Editorial

# The use of near-infrared fluorescence imaging in the surgical treatment of esophageal cancer

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## Introduction

Surgical resection with en bloc lymph node dissection remains the cornerstone of curative treatment in esophageal cancer. Unfortunately, this procedure still has a substantial morbidity and mortality. Technical advances in the last few decades such as the introduction of minimally invasive esophagostomy (MIE) have been essential in reducing surgical trauma and thereby morbidity (1,2). Especially pulmonary complications are significantly reduced by a minimally invasive transthoracic approach with a comparable oncological outcome (2). Although there is an increasing body of evidence in favor of a minimally invasive approach, MIE is not widely adopted as a standard procedure. While MIE is performed in 64.8% of the cases in the Netherlands, it is only performed in 15.4% of the cases in the UK (3,4). The increased technical complexity of the procedure was even ground for multiple centers to stop their MIE program due to safety reasons (3).

Recently, robot-assisted minimally invasive esophagectomy (RAMIE) was introduced to address some of the limitations of standard MIE. It is believed that RAMIE will overcome some technical challenges of the procedure and thereby reduce morbidity and facilitate radical and safe oncological resection (5-7). Better, more stable 3D visualization, more precise tissue handling and superior maneuverability may be benefits. Although there is an increasing interest in and experience with RAMIE, research showing a definitive benefit over MIE is still scarce (8). The use of robot assistance may not only aid to reduce the complexity of the procedure, but also opens possibilities to access new diagnostic tools. Build in real-time fluorescence guidance, such as the Firefly system (Intuitive Surgical, Sunnyvale, CA), may be used to assess the perfusion of the gastric conduit. Hodari *et al.* nicely describe a better assessment of gastric conduit perfusion leading to a potential reduction of anastomotic complications (9). Furthermore, real-time fluorescence may also help to perform a better oncological resection.

## Near-infrared fluorescence (NIRF) for perfusion imaging and anastomotic leakage

Despite different improvements in surgical technique and perioperative care, the incidence of anastomotic leakage after esophagostomy remains high, in some studies leakage rates of up to 30% are reported (10). Anastomotic leakage is associated with an increased postoperative morbidity, longer ICU and overall hospital stay and a reduced quality of life and long-term cancer-specific survival. Several studies have identified risk factors for anastomotic leakage, such as neoadjuvant chemoradiotherapy, surgical technique, smoking and the location of the anastomosis (11,12). These multiple factors may compromise the perfusion of the gastric conduit and thereby cause anastomotic leakage. With that in mind, perfusion assessment might be a great tool to identify conduit ischemia and thus reduce the incidence of anastomotic leakage. Especially a compromised

perfusion of the proximal part of the tubularized gastric conduit, used for reconstruction, could be one of the risk factors (13). After resection, the gastric conduit must be completely vascularized by the right gastroepiploic arcade, which often does not reach the proximal tip of the graft and thereby compromises the vascular integrity at the distal part of the anastomosis. Currently, the perfusion and quality of the gastric conduit is inspected by subjective intraoperative judgement of the surgeon, based on factors like color and pulsation, leaving room for error. Objective assessment of the perfusion of the gastric conduit could aid in this respect by identifying ischemic segments at an early stage. NIRF in combination with indocyanine green (ICG) used for real-time perfusion assessment is a relatively new technique based on the light emitting properties of ICG when exposed to light at the near-infrared spectrum. The near-infrared spectrum can be made visible with the use of special camera equipment incorporated in RAMIE, but these tools are also available for conventional MIE. ICG is known to be safe and the high contrast to background ratio and high tissue penetration are a promising basis for real-time angiography (14,15). In the past decade, several studies have evaluated the feasibility of NIRF as a tool to predict anastomotic leakage. Several observational studies have demonstrated the technique to be feasible, safe and able to visualize perfusion, however alterations in conduit perfusion have not been shown to correlate with anastomotic leakage (16-18). Unfortunately, these studies have several limitations. Especially a lack of adequate power (small patient groups) and the absence of a control group make it difficult to draw definitive conclusions from these studies. Besides the lack of a high level of evidence for the use of NIRF, the techniques and study designs come with other limitations such as the multifactorial risk factors for the development of anastomotic leakage. Furthermore, the question remains how to interpret the perfusion information provided by NIRF. A complete lack of colorization of parts of the gastric conduit is easy to distinguish, but more subtle changes in fluorescence intensity are more difficult to detect. Besides this, baseline intensity of the entire gastric conduit and other tissues could be altered by a variety of factors like the speed of infusion and cardiac output and might influence proper assessment furthermore. Therefore, software for the objective measurement of intensity alterations could be a helpful tool to accompany subjective assessment, at least for research purposes. Other factors, such as specific flow patterns could be of interest. Koyanagi *et al.* showed a correlation between delayed flow speed and anastomotic leakage in 40 patients undergoing an esophagectomy (19). However, it has to be kept in mind that it is unclear what interventional options are possible after observation of a compromised vascularization.

## Future perspective

Besides assessment of tissue perfusion, fluorescence guidance for the improvement of oncologic outcome has gain special interest of different study groups. Several studies have shown a use for NIRF imaging of the sentinel node in different types of cancer, including colon, gastric and breast cancer. A systematic review, looking at ICG NIRF imaging for sentinel node procedures in breast cancer, shows an equal or possibly even better detection rate with the use of NIRF compared to traditional techniques (20). The first results of sentinel node mapping in both gastric and early stage colon cancer are promising, but further research is needed (21-23).

The latest developments focus on oncologic visualization with the use of tumor specific NIR tracers to improve the identification of tumor cells in ovarian-, colorectal- and pancreatic cancer. Identification of the resection margin is key in the curative intent of a surgical approach and perioperative imaging with the use of NIRF tracers could be a helpful tool for guidance in achieving a curative resection. The use of a fluorescent agent bound to folate receptor alpha was recently shown to be feasible and possibly beneficial in patients with ovarian cancer (24). In line with these results, different tracers, such as a CEA-targeted NIRF tracer, are currently developed and tested showing promising results, but definitive results remain to be awaited (25).

## Conclusions

The introduction of MIE has shown several benefits in the surgical treatment of esophageal cancer with reduced morbidity and comparable oncological outcome. MIE can be technically demanding and is therefore not yet adopted as a standard surgical technique. To address some of the challenging issues of MIE, RAMIE has gain special interest by several surgeons. RAMIE not only facilitates technical challenges in surgery, but also opens opportunities to use image guided tools, which are also available for MIE. Perfusion assessment shows promising results, but the technique needs further elaboration and a stronger body of evidence before definitive implementation in current

 

practice may take place. Recent developments in the use of NIRF for sentinel lymph node mapping and tumor targeting tracers are very promising and could possibly be translated to patients with esophageal cancer.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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