Esophagus (2011) 8:259–266
DOI 10.1007/s10388-011-0291-7

ORIGINAL ARTICLE

Usefulness of blood supply visualization by indocyanine green fluorescence for reconstruction during esophagectomy

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Received: 6 May 2011 / Accepted: 18 August 2011 / Published online: 10 September 2011

Abstract
Background Adequate blood supply for the reconstructed organ is important for safe esophagogastric anastomosis during esophagectomy. Recently, indocyanine green (ICG) has been used for visualization of the blood supply when anastomosis is performed in vascular surgery. To visualize the blood supply for reconstruction, we employed ICG fluorescence during esophagectomy.
Methods From August 2008, 40 patients received cervical or thoracic esophagectomy. They consisted of 33 patients having esophagectomy for thoracic esophageal cancer, 3 being treated for cervical esophageal cancer, and 4 with double cancer of the thoracic and cervical regions. Before and after pulling up the reconstructed organ, 2.5 mg of ICG was injected as a bolus. Then ICG fluorescence was detected by a camera and recorded.
Results ICG fluorescence was easily detected in all patients at 1 min after injection. The vascular network was well visualized in the gastric wall, colonic grafts, and free jejunal grafts. In five patients, we also performed anastomosis between the short gastric vein and the external cervical vein or superficial cervical vein. The intraoperative and postoperative course of all patients was uneventful apart from three anastomotic leakages.
Conclusions ICG fluorescence can be employed to evaluate the blood supply to reconstructed organs and can be useful in selecting the patients who do not need additional vessel anastomosis. However, anastomotic leakage was not reduced, so the microcirculation detected by ICG fluorescence did not necessarily provide appropriate blood supply for a viable anastomosis.

Keywords Anastomotic leakage · Vessel anastomosis · Microcirculation

Introduction

Reconstruction of the gastrointestinal tract is still a major issue in patients with gastrointestinal malignancies. In esophageal cancer surgery, anastomotic leakage is one of the important causes of death [1], and the rate of anastomotic leakage ranges from 6.2 to 27% [2–8]. Among several causes of anastomotic leakage, ensuring an adequate blood supply is the most important point for performing anastomosis safely after esophagectomy. In 1986, we introduced the EEA stapler for esophago-gastrostomy after resection of part of the sternum following subtotal esophagectomy [9], and the average anastomotic leakage rates from 1994 to 2008 were 4.8% (20/416).

Although all of these patients recovered, a method for effective evaluation of the blood supply to the reconstructed organs would be useful.

To assess the blood supply in reconstructed organs, laser Doppler flowmetry has been used, but sufficiently reliable measurements are not obtained [10, 11].

Indocyanine green (ICG) has long been used for the evaluation of liver function. Recently, ICG fluorescence has also been used for the detection of sentinel lymph

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nodes in breast cancer surgery, gastrectomy, or colorectal cancer surgery, and for visualization of the blood supply after anastomosis during vascular surgery [12–17]. To visualize the blood supply of reconstructed organs during esophagectomy, we started to use ICG fluorescence in July 2008. This study was done to evaluate the efficacy of ICG fluorescence based on our experience so far.

Methods

Patient characteristics

The patients consisted of 33 having esophagectomy for thoracic esophageal cancer, 3 who were treated for cervical esophageal cancer, and 4 with double cancer of the thoracic and cervical regions. (Table 1). There were 32 men and 8 women with an average age of 66 years (range 49–81 years). Ten patients received preoperative chemotherapy, one patient received preoperative chemo-radiotherapy, and two patients had received radiotherapy several years before surgery.

Table 1 Characteristics of the patients

	Number
Age	66 (49–81)
Sex	
Male	32
Female	8
Tumor location	
PhMt	2
CeMt	2
Ce	3
Ut	2
Mt	19
Lt	12
TNM stage[a]	
1	10
2a	5
2b	5
3	18
4	2
Preoperative treatment	
Chemotherapy	10
Chemoradiotherapy	1
Radiotherapy	2
None	27

Ph pharynx, *Ce* cervical esophagus, *Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *Ae* abdominal esophagus

[a] UICC TNM 6th edition

Operative procedures

After esophagectomy, we made a gastric tube or colonic graft and pulled it up via the retrosternal, posterior mediastinal, or subcutaneous route depending on the patient. We routinely used the retrosternal route. A gastric tube with a width of 4 cm was usually fashioned. Anastomosis was done in the cervical region by hand sewing or circular stapler (25 mm EEA) [9]. When a free jejunal graft was used, we first made a hand sewn pharyngo-jejuno anastomosis and then performed microvascular anastomosis. Finally, the jejuno-esophago anastomosis was done.

Modified procedure

After preparation of the gastric tube, the end of the short gastric vein was cut, and we checked the status of bleeding. If bleeding was not continuous or was very weak, there was a possible need for additional venous drainage. In order to decide whether additional drainage was likely to be effective, we performed ICG fluorescence of the gastric tube. If ICG fluorescence showed a strong microvascular network, we concluded that the gastric tube did not need additional venous drainage or arterial anastomosis. If ICG fluorescence first appeared or became stronger after cutting the short gastric vein, we concluded that additional venous drainage would be effective. If ICG fluorescence did not appear after cutting the short gastric vein, additional arterial anastomosis was added. If additional drainage or anastomosis was needed, anastomosis was performed between the short gastric vein or artery and the external cervical or superficial cervical vein.

ICG imaging

Before and after pulling up the reconstructed organ, 2.5 mg of ICG dye (Diagnogreen; Dai-Ichi Pharm, Tokyo, Japan) was injected as a bolus. Then ICG fluorescence imaging was performed with a near-infrared camera system (Photodynamic Eye; Hamamatsu Photonics K.K, Hamamatsu, Japan), and the images were 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 of wavelengths below 820 nm before detection [18] (Fig. 1). Images were sent to a digital video processor and then were displayed on a monitor.

Results

Twenty-three patients underwent thoracoscopic-assisted right thoracotomy in the left lateral position, 1 patient

Fig. 1 Near-infrared camera system

Table 2 Summary of the operative procedures

	Number
Reconstruction method	
Gastric tube	36
Free jejunal graft + gastric tube	1
Free jejunal graft	2
Ileo-colonic graft	1
Reconstruction route	
Retrosternal	31
Posterior mediastinal	2
Subcutaneous	5
Cervical	2
Additional vascular anastomosis	
Yes	5
No	35
Surgical position	
Lateral	24
Prone	14
Supine	2

received left thoracotomy because of a right aortic arch, 14 patients had esophagectomy in the prone position, and 2 patients received cervical esophagectomy in the supine position. With regard to the method used for reconstruction of the esophagus, a gastric tube was employed in 36 patients, a gastric tube plus free jejunal graft in 1 patient, a free jejunal graft in 2 patients, and an ileo-colonic graft in 1 patient. In 2 patients, reconstruction was done via the posterior mediastinal route, while 5 patients were treated by the subcutaneous route, and the retrosternal route was used in 31 patients (Table 2).

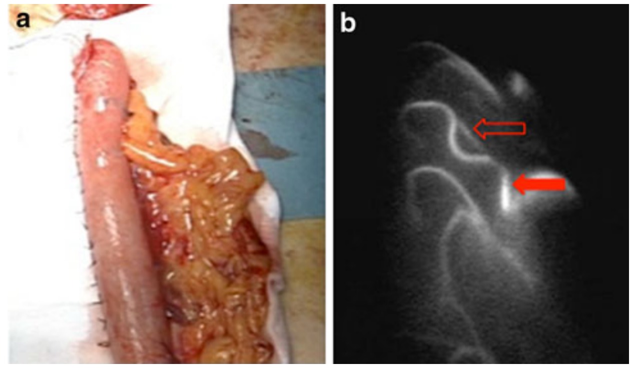

Fig. 2 ICG fluorescence image of a gastric tube before anastomosis. Blood flow in the arteries and veins is well visualized. **a** The gastric tube. **b** ICG fluorescence image. A *closed arrow* indicates an artery and an *open arrow* indicates a vein

Fluorescence of the reconstructed esophagus was easily detected in all patients at 1 min after ICG injection. Both arteries and veins were effectively visualized (Fig. 2a, b). Furthermore, microvessels of the gastric wall were well visualized about 2 min after ICG injection (Fig. 3a, b). The blood supply of the free jejunal grafts was also well visualized (Fig. 4a, b).

In five patients, an anastomosis was added between the short gastric vein and vessels in the neck based on the ICG fluorescence findings. Subsequently, one patient required re-anastomosis because poor circulation was revealed by ICG fluorescence (Fig. 5a, b). We could also effectively visualize blood flow in the colonic graft (Fig. 6a, b).

During this study we evaluated ICG fluorescence using the detection of microcirculation; however, retrospective re-evaluation of the fluorescence status after the period of this study revealed that small vessels were observed in the stump of the reconstructive organ's wall in 22 cases, (Table 3).

There were no severe complications in this series, but two minor and one major anastomotic leakage. In all of the leakage patients, the subcutaneous route was used for reconstruction. Retrospective analysis revealed that there was no anastomotic leakage in the cases where we could observe small vessels in the reconstructive organ's wall. On the other hand, in 15 out of 18 cases in which we could not observe small vessels in the organ's wall, anastomotic leakage did not occur. (Table 3).

Discussion

Although surgical techniques have improved in recent decades and the incidence of anastomotic leakage has decreased to less than 10%, leakage is still one of the factors that influences the postoperative course and

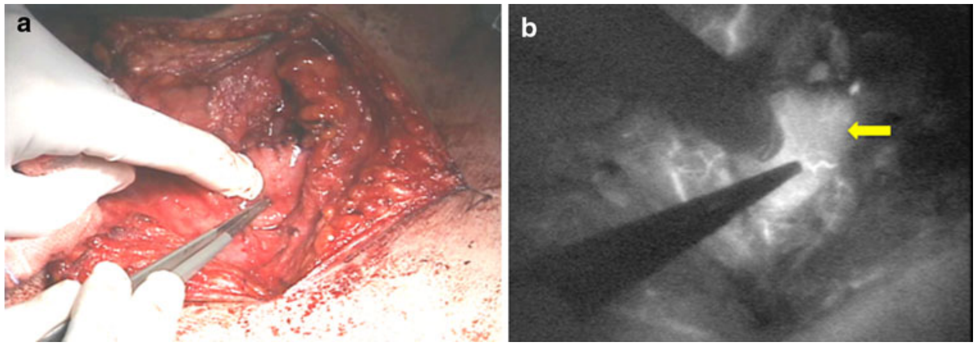

Fig. 3 Microvessels in the gastric wall are well visualized about 2 min after ICG injection. **a** Image obtained under normal light. **b** Blood vessels and microcirculation of the gastric tube. The *forceps* indicates a small blood vessel in the gastric wall and *closed arrow* indicates microcirculation

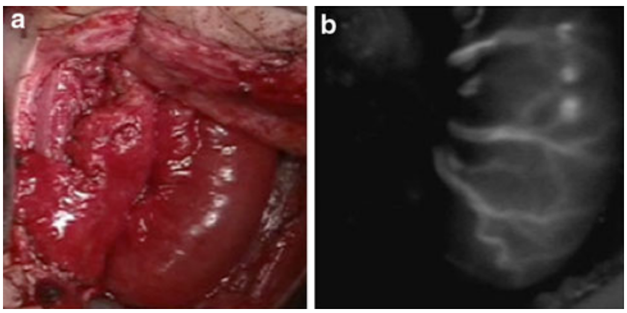

Fig. 4 ICG fluorescence image of a free jejunal graft. **a** Edematous graft with repeated vascular anastomosis. **b** Although the graft is edematous, ICG fluorescence can visualize blood flow

survival after en bloc resection of esophageal cancer [19]. Thus, in order to improve the outcome, reducing the occurrence of anastomotic leakage is a major issue in the field of esophageal surgery. The most important predictors of anastomotic leakage are ischemia of the gastric conduit and a low blood oxygen level [20]. Several reports have also suggested that tissue blood flow is worse during the intra-operative and postoperative periods among patients with leakage than those without leakage [10, 11]. Epidural anesthesia may improve blood flow to the gastric tube and reduce the occurrence of anastomotic leakage [20].

To assess the blood supply of reconstructed organs, several studies have employed laser Doppler flowmetry [10, 11, 21]. Recent progress has led to intraoperative fluorescent imaging (IFI) using the SPY system, which allows the evaluation of coronary artery bypass graft patency intraoperatively based on the detection of indocyanine green (ICG) fluorescence [15, 22–24].

In the gastrointestinal field, ICG fluorescence has already been used for navigation surgery and for

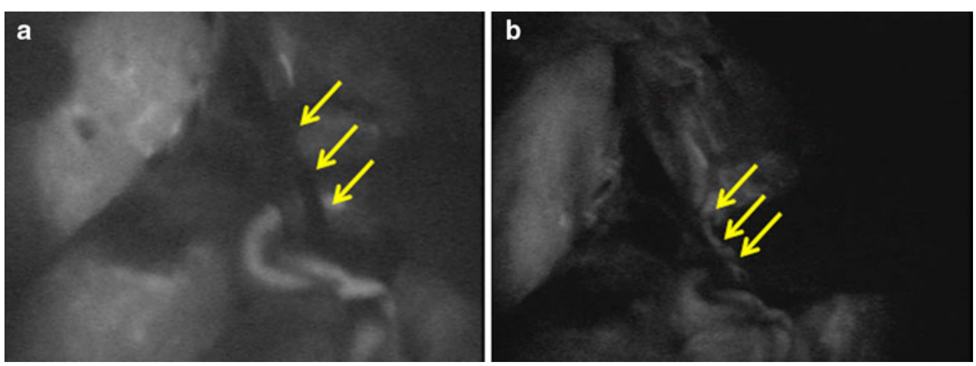

Fig. 5 Before and after re-anastomosis between the short gastric vein and cervical vein. **a** ICG fluorescence shows no blood flow in the anastomosed vessel. **b** ICG fluorescence shows blood flow in the vessel after repeat anastomosis

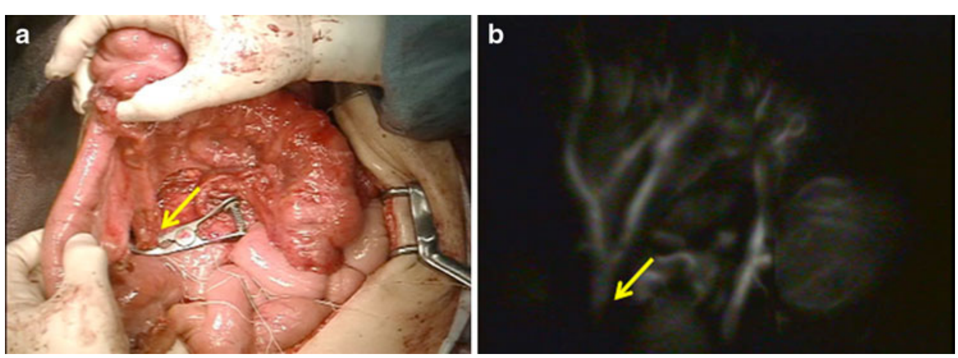

Fig. 6 ICG fluorescence images of a colonic graft. **a** The ileo-colic vessels. **b** There is good blood flow from the middle colic vessels

Table 3 The outcome of each patient

Patient no.	Age/gender	Stage	Tumor location	Reconstruction method	Pull-up route	Method of thoracotomy	Preoperative treatment	Associated conditions	Vascular anastomosis	Anastomotic leakage	ICG (microcirculation in the stump)	ICG (small vessel in the stump)
1	59/M	T3N0M0 stage 2a	Mt	G	R	L	–	–	–	–	Observed	Observed
2	59/M	T3N1M0 stage 3	Mt	G	P	L	FP × 2	Funnel chest Rectal cancer	–	–	Observed	Observed
3	66/M	T3N0M0 stage 2a	Lt	G	R	L	–	Obesity (BMI 30)	–	–	Observed	Observed
4	70/M	T1N0M0 stage 1	PhMt	G	R	L	–	Pharyngeal cancer, DM	–	–	Observed	Observed
5	62/M	T1N1M0 stage 2b	Lt	G	R	L	–	Renal failure	+	–	Observed	Not observed
6	70/M	T3N1M0 stage 3	Mt	G	R	L	FP × 2	–	–	–	Observed	Not observed
7	76/F	T3N1M0 stage 3	Mt	G	R	L	FP + 40 Gy	–	–	–	Observed	Not observed
8	58/M	T3N1M0 stage 3	Lt	G	R	L	–	–	–	–	Observed	Not observed
9	70/M	T3N1M0 stage 3	Lt	G	S	L	–	Colon cancer	+	+	Observed	Not observed
10	78/M	T3N1M0 stage 3	Mt	G	R	L	–	–	–	–	Observed	Not observed
11	56/F	T4N1M0 stage 3	Mt	G	R	L	–	–	–	–	Observed	Observed
12	76/M	T1N0M0 stage 1	Ce	J	–	–	60 Gy (9 years before)	–	+	–	Observed	Observed
13	56/F	T2N0M0 stage 2a	Ce	J	–	–	FP	–	+	–	Observed	Observed
14	68/M	T1N1M0 stage 2b	Mt	G	R	L	FP	–	–	–	Observed	Observed
15	62/M	T1N1M0 stage 2b	PhMt	G + J	R	L	FP	Pharyngeal cancer	+	–	Observed	Observed
16	71/M	T2N0M0 stage 2a	Mt	G	S	R	–	Right aortic arch	–	+	Observed	Not observed
17	81/M	T3N1M0 stage 3	Lt	G	R	L	–	–	–	–	Observed	Observed
18	67/M	T4N1M0 stage 3	CeMt	G	R	L	–	–	+	–	Observed	Not observed
19	54/M	T1N0M0 stage 1	Mt	G	R	L	–	–	–	–	Observed	Observed
20	67/M	T1N0M0 stage 1	Mt	C	S	L	–	–	–	–	Observed	Observed
21	76/M	T1N1M0 stage 2b	Mt	G	R	L	–	–	–	–	Observed	Observed
22	79/M	T2N0M0 stage 2a	Mt	G	R	L	–	Lung cancer	–	–	Observed	Not observed
23	61/F	T1N0M0 stage 1	Mt	G	R	L	–	–	–	–	Observed	Observed
24	60/M	T1N1M1 stage 4	CeMt	G	R	L	60 Gy	–	+	–	Observed	Not observed
25	67/M	T1N0M0 stage 1	Ce	G	P	L	–	–	+	–	Observed	Not observed
26	64/M	T2N1M0 stage 2b	AeLt	G	R	L	–	–	–	–	Observed	Not observed
27	58/M	T3N1M0 stage 3	Lt	G	R	P	–	–	–	–	Observed	Observed
28	74/M	T1N0M0 stage 1	Mt	G	R	P	–	–	–	–	Observed	Not observed
29	68/F	T1N0M0 stage 1	AeLt	G	R	P	–	–	–	–	Observed	Observed

Table 3 continued

Patient no.	Age/gender	Stage	Tumor location	Reconstruction method	Pull-up route	Method of thoracotomy	Preoperative treatment	Associated conditions	Vascular anastomosis	Anastomotic leakage	ICG (microcirculation in the stump)	ICG (small vessel in the stump)
30	65/M	T1N0M0 stage 1	UtMtLt	G	R	P	–	–	–	–	Observed	Observed
31	71/F	T3N1M0 stage 3	Mt	G	R	P	FP	Bilateral breast cancer	–	–	Observed	Not observed
32	67/M	T4N1M0 stage 3	Mt	G	S	P	DCF	–	–	+	Observed	Not observed
33	49/F	T3N1M0 stage 3	Mt	G	R	P	–	–	–	–	Observed	Observed
34	61/F	T1N1M1 stage 4	Mt	G	R	P	FP	–	–	–	Observed	Observed
35	70/M	T3N1M0 stage 3	Lt	G	S	P	–	–	–	–	Observed	Not observed
36	63/M	T3N1M0 stage 3	LtAe	G	R	P	–	–	–	–	Observed	Observed
37	67/M	T3N1M0 stage 3	Mt	G	R	P	FP	–	–	–	Observed	Not observed
38	60/M	T3N1M0 stage 3	LtAe	G	R	P	–	–	–	–	Observed	Observed
39	47/F	T3N1M0 stage 3	LtAe	G	R	P	DCF	–	–	–	Observed	Observed
40	68/M	T1N0M0 stage 1	Ut	G	R	P	–	Gastric cancer	–	–	Observed	Not observed

G gastric tube, *J* free jejunal graft, *C* colonic graft, *R* retrosternal, *P* posterior mediastinal, *S* subcutaneous, *L* left lateral position with VATS, *R* right lateral position with VATS, *S* supine position, *P* prone position, *FP* 5-FU plus cisplatin, *DCF* FP plus docetaxel

intraoperative detection of hepatocellular carcinoma [18, 25, 26]. In addition, Sekijima et al. [27] introduced ICG fluorescence for organ transplantation. However, detection of the microcirculation in gastrointestinal organs has not been studied much so far [28, 29].

Our results revealed that ICG fluorescence could detect organ blood flow before reconstruction and assist in evaluating the appropriate anastomotic sites. However, the incidence of anastomotic leakage was not reduced. Thus, the microvessels detected by ICG fluorescence did not always provide enough blood for a viable anastomosis. On the other hand, retrospective re-analysis revealed that there was no anastomotic leakage in cases in which we could observe small vessels in the stump of the reconstructive organ's wall. Thus, observation of microcirculation and small vessels indicates an appropriate organ for anastomosis. However, we could observe microcirculation and small vessels in only about half of our series.

Intraoperative prostaglandin E1 treatment is also not effective for preventing anastomotic insufficiency [10]. Furthermore, gastric perfusion of less than 70% can predict the occurrence of anastomotic stricture but does not predict leakage [21]. Factors other than perfusion may also influence the process of anastomotic healing [21]. Thus, not only the blood supply, but also factors such as the route of anastomosis (retrosternal vs. posterior mediastinal or subcutaneous), the type of gastric tube (narrow or wide), the method of anastomosis (hand sewing, circular stapler, or triangulating stapling) and the tension at the anastomotic site may influence the healing of an anastomosis [10, 11, 20, 30–32].

In our series, the subcutaneous route was used in five patients because of the condition of the gastric tube or various anatomical problems, and three of these five patients had leakage. Thus, the need to employ the subcutaneous route may be one of the risk factors for anastomotic leakage [7].

With regard to additional microvascular anastomosis, a significant increase of tissue blood flow was observed after additional venous anastomosis (mean 19%) and also after combined arterial and venous anastomosis (mean 43%) [33]. Thus, additional anastomosis between the short gastric vessels and vessels in the neck resulted in the reduction of anastomotic leakage [34]. We had a good outcome in the present series, so ICG fluorescence may provide useful information to the surgeon about whether patients require additional microvascular anastomosis or not.

Finally, imaging with the photodynamic eye has the following benefits. First, ICG is almost completely washed out within 20 min after injection, so ICG fluorescence can be assessed several times during surgery. Second, we can detect the microcirculation of a target organ as well as the adjacent organs. Third, we can select the patients who do not need additional vessel anastomosis.

In conclusion, imaging of ICG fluorescence can be used to evaluate the blood supply of reconstructed organs and can be useful in selecting the patients who do not need additional vessel anastomosis. However, the microcirculation detected by ICG fluorescence does not necessarily provide enough blood flow to maintain a viable anastomosis. In order to establish more detailed and appropriate ICG fluorescence criteria, an additional and larger study is needed.

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