Anastomotic leakage after esophagectomy for esophageal cancer: risk factors and operative treatment

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: S Ubels, M Verstegen; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Esophagectomy with gastric tube reconstruction is the cornerstone of curative treatment for patients with esophageal or gastro-esophageal junction (GEJ) cancer. Anastomotic leakage is a major complication, and may result in major morbidity or mortality. Moreover, anastomotic leakage after esophagectomy may impact on recovery of long-term quality of life and is associated with worse oncologic outcomes. The presentation and consequences of anastomotic leakage represents a spectrum, ranging from a small leak with mild symptoms to a large defect with extensive contamination and fulminant sepsis. Incidence rates and risk factors of anastomotic leakage are well reported, but the literature on factors associated with the outcome of anastomotic leakage and optimum management is scant. Although multiple treatment options for anastomotic leakage, consisting of conservative, radiologic, endoscopic and surgical interventions, are available, there is a large variation in treatment of anastomotic leakage and an evidence-based treatment guideline is currently lacking. The aim of this review is (I) to discuss the literature on factors influencing the occurrence of anastomotic leakage and factors affecting the outcome of patients with anastomotic leakage, and (II) to review the recent literature on the role of surgical management of anastomotic leakage after esophagectomy. New trials and experimental treatments for anastomotic leakage are presented and future directions towards evidence-based treatment of anastomotic leakage are proposed.

Keywords: Anastomotic leakage; esophagectomy; risk factors; surgical treatment

Received: 27 May 2020; Accepted: 29 June 2020; Published: 25 March 2021.
doi: 10.21037/aoe-2020-18
View this article at: http://dx.doi.org/10.21037/aoe-2020-18

Introduction

Worldwide, the incidence of esophageal and gastro-esophageal junction (GEJ) cancer is increasing and it is the sixth most common cause of cancer related deaths (1,2). Esophagectomy is the cornerstone of curative treatment, most often in combination with neoadjuvant chemoradiotherapy or perioperative chemotherapy (3,4). The most frequently performed surgical techniques for esophagectomy are the Orringer procedure (transhiatal with cervical anastomosis), the McKeown 3-stage procedure (transthoracic with cervical anastomosis) and the Ivor Lewis procedure (transthoracic with intrathoracic anastomosis). All procedures can be performed by either an open, hybrid, totally minimally invasive, or robotic- assisted approach.

Irrespective of surgical approach, esophageal cancer resection is associated with a significant risk of morbidity. From a surgeon's perspective perhaps the most dreaded complication is leakage of the esophagogastric anastomosis, which occurs in between 5% to 30% of patients (5,6). Anastomotic leakage is a major cause of morbidity and

Table 1 Classification of anastomotic leakage severity according to the ECCG

Leakage severity	Criteria
Grade 1	Local defect requiring no change in therapy or treated medically or with dietary modification
Grade 2	Localized defect requiring interventional but not surgical therapy, for example, interventional radiology drain, stent or bedside opening, and packing of incision
Grade 3	Localized defect requiring surgical therapy

Classification of anastomotic leakage according to the Esophagectomy Complications Consensus Group (ECCG), published by Low *et al.* 2015 (18).

mortality (6-12). Moreover, it may impact on recovery of quality of life and be associated with worse oncologic outcomes (13-15). Accordingly, its prevention and optimal management are of great importance.

There is a wide spectrum of treatment modalities for anastomotic leakage, from simple non-intervention conservative measures and antibiotics, to more invasive treatment modalities such as radiologic or endoscopic approaches, to surgical interventions. Surprisingly, good evidence to base management decisions on the optimum approach is lacking. A recent international survey for instance revealed significant variation in the approach (16). A systematic review on studies up to 2017 concluded that due to small cohorts, heterogeneity between studies, and lack of data regarding patient and leakage characteristics, no evidence-based treatment strategy exists (17). As a result, the current treatment of anastomotic leakage is highly variable, and what evidence exists is based on expert opinion rather than on a proven treatment algorithm.

A part of the difficulty in establishing a clear pathway in management is because the clinical presentation of patients can be wide-ranging. For example, some patients present with a small leak, mild symptoms and without significant intrathoracic manifestations, whilst others present with a large defect of the anastomosis with fulminant sepsis and (multi) organ failure. It is plausible and understandable that surgeons adopt different patient and leakage characteristics into consideration when choosing for a treatment approach. However, it is currently unknown which patient and/or leakage characteristics contribute to anastomotic leakage severity.

This review has two aims. First, to describe factors that influence the occurrence of anastomotic leakage and consequent clinical outcomes. Second, to review the recent literature on the role of surgical management of anastomotic leakage.

Anastomotic leakage: definition and influencing factors

According to the recent Esophagectomy Complications Consensus Group (ECCG) consensus definition, anastomotic leakage is defined as a "full thickness gastrointestinal defect involving esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification" (18). A conventional classification of the severity of anastomotic leakage is based on the invasiveness of the treatment for anastomotic leakage, also described by the ECCG (*Table 1*) (18).

Relevant factors underpinning the risk can be divided into patient, oncological, and peri-operative factors (*Table 2*). In addition, different surgical techniques and interventions have been shown to affect the incidence of anastomotic leakage (*Table 3*).

When a leak occurs, some factors are known to influence the outcome. For instance, a low serum albumin is associated with higher failure rates of conservative leak treatment and longer time to recovery (7,39). In addition, older age and ASA classification may increase the risk of mortality in patients with anastomotic leakage (40). These associations may be explained by the reduced ability to respond to physiological stress and catabolism which may accompany a leak. Factors associated with more invasive treatment, longer hospital and ICU admission and longer anastomotic healing time include uncontained leaks accompanied by intrathoracic and/or mediastinal contamination (8,39,41,42). Furthermore, one study reported that early leakage (<7 days) and clinical apparent leaks were associated with higher mortality in patients with anastomotic leakage (40). Notwithstanding, most studies were retrospective, the associations varied in strength and sample sizes were limited, hence conclusions are based on relatively weak data.

Technical factors reported to be associated with outcome of anastomotic leakage are the site of the anastomosis and the use of an omentoplasty to reinforce the anastomosis. A cervical anastomosis is associated with a higher incidence of anastomotic leakage as compared to an intrathoracic anastomosis. Advocates of esophagectomy with cervical anastomosis, by either a transthoracic (McKeown esophagectomy) or a transhiatal (Orringer esophagectomy) approach, accept this risk as the tradeoff because they believe the sequelae of cervical anastomotic leakage might be less severe because the leak can drain through the cervical wound, preventing mediastinal and intrathoracic manifestations, severe sepsis and mortality. Although these arguments will continue, a meta-analysis of randomized controlled trials revealed no difference in postoperative mortality after a McKeown or Ivor Lewis resection notwithstanding these anastomotic considerations (13). Outcomes of anastomotic leakage in patients after Orringer compared to McKeown and Ivor Lewis esophagectomy is subject of ongoing research by our group in Nijmegen. With respect to omentoplasty as a support to reduce leaks, their severity, and risk of re-operation and associated mortality, although supported by some studies (43-45) this was not confirmed by a recent meta-analysis and therefore lacks compelling evidence (46).

Table 2 Factors associated with incidence of anastomotic leakage

Contributing factors
Patient
Hypoalbuminemia (19,20)†
Older age (21)
Alcohol abuse (21)
Obesity (BMI >30 kg/m^2) (21-24)
Comorbidities: diabetes, hypertension, chronic kidney disease, COPD myocardial infarction, heart failure, cardiac arrhythmia (21,25,26)
Celiac artery calcifications and systemic atherosclerosis (21,27)†
Steroid or immunosuppressant use (21)
Oncological
Radiation therapy: radiation of gastric fundus (28,29) or in field anastomosis (30)†
Anti-angiogenic therapy (i.e., bevacizumab) (31)†
Perioperative
Prolonged mechanical ventilation (32)
Gastric distention and delayed gastric emptying (32,33)
Intraoperative hypotension (21)
Need for blood transfusion (21)

†, possible factor, contradicting evidence or still under investigation. BMI, body mass index; COPD, chronic obstructive pulmonary disorder.

In summary, evidence to date suggests that several patient, oncological and peri-operative factors are associated with anastomotic leakage incidence and that different (surgical) interventions reduce the incidence of anastomotic leakage. However, there is a paucity of data regarding factors that are associated with a worse outcome in patient with anastomotic leakage. Gaining insight into these factors is crucial for designing an evidence-based treatment algorithm that will help guiding clinicians at the time of anastomotic leakage diagnosis.

Anastomotic leakage: treatment

In recent decades, the range of interventions for anastomotic leakage has steadily increased, including non-invasive and

Table 3 Surgical techniques and interventions to reduce anastomotic leakage incidence

Factor	Intervention
Operation approach	Favors transthoracic over transhiatal (21)
Anastomosis location	Favors intrathoracic over cervical anastomosis (21)
Anastomosis technique	Favors stapled over handsewn (21,34,35)†
Anastomotic reinforcement	Omentoplasty (21)
Conduit vascularization	Preoperative ischemic preconditioning (i.e., laparoscopic ligation, radiologic embolization) (36)†
	Intraoperative vascular-enhanced anastomosis (37,38)†

†, possible factor, contradicting evidence or still under investigation.

minimally-invasive management treatment modalities. Even though immediate surgery for anastomotic leakage has previously been suggested by some authors (47), more recent studies suggest that the treatment should be a step-up approach in which surgical treatment is reserved in most clinical scenarios for patients in whom non-invasive, radiologic or endoscopic treatment has failed (7,8,39,48). Some general principles apply to all patients with anastomotic leakage. Early recognition of a deviation from the normal course of recovery, and swift diagnosis remain key (48-50). Currently, an evidence-based diagnostic algorithm is lacking and there is no consensus regarding a routine diagnostic protocol to monitor patients' recovery after esophagectomy in the context of early identification of leaks. Multiple clinical, laboratory and imaging examinations may be deployed to aid early diagnosis of anastomotic leakage and enable early management (51,52). However imaging should be performed only in patients with suspected anastomotic leakage, as routine endoscopy, contrast esophagram or computed tomography has not shown to be effective in patients without a clinical suspicion (53-57). Once a leak has been diagnosed, obtaining adequate drainage and providing source control to stop further leakage and control progressive sepsis are crucial principles to adopt (58).

Non-invasive treatment

Conservative non-invasive approaches include nil by mouth, antibiotics, placement or maintaining a nasogastric tube, maintaining drains if effective, and nutritional support. Previous studies suggest that antibiotic treatment and measures to secure continued feeding, preferably enteral, should be deployed at an early stage in all patients (48,59). Successful conservative treatment has been reported in many cases of cervical as well as intrathoracic anastomotic leakage (39,41,53,60-62). Manghelli *et al.* performed a retrospective study of 61 patients who had leakage after esophagectomy with either cervical or intrathoracic anastomosis, and reported that of 46 patients (75%) who were initially treated conservatively, only 11 patients required further interventional treatment such as stenting or reoperation, irrespective of anastomotic location (39). In addition, no differences regarding mortality and length of ICU-stay were found between patients who underwent initial surgical treatment and patients who underwent surgery after failure of initial conservative treatment. Accordingly, despite small cohorts and lack of comparative studies, a non-invasive treatment with step-up to more invasive treatment modalities when non-invasive treatment fails seems to be feasible and successful.

Endoscopic management

A variety of endoscopic treatments are now established in the armamentarium to manage anastomotic leakage. Endoscopic drain placement through the anastomotic defect may be used for drainage of fluid cavities that cannot be drained using a chest tube or percutaneous drainage (61-64). In addition, the insertion of a fully covered self-expanding stent may be used to prevent further leakage in patients with limited contamination, or when this has been drained adequately (45-47). However, some patients may require (endoscopic) reintervention due to stent migration or other stent-related complications. More recently, endoluminal vacuum assisted closure devices (E-VAC or EsoSponge) have emerged. These devices are advocated to be more effective compared to stent placement by different authors through combining effective drainage with stimulation of anastomotic healing (65-67). Some authors have suggested that combining E-VAC treatment with stent placement may yield even better outcomes (68,69). However, endoscopic stenting or E-VAC therapy is believed not be sufficient in patients with extended intrathoracic contamination and these patients will need additional drainage of collections (9,70). The endoscopic approaches for management of anastomotic leakage and their outcomes are discussed in detail in an accompanying paper in this Journal.

Surgical management

The goal of surgical treatment is to obtain adequate drainage of contaminated areas and/or to surgically repair the anastomosis or to perform proximal esophageal diversion. Once surgical intervention is determined to be clinically indicated, existing evidence suggests it is important not to delay the procedure (71). Surgical treatment of anastomotic leakage consists of bedside chest tube placement, surgical drainage via reoperation, performing reoperation with re-anastomosis and reoperation with taking down the anastomosis in combination with esophageal diversion. Reoperations can be performed by either an open (i.e., laparotomy, thoracotomy) or minimally invasive approach [i.e., laparoscopy, thoracoscopy, video-assisted thoracoscopy (VATS)] approach.

Surgical drainage

Methods for draining depend on the location and extent of the contamination and may differ depending on the site of the anastomosis. A recent retrospective cohort study presented the outcomes of 60 patients with anastomotic leakage after esophagectomy with a cervical anastomosis (42). Interestingly, 40 percent of cases had leakage contained to the cervical area, highlighting how often an anastomosis fashioned in the neck can reside in the mediastinum. Surgical drainage by opening the cervical wound was the treatment of choice in all patients. While drainage of the cervical wound was effective in all patients with a leak contained to the neck, more than half of the patients with intrathoracic manifestations required additional transthoracic drainage. Intrathoracic contamination was associated with development of sepsis and prolonged ICU- and hospital admission. Although a higher mortality rate was found in patients with a leak with intrathoracic manifestations, this finding was not statistically significant. In line with this study, others have also suggested that drainage by opening the cervical wound may suffice when a leak is contained to the cervical region, but when intrathoracic contamination is present further surgical drainage is indicated (8).

Specifically for intrathoracic anastomotic leaks, a retrospective cohort study reported their outcomes of a "three-tube" strategy, in which nasogastric decompression tube, nasojejunal feeding tube and chest tube placement was performed (7). Compared with patients who underwent surgical re-exploration, the healing time of the leak was shorter and this strategy was effective in patients with both contained intrathoracic leaks and patients with uncontained leaks, i.e., gross contamination of the pleural cavity, the presence of an abscess, mediastinitis, pyothorax or sepsis. However, the proportion of uncontained leaks was higher in patients who underwent surgical re-exploration whilst no clear indications for either treatment were described. Also, others suggest that chest tube placement may be indicated when intrathoracic fluid collections are present, but encapsulated collections should be combined with surgical debridement using a thoracoscopy, VATS or thoracotomy (72). This may also be the case for mediastinal collections, which often cannot be drained using chest tubes. In conclusion, a step-up approach consisting of local, endoscopic or percutaneous drainage followed by surgical drainage and exploration as needed seems supported by available evidence.

Surgical repair and deviation

Although a step-up approach, in which surgical treatment is reserved for patients failing non-operative treatment, may be feasible for the majority of patients, some studies suggest indications for direct surgical treatment as the primary approach. In patient with evident leaks within the first 72 hours, prior to any major sepsis developing, repair of the anastomotic defect using sutures may suffice (71,73). In some cases, a re-anastomosis may be required. In these cases, it is important that the conduit is vital and of sufficient length to allow a tension-free re-anastomosis to be performed. In a retrospective cohort study reporting on the outcomes of patients with a mediastinal localization of the leak, re-exploration was the primary treatment strategy in almost 40 percent of the patients (71). Surgical debridement, re-anastomosis or esophageal diversion was performed promptly, before signs of sepsis were apparent. The other patients were primarily treated using either conservative or endoscopic treatment. In these patients, surgery was only indicated in case of an ischemic anastomosis, sepsis or failure of initial treatment. The study found a higher mortality rate in patients who underwent initial surgical treatment compared to patients who underwent conservative or endoscopic treatment, however the authors acknowledge significant bias in that comparison.

If the defect does not allow primary repair, closure and anastomotic reinforcement using pedicled chest wall muscles, omentum, pleura or pericardial fat may be utilized (9,74). A study reported outcomes of 19 patients who underwent anastomotic repair after suffering esophageal leakage of various etiologies. A muscle flap repair was performed as primary treatment or secondary treatment using either diaphragm, latissimus dorsi, serratus anterior or pectoralis muscle flaps depending on the location of the leak (74). Although four patients developed respiratory insufficiency and four patients required reintervention, there was no postoperative mortality. Next to repair of the defect using autologous material, recently one study investigated repair using a bovine pericardial patch in patients with persistent cervical fistulas following anastomotic leakage (75). Although the study only included 7 patients, all patients recovered and no recurrent anastomotic leakage was reported. While surgical repair of the anastomosis seems safe and effective, only one of the studies has compared the outcomes of patients treated surgically with patients who were treated conservatively or endoscopically. In addition, the pathologies of patients included, indications for surgical treatment and surgical procedures performed are all heterogeneous, hence firm conclusions are difficult to draw.

Excision and diversion is reserved for the most fulminant cases, particularly where sepsis is progressive, and tissues are unhealthy and unsafe to utilize, with partial or complete gastric necrosis (39,76). Other indications for anastomotic disconnection and esophageal diversion may include, a large (>2 cm) or near-circumferential leak, diffuse contamination of the thoracic cavity and failure of previous therapies (39,50,76,77). A common technique for diverting the esophagus is performing an end-esophagostomy (8,76,78). Alternatively, a double-barrel esophago-gastrostomy has also been described (47). The gastric tube may be stapled off proximally and temporarily stored intra-abdominally or resected, depending on the condition of the conduit. After diversion procedures, restoring gastro-intestinal continuity may represent a major challenge. For restoration of the gastro-intestinal continuity the stomach is the preferred conduit (78). However, after an esophageal diversion the stomach may have been resected, of insufficient length or otherwise not suitable for reconstruction. In those cases, colonic interposition is usually preferred to jejunal interposition (76,78). The timing of reconstruction is debatable, but it is rarely done before 6 months (47,78), although cases of successful earlier reconstructions have been described (76). Regardless of the precise timing, authors agree that reconstruction should only be performed once infectious, nutritional and physical status has been optimized (47,76,78).

In summary, no evidence supporting a specific treatment for anastomotic leakage was found in currently available literature due to small cohorts in the included studies and heterogeneity between studies. We recommend that the treatment of anastomotic leakage in all patients includes nil by mouth, intravenous antibiotics and adequate feeding preferably by nasojejunal feeding tube or jejunostomy. Furthermore, adequate drainage of the leak should be obtained which is preferably performed by opening the cervical wound in case of a cervical anastomosis and/or radiologic, endoscopic and/or surgical drainage. Reoperation on the anastomosis or taking down the anastomosis and diverting the esophagus should be reserved for specific indications (e.g., anastomotic leakage in combination with gastric conduit necrosis) (8,42,47,48,77). In the absence of an evidence-based treatment algorithm, we recommend an individualized treatment based on the condition of the patient and the sequalae of the leakage at diagnosis.

Ongoing trials and experimental treatments

A variety of novel interventions and experimental treatments to prevent or improve healing of leaks are currently undergoing investigation. Based on a strong theoretic rationale, ischemic preconditioning of the stomach to improve gastric perfusion prior to resection has been evaluated. The approach involves either ligation or occlusion of the left gastric artery at least 2 weeks prior to resection by respectively laparoscopic arterial ligation or radiological arterial embolization (79,80). Results are variable to data, for instance, a recent meta-analysis for instance showed no evidence of reduced anastomotic leak rates, however it concluded that these interventions are feasible and that randomized trials are warranted (36). The results of two new randomized trials and one prospective cohort study currently investigating ischemic preconditioning are eagerly awaited (NCT04268654, NCT02432794, NCT03896399) (81-83).

Another approach to improve gastric perfusion, particularly in high risk patients based on vascular disease, is to perform (micro)vascular anastomoses between arteries of the conduit and surrounding thoracic or cervical arteries. This technique, often referred to as "supercharging", is predominantly used in reconstruction with jejunal or colonic interpositions (84), but has also been described for reconstruction with a gastric conduit (37,38). One retrospective study including 44 patients reported significantly lower rates of anastomotic leakage compared to their routine procedure (37). The study did not describe why patients were selected to undergo a supercharged anastomosis. Although not proven conclusively at this time, supercharging may find a role in patients who have vascular disease and are at high risk of ischemia following a routine gastric conduit formation.

Intra-operative assessment of conduit perfusion via intraoperative perfusion monitoring is increasingly being studied (85). The most common mode of assessment is fluorescent imaging using indocyanine green (ICG). A recent meta-analysis reported that intraoperative ICG fluorescence imaging leads to a change in management in about 25% of cases (86). A change in management consisted of resection of a part of the gastric conduit or change in the anastomotic site, and a lower rate of anastomotic leakage was reported where ICG fluorescent imaging was utilized. However, in line with much of the literature on this topic, the quality of reported studies is poor, and no randomized controlled trials exist, therefore a control cohort is lacking from most studies. A further bugbear of this approach is the lack of reliable quantitative measures currently (85,86).

Stem cell therapy is an interesting theoretic approach for the treatment of anastomotic leakage. In a study from China, a mixture of autologous mesenchymal stem cells in a fibrin solution was injected around a cervical anastomotic leak in an animal model, and compared to fibrin injection alone (87). A higher healing rate and decreased wound infection rate was seen in the interventional group. However, the safety and efficacy are yet to be investigated in humans. The concept of an 'anastomotic glue' is not new, and fibrin glue (without stem cells) has been previously investigated for preventing anastomotic leakage in gastrointestinal and especially colorectal surgery, with no proven efficacy at this time (88,89). A randomized trial is currently being conducted to investigate the efficacy of a porcine fibrin sealant (Bioseal®) in preventing anastomotic leakage in patients after McKeown esophagectomy and results are expected in 2023 (NCT03529266) (90).

Discussion

The current review has described factors associated with the incidence and outcome of anastomotic leakage after esophagectomy, and treatment approaches, in particular surgical therapy, and the prospects of novel approaches. Reviewing the available literature, several factors associated with an increased incidence of anastomotic leakage were identified, but little is known about factors associated with the outcome of anastomotic leakage. Currently, an evidence-based treatment algorithm is lacking. A reasonable conclusion, based on available literature, is that a step-up approach from non-invasive to more invasive treatment provides the best available algorithm and we have highlighted some exceptions to this approach where immediate surgery is the optimal approach. However, clearly the evidence-base is weak and mostly based on expert opinion. Research should establish new algorithms based on the timing of leakage, and the severity of leakage and associated septic response and organ failure.

This review has highlighted the limitations of current available literature. First, the majority of the studies reporting on the treatment of anastomotic leakage are retrospective, non-comparative cohort studies including small number of patients with consequent substantial risk of bias. Second, there is substantial heterogeneity between studies, both in inclusion criteria and reporting of outcome parameters, limiting comparability of studies and firm conclusions. Third, most patients in the current studies underwent open esophagectomy, while MIE is increasingly being performed in current practice and this may limit the generalizability of the findings of these studies. Finally and more general, there is an absence of an anastomotic leakage severity classification that can be used at time of diagnosis and that is therefore clinically relevant. Though the current anastomotic severity classification by the ECCG classification is useful in many different ways and will improve standard reporting (18), this classification is not useful in decision making at the time of diagnosis since it classifies anastomotic leakages according to the treatment provided. There is clearly an unmet need for a clinically relevant leakage severity classification based on clinical and leakage characteristics, and international networks will hopefully fill these gaps in knowledge and provide a more robust evidence base and algorithm in the future.

In this regard, EsoBenchmark is an international initiative of high-volume centers established to define the best outcomes in total minimally invasive transthoracic esophagectomy (91). EsoData is another international collaboration aiming to compare outcomes after esophagectomy initiated by the ECCG under the auspices of the International Society for the Diseases of Esophagus (ISDE) (92). Recently, a global multicenter cohort study was initiated by the Oesophago-Gastric Anastomosis Audit (OGAA) (93). Beyond dispute, this study will provide valuable answers on questions regarding international variation in anastomotic leakage rate and the relationship between anastomotic technique and patient outcome. However, this study is not powered to investigate factors that are associated with anastomotic leakage outcome or the effectiveness of different anastomotic leakage treatments. In an attempt to provide answers on these two questions, the TENTACLE-Esophagus study (treatment of anastomotic leakage after esophagectomy) is currently being conducted (NCT03829098) (94). The first aim of the TENTACLE study is to investigate which factors contribute to anastomotic leakage severity, and to compose an evidence-based anastomotic leakage severity score. The second aim is to investigate which characteristics of leaks are associated with success of different treatments, and to compare the effectiveness of different initial treatments classified according to severity characteristics. According to the sample size calculation 680 patients needed to be included. However, already over 1,500 patients are included and the results are expected in the beginning of 2021.

In conclusion, despite anastomotic leakage after esophagectomy being relatively common, the currently available literature does not provide a strong evidence base to provide clear recommendations on the management of leaks, or a clear approach based on the nature of the leak and severity of sepsis. This provides a major research opportunity, and hopefully TENTACLE-esophagus and other studies will significantly advance knowledge that will underpin treatment guidelines for anastomotic leakage.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Riccardo Rosati) for the series "Current issues on GEJ adenocarcinoma" published in *Annals of Esophagus*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at: http://dx.doi.org/10.21037/aoe-2020-18). The series "Current issues on GEJ adenocarcinoma" was commissioned by the editorial office without any funding or sponsorship. JVR serves as an unpaid editorial board member of *Annals of Esophagus* from Sept 2019 to Aug 2021. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aoe-2020-18
Cite this article as: Ubels S, Verstegen MHP, Rosman C, Reynolds JV. Anastomotic leakage after esophagectomy for esophageal cancer: risk factors and operative treatment. Ann Esophagus 2021;4:8.

