Intraoperative Assessment of Perfusion of the Gastric Graft and Correlation With Anastomotic Leaks After Esophagectomy

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Objective: The aim of the study was to evaluate laser-assisted fluorescent-dye angiography (LAA) to assess perfusion in the gastric graft and to correlate perfusion with subsequent anastomotic leak.

Background: Anastomotic leaks are a major source of morbidity after esophagectomy with gastric pull-up (GPU). In large part, they occur as a consequence of poor perfusion in the gastric graft.

Methods: Real-time intraoperative perfusion was assessed using LAA before bringing the graft up through the mediastinum. When there was a transition from rapid and bright to slow and less robust perfusion, this site was marked with a suture. The location of the anastomosis relative to the suture was noted and the outcome of the anastomosis ascertained by retrospective record review.

Results: Intraoperative LAA was used to assess graft perfusion in 150 consecutive patients undergoing esophagectomy with planned GPU reconstruction. An esophagogastric anastomosis was performed in 144 patients. A leak was found in 24 patients (16.7%) and were significantly less likely when the anastomosis was placed in an area of good perfusion compared with when the anastomosis was placed in an area of less robust perfusion by LAA (2% vs 45%, $P < 0.0001$). By multivariate analysis perfusion at the site of the anastomosis was the only significant factor associated with a leak.

Conclusions: Intraoperative real-time assessment of perfusion with LAA correlated with the likelihood of an anastomotic leak and confirmed the critical relationship between good perfusion and anastomotic healing. The use of LAA may contribute to reduced anastomotic morbidity.

Keywords: anastomotic leak, esophageal resection, esophagectomy, gastric pullup, graft perfusion

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Esophagectomy is associated with a high morbidity rate, in large part related to the reconstruction. Typically reconstruction is done with a tubularized gastric graft perfused by the right gastroepiploic arcade. Perfusion at the proximal portion of the graft, in the area where the anastomosis is typically created, is variable but often tenuous because the gastroepiploic arcade rarely reaches the tip of the graft. Instead, the most proximal portion of the graft is typically perfused by intramural capillaries within the wall of the stomach and small vessels in the omentum along the greater curvature. It has been shown that cervical esophagogastric anastomotic complications are increased in patients with a history of cigarette smoking, neoadjuvant radiotherapy to the fundus of the stomach, hypertension, and diabetes.[1] These factors may affect perfusion in the area of the proposed anastomosis by interfering with microvascular integrity.

Leak rates after a cervical esophagogastrostomy are among the highest of any gastrointestinal anastomosis.[2] Compromised microperfusion in the area where the anastomosis is sited likely contributes to leaks, but until recently there has not been an easy and reliable technique to intraoperatively evaluate microperfusion. Laser-assisted angiography (LAA) with the SPY Imaging System (Novadaq, Ontario, Canada) provides real-time intraoperative assessment of both gross and microperfusion. The SPY system was developed for cardiac surgery but has been applied in plastic surgery to evaluate perfusion in flaps and tissue transfers.[3–5] We hypothesized that this technology might provide valuable real-time information about perfusion in a gastric graft during an esophagectomy with reconstruction. The aim of the study was to review our experience with the SPY system during esophagectomy and gastric pull-up (GPU) and to correlate our assessment of perfusion at the proposed site of the anastomosis with subsequent anastomotic healing and leak rates.

METHODS

After initially using intraoperative LAA on several esophagectomies with GPU we saw that perfusion in the tip of the gastric graft as assessed visibly with the SPY system was variable. In some patients, the entire graft showed rapid, bright perfusion by LAA (Fig. 1). Often, though, there was a point of demarcation where rapid and bright perfusion transitioned into slower and less robust perfusion. We prospectively decided to evaluate the utility of LAA by placing a suture at the site of this transition if present, and recording in the operative note the location of the anastomosis relative to the suture (proximal vs distal to the stitch) (Fig. 2). During this time, we used standard techniques including our clinical judgment and Doppler to evaluate graft perfusion for placement of the anastomosis. In addition to noting the site of a transition in perfusion by LAA if present, we also noted the proximal-most extent of the Doppler signal. We subsequently evaluated the outcome of these anastomoses by retrospectively reviewing the records of these patients. The study was approved by the University of Southern California institutional review board.

Laser-assisted Indocyanine Green Fluorescent-Dye Angiography

The SPY Imaging System is designed to acquire fluorescence images. This is achieved using a fluorescent agent, indocyanine green (ICG), which upon intravascular administration is rapidly and extensively (>98%) bound to plasma proteins. The ICG is a sterile, water soluble, tricarbocyanine dye with a peak spectral absorption at 800 to 810 nm in blood. It is taken up by the liver and excreted unchanged into the bile. The plasma half-life of ICG is 3 to 5 minutes. The ICG is caused to fluoresce by illumination with a laser at 806 nm. The ICG molecules absorb the light, get “excited,” drop back to an “unexcited” state, and emit light in a longer wavelength. Fluorescence

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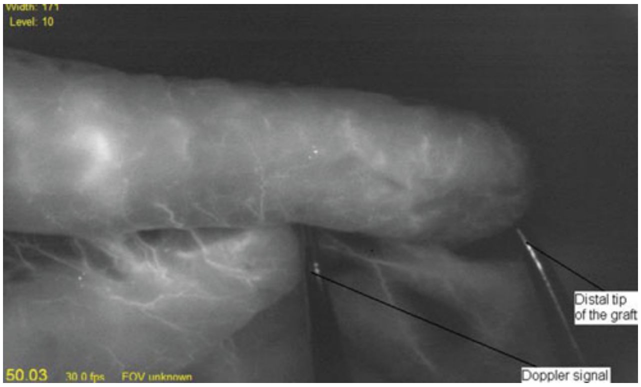

FIGURE 1. Rapid and bright perfusion of the entire gastric graft by LAA.

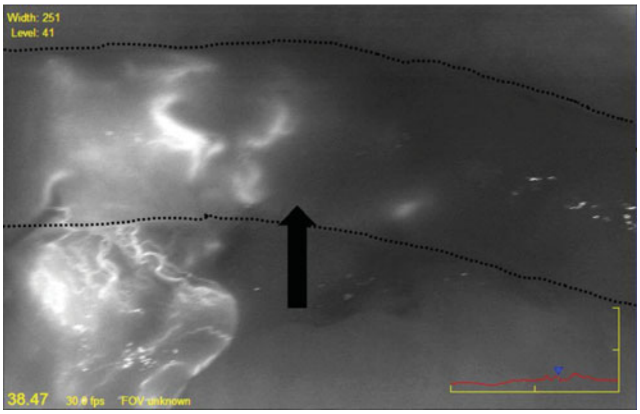

FIGURE 2. A transition point is seen between rapid and bright versus slower, less robust perfusion (arrow). A suture is placed at the site of this transition point and if possible the anastomosis was placed proximal to this suture in an area of good perfusion by LAA.

images of the GPU graft are acquired using a charge coupled device video camera, sensitive into the near infrared, and equipped with an edge filter to permit efficient transmission of fluorescent light (in the range 815–880 nm) while blocking laser and room light. The images are visible in real-time on a monitor and are captured to hard drive for analysis, future review, and archiving.

Safety of Indocyanine Green

Indocyanine green (ICG) has been approved for use in humans and has been extensively used for determining cardiac output, hepatic function, liver blood flow, for ophthalmologic angiography, and during cardiac bypass and plastic and reconstructive surgery. The incidence of adverse reactions to ICG is low and most are mild (sore throat, feeling of warmth). Rare reports describe hypotension requiring treatment with epinephrine. Caution is recommended in patients with iodine or shellfish allergy.

Surgical Procedure

All patients underwent esophagectomy with a transhiatal, en bloc transthoracic, minimally invasive thoracoscopic/laparoscopic or vagal-sparing approach. The tubularized gastric graft was brought up through the posterior mediastinum and a handsewn single-layer cervical anastomosis onto the anterior wall of the gastric pull-up was performed in all patients.

Intraoperative Assessment of Graft Perfusion and Placement of the Anastomosis

After creating a 3- to 4-cm wide gastric tube, but before bringing the graft up to the neck, the SPY system was used to assess graft perfusion. The time between gastric tube creation and LAA was approximately 15 minutes. Images were obtained beginning 5 seconds after intravenous central-line injection of 2.5 mg of ICG followed by a 5 mL flush of saline. This dose was recommended by Novadaq and provided excellent visualization of microperfusion in the gastric grafts. After LAA assessment of perfusion and placement of a suture, if a transition point was seen, the graft was brought up to the neck through the posterior mediastinum. The anastomosis was placed in a suitable area of the anterior wall of the gastric graft, and the location of the anastomosis relative to the suture, if present, was recorded in the operative note. An effort was always made to place the anastomosis proximal to the suture, in an area of good perfusion by LAA, but in patients where the anastomosis would not reach to a portion of stomach proximal to the suture it was placed at or distal to the suture.

Assessment of Anastomotic Healing

A videoesophagram was routinely obtained at 5 to 7 days postoperatively, and if there was evidence of a leak or abnormality, or when indicated by clinical deterioration of the patient, upper endoscopy was performed. If a leak was evident either by videoesophagram or by upper endoscopy, the patient was classified as having an anastomotic leak. Furthermore, for this study, the leak was defined as minor when conservative treatment with antibiotics or nil per os was sufficient to lead to healing and major when an intervention (endoscopic stenting) or reoperation was necessary.

Comorbidities and risk factors for poor anastomotic healing that were evaluated included cardiac disease, hypertension, diabetes, chronic obstructive pulmonary disease, current cigarette smoking, or alcohol abuse.

Statistical Analysis

Data are expressed as medians and interquartile range. Comparisons of proportions were performed using the Fisher exact test. A $P < 0.05$ was considered significant. Univariate and multivariate analysis were performed using Prism software (GraphPad, La Jolla, CA).

RESULTS

There were 150 consecutive patients that had intraoperative LAA assessment of perfusion during esophagectomy with GPU using the SPY system from March 2008 until July 2011. The median age of the patients was 66.7 years (interquartile range: 57–74). There were 125 men and 25 women. The indication for esophagectomy was cancer in 133 patients and end-stage benign disease in 17 patients. The type of esophagectomy was en bloc in 88 patients, transhiatal in 26, minimally invasive in 24 and vagal-sparing in 12 (open 10, laparoscopic 2). Major complications occurred in 22% and there was one mortality (Table 1). The median hospital stay in all patients was 14 days. The median hospital stay was significantly longer in patients with a leak (20 days with leak vs 13 days with no leak; $P = 0.0096$) and in those with a major versus a minor leak (40.5 days with a major leak vs 18 days with a minor leak, $P = 0.0198$).

Intraoperative injection of ICG was well-tolerated by all patients with no adverse events or noticeable adverse effects. There were no technical difficulties and images were obtained in all patients. The entire graft was noted to have good perfusion in 66 of 150 patients (44%), whereas in 84 (66%) patients a line of demarcation was noted between rapid, bright perfusion and slower, less robust perfusion in the fundus of the gastric tube. In these 84 patients, the anastomosis was placed proximal to the stitch in 29 patients, at or distal to the stitch in 49 patients and in 6 patients no anastomosis was performed. These 6 patients all had significant comorbid conditions and poor perfusion by LAA in the area where the anastomosis was to be performed, and we elected to delay the reconstruction until ischemic conditioning led to better graft perfusion. In these patients, the graft was brought up to the neck and sutured to the sternocleidomastoid muscle as has been previously described.[6] Subsequent reconstruction was done once the patient had satisfactorily recovered from the esophagectomy, usually at about 8 to 12 weeks.

Anastomotic leaks occurred in 24 (16.7%) of the 144 patients who had an anastomosis and were classified as major in 8 and minor in 16 patients. Patients in whom the anastomosis was placed at or distal to the site of the suture were significantly more likely to have a leak compared with those in whom no suture was placed (entire graft well-perfused) or where the anastomosis was placed proximal to the transition point in an area of good perfusion by LAA (45% vs 2%, $P < 0.0001$) (Fig. 3). Similarly, major leaks were significantly more common when the anastomosis was not placed in an area of good perfusion by LAA (15% vs 0; $P = 0.0002$). Major leaks were treated with an endoscopic stent in 4 patients and reoperation with neck drainage in 4 patients. No patient required graft takedown. All leaks except 1 occurred in patients with cancer, and all patients with leaks had at least 1 comorbid condition. On univariate analysis, placement of the anastomosis at or distal to the suture and a history of hypertension were significantly associated with an anastomotic leak (Table 2). By multivariate analysis, anastomotic placement at or distal to the suture was the only significant factor associated with a leak.

TABLE 1. Minor and Major Complications (n = 150)

	52 (34.7%)
Minor complications	
Wound infection	10 (6.7%)
Wound hematoma, dehiscence	2 (1.3%)
Urinary tract infection	2 (1.3%)
Atrial fibrillation	24 (16%)
Pulmonary complications	13 (8.6%)
Deep venous thrombosis	1 (0.7%)
Major complications	33 (22%)
Perforation with NG tube	1 (0.7%)
Leakage (minor/major)	24 (16/8)
Chylothorax	7 (4.6%)
Pulmonary Embolism	1 (0.7%)
Mortality	1 (0.7%)

DISCUSSION

Adequate perfusion is a prerequisite for reliable healing of a gastrointestinal anastomosis. One of the most tenuous anastomoses in all of gastrointestinal surgery is the cervical esophagogastric anastomosis during esophagectomy with gastric reconstruction. Leaks are reported in 20% to 35% of these patients and are a major source of short- and long-term morbidity and occasionally mortality.[7] Intraoperative assessment of gastric graft perfusion has typically been on the basis of color, temperature, and Doppler signal. A bluish color and cool temperature are unsettling but lack specificity, and although the Doppler is good for gross perfusion, it is unreliable for microperfusion. Seldom is there a discernible Doppler signal beyond about two thirds the way up the greater curvature of the gastric tube and thus the Doppler is not useful to assess perfusion in the area where the anastomosis is likely to be performed in most patients. In this study, we found that the Doppler signal always disappeared proximal to the site of demarcation by LAA (if present) and could not differentiate grafts with complete microperfusion to the tip versus those with a zone of demarcation as seen using the SPY technology (data not shown).

We started using the SPY system to see if it would provide real-time information about perfusion, particularly microperfusion, that could be useful to assess gastric grafts during esophagectomy. Because we were uncertain of the significance of perfusion as visually assessed with the SPY system, we decided to place a stitch if there was a transition by LAA between fast and bright versus slower and less robust perfusion. We found that an anastomosis was unlikely to leak in patients with no transition point or when it was placed proximal to the transition point when present, in an area of good LAA perfusion. The leaks that occurred in these patients were all minor and healed with conservative therapy. In contrast, 45% of patients with an anastomosis

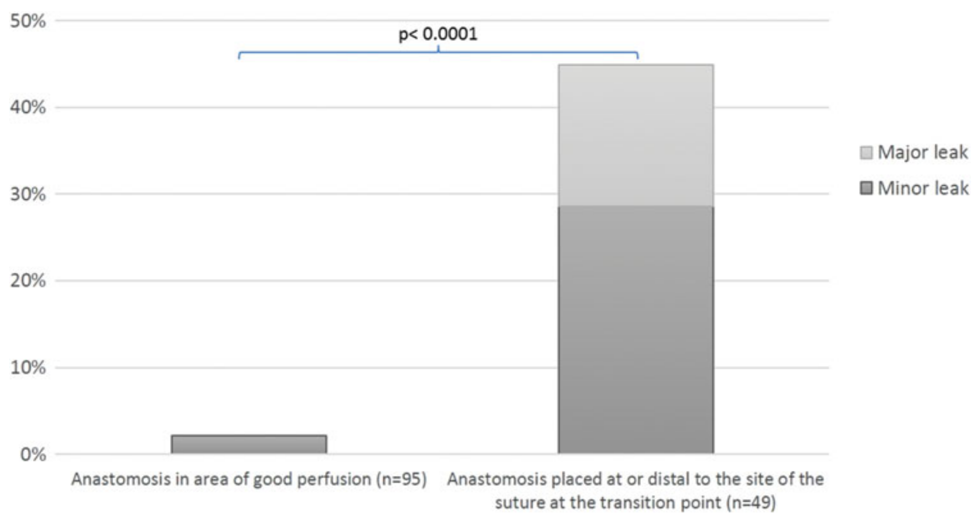

FIGURE 3. The frequency of major and minor leaks in patients where the anastomosis was placed in an area of good perfusion by LAA [either entire graft with good perfusion (n = 66) or anastomosis placed proximal to suture at site of transition (n = 29)] versus those patients that had an anastomosis placed at or distal to the site of the suture at the transition point (n = 49) (2% vs 45%, $P < 0.0001$).

TABLE 2. Univariate Analysis of Factors Potentially Associated With Leak (n = 144)

	No Leak (n = 120)	Leak (n = 24)	*P*
Anastomosis at or distal to suture	27	22	<0.0001
Cancer diagnosis	104	23	0.31
Diabetes	23	5	0.78
Hypertension	57	18	0.0149
Coronary artery disease	25	3	0.41
Active or recent smoking	51	14	0.18
Neoadjuvant therapy	52	15	0.12

placed at or distal to the stitch, in an area of slower and less robust perfusion by LAA, had an anastomotic leak. Furthermore, 36% of these leaks were major leaks that required an intervention.

There are several important issues in relation to this finding. First, when perfusion to the site of the planned anastomosis was good by LAA leaks were unlikely and minor if they occurred. These patients may be considered for fast tracking or elimination of a barium swallow in the absence of any clinical suggestion of a leak. In contrast, when the anastomosis had to be placed at or distal to a transition point in perfusion by LAA, a leak will develop in almost one-half of the patients, and some of these leaks will require an intervention. These patients should be monitored closely and evaluated promptly for any evidence of clinical deterioration. Furthermore, in these patients, planned graft evaluation with an upper endoscopy at 5 to 7 days after reconstruction may be useful to address a leak before it becomes clinically significant. We have previously shown the safety and efficacy of early endoscopy after esophagectomy and reconstruction.[8] It is important to recognize that in these patients with an anastomosis at or distal to the transition site healing without leak occurred in more than half of the patients. Therefore, when faced with this situation factors such as the patient's ability to tolerate a leak should be taken into consideration.

If there were no intraoperative options then defining perfusion with the SPY system would be informative for postoperative care but would not be clinically useful at the time of the operation. However, since understanding the implications of putting the anastomosis in an area of less robust perfusion, we now will alter our operative plan in patients at high risk for doing poorly with a leak. These patients include those with significant comorbid conditions or very elderly patients who tend to have little reserve for major complications. In this series, we had 6 such patients in whom we elected to delay the reconstruction. With this technique, the graft is left in the neck but no anastomosis is performed. Over several weeks, ischemic conditioning leads to improved perfusion in the graft and the subsequent anastomosis typically heals reliably in these patients.[6,9] Alternatively, in some cases, we will now resect a portion of the manubrium and first rib and place the anastomosis proximal to the stitch either with the graft in the posterior mediastinum or in a substernal location. Using this strategy, we can assess the risk for anastomotic leak and tailor the operative plan as necessary when the perfusion by LAA or condition of the patient indicates it appropriate to do so.

In an effort to further refine assessment of perfusion and to move from qualitative to quantitative assessment, the SPY-Q system has been introduced (Fig. 4). Efforts are underway to define a threshold of perfusion below which the majority of anastomoses will not heal. In this way, the risk of anastomotic leak can be defined even more precisely and operative decisions tailored more specifically for an individual patient. Since gaining confidence with the SPY system, we have expanded use of LAA to all types of reconstruction after esophagectomy including colon and jejunal grafts and have found it equally useful to evaluate perfusion in these grafts. Furthermore, the recent introduction of the Pinpoint (Novadaq Ontario, Canada) and Firefly (Intuitive Surgical, Sunnyvale, CA) systems allow LAA perfusion assessment during minimally invasive and robotic procedures.

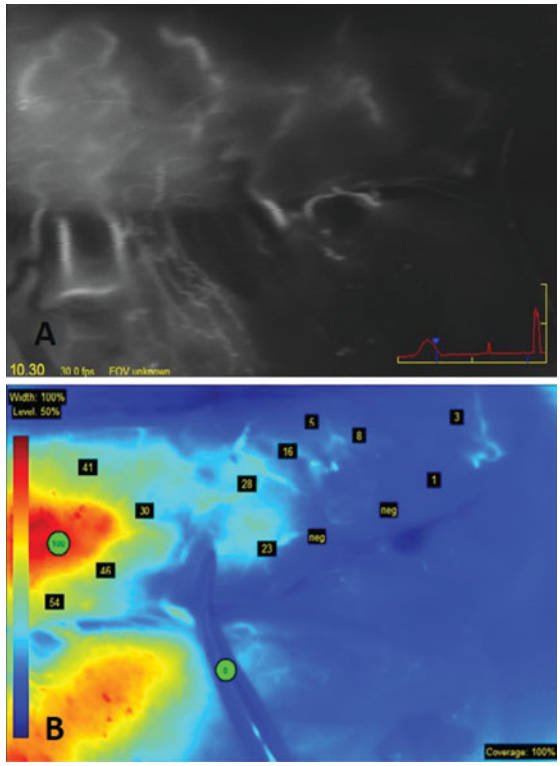

FIGURE 4. Perfusion by LAA shown in (A) qualitative mode versus (B) with quantitative (SPY-Q) overlay.

A limitation of this study is that the evaluation of the SPY images is largely qualitative at this point, and as we have gained experience with the images and perfusion implications we undoubtedly altered our practice, which may have impacted the results of this retrospective review. However, if anything these alterations would likely have led to a reduced rate of leaks since with experience, we began making even greater efforts to place the anastomosis proximal to the suture or alter the surgical plan. Furthermore, our overall small number of leaks prohibited an evaluation of the impact of operative approach on anastomotic healing and likely masked the role of important comorbid conditions that contribute to leaks.

CONCLUSIONS

Perfusion is critical for anastomotic healing after esophagectomy and gastric pull-up. Intraoperative real-time assessment of perfusion with LAA correlated with the likelihood of an anastomotic leak, and the cervical anastomotic leak rate was trivial when the anastomosis was placed in an area of the graft shown to have good perfusion. The use of LAA during esophagectomy with gastric pull-up may lead to an altered surgical plan in some patients and contribute to reduced anastomotic morbidity and better overall patient outcomes.

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