Indocyanine Green (ICG) fluorescence angiography of gastric conduit for reconstruction after esophagectomy: a single center prospective study

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Abstract

Introduction: Esophageal cancer ranks among the most aggressive neoplasms worldwide and is a significant contributor to cancer-related mortality. Surgical intervention through esophagectomy with radical lymph node dissection remains a cornerstone in the curative treatment of mid and lower esophageal and gastroesophageal junction tumors, often preceded by neoadjuvant therapy tailored to histological type. Anastomotic leak (AL) following gastroesophageal anastomosis is a major complication associated with substantial morbidity and mortality.

Methods: A prospective study was conducted on 30 patients undergoing esophagectomy with gastric conduit reconstruction from May 2023 to April 2024. Gastroesophageal anastomosis was placed at neck. Intraoperatively, indocyanine green (ICG) fluorescence angiography was employed to assess gastric conduit perfusion. The anastomosis site was selected based on ICG fluorescence dynamics, aiming for anastomosis within 45 seconds of ICG enhancement.

Results: The study cohort comprised predominantly male patients (60%) with a mean age of 60.67 years. Most patients presented with squamous cell carcinoma (66.67%), primarily located in the lower esophagus and minimally invasive surgery was predominantly performed. Mean ICG fluorescence angiography time was 32.1 seconds. Anastomotic leak occurred in 23.3% of patients, correlating with significantly longer hospital stays (p=0.005). Although ICG fluorescence angiography was used to guide anastomosis based on perfusion assessment, there was no statistically significant reduction in AL rates observed in this study (p=0.471).

Conclusion: In conclusion, while ICG fluorescence angiography represents an innovative approach to evaluating gastric conduit perfusion during esophagectomy, its direct impact on reducing AL in our study was not statistically significant.

Keywords: *Esophagectomy, gastric conduit reconstruction, indocyanine green fluorescence angiography, anastomotic leak*

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Introduction

Esophageal cancer is one of the most aggressive neoplasms and the sixth leading cause of cancer deaths.[1] Esophagectomy with radical lymph node dissection is performed for the curative treatment of mid and lower esophagus and gastroesophageal junction (GEJ) tumors. Neoadjuvant therapy following surgery is standard treatment. Preoperative chemoradiation is usual protocol for squamous cell carcinoma and perioperative chemotherapy for adenocarcinoma.[2]

There are various techniques of esophagectomy, but whatever the technique gastric conduit is mostly used for the reconstruction after surgery and the anastomosis is performed in chest or in neck. Esophagectomy is the major procedure associated with high rate of complications and morbidity up to 59.8% has been reported.[3] Anastomotic leak is a serious complication associated with increased morbidity and mortality. Among the gastrointestinal anastomosis, esophago-gastric anastomosis is more prone to leak with anastomotic leak rate reported up to 10.6% (12.3% for cervical anastomoses and 9.3% for intrathoracic anastomoses).[4] The most important factor for the anastomotic leak remains the ischemia of the gastric conduit.[5] The blood supply of the gastric conduit is dependent on only right gastroepiploic artery and right gastric artery. The vascular arcade is absent at the tip of gastric conduit where the anastomosis is performed and it is only supplied by the submucosal plexus.[6,7] The perfusion of anastomotic site has been evaluated by visual inspection of color of gastric conduit, bleeding at edges, palpation of warmth and pulse, but these are unreliable methods. Various techniques like tissue pulse oximetry, computed tomography angiography, laser doppler flowmetry, laser speckle(contrast) imaging, near infrared spectroscopy has been introduced but its feasibility in day-to-day surgical practice is questionable. Newer techniques like side stream dark field microscopy and optical coherence tomography gives quantitative measurement of gastric perfusion, however patient studies are lacking.[8]

Reduction of anastomotic leakage or gastric tube necrosis may be possible if anastomosis is made at a site with a good blood flow according to ICG fluorescence angiography (ICG-FA). Kumagai Y. et al[9] established application of the 90-second rule using ICG fluorescence angiography and Yamaguchi K. et al[10] confirmed the usefulness of the “90-to 60-s rule” for gastric tube reconstruction after esophagectomy in a multicenter prospective study. The aim of our study is to reduce the time to 45 seconds and make the anastomosis in gastric conduit at neck to further reduce the possibility of anastomotic leak.

Methods

A prospective study was conducted on patients undergoing esophagectomy with gastric conduit reconstruction from May 2023 to April 2024. The inclusion criteria included:

1. Squamous cell carcinoma or adenocarcinoma of middle and lower esophagus and gastroesophageal junction (GEJ) Siewert I/II

2. ECOG: 0-1
3. Medically fit to tolerate esophagectomy
4. Clinical stage (UICC 8th edition): T1-4aN0-1M0
5. Gastroesophageal anastomosis at neck

The exclusion criteria included cancer of upper esophagus and anastomosis in chest.

Patients were evaluated preoperatively with contrast enhanced CT of chest and abdomen, esophagogastroscopy, tissue biopsy and other routine blood investigations. Patients with squamous cell carcinoma underwent neoadjuvant chemoradiation followed by surgery and patients with adenocarcinoma underwent neoadjuvant chemotherapy followed by surgery for bulky disease and for resectable cases upfront surgery ± adjuvant chemotherapy was done.

Surgery was planned according to the tumor location. If tumor was located in mid and lower esophagus or GEJ Siewert I, Thoracoscopic three incision esophagectomy was performed. If the tumor was located in GEJ Siewert II, transhiatal esophagectomy was performed. Gastric conduit was used for reconstruction in all patients. A gastric tube of 4-5cm diameter was made with preserved right gastroepiploic and right gastric artery. Omentum was preserved at the proposed site of anastomosis for wrapping the anastomosis.

Method of ICG fluorescence angiography:

ICG was used for evaluation of the blood flow in gastric conduit. A test dose of 0.1ml was injected intradermally 30minutes prior to surgery to check for hypersensitivity. After preparing the gastric conduit, 5-10mg of ICG (diluted in 10ml saline) was injected intravenously followed by instant bolus injection of 10ml of normal saline. Stryker laparoscopic set (model 1588) was used to determine the vascular course using near infrared light mode. The perfusion of the gastric conduit and the omentum was checked and the timing was noted just after injection of normal saline bolus. Anastomotic site was determined at 45 seconds of perfusion. If the conduit length is inadequate at 45seconds then well perfused segment was used for anastomosis, preferably <60seconds. The gastric conduit was then pulled to neck and hand sewn or stapled gastroesophageal anastomosis was done at neck. Omental pedicle was wrapped around the anastomosis. Feeding jejunostomy was made for enteral feeding. Oral feeding was started on 5^{th} – 7^{th} postoperative day if there was no leak. Anastomotic leak (AL) was confirmed clinically if there was discharge from neck wound other than seroma or pus. FJ feeding was continued in case of leak until it healed.

Data collection technique: Data was collected and analyzed using SPSS version 23.

Ethical consideration: Ethical approval was taken from Institutional Review Committee (Ref. No. 106/2080/081) prior to conducting the study. An informed consent was taken from every patient enrolled in the study.

Results

Thirty patients underwent esophagectomy for esophageal carcinoma with gastric conduit reconstruction from May 2023 to April 2024. ICG fluorescence angiography was done in all patients to evaluate blood flow of the gastric conduit. The patient demographics, tumor characteristics, and operative details are summarized in Tables 1 and 2. The mean age of the patients was 60.67 ± 10.48 years. Majority of the patients were male (60%). Most of patients had low BMI with mean BMI of 19.1 kg/m^2 and mean weight loss of

6.6kg. Dysphagia was the predominant symptom, with 60% of patients having Grade 3 dysphagia and a mean duration of 4.7 months. Fifty percent of the patients were smoker and 36.7% patients consumed alcohol. Hospital stay and postoperative stay was significantly higher in patients with anastomotic leak (p=0.005).

Squamous cell carcinoma was the most common histology (66.67%), and lower esophageal tumors were the most frequent location (53.3%). Minimally invasive surgery was predominantly performed which included VATS 3- incision esophagectomy and laparoscopic transhiatal esophagectomy. Mean ICG time was 32.1 seconds and mean operative time was 251.3 ± 48 minutes. Median intraoperative blood loss was 235ml.

Table 1: Basic Parameters

	All patients (N=30)	No Anastomotic Leak (N=23)	Anastomotic Leak (N=7)	p-value
Age (Mean ± SD)	60.67 ± 10.48	60.52 ± 11.7	61.14 ± 5.1	0.894
Sex (Male:Female)	18:12	15:8	3:4	0.392
BMI (Mean ± SD) Underweight Normal	19.1 ± 3.6 17 13	18.6 ± 3.2 14 9	20.5 ± 4.9 3 4	0.666
Dysphagia Grade 2 Grade 3 Grade 4	11 (36.7%) 18 (60%) 1 (3.3%)	8 14 1	3 4 0	0.814
Duration of Dysphagia (in months)	4.7 ± 3	5.13 ± 3.3	3.29 ± 1.4	0.204
Weight loss (kg)	6.63 ± 5.81	7.65 ± 5.9	3.29 ± 4.35	0.106
Alcohol consumption	11 (36.6%)	9	2	1.00
Smoker	15(50%)	12	3	1.00
Hemoglobin	11.5 ± 1.6	11.7 ± 1.6	10.7 ± 1.6	0.156
Albumin	3.8 ± 0.3	3.82 ± 0.3	3.74 ± 0.28	0.527
Hospital Stay	19.1 ± 6.9	17.2 ± 3.3	25.3 ± 11.5	0.005
Post operative stay	16 ± 6.6	14.2 ± 3.5	21.86 ± 10.6	0.005

Table 2: Operative characteristics

	All patients (N=30)	No AL (N=23)	AL (N=7)	p-value
Location of tumor				0.231
Mid esophagus	7 (23.3%)	6	1	
Lower Esophagus	16 (53.3%)	11	5	
GEJ I	1 (3.3%)	1	0	
GEJ II	6 (20%)	5	1	
Histopathology				0.843
Squamous cell carcinoma	20 (66.67%)	15	5	
Adenocarcinoma	9 (30%)	7	2	
Poorly differentiated carcinoma	1 (3.33%)	1	0	
Treatment Protocol				0.198
S-CT *	7 (23.3%)	7	0	
CT-S-CT†	13 (43.3%)	10	3	
CT-S‡	1 (3.3%)	1	0	
CTRT-S§	9 (30%)	5	4	
Neoadjuvant Chemoradiation				Odds ratio
Yes		5	4	4.8
No		18	3	
Response to Neoadjuvant treatment				0.249
Partial Response				
Complete Response	22 (73.3%)	15	7	
Not applicable	1 (3.3%)	1	0	
	7 (23.3%)	7	0	
Approach to surgery				1.00
Open	5 (16.7%)	4	1	
MIS‖	25 (83.3%)	19	6	
Type of surgery				1.00
3-incision Esophagectomy	23 (76.7%)	18	5	
Transhiatal Esophagectomy	7 (23.3%)	5	2	
Nodal dissection				0.637
Sampling	6 (20%)	5	1	
2-FD¶	24 (80%)	18	6	
Intraoperative blood loss	262 ± 125	250 ± 123.5	301 ± 130.6	0.226
Operative time (Mean ± SD)	251.3 ± 49.4	248.9 ± 48	259.3 ± 57	0.413
ICG time (Mean ± SD)	32.1 ± 12.5	32.8 ± 13.1	29.57 ± 10.47	0.471

*S-CT: Surgery f/b adjuvant chemotherapy

†CT-S-CT: Neoadjuvant chemotherapy f/b surgery f/b adjuvant chemotherapy

‡CT-S: Neoadjuvant chemotherapy f/b surgery

§ CTRT-S: Neoadjuvant chemoradiation f/b surgery

‖MIS: Minimally invasive surgery

¶ 2-FD: 2 field lymph node dissection

Post operative complications are shown in Table 3. Most common complication was hoarseness of voice due to recurrent laryngeal nerve palsy in 11 patients. Anastomotic leak occurred in 7 patients (23.3%). There was one mortality due to postoperative pneumonia. One patient had chylothorax which was managed conservatively with prolonged chest tube drain and dietary modification.

While comparing ICG time with anastomotic leak no significant difference was seen. Patients who received neoadjuvant chemoradiation (CTRT-S) had 4.8 times higher odds of having anastomotic leak (44.4% vs 14.3%).

Table 3: Post operative complications

	Frequency	Percentage
Anastomotic Leak (AL)	7	23.3%
Recurrent laryngeal nerve palsy (RLN palsy)	11	36.7%
Surgical site infection	5	16.7%
Chylothorax	1	3.3%
Pneumonia	1	3.3%
Mortality	1	3.3%

Table 4: ICG time Vs Anastomotic leak

	No AL (N=18)	AL (N=7)	p value
ICG time (sec) (Mean ± SD)	32.8 ± 13.1	29.57 ± 10.47	0.471

Discussion

The present study provides a comprehensive analysis of patient demographics, tumor characteristics, operative details, and postoperative outcomes following esophagectomy with gastric conduit reconstruction for esophageal carcinoma.

In this study, there were no significant differences observed in most clinical parameters and operative characteristics between patients who experienced anastomotic leak (AL) and those who did not. Anastomotic leak was mostly seen in patients who received neoadjuvant chemoradiation with odds ratio of 4.8 which was similar to the study of 393 cervical anastomosis patients by Briel et al. revealing a higher incidence of AL in those who underwent neoadjuvant therapy(OR: 2.2 [95% CI 1.1–4.5]).[11]

During esophagectomy, ICG angiography has grown in importance as a technique for evaluating tissue perfusion. It has been demonstrated to considerably lower the risk of AL when used to assess GC perfusion prior to anastomosis. Anastomosis made in a well-perfused area has shown to decrease AL.

In our study, although mean ICG time was 32.1 seconds, anastomotic leak occurred in 23.3% of patients. In our previous studies, anastomotic leak was 3.5-7% while using ICG angiography and up to 16% in those without using ICG angiography.[12,13] Lou and colleagues reported similar findings in McKeown minimally invasive esophagectomy, achieving a low AL rate of 1.2% when performing anastomosis within the ICG-FA visualized zone within 60 seconds. The perfusion time exceeding 60 sec indicated a poor tissue perfusion and presented higher AL rates of up to 10.4%.[14]

In a multicentric study by Yamaguchi et al. AL rate was 4.1% when anastomotic site was within 90 sec of enhancement and 2.4% when it was within 60 sec using ICG-FA.[10] Various meta-analyses have reported AL incidence rates ranging from 11% to 14% following intraoperative ICG-FA.[15-17]

ICG angiography does not appear to lower the incidence of AL, according to several other research. For example, regardless of the fluorescence imaging, Casas et al.[18] showed a similar AL incidence in patients having minimally invasive esophagectomy with intrathoracic anastomosis. The use of ICG was linked to a higher death rate and an increased leak rate, according to a study by Banks et al. [19]. The use of ICG was not able to significantly lower the AL rate (31.0% vs. 37.5%) in the study by Nguyen et al.[20] .Our study's AL rate was comparable to that of other earlier studies.[20-24]

While ICG fluorescence is helpful in assessing arterial blood flow, it is challenging to evaluate venous outflow, and venous congestion may be related to AL.[20] Recent study has demonstrated that blood flow reduces dramatically from the GC creation phase to the anastomotic phase, and tension or compression caused by pulling up the GC via the posterior mediastinal or retrosternal route may further impact blood perfusion.[25] The application of ICG fluorescence both before and after GC creation is more effective in preventing AL.[26] These factors may have resulted in higher anastomotic leak in our study.

Further, quantitative assessment of perfusion by ICG-FA is feasible as shown by several studies[27-30] which may help to select proper anastomotic site in gastric conduit leading to decreased anastomotic leak.

Limitations

Several limitations warrant consideration in interpreting the study findings. Although this was a prospective study, relatively small sample size may limit generalizability and statistical power to detect subtle associations. Furthermore, the single-center design and inherent variability in surgical techniques and perioperative management introduce potential biases. Future studies with larger, multi-centric cohorts and standardized protocols for ICG fluorescence angiography could provide further insights into its utility in predicting anastomotic leak and optimizing surgical outcomes.

Conclusion

In conclusion, while ICG fluorescence angiography shows promise as a tool to assess gastric conduit perfusion during esophagectomy, its direct impact on reducing anastomotic leaks in this study was not statistically significant. The findings emphasize the complexities of optimizing surgical outcomes in esophageal carcinoma patients and highlight the need for integrated approaches combining advanced imaging technologies with comprehensive perioperative management strategies to mitigate complications and enhance patient care.

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