Chapter

Prevention of Anastomotic Leak in Minimally Invasive Esophagectomy: The Role of Anastomotic Technique and Adjuvant Surgical Strategies

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Abstract

Ivor-Lewis esophagectomy is followed by a considerable anastomotic leakage rate, which is a potentially fatal complication, followed by increased morbidity and mortality. The emergence of minimally invasive surgery led to a wide variety of anastomotic techniques, three of which are mainly preferred. Hand-sewn anastomoses can be performed in an end-to-end or end-to-side manner, while stapled end-to-end or end-to-side anastomoses are conducted either as circular-stapled anastomoses using a transorally inserted anvil (Orvil™) or as hand-sewn purse-string stapled anastomoses. In addition, side-to-side esophagogastrostomy with a linear stapler is presented as a promising technique. Hybrid techniques are also reported. No consensus has been achieved upon optimal technique and the decision relies on surgeon preference and skills, cost, and length of the available conduit. Furthermore, numerous techniques have been proposed to prevent anastomotic leakage (AL), including appropriate submucosa apposition, omentoplasty of the anastomosis, wide gastric and duodenal mobilization, sufficient esophageal hiatus enlargement, gentle conduit manipulation, reinforcement of staple line, intraoperative fluorescence angiography, as well as preoperative ligation of the left gastric artery. This chapter aims to provide a critical appraisal of the various anastomotic techniques and the tips and tricks described for reducing the anastomotic leak rate during minimally invasive Ivor-Lewis esophagectomy.

Keywords: anastomotic leakage, anastomotic technique, prevention, esophagogastric anastomosis, minimally invasive esophagectomy, minimally invasive Ivor-Lewis, esophageal cancer

1. Introduction

Esophageal cancer is an aggressive neoplasm with a higher prevalence among the male gender, associated with high rates of cancer-related mortality. The two histological subtypes mainly described in the literature include squamous cell carcinoma and adenocarcinoma [1]. Esophageal cancer represents the eighth most common type of cancer and the sixth leading cause of mortality due to neoplasia, with a 5-year survival of less than 25% [2]. Management strategy for patients with esophageal cancer is multidisciplinary, depending on the neoplasia stage, and includes endoscopic procedures such as radiofrequency ablation, endoscopic mucosal resection, and endoscopic submucosal dissection and/or chemoradiotherapy (CRT) as an esophagus-preserving treatment for early esophageal cancer, while most cases are treated with surgical resection, combined with chemoradiotherapy [3]. The advent of minimally invasive esophageal surgery has led to lower rates of morbidity, mortality, shorter hospital stay, enhanced life quality, as well as better long-term oncological outcomes, compared with open esophagectomy [4, 5].

Commonly performed minimally invasive esophageal procedures include Ivor-Lewis, McKeown, and transhiatal esophagectomy. Ivor-Lewis esophagectomy has been associated with a shorter length of hospital stay, lower rate of postoperative complications, and lower readmission rates compared to the McKeown esophagectomy [5]. Moreover, advances in anastomotic leak management options, including endoscopic stent placement or endoscopic vacuum-assisted closure device placement, led to wider and more confident adoption of intrathoracic anastomosis, rendering minimally invasive Ivor-Lewis the most common approach performed in clinical practice [6]. Nowadays, robotic-assisted minimally invasive esophagectomy (RAMIE) has also emerged as an alternative approach to totally and hybrid minimally invasive esophagectomy (MIE), followed by enhanced tissue manipulation ability, better lymph node dissection, superior intraoperative image quality as well as reduced morbidity and mortality rates and improved postoperative outcomes [7]. However, RAMIE is also combined with lack of experience, longer operative times, and higher costs [7].

Anastomosis construction is considered the most crucial step during esophagectomy. Despite the advantages offered by the adoption of minimally invasive Ivor-Lewis esophagectomy and the development of high-tech anastomotic staplers, anastomotic leakage (AL) remains a serious and possibly fatal complication after esophagectomy, with incidence higher than the open approach in numerous studies [4, 8]. AL is defined as a "full-thickness gastrointestinal defect involving the esophagus, anastomosis, staple line, or conduit, irrespective of presentation or method of identification" by the Esophagectomy Complications Consensus Group and is classified into three types, depending on the management approach [9]. AL is the main cause of perioperative mortality, prolonged hospital stay, delayed oral feeding, need for reintervention, decreased overall survival, and increased risk of recurrence [10]. The steep learning curve of minimally invasive Ivor-Lewis esophagectomy is proposed as the main factor contributing to higher rates of AL, since AL incidence is limited to 4.5 % after the learning curve plateau had been achieved [4].

A thorough investigation of pathophysiology and risk factors for anastomotic leakage is necessary for the optimization of perioperative results as well as for the development of preventive strategies. The anatomic location of anastomosis has been proven as a factor affecting AL rate, since cervical anastomosis is followed by a higher rate of AL (10–25%), compared to intrathoracic anastomosis (<10%) [11]. Reasons leading to increased AL rate apart from cervical anastomosis include compromised perfusion of the fundus, increased risk of tension, local compression, and neoplasia characteristics, such as neoadjuvant radiation or extended resection [6]. The serosal status may also affect the rate of AL [12]. Preoperative irradiation has a conflicting effect on AL rate, while patient characteristics, including obese or underweight patients, preoperative malnutrition, cardiovascular comorbidities, diabetes mellitus, renal failure, and tobacco and steroid use have been associated with increased AL risk [6]. Finally, the anastomotic technique has not been proven to influence the AL rate [6]. AL related complications remain the main cause of perioperative morbidity and mortality, as well as poor quality of life after open and minimally invasive esophagectomy [13]. In addition, management of an intrathoracic anastomotic leak, contrary to the cervical anastomosis, demands more aggressive interventions, such as re-operation, thoracotomy, thoracoscopic drainage, or complete gastrointestinal diversion [10].

In conclusion, intrathoracic anastomosis, although more challenging technically, is associated with a series of advantages including lower anastomotic leak rate, lower stricture formation rate, decreased nerve injury rate, and improved oncological outcomes [10]. In addition, the emergence of interventional methods for the management of anastomotic leakage have led to wide adoption of intrathoracic anastomosis [14]. As a result, Ivor-Lewis MIE now ranks first as the most common approach to MIE used clinically [10]. No consensus has been achieved regarding the optimal esophageal anastomotic method. This chapter aims to provide a critical review of current strategies for intrathoracic anastomosis creation during minimally invasive Ivor-Lewis esophagectomy, as well as to discuss the methods proposed for minimizing anastomotic leakage.

2. Techniques for esophagogastric anastomosis

2.1 General principles

Esophageal anastomosis healing follows the main phases of tissue healing: inflammation (day 0 to day 4), proliferation (day 5 to day 10), and remodeling (after day 10) phase, with the maximum strength being achieved between day 10 and 14 [15]. A series of technical general principles must be followed during esophagogastric anastomosis creation. First of all, appropriate apposition of esophageal submucosa with the gastric wall is necessary, since submucosa collagen mainly contributes to the integrity and the mechanical strength of the anastomosis [10].

The esophagogastric anastomosis can be hand-sewn, completely stapled, using either a circular or linear stapler, or semi-mechanical, where a linear stapler is preferred for posterior wall reconstruction, while the anterior wall of the anastomosis is performed in a hand-sewn fashion [14]. Based on the anatomic relationship of the esophageal stump and the gastric conduit after the anastomosis, end-to-end, end-to-side, and side-to-side anastomoses are described.

The first step during the thoracoscopic phase of Ivor-Lewis esophagectomy is the division of the esophagus, which should be done at the level of the arch of the azygos vein. In addition, it is proposed to create an esophagotomy at the anterior wall rather than transect the esophagus, to achieve better traction for anvil insertion, when the OrVil technique is not selected [16]. The absence of tension or torsion on the anastomosis, as well as gentle tissue manipulations, are necessary to maintain adequate perfusion [16].

2.2 Handsewn anastomosis techniques

The decision to perform an intrathoracic esophagogastric anastomosis via a thoracoscopic hand-sewn technique demands advanced technical skills and is associated with prolonged operative time [10]. An end-to-end or end-to-side anastomosis is performed between the distal esophagus and the greater curvature of the gastric conduit. Absorbable or nonabsorbable sutures can be selected and the anastomosis may be performed in a continuous or interrupted fashion, in a single or double-layer technique. Single-layer anastomosis is conducted with absorbable or nonabsorbable sutures occupying all wall layers, while the double layer-technique uses an outer row of sutures on the seromuscular layer, followed by an additional inner absorbable suture layer for mucosa inversion after gastrostomy on the great curvature has been performed. It is advisable to place Connell sutures at both ends of the posterior wall to ensure mucosal apposition before proceeding to the anterior wall. After nasogastric tube placement, anterior wall reconstruction is performed [17].

Limited literature exists on hand-sewn esophagogastric anastomosis in the era of minimally invasive esophagectomy [18]. Charalabopoulos et al. published a large cohort study of laparoscopic two-stage esophagectomy with a completely hand-sewn intrathoracic anastomosis, with promising results. The surgical procedure involved the creation of a two-layer end-to-side esophagogastric anastomosis. Outcomes were promising, reporting an anastomotic leak incidence of 2.5 (2 out of 80 patients) and 90-day mortality of 5%. Finally, 10 out of 80 patients presented anastomotic strictures and were treated with endoscopic balloon dilatations. The authors conclude that intrathoracic manual anastomosis is a safe and easily reproducible technique during minimally invasive Ivor-Lewis, with satisfactory oncological short and long-term outcomes when performed in specialized esophageal cancer centers [18]. Carr et al. report reduced incidence of anastomotic leak and postoperative stricture by performing double-layer anastomosis, although they are associated with longer operative time and higher costs [10].

In their prospective cohort study, Ramirez et al. presented the outcomes of intracorporeal hand-sewn anastomosis in 27 patients who underwent laparoscopic Ivor-Lewis esophagectomy. The anastomosis technique included two PDS running suture layers in the posterior wall and one PDS running layer in the anterior wall, followed by omentoplasty. An articulated needle holder (FlexDex) for better surgical ergonomics was also used. The mean operative time needed for anastomosis creation was 60 minutes. The authors report an anastomotic rate of 14.8%, while in 7.4% of participants, reoperation was performed [19].

Intracorporeal hand-sewn esophagogastric anastomosis carries the burden of a steep learning curve, since manual anastomosis demands a higher level of technical skills, experience, and background compared to mechanical staplers [19].

In addition, the literature contains reports of hand-sewn esophagogastric anastomosis during robot-assisted Ivor-Lewis esophagectomy with excellent outcomes regarding anastomotic leak rate [20]. Notably, the advent of robotic esophagectomy has triggered the interest back in hand-sewn anastomosis due to increased degrees of freedom offered compared to conventional thoracoscopy [16, 21].

In conclusion, thoracoscopic hand-sewn anastomosis, although challenging, is a feasible and safe technique, presenting relatively low rates of anastomotic leak and stricture rate, even during the learning curve period. The emersion of flexible ergonomically advantageous tools may facilitate manual anastomosis creation (**Figure 1**).

2.3 Stapled anastomosis techniques

The advent of mechanical stapled anastomotic devices in 1977 offered the advantage of reduced operative time and technical feasibility independently of the surgeon's

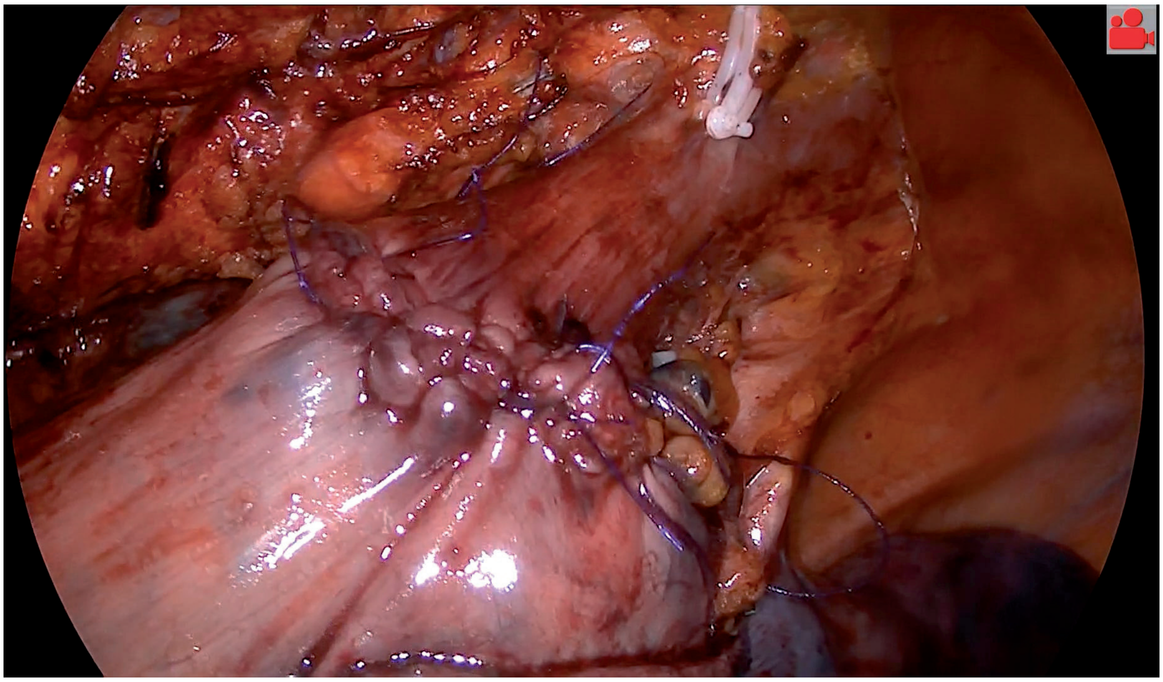

Figure 1.
Final result of a hand-sewn end-to-side esophagogastric anastomosis during laparoscopic Ivor-Lewis esophagectomy.

experience and skills [22]. Mechanical esophagogastric anastomosis is mainly performed with the use of a circular end-to-end anastomosis stapler (EEA stapler) or a linear cutting gastrointestinal stapler (GIA stapler) [10]. In esophageal surgery, the use of circular staple anastomosis has been adopted since the 1990s, while linear stapled anastomosis was introduced in 1998 [23].

2.3.1 Linear side-to-side stapled anastomosis

To create an intrathoracic side-to-side functional anastomosis, usually a 30- or 45-mm gastrointestinal anastomosis (GIA) stapler is selected, securing the anastomotic site with a triple row of titanium staples [10]. After gastric conduit mobilization and alignment of the esophageal posterior wall and gastric anterior wall, the large jaw of an Endo GIA stapler is placed into the gastrostomy and the thin jaw is inserted into the esophagotomy [10]. After stapler firing, the posterior wall of the anastomosis has been created and nasogastric tube has been inserted and the anterior wall can be reconstructed with another staple firing [10]. Alternatively, after stapling of the opposing walls and creation of a V-shaped anastomosis, anterior walls are sutured in a single-layer running fashion [23]. The side-to-side linear anastomosis technique presents numerous advantages, since the linear stapler is easily inserted and used into the thoracic cage, creating a wide anastomosis with a low stricture creation rate [10]. Furthermore, it is an easily standardized technique with a low rate of technical errors [24]. However, sufficient esophageal stump length is needed and the retention of a gastric conduit stump leads to a higher rate of ischemic anastomotic fistula formation [25]. In addition, special technical skill is required for closing sites of initial gastrostomy and esophagotomy discourages surgeons from choosing it during minimally invasive intrathoracic anastomosis formation [25].

2.3.1.1 Linear vs. circular anastomosis

A meta-analysis by Zhou et al. was the first to compare linear with circular-stapled esophagogastric anastomosis during open Ivor-Lewis esophagectomy. Outcomes favored linear anastomosis regarding postoperative anastomotic stricture, while no statistically significant difference was proved regarding anastomotic leakage rate and 3-month mortality [23].

2.3.1.2 Linear vs. handsewn anastomosis

According to a meta-analysis by Deng and colleagues, esophagogastric anastomosis created in a linear fashion presents a lower incidence of anastomotic leak compared to the handsewn anastomosis. Possible mechanisms for this outcome include the less traumatic character of mechanical staplers to tissues, the reduced tension on the anastomosis due to lateral stay sutures, and, finally, the three layers of titanium staplers, which contribute to the mechanical strength of the anastomosis. At the same time, the linear-stapled technique is superior to hand-sewn anastomosis regarding anastomotic stricture rate [24].

The literature contains insufficient data regarding the clinical outcomes of linear-stapled esophagogastric anastomosis after minimally invasive esophagectomy for esophageal cancer. Gao et al. studied the short-term outcomes of 34 consecutive patients, in whom the creation of a mechanical side-to-side linear stapled anastomosis was decided for minimally invasive Ivor-Lewis. The results were promising, with no mortalities or serious postoperative complications noted. Anastomotic leakage presented in only one patient (2.9%) and was treated without intervention, while no conversion to an open approach was needed. In conclusion, the authors suggest that linear-stapled esophagogastric anastomosis is a safe and feasible option regarding short-term outcomes, although associated with a steep learning curve [25].

2.3.2 Circular stapled anastomosis

Mechanical circular stapled anastomosis technique is the most frequently used method for intrathoracic esophagogastric anastomosis in the era of minimally invasive Ivor-Lewis. The surgical procedure includes the insertion of an anvil into the esophageal stump, followed by apposition and application of the anvil rod with the stapler shaft of an intraluminal EEA placed into the gastric conduit. Based on the method of anvil introduction, circular stapled intrathoracic anastomoses are performed with the transorally inserted anvil technique, using the Orvil™ device, or with the hand-sewn purse-string stapled anastomosis technique [26]. With the aforementioned procedure, an end-to-end esophagogastrostomy is performed, enhanced by a double row of staplers in a circular fashion. Anvil size is selected based on esophagus diameter and literature reports no relationship between anvil size and risk for anastomotic leak [10].

2.3.3 Circular-stapled anastomosis using a transorally inserted anvil (Orvil™)

The first use of Orvil EEA for the creation of end-to-side esophagogastric anastomosis for Ivor-Lewis MIE is reported by Nguyen et al. in 2008 [27]. The transoral OrVil circular-stapled technique presents a safe, time-efficient, and reproducible method for esophagogastric anastomosis. However, the cost associated with OrVil renders this technique too expensive, while transoral insertion of the anvil may cause thoracic infection and throat injury [28]. In addition, the OrVil anvil comes only in the size of 25 mm.

OrVilTM is preconnected to a long PVC nasogastric-like tube with anchoring sutures [10]. After esophageal resection using a linear stapler and advancement of the OrVil up to the end of the esophageal stump, an incision is made at the esophageal staple line and the blue sutures are transected. The anvil is separated from the orogastric tube, is orientated appropriately and anastomosis is performed, by docking the anvil to the EEA spike and firing the stapler.

According to a retrospective observational study by Zhang et al., which included patients undergoing Ivor-Lewis minimally invasive esophagectomy, no statistically significant difference was noticed regarding minor and major leakage rates, as well as anastomotic stricture rates when the transoral Orvil technique group was compared to purse-string technique group.

Due to its mechanical similarity with a nasogastric tube, misplacement of the OrVil through the patient's nostril may be done in case of sparse education and communication with the person assisting. In addition, several maneuvers are necessary to avoid obstacles during the advancement of the anvil portion up to the esophageal stump. There are specific maneuvers to prevent and resolve these occurrences. First of all, the smooth portion of the disk should face the patient's hard palate. Secondly, lifting and shaking the patient's jaw can help advance the anvil at the point of the piriform sinus, Furthermore, an obstacle at the level of the aortic arch can be overcome by a tugging back and forth between the surgeon at the chest and the assistant at the head of the patient. Last but not least, the cuff of the endotracheal balloon can be transiently deflated during anvil advancement [17]. In addition, one should be careful during the insertion of the stapler through the trocar, since a position perpendicular to the vertebral plane is necessary [16]. What is more, a 10 mm laparoscopic fan retractor for lung parenchyma may be useful to achieve better exposure to upper mediastinum and facilitate anvil and stapler engagement. Control of the anvil by holding it in its proximal part can also be achieved using a laparoscopic grasper, to avoid any damage to flanges. During engagement, attention should be paid to avoid incorporating any adjacent tissues, as well as to hold in the engagement place for 30 seconds before firing, to achieve complete tissue compression. Finally, in cases of very proximal tumors and insufficient length of gastric conduit, Grubic et al. propose complete gastric mobilization including the duodenal Kocher maneuver, to achieve a tension-free anastomosis [29]. Gentle manipulations are required, to avoid dissociation of the anvil from the tube. In case of dissociation, the anvil can be retrieved using the blue retrieval suture [17].

2.3.4 Hand-sewn purse-string stapled anastomosis

The circular stapled end-to-end intrathoracic anastomosis (EEA) is less time consuming than the hand-sewn technique and is feasible even with a shorter length of gastric conduit available compared to the linear-stapled technique. While hand-sewn purse-string stapled anastomosis is a popular technique in open esophagectomy, it is technically challenging under thoracoscopy [28].

After sharp dissection of the esophagus, the anvil of an EEA is inserted into the esophageal stump under proper pressure. Attention should be made to use the largest anvil size the esophageal stump can accommodate, to avoid postoperative anastomotic strictures. Usually, a 25 mm anvil is used. Esophageal intraoperative dilation may be beneficial in cases of difficulty while inserting the anvil. After anvil placement, a baseball stitch fashion suture is placed to secure the anvil position, including esophageal mucosa. A second purse-string suture is placed outside the previous suture. After insertion of the EEA handle through a 2–2.5 cm gastrostomy, the spike of the EEA is advanced through the gastric wall and is engaged with the anvil and the handle is fired [17]. Resection of the open end of the gastric conduit is performed after anastomosis inspection. After anastomosis creation, a nasogastric tube is advanced to the gastric conduit under manual guidance [10].

The most difficult step during thoracoscopic hand-sewn purse-string stapled anastomosis is to deliver successfully the anvil into the esophageal stump. Various techniques have been proposed. A special purse-string clamp device was used by Xie et al. to insert a purse-string suture over the esophageal stump. This method is challenging technically at the high level of the thorax and also requires special equipment [30]. Zhan et al. proposed a modification of hand-sewn circular stapled anastomosis, using a zero-silk suture at 5 cm proximal to the tumor, and placing the first stitch at the 3 o'clock position of the esophageal wall, the second at the 12 o'clock position, and the third at the 9 o'clock position, and finally, the fourth stitch at the 3 o'clock position, after esophagus rotation. After securing the suture with two knots, the anterior esophageal wall is resected and the anvil is inserted. Mean anvil fixation time was 7.1 minutes, compared to the range of 10–18 reported in the literature [28].

It is important to line up the staple line with the body of the gastric conduit and to leave at least a centimeter free between the anastomosis site and the end of the linear staple line [17].

3. Intraoperative techniques to reduce anastomotic failure

3.1 Omentoplasty of the anastomosis

The omentum is an organ with widely described properties, including control of intra-abdominal infectious and inflammatory processes, angiogenesis, and wound healing promotion, as well as a key role in tumor spread, thus being characterized as "the abdominal policeman" [31]. It also holds a crucial role as a reconstructive tool, since omental flaps are commonly used for reinforcement of esophagogastric anastomosis after open or minimally invasive esophagectomy, taking advantage of its anatomical and physiological characteristics [10]. Production of high levels of vascular endothelial growth factor (VEGF) under hypoxic circumstances is thought to be the main pathophysiologic mechanism for neoangiogenesis induction [32].

The technique of omentoplasty includes the creation of a pedicled omental flap originating from perforators of the right gastroepiploic artery that covers the esophagogastric anastomosis and the gastric staple line and is sutured with interrupted sutures including the superficial muscular and serosal layers near the anastomosis [10, 12]. Additional time added to the surgical procedure varies from 7–8 minutes up to 20 minutes [12]. In a meta-analysis including 1608 patients, among them 1087 were treated with an intrathoracic anastomosis after resection, Tuo et al. conclude that omentoplasty reduced the AL for intrathoracic anastomosis by 2-fold and led to statistically significant shorter length of hospital stay, without leading to statistically significant difference regarding anastomotic stricture development [12]. Towards the same orientation, Lu et al. studied the role of omentoplasty for intrathoracic esophagogastric anastomosis protection in minimally Ivor-Lewis esophagectomy for patients having received neoadjuvant chemoradiation. However, data exported from this study failed to prove any statistically significant difference regarding the protective role of omentoplasty against anastomotic dehiscence and the associated mortality, probably due to damage of omental flap viability due to radiation [32]. In contrary, the beneficial role of omental wrap use in minimally invasive esophagectomy has been highlighted by Van Workum et al., who detected no anastomotic leakage in groups who were treated with omental flap versus group with intrathoracic anastomosis, without omentoplasty. The volume of the omental flap has also clinical significance, since a smaller omental wrap volume combined with intravenous dexamethasone administration resulted in lower pulmonary complications [33].

In conclusion, omentoplasty after performance of esophagogastric anastomosis offers physical protection of a compromised anastomosis from an early leakage, but also promotes granulation formation and enhances neovascularization for later wound healing [12]. Larger clinical studies are needed to identify the role of omentoplasty in the era of minimally invasive esophagectomy and neoadjuvant therapy.

3.2 Anastomosis sealing

Fibrin glue has also been proposed to prevent anastomotic leakage after minimally invasive esophagectomy with esophagogastric anastomosis [16]. Sdralis and colleagues, after the application of fibrin sealant (Tisseel) on esophagogastric anastomosis during hybrid Ivor-Lewis esophagectomy, conclude that no statistically significant difference emerges from fibrin sealant use regarding anastomosis integrity [34]. In contrary, Lin et al., based on a cohort study with 57 patients undergoing open or minimally invasive McKeown esophagectomy, presented promising results regarding the effect of porcine fibrin sealant in preventing anastomotic failure [35]. Based on the aforementioned study, further randomized clinical trials with a greater number of patients are necessary to establish the role and application fashion of fibrin sealant in intrathoracic anastomoses.

3.3 Preemptive endoluminal vacuum therapy

Intraoperative application of preemptive endoscopic vacuum therapy (pEVT) is an well accepted method for promoting healing through granulation tissue formation and reducing anastomotic leak rate during minimally invasive Ivor-Lewis esophagectomy. Gubler et al. report promising results from their case series, where pEVT was applied to 19 patients undergoing minimally invasive esophagectomy with intrathoracic anastomosis, after anastomosis creation, and was removed 5 days postoperatively. One anastomotic leakage was noted, which was resolved after reoperation and reapplication of pEVT, while no severe adverse effects were reported. In conclusion, the adoption of pEVT may lead to a crucial reduction of anastomotic leakage, especially in high-risk patients [36]. Similar outcomes are reported by a case series of 67 patients, with an overall AL rate of 7.5%, presenting pEVT as a useful tool to reduce anastomotic leak rate [37].

3.4 Gastric conduit perfusion evaluation-intraoperative fluorescence angiography

During gastric conduit creation and pullup, ligation of the left gastric, left gastroepiploic, and short gastric vessels is necessary, leaving the right gastroepiploic artery as the main feeding vessel of the gastric conduit. This may lead to insufficient arterial supply or venous congestion at the anastomotic site, leading consequently to anastomotic complications, such as anastomotic leakage, benign stricture, and graft necrosis [38]. Esophagogastric anastomotic strength and, thus anastomotic complications after esophagectomy depend mainly on the preservation of the right gastric and right gastroepiploic arteries, which provide adequate perfusion to gastric conduit [39]. In addition, the tip of the gastric conduit is the most vulnerable site of ischemia due to insufficient perfusion by the gastroduodenal artery. Apart from adequate arterial perfusion, gastric conduit perfusion may be affected by rough manipulations, poor preparation, and suboptimal surgical technique [10].

Numerous intraoperative methods have been proposed for the assessment of gastric conduit perfusion and optimal anastomotic site selection. Among them, fluorescence angiography (FA) using indocyanine green has been adopted widely. Slooter and colleagues tried to identify a threshold of FA using ICG for facilitating intraoperative decision-making and identifying high-risk patients for anastomotic leakage. For Ivor-Lewis esophagectomy, FA was performed after gastric pullup into the thorax and decision of anastomotic site. After intravenous ICG injection, the first fluorescent enhancement time point in the lungs, at the base of the gastric conduit, at the planned anastomotic site, and at the ICG watershed or in the tip of the gastric conduit were recorded. Follow-up revealed anastomotic leakage in 9 out of 67 patients (13.4%) with intrathoracic anastomosis. In conclusion, the authors suggest that the time between ICG injection and enhancement at the tip of the gastric conduit, with a cut-off value of 98 seconds, can be used as a threshold to predict anastomotic leakage after esophagectomy. However, it should be highlighted that anastomotic leakage was noticed in two out of two patients who underwent additional gastric conduit resection based on FA findings. In other words, excessive gastric resection based on FA outcomes may lead to anastomotic leakage due to tension at the anastomosis [38].

Using the Near-Infrared (NIR) laparoscopic PINPOINT® endoscopic fluorescence imaging system (NOVADAQ®, Mississauga, ON, Canada), which provides ICG fluorescence angiography images over white light in a dynamic fashion, Pather et al. reported their experience in indocyanine green fluorescence angiography-assisted minimally invasive Ivor-Lewis esophagectomy. After intravenous administration of 7.5 ml of ICG, a surgeon-based assessment of conduit perfusion was performed, as good perfusion, when visualization of the ICG-FA up to the tip of the gastric conduit was noticed, or non-perfusion, if any area of perfusion demarcation was noticed. In the latter category, the operative plan was changed and the poorly-enhanced part of gastric conduit was resected before anastomosis. Anastomotic leak was noticed in 6 out of 100 patients and was managed with endoscopic stent placement. The authors conclude that non-perfusion was independently associated with anastomotic leak postoperatively. However, anastomotic leakage remains a multifactorial complication, and ICG-FA should be used as a tool for recognizing high-risk patients, parallel to patient preoperative optimization [39].

FA with ICG is also proposed to be of great value for the assessment of gastric fundus perfusion in patients who previously received neo-adjuvant radiation [16]. Apart from perfusion assessment, Gubric et al. use FA with ICG for anastomosis tension assessment, where delayed perfusion in a previously well-perfused gastric conduit tip reveals excessive tension [29]. However, this technique also presents a series of limitations. First of all, interpretation of the outcomes is mainly subjective and no consensus has been reached regarding perfusion-related cut-off point for fluorescence. In addition, gastric conduit fluoresces green under circumstances of venous congestion, since arterial perfusion is intact [38]. In conclusion, a FA threshold may be used for detecting high-risk patients for anastomotic leakage and adopting prophylactic measures to avoid it [38].

3.5 Ischemic preconditioning of the stomach

The concept of gastric ischemic pre-conditioning preoperatively to reduce anastomotic leakage was first introduced by Akijama et al., who performed preoperative embolization therapy (PET). After femoral artery catheterization, embolization of the left gastric artery was performed and the right gastroepiploic artery was the remaining feeding artery of the stomach. Blood flow of the gastric tube was measured to be 67% of the measure just after laparotomy was performed, compared to the non-PET group, where the respective value of blood flow was 33%. Similar outcomes were noticed regarding the anastomotic leakage rate among the two groups [39]. Nowadays, the idea of ischemic preconditioning has been extended apart from preoperative embolization also to pre-operative laparoscopic ligation of the left gastric and left gastroepiploic arteries during the staging laparoscopy in type II junction tumors [16]. Occasionally, ligation or embolization of short gastric vessels is also performed [2].

The pathophysiological mechanism is based on preoperative redistribution of gastric blood supply and increased tissue perfusion at the site of the esophagogastric anastomosis. Michalinos et al. performed a systematic review and meta-analysis to investigate the role of gastric ischemic preconditioning, including both techniques of embolization and ligation, to postoperative anastomotic leakage rate, as well as morbidity and mortality. Outcomes revealed a statistically significant association between gastric preconditioning and reduced overall rate of anastomotic leakage, as well as severe anastomotic leakage. On the contrary, no statistically significant relationship was established between ischemic precondition and anastomotic stricture, major postoperative morbidity, or mortality. Results were similar among the two methods of ischemic preconditioning, while authors also suggest that increasing the interval time period between preconditioning and esophagectomy as well as the number of vessels embolized or ligated may lead to better outcomes regarding conduit perfusion. [2]. In addition, it is investigated whether patients with calcifications of the thoracic aorta and stenosis of the celiac trunk, who are at risk of higher anastomotic leakage rate due to reduced micro or macro perfusion of the gastric conduit, may benefit significantly from gastric ischemic preconditioning performance [40].

4. Conclusion

Despite technological improvement and adoption of minimally invasive techniques, the fashion of esophagogastric anastomosis remains a point of controversy as well as the Achilles heel of minimally invasive esophagectomy. More multicenter randomized clinical trials are necessary to establish the indications of each technique as well as basic principles of patient safety. In addition, apart from the debate regarding optimal anastomosis technique, attention should be paid to the learning curve of the described methods, which should be smoothed through well-structured training programs.

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Conflict of interest

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