Consequences of anastomotic leaks after minimally invasive esophagectomy: A single-center experience

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A B S T R A C T
Background: Anastomotic leak (AL) after minimally invasive esophagectomy (MIE) is a well-described source of morbidity for patients undergoing surgical treatment of esophageal neoplasm. With improved early recognition and endoscopic management techniques, the long-term impact remains unclear.

Methods: A retrospective review was conducted of patients who underwent MIE for esophageal neoplasm between January 2015 and June 2021 at a single institution. Cohorts were stratified by development of AL and subsequent management. Baseline demographics, perioperative data, and post-operative outcomes were examined.

Results: During this period, 172 MIEs were performed, with 35 of 172 (20.3%) complicated by an AL. Perioperative factors independently associated with AL were post-operative blood transfusion (leak rate 52.9% versus 16.8%; p = 0.0017), incompleteness of anastomotic rings (75.0% vs 19.1%; p = 0.027), and receiving neoadjuvant therapy (18.5% vs 30.8%; p < 0.0001). Inferior short-term outcomes associated with AL included number of esophageal dilations in the first post-operative year (1.40 vs 0.46, p = 0.0397), discharge disposition to a location other than home (22.9% vs 8.8%, p = 0.012), length of hospital stay (17.7 days vs 9.6 days; p = 0.002), and time until jejunostomy tube removal (134 days vs 79 days; p = 0.0023). There was no significant difference in overall survival between patients with or without an AL at 1 year (79% vs 83%) or 5 years (50% vs 47%) (overall log rank p = 0.758).

Conclusions: In this large single-center series of MIEs, AL was associated with inferior short-term outcomes including hospital length of stay, discharge disposition other than to home, and need for additional endoscopic procedures, without an accompanying impact on 1-year or 5-year survival.

Key message: In this large, single-center series of minimally invasive esophagectomies, anastomotic leak was associated with worse short-term outcomes including hospital length of stay, discharge disposition other than to home, and need for additional endoscopic procedures, but was not associated with worse long-term survival. The significant association between neoadjuvant therapy and decreased leak rates is difficult to interpret, given the potential for confounding factors, thus careful attention to modifiable pre- and peri-operative patient factors associated with anastomotic leak is warranted.

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Introduction

More than 18,000 new cases of esophageal cancer were diagnosed in the United States in 2020 [1]. Although the annual incidence has largely remained stable over the past decade, it remains one of the most aggressive forms of cancer, with 5-year survival approaching 20% [2,3]. Esophageal resection is an integral component of the trimodal approach to management, with more surgeons adapting minimally invasive esophagectomy (MIE) due to its association with improved post-operative morbidity and mortality compared to open techniques [4,5]. Anastomotic leak (AL) between the proximal esophageal margin and the gastric conduit nonetheless remains a feared complication, with an incidence of 10–20% in several large series and an associated mortality as high as 35% [6–8].

Numerous attempts have been made to elucidate the risk factors associated with AL as well as their effect on other post-operative...
outcomes. Baseline patient demographics and pre-operative comorbidities, such as age, sex, type 2 diabetes mellitus, nutrition, and smoking status, have not consistently shown an association with AL [8–13]. Tumor characteristics, including staging and location, however, have more reliably demonstrated an association with AL [8,14,15]. The timing of neoadjuvant chemoradiation administration and its effect on AL is an area of active research [16–18]. In addition to variable relationships with different risk factors, the relationship between AL and postoperative outcomes, including overall survival, remains unclear [19,20].

In this study, we aimed to examine the association between perioperative factors and AL after MIE, as well as to better define the effect of AL on short and long-term morbidity and mortality.

Patients and methods

Patient population. After obtaining institutional review board approval (IRB2015-0266), the STS database was queried retrospectively for esophagectomy patients at our single, large-volume, academic institution over the 5.5 year period from January 1st, 2016 to June 30th, 2021. A total of 294 patients underwent esophagectomy for any indication and with any surgical approach during the above period (Fig. 1). Of these, 103 patients underwent surgical intervention including at least one open approach (thoracotomy and/or laparotomy) and were excluded, yielding only those who underwent a totally minimally invasive (thoracoscopic and laparoscopic) Ivor-Lewis or McKeown esophagectomy for any indication. Because there were only three patients who underwent McKeown esophagectomy in our cohort, no subgroup analysis was performed for this surgical technique. Nineteen patients with a surgical indication other than a malignant neoplasm were then excluded from this cohort, leaving 172 patients in our study population. Of these, 35 patients demonstrated a post-operative AL (defined below) with four repaired surgically, 26 managed with endoscopic stent placement, and five managed medically only. Due to the relatively small cohort managed surgically or medically, separate stratification by management strategy was not performed. Median follow-up interval was 22.5 months for the non-AL group and 18.6 months for the AL group.

Anastomotic leak definition and routine perioperative care. During Ivor-Lewis or McKeown MIE, all esophagogastric anastomoses were created in an end-to-side fashion using the Covidien EEA 25 mm–4.8 mm XL circular stapler and Covidien EEA 25 mm OrVil Transoral Circular

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**Fig. 1.** CONSORT Diagram for retrospective review of minimally-invasive esophagectomy patients at a single institution.
Statistical analysis. The primary outcome was overall survival following esophagectomy. Secondary outcomes included initial disposition (i.e. general care, intermediate care unit [IMC], or intensive care unit [ICU]); ICU length of stay; inpatient length of stay; days until jejunostomy tube removal; endoscopic balloon dilatations within the first postoperative year; and discharge disposition location. “Unanticipated post operative complications” were defined as the following variables being positive in the STS database within the index hospitalization: chylothorax, air leak greater than five days, atelectasis requiring bronchoscopy, post-op pleural effusion requiring drainage, pneumonia, acute respiratory distress syndrome, respiratory failure, bronchopleural fistula, pulmonary embolus, pneumothorax requiring chest tube, initial vent support > 48 h, tracheostomy, other pulmonary event, atrial or ventricular arrhythmia requiring treatment, myocardial infarction, deep vein thrombosis requiring treatment, other cardiovascular event, ileus, delayed conduit emptying requiring intervention, clostridium difficile infection, any other GI event, urinary tract infection, urinary retention requiring catheterization, discharge with Foley catheter, surgical site infection, sepsis, other infection requiring antibiotics, new central neurological even, recurrent laryngeal nerve paresis, delirium, other neurologic event, renal failure, other events requiring OR with general anesthesia, and unexpected ICU admission. Statistical comparisons between groups were performed using Fisher’s exact test, pooled t test, or Satterthwaite t test where appropriate. Kaplan–Meier survival analysis was performed to compare overall survival between the two groups. Statistical analyses were performed using SAS (version 9.2; SAS Institute, Inc., Cary, North Carolina, USA). The Kaplan–Meier curve was constructed using IBM SPSS Statistics (version 27.0; IBM, Inc., Armonk, New York, USA).

Results

Perioperative risk factors for anastomotic leak. Overall, of the 172 patients included for analysis, 35 (20.3%) developed an AL. Baseline patient demographics and pre-operative comorbidities are shown in Table 1. Information was not available for serum creatinine (n = 2). The non-AL group had an average age of 64.4 years, pre-operative BMI of 26.7, and was 81.0% male. The AL group had an average age of 61.5 years, pre-operative BMI of 29.0, and was 74.3% male. There was no statistically significant difference between the two groups with regard to age, BMI, or sex. Pre-operative comorbidities, including smoking history (p = 0.6857), diabetic history (p = 0.216), CAD (p = 0.1996), prior cardiac surgery (p = 0.7676), mean weight loss 90 days prior to index procedure (p = 0.2582), and ASA classification (p = 0.2054) also were not associated with a higher incidence of AL.

Neoplasm characteristics and pre-operative treatment regimens were reviewed (Table 2). There was not a statistically significant association between AL and tumor subtype (p = 0.4486) or tumor location (p = 0.5403). Clinical and pathologic TNM staging and histologic grading also did not demonstrate a significant association with AL. Neoadjuvant therapy was negatively associated with the development of an AL. Of the 146 patients who underwent neoadjuvant therapy, only 27 (18.5%) developed an AL compared with 8 of 26 patients (30.8%) who received no neoadjuvant therapy (p < 0.0001). Additionally, of the 50 patients who received neoadjuvant chemotherapy only without the inclusion of radiation, none went on to develop a post-operative AL. Luminar obstruction by neoplasm identified on initial EGD was negatively associated with AL: patients with obstruction had a leak rate lower than those without obstruction (11.7% vs 27.3%, p = 0.0131). Receiving post-operative red blood cell (RBC) transfusion was associated with a higher rate of AL (52.9% vs 16.8%, p = 0.0017) while intraoperative
Post-operative outcomes following anastomotic leak. Table 3 summarizes the associations between AL and short-term post-operative outcomes, including hospital course following the index operation and additional interventions such as endoscopic stricture dilations. The development of an AL was associated with longer index hospitalization (17.7 days vs 9.56 days; p = 0.0002), discharge disposition to a location other than home (22.9% vs 8.8%, p = 0.012), a greater number of endoscopic balloon dilations in the first post-operative year (1.40 dilations vs 0.46 dilations; p = 0.0397), and time until jejunostomy tube removal (134 days vs 79 days, p = 0.0023). There was no association between AL and initial post-operative level of care (i.e. general care, IMC, or ICU), ICU length of stay, or additional unanticipated post-operative outcomes such as new-onset cardiac or pulmonary comorbidities.

Overall post-operative survival is shown in Fig. 2. There was no association between AL and overall survival at 1 year (79% vs 83%) or 5 years (50% vs 47%) (log rank p = 0.798).

**Discussion**

Numerous studies have demonstrated the advantages of MIE over open esophagectomy, including reduced intraoperative blood loss, post-operative cardiovascular and pulmonary complications, and decreased length of stay [21–23]. Despite these advantages, the rate of AL between the distal esophagus and gastric conduit remains similar across operative techniques and is a significant source of postoperative morbidity and mortality [24–26]. Gaining a better understanding of the risk factors associated with AL development, as well as the impact of AL on other post-operative outcomes, may help determine the benefit of preoperative interventions such as nutritional prehabilitation, and guide the use of AL management techniques such as prophylactic intraoperative stenting and omentoplasty [27,28].

In this large, single-center experience of 172 patients over five years, we identified AL in 20.3% of patients, which is comparable to other large

| Variables* | No anastomotic leak (n = 137) | Anastomotic leak (n = 35) | p-Valueb |
|------------|-------------------------------|--------------------------|---------|
| Tumor subtype | Squamous carcinoma | 10 (7.3) | 4 (11.4) | 0.4486 |
|          | Adenocarcinoma | 125 (91.2) | 30 (85.7) | |
|          | Other | 2 (1.5) | 1 (2.9) | |
| Tumor location | Cardia | 84 (61.3) | 23 (65.7) | 0.5403 |
|          | Lower 1/3 | 51 (37.2) | 11 (31.4) | |
|          | Middle 1/3 | 2 (1.5) | 1 (2.9) | |
| Clinical staging (T) | T1s | 1 (0.7) | 0 (0) | 0.0944 |
|          | T1 | 14 (10.2) | 4 (11.4) | |
|          | T2 | 17 (12.4) | 10 (28.6) | |
|          | T3 | 105 (76.6) | 21 (60.0) | |
| Pathologic staging (T) | T0 | 37 (27.0) | 7 (20.0) | 0.138 |
|          | Tis | 1 (0.7) | 1 (2.9) | |
|          | T1a | 7 (5.1) | 6 (17.1) | |
|          | T1b | 17 (12.4) | 6 (17.1) | |
|          | T2 | 20 (14.6) | 4 (11.4) | |
|          | T3 | 55 (40.1) | 13 (31.4) | |
| Clinical staging (N) | N0 | 60 (43.8) | 15 (42.9) | 1 |
|          | N1 | 77 (56.2) | 20 (57.1) | |
| Pathologic staging (N) | N0 | 92 (67.2) | 24 (68.6) | 0.6483 |
|          | N1 | 29 (21.2) | 5 (14.3) | |
|          | N2 | 12 (8.8) | 5 (14.3) | |
|          | N3 | 4 (2.9) | 1 (2.9) | |
| Clinical staging (M) | M0 | 135 (98.5) | 34 (97.1) | 0.4969 |
|          | M1 | 2 (1.5) | 1 (2.9) | |
| Pathologic staging (M) | M0 | 135 (98.5) | 33 (94.3) | 0.1844 |
|          | M1 | 2 (1.5) | 5 (7.3) | |
| Histologic grading | GX | 33 (24.1) | 5 (14.3) | 0.4972 |
|          | G1 | 25 (18.2) | 8 (22.9) | |
|          | G2 | 46 (33.6) | 15 (42.9) | |
|          | G3 | 33 (24.1) | 7 (20.0) | |
| Neoadjuvant chemoradiation | No neoadjuvant treatment | 18 (13.1) | 8 (22.9) | <0.0001 |
|          | Chemotherapy only | 50 (36.5) | 0 (0) | |
|          | Chemoradiation | 69 (50.4) | 27 (77.1) | |
| J-tube placed pre/intraoperatively | No | 37 (27.0) | 10 (28.6) | 0.8346 |
|          | Yes | 100 (73.0) | 25 (71.4) | |
| Luminal obstruction by neoplasm | No | 69 (50.4) | 26 (74.3) | 0.0131 |
|          | Yes | 68 (49.6) | 9 (25.7) | |
| Surgical anastomotic rings complete | No | 1 (0.7) | 3 (8.6) | 0.027 |
|          | Yes | 136 (99.3) | 32 (91.4) | |
| Intraoperative RBC transfusion | No | 136 (99.3) | 35 (100.0) | 1 |
|          | Yes | 1 (0.7) | 0 (0) | |
| Postoperative RBC transfusion | No | 129 (94.2) | 26 (74.3) | 0.0017 |
|          | Yes | 8 (5.8) | 9 (25.7) | |
| Operative time, min | 278 ± 101 | 283 ± 109 | 0.7646 |

J-tube = jejunostomy tube; RBC = red blood cell.

* The sample mean ± SD is given for continuous variables, and number (percent) is given for categorical variables.

b p-Values were obtained using Fisher’s exact test or pooled t test.

d J-tube transfusion was not (0 vs 0.20%, p = 1). Incomplete anastomotic rings were associated with a higher AL rate than complete anastomotic rings (75% vs 19%, p = 0.027). There was no association between AL and operative time or the addition of jejunostomy tube placement at the time of esophagectomy.
series of MIE [29]. Similar to these other large series, we did not identify a reliable association between AL and patient demographics, preoperative comorbidities, or neoplasm characteristics (histology, location, or TNM staging). While the average BMI was higher in the AL group and patients insulin dependent diabetes pre-operatively did have a high overall rate of AL (33%), neither of these findings reached statistical significance. That said, our review did identify a number of interesting associations between operative variables and the development of AL.

We found that the type of neoadjuvant therapy administered was associated with the AL. Specifically, those patients who received neoadjuvant therapy had a lower AL rate (18.5%) than those who did not (30.8%), and none of the fifty patients who received only neoadjuvant chemotherapy without radiation developed AL. This negative association is contrary to multiple studies, which predominately report either no difference or a positive association with AL following neoadjuvant treatment [18,30–35]. The reason this divergence from prior reports is difficult to identify is due to the differences in treatment regimens and disease characteristics existing both within our patient populations and those examined elsewhere, which introduce potential confounding variables. Pennathur et al. outlined the limitations of studies examining survival in patients treated with surgical resection with or without neoadjuvant chemotherapy or chemoradiation, including neoplasm histology and location, CT staging prior to treatment, and poor accrual [36]. There also exists an intimate relationship between neoadjuvant treatment and nutritional status in esophageal cancer, as most patients presenting with symptoms of locally advanced disease, such as dysphagia, receive neoadjuvant treatment with or without interventions for enteral support [37,38]. Our study did not specifically control for this potential confounder; however, it should be noted that 96% of patients presenting with obstructing symptoms or tumor obstruction visualized on initial EGD received either neoadjuvant chemotherapy or chemoradiation. Although the proxy for nutritional status (weight loss 90 days prior to index operation) used in this study, did not demonstrate an association with AL, the positive correlation between malnutrition and AL has been well-documented elsewhere [39]. Therefore, improved nutritional status prior to the index operation thus is one potential explanation for the negative association between neoadjuvant chemotherapy and AL seen in this study, as relief of dysphagia has been reported in patients with esophageal obstruction during neoadjuvant treatment [40]. Taken together, the inconsistencies within the literature at large suggest a need for a more standardized approach that controls for confounders such as nutritional status and treatment regimen when attempting to quantify the effects of neoadjuvant treatment on AL. It is also possible that there is some selection bias in the patients who did not receive neoadjuvant therapy: some patients may have been unable to tolerate chemoradiation but still ultimately underwent esophagectomy due to ongoing obstruction, bleeding, or other surgical indication outside of the standard trimodal therapy paradigm.

We also identified a positive correlation between post-operative RBC transfusion and AL development, with 53% of patients who received post-operative transfusion developing an AL. Due to limitations with data collection, the temporal relationship between RBC transfusion and AL is difficult to discern. There is, therefore, the possibility of AL developing initially and resulting in the need for a transfusion, but this has not been shown to consistently occur in the literature [41]. Nonetheless, the association between these events has been documented previously [8]. Given the low incidence of intraoperative blood transfusions in our cohort (n = 1), one of the factors influencing the need for postoperative RBC transfusion may be pre-operative anemia rather than intraoperative blood loss. The relationship between pre-operative anemia and AL has also been described in the literature, suggesting that optimization prior to surgery may reduce the incidence of AL [42,43].

Analysis of post-operative outcomes demonstrated an association between AL and inferior short-term outcomes. Patients with AL experienced a longer inpatient hospitalization (17.7 days vs 9.56 days), and were more likely to be discharged to a location other than home (20.6% vs 7.4%). These results were expected because management of AL frequently required endoscopic stenting or more rarely surgical intervention, both of which can delay the attainment of nutritional or physical therapy goals requisite for timely discharge to home. Patients with AL were also more likely to maintain dependence on tube feeds for adequate nutrition, resulting in the longer time to discontinuation of the jejunostomy tube in the AL cohort (134 days vs 79 days). While the presence of a jejunostomy tube had no effect on overall survival following AL in the literature, its use was associated with an expedited recovery and allowed for home enteral nutrition, supporting its prolonged use in our cohort [44,45]. Our study also found an increased number of endoscopic balloon dilations in the first postoperative year following an AL (1.40 vs 0.46). This increase is most likely due to the known association between AL on stricture formation at the anastomosis [46].

While there was an association between AL and short-term outcomes, there was no effect of AL on in-hospital mortality (1.5% vs
2.9%) or overall survival at 1 year (83% vs 79%) following MIE. These findings are consistent with previously reported data [47,48]. Although there is no statistically significant difference concerning AL and 5-year survival in our analysis (47% vs 50%), our ability to draw conclusions is limited given a median follow-up time of 18.6 months, requiring further investigation. Should these results hold with a longer follow-up interval in future analyses, they would be similar to previously reported data as well [49,50].

Limitations. As a retrospective review of a single center experience in MIE, this study has several inherent limitations. Particularly, it is impossible to know the extent of surgeon bias and case-by-case analysis of patient selection and post-operative management especially in making comparisons between our cohorts. Notably, while the vast majority of these procedures were performed by a single surgeon, practice and management patterns varied considerably during the examined period with regard to jejunostomy placement, timing of post-operative esophagogram imaging, and whether oral feeds were initiated during the index hospitalization. Given the retrospective nature of the study, it is also difficult to determine the significance of the association between certain pre- and peri-operative factors and the development of AL. Long-term survival data was not also available for all patients.

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Ethics approval
This manuscript and the data collection required for its creation has been approved and overseen by the appropriate ethical committees at our institution and the subjects involved have given informed consent.

CRediT authorship contribution statement
Grigor S Simitian assisted with data acquisition, data analysis, and manuscript construction. David J Hall assisted with manuscript construction and advised on perioperative management techniques elaborated upon in the manuscript. Glen Leveson assisted with data analysis. Entela B Lushaj assisted with data analysis. Erik Lewis assisted with manuscript construction and advised on perioperative management techniques elaborated upon in the manuscript. Kelsey A Musgrove assisted with manuscript construction and advised on perioperative management techniques elaborated upon in the manuscript. Daniel P McCarthy and James D Maloney supervised and assisted with all aspects of the manuscript as necessary. All authors edited, reviewed, and approved the final manuscript as necessary. All authors authorized publication.

Declaration of competing interest
There are no declarations or conflicts of interest by any authors of this manuscript.

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