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Optimal approach to the management of intrathoracic esophageal leak following esophagectomy: a systematic review

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Abstract

Background—Recently, endoscopic interventions, e.g. esophageal stenting, have been successfully utilized for the management of intrathoracic leak. The purpose of this systematic review was to assess the safety and efficacy of techniques used in the management of intrathoracic anastomotic leak.

Data Sources—We performed a systematic review of MEDLINE, EMBASE, and PubMed to identify eligible studies analyzing management of intrathoracic esophageal leak following esophagectomy.

Conclusions—Intraoperative anastomotic drain placement was associated with earlier identification and resolution of anastomotic leak (mean 23.4 vs 80.7 days). In addition, reinforcement of the anastomosis with omentoplasty may reduce the incidence of anastomotic leak by nearly 50%. Endoscopic stent placement was associated with leak resolution in 72%; fatal complications were reported, however, and safety remains to be proven. Negative pressure therapy, a potentially useful tool, requires further study. If stenting and wound vacuum are used, undrained mediastinal contamination and persistent leak requires surgical intervention.

Keywords

Esophagectomy; Postoperative Complications; Anastomotic Leak; Review, Systematic; Assessment, Outcomes

Introduction

Esophagectomy is the mainstay of therapy in the management of patients with locoregionally advanced esophageal cancer, but carries significant risk of associated morbidity and mortality. The incidence of anastomotic leak varies widely in the current

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literature but has been reported to be up to 50%, [1] with mortality rates as high as 30-60%. [2-4] Compared to cervical anastomosis, intrathoracic anastomoses have a lower incidence of anastomotic leak and stricture rate. Presentation ranges from asymptomatic and clinically silent to overwhelming sepsis and death; patient prognosis after intrathoracic anastomotic leak depends on the extent of contamination and time interval to diagnosis. Regardless of the severity, the presence of an anastomotic leak following esophagectomy has a substantial impact on postoperative length of stay, overall morbidity, stricture formation, and dysphagia.[5 6]

The treatment of anastomotic leak remains controversial, as the indications for surgical, conservative and endoscopic therapy remain non-standardized.[7 8] Strategies described in the literature include conservative management (consisting of strict NPO, initiation of intravenous antibiotics and drainage), early and late surgical exploration, endoscopic management with stenting, as well as prophylactic omental reinforcement. Determining the optimal therapy for such patients requires examining all available options as there are few retrospective and prospective studies comparing these techniques.

To determine the optimal management of intrathoracic anastomotic leak, we performed a systematic review of the literature analyzing endoscopic approaches to management and published outcomes. Specifically, we sought to determine: 1) whether intraoperative drain placement at the anastomosis impacts leak rate and/or duration; 2) whether reinforcement of the esophagogastric anastomosis after esophagectomy with omentoplasty reduces leak rate or need for reintervention; 3) the safety, efficacy, and indications for endoscopic interventions (stenting and negative pressure therapy) in leak management.

Data Sources

Eligible studies for inclusion were identified using a systematic search strategy. (Table 1) Titles and abstracts of 465 articles were reviewed and all English-language studies examining intrathoracic esophageal anastomotic leak after esophagectomy were identified for inclusion. Articles were excluded if they were published in abstract only, reported leaks predominately for operations other than esophagectomy and esophagogastric anastomosis, were case reports with <3 patients, or did not include anastomotic leak as a major focus of the article. Review articles other than systematic reviews and meta-analysis were also excluded. If more than one publication was found from the same institution, only the largest series was included. Because the outcomes of interest are leak resolution and leak-related mortality, articles that did not report success rate or mortality rate after use of a stent to treat anastomotic leaks were also excluded. To further limit the scope of the systematic review, we excluded articles focused on cervical anastomotic leaks, approach to anastomosis and leak, and ischemic preconditioning and leak. Additional references from article bibliographies were included as appropriate. A total of 51 articles were included in the final review.

Prophylactic management of anastomotic leak after esophagectomy: the role for intraoperative drain placement and pedicled omental reinforcement of the anastomosis

Due to the high mortality and morbidity associated with anastomotic leak, several authors have argued for the use of prophylactic interventions to reduce the impact and/or incidence of anastomotic leak. These include ischemic preconditioning, debates regarding the location (thoracic vs cervical) and approach to anastomosis (hand-sewn vs stapled), type of conduit (stomach, jejunum, or colon), intraoperative drain placement, and vascularized tissue reinforcement of the anastomosis at the time of initial operation. For this systematic review, we focused our question on whether intraoperative drain placement at the anastomosis impacts leak rate and/or duration and whether reinforcement of the esophagogastric anastomosis after esophagectomy with omentoplasty reduces leak rate or need for reintervention.

It is widely accepted that adequate drainage is a critical principles guiding management of anastomotic leak, with mortality rates as high as 80% in the setting of uncontrolled, inadequately drained leak.[9] Despite wide acceptance of the role for prophylactic intraoperative perianastomotic drain placement, the available literature analyzing the role for this approach is limited. Only 1 article was identified that focused on the role of intraoperatively placed drains in the evaluation and management of anastomotic leak. Tang and colleagues, in a retrospective review of 414 patients who underwent esophagectomy with intrathoracic anastomosis, analyzed the role of prophylactic placement of a drainage tube adjacent to the anastomosis at time of surgical resection in addition to standard tube thoracostomy. A prophylactic drain adjacent to the anastomosis were placed in 112 patients and leaks were identified in this group through detection of increased drain volume, odor, and turbidity and were no longer able to hold suction. Confirmation of leak was achieved upon suspicion of leak at the bedside with methylene blue ingestion and immediate discoloration of the drain. In contrast, 5 of 11 patients with leaks without prophylactic drain required further assessment with computed tomography and oral contrast to establish the diagnosis. Of the remaining 6 patients, methylene blue with drainage into the chest tube established the diagnosis; however, one patient required 3 doses. Eight patients in the no drain group required placement of additional drains to control the leak compared to none in the prophylactic drain group. Resolution of anastomotic leak was significantly faster in the prophylactic drain group (mean 23.4 vs 80.7 days; $p<0.05$) as was return to oral intake (mean 32.2 vs 98 days).[10] Perianastomotic drain placement permitted bedside assessment for leak using methylene blue and minimized the time delay in diagnosis that accompanies radiographic imaging. Use of drain amylase levels for confirmation of leak may be another advantage of perianastomotic drain placement, but only one abstract (not published in manuscript form) was identified in the systematic review.[11] It is important to note, however, that intraluminal migration of surgical drains can occur after esophagectomy.[12] Wilmot and colleagues reviewed 254 patients who underwent esophagectomy; 57 patients had anastomotic leak postoperatively and all 57 had perianastomotic drains in place at the time of leak diagnosis. Four of the 57 patients had radiographic evidence of intraluminal migration of the surgical drain, either at or near the anastomosis an average of 19 days after

esophagectomy. Proper drain position had previously been documented in all 4 patients, but only two of the four patients had previously documented leaks prior to migration of the drain into the anastomotic defect. Healing of the leak in all 4 patients was achieved after withdrawing the drain. Given these findings, perianastomotic drain placement likely facilitates earlier diagnosis and reduces the need for subsequent intervention in some patients with low risk of drain associated complications, but the quality of data supporting the use of intraoperative perianastomotic drain placement is weak.

Use of perianastomotic drainage may facilitate diagnosis and management of anastomotic leak but does not minimize the occurrence of the leak. In contrast, pedicled omental reinforcement of the thoracic esophagogastric anastomosis has been proposed by several authors as a means to decrease the incidence of anastomotic leak. (Table 2) During formation of the gastric conduit, a 2 or 3 vessel segment of omentum is retained on the greater curvature near the anticipated location of the anastomosis. This segment is used to encircle the anastomosis, providing a buttress for the staple line and containing endoluminal contents in the event of anastomotic dehiscence. Systematic review revealed three randomized controlled trials, a retrospective review, and a Cochrane database review, which compared anastomotic complications in cases with omentoplasty reinforcement to those without reinforcement.[13-17] In 2006, Bhat and colleagues published their experience of 184 patients randomized to receive omental reinforcement of the esophageal anastomosis versus no reinforcement, and demonstrated a decrease in leak rate from 3.4% vs 14.4%. The authors reported no complications related to omental pedicle mobilization.[13] Dai and colleagues reported their experience with 255 patients, 127 of whom were randomized to receive anastomotic omental reinforcement. This study demonstrated a leak rate of 1% compared to 6% in patients without omental reinforcement.[14] Neither the Bhat trial nor the Dai trial demonstrated significant differences in postoperative complication rates, hospital mortality or length of stay or incidence of anastomotic strictures. In 2010, Sepsi and colleagues published a retrospective review of their experience with thoracic transposition of an omental flap; the incidence of leak with omentoplasty was 4.7% versus 10.5% without. The need for reintervention was also decreased in the omentoplasty cohort. Mobilization of the omentum from the transverse colon and creation of the pedicle added approximately 20 minutes to the operative time, and did not demonstrate any additional morbidity.[15]

The trials by Bhat and Dai were included in the Cochrane review on the topic, published in 2012, which concluded that omentoplasty after esophagectomy may provide benefit with regard to decreasing the incidence of anastomotic leak. The review indicated that more randomized trials were needed.[16] In keeping with this finding, the most recent randomized trial on the topic was published in 2013 by Zheng and colleagues with 184 patients randomized to omentoplasty (n=92) or non-omentoplasty (n=92).[17] Similar to Bhat and Dai, they observed a significant reduction in leak rate (9.8% vs 3.3%; $p<0.05$). Uncontrollable leak with empyema and mediastinitis with subsequent death occurred in 2 patients in the non-omentoplasty group experienced compared to none in the omentoplasty group; this difference was not significantly different due to small numbers. Hospital stay was significantly longer (21 vs 23 days; $p=0.01$). Taken together, these studies suggest that routine reinforcement of the thoracic anastomosis with pedicled omental flap may reduce the incidence of anastomotic leak; recommendations based on this data can be made with

moderate strength, but further studies are needed to determine which patients and surgical approaches are most likely to benefit from the additional intervention.

Analysis of data regarding the safety, efficacy, and indications for endoscopic interventions (stenting and negative pressure therapy) in leak management

Historically, the approach to anastomotic leak has been to control drainage, nil per oral (NPO), and antibiotic therapy. In the setting of mediastinitis or empyema, surgical debridement was utilized. Recently, however, endoluminal therapy with stenting and negative pressure therapy has been used successfully for management of intrathoracic anastomotic leak. Systematic review for use of stent in the management of anastomotic leaks revealed 25 articles, of which none were randomized controlled trials; there was 1 systematic review focusing on comparisons between types of stents. Five articles described the use of negative pressure therapy for leak management.

Endoscopic placement of stents for management of anastomotic leak was successful in 72% of patients, aggregating results from the 25 articles (299/414 cases). Overall mortality was 15% when stents were used compared to 3.3-11.6% for surgical repair. Data for each series are summarized in Table 3. Types of stents utilized included partially and completely covered self-expanding metal stents (SEMS), self-expanding plastic stents (SEPS), and Montgomery salivary tubes. A systematic review of 25 studies, including 267 patients, was performed by van Boeckel and colleagues to assess the clinical effectiveness and safety of temporary placement of stents for anastomotic leak. They performed a pooled analysis of clinical outcomes, complications and survival comparing fully and partially covered SEMS with SEPS. Clinical success was reported in 85% of patients and did not differ by stent type. The average time for SEPS to remain in place was 8 weeks, whereas SEMS remained only 6 weeks. Stent-related complications, including migration, bleeding, perforation, and tissue ingrowth, occurred in 34% of patients. Migration was more common with SEPS and fully-covered SEMS than with partially covered SEMS (31% and 26% vs 12%, respectively), resulting in significantly higher rates of endoscopic re-intervention for the former two stents compared to the partially covered SEMS.[18]

While it was not possible to separate the intrathoracic anastomotic leaks from the other esophageal leaks reported in the 25 articles with regard to the reporting of complications, they are important to note; serious complications included 11 patients with erosion of the stent into large vessels (e.g. aorta) with hemorrhage that was usually fatal,[19-24] and 6 patients who suffered extension of the anastomotic dehiscence with worsening of the leak. [20 23 25 26] Perforation of the stent through the conduit into the trachea was noted in 1 patient, [27] airway obstruction from the stent in 2 patients,[20] and left atrial compression in 1 patient.[28] Stent erosion, not otherwise specified, was reported in 3 patients,[23 28] esophageal necrosis at the proximal stent resulting in patient death in another.[29] Stent migration was a common problem, requiring repeat endoscopic intervention and resulting in 2 reported bowel obstructions without perforation.[28]

These data suggest that stenting for esophageal anastomotic leaks is potentially beneficial but not without significant potential risk. In general, endoscopic stenting is limited to leaks involving <30% of the anastomotic circumference and without extensive necrosis of the gastric conduit. Patients with extensive devitalization of esophageal anatomy, large leaks, or a nonviable conduit are not suitable for endoscopic management with stent placement. If para-anastomotic and pleural drainage with existing thoracostomy tubes is inadequate, insertion of additional drains under thoracoscopic or CT guidance may be required. A significant caveat of endoscopy is that it carries the risk of exacerbating an anastomotic defect. Due to the risk of mediastinal contamination during endoscopy, it is recommended that esophageal stents be placed at time of initial endoscopic diagnosis.[30] The morbidity associated with endoscopic management and stenting extends to the required follow-up and often the need for repeat interventions. Serial surveillance chest radiography is required to monitor for stent migration, and when detected, repeat endoscopy is required to reposition the stent. Finally, endoscopic removal of the stent is the only definitive method to assess healing of the defect. Dai and colleagues demonstrated that in their series, repeat stenting was necessary in 33 of 40 patients, the mean number of stents per patient was 3.2, and the mean time to healing was 30 days.[30] The principle advantage of endoscopic stenting is immediate coverage of the anastomotic defect with shorter time to oral intake. Freeman and colleagues demonstrated that 82% of patients were able to resume oral intake within 72 hours of stent placement.[31]

Although multiple studies have demonstrated the successful use of endoscopic stenting for the management of anastomotic leaks, these studies are limited by small study populations with heterogeneous patient selection, lack of randomized trials, use of a variety of stent types, varying management algorithms and, importantly, different underlying pathology. Limiting factors for the use of endoscopic stenting may include the extent of the defect, delay in diagnosis and treatment, clinical condition of the patient and underlying malignant disease. Unfortunately, determining the efficacy of endoscopic stenting is difficult as no standardized reporting system or clinical trials exist. Many studies report the ability of a stent to seal but not heal the leak and mortality associated with anastomotic leak, even when managed with early endoscopic stenting, continues to be substantially higher than mortality for esophagectomy in general. For now, endoscopic stenting for the management of intrathoracic leak remains experimental therapy and providers should be fully aware of the associated risks and inform their patients accordingly.

The goal of endoscopic stenting is to eliminate extra-anastomotic contamination of the mediastinum and pleura while the dehiscence heals by secondary intention. Another option that may prove viable for achieving this same goal is to use endoscopically placed, transluminal vacuum therapy. This technique was reported in 5 articles (two were updates of the previous experience at the same institution and the most recent, largest report was included) as an adjunct to surgical management of anastomotic leak. (Table 4). Similar to wound vacuum, which has been used with great success for abdominal wound dehiscence and other large wounds with cavitory components, transluminal vacuum therapy involved placement of a sponge into the anastomotic defect cavity with suction provided by a transnasal catheter. In the 3 articles included in this systematic review, 37 of 40 (93%) patients were successfully managed with endoscopic vacuum therapy. There were no

episodes of significant bleeding or erosion reported. The wound vacuum sponge was changed at varying intervals, but on average between 2 and 3 times per week. While still experimental and not yet available in the United States, Schorsch and colleagues argue that endoscopic vacuum drainage can be used for a wide range of defect sizes within the entire length of the esophagus and provides an opportunity for direct visualization of the inner wound at each vacuum system change.

Conclusions

Early recognition and appropriate management of intrathoracic anastomotic leaks have decreased leak-associated mortality, yet morbidity associated with the complication remains significant. Over the past several decades there has been a shift in management of anastomotic leaks from aggressive surgical intervention to conservative management, and more recently to increasing utilization of endoscopic interventions. The basic principles of these management strategies remain the same, including closure or coverage of the defect, containment of the leak and drainage of the contaminated paraesophageal and mediastinal space. Based on a systematic review of the available literature, there appears to be weak evidence supporting prophylactic drain placement for early identification and control of the leak and omental reinforcement to reduce the incidence and minimize contamination of the mediastinum. There is moderate evidence for the efficacy of endoluminal stents in appropriate patients, but the safety of stent use remains in question and further research is needed to better understand the appropriate use of endoscopic stents for management of intrathoracic anastomotic leaks. Negative pressure wound vacuum therapy may become an important tool in the management of anastomotic leaks, but further study is needed and both stenting and wound vacuum should continue to be regarded as experimental therapy at this time. To date there are no guidelines for endoscopic stent selection nor treatment window for stenting.

The patient's clinical presentation, time to diagnosis, etiology and size of the anastomotic defect should each be considered in the clinician's choice of management strategy. All patients with loss of anastomotic integrity should be treated with intravenous antibiotics, adequate drainage and nutritional support. Patients with leaks diagnosed early, absence of significant mediastinal contamination, smaller defects and asymptomatic presentation may be amenable to endoscopic management with stent placement.

Due to the high morbidity and mortality associated with a second operation, surgical intervention should be reserved for patients with symptomatic or uncontained intrathoracic anastomotic leaks and those in whom conservative or endoscopic management has failed. It is important for the esophageal surgeon to be familiar with the options for surgical management. It is equally important that endoscopic management be quickly abandoned in a patient who is not thriving after endoscopic therapy, as this is likely an indication that the leak is not controlled. Options for surgical intervention include primary repair of the anastomosis or gastric conduit, revision and augmentation with the use of a reinforcing flap such as chest wall muscle, omentum, pleura, pericardial fat or complete surgical revision including gastrointestinal diversion with takedown of the gastric conduit, replacement to an intraabdominal position and creation of an end-esophagostomy. Esophageal exclusion and

creation of end-esophagostomy is often reserved for cases of uncontained leaks, near-circumferential breakdown of the anastomosis or the presence of a large leak (>2 cm) along the anastomosis or gastric conduit staple line. [32 33]

In summary, post-esophagectomy anastomotic leak is associated with increased morbidity, mortality and decreased quality-of-life. Outcomes are improved with intraoperative drain placement and endoscopic stent placement may be beneficial for leaks with defects smaller than 30% of the anastomotic circumference. Undrained mediastinal contamination and persistent leak after stent placement mandates a change in strategy to surgical intervention.

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Table 1
Systematic Literature Search for management of anastomotic leaks

Search Terms	Number of articles
1) 'esophagectomy' AND (anastomosis OR anastomotic) AND leak AND ('complication'/exp/mj OR complication) AND [humans]/lim AND [english]/lim AND [2000-2014]	326
2) 'esophagectomy'/exp AND ('anastomosis'/exp OR anastomotic) AND leak AND 'stent'/exp AND [humans]/lim AND [english]/lim AND [2000-2014]	70
3) 'esophagectomy'/exp AND ('anastomosis'/exp OR anastomotic) AND oment* AND [humans]/lim AND [english]/lim AND [2000-2014]	28
4) 'esophagus' AND ('resection'/exp/mj OR 'resection') AND 'anastomosis dehiscence'	98
Total number of articles	522
Total number after removal of duplicates	465
Final number after review for inclusion and exclusion criteria and addition of articles from review of references^a	51

^aExclusion criteria: abstract only; operations other than esophagectomy; anastomotic leak not a major focus of article; not published in English; case reports with <3 patients; review articles other than systematic reviews and meta-analysis; other than esophagogastric anastomosis

Table 2
Review of omental reinforcement following esophagectomy

Author, year	Number of patients	Anastomotic Technique	Leak Rate n (%)		Stricture Formation n (%)		Length of Stay (days +/- SD)	
			Omental Flap	No Omental Flap	Omental Flap	No Omental Flap	Omental Flap	No Omental Flap
Bhat et al., 2006[13]	194	Hand-sewn	3/97(3)	14/97(14)	10/97(10)	7/97 (7)	22 +/- 6	
Dai et al, 2011[14]	255	Circular Stapled	1/128(1)	7/127(6)	8/128(6)	20/127(16)	20.4 +/- 11.5	23.1 +/- 15.2
Sepesi et al., 2012[15]	607	Stapled	10/215(5)	41/392(11)	Not reported		9	11
Zheng et al., 2013[17]	184	Hand-sewn	3/92(3)	9/92(10)	4/92(4)	2/92(2)	21 +/- 5	23 +/-6

Abbreviations: OFR=omental flap reinforcement

Table 3
Analysis of outcomes after stent placement for management of anastomotic leak after esophagectomy

Author	Year	Type of Stent	Number of patients	Anastomotic Technique	Heal Success n (%)	Mortality n (%)
Doniec et al.[34]	2003	pcSEMS	10	Not reported	8(80)	1(10)
Evrard et al.[35]	2004	SEPS	4	Not Reported	4(100)	0
Gelbmann et al.[25]	2004	SEPS	5	Not reported	3(60)	2(40)
Hunerbein et al.[36]	2004	SEPS	9	Stapled	9(100)	0
Langer et al.[26]	2005	SEPS	24	Not reported	16(67)	3(13)
Schubert et al.[37]	2005	SEPS	12	Circular stapled	11(92)	0
Han et al.[22]	2006	cSEMS	8	Not reported	6(75)	2(25)
Kauer et al.[38]	2008	cSEMS	10	Not reported	7(70)	2(20)
Kim et al.[21]	2008	MSBT	4	Not reported	4(100)	0
Pennathur et al.[20]	2008	SEPS	5	Not reported	2(40)	Not reported
Tuebergen et al.[39]	2008	cSEMS	19	Not reported	14(74)	1(5)
Zisis et al.[40]	2008	cSEMS	9	Not reported	7(78)	2(22)
Kotzampassakis et al.[24]	2009	Not reported	3	Not reported	3(100)	0
Leers et al.[41]	2009	cSEMS	15	Not reported	13(87)	1(7)
Bona et al.[42]	2010	cSEMS	3	Not reported	2(67)	0
Dai et al.[30]	2011	fcSEPS	18	Not reported	16(89)	2(11)
David et al.[28]	2011	cSEMS	5	Not reported	4(80)	1(20)
D'Cunha et al.[23]	2011	cSEMS or SEPS	22	Not reported	13(59)	4(18)
Feith et al.[27]	2011	fcSEMS	115	Not reported	81(70)	10(9)
Freeman et al.[31]	2011	SEPS & cSEMS	17	Not reported	16(94)	0
Nguyen et al.[43]	2011	cSEMS	9	Not reported	9(100)	0
Schweigert et al.[19]	2013	cSEMS	22	Stapled	17(77)	5(23)
Brangewitz et al.[29]	2013	cSEMS or SEPS	39	Not reported	21(54)	11(28)
Leenders et al.[44]	2013	SEMS- mix	15	Hand-sewn	11(73)	5(33)
Schniewind et al.[45]	2013	SEMS & SEPS	12	Not reported	2(17)	10(83)
Total			414		299(72)	62(15)

Abbreviations: cSEMS = covered self-expanding metal stent, pcSEMS = partially covered self-expanding metal stent, fcSEMS = fully covered self-expanding metal stent, bd = biodegradable stent, SEPS = self-expanding plastic stent, MSBT = Montgomery salivary bypass tube^{e+}

Heal success means that the stent is reported to heal the leak and not just seal with radiograph. The seal rate will always be higher than the actual heal rate.

Table 4
Outcomes of Endoscopic Vacuum Sponge Therapy for Anastomotic Leak

Author, year	Number of patients	Anastomotic Technique	Treatment success n (%)	Duration of Therapy	Exchange Interval	Post-treatment outcomes	
						Symptomatic Dysphagia n (%)	Stricture formation noted on endoscopy n (%)
Schniewind et al., 2013[45]	17	Not reported	15(88)	Once diameter of wound cavity <2cm.	Week 1: 3x/week Subsequent weeks: 2x/wk		Not reported
Schorsch et al., 2013[46]	17	Not reported	16(94)	12 days	1-7 days	Not reported	1(6)
Weidenhagen et al., 2010[47]	6	Circular stapled	6(100)	13.5 days	48-72 hours		Not reported