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Association Between Quantitative Blood Flow Measurement Using SPY-QP Software and Prevention of Anastomotic Leakage in Esophageal Cancer Surgery

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Abstract

Background Anastomotic leakage is a severe complication of curative surgery for esophageal cancer, mostly because blood supply to the gastric tube is poor. Although qualitative indocyanine green (ICG) fluorescence imaging has been used to assess blood flow, the subjective nature of this approach poses a challenge. Recently, use of the SPY-PHI system with the SPY-QP software has allowed objective, semiquantitative fluorescence evaluation; however, its utility remains unclear. We investigated the utility of intraoperative SPY-QP-based quantitative perfusion fluorescence imaging for assessing blood flow in the gastric tube and optimizing the anastomotic site to prevent anastomotic leakage in esophageal cancer surgery.

Methods This retrospective, single-center study (January 2017 to December 2024) compared two groups of patients who underwent subtotal esophagectomy: the conventional group with qualitative fluorescence assessment ($n = 72$) and the quantitative group with SPY-QP fluorescence assessment ($n = 55$). We collected and compared preoperative, intraoperative, and postoperative data, including complications (Clavien–Dindo grade ≥ II) and anastomotic leakage.

Results The quantitative group had a significantly higher proportion of patients who underwent preoperative chemotherapy ($p < 0.001$), retrosternal reconstruction ($p = 0.046$) and, Gambee/single-layer anastomoses ($p < 0.001$), and had significantly less intraoperative blood loss ($p < 0.001$). This group also showed a significantly lower incidence of overall postoperative complications and anastomotic leakage, along with a shorter postoperative hospital stay ($p < 0.001$). In multivariate analysis, quantitative SPY-QP fluorescence was identified as a favorable independent factor for reducing anastomotic leakage ($p = 0.009$).

Conclusions Quantitative blood flow measurement using SPY-QP may contribute to a reduction in the incidence of anastomotic leakage following esophageal cancer surgery by facilitating the objective selection of the optimal anastomotic site.

Keywords Esophageal cancer · Esophagogastric junction cancer · Gastric tube blood flow · Quantitative fluorescence signal assessment · SPY-QP

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Esophageal cancer is the 11th most common cancer worldwide and the 7th leading cause of cancer-related deaths annually.[1] More than 500,000 new cases and an estimated 400,000 deaths are recorded worldwide each year.[1] The standard treatment for esophageal cancer involves subtotal esophagectomy with radical lymph node dissection and reconstruction using a gastric tube.[2,3] However, in various malignancies, including esophageal cancer, postoperative complications are associated with decreased survival rates as well as with an increased recurrence risk.[4,5] Postoperative anastomotic leakage occurs in approximately 15% of

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esophageal cancer surgeries.[6] Various measures are being implemented to mitigate this risk.

In Japan, cervical esophagogastric anastomosis is the most widely used reconstruction procedure after esophagectomy for esophageal cancer.[7] To prevent anastomotic leakage, intraoperative indocyanine green (ICG) staining has been used to evaluate blood flow to the elevated gastric tube in order to select the anastomosis site. Evaluation of blood flow by ICG has reportedly been useful but is a qualitative and subjective approach that is dependent on the surgeon's experience, posing a challenge.[8–10] Recently, Stryker's SPY Portable Handheld Imaging (SPY-PHI) fluorescence imaging system (Kalamazoo, MI), which uses SPY-QP software, has enabled the semiquantitative evaluation of blood flow by visualizing the relative ICG fluorescence signal intensity under near-infrared light. However, whether this method could be useful for esophageal cancer surgery remains unclear.

To gain insight into the clinical utility of the quantitative SPY-QP-based fluorescence assessment method in esophageal cancer surgery, we compared this method with a conventional, qualitative fluorescence assessment method in patients who had undergone surgery for esophageal or gastroesophageal junction cancer.

Patients and Methods

Ethics Approval

Prior to commencing this retrospective, noninterventional, observational study, approval was obtained from the institutional review board of Yokohama City University Medical Center (approval number: B201000012). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients

In this study, we investigated consecutive patients with esophageal or gastroesophageal junction cancer who underwent subtotal esophagectomy at Yokohama City University Medical Center between January 2017 and December 2024. The eligibility criteria were as follows: (1) diagnosis of primary esophageal or gastroesophageal junctional cancer made according to the 12th edition of the Japanese Classification of Esophageal Cancer[11] and the 15th edition of the Japanese Classification of Gastric Carcinoma[12]; (2) curative subtotal esophagectomy (R0 resection) performed with radical lymph node dissection; (3) gastric tube reconstruction; and (4) intraoperative gastric tube blood flow assessment conducted using fluorescence imaging. The exclusion criteria were as follows: (1) salvage surgery performed after definitive chemoradiotherapy; (2) presence of unresectable disease; (3) lower esophagectomy; and (4) use of reconstruction methods other than a gastric tube.

Treatment Procedure

Neoadjuvant chemoradiotherapy (NAC) was administered preoperatively to patients with clinical stage II or III esophageal cancer, in accordance with the Japan Clinical Oncology Group (JCOG) 9907 study, JCOG1109 study, and other relevant clinical trials.[2,3,13] In addition, we performed percutaneous endoscopic gastrostomy or inserted a nasal feeding tube for patients with esophageal cancer with severe stenosis (dysphagia score ≥ 3) prior to commencing chemotherapy.[14–16] NAC consisted of two cycles of cisplatin and 5-fluorouracil (CF) or three cycles of cisplatin, 5-fluorouracil, and docetaxel (DCF) administered every 3 weeks.

Surgical resection was performed at 4–6 weeks after chemotherapy had been completed. The surgical procedure consisted of an open subtotal esophagectomy conducted via a right thoracotomy or a thoracoscopic/robot-assisted subtotal esophagectomy, gastric tube reconstruction via the retrosternal or posterior mediastinal route, and cervical anastomosis. The reconstruction route was determined in a multidisciplinary conference. The retrosternal route was selected for patients with severe comorbidities or poor nutritional status. Overall, three-field lymphadenectomy was performed, although two-field lymphadenectomy was selected for cases with lower esophageal or esophagogastric junction cancers. A feeding tube was routinely inserted into the duodenum and enteral nutrition was initiated postoperatively.

Reconstruction Methods

We use a simple and reproducible reconstruction method. The key steps of the method include the following: (1) preserving the right gastric and gastroepiploic arteries and veins; (2) dividing the lesser curvature side of the stomach with a linear stapler to create a 3.5-cm–wide gastric tube; (3) intraoperative evaluation of blood flow to the gastric tube using ICG fluorescence imaging; (4) ensuring that the gastric tube has sufficient length to reach the anastomotic site, and creating the anastomosis as distally as possible on the gastric tube; and (5) performing esophago-gastrostomy by using Albert–Lembert sutures from November 2017 to February 2019, modified Gambee sutures from March 2019 to September 2021, and single-layer interrupted sutures with mucosal inversion thereafter.

Assessment of the Blood Flow to the Gastric Tube

ICG imaging has been performed at our institution since January 2017. Initially, the anastomosis site for esophageal

cancer surgery was selected based on a qualitative assessment of ICG fluorescence to identify regions of diminished blood flow (Fig. 1a). However, with the introduction of Stryker's Pinpoint® fluorescence imaging system in June 2020, we transitioned to quantitative assessment of perfusion.

Pinpoint® System

Stryker received Food and Drug Administration approval for the SPY-PHI system in November 2019. The SPY-PHI is a handheld imaging device used for intraoperative fluorescence angiography and employs SPY-QP fluorescence assessment software. To visualize the vascular contrast, a single bolus of 12.5 mg of ICG dye was administered intravenously. Thereafter, the SPY-PHI captures and displays real-time fluorescence images, enabling visual assessment of blood flow and objective evaluation of tissue perfusion during surgical procedures. The Pinpoint® system was used to evaluate the blood supply at the planned anastomotic site relative to that at the antrum. We then compared blood perfusion between the planned anastomosis site and the gastric antrum, establishing the anastomosis line at a site demonstrating ≥50% of the antral perfusion. After quantitative evaluation of the ICG blood flow, the planned anastomotic site was adjusted (Fig. 1b, Supplemental Video 1). The evaluation method was determined chronologically by the introduction of the SPY-QP software. Prior to June 2022, all patients underwent conventional qualitative ICG assessment. Starting in June 2022, we implemented a standardized protocol for consecutive quantitative measurement for all patients. Notably, quantitative assessment was successfully

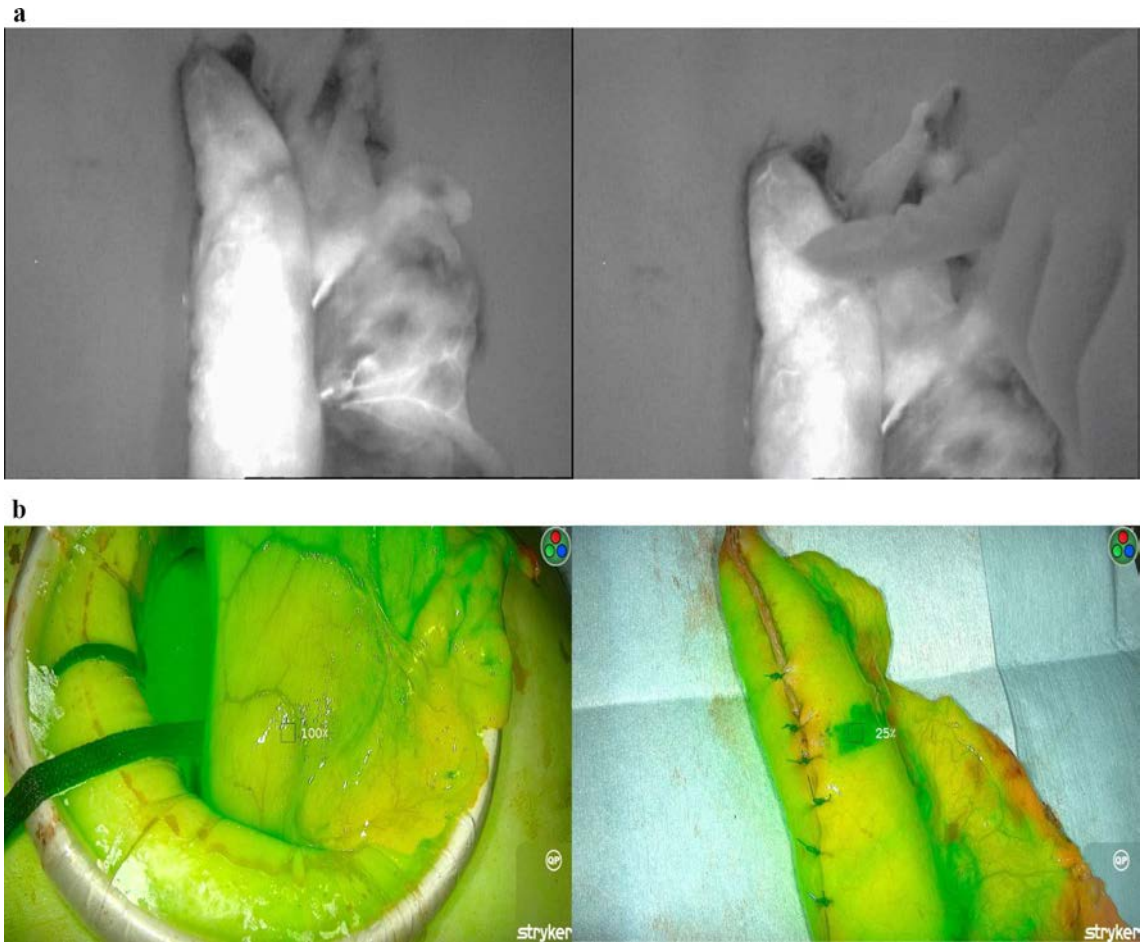


Fig. 1 Indocyanine green (ICG) blood flow evaluation in both groups. **a** A representative case assessed using the conventional method, in which the fluorescence signal was not quantified. The anastomotic site was selected based on subjective assessment of areas with poor blood flow. **b** A representative case assessed using the quantitative method. Prior to the ICG blood flow evaluation, both the planned anastomotic site and the last branch of the gastroepiploic vessels were marked. The fluorescence signal was quantified by using SPY-QP quantitative perfusion fluorescence imaging. In this case, although ICG fluorescence appeared to be adequate, the quantified relative value was only 20%. The planned anastomotic site was changed to a location in which the quantified relative value 50%. Anastomosis was still performed at the 50% site, and no postoperative anastomotic leakage was observed

completed in all cases during this period, with no patients excluded due to technical failures in data acquisition. This approach ensured that the selection of the evaluation method was not subject to surgeon bias but was dictated strictly by the timeline of technological implementation, establishing a historical cohort comparison.

Data Collection

All clinicopathological, surgical, and laboratory data were retrospectively extracted from the patients' medical records using the institutional clinical database. Body mass index, prognostic nutritional index, and American Society of Anesthesiologists physical status data were assessed preoperatively.[17,18] Postoperative complications occurring during hospitalization or within 30 days of surgery were retrospectively identified from patient records and were defined as grade II or higher according to the Clavien–Dindo classification.[19]

Anastomotic Leakage

Anastomotic leakage was defined and graded according to the Esophagectomy Complications Consensus Group (ECCG) criteria.[20] In this study, the diagnosis of anastomotic leakage was strictly confirmed by radiological findings, specifically the identification of contrast extravasation on an esophagogram using thin barium. Following the ECCG framework, we focused on clinically significant leaks requiring intervention: Type II (leaks requiring nonsurgical intervention, such as radiologic drainage, endoscopic therapy, or bedside opening of the cervical wound) and Type III (leaks requiring surgical intervention). These definitions correspond to Clavien–Dindo Grade ≥ II complications. In the current study, anastomotic leakage refers specifically to these ECCG Type II/III events.

Statistical Analyses

Data are presented as medians and interquartile ranges unless otherwise stated. We compared patient characteristics by using Fisher's exact test and the chi-square test. Multivariate analysis was performed to identify independent factors associated with a reduced risk of anastomotic leakage. Variables with a p-value < 0.1 in the univariate analysis, along with clinically essential factors, such as surgical approach, tumor location, and blood loss, were included in the multivariable model. We intentionally limited the number of independent variables to maintain model stability and avoid overfitting, strictly adhering to the events per variable principle. Nonsignificant background factors, including age and sex, were excluded. Furthermore, factors that caused statistical instability due to zero-event cells (e.g., PNI) or insufficient variance (e.g., ASA-PS) were also excluded to ensure the reliability and convergence of the estimated hazard ratios. Administration of NAC, the anastomotic method, reconstruction route, and fluorescence signal evaluation method use were included as covariates. Multicollinearity among all independent variables was assessed by using the variance inflation factor (VIF), with a threshold of 5.0. Statistical significance was set at $p < 0.05$. EZR ver. 1.37 software (Jichi University, Tochigi, Japan) was used for all statistical analyses.[21]

Results

The study included 127 patients, 72 of whom were classified into the conventional method group and 55 of whom were classified into the quantitative method group. Figure 2 shows the patient flow diagram of this study.

Table 1 summarizes the clinicopathological characteristics of the patients. The incidence of preoperative

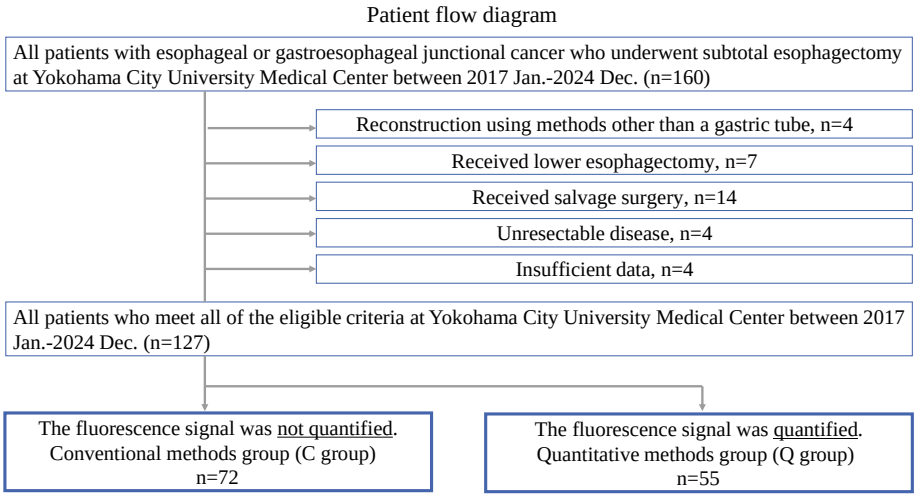


Fig. 2 Overall, 127 patients who underwent subtotal esophagectomy at our institution between January 2017 and December 2023 met the eligibility criteria. These patients were divided into two groups based on the method used for gastric tube blood flow assessment: 72 patients comprised the non-quantified, conventional group, and 55 patients comprised the quantified ICG fluorescence imaging group

Table 1 Association between fluorescence signal evaluation methods and clinicopathological features

	All patients ($n = 127$)	Fluorescence signal evaluation methods		p
		Conventional group ($n = 72$)	Quantitative group ($n = 55$)	
Age (years), median (IQR)	67 (36-84)	67 (36-83)	69 (39-84)	0.477
Sex				0.508
Female	26 (20.5%)	13 (18.1%)	13 (23.6%)	
Male	101 (79.5%)	59 (81.9%)	42 (76.4%)	
BMI (kg/m^2), median (IQR)	22 (15-47)	22 (15-32)	21 (15-47)	0.883
PNI, median (IQR)	49 (35-63)	50 (40-63)	47 (35-60)	0.073
ASA-PS				0.726
1	6 (4.7%)	5 (6.9%)	1 (1.8%)	
2	113 (89%)	63 (87.5%)	50 (90.9%)	
3	8 (6.3%)	4 (5.6%)	4 (7.3%)	
Main tumor location				0.750
Ut	16 (12.6%)	10 (13.9%)	6 (10.9%)	
Mt	65 (51.2%)	36 (50.0%)	29 (52.7%)	
Lt	31 (24.4%)	18 (25.0%)	13 (23.6%)	
Jz	15 (11.8%)	8 (11.1%)	7 (12.7%)	
Tumor size (mm), median (IQR)	50 (8-128)	50 (8-128)	50 (10-100)	0.595
Histological type				0.052
Squamous	107 (84.3%)	56 (77.8%)	51 (92.7%)	
Adenocarcinoma	17 (13.4%)	13 (18.1%)	4 (7.3%)	
Others	3 (2.3%)	3 (4.1%)	0 (0.0%)	
Clinical T factor*				0.419
T1	39 (30.7%)	24 (33.3%)	15 (27.3%)	
T2	22 (17.3%)	14 (13.9%)	8 (14.5%)	
T3r	57 (44.9%)	31 (43.1%)	26 (47.3%)	
T3br	9 (7.1%)	3 (4.2%)	6 (10.9%)	
Clinical N factor*				0.853
N0	58 (45.7%)	31 (43.1%)	27 (49.1%)	
N+	69 (54.3%)	41 (56.9%)	28 (50.9%)	
Clinical M factor*				1.000
M0	125 (98.4%)	71 (98.6%)	54 (98.2%)	
M1	2 (1.6%)	1 (1.4%)	1 (1.8%)	
Preoperative chemotherapy				**<0.001**
Absent	62 (48.8%)	44 (61.1%)	18 (32.7%)	
Present	65 (51.2%)	28 (38.9%)	37 (67.3%)	
Preoperative enteral nutrition				0.204
Absent	117 (92.1%)	69 (95.8%)	48 (87.3%)	
ED tube	4 (3.1%)	1 (1.4%)	3 (5.5%)	
PEG	6 (4.7%)	2 (2.8%)	4 (7.3%)	

Values in bold indicate statistical significance ($p < 0.05$)

IQR Interquartile range; *BMI* Body mass index; *PNI* Prognostic nutritional index; *ASA-PS* American Society of Anesthesiologists Physical Status; *ED tube* Elemental diet tube; *PEG* Percutaneous endoscopic gastrostomy

*Includes postoperative chemotherapy cases

chemotherapy was significantly higher in the quantitative method group than in the conventional method group ($p < 0.001$).

The annual trend analysis (Fig. 3) revealed that the anastomotic leakage rate peaked in 2020 at 46.2%. Following the standardized introduction of quantitative SPY-QP assessment in June 2022, the leakage rate showed a dramatic, stepwise reduction to 4.2% in 2022, and reached 0% in 2023. This trend remained stable at 4.2% in 2024, despite the increasing complexity of cases.

The operative findings are shown in Table 2. The quantitative method group had a significantly higher incidence of retrosternal reconstruction methods ($p = 0.046$) and Gambee/single-layer anastomoses ($p < 0.001$) than did the conventional method group. Intraoperative blood loss was significantly lower in the quantitative method than in the conventional method group ($p < 0.001$). Additionally, the median relative blood flow evaluation value at the planned anastomotic site relative to the gastric antrum was 67.5% (40–100%) in the quantitative methods group.

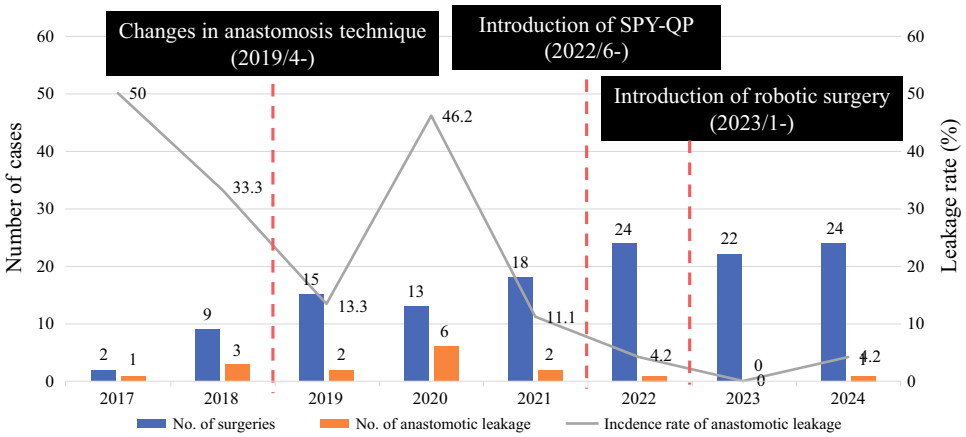


Fig. 3 Annual trends of surgical volume and anastomotic leakage rates. Bars represent the annual number of esophagectomies (blue) and cases of anastomotic leakage (orange). The gray line indicates the leakage rate. A sharp decline in the leakage rate is observed following the implementation of quantitative SPY-QP assessment in June 2020

Table 2 Association of fluorescence signal evaluation methods and operative findings

	All patients ($n = 127$)	Fluorescence signal evaluation methods		p
		Conventional group ($n = 72$)	Quantitative group ($n = 55$)	
Surgical procedure				0.505
Open	2 (1.6%)	2 (2.8%)	0 (0%)	
MIS	125 (98.4%)	70 (97.2%)	55 (100%)	
Reconstruction route				**0.046**
Posterior mediastinal	101 (79.5%)	62 (86.1%)	39 (70.9%)	
Retrosternal	26 (20.5%)	10 (13.9%)	16 (29.1%)	
Anastomosis method				**<0.001**
Albert–Lembert	13 (10.2%)	13 (18.1%)	0 (0%)	
Gambee/single-layer	114 (89.8%)	59 (81.9%)	55 (100%)	
Thoracic operation time (min), median (IQR)	217 (98-408)	222 (151-386)	210 (98-408)	0.763
Intraoperative blood loss (ml), median (IQR)	193 (0-2,746)	219 (0-2,746)	147 (0-1,053)	**<0.001**
Blood transfusion				1.000
Absent	123 (96.9%)	70 (97.2%)	53 (96.4%)	
Present	4 (3.1%)	2 (2.8%)	2 (3.6%)	
No. lymph nodes dissected, median (IQR)	43 (12-90)	44 (13-90)	43 (12-78)	0.734

Values in bold indicate statistical significance ($p < 0.05$)

MIS Minimally invasive surgery; *IQR* Interquartile range

Table 3 shows the morbidity and length of postoperative stay of patients in the two groups. The incidence of postoperative complications ($p < 0.001$), particularly of anastomotic leakage ($p < 0.001$), was significantly lower in the quantitative method than in the conventional method group. Additionally, the postoperative length of hospital stay was significantly shorter in the quantitative method than in the conventional method group ($p < 0.001$). Notably, the maximum stay in the C group reached 1443 days due to a single patient who developed a refractory esophagopulmonary fistula. This complication followed a partial resection of the right upper lobe, which was necessitated by a lung injury sustained during the dissection of dense adhesions. This outlier required exceptionally prolonged hospitalization primarily for social reasons and long-term rehabilitation rather than ongoing acute surgical management. Excluding this case, the clinical course was comparable between the groups.

Multivariate analysis, adjusted for covariates, including main tumor location, preoperative chemotherapy, lymph node dissection area, surgical approach, and intraoperative blood loss, confirmed that the conventional fluorescence evaluation method remained a significant independent risk factor for anastomotic leakage (hazard ratio (HR) 26; 95% confidence interval (CI) 2.36–286; $p = 0.008$) (Table 4). Conversely, the use of the retrosternal reconstruction route was also identified as an independent risk factor for increased leakage (HR 5.83; 95% CI 1.21–28.2; $p = 0.028$) (Table 4). All VIF values for the independent variables were <2 (range 1.22–1.92), indicating that multicollinearity, including that between the anastomotic technique and reconstruction route, did not significantly impact the stability of the regression model.

Discussion

In this study, we revealed the clinical utility of intraoperative SPY-QP-base quantitative perfusion fluorescence imaging for assessing gastric tube blood flow and reducing the anastomotic leakage rate in patients undergoing subtotal esophagectomy for primary esophageal or esophagogastric junction cancer. We demonstrated that this imaging modality allows surgeons to identify the most suitable anastomotic location objectively, contributing to reduced anastomotic leakage and shorter length of postoperative stay in our patients. In multivariate analysis, use of this assessment approach was the single independent predictor of the absence of postoperative anastomotic leakage.

Table 3 Association of fluorescence signal evaluation methods and postoperative findings

	All patients ($n = 127$)	Fluorescence signal evaluation methods		p
		Conventional group ($n = 72$)	Quantitative group ($n = 55$)	
Postoperative complication (CD ≥ Gr II)				**<0.001**
Absent	73 (57.5%)	33 (45.8%)	40 (72.7%)	
Present	54 (42.5%)	39 (54.2%)	15 (27.3%)	
Anastomotic leakage				**<0.001**
Absent	111 (87.4%)	57 (79.2%)	54 (98.2%)	
Present	16 (12.6%)	15 (20.8%)	1 (1.8%)	
Recurrent laryngeal nerve palsy				0.512
Absent	117 (92.1%)	65 (90.3%)	52 (94.5%)	
Present	10 (7.9%)	7 (9.7%)	3 (5.5%)	
Pneumonia				0.512
Absent	117 (92.1%)	65 (90.3%)	52 (94.5%)	
Present	10 (7.9%)	7 (9.7%)	3 (5.5%)	
SSI				0.512
Absent	117 (92.1%)	65 (90.3%)	52 (94.5%)	
Present	10 (7.9%)	7 (9.7%)	3 (5.5%)	
Postoperative hospital stay (days), median (IQR)	16 (11-1,443)	20 (11-1,443)	15 (12-53)	**<0.001**

Values in bold indicate statistical significance ($p < 0.05$)

One patient in the conventional group had an exceptionally prolonged hospital stay (1,443 days) due to severe postoperative complications, including a refractory esophagopulmonary fistula following combined partial resection of the right upper lobe. This case required extended institutional care primarily for social reasons and long-term rehabilitation rather than ongoing acute surgical management

CD Clavien–Dindo classification; *SSI* Surgical site infection; *IQR* Interquartile range

Table 4 Univariate and multivariate analyses of the clinicopathological and operative features related to anastomotic leakage

	No. patients	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*	HR	95% CI	*p*
Main tumor location			0.432			0.138	
Mt/Lt/Jz	111	1			1		
Ut	16	1.74	0.437–6.93		3.65	0.659–20.2	
Preoperative chemotherapy			0.247			0.937	
Absent	62	1			1		
Present	65	0.529	0.18–1.56		1.06	0.255–4.39	
Lymph node dissection (area)			0.924			0.836	
2	49	1			1		
3	78	1.05	0.357–3.11		0.868	0.226–3.33	
Anastomosis method			**0.007**			0.292	
Gambee/single-layer	114	1			1		
Albert–Lembert	13	5.85	0.889–21		2.79	0.413–18.9	
Reconstruction route			0.079			**0.028**	
Posterior mediastinal	101	1			1		
Retrosternal	26	2.73	1.252–8.38		5.83	1.21–28.2	
Intraoperative blood loss (ml)			0.617			0.301	
<193	63	1			1		
≥193	64	1.31	0.456–3.76		0.475	0.116–1.95	
Fluorescence signal evaluation methods			**0.012**			**0.008**	
Quantitative method	55	1			1		
Conventional method	72	14.2	1.81–111		26	2.36–286	

Values in bold indicate statistical significance ($p < 0.05$)

HR Hazard ratio; *CI* Confidence interval; *PNI* Prognostic nutritional index; *ASA-PS* American Society of Anesthesiologists physical status

Anastomotic leakage is one of the most serious complications of esophageal cancer surgery. Various surgical and patient factors are recognized as risk factors, including the patient's preoperative nutritional status, the anastomotic site and technique employed, insufficient blood supply to the reconstructed organ, anastomotic tension, and the reconstruction route used.[22,23] Notably, inadequate blood flow to the reconstructed organ is considered as the primary risk factor for anastomotic leakage.

Although the utility of conventional qualitative ICG fluorescence imaging has frequently been reported, its subjective visual assessment poses challenges in achieving a consistent evaluation.[8–10] Furthermore, while recent reports have described quantitative evaluation methods, the requirement for analyzing images captured over several minutes with dedicated software, either intraoperatively or postoperatively, to generate time–fluorescence intensity curves has limited their adoption.[24–29]

SPY-PHI is a portable imaging device that addresses the abovementioned challenges, enabling real-time and objective blood flow assessment using the SPY-QP fluorescence evaluation software. This software quantifies blood flow by capturing time-dependent changes in fluorescence intensity and by calculating parameters, such as time to peak, maximum fluorescence intensity, and fluorescence arrival time. As the SPY-PHI device is portable, it can be easily operated in the confined space of the operating room, facilitating rapid decision-making without the need for a complex setup or lengthy image processing. By acquiring and displaying real-time fluorescence images within 1 min after intravenous ICG administration, SPY-PHI allows rapid, simple, visual, and objective assessment of intraoperative blood flow and tissue perfusion.

Our results suggest that SPY-PHI-guided blood flow assessment appears to reduce the incidence of postoperative complications, particularly anastomotic leakage, significantly as compared with conventional methods. As shown in a representative case in Fig. 1b, the SPY-QP blood flow assessment revealed insufficient perfusion, although the blood flow appeared visually adequate on the system. Therefore, using SPY-QP software for blood flow evaluation provides a more accurate and objective assessment of tissue perfusion. This offers the advantage of objective decision-making, rather than relying on a subjective visual assessment based on the surgeon's experience and intuition, and can contribute to provision of consistent medical care.

Recent studies have increasingly emphasized the importance of quantitative ICG assessment to overcome the

limitations of subjective visual evaluation.[30] For instance, Ishikawa et al. reported that the relative blood flow ratio at 5 cm from the gastric tube tip was significantly lower in patients with anastomotic leakage compared to those without (35.9% vs. 44.9%).[31] Based on these findings, we established a more conservative threshold of 50% relative to antral perfusion. By setting this higher cutoff, we aimed to incorporate a robust safety margin that compensates for unpredictable postoperative factors, such as local tissue edema or systemic hemodynamic changes. Notably, in our single case of leakage in the quantitative group, the perfusion value was actually >50%. This suggests that while arterial inflow is a primary determinant of healing, other factors—such as venous congestion, mechanical tension on the anastomosis, or patient-specific comorbidities—may also play a critical role in the multifactorial nature of anastomotic failure.

The retrosternal reconstruction route carries a higher risk of anastomotic leakage than does the posterior mediastinal route.[32] Tables 1 and 4 showed that the retrosternal route was frequently used in the quantitative group. Moreover, multivariate analysis identified this route as an independent risk factor for anastomotic leakage. Despite the frequent use of the retrosternal route, with its concomitant increased risk for anastomotic leakage, our findings indicated that intraoperative SPY-QP quantitative perfusion fluorescence imaging helped to reduce the incidence of postoperative anastomotic leakage. This finding further provides evidence that SPY-QP-based assessment can contribute to lowering the rate of anastomotic leakage after esophagectomy.

Concerns regarding this method include the potential variability in fluorescence intensity and distribution arising from differences in ICG dosage or administration timing, as well as the influence of tissue thickness and blood flow status on fluorescence transparency and the detected intensity. Furthermore, subtle variations in the surgeon's observation angle and distance can affect visual assessment, necessitating the use of standardized techniques.[33] Additionally, even if the SPY-QP software identifies an optimal perfusion site, it does not necessarily guarantee that safe anastomosis can be performed at that location, particularly if the distal gastric tube cannot be sufficiently elevated to reach the ideal site. Under these circumstances, Kocher mobilization, further mobilization of the transverse mesocolon, and dissection of physiological adhesions between the stomach and head of the pancreas are required to mobilize the gastric tube more extensively to elevate it as much as possible. Nevertheless, anastomosis at a low level, near the mediastinum, may be necessary, in which case the handsewn technique may be challenging. Under these circumstances, assessment of blood flow to the reconstructed gastric tube is crucial, which emphasizes the importance of achieving high reproducibility in real-time blood flow evaluation.

It is important to acknowledge that practice evolution, including the refinement of minimally invasive techniques and the accumulation of institutional experience, may account for part of the outcome improvement observed in the quantitative group. However, we contend that the improved outcomes were not merely a reflection of a traditional surgical learning curve. As demonstrated in Fig. 3, the precipitous drop in the anastomotic leakage rate occurred specifically following the implementation of SPY-QP, rather than as a result of a gradual, linear decline over several years. Notably, the leakage rate remained high (46.2%) in 2020 despite the earlier adoption of the modified Gambee suture technique in 2019. This temporal decoupling between surgical technique refinement and the sudden improvement in outcomes further supports the specific, transformative impact of quantitative perfusion assessment on surgical safety.

This study had some limitations. First, because this was a single-center retrospective analysis involving a limited patient cohort, the influence of incidental confounding factors could not be excluded. Therefore, caution should be exercised when generalizing these results. Second, we had implemented various strategies for esophageal cancer surgery over the years. The choice of the anastomotic route and method is an example of this variation. Anastomotic techniques have also evolved over time. Differences in blood loss may be related to surgical advances. The use of preoperative chemotherapy differed between the two groups due to changes in the standard treatment. These historical and technical shifts may thus have influenced patient outcomes. Third, the optimal cutoff values for quantitative perfusion fluorescence assessment using SPY-QP software have not yet been defined. Establishing optimal cutoff values linking specific fluorescence intensities or their rates of change to the risk of anastomotic leakage is anticipated to allow more personalized intraoperative decision-making. Although the optimal physiological threshold remains a subject of debate, the clinical utility of our approach lies in shifting from empirical judgment to a standardized, reproducible metric. Future large-scale studies utilizing ROC curve analyses are essential to further refine these quantitative benchmarks. Finally, this study has statistical limitations. The results of the multivariable analysis—particularly the markedly high hazard ratio and wide confidence intervals for the quantitative method—should be interpreted with caution. These values likely reflect statistical instability due to the low number of events in the quantitative group, suggesting a potential risk of model overfitting. Therefore, our statistical findings should be regarded as exploratory rather than definitive, serving as a foundational basis for future large-scale prospective validation studies. Further prospective studies are required to validate and generalize these findings.

Conclusions

The findings of this study support the potential clinical utility of quantitative fluorescence signal assessment of gastric tube blood flow using SPY-QP software in identifying optimal anastomotic sites, which may contribute to a reduction in the incidence of anastomotic leakage after performance of esophagectomy and gastric tube reconstruction for esophageal or esophagogastric junction cancers. Further case accumulation and multi-institutional prospective studies are essential to validate and generalize these findings.

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