Intraoperative fluorescence imaging in esophagectomy and its application to the robotic platform: a narrative review

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Background and Objective: Robotic-assisted esophagectomy is an approach to minimally invasive esophagectomy (MIE) that has demonstrated equivalent or improved outcomes relative to open and other minimally invasive techniques. The robotic approach also allows unique opportunities to improve complications following esophagectomy through use of enhanced visualization tools, including intraoperative fluorescence imaging. In this review, we summarize the specific uses of intraoperative fluorescence imaging as an adjunct tool during esophagectomy and discuss its application to the robotic platform.

Methods: A literature search was conducted via PubMed in February 2022 with the following keywords: esophagectomy, esophageal cancer, infrared, near-infrared (NIR) and fluorescence. Peer-reviewed academic journal articles published in English between 2000 and 2021 were included.

Key Content and Findings: There is a growing body of literature evaluating the use of intraoperative fluorescence imaging in robotic-assisted esophagectomy. This includes assessment of gastric conduit perfusion, including feasibility, creation of the gastroesophageal anastomosis, and qualification of perfusion, along with lymphatic mapping and identification of critical anatomy. These tools are uniquely leveraged using the robotic platform to standardize and quantify key technical aspects of the operation.

Conclusions: Intraoperative fluorescence imaging provides the opportunity to assess perfusion and identify anatomy for more precise and patient-specific dissection and reconstruction. Among all the operative techniques for esophagectomy, robotic-assisted esophagectomy is uniquely suited to utilize these imaging modalities to optimize outcomes and minimize risk associated with esophagectomy.

Keywords: Intraoperative fluorescence; near-infrared imaging (NIR imaging); esophagectomy; robotic-assisted

Introduction

The use of robotic-assisted esophagectomy, a type of minimally invasive esophagectomy (MIE), is increasing and a growing body of literature demonstrates its advantages over other operative techniques (1). MIE, in general, has been associated with shorter length of stay, decreased complication rates, and improved quality of life, without comprising surgical outcomes or survival (2-4). In addition, robotic-assisted esophagectomy provides the surgeon with improved visualization with 10× magnification and 3D high-definition modalities, increased mobility due to a

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Table 1 Search strategy summary

Items	Specifications
Date of search	February 20, 2022
Databases and other sources searched	PubMed
Search terms	Esophagectomy, esophageal cancer, infrared, near-infrared, fluorescence
Timeframe	2000–2021
Inclusion and exclusion criteria	Peer-reviewed academic journals published in English were included. Editorials, commentaries, abstracts and articles without full text were excluded
Selection process	A single author (MVP) reviewed the results of the initial search, along with relevant bibliographies and excluded those unrelated to the topic. All authors reviewed the final list of studies included in the review

wider range of motion of the wristed instruments and user-friendly ergonomics. Recent studies have indicated that even compared to MIE, robotic assistance has resulted in superior outcomes, including lower rates of conversion to open, shorter length of stay, higher lymph node yield, less operative blood loss, and higher rates of R0 resection (5-7).

Esophagectomy, a complex procedure with high morbidity and mortality, represents an operation with great potential for improvement with robotic techniques (8). In this procedure, the resected esophagus is replaced with a tubularized conduit, most commonly gastric, that is dependent on blood flow from the right gastroepiploic artery. Therefore, visualization of this vessel to ensure preservation during dissection, as well as assessing perfusion at the conduit tip to determine the site of the gastroesophageal anastomosis, are critical. The superior visualization by 3D technology enhances the identification of these critical structures, and the wristed instruments allow improved management of tight operative spaces, facilitating key steps including complete 3-field lymph node dissection. In addition, the use of adjunct visualization tools is optimized in the robotic setting, where 3D optics and built-in near-infrared (NIR) imaging are standard components of the robotic platform. Intraoperative fluorescence imaging has demonstrated promising preliminary results in reducing complications following esophagectomy (9). Although there are multiple fluorescence modalities available, NIR fluorescence with the use of indocyanine green (ICG) is the only modality approved by the Federal Drug Administration, and as such, is widely used for esophagectomy, along with other gastrointestinal cancers, in both open and minimally invasive settings (10).

As robotic-assisted esophagectomy becomes more routine, the reliance on adjunct visualization tools will increase. These tools allow for both standardization and quality control across surgeons and hospital centers by facilitating clear visualization of conduit perfusion, mapping of lymphatic channels, and identification of critical anatomy. The aim of this narrative review is to evaluate the specific uses of intraoperative fluorescence imaging as an adjunct tool while performing robotic-assisted esophagectomy. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-456/rc).

Methods

A literature search was conducted via PubMed in February 2022 to look specifically at the use of intraoperative fluorescence imaging in esophagectomy. The following keywords and their combinations were used: esophagectomy, esophageal cancer, infrared, NIR and fluorescence. The inclusion criteria were peer-reviewed academic journal articles published in English between 2000 and 2021. Bibliographies of relevant studies were reviewed and appropriate citations were included. Editorials, commentaries, abstracts and articles without full text were excluded (*Table 1*).

Results

Assessment of perfusion

Anastomotic leak rate following esophagectomy has been reported to be anywhere from 6–41% and is associated with significant morbidity and mortality (11). Anastomotic leaks are a result of mechanical tension and poor perfusion, which has motivated the development of adjunct tools to assess intraoperative blood flow at the anastomotic site (12).

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Prior to the development of these techniques, the risk of anastomotic leak was predicted by clinical judgement, which is not reliably correlated with clinical results (13,14). Studies have evaluated the role for intraoperative fluorescence imaging as related to feasibility, selection of anastomotic site, and defining qualitative and quantitative measures of perfusion. As we will discuss below, we would argue that these metrics are best leveraged in the robotic platform, with several groups, including our own, advancing the role of these quantitative metrics in evaluating quality and outcomes for esophagectomy.

Feasibility

Multiple studies have demonstrated the use of intraoperative fluorescence to identify the vascular network and associated conduit perfusion (15-21). Among patients undergoing robotic-assisted esophagectomy, Sarkaria *et al.* utilized ICG in a cohort of 30 patients and were able to successfully identify the termination of the vascular arcade in all patients. In addition, the use of ICG resulted in visualization of small transverse vessels, which were otherwise unidentified, and confirmation of the arcade during mobilization of the greater curve and omentum, illustrating the advantages of the improved optics and visualization capabilities of the robotic system (22).

Creation of anastomosis

The placement of the gastroesophageal anastomosis is a critical decision, as anastomosis to areas with poor perfusion threaten the integrity, increasing the risk for anastomotic breakdown and leak. Egberts *et al.* describe their fully robotic technique in 75 patients, which includes administration of fluorescing ICG in order to identify a potential deficiency in perfusion of the gastric conduit, allowing for gastric tube length adaptation as needed (23). Similarly, both Pötscher *et al.* and DeLong *et al.* illustrate their experience with the robotic system, explaining the use of fluorescence in their identification of vascular anatomy and creation of the gastric conduit and esophagogastric anastomosis, highlighting the ease, feasibility and technical advantages that come with the robotic system (24,25). Lastly, Hodari *et al.* evaluated 54 patients who underwent robotic-assisted Ivor Lewis esophagectomy, utilizing ICG and the FireFly Fluorescence Imaging system to evaluate real-time perfusion. Ultimately, only 3 patients developed a leak, and the team hypothesized that the use of ICG to evaluate real-time perfusion improved outcomes as they were able to consistently identify a demarcation zone of perfusion on the esophageal remnant and tip of esophageal mucosa, guiding their suture placement (26). The adoption of the robotic platform for MIE further enhances the scope of these findings, with the ease of the built-in Firefly camera and the opportunity to quantify perfusion intensity and time to perfusion, and to standardize these metrics across surgeons and centers.

Qualitative and quantitative measures of perfusion

Given the association of poor perfusion with development of anastomotic leak, assessing perfusion quality provides a unique opportunity to quantify the risk for anastomotic leak and the quality of the anastomosis, allowing a new level of standardization and development of quality of care metrics, which is critically important for a procedure with historically high morbidity. However, essential to improving surgical care in esophagectomy is to quantify what defines a "good" conduit in objective rather than subjective terms. Preliminary studies in open and MIE techniques have shown that longer intraoperative fluorescence visualization time and slower gastric conduit perfusion are associated with anastomotic leak, with timing thresholds ranging from 30–90 seconds (27-33). Slooter *et al.* prospectively evaluated 84 patients who underwent Ivor Lewis or McKeown esophagectomy, many of which were performed with robotic assistance. This group determined that time between ICG injection and tip enhancement was predictive for anastomotic leakage with a cut-off value of 98 seconds [specificity 98%, sensitivity 17%, positive predictive value (PPV) 50%, negative predictive value (NPV) 91%] (27). In these situations, in which seconds may lead to improved outcomes, the accuracy of timing can be ideally quantified in a robotic system, particularly with the use of the da Vinci Firefly camera, allowing for more precise and standardized measures of perfusion and enhanced monitoring of surgical technique across surgeons and hospital centers.

Nodal mapping and dissection

Lymph node dissection during esophagectomy provides improved locoregional control and has been shown to result in improved survival (34). In addition, greater lymph node harvest has been associated with improved staging and prognostic information, influencing post-operative adjuvant therapy decisions (35). Therefore, the ability to

Figure 1 Identification of the right gastroepiploic artery using ICG fluorescence in robotic-assisted esophagectomy. ICG, indocyanine green.

Figure 2 Assessment of conduit perfusion using ICG fluorescence in robotic-assisted esophagectomy. ICG, indocyanine green.

identify lymph nodes during esophagectomy is critical for optimal oncological care, especially with the continued improvement in adjuvant therapeutics, including targeted and immunotherapies. The use of intraoperative fluorescence for lymphatic mapping during esophagectomy has been well documented in several studies (36,37). Hachey *et al.* evaluated the use of endoscopic submucosal injections of ICG in a cohort of 10 patients, four of which were performed robotically, with NIR signals identified in six of the tumor sites (38). Hosogi *et al.* evaluated 15 patients who underwent robotic-assisted esophagectomy with the use of ICG, identifying 80% of patients with ICG-positive lymph node basins along the right recurrent laryngeal nerve and

73% of patients along the left recurrent laryngeal nerve. All ICG-positive lymph node basins were ultimately found within a common area encompassing the esophagus, trachea, recurrent laryngeal nerves and surrounding lymph nodes (39).

The application of these techniques in robotic esophagectomy remains to be fully established, however ICG under NIR imaging has been found to have better visualization of lymph nodes, particularly within thick fatty tissues, with the use of the robotic system (39,40). This improved visualization, particularly with the use of the da Vinci Firefly camera, allows for *en bloc* resection of lymph nodes and lymphatics without injury to these structures, thus preventing tumor cell spillage, and safe dissection of lymph node-bearing soft tissue adjacent to critical structures (41).

Identification of anatomy

Chylothorax after esophagectomy occurs in 2–12% of patients and affects not only enteral intake, but also hospital length of stay and overall survival (42). Fluorescence guided dissection, with percutaneous inguinal injection of ICG alone, has been utilized to identify the thoracic duct to avoid injury intraoperatively and in the setting of post-procedural chylothorax (43-45). Jardinet *et al.* successfully applied these techniques in robotic-assisted esophagectomy by inserting an intra-lymphatic needle in an inguinal node and injecting ICG after mobilization of the inferior pulmonary ligament. This not only identified the thoracic duct, but did so with less time for set-up, more rapid fluorescence, and longer signal duration, as compared to prior studies that did not utilize the robotic platform (46). Similarly, Barbato *et al.* and Varshney *et al.* both utilized ICG in 18 and 21 patients, respectively, with identification of the thoracic duct in all patients in the robotic setting (47,48).

Advantages in robotic-assisted esophagectomy

The robotic platform for MIE has the potential to reduce the morbidity and mortality of esophagectomy in several ways, including use of additional built-in diagnostic tools such as intraoperative fluorescence imaging. When considering the use of adjunct tools, the technical advantages of a robotic-assisted platform cannot be understated as improved optics, scaling, and built-in fluorescence camera for rapid angiography allows for a more precise and tailored dissection, and provides quantifiable metrics to define optimal perfusion of the conduit and anastomosis (22,25,38,46) (*Figures 1,2*). Firefly

represents an integrated fluorescent camera which is now standard equipment in all da Vinci Surgical Systems, and includes cameras modified for NIR light, filters and sensors for ICG, and light emitting diode (LED)-based illuminators with a NIR laser to excite ICG (49). In fact, the Firefly technology allows for evaluation of a larger spectrum of wavelengths with various imaging modes (example: white light, unprocessed fluorescence and processed fluorescence) (50).

Several limitations to robotic-assisted esophagectomy should be noted, however, including the steep surgeon learning curve, risk of conversion to open, and requisite hospital cost and maintenance, but the benefits in outcomes and potential to advance the field by quantifying optimal surgical technique are certainly worth the investment for surgeons and institutions committed to advancing the field (25,51).

Limitations and future directions

Further scholarship in the robotic platform is required for each of the uses of ICG presented above. In addition, the studies presented highlight the role for intraoperative fluorescence imaging as a tool to facilitate dissection and decrease complications after esophagectomy, but are predominantly case-control studies, with no standardization between groups. More rigorous scientific inquiry is warranted, including published and validated protocols for intraoperative ICG usage, as well as randomized control trials, when possible. In conjunction, new techniques are being developed to improve imaging through more advanced camera technology and more specific tracers. This includes protein-bound ICG formulations to prolong the half-life of intraoperative fluorescence dyes, NIR spectroscopy, thermal imaging, and incorporation of mathematical modeling and software designed specifically for the robotic platform (52-58). In addition, the use of NIR dyes as both cancer imaging and therapeutic modalities is rapidly expanding (59).

Conclusions

Over the last decade, intraoperative fluorescence imaging has demonstrated great potential to facilitate dissection and improve postoperative outcomes following esophagectomy. This technique provides the opportunity to assess perfusion and identify anatomy for more precise and patient-specific dissection and reconstruction. Robotic-assisted esophagectomy is optimally suited to utilize fluorescence imaging to enhance surgical technique, and greater adoption of the robotic approach will enable development of standard metrics to benchmark surgical outcomes of esophagectomy in order to decrease risk and improve patient outcomes of this procedure across surgeons and hospital centers, both nationally and internationally.

Footnote

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