

## Diagnosis, assessment, and management of surgical complications following esophagectomy

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### **Graphical abstract**

Surgical complications such as anastomotic leaks, fistula, postoperative pulmonary complications, and chylothorax can occur following esophagectomy. This review seeks to identify potential risk factors, modalities for early diagnosis, and novel interventions that may ameliorate the potential adverse effects of these complications.

## Abstract

Despite improvements in operative strategies for esophageal resection, anastomotic leaks, fistula, postoperative pulmonary complications, and chylothorax can occur. This review seeks to identify potential risk factors, modalities for early diagnosis, and novel interventions that may ameliorate the potential adverse effects of these surgical complications following esophagectomy.

## Introduction

Anastomotic leakage after esophageal resection is one of the most feared postoperative complications, occurring in 5% to 20% of cases,<sup>1, 2</sup> and can result in 30-day mortality of 2.1% to 35.7%.<sup>3, 4</sup> Reasons for the gravity of these complications are both the anatomy of the esophagus and the location of the anastomosis. A recent meta-analysis including nearly 3000 patients showed worse long-term prognosis in patients with severe leakage after esophagectomy.<sup>5</sup> According to a recent review of the experiences of 24 experienced centers worldwide, in a group of 2704 consecutive patients undergoing esophagectomy, 30-day and 90-day mortality were 2.4% and 4.5%, respectively, with an overall complication rate of 59%, including pneumonia and leak rates of 15% and 11.4%, respectively.<sup>6</sup>

Furthermore, this complication increases hospital stay, delays oral (but not necessarily enteral) feeding, and increases risks of both stricture formation and reoperation. Anastomotic leakage has been associated with poorer quality of life, increased cancer recurrence rates, and subsequently worsened long-term survival.<sup>5, 7-9</sup> Despite the increasing utilization of intrathoracic anastomosis, the rate of cervical anastomosis use remains approximately 40% in a large cohort of patients treated between January 2015 and December 2016 by dedicated esophageal surgeons.<sup>6</sup> In view of these data, is cervical anastomosis still an important technique to master in the arsenal of esophageal surgeons?

Multiple risk factors for leakage have been proposed in the literature.<sup>10</sup> Treating co-morbidities (malnutrition,<sup>11</sup> diabetes,<sup>12</sup> smoking cessation, and reduction of steroid use) whenever possible is obviously important. Placing the anastomosis in previously irradiated, and thus vascular-compromised, tissue<sup>13</sup> could also be a risk factor, but also of necessity given the importance of combined modality treatment to optimize the oncological outcomes for esophageal cancer treatment. Limiting trauma to the gastric conduit and to the vascular axis alongside the greater curvature by using gentle surgical and no-touch technique is of the utmost importance. Great care should be taken to mobilize adjacent omentum with the vascular axis consisting of the right gastroepiploic arcade, staying as far away as possible from this axis during dissection to avoid damage to collateral circulation. Increased vascularization through ischemic preconditioning has so far failed to show a significant decrease in leakage rate<sup>14</sup> but enhanced visualization of conduit vascularization in an attempt to define the non-ischemic zone for placing the anastomosis seems promising. Several types of anastomosis have been reported and compared (hand-sewn vs stapled, circular vs triangular, end-to-end vs end-to-side) but no single technique has been shown to be superior to others in terms of leakage, although non-circular anastomosis (triangular or semi-mechanical) seems to increase the quality of life in the first postoperative year and decreases the risk of stricture and subsequent need for dilatation.<sup>15</sup>

Not only safe anastomosis, but also timely identification of anastomotic or other surgical complications are essential to reduce morbidity, prolonged hospitalization, mortality, and consequently additional medical costs.<sup>16-18</sup> Both surgical expertise and experience are key elements for limiting the leakage rate and managing its consequences after esophagectomy, and it is argued that centralizing surgical care may be a key determinant of lower leakage rates.<sup>5, 19</sup> Our goal is to provide a succinct review of key principles and current knowledge relating to risk factors, modalities to identify and manage anastomotic leakage as well as

associated technical complications, particularly airway fistula, respiratory failure, and chylothorax, that can impact development of a leak in patients undergoing esophagectomy.

## **Risk Factors**

### *Impact of anastomotic location*

While there are several confounding factors, such as anastomotic technique (stapled versus hand-sewn) or minimally-invasive versus open approaches, the location of the anastomosis based on tumor location, patient performance status, and functional results remains an important determinant of anastomotic leaks. Cervical anastomoses have been associated with greater leakage rates (25-45%) compared to intrathoracic anastomoses (5-15%)<sup>20, 21</sup> and may lead to increased recurrent nerve palsy and longer hospital stays.<sup>22</sup> A cervical anastomosis requires a longer gastric conduit and is more likely positioned in the fundus, where vascularity is limited. Although anastomotic leaks are more frequent with cervical anastomoses, such leaks are easier to manage and are less likely to result in profound sepsis. The functional results, however, are thought to be better after an intrathoracic anastomosis despite a lack of clear evidence in the literature. More recent nonrandomized trials show similar results with an intrathoracic leakage rate between 3.5% and 23% compared to a leakage rate between 28% and 33% in the neck.<sup>23-25</sup> Minimally invasive surgery has been introduced to minimize surgical trauma and reduce the perioperative complication rate. Different operative techniques exist, including robotic surgery, and reports of early experiences have been published. However, a recent publication from the Netherlands, assessing a total of 866 patients, reported higher anastomotic leakage in the minimally-invasive group (21.2% vs. 15.5%).<sup>2</sup> Subgroup analysis showed a lower leakage rate in the intrathoracic anastomosis group for both the open (10% vs 17%) and the

minimally-invasive (21% vs 23%) procedures, with an overall complication rate of 63% and 67%. A randomized trial assessing this endpoint in minimal invasive esophagectomy is in progress.

Four randomized trials have shown lower anastomotic leakage (4-7% vs 2-39%) and less recurrent nerve palsy in favor of intrathoracic anastomosis,<sup>26-29</sup> although mortality rates were similar (2-17% vs 2-14%).<sup>30</sup> One interpretation is that cervical anastomotic leaks are easier to manage and carry a lower systemic burden for the patient whereas intrathoracic leaks are more likely to have a detrimental impact on the patient, despite modern therapeutic options. The potential systemic burden of such complications might result in a similar mortality between the two techniques. Of note, the latest randomized trial was published in 2007 before endoluminal sponge therapy and other techniques were available. Data assessing anastomotic level in minimally-invasive esophagectomy are needed and have currently been submitted for publication.

In conclusion, although cervical esophageal anastomoses are associated with higher leakage rates compared to intrathoracic anastomoses, similar perioperative mortality suggests that a cervical leak has less risk for mortality. The implementation of advanced endoscopic treatments for anastomotic leaks could modify the impact of leaks on morbidity and mortality.

#### *Ischemic pre-conditioning and subsequent risk for anastomotic leak*

The prevention and treatment of anastomotic leaks is important due to the associated mortality. There are several determinants of anastomotic leaks, such as: (1) the intrinsic anatomic factors of the esophagus, (2) the negative pressure within the thoracic cavity and (3) anastomotic technique, including either hand-sewn or stapled anastomoses.

Esophageal reconstruction mostly involves the stomach (more than 90% of cases). Various techniques and modalities that prevent anastomotic leakage have been introduced and assessed, including preoperative partial gastric devascularization, i.e. ischemic conditioning of the stomach, and subsequent delayed esophagogastric anastomosis.<sup>31</sup> Kechagias and colleagues<sup>14</sup> summarized the experimental and clinical studies with the purpose of assessing the current role of the ischemic conditioning technique. Their report did not identify any significant reduction in the incidence of anastomotic leakage after esophagectomy despite staged ischemic conditioning.

The prevention of anastomotic leak should focus on preoperative nutritional status, intraoperative maneuvers that minimize direct trauma to the conduit, and postoperative management. The longer the gastric conduit is made, the more prone it will be to ischemia at its tip. Maintaining the conduit's blood supply and the ease of operation need to be balanced. The gastric conduit is perfused only via the right gastroepiploic artery which provides blood to 60% of the distal stomach, whereas the remaining 40% of the more proximal stomach depends on its vascular supply from a submucosal network of small vessels (Figure 1). The stomach is tailored to form a 4-cm-wide neo-esophagus to obtain a tubular-shaped conduit, with resection of the poorly vascularized fundus, permitting anastomosis closer to the right gastroepiploic artery branches.<sup>32</sup> Moreover, a tubular-shaped conduit promotes alignment of the anastomosis and pylorus to address the anatomical and mechanical problems of gastric retention and emptying, thereby reducing the risk of anastomotic leakage.<sup>32</sup> Additionally, improving perioperative management and resuming early postoperative enteral nutrition, pulmonary physiotherapy, as well as preventing hypoxemia and hypotension, are all important measures to reduce the occurrence of an anastomotic leak.<sup>32</sup>

## Definitions and classifications of anastomotic leak

Anastomotic leaks are typically defined as the presence of contents emerging at the wound and associated systemic complications,<sup>33</sup> although nearly half of leaks initially are clinically silent. The Esophagectomy Complications Consensus Group (ECCG) defines anastomotic leaks as a “full-thickness gastrointestinal defect involving esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification.”<sup>34</sup> This same group classifies leaks into three types:

- Type I: Local defect requiring no change in therapy or treated medically
- Type II: Localized defect requiring interventional but not surgical therapy
- Type III: Localized defect requiring surgical therapy

Lerut *et al.* used a modified classification from the Surgical Infection Study Group, dividing leaks into 4 grades:<sup>35</sup>

- Grade 1 (radiologically or endoscopically detected): without clinical signs
- Grade 2 (minor clinical): local inflammation
- Grade 3 (major clinical): severe disruption with sepsis
- Grade 4 (conduit necrosis): confirmed by endoscopy

To properly diagnose a leak, two issues should be taken into consideration. First, that the leak should not only be confirmed but also be graded simultaneously. Second, that there is a significant difference between diagnosing suspected leaks, where the best test(s) are

needed in terms of sensitivity and specificity, and diagnosing an unsuspected leak, where the usefulness of routine tests should be evaluated.

### **Diagnosis of anastomotic leak and fistula**

Clinical signs of a leak can vary significantly and range from no clinical signs to pleural collection to fulminant sepsis. A gold standard for diagnosing leakage has not yet been established. If this complication is suspected, it is crucial that further medical tests are administered directly as any delay can significantly affect the patient's prognosis. In contrast to a cervical leak, diagnosis of a thoracic anastomotic leak can be more difficult, and a standardized international definition does not exist.<sup>36</sup> If an anastomotic leak is suspected, two aspects should be considered: the clinical signs of the patient and the available diagnostic tools. The question remains as to when does one need to investigate and what tool(s) should one use. Various modalities to diagnose anastomotic leaks have been proposed:

- Clinical signs, drain fluid, and blood tests
- Upper endoscopy
- Contrast esophagogram
- Computed tomography scan (with or without oral contrast)

*Clinical signs, drain fluid, and blood tests*

Early signs of complications, although sometimes subtle, should be pursued. Such patients often present initially with postoperative fever or leukocytosis. The development of erythema or induration along the neck incision (if present) may alert the surgeon of an underlying leak and trigger further diagnostic studies. Changes in heart rate, often in form of atrial fibrillation, can be the first and only indicator of a leak,<sup>37</sup> as well as unexplained high levels of inflammation markers in the blood (white blood count, C-reactive protein).<sup>38</sup> The serum level of C-reactive protein can allow detection of leaks on postoperative days 3 or 4.<sup>39</sup> The presence of saliva or gastric contents in a drain are obvious signs of a leak, but the routine analysis of drain amylase levels on day 4 may detect leaks earlier and even more accurately than barium esophagogram.<sup>40</sup> In addition to clinical signs, there are several diagnostic methods that can help determine whether the patient has developed anastomotic leak: endoscopy, contrast swallow examination or computed tomography (CT).

#### *Upper endoscopy*

Many surgeons hesitate to perform upper endoscopy because of the risk of disrupting the anastomosis. Recent studies in an *in vivo* porcine model demonstrated that intraluminal pressure greater than 80 cm H<sub>2</sub>O is needed to disrupt an esophagogastric anastomosis. Endoscopic air insufflation should always be gentle and progressive but even with maximum insufflation the intraluminal pressure at the anastomosis never increases beyond 9 cm H<sub>2</sub>O, with minimal disturbance of the blood flow in the conduit.<sup>41</sup>

Clinical studies have confirmed that upper endoscopy performed within 1 week after esophagectomy is safe and can be performed at the bedside, even in a patient who is intubated,<sup>12, 42</sup> without worsening an already existing leak.<sup>20</sup> The sensitivity of endoscopy is

relatively high not only to assess the anastomosis but also to identify any degree of alteration of the integrity of the conduit, from mucosal ischemia to necrosis, and to provide information about the vitality of the gastric conduit.<sup>7</sup> In a prospective non-randomized trial comparing other modalities and endoscopy to identify EAL after esophagogastric surgery, Hogan *et al.* did not observe any complication due to endoscopy<sup>43</sup> and confirmed the safety and feasibility of early endoscopy in case of a suspected anastomotic leak. Endoscopy should be considered in patients with suspected anastomotic leak as it may be helpful to select those who might need surgical revision of the anastomosis.

Endoscopic evaluation must be performed carefully with low insufflation pressure<sup>7</sup> by an experienced gastroenterologist or surgeon in order to limit the theoretical risk of worsening the defect and/or the perianastomotic sepsis. Upper endoscopy has a few drawbacks. Its use with sedation may lead to aspiration in some patients, and is performed under general anesthesia in many centers. In addition, although its sensitivity is relatively high as a routine test for detecting intrathoracic leaks, a recent study of cervical anastomotic leaks compared the routine use of endoscopy and esophagogram and found a sensitivity of 56% and 20%, respectively.<sup>44, 45</sup> Therefore, its routine use in patients without clinical suspicion of cervical leakage is controversial.

In summary, endoscopy is a very useful diagnostic method and can effectively complement, if not altogether replace, other diagnostic means.<sup>12, 45</sup> In spite of the high specificity and sensitivity of endoscopy, it still is not recommended as a routine means of detecting leaks in the post-operative phase.<sup>46</sup>

*Contrast esophagogram*

The traditional approach to diagnose an esophageal leak has been to begin the study using a water-soluble contrast agent (such as Gastrografin) to prevent exacerbation of cervical sepsis by the leaked barium. While this is an inexpensive and relatively safe method, this test only fulfills its diagnostic potential when the execution of the test and the interpretation of the results is undertaken by an experienced radiologist.<sup>47</sup> Gastrografin can cause severe chemical pneumonitis if aspirated. Esophagectomy patients frequently have altered swallowing function and these exams should be avoided in case of impaired consciousness because of the risk of aspiration. A normal study with a water-soluble agent should be followed by thin barium to improve sensitivity for detection of a leak by 15%.<sup>47</sup> Even a negative barium study does not rule out a leak because of its sensitivity of only 40% (33-52%) in patients with cervical anastomosis.<sup>48, 49</sup> These rates are worse than those for intrathoracic leaks (93%), but specificity rates greater than 90% have been reported for such evaluation of both cervical and thoracic anastomoses.<sup>50</sup> Given that nearly a third of the patients diagnosed with leakage have their cervical wounds opened based upon clinical suspicion prior to scheduled contrast swallow, this test changes patient management in only 1.5% of the cases.<sup>48, 49</sup> Further limitations of this method include an insufficient intake of the contrast agent or aspiration.<sup>12, 51, 52</sup> Consequently, this method should be regarded as an inadequate routine diagnostic modality when aiming to diagnose a leakage.<sup>53</sup> Nevertheless, its high specificity rates imply a potential ongoing role for confirming clinical suspicion of a leak, but its low sensitivity implies a less prominent role.

### *Computed tomography*

CT with or without oral contrast is a unique modality as it allows visualization of the neck, thorax, and abdomen on a single examination. In addition to the diagnosis of an anastomotic

leak, CT scan provides the location and extent of peri-anastomotic collections and covers a broader differential diagnosis than leakage alone (e.g., pulmonary complications).<sup>43, 54</sup> The sensitivity of CT in detecting fistula, wall discontinuity, and mediastinal fluid or air is up to 80%.<sup>55</sup> CT imaging is non-invasive, fast, and safe in critically ill patients.

The assessment of a postoperative CT scan remains challenging because of the anatomic changes and residual air caused by esophagectomy, and lack of consensus on radiographic findings associated with leakage. This is supported by the large difference in published diagnostic values from studies that have assessed the clinical diagnostic ability of CT imaging for the detection of anastomotic leakage. Reported sensitivity and specificity by these studies range from 52% to 88% and 33% to 100%, respectively.<sup>43, 52, 54-56</sup> In most of these studies, one or two radiologists independently determined their own definition of anastomotic leakage based upon a variety of radiologic findings.<sup>43, 52, 54-56</sup>

Two studies have assessed the association of specific postoperative CT findings with anastomotic leakage after esophagectomy. In these studies, the presence of mediastinal air, mediastinal fluid, and contrast leakage were associated with anastomotic leakage.<sup>52, 56</sup> However, these studies found that using solitary CT findings for diagnosis of anastomotic leakage resulted in lower diagnostic accuracy compared to assessment by independent radiologists who determined their own definition of leakage.<sup>52, 56</sup> This is likely because single CT features are either too specific and not very sensitive, or vice versa. For example, contrast leakage after esophagectomy is a very specific finding for the presence of an anastomotic leak. In many patients with leakage, however, extravasation of contrast can be absent, consequently resulting in a low sensitivity.<sup>52</sup> On the other hand, presence of mediastinal air near the anastomosis is highly sensitive for the presence of leakage, but because this can be a frequent finding after esophagectomy this finding is not specific.<sup>52, 56</sup>

A recent study that assessed 122 patients who underwent CT imaging for clinical suspicion of anastomotic leakage identified a risk score to overcome these limitations.<sup>55</sup> In this study, the potential findings of mediastinal fluid, mediastinal air, and anastomotic wall discontinuity and fistula were significantly associated with anastomotic leakage (Figure 2). Based on these factors an anastomotic leakage prediction score (ALP score) was developed with a sensitivity of 80% and specificity of 84% for the detection of leakage. The ALP score significantly outperformed the original clinical interpretation by radiologists (reported sensitivity of 52% and specificity of 84%, respectively).<sup>55</sup>

These data suggest that combining different well-recognizable CT findings in a risk score can improve the diagnostic accuracy of CT imaging for the diagnosis of anastomotic leakage after esophagectomy. In cases when the results of a CT scan remain uncertain, endoscopy could be performed, as this has proven to be an accurate test for the diagnosis of leakage.<sup>55</sup>

Unlike symptomatic patients, sensitivity of a CT scan performed routinely on postoperative day 7 after intrathoracic anastomosis in asymptomatic patients was estimated in a study by Strauss *et al.* at 54.5%, compared to 45.4% for esophagogram.<sup>52</sup> These rates are worse when evaluating cervical leaks only. As a consequence, rather than being performed routinely, these exams should probably be undertaken only when a leak is suspected. Unlike upper endoscopy, CT scan does not provide information about gastric conduit viability; as with endoscopy, which includes options for therapy, CT imaging also can identify mediastinal fluid collections that might be accessible for percutaneous drainage.

*Order of investigation*

Typically asymptomatic patients are to be followed clinically, including measurements of serum C-reactive protein and drain amylase levels. Contrast esophagogram done routinely between days 4 and 7 has low sensitivity, but provides information on the conduit and gastric emptying. Upper gastro-intestinal endoscopy has better sensitivity and specificity (100% and 100%, respectively) versus 87.5% and 90% for swallow test and 87.5 and 100% for CT scan.<sup>43</sup> When a leak is suspected, both endoscopy and CT scan should be considered. In addition to confirming the diagnosis of leakage, these methods provide essential information for initial treatment. Endoscopy is the only method that can assess the viability of the conduit and CT identifies peri-anastomotic collections. Even if exploration of a cervical wound is planned for confirmation of conduit viability and drainage of any fluid collection or abscess, endoscopy and CT are necessary to assess the thoracic extension of these conditions.

#### *Leak management*

In treating a suspected or confirmed anastomotic leak, the general principles include control of sepsis (with drainage as needed), ensuring adequate nutrition, and consideration of antimicrobial therapy. The primary aim of early endoscopy is to identify a leak due to conduit ischemia. In case of severe ischemia or necrosis, emergency salvage surgery, including reversal of the anastomosis and conversion to an end esophagostomy, is mandatory. In case of mild ischemia without anastomotic leakage, endoscopy should be repeated within several days (as determined by patient stability). In case of an anastomotic leakage with mild ischemia, either non-operative treatment or anastomosis revision can be considered. In case of a leak without ischemia, management includes (1) nasogastric drainage, (2) endoscopic treatment (pig tail or prosthesis) or revision of the anastomosis, or (3) administration of anti-

acid drugs. Early endoscopy is safe when performed cautiously, including low insufflation pressure, by an experienced endoscopist or the operating surgeon. With a very low complication rate, it is the most sensitive test for diagnosis of EAL and gastric conduit viability.

### **Detection of gastric conduit ischemia**

One of the major factors contributing to the risk of esophagogastric anastomotic leakage following esophagectomy is the detection of gastric conduit ischemia. The native stomach has a rich blood supply derived from the right and left gastric arteries, right and left gastroepiploic arteries, and short gastric arteries. During routine esophagectomy, the stomach is fully mobilized, requiring division of at least the left gastric, left gastroepiploic, and short gastric arteries. Consequently, the fundus of the stomach becomes a watershed zone of potentially compromised blood flow. The fundus also serves as the primary target site for anastomosis to the cervical or thoracic esophageal remnant. Although complete conduit necrosis is rare, it is a devastating complication occurring in less than 2% of esophagectomies. Avoidance of conduit ischemia, defined as inadequate tissue perfusion, is one of the most important criterion for successful esophageal reconstruction.<sup>10, 57</sup>

Several factors appear to contribute to lower risk of complications following esophagectomy for malignancy. These include participation of multidisciplinary care teams, early surgical consultation prior to initiation of treatment, assessment of nutritional status with enteral support via oral or feeding tube supplementation, smoking cessation, diabetes management, epidural pain management, and judicious perioperative fluid management. Intraoperative decision-making should include careful assessment of the gastric blood supply, particularly

in the setting of prior operations; abdominal adhesions can obscure identification and preservation of the right gastroepiploic arcade. If gastric conduit reconstruction is not available or fails, alternative esophageal replacement strategies should be considered.<sup>58, 59</sup>

Intraoperative detection of conduit ischemia has traditionally depended on clinical judgment, with questionable reliability. A variety of other methodologies have been used clinically to assess tissue perfusion, but none have achieved widespread acceptance. Fluorescein angiography with Wood lamp is cost-efficient and widely available, but is limited to a one-time injection with >12-hour half-life and dye extravasation into the extracellular space. Conventional angiography is time-consuming and difficult to perform in the operating room setting. Use of the handheld Doppler probe, optical fiber spectroscopy, and measurement of transmucosal oxygen saturation are technologies that are either limited to microvasculature assessment or unable to show variations in regional conduit perfusion. Intraoperative esophagogastroduodenoscopy risks injury to the newly created anastomosis and does not demonstrate gastric conduit vasculature.<sup>60, 61</sup>

The reintroduction of laser-induced indocyanine green (ICG) fluorescence for both open and minimally-invasive surgery has attracted new enthusiasm for the intraoperative detection of conduit ischemia. This vascular imaging technology has several advantages, including real-time assessment of both the microvasculature network and a macroscopic view of regional organ perfusion without radiation exposure. With a short plasma half-life of 3–5 minutes, ICG has rapid tissue clearance and can be readministered during the same operation for pre- and post-reconstruction evaluation. Indocyanine green is eliminated solely by bile excretion, permitting its use in patients with chronic renal disease.<sup>61</sup> Of note, this dye is contraindicated for patients with allergic reactions to iodinated agents. Zehetner *et al.* utilized

this technology to assess regional perfusion of the gastric conduit and correlated perfusion findings with subsequent anastomotic leaks in 150 consecutive patients undergoing esophagectomy.<sup>62</sup> Although the overall anastomotic leakage rate was 16.7%, the leakage rate was only 2% when the anastomosis was placed in an area of robust perfusion, as determined by ICG fluorescence. In comparison, when anastomoses were constructed in an area of diminished perfusion, anastomotic leaks occurred at a rate of 45% ( $P < 0.0001$ ), confirming a critical relationship between conduit ischemia and risk of anastomotic leak.

Intraoperative real-time assessment of gastric conduit perfusion with laser-assisted ICG fluorescence may increase the sensitivity for detecting gastric conduit ischemia compared to other methodologies or clinical judgment alone. Such information can help guide critical decision making for esophageal reconstruction and may contribute to reduced risk of anastomotic leakage and its associated morbidity following esophagectomy.

## **Treatment considerations**

### *State of the art management of anastomotic leakage*

According to the current literature, cervical leakage is significantly higher than intrathoracic anastomotic insufficiency (32% vs. 15%).<sup>24, 63-66</sup> Possible contributing factors include the longer distance of the gastric interponat needed for cervical anastomosis, greater anastomotic tension, worse microcirculation at the tip of the esophageal substitute, and higher risk of compression at the thoracic inlet. However, cervical leaks are associated with less life-threatening complications, especially those with infectious presentations, such as mediastinitis, sepsis, erosion, bleeding, and aerodigestive fistulae, as compared to intrathoracic leaks.

Division of the interclavicular ligament beneath the sternum with resection of the left sternoclavicular joint might prevent compression of the gastric conduit.<sup>67</sup> Randomized controlled trials (RCTs) comparing end-to-end vs. end-to-side cervical anastomoses revealed increased leakage in the latter,<sup>68</sup> yet there were no differences in cervical anastomotic leak rates between hand-sewn vs. stapled side-to-side anastomoses.<sup>15, 69</sup> To date, no definitive technique aiming at prevention of cervical leakage can be recommended with respect to the evidence.<sup>59</sup> In analogy to intrathoracic anastomotic insufficiency, cervical leaks are classified clinically according to Lerut *et al.*,<sup>35</sup> Siewert *et al.*,<sup>20</sup> Veeramootoo *et al.*,<sup>70</sup> or Nishikawa *et al.*<sup>71</sup> Nishikawa *et al.* reported an endoscopic mucosal classification that considers the extent of mucosal impairment (from intact mucosa, to mild to severe mucosal degeneration) and correlates well with the occurrence of postoperative anastomotic complications, offering an approach to individualized therapy.<sup>71</sup> State-of-the-art management of anastomotic leakage is built upon three main pillars (Table 1): (1) conservative measures to address the vast majority of these complications; (2) endoscopic interventional treatment; and (3) surgical revision. These principles depend on the extent of circumferential involvement, the control of sepsis, and the presence of ischemia/necrosis of the gastric conduit.<sup>59, 64</sup> The treatment of cervical or intrathoracic anastomotic leakages follow the same principles, including adequate drainage. However, due to the anastomotic location, the access for drainage is different and explains the different trends for treatment, for example, opening of the cervical wound vs. intrathoracic endosponge treatment.

The placement of self-expandable stents has proven to be a viable and effective treatment for anastomotic leakage.<sup>72</sup> While technically straightforward, stent placement requires several considerations. Anastomotic leakage or subsequent stricture within 2 cm of the cricopharyngeus muscle may not be amenable to stenting as the patient may experience an intolerable globus sensation. Angulation of the conduit or anastomosis also can affect

adequate stent placement.<sup>73</sup> Stent migration is a common complication for which the use of large diameter stents (22–25 mm)<sup>74</sup> and even colonic stents with a flange diameter of up to 32 mm have been reported.<sup>75</sup> Others have used endoscopically deployed sutures<sup>76</sup> or placed a silk thread affixed to the nose or ear lobe<sup>77, 78</sup> to prevent stent migration. A 4- to 8-week (or even shorter) period of stenting is usually adequate for healing of most anastomotic leaks.<sup>74, 79</sup> Stenting for 2 weeks may be sufficient for management of most anastomotic leaks and also might reduce the frequency of stent-related complications, such as fistulization (to airway or vascular structures), migration with distal bowel obstruction, esophageal necrosis, and stent fracture or degradation.<sup>79</sup>

Among endoscopic interventions, endoscopic vacuum therapy (EVT)/endosponge therapy (EST)<sup>80-82</sup> seems to be more favorable and technically easier as compared to the use of self-expandable metal stents (SEMS).<sup>83</sup> Current data regarding outcomes of EVT/EST *versus* SEMS do not differentiate between cervical and intrathoracic anastomotic insufficiency and include mixed cohorts, including Ivor Lewis (intrathoracic anastomosis) and McKeown (cervical anastomosis) esophagectomies, as well as gastrectomies.<sup>81, 83</sup> The stent-over-sponge (SOS) therapy has similar problems for cervical anastomoses as the above-mentioned drawbacks of SEMS.<sup>84</sup> The “bear claw”/over-the-scope-clip (OTSC®) system might be an option in a newly opened dehiscence with viable mucosa and strong tissue quality in both components of the anastomosis,<sup>85</sup> with the respective risk of injuring adherent cervical structures such as the carotid artery, the trachea, or the recurrent laryngeal nerve (RLN). Application of the OverStitch™ can be technically difficult when applied in the cervical esophagus but may be a better option for leaks in the middle or distal third of the esophagus, although this is described only in anecdotal reports,<sup>86</sup> whereas there have been reports of this approach for other types of esophageal fistulae.<sup>87</sup> Combined fibrin glue and vicryl plug

can be applied in small defects only and usually requires multiple repetitions of the procedure.<sup>88</sup>

Endosponge treatment (endoscopic vacuum-assisted closure or Endo-VAC) has been used to treat esophageal anastomotic leaks successfully over ten years.<sup>89</sup> The first retrospective and prospective studies including over 50 patients show that endosponge treatment is equivalent or even superior to endoscopic esophageal stent treatment.<sup>80, 90</sup> It has also been shown that even complex anastomotic leaks can be treated using a combination of endosponge and esophageal stent treatment (Table 1).<sup>84</sup>

As an example of endosponge utilization, the perioperative outcomes of one referral center for gastric and esophageal cancer surgery in Mainz, Germany include an intra-thoracic anastomotic leakage rate below 15% for patients undergoing minimally invasive laparoscopic/thoracoscopic and robotic-assisted Ivor Lewis resections. Of 17 cases of intrathoracic anastomotic leaks treated with endosponge at the University of Mainz, 16 patients were successfully treated using endosponge alone, while one patient required esophageal stent placement after downsizing the leak with the endosponge. In addition, endosponge therapy for complex postoperative perforations, such as an acquired tracheoesophageal fistula, may be used and can avoid surgical removal of an interponat (P.P. Grimminger, personal communication). Although the endosponge may become the first choice for management of esophageal perforations and anastomotic leaks, esophageal stents, fibrin glue injection, and other endoscopic tools remain important for second-line treatment.

Surgical options include pedicled muscle flap (such as sternocleidomastoid, pectoralis major, or, as described below, intercostal muscle) repair for complex cervical fistulas/leaks.<sup>91,92</sup> If gastric fundic tip necrosis (local ischemia) is present, resection of the necrotic tissue and

refashioning of the anastomosis, if possible, are necessary.<sup>59</sup> In the face of gross or diffuse ischemia of the gastric conduit, diversion surgery, dismantling the gastric pull-up, and placing a temporary esophagostomy with staged colonic interposition is inevitable.<sup>59, 64</sup>

Initial management for intrathoracic anastomotic leakage typically is not operative. There has been a paradigm shift in the management of intrathoracic leaks due to advances in early diagnosis, improved critical care, and endoscopic diagnostic and therapeutic strategies that has tilted the balance from aggressive surgical intervention to conservative management.

The factors which govern management include:

- Type of presentation
- Magnitude of leak
- Time of recognition
- Status of the patient
- Status of esophagus and conduit
- Operative expertise

The presentation of an intrathoracic anastomotic leak, as defined earlier in this review, could be evident clinically or as an endoscopic diagnosis, depending upon the magnitude of the leak. The extent of leakage also dictates the general condition and status of the patient. Major determinants of outcome are the status of the remnant esophagus and gastric conduit. Compounding factors include integrity of the anastomotic or conduit staple lines and the presence of distal obstruction.

Use of systemic antimicrobial therapy, closing or occluding the defect at the earliest possible time, draining the fluid collection, preventing or relieving distal obstruction, ensuring lack of factors keeping the perforation open, and, finally, esophageal diversion or resection if sepsis is poorly controlled, are the major steps in management of an intrathoracic anastomotic leak.<sup>93</sup>

The surgical technique adopted depends upon the magnitude of leakage and the presence of ischemia of the esophageal remnant or gastric conduit, with the extreme being total conduit necrosis. Anastomotic disruption without conduit ischemia can be managed by revision of the anastomosis with reinforcement using a pedicled pleural, pericardial, or viable intercostal muscle flap as described below. Completion gastrectomy and end cervical esophagostomy can limit the consequences of sepsis related to a severe anastomotic leak or conduit necrosis. Reoperation for subsequent reconstruction is technically challenging and should be undertaken once the patient's functional status has been optimized and restaging evaluations confirm no evidence of recurrent or metastatic disease.

#### *Surgical treatment of a tracheoesophageal fistula after esophagectomy using an iinterposition flap*

Aerodigestive fistula is a rare life-threatening complication of the surgical treatment of esophageal cancer. A perioperative fistula is defined as that caused by major airway injury during esophagectomy or occurring after operation. A variety of strategies have been recommended for treatment, likely due to the differing anatomic levels of presentation. Few case reports and case series have described successful management. Hence, the optimal treatment remains elusive. Neoadjuvant radiation therapy must be taken into consideration when reoperation is necessary. Two major strategies can be adopted when the diagnosis of

an aerodigestive fistula is confirmed: endoscopic treatment with a fully covered self-expanding stent or surgical treatment using an interposition flap.

Of 530 articles initially identified by systematic review,<sup>94</sup> 9 studies (Figure 3) described outcomes for 27 patients, 17 of whom had flaps (total, 18) placed. Of the 17 patients, 13 were alive at the time of reporting. Various tissue flaps were described, including three latissimus dorsi flaps,<sup>95-97</sup> five pectoralis major flaps,<sup>92, 97-99</sup> two sternocleidomastoid muscle flaps,<sup>100, 101</sup> one intercostal muscle flap,<sup>97</sup> one sternohyoid muscle flap,<sup>102</sup> one skin perforator pedicled by an intercostal muscle flap,<sup>103</sup> five pericardial flaps,<sup>101</sup> and one pleural flap.<sup>102</sup> No clear evidence supports the superiority of any one operative approach.

The institutional experience at Rennes University Hospital from June 2016 through August 2017 included six patients who developed tracheobronchoesophageal fistula after treatment for esophageal carcinoma. All six patients had received neoadjuvant chemotherapy and five had received radiation therapy (<50 Gy). One patient had sustained an intraoperative injury of the left main stem bronchus and the remaining five developed postoperative fistulae at a mean of  $15.8 \pm 7.8$  days after surgery. At the time of diagnosis, before reoperation, five patients were in septic shock and required mechanical ventilation ( $n = 4$ ), vasopressor or inotropic support ( $n = 3$ ), and/or respiratory assistance via extracorporeal membrane oxygenation (ECMO;  $n = 2$ ).

All patients were treated using an interposition flap with a skin perforator flap pedicled with intercostal muscle harvested from sites depending on the location of the perforator flap and previous operations.<sup>103</sup> Using an 8-MHz handheld Doppler ultrasonographic device, the cutaneous perforator vessels in the right fifth to eighth intercostal spaces were identified. An elliptical skin flap was fashioned around the vessels to allow primary closure of the donor site. The skin flap was harvested and the intercostal muscle elevated after ligating the

intercostal pedicle anteriorly to the perforator vessel. The subperiosteal muscle flap was separated from the adjacent rib, maintaining continuity with the parietal pleura. The latissimus dorsi muscle was preserved, offering an alternative flap. While maintaining the epithelium in an area of the size of the fistula, the remaining skin layer was de-epithelialized to facilitate adherence to the airway mucosa (Figure 4).

For this particular report, the gastric tract was preserved in five patients. In one patient, preparation of a second muscle flap was required when intraoperative dissection revealed that the intercostal pedicle for the planned flap had been sectioned by a suture from prior thoracotomy, despite harvesting of the initial flap from two intercostal spaces inferiorly. Of these six patients, three were alive and required reoperation for residual fistula. Three patients had died due to massive gastrointestinal bleeding, mesenteric ischemia, and multiorgan failure, respectively. These three patients required vasopressor support preoperatively, and two had also received ECMO.

Tracheobronchoesophageal fistula is a rare and life-threatening complication of the surgical treatment of esophageal cancer. Fistulae lead to microbial overgrowth, resulting in pulmonary infection, septic shock, and, ultimately, organ failure. As multiorgan failure severe enough to require vasopressor or ECMO support is associated with greater morbidity and mortality, rapid and precautionary diagnosis and surgical intervention before visceral failure are imperative. Currently, no guideline specifies the best strategy; endoprosthesis treatment is often chosen as a first-line therapy because of its availability and relative ease, although the outcome of stent coverage is poor.<sup>104</sup> In contrast, interposition flap repair is more complex and often deferred to a specialized team but should be considered. After initial stabilization, an intercostal pedicled flap can be prepared as an initial phase of reoperation, allowing direct closure of the donor site. The flap has a long pedicle with a pivot point close

to the trachea that enables preservation of the gastric conduit and avoids tracheoesophageal compression.

### **Other complications that may impact the conduit or anastomosis**

#### *Pathophysiology of post-operative pulmonary complication (POPC)*

The reported incidence of POPC ranges from 8% to 36%; this variation may arise from the differences in definition for POPC.<sup>105</sup> In some reports, respiratory complications are defined by therapeutic criteria such as the use of interventions, including the need for and the duration of ventilatory assistance.<sup>106</sup> It also is defined as an ICU stay longer than 5 days.<sup>107</sup> In some reports, all abnormalities in the lungs and pleura after esophageal resection are defined as respiratory complications.<sup>108</sup> The lack of standardized definitions of POPC precludes valid comparisons of incidence rates across such studies. Defined grading of surgical complications, consisting of five tiers of increasing severity, has been suggested to standardize the definition of surgical complications and to increase comparability of the data from different studies.<sup>109</sup> This schema does not distinguish respiratory complications related to the technical aspects of the surgical procedure from respiratory complications due to other factors.

Preoperative, intra-operative, and post-operative factors have been associated with pulmonary complications after esophagectomy for cancer. Preoperative factors for POPC include age, nutritional status, use of induction therapy, baseline pulmonary function, ethanol use, smoking history, and poor performance status. Intraoperative details include stage, location of tumor, surgical approach, estimated blood loss, length of surgical procedure, entry into two separate body cavities, and disruption of bronchial innervation or lymphatic

circulation. Postoperative causes include pulmonary hygiene, vocal cord paralysis, RLN palsy, and postoperative respiratory muscle dysfunction.<sup>110</sup>

Aged patients are more likely to have underlying, subclinical swallowing disorders, thus predisposing such patients to postoperative complications such as aspiration and pneumonia.<sup>111</sup> The high-risk factors for POPC in the elderly were identified as presence of comorbid diseases such as tuberculosis, COPD, pleural adhesion, or lung fibrosis. Preoperative induction chemoradiation was reported to be associated with more pneumonia, impaired pulmonary gas exchange, lower carbon dioxide diffusing capacity of the lungs, and development of ARDS. This latter complication can lead to prolonged postoperative mechanical ventilation and results in higher in-hospital mortality.<sup>110</sup>

Among intra-operative factors, greater blood loss and longer operation duration were reported to be associated with more postoperative pulmonary complications and mortalities. Tumor location and the type and level of anastomosis also affect POPCs. POPC was four-fold higher for three-field incision resections for more proximal tumors than Ivor Lewis esophagectomy for distal esophageal tumors, possibly related to the greater prevalence of RLN injuries for patients whose operation included cervical dissection.<sup>112,113</sup>

Postoperatively, incisional pain was reported to be associated with more POPCs, which may be reduced by avoidance of thoracic incisions such as transhiatal esophagectomy (THE), or reduced incisions such as minimally invasive esophagectomy (MIE).<sup>114</sup> Disorders including swallowing abnormalities, dysphagia, and poor airway protection are the most prevalent causes of respiratory complications after esophagectomy. Postoperative laryngopharyngeal dysfunction is most commonly attributed to RLN injury during surgery with resultant vocal cord dysfunction and manifests clinically by hoarseness, ineffective cough, dysphagia, and aspiration.<sup>115</sup> It is reported that 15.6%-33.0% of patients who underwent esophagectomy

had RLN injury or vocal-cord paralysis by indirect laryngoscopy. Nearly 50% of patients who had vocal cord paralysis developed respiratory complications, compared with 27% of those who did not have documented RLN injury.<sup>116</sup>

Strategies to reduce pulmonary complications after esophagectomy should be implemented and directed to minimize the above risk factors. In turn, reduction of pulmonary complications also may minimize anastomotic complications.<sup>117, 118</sup> Preoperative cardiopulmonary rehabilitation may help reduce rates of pulmonary complications for patients with poor cardiopulmonary reserve in some studies. Breathing exercises, including deep and slow abdominal breathing and coughing, can promote clearance of respiratory secretions. Cessation of smoking 4 weeks before esophagectomy has been shown to reduce rates of pulmonary complications. The use of expectorant, bronchodilator, inhaled steroids, and antimicrobial therapy as appropriate may reduce the incidence of POPCs.<sup>119</sup> During operation meticulous surgical technique should be performed to avoid RLN injury and blood loss, while reducing the operating time as much as possible. Adequate postoperative analgesia utilizing epidural analgesia can reduce pulmonary complications. Vocal cord medialization after RLN injury can improve outcomes such as hoarseness, dysphagia, dyspnea, aspiration, pneumonia, and weight loss. Vocal cord interventions should be performed as soon as possible after recognition of RLN injury.<sup>120, 121</sup>

#### *Indications for lymphangiography in the treatment of chylothorax after esophagectomy*

In the modern era of upper gastrointestinal surgery, postoperative chylothorax is a dramatic complication which occurs between 1% to 9%<sup>122-124</sup> after esophagectomy for cancer.<sup>123-125</sup> Although a rare event, chylothorax impacts the postoperative morbidity by promoting the

occurrence of pneumonia, with respiratory failure, malnutrition, and death in 20 percent of cases.<sup>125</sup> Currently the debate is not completely resolved whether to perform systematic dissection of the thoracic duct, although this practice can prevent the occurrence of severe chylothorax.<sup>126</sup> Many therapeutic options for postoperative chylothorax, including conservative treatment, lymphangiography, and surgical revision have been described. The optimal management is still under debate both in terms of timing and treatment modalities.

Postoperative chylothorax can be classified into three categories according to the daily output (volume/kg): low, medium, and high drain output.<sup>124</sup> Brinkmann *et al.* and Dugue *et al.* advocate a daily output threshold of 10 ml/kg body weight before considering thoracic duct ligation,<sup>124, 127</sup> but the timing for surgical revision after failure of conservative treatment, which can include total parenteral nutrition or medium chain triglyceride diets, is still unclear.<sup>128-130</sup> Among patients with high or medium output chylothorax, high mortality rates associated with non-operative management dictate earlier surgical revision, which has clinical success of up to 100%. The optimal management of patient with low volume chylothorax also is more questionable, although the prolonged wait time that accompanies non-operative treatment is not without consequences.

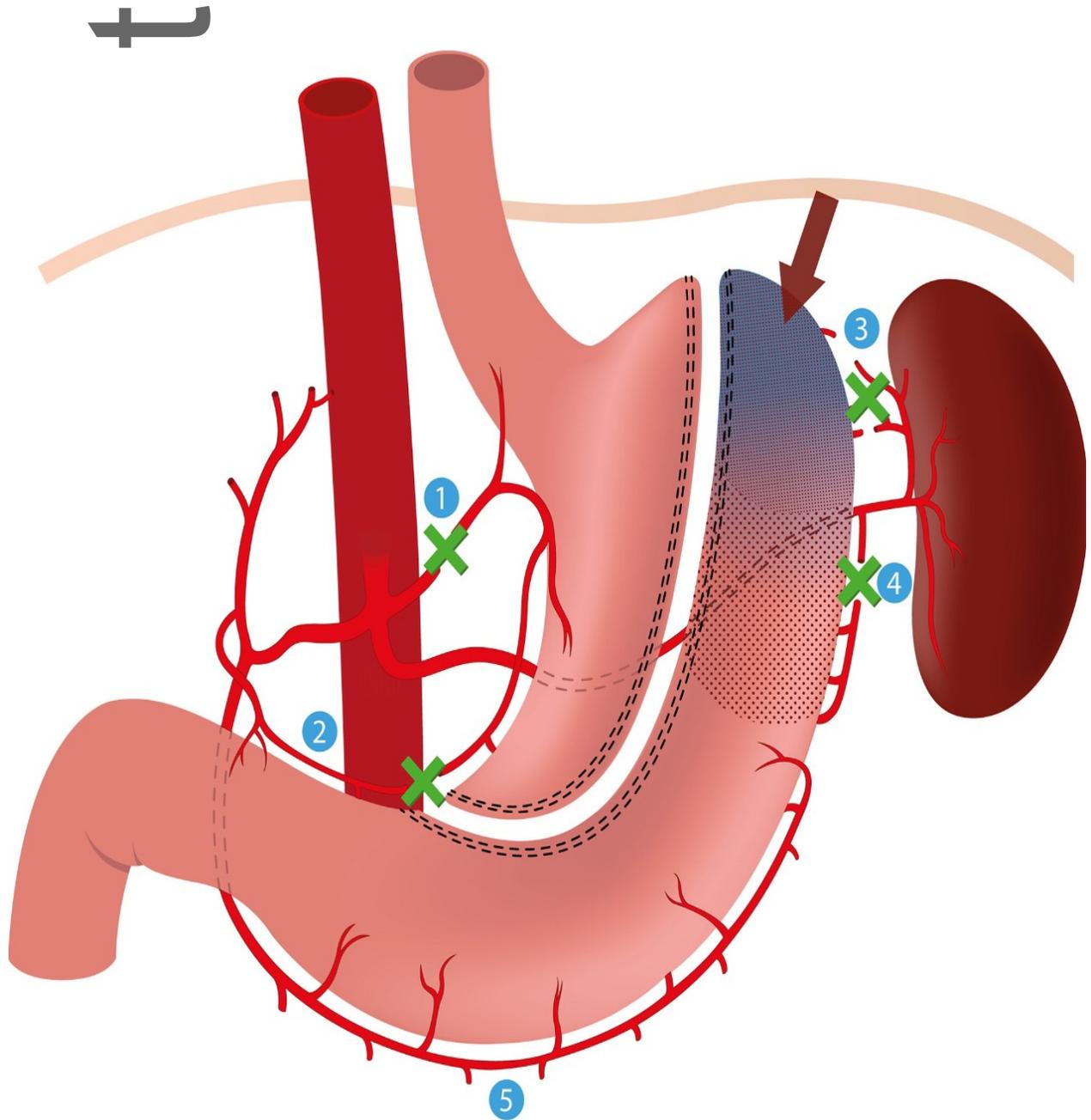
Lymphangiography has been considered an alternative to surgical intervention with reported success rates of pedal lymphangiography approaching 51%.<sup>131</sup> The technical expertise needed for this approach has limited its development and probably the success of pedal lymphangiography. Recently, percutaneous inguinal ultrasound-guided intranodal lymphangiography has been shown to be effective for management of chylothorax. The inguinal approach (Figure 5A), contrary to pedal lymphangiography, which can be time-consuming and requires an experienced operator, is relatively easy, minimally invasive, rapid, and reliable. As described, this procedure does not require thoracic duct catheterization<sup>132</sup> and simplifies catheter-based management considerably. The

inflammatory reaction caused by the lipiodol injectate acts as both a sclerosant as well as an embolic agent (Figure 5B).<sup>131</sup> Efficacy cannot be assessed until 3 weeks, based on complete symptom regression and/or effusion regression on CT or in the chest tube. In our experience, the technical success rate is 100%, although in some cases repeat lymphangiography is needed to approach a clinical success around 80%. This technique can be easily repeated in cases of incomplete resolution but the maximum cumulative dose of lipiodol injected should be 20 ml. Above this dose, a risk of toxicity exists with symptomatic pulmonary arterial embolization of the lipiodol.<sup>133</sup> Lymphangiography can be proposed also in cases of repeat surgery failure.<sup>134</sup> This approach represents an encouraging alternative to non-operative conservative treatment and should be considered after failure of redone thoracic duct ligation or even as primary therapy for postoperative chylothorax. The consequences of postoperative chylothorax should not be discounted and this approach can be safely proposed for treatment of patients with refractory medium/low output chylothorax after esophagectomy. While the timing for such interventions should be defined by robust studies, this is limited by the low prevalence of this postoperative complication. A treatment algorithm strategy to manage chylothorax after esophagectomy is described (Figure 6).

### Figure legends

**Figure 1.** Illustration showing the arterial supply of the stomach after constructing the gastric tube for reconstruction in esophageal surgery. During mobilization of the stomach, ligation (green crosses) of the left (1) and right (2) gastric artery, short gastric arteries (3), and left gastroepiploic artery (4) causes the gastric tube to be supplied exclusively by the right gastroepiploic artery (5). This results in compromised blood flow in the most cranial part of

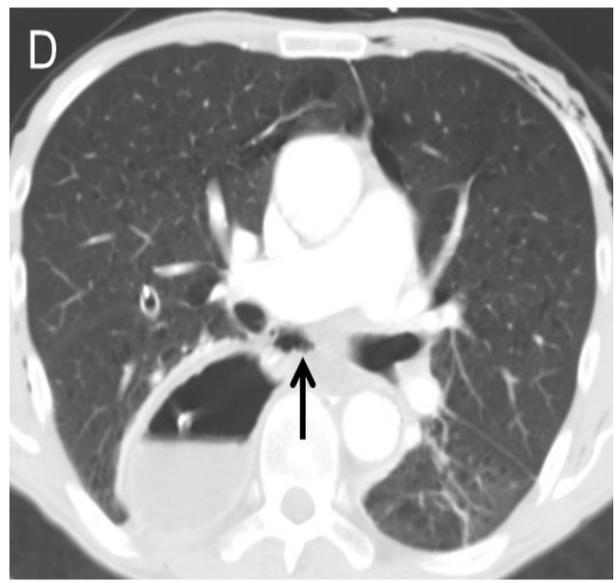
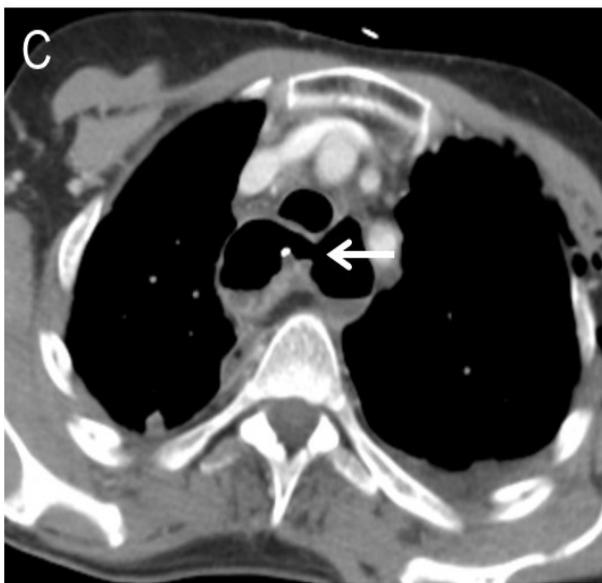
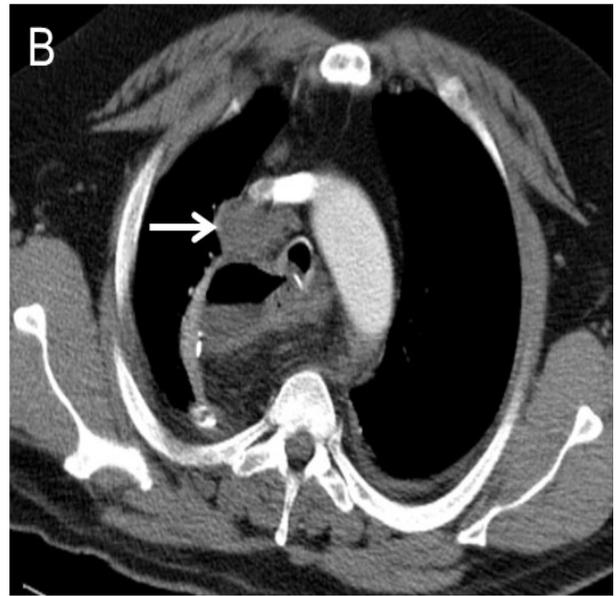
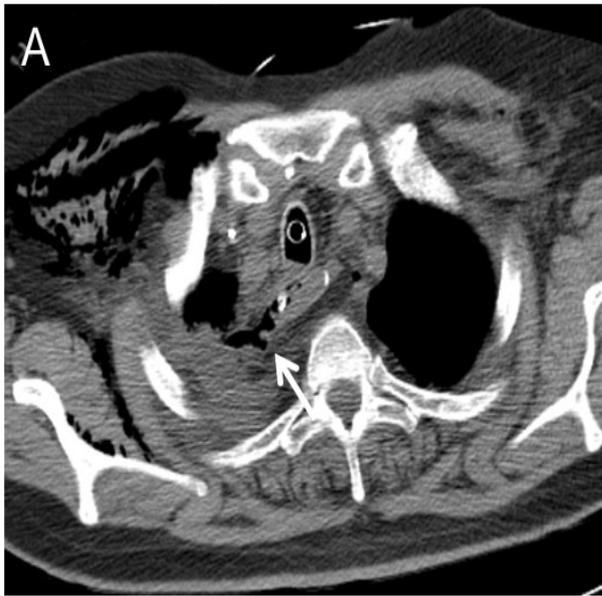
the gastric tube (arrow), which is used to create the cervical anastomosis. Reprinted with permission from Ref. 135.



**Figure 2.** Examples of CT findings associated with the presence of anastomotic leakage after esophagectomy. A. Image shows a fistula between the gastric tube and right pleural cavity (arrow). B. Image shows a fluid collection (arrow) in the mediastinum. C. Image shows a visible discontinuity of the esophagogastric wall

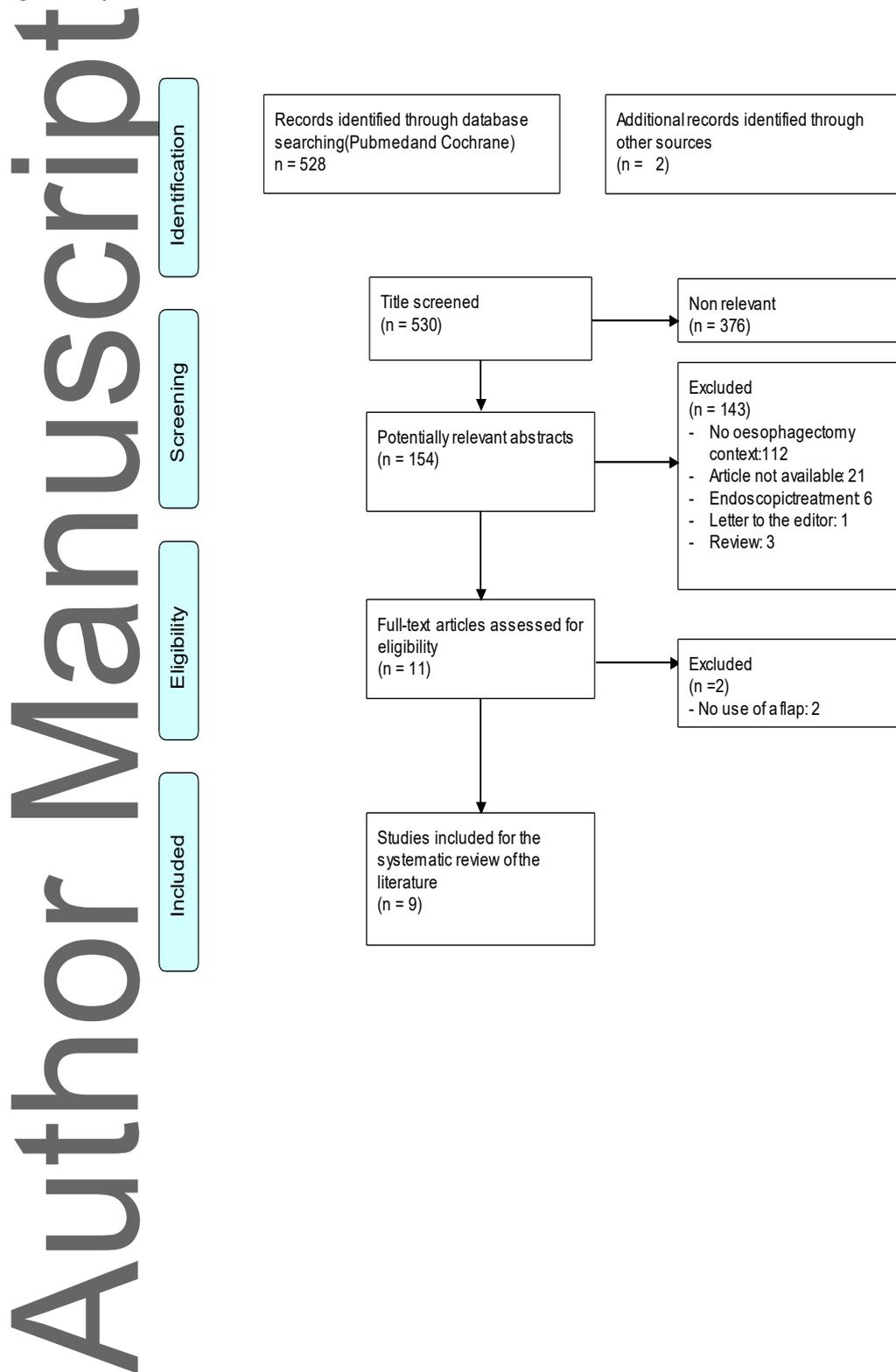
(arrow). D. Image shows a mediastinal air cavity (arrow) after esophagectomy.

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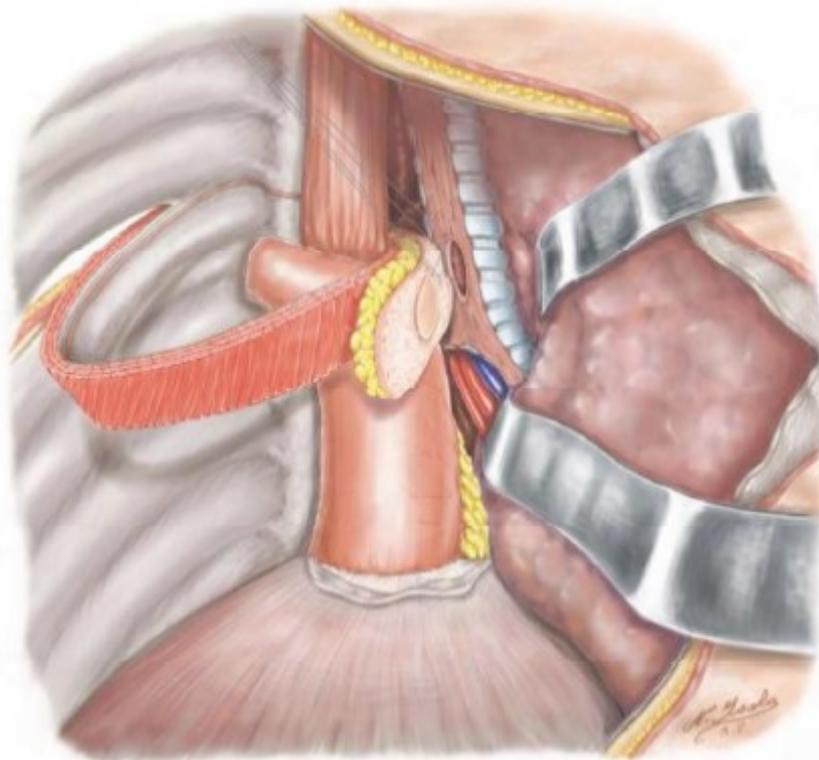


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**Figure 3.** PRISMA flow chart for repair of acquired aerodigestive tract fistula following esophagectomy.



**Figure 4.** Skin perforator flap pedicled by intercostal muscle.

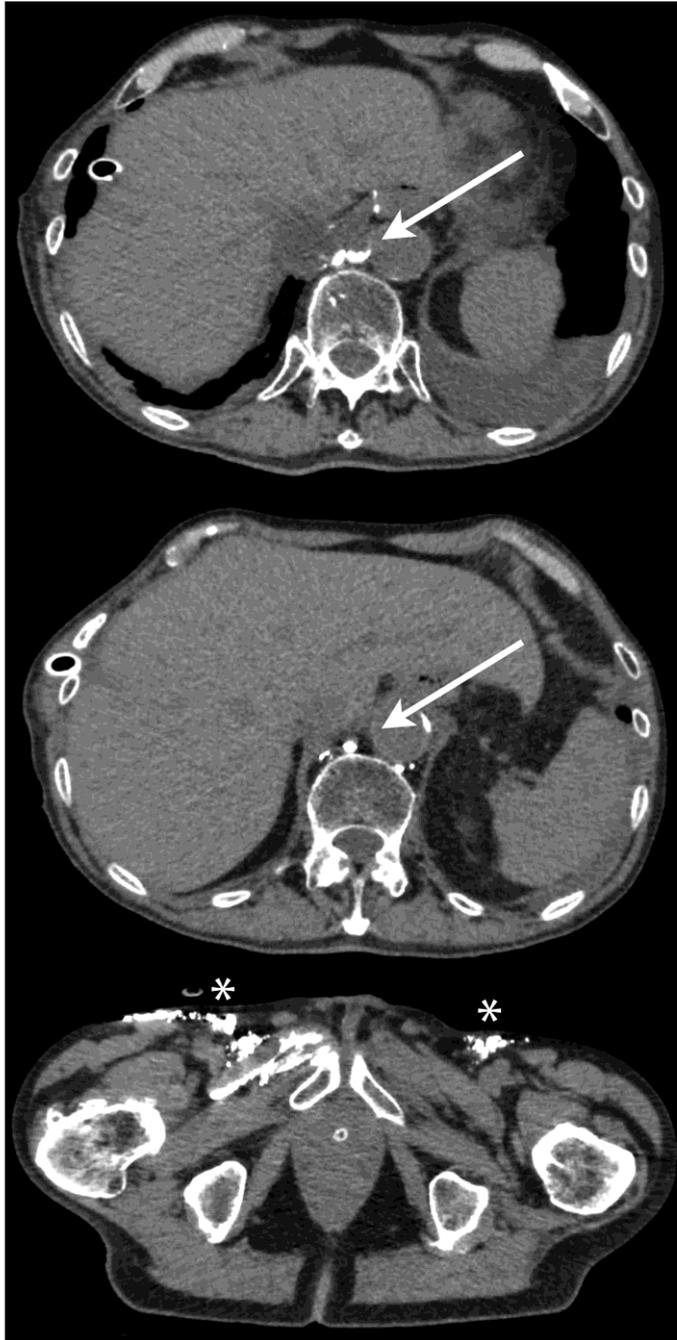


**Figure 5.** Percutaneous management of postoperative chylothorax. A. Lymphangiography demonstrating opacification with lipiodol; efferent lymphatics were monitored by fluoroscopy until the lipiodol reached L3. B. Control CT scan. Visualization of the lipiodol in the thoracic duct (arrow) several days after the procedure and in the inguinal node (asterisk).

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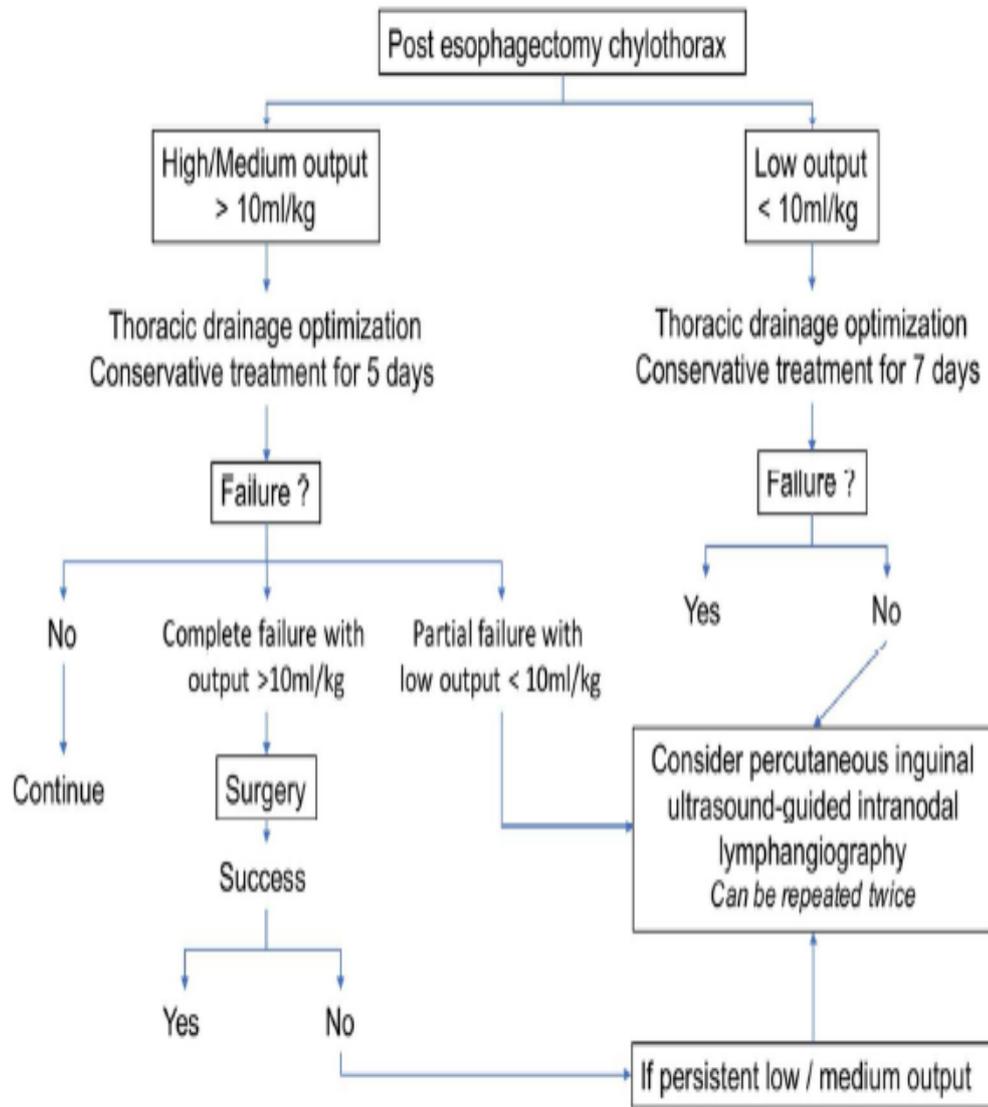


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**Figure 6.** Treatment algorithm proposed to manage post-esophagectomy chylothorax.



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**Table 1.** The three pillars for managing anastomotic leaks

Conservative measures	Endoscopic interventional treatment	Surgical revision
<ul style="list-style-type: none"> <li>• Nasogastric tube/jejunostomy</li> <li>• Parenteral feeding</li> <li>• IV antibiotics (antimycotics)</li> <li>• Opening of the cervical wound, rinsing, possibly interventional mediastinal drainage</li> <li>• Early dilatation of the anastomosis/pylorus</li> <li>• IV anticholinergics (to reduce saliva)</li> </ul>	<ul style="list-style-type: none"> <li>• Endoscopic vacuum therapy (EVT) (intraluminal/intracavitary)/endoscopic therapy (EST)</li> <li>• Self-expandable metallic stents (SEMS)</li> <li>• Stent-over-sponge (SOS) therapy</li> <li>• “Bear claw”/over-the-scope-clip (OTSC) system</li> <li>• OverStitch</li> <li>• Fibrin glue, combined with vicryl plug</li> </ul>	<ul style="list-style-type: none"> <li>• Sternocleidomastoid (SCM) flap repair for complex cervical leak</li> <li>• Left pectoralis major muscle flap to cover complex leaks (e.g., with esophagotracheal fistula)</li> <li>• Resection of gastric fundic tip necrosis and refashioning of the anastomosis (local ischemia)</li> <li>• Diversion surgery dismantling the gastric conduit and esophagostomy (diffuse ischemia, gastric conduit necrosis)</li> </ul>

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