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REVIEW ARTICLE

# Indocyanine green for the prevention of anastomotic leaks following esophagectomy: a meta-analysis

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## Abstract

**Background** Intraoperative evaluation with fluorescence angiography using indocyanine green (ICG) offers a dynamic assessment of gastric conduit perfusion and can guide anastomotic site selection during an esophagectomy. This study aims to evaluate the predictive value of ICG for the prevention of anastomotic leak following esophagectomy.

**Methods** A comprehensive search of electronic databases using the search terms "indocyanine/fluorescence" AND esophagectomy was completed to include all English articles published between January 1946 and 2018. Articles were selected by two independent reviewers. The quality of included studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS) instrument.

**Results** Seventeen studies were included for meta-analysis after screening and exclusions. The pooled anastomotic leak rate when ICG was used was found to be 10%. When limited to studies without intraoperative modifications, the pooled sensitivity, specificity, and diagnostic odds ratio were 0.78 (95% CI 0.52–0.94; $p=0.089$), 0.74 (95% CI 0.61–0.84; $p=0.012$), and 8.94 (95% CI 1.24–64.21; $p=0.184$), respectively. Six trials compared ICG with an intraoperative intervention to improve perfusion to no ICG. ICG with intervention was found to have a risk reduction of 69% (OR 0.31, 95% CI 0.15–0.63).

**Conclusions** In non-randomized trials, the use of ICG as an intraoperative tool for visualizing microvascular perfusion and conduit site selection to decrease anastomotic leaks is promising. However, poor data quality and heterogeneity in reported variables limits generalizability of findings. Randomized, multi-center trials are needed to account for independent risk factors for leak rates and to better elucidate the impact of ICG in predicting and preventing anastomotic leaks.

**Keywords** Esophageal surgery · Esophageal cancer · Anastomotic leak · Perfusion · Imaging · Meta-analysis

Anastomotic leak following esophageal resection continues to be a source of considerable morbidity and mortality [1]. In high volume centers, leak rates range from 5 to 40% [2–5] despite surgical advances and preoperative optimization. Ischemia of the conduit is felt to be the single most important determinant of anastomotic disruption [6, 7].

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There are many factors thought to influence the integrity of the conduit and have been summarized in Fig. 1 [8, 9]. Unique to the esophageal anastomoses is its tenuous blood supply, particularly at the tip of the conduit where the gastroepiploic artery often does not reach, making it vulnerable to ischemia relative to other gastrointestinal anastomoses [10]. Thus, it becomes important for esophageal anastomoses to factor in and ameliorate modifiable risk factors for poor perfusion.

At present, perfusion to the gastric conduit is subjectively assessed by way of color, temperature, and pulsation of vessels; however, these parameters do not reliably correspond to perfusion [11–13]. Instead, objective, intraoperative measures have been sought to better evaluate the adequacy of perfusion and guide site selection. Laser Doppler flowmetry and tissue pulse oximetry emerged as some of the first tools to detect microperfusion; however, lack of reproducibility

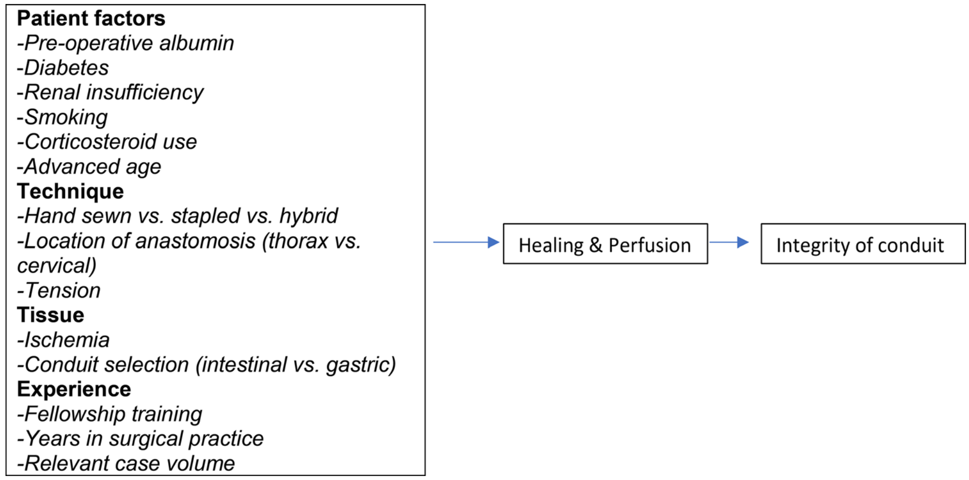


**Fig. 1** Factors impacting the integrity of the reconstructed conduit following esophagectomy

and poor correlation between blood flow assessment and anastomotic leakage has discouraged its use [14–16]. In the last decade, there has been growing interest in the use of indocyanine green (ICG) fluorescence angiography for intra-operative evaluation of gastrointestinal anastomoses. ICG is an amphiphilic, tricarbocyanine iodide dye that can be safely injected intravenously [17]. Its fluorescent properties are the result of molecular excitation brought about by use of a laser or near-infrared light at wavelengths exceeding 820 nm [18]. It can then be detected using specifically designed scopes or cameras. ICG is FDA approved in neurosurgical research and cardiac vessel angiography [18], with ongoing trials to discern its utility in plastic surgery and general surgery [19–22]. Multimodal studies are currently underway in colorectal surgery where fluorescent imaging is being evaluated for its role in tumor localization in emergent situations, sentinel lymph node chain identification, and lymphatic mapping to enable more accurate oncologic resection [23, 24].

ICG fluorescence angiography for esophagectomy and conduit reconstruction is actively being studied. The objective of this study is to systematically review the current literature to determine the value of ICG in predicting and preventing anastomotic leaks.

## Methods

### Search strategy

A comprehensive search of electronic databases MEDLINE, EMBASE, SCOPUS, Web of Science, and the Cochrane Library using the search terms "indocyanine/fluorescence" AND esophagectomy was completed to include all English articles published between January 1, 1946 and January 1, 2018. The reference lists of included articles were also reviewed to identify articles missed in the primary search.

### Inclusion and exclusion criteria

Articles were selected by two independent reviewers (FL, JD) based on the following major inclusion criteria: (1) esophagectomy with gastric conduit reconstruction; (2) use of fluorescence angiography with indocyanine green to assess perfusion; (3) age ≥ 18 years; (4) sufficient outcome data for the calculation of leak rates; and (5) sample size ≥ 5.

### Outcome of interest

The primary outcome of interest was anastomotic leak, identified clinically, radiologically, or endoscopically.

### Data extraction and quality evaluation

The following data were extracted from the selected studies: first author, year of publication, country of origin, sample size, participants' characteristics, ICG concentrations, injected volumes, ICG-related adverse reactions, number of patients with successful fluorescence imaging, measures of test performance for ICG angiography including true-positive, true-negative, and false-negative results as it relates to anastomotic leaks. Data extraction was performed by one reviewer (FL) and accuracy was ensured by a second reviewer (JD).

The quality of each study was quantified using the Methodological Index for Non-Randomized Studies tool (MINORS, score from 0 to 24). MINORS is a 12-point validated tool designed specifically to evaluate the methodological quality of non-randomized surgical trials, whether comparative or non-comparative. For comparative trials, the ideal score is 24 and for non-comparative studies, it is 16 [25]. Any discrepancies between the reviewers were discussed and resolved by consensus.

### Statistical analysis

Descriptive statistics and tabulation frequencies were used to summarize the articles. The predictive value of ICG was characterized in terms of detection rate, sensitivity, specificity, diagnostic odds ratio (DOR), the summary receiver operator characteristic (SROC) curve, the area under the curve (AUC), and the Q* index. The closer the AUC is to 1.0, the better the diagnostic method. The Q* index is a statistical value defined by the point on the SROC curve where sensitivity and specificity are equal. The Mantel–Haenszel random-effects model was used to obtain the summarized detection rate, DOR, sensitivity, and specificity, considering the differences in patient characteristics, technical details, and operators' experiences. The Q* index was subsequently produced from the SROC curve of all the included studies.

The statistical heterogeneity among studies was evaluated using Cochran's Q statistic and $p$ values. Heterogeneity was considered significant if $p < 0.05$. The sensitivity and specificity of each study was calculated by $2 \times 2$ contingency tables assessing leak rates in good and poor perfusion.

Meta-analysis was conducted to compare ICG with intraoperative, perfusion-improving interventions to no ICG. The estimated effects were calculated using the Revman 5.3 obtained from the Cochrane website [26]. Included studies were then tested for heterogeneity using the $X^2$ test with significance set at $p < 0.10$ and the amount of heterogeneity quantified by the $I^2$ statistic: (1) low at 25%; (2) moderate at 50; and (3) high at 75% [27].

## Results

Literature search identified 228 potential studies. After removal of duplicate studies, languages other than English, animal studies, conference proceedings, and review articles, 22 studies remained for full-text review (Fig. 2). After full-text review, an additional 5 articles were excluded on the basis of relevance, duplicate data, study design (case report), and inclusion of adjuncts such as flap use for improved blood supply to the conduit, leaving 17 articles.

### Study characteristics

Included studies were published between 2011 and 2017. Nine studies were published in Japan, six in the USA, and two in Germany. All were single center, observational studies: 9 included a control group, 9 were prospective cohort studies, and 8 were retrospective cohort studies. Only six studies made explicit mention of intraoperative modifications based on ICG findings. These ranged from resection of devitalized segments to the addition of vessel anastomoses to improve perfusion (Table 1).

ICG was assessed using one of three imaging modalities: PhotoDynamic Eye (PDE, Hamamatsu photonics, Japan), SPY (Novadaq, Ontario, Canada), and Hyper Eye Medical System (HEMS, Mizuho Ikakogyo Co., Ltd., Tokyo, Japan). All imaging technology modalities are commercially available, and no prototype devices were used.

### Incident leak rate

The number of participants totaled 1067, 436 of which made up the control group. When all studies were considered, the incident leak rate was 10.8%. When restricted to the six studies that specified an intraoperative intervention to correct for poor ICG-assessed perfusion, the incident leak rate was 5.7% (15/261), compared to an incident leak rate among the control group of 22.9% (89/388) (Table 2).

### Predictive utility of ICG

In the studies presented, ICG is used as an intraoperative tool for mitigation of anastomotic leaks based on the premise that anastomoses placed in adequately perfused areas are less likely to leak. With this in mind, the sensitivity of the tool is most accurately reflected in studies that made no intraoperative changes based on ICG findings. As such, a leak in an area of poor perfusion would constitute a true positive. Similarly, a true negative would be the absence of leak in an area of good perfusion. Using these definitions, the pooled sensitivity and specificity of ICG for predicting postoperative leak were 0.78 (0.52–0.94; $p = 0.0889$) and 0.74 (0.61–0.84; $p = 0.0116$), respectively. The DOR was 8.94 (1.24–64.21; $p = 0.1841$).

The Mantel Haenszel model was used to generate the absolute risk reduction (ARR) associated with ICG. The model was limited to comparative studies reporting intraoperative interventions (six studies) with the understanding that this cohort most accurately reflects the added advantage offered by ICG. The ARR with ICG was significant and was found to be 69% (OR 0.31, 95% CI 0.15–0.63, $p = 0.001$) with low heterogeneity among studies ($I^2 = 17\%$, $p = 0.31$) (Fig. 3).

### Study quality assessment

MINORS criteria were used to evaluate the quality of included studies. All studies were rated as being of poor quality given their observational study design, the absence of control groups in 10 of 16 studies, omission of sample size calculations, and inconsistently and poorly defined endpoints. It should also be noted that among studies with

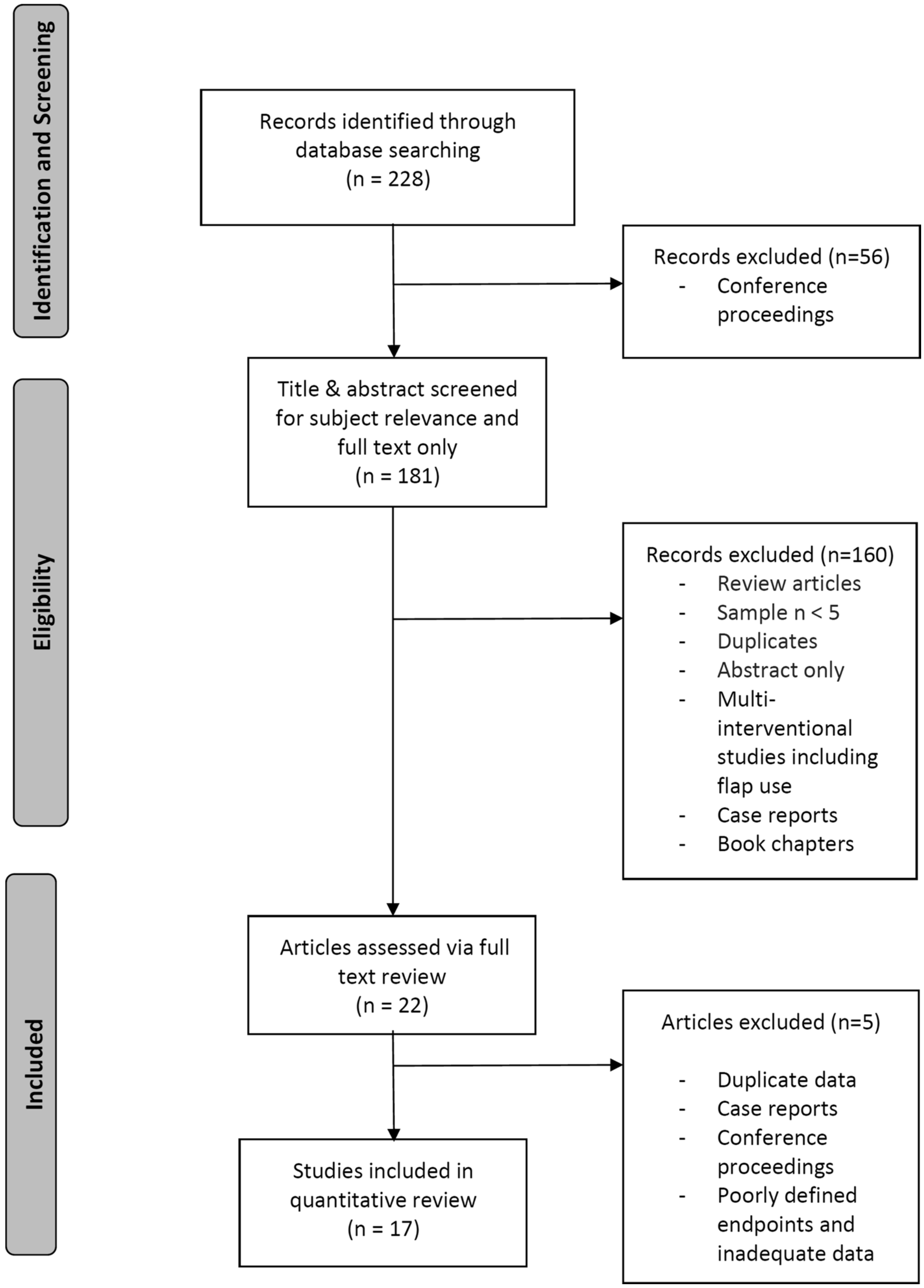


**Fig. 2** PRISMA flow diagram

a control group, conduit viability in the controls was determined based on subjective evaluation of pulse, color, and peristalsis (Table 3).

## Discussion

This is the most up-to-date meta-analysis focused on the use of ICG for the prevention of anastomotic leaks following esophagectomy. In our meta-analysis, we identified 17 studies, comprising 1067 cases, with a pooled leak rate of 10.8%. This implies that just over 1 in 10 people in which ICG was used for evaluation of conduit perfusion experienced a leak, a rate that minimally differs from the average expected leak rate in the absence of ICG (12.3% in cervical anastomoses, 9.3% in thoracic anastomoses) [2, 8]. Among studies with a control group and intraoperative modification for poor perfusion, the impact of ICG is better elucidated, demonstrating an absolute risk reduction of 69%. This is a promising finding, with the potential to obviate the significant morbidity and mortality known to accompany anastomotic leaks.

**Table 1** Summary of included studies

| Study | Enrollment period | Country | Design | Sample size (M:F) | Age range | Operative procedure | Near-infrared system |
|---|---|---|---|---|---|---|---|
| Campbell et al. [28] | 2008 | Japan | Prospective | 40 (32:8) | 49–81 | Gastric conduit in 36, jejunal graft + gastric tube in 1, free jejunal graft in 2, ileocolonic graft in 1 | PDE |
| Dalton et al. [29] | 2014–2016 | USA | Retrospective | 40 (32:8) | 50–70 | Gastric conduit with end-to-end stapled anastomosis | SPY |
| Karampinis et al. [30] | 2010–2016 | Germany | Retrospective | 90 (65:23) | 60–74 | Gastric conduit with circular stapler for distal esophageal cancer or cervical end-to-end hand sewn | PinPoint System |
| Kitagawa et al. [31] | 2011–2017 | Japan | Retrospective | 72 (57:15) | 59–73 | Gastric conduit | HEMS |
| Koyanagi et al. [32] | Jan 2014–Oct 2015 | Japan | Prospective | 40 (34:6) | 26–82 | Gastric conduit with cervical anastomosis (stapled/hand sewn) | PDE |
| Kubota et al. [33] | Sept 2011–March 2015 | Japan | Retrospective | 51 (41:10) | 43–81 | Gastric conduit with cervical anastomosis using a circular stapler | HEMS |
| Kumagai et al. [34] | Sept 2007–Feb 2013 | USA | Retrospective | 90 (74:16) | 22–81 | Gastric conduit with thoracic anastomosis using a circular stapler | SPY |
| Murawa et al. [35] | June 2010–May 2011 | Japan | Prospective | 5 (4:1) | 64–71 | Gastric conduit in 4 cases and ileocecal in 1 case | HEMS |
| Noma et al. [36] | 2010–2016 | Japan | Retrospective | 285(244: 41) | 57–73 | Gastric conduit and Anastomosis with end-to-end or end-to-side anastomosis (stapled/hand sewn) | PDE |
| Ohi et al. [37] | n.r | USA | Prospective | 5 (3:2) | 56–70 | Gastric conduit with stapled side-to-side anastomosis | IMAGE1 STORZ |
| Pacheco et al. [38] | June 2010–May 2011 | Japan | Prospective | 20 (16:4) | 50–79 | Gastric conduit with cervical anastomosis | PDE |
| Rino et al. [39] | 2009–2010 | Germany | Prospective | 15 (13:2) | 54–74 | Gastric conduit with hand-sewn cervical anastomosis | ICVIEW |
| Sarkaria et al. [40] | Jan 2000–Dec 2015 | Japan | Retrospective | 120 (101:19) | IQR 63–74 | Gastric conduit with cervical anastomosis | PDE |
| Schlottmann et al. [41] | 2009 | Japan | Prospective | 33 (29:4) | Mean 67.8 | Gastric conduit with stapled anastomosis | PDE |
| Shamida et al. [42] | 2010–2011 | USA | Retrospective | 11 | 42–72 | Gastric conduit with hand-sewn anastomosis | SPY |
| Yukaya et al. [43] | 2012–2013 | USA | Prospective | 42 (22:20) | 37–76 | Robotic-assisted minimally invasive esophagectomy | SPY |
| Zehetner et al. [44] | 2008–2011 | USA | Prospective | 150 (125:25) | 57–74 | Gastric conduit with use of Doppler in addition to ICG | SPY |

Indocyanine green was first introduced in the late 1950s as a means of measuring hepatic function [45]; however, its fluorescent properties have only recently been used for intraoperative evaluation of tissue perfusion [45–47]. In the setting of anastomotic assessment, ICG has gained widespread attention for its relative ease of use, low cost, and good safety profile relative to other intraoperative modalities. It has also been shown to be compatible in open, laparoscopic, and robotic-assisted procedures, providing surgeons with versatility of use.

The present meta-analysis highlights the role of ICG in ameliorating the risk of anastomotic leak following

**Table 2** Anastomotic leak stratified by adequacy of perfusion and related interventions

| Study | Definition of leak | Adequacy of perfusion | *n* | # of leaks | Leak in good perfusion | Leak in poor perfusion | No leak in good perfusion | No leak in poor perfusion | Intraoperative intervention for poor ICG perfusion |
|---|---|---|---|---|---|---|---|---|---|
| Campbell et al. [28] | Clinical, drain findings, radiological | n.r | 30 | 0 | 0 | 0 | 30 | 0 | Y |
| Dalton et al. [29] | n.r | Control: pulse, color, peristalsis<br>Experimental: marking stitch based on fluorescence | 20 | 2 | 2 | 0 | 18 | 0 | Resection of poorly perfused segment |
| Karampinis et al. [30] | n.r | "Optizone" based on fluorescence | 35 | 3 | 1 | 2 | 32 | 0 | Resection of poorly perfused gastric tip |
| Kitagawa et al. [31]* | Endoscopy, radiological | Experimental: good: perfused to top of GT; moderate: perfused to anastomosis; poor: weak fluorescence pre- anastomosis** | 46 | 3 | 3 | 0 | 42 | 4 | End to end in poor perfusion; end to side for insufficient length |
| Kitagawa et al. [31]* | Endoscopy, radiological | "Control": definitions for perfusion sufficiency not provided | 26 | 4 | n.r | n.r | n.r | n.r | n.r |
| Koyanagi et al. [32] | Clinical, radiological | n.r | 40 | 7 | 0 | 7 | 25 | 8 | None |
| Kubota et al. [33] | n.r | n.r | 5 | 0 | 0 | 0 | 5 | 0 | None |
| Kumagai et al. [34] | n.r | Time to perfusion of gastric tip | 20 | 0 | 0 | 0 | 9 | 11 | None |
| Murawa et al. [35] | n.r | n.r | 15 | 1 | 1 | 0 | 10 | 4 | End-to-side anastomosis in poor perfusion |
| Noma et al. [36] | Clinical, radiological | Perfusion within 30 s— adequate. Distal to 30 s—poor | 71 | 6 | 6 | 0 | 64 | 1 | Free jejunal transfer, Roux-en-y |
| Ohi et al. [37] | Clinical | Rapid and slow perfusion—adequate vs. low perfusion | 59 | 1 | 0 | 1 | 53 | 5 | End-to-end hand-sewn anastomosis between short gastric vein and neck vessels in poor perfusion |
| Pacheco et al. [38] | Clinical, esophagram | n.r | 11 | 2 | 1 | 1 | 10 | 0 | None |
| Rino et al. [39] | n.r | n.r | 33 | 5 | 6 | 0 | 28 | 0 | None |
| Sarkaria et al. [40] | n.r | n.r | 30 | 2 | 2 | 0 | 28 | 0 | Addition of venous drainage and/or arterial anastomosis |
| Schlottmann et al. [41] | n.r | n.r | 5 | 0 | 0 | 0 | 5 | 0 | Resection of devitalized segments |

**Table 2** (continued)

| Study | Definition of leak | Adequacy of perfusion | $n$ | # of leaks | Leak in good perfusion | Leak in poor perfusion | No leak in good perfusion | No leak in poor perfusion | Intraoperative intervention for poor ICG perfusion |
|---|---|---|---|---|---|---|---|---|---|
| Shamida et al. [42] | n.r | Perfusion within 1 min with retrospective microcirculation assessment | 40 | 3 | 0 | 3 | 22 | 15 | Additional drainage or arterial anastomosis based on sufficiency of microvascular networks among GTs with weak or no bleeding post cutting of gastric vein |
| Yukaya et al. [43] | Clinical, esophagram | Time to perfusion—normal, delayed inflow, delayed outflow | 27 | 9 | 3 | 6 | 10 | 8 | None |
| Zehetner et al. [44] | Upper endoscopy, esophagram | Transition point based on fluorescence | 144† | 24 | 2 | 22 | 93 | 27 | No anastomosis in 6 patients |
| Total | | | 654 | 69 | 28 | 42 | 506 | 83 | |

Clinical: leukocytosis, fever, redness of the wound, swelling of the wound, and pus discharge from the wound

Radiological: Mediastinitis, empyema on CT, swallowing study (barium, esophagram)

Drain findings: elevated amylase

*GT* gastric tube, *HEMS* Hyper Eye Medical System, *PDE* PhotoDynamic Eye

*No true control group. Experimental group involved ICG before and after creating GT and "control" group performed ICG only after GT creation. Groups are presented separately

**Moderate and good classified as good perfusion; poor as poor perfusion

†Six cases omitted as no anastomosis performed secondary to poorly perfused conduit

| Study or Subgroup | ICG intervention Events | ICG intervention Total | No ICG intervention Events | No ICG intervention Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Campbell 2015 | 0 | 30 | 12 | 60 | 6.0% | 0.06 [0.00, 1.11] |
| Dalton 2017 | 2 | 20 | 0 | 20 | 5.2% | 5.54 [0.25, 123.08] |
| Karampinis 2017 | 3 | 35 | 10 | 55 | 21.7% | 0.42 [0.11, 1.66] |
| Kitagawa 2017 | 3 | 46 | 4 | 26 | 17.2% | 0.38 [0.08, 1.87] |
| Noma 2017 | 6 | 71 | 54 | 214 | 39.3% | 0.27 [0.11, 0.67] |
| Ohi 2017 | 1 | 59 | 9 | 61 | 10.6% | 0.10 [0.01, 0.81] |
| **Total (95% CI)** | | **261** | | **436** | **100.0%** | **0.31 [0.15, 0.63]** |
| Total events | 15 | | 89 | | | |

Heterogeneity: Tau² = 0.14; Chi² = 5.99, df = 5 (P = 0.31); I² = 17%
Test for overall effect: Z = 3.21 (P = 0.001)

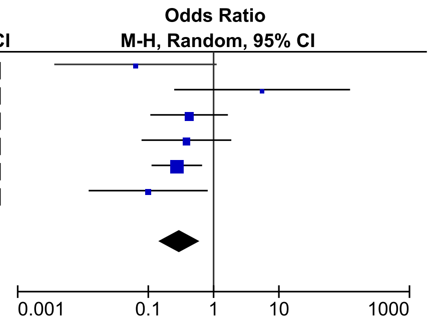


**Fig. 3** Absolute risk reduction afforded by ICG provoked interventions, using the Mantel Haenszel Model

esophagectomy as demonstrated by a significant reduction in leak rate. Previous meta-analyses on ICG and esophagectomy either do not include an absolute risk reduction or use a composite measure that does not discern between patients undergoing interventions related to ICG findings and those who do not. By limiting our analysis to patients who had perfusion-improving interventions, we are able to show the impact that ICG can have on reducing anastomotic failure. The specific interventions and their associated impact on perfusion have not yet been studied but warrant further investigation.

Despite the theoretical potential of ICG for preventing anastomotic leak, its value in evaluating esophageal anastomoses remains controversial. The findings of this meta-analysis draw attention to major flaws in data quality among the studies supporting its use. First, all studies were observational cohort studies with small sample sizes and none employed a sample size calculation to determine the minimum number of patients required to detect an effect. This limits both power and generalizability of their findings. Second, timing of intraoperative assessment of the gastric conduit differed across studies. Specifically, some studies used ICG to guide anastomotic site selection or to judge the need for additional vascular anastomoses, while others evaluated the conduit following anastomotic creation. With the latter, it would be difficult to draw conclusions regarding the utility of ICG as perfusion prior to anastomosis is not known. Third and most notably, the delineation between "good" and "poor" perfusion was specified only in one study where an arbitrary cutoff of 75% was used. Though objective measures exist, they are inconsistently used, making comparison across studies impossible and subject to inter-observer variability [32, 43]. Further, without this information, we cannot discern the minimum level of perfusion required to support the anastomosis, limiting informed application of this tool in the future. Given that different operative interventions (either altering the location of anastomosis or the use of vascular anastomoses) were used in response to the finding of poor perfusion, it is difficult to conclude what the ideal approach is, especially since the two strategies vary greatly in their technical complexity. Finally, the outcome variable was not uniformly defined nor assessed. Some studies relied on clinical evidence of leak, while others performed esophagrams prior to oral intake, reflecting known variations in clinic practice. These concerns culminated in low MINORS scores for all included studies.

In addition to limitations on available data, a discussion around interpretation of ICG findings is warranted. As mentioned above, there is no operational definition for adequate perfusion of the gastric conduit. With the exception of one study that used 75% as a cutoff, the studies included in this meta-analysis relied on subjective assessment of the arcade, with intensity and time as their guide. The lack of objective quantification is of critical importance as we consider the practical and routinized application of this tool. In other settings, efforts are underway to create more specific criteria around perfusion adequacy. For example, Moyer et al. generated a Gaussian distribution for flap perfusion using Spy-Q computer software, which designates a perfusion percentage score based on emission. It was determined that skin with 25% or less perfusion (perfusion score, <=25%) was not viable 90% of the time, and areas with greater than or equal to 45% perfusion would survive 98% of the time [48]. SPY technology has also been used in colorectal surgery; however, specific cutoffs have not been established [49]. This level of specificity can increase the clinical utility and accuracy of ICG.

It is also important to consider aspects of the procedure that may not directly relate to perfusion but nonetheless compromise conduit viability. As seen in this study, leaks were present even in well-perfused areas. Tension, distal (pyloric) obstruction, and technique/proficiency in sewing/stapling the anastomosis are all well-known surgical principles for any anastomosis with the potential to impact anastomotic healing. Additionally, surgeon experience has been described as a critical determinant of anastomotic leak. Van Workum et al. [50] retrospectively reviewed patients undergoing minimally invasive Ivor-Lewis esophagectomy in four centers. Their study showed marked reduction in leak rates

**Table 3** Methodological quality of included studies using the MINORS tool

| Author | Non-comparative studies | | | | | | | | Additional criteria for comparative studies | | | | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Stated aim | Inclusion of consecutive patients | Prospective data collection | Endpoint appropriate for study | Unbiased assessment of study endpoint | F/U period appropriate for study | Loss to follow up < 5% | Prospective calculation of study size | Adequate control group | Contemporary groups | Baseline equivalence of groups | Adequate statistical analysis | |
| Campbell et al. [28] | 2 | 2 | 0 | 1 | 0 | 1 | 2 | 0 | – | – | – | – | 7 |
| Murawa et al. [35] | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 0 | – | – | – | – | 11 |
| Ohi et al. [37] | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 0 | – | – | – | – | 12 |
| Rino et al. [39] | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 0 | – | – | – | – | 11 |
| Schlottmann et al. [41] | 2 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | – | – | – | – | 6 |
| Shamida et al. [42] | 2 | 0 | 0 | 2 | 0 | 2 | 2 | 0 | – | – | – | – | 8 |
| Yukaya et al. [43] | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 0 | – | – | – | – | 10 |
| Zehetner et al. [44] | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 0 | – | – | – | – | 13 |
| Dalton et al. [29] | 2 | 2 | 0 | 1 | 1 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 17 |
| Karampinis et al. [30] | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 0 | 2 | 2 | 2 | 2 | 19 |
| Kitagawa et al. [31] | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 2 | 2 | 0 | 2 | 16 |
| Koyanagi et al. [32] | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 2 | n/a | n/a | n/a | n/a | 14 |
| Kubota et al. [33] | 2 | 2 | 0 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 1 | 1 | 18 |
| Kumagi et al. [34] | 2 | 2 | 0 | 1 | 0 | 2 | 2 | 0 | 1 | 2 | 2 | 2 | 16 |
| Noma et al. [36] | 2 | 2 | 0 | 0 | 0 | 2 | 2 | 0 | 2 | 0 | 0 | 1 | 11 |
| Pacheco et al. [38] | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 13 |
| Sarkaria et al. [40] | 2 | 2 | 0 | 2 | 0 | 2 | 2 | 0 | 2 | 2 | 0 | 1 | 15 |

Items are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). Global ideal score being 16 for non-comparative studies and 24 for comparative studies

In comparative studies, the conduit viability relies on clinician assessment—pulse, color

*Comorbidities known to impact anastomotic viability differed between the control and experimental groups as surgeon experience increased (18.8% during the learning phase to 4.5% during the plateau phase). None of the studies included in this meta-analysis commented on surgeon experience or hospital volume, which may be a large confounder particularly when other factors were optimized.

## Conclusions

This systematic review offers encouraging evidence for the use of ICG in gastric conduit reconstruction as evidenced by a 69% reduction in anastomotic leaks when combined with intraoperative interventions. Tools for quantitative assessment of perfusion are available and can provide an objective and standardized approach to evaluating the effectiveness of ICG. Future studies should incorporate these measures in randomized controlled trials to generate more robust evidence in this area. ICG has shown tremendous promise in other areas and has the potential for successful risk reduction among esophagectomy patients.

### Compliance with ethical standards

**Disclosures** Drs. Farah Ladak, Jerry Dang, Noah Switzer, Valentin Mocanu, Chunhong Tian, Daniel Birch, Simon Turner, and Shahzeer Karmali have nothing to disclose.

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