REVIEW ARTICLE

Dear Editor and reviewers, thank you for your time and effort. You can herby find the alterations we made to the manuscript based on your suggestions.

Sincerely

The authors

Reviewer 1:

Comment 1: abbreviations in the text without their primary explanation

Answer 1: We have corrected this in the manuscript

Comment 2: abbreviations have not been used consistently

Answer 2: We have corrected this in the manuscript

Comment 3: comment on a randomized controlled trial and the ethics of an ICGA poor perfused control group

Answer 3: added to the conclusion

Changes 3: Reducing AL after esophageal reconstruction is an ongoing goal of the esophageal surgical community, this easy and safe new technique of perioperative perfusion assessment has the potential to reduce AL rate and its associated mortality but randomized trials are needed to confirm these retrospective results. However a prospective randomized study can only compare ICGA guided surgery versus non ICGA guided surgery and that implies a large sample size demanding a multicentre study. Comparing in a randomized fashion ICGA good perfused anastomoses versus ICGA poor perfused anastomosis would be scientifically perfect but ethically impossible. At present, there are no ongoing randomized trials listed on clinical trial.gov.

Reviewer 2:

Comment 1: Introduction section: additional referral in esophageal cancer an surgical interventions is recommended

Answer 1: We have added this to the introduction

Changes 1: page 7: At present ICGA is not a standard guideline during esophageal surgery because of the lack of prospective randomized studies, but many expert centers already incorporate perioperative ICGA as a routine step during esophageal reconstruction.

Comment 2: Result section: size of the text should be reduced and information included in the tables should be excluded
Answer 2: We have corrected the text size and reduced the results section

Comment 3: Discussion section: additional comparative evaluation of relevant surveys is implemented
Answer 3: We have looked for relevant surveys concerning ICGA in esophageal surgery but we could not find anything. We thank the reviewer for this nice suggestion and we will propose a Delphi round survey for expert surgeons on the use of ICGA during esophageal surgery in the near future.
Changes 3: None.

Comment 4: Table 1
Answer 4: We have altered table 1
Changes 4: Page 20-21

Editorial office:
Comment 1: crosschecking for similar sentences
Answer 1: crosschecking showed 8% of the sentences (mainly in the introduction) to be similar to an article published in Medicine. The published article is a study protocol written and published by the same authors as this review. Therefor it cannot be considered as plagiarism. We did not alter these sentences in the manuscript. The crosschecking did also show a 1% similarity with two other (referred) articles. Both of these sentences were rewritten in the manuscript
Changes 1: altered in the manuscript

Comment 2: Running Title

Answer 2: Near-Infrared Fluorescence guided esophageal surgery

Changes 2: Added on page 1

Comment 3: ORCID numbers

Answer 3: added to the manuscript

Changes 3: Added on page 2

Comment 4: Abstract and background

Answer 4: the background was added and the abstract was altered to an informative, unstructured abstract of 200 words on page 4.

Changes 4: After an esophagectomy, the stomach is most commonly used to restore continuity of the upper gastrointestinal tract. These esophago-gastric anastomoses are prone to serious complications such as leakage associated with high morbidity and mortality. This review evaluates feasibility and effectiveness of Indocyanine green fluorescence angiography (ICGA) as an assessment tool for gastric tube (GT) perfusion and as a predictor of anastomotic leakage (AL). Pubmed and Embase were searched for studies presenting data on intraoperative ICGA perfusion assessment during esophago-gastric reconstruction. The 19 included studies all described ICGA as a safe and easy method for graft perfusion. AL occurred in 10% in the ICG guided group and 20.6% in the control group ($p<.001$). The AL rate in the group with an altered surgical plan based on the ICG image is similar to the well perfused group, suggesting that the technique is able to identify and alter a potential bad outcome. This review proves that ICGA is a safe, feasible and promising method to assess graft perfusion. The differences in AL rate between the well perfused and poor perfused anastomotic sites clearly suggest that a good fluorescent signal is a predictor of good outcome.

Comment 5: Keywords

Answer 5: Keywords were added on page 4

Changes 5: Indocyanine green, angiography, fluorescence, esophagectomy, anastomotic leak, Near-infrared spectroscopy, esophageal neoplasms, and esophageal cancer.

Comment 6: Core tip

Answer 6: Core tip was added

Changes 6: Esophagectomy is a surgery known for its complexity and potentially high morbidity associated with postoperative AL. This review evaluates ICGA as a safe, feasible and promising method to assess graft perfusion during esophageal reconstructive surgery. We discuss the safety, the methodology and the effectiveness of ICGA and its potential to reduce AL rate.

Comment 7: Audio Core tip

Answer 7: Audio Core tip was added

Changes 7: Esophagectomy with gastric graft reconstruction is a surgery known for its complexity and potentially high morbidity associated with postoperative AL. This review evaluates ICGA as a method to assess graft perfusion during esophageal reconstructive surgery. We discuss the safety, the methodology and the effectiveness of ICGA and its potential to reduce AL rate. The differences in AL rate between the well perfused and poor perfused anastomotic sites clearly suggest that a good fluorescent signal is a predictor of good outcome.

Comment 8: references should be in square brackets

Answer 1: corrected in the manuscript

Changes 1: altered in the manuscript

Comment 9: crosschecking for similar sentences

Answer 9: The crosschecking did also show a 1% similarity with a (referred) articles. This sentence was rewritten in the manuscript.

Changes 9: Age, male gender, smoking, alcohol abuse, American Society of Anaesthesiologists score, obesity, emergency surgery, prolonged operative time, intraoperative blood loss, diabetes, renal failure, use of corticosteroids and

cardiovascular disease are identified as risk factors for AL, potentially through impaired perfusion of the gastric graft [2, 4–6, 8-11].

Comment 10: crosschecking for similar sentences
Answer 10: crosschecking showed 8% of the sentences (mainly in the introduction) to be similar to an article published in Medicine. The published article is a study protocol written and published by the same authors as this review. Therefor it cannot be considered as plagiarism. We did not alter these sentences in the manuscript.
Changes 10: none

Comment 11: Article highlights
Answer 11: added as a Conclusions and perspectives:
Changes 11: Conclusions and perspectives:
The present review suggest that ICGA is a safe, feasible and promising method to assess graft perfusion that might help reducing AL. At present optimal doses of 0.2-0.5 mg/kg are mentioned in literature, but based on this review a bolus dose of 2.5 mg is a sufficient optimal dose for visualization of esophagogastric anastomotic perfusion.
A few authors have attempted to quantify the method, but rarely in esophageal surgery and without comparison with a golden standard method, stressing the need for objective quantification of the ICGA with validated cutoff levels for sufficient graft perfusion in esophageal surgery. No studies mentioned validation of the method. Objective, in depth assessment of tissue perfusion using NIRF imaging during creation of the esophagogastric anastomosis in EC surgery is lacking. Therefore, we propose a clinical study that uses NIRF dynamic images to calculate physiologically relevant parameters (blood flow, blood volume, vascular leakage) and generate pseudocolor coded parametric maps using advanced curve analysis and compartmental modelling (adiabatic approximation to tissue homogeneity model, AATH) [45,46]. In addition, this study would be the first to validate imaging based perfusion assessment of the stomach graft using tissue, serum, and cellular

hallmarks of hypo-perfusion and hypoxia during esophagectomy [47]. The study is registered in Clinicaltrials.gov as NCT03587532 and is currently recruiting.
The differences in AL rate between the well perfused and poor perfused anastomotic sites clearly suggest that a good fluorescent signal is a predictor of good outcome. The AL rate in the group with an altered surgical plan based on the ICG image was similar to the well perfused group and significantly less than the poorly perfused group, suggesting that the technique is able to predict and remedy a potentially worse outcome. Reducing AL after esophageal reconstruction is an ongoing goal of the esophageal surgical community, this easy and safe new technique of perioperative perfusion assessment has the potential to reduce AL rate and its associated mortality but randomized trials are needed to confirm these retrospective results. At present, there are no ongoing randomized trials listed on clinical trial.gov.

Comment 12: Location of fig 2
Answer 12: Corrected in the text
Changes 12: Corrected in the manuscript on page 13
AL rates are summarized in Figures 2 and 3.

Comment 13: PubMed citation numbers and DOI
Answer 13: Corrected in the text
Changes 13: Corrected in the manuscript on page 23-28.