The Impact of Severe Anastomotic Leak on Long-term Survival and Cancer Recurrence After Surgical Resection for Esophageal Malignancy

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Objective: The aim of this study was to the determine impact of severe esophageal anastomotic leak (SEAL) upon long-term survival and locoregional cancer recurrence.

Background: The impact of SEAL upon long-term survival after esophageal resection remains inconclusive with a number of studies demonstrating conflicting results.

Methods: A multicenter database for the surgical treatment of esophageal cancer collected data from 30 university hospitals (2000–2010). SEAL was defined as a Clavien-Dindo III or IV leak. Patients with SEAL were compared with those without in terms of demographics, tumor characteristics, surgical technique, morbidity, survival, and recurrence.

Results: From a database of 2944 operated on for esophageal cancer between 2000 and 2010, 209 patients who died within 90 days of surgery and 296 patients with a R1/R2 resection were excluded, leaving 2439 included in the final analysis; 208 (8.5%) developed a SEAL and significant independent association was observed with low hospital procedural volume, cervical anastomosis, tumoral stage III/IV, and pulmonary and cardiovascular complications. SEAL was associated with a significant reduction in median overall (35.8 vs 54.8 months; $P = 0.002$) and disease-free (34 vs 47.9 months; $P = 0.005$) survivals. After adjustment of confounding factors, SEAL was associated with a 28% greater likelihood of death [hazard ratio = 1.28; 95% confidence interval (CI): 1.04–1.59; $P = 0.022$], as well as greater overall (OR = 1.35; 95% CI: 1.15–1.73; $P = 0.011$), locoregional (OR = 1.56; 95% CI: 1.05–2.24; $P = 0.030$), and mixed (OR = 1.81; 95% CI: 1.20–2.71; $P = 0.014$) recurrences.

Conclusions: This large multicenter study provides strong evidence that SEAL adversely impacts cancer prognosis. The mechanism through which SEAL increases local recurrence is an important area for future research.

Keywords: anastomotic leak, esophageal neoplasms, general surgery, local, neoplasm recurrence, review, survival

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The overall European pooled relative 1-year and 5-year survival rates for esophageal cancer from the EUROCARE-4 study has previously been shown to be approximately 33.4% [95% confidence interval (CI): 32.9%–33.9%] and 9.8% (95% CI: 9.4%–10.1%), respectively .[1] Treatment of locoregional esophageal cancer is most commonly by surgical resection with or without neoadjuvant or adjuvant chemo- or radiotherapy .[2] Despite recent improvements in perioperative optimization, surgical technique, intraoperative monitoring, and postoperative care, esophagectomy remains one of the most demanding surgical procedures and is associated with a significant rate of morbidity and mortality. Further in-hospital mortality after esophagectomy remains among the highest of all cancer resections[3]; however, improvements associated with centralization of services have seen mortality from esophagectomy decreasing to less than 5% in high-volume centers.[4] Despite these improvements in postoperative mortality, major morbidity after esophagectomy remains high and may impact long-term quality of life and long-term survival.[5]

Esophageal anastomotic leak (EAL) remains one of the most devastating complications after esophagectomy with a wide range of reported incidence from 0 to 35%.[6] Previously it has been shown that the odds ratio of postoperative death within 90-days after intrathoracic anastomotic leak was increased threefold compared with those without such a complication.[7] The impact of severe EAL (SEAL) upon long-term survival after esophageal resection remains inconclusive with a number of studies demonstrating conflicting results.[7–12] However, it is important to acknowledge that because of variation in follow-up patterns, lack of an objective standardized definition of SEAL and small sample sizes with a low incidence of SEAL included, these studies are underpowered and poorly designed to demonstrate a difference in long-term survival associated with SEAL.

The aim of this study was to the determine impact of SEAL upon long-term survival and locoregional cancer recurrence.

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METHODS

Patient Eligibility Criteria

Data from 2944 consecutive adult patients undergoing surgical resection for esophageal cancer (including Siewert type I and II junctional tumors) with curative intent in 30 French-speaking European centers between 2000 and 2010 were retrospectively collected through a dedicated Web site (http://www.chirurgie-viscerale.org), with an independent monitoring team auditing data capture to minimize missing data and to control concordance, and inclusion of consecutive patients. Data collected included demographic parameters, details regarding perioperative and surgical treatments, postoperative outcomes, histopathological analysis, and long-term oncological outcomes. Missing or inconsistent data were obtained from e-mail exchanges or phone calls with the referral center. The focus of this study was the assessment of long-term outcomes after esophagectomy; therefore, patients who died within 90 days of surgery (n = 209, 7.1%) and patients with a noncurative resection (R1 or R2, n = 296) were excluded, leaving 2439 included in the final analysis.

SEAL was defined as a symptomatic (mediastinal abscess, mediastinitis or digestive content in the chest drain) disruption of the intrathoracic anastomosis, classified as grade III or IV according to the Clavien-Dindo classification.[13] Postoperative barium swallow was not routinely performed.

Data Collection

Patient demographic data that was collected included patient age, sex, American Society of Anesthesiology grade (ASA), and nutritional status. Patient malnutrition was defined by weight loss of more than 10% over a 6-month period before surgery. Hospital procedural volume was also collected during the study period, with hospitals divided into 3 groups on the basis of the number of patients operated on during the study period; less than 50 defining low-volume centers, 50 to 99 defining medium-volume centers, and 100 or more patients defining high-volume centers. These thresholds ensured that on average centers classified as low volume performed no more than 5 resections per year, which is consistent with the published literature for esophagectomy.[14] Data regarding tumor location (upper, middle, or lower esophagus), clinical stage, and use of neoadjuvant and adjuvant therapy was also collected. As recommended by French national guidelines,[15] approach to clinical staging used a combination of endoscopic ultrasound for traversable tumor, computerized tomography (CT) and, on demand, positron emission tomography. Approach to surgery varied between 3 techniques being Ivor Lewis, 3-stage, or transhiatal esophagectomy. Postoperative morbidity was assessed including EAL, surgical site infection, chylothorax, gastroparesis, pulmonary, cardiovascular, thromboembolic, neurological complications, and reoperation. The Clavien-Dindo scale was used to grade severity of all postoperative morbidity.[13]

Histologic staging of tumors was based on the seventh edition of the Union Internationale Contre le Cancer/TNM classification.[16] Tumor differentiation and pT and pN stage along with tumor regression grade by Mandard scale were also collected.[17]

Follow-up—Survival and Recurrence

All patients surviving 90 days from surgery were followed until death or time of database closure (2013). During follow-up, clinical examination and thoracoabdominal CT every 6 months for 5 years were recommended, with upper endoscopy at 2 years.[15] In cases of suspected recurrence, thoracoabdominal CT scan and upper gastrointestinal endoscopy were performed. Histologic, cytologic, or unequivocal radiological proof was required before a diagnosis of recurrence was made. The first site of recurrence was used to define whether a locoregional or distant relapse had occurred. Locoregional recurrence comprised cancer relapse within area of resection including local anastomotic sites. Distant recurrence included solid organ metastases, peritoneal recurrence, and nodal metastases beyond the regional lymph nodes. Mixed recurrence was used to describe the situation when locoregional and distant recurrences were discovered simultaneously.

Outcomes

The primary outcome of the study was to determine the effect of SEAL upon long-term survival after esophagectomy for cancer. The secondary outcomes of the study were to determine preoperative and intraoperative factors associated with SEAL and to evaluate the incidence and pattern of disease recurrence in patients with SEAL.

Statistical Analysis

Statistical analysis was performed using SPSS version 19.0 software (SPSS, Chicago, IL). Data are presented as prevalence (percentage), median (range), and for survival as median (95% CI). Data between patients who developed a SEAL were compared with data in patients who had no evidence of a SEAL after esophagectomy. Continuous data were compared using the Mann-Whitney *U* test. Discrete data were compared using the χ^2 test or the Fisher exact test as appropriate. Overall and disease-free survivals were estimated using the Kaplan-Meier method. The log rank test was used to compare survival curves. The factors associated with survival were analyzed by Cox proportional hazard regression analysis using a stepwise procedure; the 0.1 level was defined for entry into the model. Factors associated with recurrence were identified using a forward binary logistic regression model. All statistical tests were two sided, with the threshold of significance set at a *P* value of less than 0.05. The study was accepted by the regional institutional review board on July 15, 2013, and the database was registered on the Clinicaltrials.gov Web site under the identifier NCT 01927016.

RESULTS

Demographics of Study Population

In total, 2439 patients who underwent surgical resection for esophageal cancer were included, of whom 274 developed an EAL (11.2%), graded I (1.8%), II (22.2%), IIIa (13.2%), IIIb (27.0%), IVa (24.9%), and IVb (10.9%) according to the Clavien-Dindo classification. Only the clinically significant SEAL, defined as grade III and IV anastomotic leak, was considered in this study (n = 208, 8.5%). The median age of the study group was 60.6 (21–88) years, with 82.0% being male, 58.4% were ASA grade II, and 19.2% of patients showed evidence of preoperative malnutrition. The majority of patients (59.6%) were operated on in high-volume centers, with Ivor-Lewis being the most commonly utilized surgical approach in 75.9% of cases, and neoadjuvant chemotherapy used in 46.3% of cases and in combination with radiotherapy in 28.6% of cases. Clinical stage III disease was seen in 46.8% of patients, with the lower esophagus most often involved (54.5%).

Factors Associated With Esophageal Anastomotic Leak

An increasing number of esophageal resections performed by the center were associated with a reduced rate of SEAL, with a higher rate in low-volume centers (13.0%) when compared with medium- (8.7%) or high-volume centers (7.6%) ($P = 0.012$) (Table 1). There

TABLE 1. Patient Demographics and Preoperative Variables

Variables	Total, n (%) (N = 2439)	SEAL, n (%) (N = 208)	No Anastomotic Leak, n (%) (N = 2231)	*P*
Age, median (range), yrs	60.6 (21–88)	61.0 (32–81)	61.0 (21–88)	0.882
Age, yrs				
<60	1192 (48.9)	102 (8.6)	1090 (91.4)	0.960
≥60	1247 (51.1)	106 (8.5)	1141 (91.5)	
Sex				
Male	2000 (82.0)	170 (8.5)	1830 (91.5)	0.916
Female	439 (18.0)	38 (8.7)	401 (91.3)	
ASA grade				
I	414 (17)	29 (7.0)	385 (93.0)	0.036
II	1425 (58.4)	111 (7.8)	1314 (92.2)	
III	576 (23.6)	66 (11.5)	510 (88.5)	
IV	24 (1.0)	2 (8.3)	22 (91.7)	
Malnutrition at initial diagnosis				
No	1495 (61.3)	122 (8.2)	1373 (91.8)	0.680
Yes	468 (19.2)	44 (9.4)	424 (90.6)	
Unknown	476 (19.5)	42 (8.8)	434 (91.2)	
Study period				
2000–2005	1204 (49.4)	94 (7.8)	1110 (92.2)	0.208
2006–2010	1235 (50.6)	114 (9.2)	1121 (90.8)	
Hospital volume*				
<50	277 (11.4)	36 (13.0)	241 (87.0)	0.012
50–99	708 (29.0)	62 (8.8)	646 (91.2)	
≥100	1454 (59.6)	110 (7.6)	1344 (92.4)	
Surgical technique				
Ivor Lewis	1850 (75.9)	134 (7.2)	1716 (92.8)	<0.001
3 stage	267 (10.9)	35 (13.1)	232 (86.9)	
Transhiatal	322 (13.2)	39 (12.1)	283 (87.9)	
Tumor location				
Upper	281 (11.5)	41 (14.6)	240 (85.4)	<0.001
Middle	828 (33.9)	69 (8.3)	759 (91.7)	
Lower	1330 (54.5)	98 (7.4)	1232 (92.6)	
Clinical tumoral stage				
I	638 (26.2)	53 (8.3)	585 (91.7)	0.005
II	635 (26.0)	75 (11.8)	560 (88.2)	
III	1142 (46.8)	78 (6.8)	1064 (93.2)	
IV	24 (1.0)	2 (8.3)	22 (91.7)	
Neoadjuvant treatment	1129 (46.3)	93 (8.2)	1036 (91.8)	0.633
Radiotherapy	698 (28.6)	63 (9.0)	635 (91.0)	0.577
Chemotherapy	1129 (46.3)	93 (8.2)	1036 (91.8)	0.633

*Number of cases operated on per center over the study period.

were also significant differences between patients who developed a SEAL and those who did not in terms of ASA grade, surgical technique, tumor location, and clinical stage. However, there were no significant differences between the groups in terms of age, sex, malnutrition, study period (before or after 2006), utilization of neoadjuvant therapy, pathological staging, tumor differentiation, histology (adenocarcinoma vs squamous cell carcinoma), or tumor regression as assessed by Mandard grading. By multivariable analysis, factors associated independently with SEAL were low-volume center (OR = 1.92; 95% CI: 1.28–2.88; $P = 0.007$), cervical anastomosis after either 3 stage or transhiatal resection (OR = 1.69; 95% CI: 1.14–2.50; $P = 0.009$), upper third tumoral location (OR = 1.77; 95% CI: 1.12–2.81; $P = 0.015$), and ASA score (OR = 1.63; 95% CI: 1.03–2.59; $P = 0.038$).

EAL and Other Complications

Pulmonary, cardiovascular, and neurological complications and surgical site infections were significantly associated with a SEAL (Table 2). As expected, SEAL was significantly associated with reoperation ($P < 0.001$) and resulted in a greater median length of hospital stay [45 (11–261) vs 18 (7–234) days; $P < 0.001$]. The percentage of patients who received adjuvant therapy was significantly reduced after SEAL (11.5% vs 21.6%; $P = 0.001$).

Survival—Overall and Disease Free

The median follow-up was 54.0 (0.5–156.7) months. SEAL was associated with a significant reduction in median overall [35.8 (26.3–45.3) vs 54.8 (48.3–61.3) months; $P = 0.002$] (Fig. 1) and disease-free [34.9 (27.4–42.5) vs 47.9 (43.5–52.2) months; $P = 0.005$] (Fig. 2) survivals. Analysis of stage-specific survival showed that overall and disease-free survivals for stage 0 and stage III disease were both significantly reduced after SEAL (Table 3). When SEAL was subdivided by severity (Clavien-Dindo III vs IV), no significant differences in overall or disease-free survivals were noted between the groups. From univariable analysis, 15 variables were related to survival and taken forward to the multivariable model. Of these, 10 variables, including SEAL (hazard ratio = 1.28; 1.28; 95% CI: 1.04–1.59; $P = 0.022$), were found to be independently associated with a poor prognosis (Table 4): surgery before 2006, patient age 60 years or more, ASA score III–IV, malnutrition at diagnosis, absence of neoadjuvant chemoradiotherapy, postoperative pulmonary complication, squamous cell carcinoma histological

TABLE 2. Postoperative Outcomes and Histology

Variables	Total, n (%) (N = 2439)	SEAL, n (%) (N = 208)	Anastomotic Leak, n (%) (N = 2231)	*P*
Overall complications	1266 (51.9)	208 (16.4)	1058 (83.6)	<0.001
Surgical site infections	250 (10.3)	208 (83.2)	42 (16.8)	<0.001
Chylothorax	57 (2.3)	0 (0)	57 (100)	0.006
Gastroparesis	33 (1.4)	0 (0)	33 (100)	0.052
Pulmonary complications	841 (34.5)	123 (14.6)	718 (85.4)	<0.001
Cardiovascular complications	235 (9.6)	42 (17.9)	193 (82.1)	<0.001
Thromboembolic event	58 (2.4)	9 (15.5)	49 (84.5)	0.054
Neurological complications	13 (0.5)	2 (15.4)	11 (84.6)	0.033
Other medical complications	46 (1.9)	11 (23.9)	35 (76.1)	<0.001
Sepsis	73 (3)	2 (2.7)	71 (97.3)	0.044
Reoperation	297 (12.2)	118 (39.7)	179 (60.3)	<0.001
Length of hospital stay, d	18.0 (7–261)	45.0 (11–261)	18.0 (7–234)	<0.001
Adjuvant treatment	507 (20.8)	24 (4.7)	483 (95.3)	0.001
Histology				
Adenocarcinoma	1260 (51.7)	97 (7.7)	1163 (92.3)	0.290
Squamous cell carcinoma	1105 (45.3)	105 (9.5)	1000 (90.5)	
Others	74 (3.0)	6 (8.1)	68 (91.9)	
Tumor differentiation				
Good	747 (30.6)	71 (9.5)	676 (90.5)	0.513
Average	824 (33.8)	67 (8.1)	757 (91.9)	
Poor	385 (15.8)	27 (7.0)	358 (93.0)	
Not reported	483 (19.8)	43 (8.9)	440 (91.1)	
pT stage				
pT0	329 (13.5)	30 (9.1)	299 (90.9)	0.540
pT1a	334 (13.7)	31 (9.3)	303 (90.7)	
pT1b	351 (14.4)	29 (8.3)	322 (91.7)	
pT2	489 (20.0)	41 (8.4)	448 (91.6)	
pT3	871 (35.7)	71 (8.2)	800 (91.8)	
pT4a	63 (2.6)	5 (7.9)	58 (92.1)	
pT4b	2 (0.1)	1 (50.0)	1 (50.0)	
pN stage				
pN0	1347 (55.2)	110 (8.2)	1237 (91.8)	0.512
pN1	560 (23.0)	56 (10.0)	504 (90.0)	
pN2	335 (13.7)	28 (8.4)	307 (91.6)	
pN3	197 (8.1)	14 (7.1)	183 (92.9)	
pTNM stage				
0	269 (11.0)	23 (8.6)	246 (91.4)	0.625
I	774 (31.7)	64 (8.3)	710 (91.7)	
II	570 (23.4)	56 (9.8)	514 (90.2)	
III	826 (33.9)	65 (7.9)	761 (92.1)	
TRG mandard (n = 698)				
TRG 1	269 (38.5)	24 (8.9)	245 (91.1)	0.707
TRG2	109 (15.6)	9 (8.3)	100 (91.7)	
TRG3	132 (18.9)	15 (11.4)	117 (88.6)	
TRG4	131 (18.8)	11 (8.4)	120 (91.6)	
TRG5	57 (8.2)	4 (7.0)	53 (93.0)	

TRG indicates tumor regression grade, among patients who received neoadjuvant chemoradiation.

subtype, poor tumoral differentiation, and pathological TNM stage III/IV.

Recurrence—Overall, Local, Distant, and Mixed

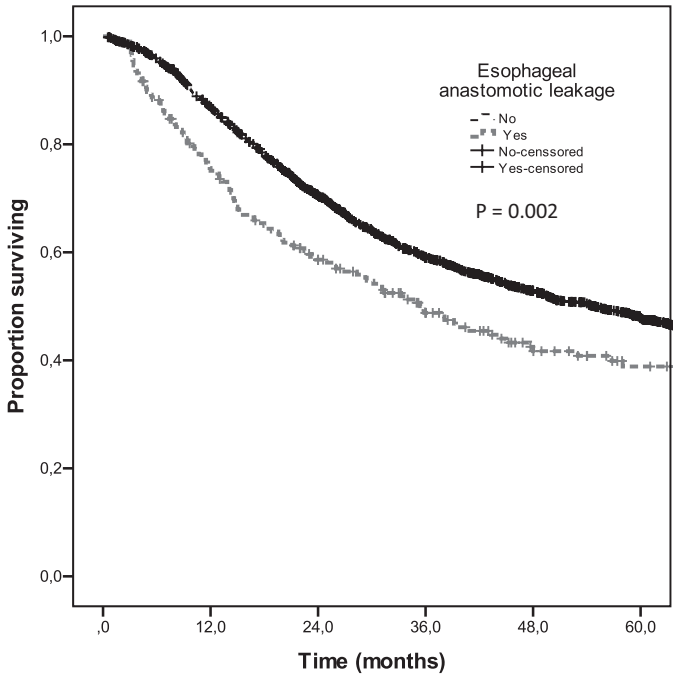
At 5 years follow-up, the incidences of cumulated overall (56.1% vs 48.5%; $P = 0.009$), locoregional (23.8% vs 18.5%; $P = 0.044$), and mixed (19.0% vs 13.3%; $P = 0.012$) recurrences were all significantly increased after esophagectomy complicated by SEAL, with however no significant impact on distant recurrence incidence (28.9% vs 26.4%; $P = 0.341$). The median time to recurrence after surgery was also reduced in patients who developed a SEAL [9.0 (1.0–42.0) vs 11.0 (0–180.0) months; $P = 0.010$]. Multivariable analysis also confirmed that SEAL was independently associated with overall (OR = 1.35; 95% CI: 1.15–1.73; $P = 0.011$), locoregional (OR = 1.56; 95% CI: 1.05–2.24; $P = 0.030$), and mixed recurrence (OR = 1.81; 95% CI: 1.20–2.71; $P = 0.014$), but not distant recurrence (OR = 1.23; 95% CI: 0.86–1.76; $P = 0.255$) (Tables 5 and 6).

Outcomes of Grades I and II EAL

A subset analysis was conducted to look at the impact of grades I and II EAL on outcomes. Considering 66 patients who experienced a nonclinically relevant EAL, no impact was observed according to the presence or absence of EAL regarding overall (medians of 72.0 vs 51.2 months, respectively, $P = 0.263$) or disease-free survivals (medians of 68.4 vs 49.7 months, respectively, $P = 0.334$).

DISCUSSION

The primary aim of this study was to determine the influence of SEAL after surgery for esophageal cancer upon long-term clinical outcomes including survival and cancer recurrence. The overall



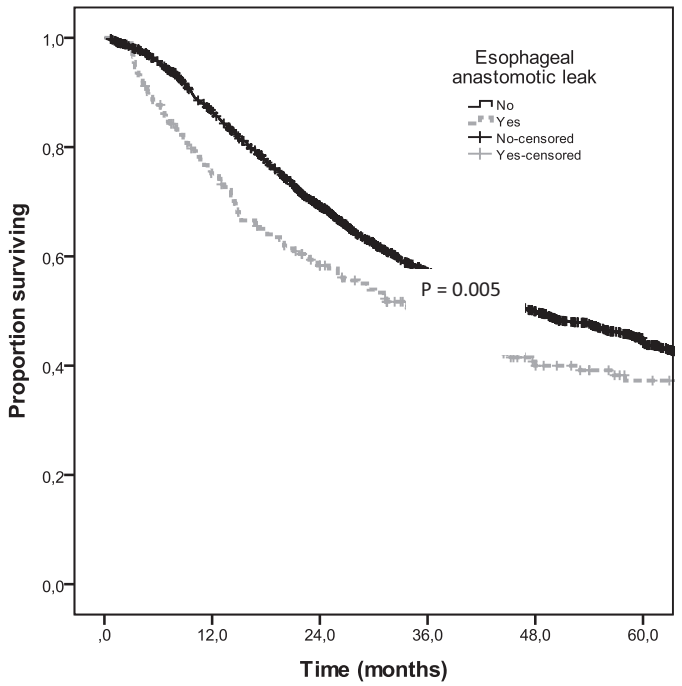
SEAL group	208	148	109	77	52	38
Absence of SEAL group	2231	1826	1378	1006	762	563

Figure 1. The overall survival curves in the SEAL group (n = 208) and absence of SEAL group (n = 2231). The number of subjects at risk in each interval is shown in the table at the bottom of the graph.

incidence of SEAL after esophagectomy in the present large-population study was 8.5%. The results of the study suggest that SEAL was significantly associated with an adverse impact upon overall and disease-free survivals, and it was also associated with an increase in the incidence of overall, locoregional, and mixed cancer recurrences. However, SEAL did not influence distant cancer recurrence. When SEAL was subdivided by severity (Clavien-Dindo III vs IV), no significant differences in overall or disease-free survivals were noted between the groups. Clinically significant differences in survival were seen in all stages; however, this reached statistical significance only for stage 0 and stage III. This is likely to be a reflection of sample size in each stage as the absolute difference in survival in months between the groups was seen to decrease with increasing stage (Table 3). The incidence of SEAL was independently associated with low hospital procedural volume, cervical anastomosis, upper third tumoral location, and ASA score III/IV in multivariable analysis.

Previous studies in the setting of esophagectomy have failed to conclusively demonstrate a long-term adverse impact on survival associated with EAL (Table 7). Rutegard et al[12] performed an analysis of 567 patients, 47 of whom developed an EAL, with no effect on long-term survival (median 22 vs 24.4 months). Similarly other publications in smaller sample sizes to the present study have failed to show a significant difference in long-term survival associated with EAL (Table 7). In contrast, Rizk et al,[5] in a study of 531 patients with a focus on technical complications, suggested that of all technical complications, EAL had the largest impact on long-term survival. Meta-analysis of large data sets from the colorectal literature have suggested that anastomotic leak after resection had a negative prognostic impact on local recurrence and reduced long-term cancer-specific survival, with no effect on distal recurrence.[18] This study includes analysis of 2439 patients and is the largest contribution to the esophagectomy literature on this subject, with findings that mirror what has been previously observed from meta-analysis of colorectal studies. The finding of anastomotic leak adversely impacting survival and locoregional recurrence across cancer types is important, as this suggests a common mechanism and furthermore the significance of this issue in cancer surgery.

It is likely that the etiology of increased locoregional recurrence and reduced survival after EAL is multifactorial. Previously, authors have suggested that for colorectal surgery, colorectal cancer cells are detectable in the bowel lumen and on the suture or staple lines during resection, with in vitro and animal models demonstrating these cells retain their metastatic potential.[19–21] Therefore following a similar hypothesis may be suggested for esophagectomy, with the spillage of viable esophageal cancer cells following EAL, provides a nidus for locoregional tumor recurrence. Leakage of enteric contents into the mediastinum sets up a proinflammatory environment with the release of a variety of acute phase reactants and cytokines. Previous studies have suggested IL-32, TNF-α, IL-6, and IL-1β expression are all increased in patients with esophageal cancer and maybe associated with tumor proliferation, survival, and progression to metastasis.[22–24] The hypothesis of an inflammatory response to EAL may set up an environment that enhances esophageal cancer recurrence is further supported by examples from other cancers including colorectal and breast.[25,26] Therefore the increased locoregional recurrence after SEAL may be the result of spillage of viable tumor cells from anastomotic stapled or sutured lines, with a proinflammatory response promoting tumor growth. Future research specifically in the setting of esophageal cancer is required to determine the viability of esophageal cancer cells from anastomotic



SEAL group	208	140	99	64	40	27
Absence of SEAL group	2231	1801	1325	995	650	461

Figure 2. The disease-free survival curves in the SEAL group (n = 208) and absence of SEAL group (n = 2231). The number of subjects at risk in each interval is shown in the table at the bottom of the graph.

TABLE 3. Severe Anastomotic Leak and Survival in Months

Variables	Total, mo (N = 2439)	SEAL, mo (N = 208)	No Anastomotic Leak, mo (N = 2231)	*P*
Overall survival				
All stages	52.9 (47.6–58.3)	35.8 (26.3–45.3)	54.8 (48.3–61.3)	0.002
Stage 0	123.0 (107.3–138.7)	56.8 (3.6–109.9)	125.3 (107.7–143.0)	0.024
Stage I	146.5 (115.6–177.4)	94.4 (78.9–100.1)	146.5 (116.0–177.0)	0.075
Stage II	45.1 (35.3–54.9)	34.9 (16.5–53.3)	46.2 (35.4–56.9)	0.306
Stage III	25.2 (23–27.5)	18.1 (12.6–23.6)	25.8 (23.5–28.2)	0.006
Clavien-Dindo				
IIIa	46.7 (30.6–62.7)	38.1 (11.2–65.0)	46.7 (18.2–75.1)	0.351
IIIb	55.6 (9.8–101.4)	58.0 (0–119.3)	52.9 (3.4–102.5)	0.612
IVa	31.5 (23.0–40.0)	33.3 (20.3–46.2)	31.2 (19.9–42.4)	0.766
IVb	14.3 (9.4–19.2)	7.7 (0–17.1)	16.8 (5.3–28.3)	0.507
Disease-free survival				
All stages	46.2 (41.8–50.5)	34.9 (27.4–42.5)	47.9 (43.5–52.2)	0.005
Stage 0	108.0 (81.0–135.0)	56.8 (3.6–109.9)	110.9 (81.4–140.5)	0.029
Stage I	112.0 (94.3–129.7)	94.4 (69.9–118.9)	114.7 (95.1–134.2)	0.162
Stage II	40.8 (34.4–47.1)	34.9 (24.7–45.1)	42.0 (35.0–49.0)	0.410
Stage III	23.7 (21.8–25.6)	18.1 (11.8–24.5)	24.9 (22.8–26.9)	0.005
Clavien-Dindo*				
IIIa	38.1 (24.4–51.8)	35.8 (7.7–63.8)	39.4 (21.9–56.9)	0.517
IIIb	50.4 (34.7–66.1)	53.0 (0–107.6)	45.3 (26.8–63.8)	0.691
IVa	30.3 (22.8–37.8)	33.3 (22.0–44.6)	29.5 (20.3–38.8)	0.675
IVb	12.8 (7.9–17.7)	7.7 (0–17.1)	16.0(4.5–27.5)	0.594

All survival values presented as median (95% confidence interval).

*Clavien-Dindo IIIa—Requiring surgical endoscopic or radiological intervention not under general anesthesia; Clavien-Dindo IIIb—Requiring surgical endoscopic or radiological intervention under general anesthesia; Clavien-Dindo IVa—Life-threatening single-organ dysfunction requiring ICU management; Clavien-Dindo IVb—Life-threatening multiorgan dysfunction requiring ICU management.

TABLE 4. Cox Regression Analysis for Identifying Factors Associated With Overall Survival

	Survival	
Variable	**Hazard Ratio (CI)**	***P***
SEAL	1.28 (1.04–1.59)	0.022
Surgery after 2006	0.84 (0.75–0.95)	0.006
Low-volume center	1.05 (0.96–1.14)	0.306
Age ≥ 60 yrs	1.29 (1.15–1.46)	<0.001
Male sex	1.15 (0.98–1.34)	0.088
ASA III-IV score	1.19 (1.09–1.30)	<0.001
Malnutrition	1.09 (1.09–1.30)	0.024
Neoadjuvant radiotherapy given	0.58 (0.37–0.92)	0.020
Adjuvant therapy	0.95 (0.81–1.11)	0.516
SCC histological subtype	1.47 (1.05–2.27)	0.035
Poor tumoral differentiation	1.50 (1.26–1.79)	<0.001
Pathological tumoral stage III/IV	4.20 (53.28–5.39)	<0.001
Reoperation	1.13 (0.93–1.36)	0.213
Pulmonary complication	1.32 (1.17–1.49)	<0.001
Cardiovascular complication	0.96 (0.79–1.16)	0.671

SCC indicates squamous cell carcinoma.

lines and the influence of a proinflammatory environment upon tumor growth.

Importantly when looking at the shape of the Kaplan-Meier curves for overall and disease-free survivals, it seems that the relative reduction in survival associated with SEAL occurs within 12 months after surgery, and this difference between the 2 groups was maintained over the study period. The median time to recurrence was also significantly reduced after SEAL (9.0 vs 11.0 months), which suggests that the initial immunogenic insult caused by SEAL has the maximal effect on tumor growth within the first 12 months.

Significant factors associated with SEAL in multivariate analysis included surgery performed in low-volume institutions, cervical anastomosis, upper third tumoral location, and ASA score III/IV. Given the long-term adverse effects of SEAL shown in this study, optimizing preoperative nutrition, surgical technique, preparation of the gastric conduit, and postoperative care should be assigned even greater importance.[27] A recent meta-analysis has shown the only technical factor associated with an increased incidence of EAL was a cervical location of the anastomosis, most likely due to a greater stretch placed upon the gastric conduit and impaired conduit microcirculation.[28] Studies examining the volume-outcome relationship for esophagectomy have suggested that high-volume institutions with a larger caseload and appropriate infrastructure are better prepared to deliver high-quality outcomes.[14,29,30] Centralizing esophageal and other high-risk cancer surgeries is a complex issue involving many factors including specialty certification, historical practice patterns, access to care, and cost of service delivery. Despite these challenges the reduction of EAL along with the resultant long-term consequences in high-volume centers provides a further argument in favor of centralization of esophageal cancer services. The utilization of neoadjuvant therapy and in particular neoadjuvant chemoradiotherapy did not affect the incidence of EAL as has been shown in several recent studies,[31,32] whereas its impact in decreasing recurrence rate was confirmed.[33]

There are some limitations of this study that must be considered when evaluating the significance of the outcomes presented, including its design as a retrospective, observational study. As a large multicenter database study, the results generated are dependent upon the reliability of the methodology of data collection. To minimize any bias associated with data collection methodology during this study, an independent monitoring team audited data capture to minimize missing data and to control concordance, as well as ensure inclusion of consecutive patients. Despite analysis and control for many important factors that can influence long-term survival and cancer recurrence, there are inevitably other confounding variables that were not studied. Insufficient information regarding individual medical comorbidities was available for inclusion in the analysis, and therefore ASA grade was used to compare physiological fitness for surgery between the groups. The unknown influence of these medical comorbidities upon the factors associated with SEAL is an important limitation. Further due to the large sample size, the probability of these unknown factors to be equally distributed

TABLE 5. Logistic Regression Analysis for Identifying Factors Associated With Tumor Recurrence Including Overall, Locoregional, Distant, and Mixed

	Recurrence							
	Overall		Locoregional		Distant		Mixed	
Variable	**OR (CI)**	***P***	**OR (CI)**	***P***	**OR (CI)**	***P***	**OR (CI)**	***P***
SEAL	1.35 (1.15–1.73)	0.011	1.56 (1.05–2.24)	0.030	1.23 (0.86–1.76)	0.255	1.81 (1.20–2.71)	0.014
Surgery after 2006	0.74 (0.86–1.11)	0.740	1.02 (0.80–1.30)	0.867	0.98 (0.81–1.19)	0.849	0.92 (0.70–1.20)	0.517
Low-volume center	1.08 (0.90–1.30)	0.217	1.26 (1.05–1.49)	0.014	1.24 (0.95–1.63)	0.114	1.27 (0.87–1.85)	0.221
Age ≥ 60 yrs	0.86 (0.76–0.98	0.021	0.94 (0.75–1.18)	0.603	0.77 (0.64–0.93)	0.008	0.94 (0.72–1.23)	0.664
Male sex	1.08 (0.92–1.27)	0.265	1.23 (0.92–1.65)	0.167	1.05 (0.82–1.35)	0.680	1.08 (0.78–1.49)	0.658
ASA III−IV score	1.10 (1.01–1.21)	0.035	1.05 (0.89–1.25)	0.547	1.12 (0.98–1.28)	0.111	1.16 (0.95–1.40)	0.139
Malnutrition	1.05 (0.97–1.14)	0.201	1.01 (0.88–1.16)	0.896	1.10 (0.98–1.24)	0.102	1.02 (0.86–1.21)	0.809
Neoadjuvant radiotherapy given	0.53 (0.32–0.88)	0.014	1.00 (0.32–3.17)	0.994	0.40 (0.22–0.77)	<0.001	0.43 (0.16–1.19)	0.105
Adjuvant therapy	1.01 (0.86–1.19)	0.894	0.81 (0.59–1.12)	0.201	0.98 (0.77–1.25)	0.863	0.84 (0.63–1.15)	0.265
SCC histological subtype	1.68 (1.03–2.75)	0.038	7.14 (1.73–29.51)	0.007	1.29 (1.05–1.58)	0.016	1.41 (0.55–3.59)	0.476
Poor tumoral differentiation	1.51 (1.26–1.81)	<0.001	1.14 (0.80–1.61)	0.413	1.50 (1.14–1.97)	0.004	0.29 (1.15–3.38)	<0.001
Pathological tumoral stage III/IV	4.78 (3.64–6.28)	<0.001	3.99 (2.50–6.37)	<0.001	5.05 (3.34–7.64)	<0.001	5.13 (2.79–9.45)	<0.001
Reoperation	1.01 (0.82–1.25)	0.894	0.92 (0.64–1.34)	0.678	0.96 (0.69–1.33)	0.798	1.39 (0.92–2.08)	0.117
Pulmonary complication	1.22 (1.07–1.39)	0.003	1.04 (0.81–1.33)	0.756	1.26 (1.03–1.53)	0.024	1.34 (1.01–1.77)	0.039
Cardiovascular complication	0.95 (0.78–1.17)	0.645	1.26 (0.89–1.78)	0.193	0.85 (0.62–1.16)	0.310	0.78 (0.49–1.22)	0.271

Mixed recurrence defined as local and distant recurrence occurring simultaneously.
SCC indicates squamous cell carcinoma.

TABLE 6. Anastomotic Leak and Recurrence—Overall, Locoregional, Distant, and Mixed

Recurrence Type	Time	SEAL (N = 208) (%)	No Anastomotic Leak (N = 2231) (%)	*P*
Overall				
	1 yr	21.7	10.3	0.009
	2 yrs	36.9	26.8	
	3 yrs	48.1	32.0	
	5 yrs	56.1	48.5	
Locoregional				
	1 yr	6.2	2.3	0.044
	2 yrs	11.8	7.2	
	3 yrs	18.1	12.8	
	5 yrs	23.8	18.5	
Distant				
	1 yr	11.9	5.5	0.341
	2 yrs	19.0	13.6	
	3 yrs	22.8	19.6	
	5 yrs	28.9	26.4	
Mixed				
	1 yr	5.9	2.7	0.012
	2 yrs	11.7	7.6	
	3 yrs	17.8	10.4	
	5 yrs	19.0	13.3	
Time to recurrence,* mo				
	All stages	9.0 (1.0–42.0)	11.0 (0–180.0)	0.010
	Stage 0	11.0 (4.0–36.0)	12.0 (0–180.0)	0.543
	Stage I	8.5 (2.4–38.0)	14.0 (0–100.0)	0.055
	Stage II	10.0 (2.4–42.0)	12.0 (0–78.0)	0.578
	Stage III	7.0 (1.0–28.0)	10.0 (0–100.0)	0.016

Mixed recurrence defined as local and distant recurrence occurring simultaneously.
*Presented as median (range).

TABLE 7. Published Literature Regarding the Influence of Anastomotic Leak on Long-term Survival After Esophagectomy

Author	Study Date	Patient Number (EAL)	Patient Number (No EAL)	Survival (EAL)	Survival (No EAL)	Conclusion
Escofet[8]	1998–2008	20	220	25% (5-yr OS)	38% (5-yr OS)	No significant difference ($P = 0.314$)
Hii[9]	1998–2011	51	379	30 mo (median OS) 28 mo (median DFS)	55 mo (median OS) 55 mo (median DFS)	OS: $P = 0.044$ DFS: $P = 0.010$ Significance lost in multivariable analysis
Rutegard[12]	2001–2005	47	520	22.0 mo (median OS)	24.4 mo (median OS)	HR = 1.29 (95% CI: 0.91–1.81)
Takeuchi[10]	1994–2008	16	49	22% (5-yr OS)	50% (5-yr OS)	No significant difference ($P = 0.076$)
Xia[11]	1994–2008	32	100	27.2 mo (mean OS)	28 mo (mean OS)	No significant difference ($P = 0.880$)
Rizk[5]	2001–2005	138*	393*	31% (3-yr OS)	48% (3-yr OS)	HR = 1.41 ($P < 0.001$) AL had largest impact on long-term survival (78% of technical complications)

*Number refers to patients who developed technical complications.
DFS indicates disease-free survival; HR, hazard ratio; OS, overall survival.

between groups is high. Patients with SEAL were statistically less likely to receive adjuvant treatment compared to those with no leak (11.5% vs 21.6%; $P < 0.001$), probably due to poor overall recovery and health after surgery. However, adjuvant therapy has not been shown to improve survival after esophageal cancer surgery in Western countries,[34] and it was found to be a nonsignificant factor in multivariable analysis for overall survival. A further limitation of the present analysis is that the time of diagnosis of SEAL and timing in relation to other complications (preceding or following) was not captured. Therefore, the influence of early versus late SEAL upon survival was not evaluated in this study.

CONCLUSIONS

From this large multicenter data set, SEAL after surgical resection for esophageal cancer is associated with poor overall and disease-specific survivals and an increase in overall, locoregional, and mixed cancer recurrences. The mechanism of enhanced local recurrence after SEAL is an important area for future assessment. The findings of this study highlight the long-term consequences of failure to attention to detail during anastomotic formation in esophagectomy and/or optimal host condition for surgery and further suggests short- and long-term benefits to the centralization of esophagectomy to high-volume centers.

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