Original Article

Fluoroscence Angiography for Assessment of Gastric Conduit: Initial Experience from a Tertiary Care Center

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ABSTRACT

Introduction: Anastomotic leak (AL) after surgery for esophageal cancer remains a main cause of postoperative morbidity and mortality. Poor tissue perfusion at the site of anastomosis is one of the major factors for leak. We aimed to review the results of Indocyanine Green dye (ICG) with a goal to decrease the leak rate.

Methods: Patients with cancer of esophagus and gastroesophageal junction were subjected to either upfront surgery or preoperative chemoradiation/ chemotherapy followed by surgery. Stomach was used for reconstruction. Intravenous injection of 5 mg – 10 mg ICG was given and vascular perfusion was assessed with infrared light of laparoscopic telescope. Gastroesophageal anastomosis was made at the site of adequate ICG perfusion. These patients (ICG group) was compared to the other group of patients in whom ICG was not used (Non-ICG group).

Results: 28 and 396 patients belonged to ICG and Non-ICG group, respectively. 61% in ICG group and 32% in Non-ICG group had preoperative treatment ($p < .001$). AL was observed in 7% and 16% in ICG and Non-ICG group, respectively ($p = 0.2$). Healing time of leak was 15 days in ICG group and 32 days in Non-ICG group ($p = .03$). One patient required revision of anastomotic site based on ICG finding. There was no adverse reaction related to ICG injection.

Conclusion: Fluoroscence angiography using ICG is a safe method for evaluation of vascular perfusion of gastric conduit. Though the leak rate was not statistically different in the two groups, ICG group required lesser time for complete resolution of AL, which might indicate lesser severity of anastomotic disruption.

Keywords: Indocyanine green, angiography, fluorescence, fsophagectomy, anastomotic leak.

Introduction

Surgery remains the cornerstone treatment for cancer of esophagus. Current guideline suggests neoadjuvant chemoradiation followed by surgery for squamous cell carcinoma. For adenocarcinoma of Gastroesophageal junction (GEJ), neoadjuvant chemotherapy followed by surgery is another alternative option. The stomach remains the preferred organ to restore the gastrointestinal continuity after esophagectomy. However, these esophago-gastric anastomotic sites are fragile and prone to complications as leakage, fistulas, bleeding, and stricture. Anastomotic leakage (AL) remains the main cause of postoperative morbidity and mortality in digestive reconstructive surgery. After an esophagectomy, leakage incidence ranges from 5% to 20%.[1-5] Literature reports leak-associated mortality rates from 18% to 40% compared to an

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overall in-hospital mortality of 4% to 6%.[1,6,7]

Graft perfusion is considered to be an important predictor for anastomotic integrity. Currently, tissue perfusion is assessed using subjective parameters such as tissue color and vessel pulsations. However, these parameters are known to be of limited predictive value, emphasizing the clear need for a safe, reproducible, and non- invasive method to objectively assess tissue viability and graft perfusion. Recently, near-infrared fluorescence using indocyanine green (ICG) has been introduced as a method for visualizing blood flow, and its usefulness has been reported in many types of reconstructive surgery.[8-10] In reconstruction after esophagectomy, the efficacy of ICG fluorescence imaging has already been reported by some groups evaluating the use of gastric or intestinal conduits.[11-13]

We report our results of Fluorescence angiography for assessment of gastric conduit after esophagectomy.

Methods

An observational study with the use of ICG during esophagectomy has been conducted at BP Koirala Memorial Cancer Hospital (Thoracic Unit/ Department of Surgical Oncology) during a period of 18 months (February 2018 – August 2019). Both the patients with squamous cell carcinoma and adenocarcinoma were enrolled in the study. Staging was done on the basis of clinocoradiological grounds (CT chest and abdomen). For any radiologically node positive or bulky tumor on CT film with squamous cell histology, neoadjuvant chemoradiation or neoadjuvant chemotherapy was considered. For resectable gastroesophageal junction (GEJ) adenocarcinoma, Siewert type II, upfront surgery followed by chemotherapy was considered. Bulky GEJ, Siewert II tumors underwent perioperative chemotherapy and surgery.

Tumors located in the middle or distal esophagus (Gastroesophageal junction, Siewert type I) underwent three-incision esophagectomy. Gastroesophageal junction, Siewert type – II underwent transhiatal esophagectomy. Stomach was used in all the cases for reconstruction after esophagectomy. All the vessels to the stomach except right gastroesophageal arcade and right gastric vessels were sacrificed. A gastric conduit of 4-6 cm in diameter was made. An omental pedicle at the region of proposed site of anastomosis (adjacent to fundus along the greeter curvature) was preserved.

A 25 mg vial of ICG was diluted with 10 ml of sterile water so that each ml of reconstituted solution contained 2.5 mg. Sensitivity test with 0.1 ml intradermal injection of the given solution was done. If there was no hypersensitivity reaction, 5 mg aliquot of the solution was given intravenously. Laparoscopy platform with near infrared function (Make: Stryker Inc, model 1588, USA) was used to visualize the ICG green dye traveling towards the tip of the stomach. A particular attention was given to the perfusion of omental flap which was preserved at the site of anastomosis. If needed, 5 mg of ICG was repeated. If the omental pedicle or the gastric tip was not well perfused with ICG, that part was excised till a good perfusion was confirmed. After confirmation of perfusion, the stomach was pulled upto neck and hand sewn gastroesophageal anastomosis was made. Omental pedicle was wrapped around the anastomosis. Feeding jejunostomy was inserted in all cases and feeding was started through it on second postoperative day. In case if AL happened, patient was kept nil per mouth and feeding was given through the jejunostomy tube. Oral feeding was started once there was complete healing of leak.

The study group (ICG group) was compared to the patients in whom ICG was not used (Non-ICG group). The later group were generally operated before February 2018. In non-ICG group, before year 2015, upfront surgery was practiced for squamous cell histology without any adjuvant treatment in case of R0 resection. Whereas for adenocarcinoma of GEJ Siewert – II, surgery was generally followed by either chemotherapy of chemoradiation for node positive cases.

The primary aim of the study was to evaluate the anastomotic leak rates in the two groups. Anastomotic leak was diagnosed clinically and was treated conservatively with dressing and nil per mouth. Statistical analysis was done with SPSS 18.0.

Results

A total of 424 patients were analyzed. ICG was performed in 28 patients and this group of patients was compared with 396 patients who had their gastric conduit examined visually (Non-ICG group).

Basic parameters have been shown in table 1.

Table 1. Basic parameters.

Parameters	ICG (%)	Non-ICG (%)	p-value
Mean age	60	58	0.4
Post op stay	13	14	0.2
Hb	12	12	1.0
Weight loss	8	9	0.3
Treatment overview			
Surgery only	8 (29%)	201 (51%)	
Multimodality treatment	20 (72%)	195 (49%)	
Preop ct/ ctrt – s*	17 (61%)	126 (32%)	<0.001
Operating time	218 min	239 min	.15
Minimally invasive surgery	18 (64%)	180 (45%)	.04
Radical nodal dissection	26 (93%)	338 (85%)	0.2

* preoperative chemotherapy/ chemoradiation followed by surgery.

Postoperative complications have been shown in table 2.

Table 2. Postoperative complications.

Complications	ICG	Non-ICG	p-value
SSI*	1 (4%)	19 (5%)	0.6
RLN injury**	2 (7%)	31 (8%)	0.7
Pneumonia	8 (29%)	95 (24%)	0.3
In-hospital mortality	1 (3.5%)	15 (3.8%)	1.0

* Surgical site infection.

** Recurrent laryngeal nerve injury.

Postoperative AL was observed in 2 (7%) and 64 (16%) in ICG and Non-ICG group, respectively (p = .2). Mean healing time for the leak was 15 days and 32 days, respectively in ICG and Non-ICG groups, respectively (p = .03).

One patient in ICG group had poor visualization of vessels in the omental pedicle. This patient required revision of anastomotic site more distally where there was good visualization of ICG. This patient did not develop anastomotic leak.

Discussion

Fluorescent imaging using ICG is an emerging method during cancer surgery that aids the surgeon with intraoperative decision-making. The technology is gaining clinical acceptance in many surgical fields, including esophageal cancer surgery.[14-17]

AL and graft necrosis are feared complications occurring in 5–20% after esophagectomy with continuity restoration and are associated with a high mortality. [1-5,18]

Age, male gender, smoking, alcohol abuse, American Society of Anesthesiologists score, obesity, emergency surgery, prolonged operative time, intraoperative blood loss, diabetes, renal failure, use of corticosteroids and cardiovascular disease are identified as risk factors for AL, potentially through impaired perfusion of the gastric graft.[1,3-5,7]

Among the risk factors that influence anastomotic integrity, poor perfusion is a surgically modifiable factor. Intraoperative real-time fluorescence angiography using ICG can assess perfusion, thereby enabling precise delineation of the ideal site for anastomosis and assessment of final anastomotic vitality. However, no quantitative threshold of the fluorescence signal is known for adequate perfusion.

ICG is a clinically approved Near-infra red fluorescent agent to determine cardiac output, hepatic function, and ophthalmic angiography. ICG is known for its absorption maximum around 760-780 nm, its immediate binding with plasma proteins resulting in a confinement to the vascular compartment, its low toxicity and its rapid and exclusive biliary excretion. Its excellent safety record has added to the rapid food and drug administration approval for clinical use in 1956.[19]

In a systematic review by Van Daele E et al of 1186 patients, where a primary esophagogastric anastomosis was made, 13.8% of patients suffered from AL. The leak rate was 9.9% in ICG group and 20.5% in non-ICG group (p <0.001).[20] Within the group of ICG guided esophagogastric anastomosis, 592 had a good ICG perfusion, but still resulted in 6.3% anastomotic leak rate. Ninety-three patients had a low perfusion at the tip of the stomach, for which different types of corrections were performed resulting in an adequate tip perfusion and leak rate of 6.5%, comparable to the AL rate of the well perfused cohort and significantly lower than the 47.8% leak rate in the poorly perfused group ($P < 0.001$). The difference in leak rate was even clearer considering only the cohort with a control group ($P < 0.001$).

Many groups recognize that static visualization of blood vessels by ICG may not accurately characterize the perfusion of the neo-esophageal conduit and have moved to dynamic visualization of the conduits. Specifically, they have aimed to determine if there is a target time to perfusion that would better identify the optimal zone for perfusion.

Kumagai *et al.* proposed a 90-second rule: all anastomoses were reconstructed in the area that was enhanced within 90 seconds after initial enhancement at the distal end of the gastric conduit.[21] The tip was excised in 50% (35/70), and in 18 of those 35 cases there was change in anastomotic site (initial enhancement after median 95.5 seconds to 41.0 seconds after excision). In none of the patients the anastomosis was performed at a site with enhancement after more than 90 seconds. Anastomotic leakage occurred in one out of 70 cases (1.4%) at an anastomotic site that was enhanced after 77 seconds.

Ohi *et al.* performed an ICG based study on 59 patients.[22] All patients were infused with 2.5 mg of ICG and the perfusion of the conduit was inspected from 0 to 60 seconds. Regions that perfused between 15 and 40 seconds were considered rapid perfusing and those between 40 and 60 seconds were considered slow-perfusing. Thirty-two patients had anastomosis performed in rapid perfusion areas and 18 in slow-perfusion areas. Of the remaining 9 patients who would needed an anastomosis in a zero-perfusion area—the anastomotic technique was changed in three, the anastomotic route was changed in five and one patient had a vessel supercharged to a neck vessel. Overall, only 1 patient of 59 leaked and as compared to the previous 61 patients who received esophagectomy, there was a marked decrease in leakage (14.8% *vs.* 1.7%).

In the most recent and perhaps strongest evidence for this approach is a recent report from Noma.[23] They compared the post-operative outcomes of 285 patients before and after initiation of an ICG protocol. Essentially, the gastric conduit and area of potential anastomosis was imaged after injection of 12.5 mg of ICG. Should perfusion be visualized by 20 seconds, the anastomosis was performed in this area and if anastomotic areas were perfused within 30 seconds, further mobilization was performed prior to anastomosis creation. If perfusion was not visualized in the anastomotic area by 30 seconds, the conduit was "super charged" by the addition of a microvascular anastomosis. Post-operative outcomes of the 71 patients in this protocol was compared with the 214 previous patients using propensity-matching based on age, sex, MBI, ASA, neoadjuvant therapy, route of conduit and anastomotic type. The study found that AL rates in patient in the ICG protocol were statistically lower than those before protocol initiation (8.8% *vs.* 22%, P=0.03). There was also a significant decrease in the number of intensive care unit (ICU) days by 1.1 days (P=0.02). Of note, perioperative hospital mortality was not significantly different.

In our study, the basic parameters like Hb, mean age, postoperative stay, weight loss before treatment and operating time did not differ in the two groups. Multimodality treatment was used more often in ICG group (72% vs. 49%, p < 0.001) as the recent guideline suggested neoadjuvant treatment as a standard approach. Minimally invasive approach was also used more frequently in ICG group than in Non-ICG group (64% vs. 45%, p = .04). Postoperative complications were not different in the two groups. AL rate was less in ICG group (7% vs. 16%) though it was not statistically significant (p = 0.2). Since more often preoperative chemotherapy or chemoradiotherapy was used in ICG group (61% vs. 32%, p < 0.001), it could have led to added anastomotic compromise possibly secondary to fibrotic changes at the region of anastomosis. Hence, a statistical significant difference in leakage rate could not be achieved in ICG group despite its lower incidence. A significant reduction in the healing time of the leak and resumption of oral feed was seen in ICG group, which would suggest less severe degree of anastomotic disruption. Moreover, it might result in less stricture rate in a long-term follow up. In one patient (4%), we needed to revise and resite the anastomosis on the basis of poor ICG perfusion.

This patient did not have leak, which might suggest, we prevented the leak in the patient by using ICG. There are several limitations of our study, mainly, this was an initial observational study, comparing almost matched group of patients, which were treated earlier in our hospital. The treatment protocol in the two groups was different. In earlier days, upfront surgery was the standard of care whereas now preoperative chemoradiation or perioperative chemotherapy is the standard of care. We had a small sample size and as suggested in recent studies, a time frame rule for better ICG perfusion was not followed in our study. In ICG group, none of the patient developed any complication related to ICG. It did not increase the operative time and it was very easy to use.

Based on the world literature[20], fluorescence angiography is gaining popularity because of its easiness to use, safety profile, availability and better confirmation of gastric conduit after esophagectomy. Yet, we do not have any randomized controlled trial and we have yet to develop quantitative method for assessment of perfusion.

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