred within 30 s compared to 52 s in this case [13]. Noma, et al. suggested that anastomosis on the conduit be done proximal to the point of ICG fluorescence reached in 30 s [16]. The ICG protocol used in this particular case adapted the one used by Kumagai, et al. Time from enhancement of root of RGEA to most cranial branch of LGEA was 16 s in this case report, much longer compared to the 3.5–9.8 seconds in the report by Kumagai, et al. Time from enhancement of the root of RGEA to gastric conduit tip was 48 s, within the reported range of 14.6–141.75 seconds but longer than the average 27–28 seconds. Interestingly, the 2 cases that had anastomotic leakages in that study had time to enhancement of the most cranial branch of LGEA and time to perfusion of the gastric conduit tip at 9.5–9.85 and 103.5–141.75 seconds, respectively. The study has suggested that the area of the gastric conduit not perfused with ICG beyond 90 s after initial enhancement of the RGEA was likely to develop necrosis, hence best avoided for anastomosis [6].

Timing of application of ICG in relation to gastric conduit construction also differed across studies. Kitagawa, et al. applied it prior to gastric conduit creation to mark the line for the gastric conduit border to avoid damaging the intragastric vascular networks. [24] This method was associated with non-statistically significant lower incidence of anastomotic leakage. More commonly, ICG angiography was applied after the gastric conduit has been constructed but before pull-up into the neck [22], after [26] or both [17]. In this case, perfusion was assessed before and after pull-up of the conduit into the neck. This was done to ensure that perfusion has not been compromised during the tunneling procedure. Extrinsic compression of the conduit and its blood supply and drainage can occur at the esophageal hiatus or at the thoracic inlet [8]. Stretching and tension of the gastric conduit during this process can cause intramural blood supply disruption particularly at the cranial end [20].

Studies have demonstrated the utility of ICG in evaluating arterial inflow into the gastric conduit. However, very few studies have looked into its role in evaluating venous drainage. Venous congestion of the gastric conduit is also a recognized factor in the healing of the anastomosis. [7,8,16,25] Inflow and outflow quantification by ICG fluorescence angiography was done in the study by Yukaya, et al. but failed to establish the correlation between anastomotic leakage and inflow and outflow blood flow type [22]. One study reported on the venous outflow assessment using ICG fluorescence angiography following superdrainage of gastric conduit [25]. Assessment of venous return is limited due to the marked enhancement of vessels and tissues that may last more than about 5 min [6].

4. Conclusion and learning points

As demonstrated in this case, the use of ICG fluorescence angiography is a feasible and promising adjunct to evaluate adequacy of perfusion of the gastric conduit for esophageal replacement. It can aid in choosing the most appropriate site of anastomosis to prevent ischemia-related complications such as leakage or stricture. However, there is a need to further standardize methods of its use and clearly define objective parameters and thresholds to assess perfusion using this technique. Randomized clinical trials are needed to further establish the utility and reproducibility of ICG fluorescence angiography.

This case report, being the first in our tertiary government hospital, can help strengthen our local experience with the use of ICG in esophagogastric anastomosis and other esophageal replacements such as colonic and jejunal interpositions. In our setting where our experience with esophageal replacement might not be as extensive as in other international centers, then having this additional armamentarium can aid in facilitating good postoperative outcomes, as in our case.

5. Patient perspective

"Natutuwa po ako sa ginawang operasyon sa akin dahil nakakain na po ako nang maayos. Nagpapasalamat ako sa mga doktor na nag-opera sa akin at nagbigay ng chemotherapy dahil hanggang ngayon ay wala pa rin akong bukol base sa pinakabagong CT scan ko. Naway magtuloy-tuloy na ang aking mabuting kondisyon."

(I am now happy that I am able to eat without difficulty because of the operation that was performed on me. I am very grateful for my doctors who did the surgery and who gave the chemotherapy because I am still tumor-free based on my latest CT scan. I am praying for my continued good health condition.)

Conflicts of interest

The authors have no conflict of interests to declare.

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Ethical approval

A case report is exempt from ethical approval in our institution.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

SACAM: primary surgeon of the case, study concept, data collection, writing the draft and final manuscript

SSM: second assist of the case, study concept, data collection, formal analysis, writing the draft and final manuscript, review and editing of manuscript

RBD: first assist of the case, study concept, supervision, resources, review of the manuscript

NDC: study concept, supervision, resources, review of the manuscript

Registration of research studies

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