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Original Article

Treatment of anastomotic leak after oesophagectomy for oesophageal cancer: large, collaborative, observational TENTACLE cohort study

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Abstract

Background: Anastomotic leak is a severe complication after oesophagectomy. Anastomotic leak has diverse clinical manifestations and the optimal treatment strategy is unknown. The aim of this study was to assess the efficacy of treatment strategies for different manifestations of anastomotic leak after oesophagectomy.

Methods: A retrospective cohort study was performed in 71 centres worldwide and included patients with anastomotic leak after oesophagectomy (2011–2019). Different primary treatment strategies were compared for three different anastomotic leak manifestations: interventional *versus* supportive-only treatment for local manifestations (that is no intrathoracic collections; well perfused conduit); drainage and defect closure *versus* drainage only for intrathoracic manifestations; and oesophageal diversion *versus* continuity-preserving treatment for conduit ischaemia/necrosis. The primary outcome was 90-day mortality. Propensity score matching was performed to adjust for confounders.

Results: Of 1508 patients with anastomotic leak, 28.2 per cent (425 patients) had local manifestations, 36.3 per cent (548 patients) had intrathoracic manifestations, 9.6 per cent (145 patients) had conduit ischaemia/necrosis, 17.5 per cent (264 patients) were allocated after multiple imputation, and 8.4 per cent (126 patients) were excluded. After propensity score matching, no statistically significant differences in 90-day mortality were found regarding interventional *versus* supportive-only treatment for local manifestations (risk difference 3.2 per cent, 95 per cent c.i. −1.8 to 8.2 per cent), drainage and defect closure *versus* drainage only for intrathoracic manifestations (risk difference 5.8 per cent, 95 per cent c.i. −1.2 to 12.8 per cent), and oesophageal diversion *versus* continuity-preserving treatment for conduit ischaemia/necrosis (risk difference 0.1 per cent, 95 per cent c.i. −21.4 to 1.6 per cent). In general, less morbidity was found after less extensive primary treatment strategies.

Conclusion: Less extensive primary treatment of anastomotic leak was associated with less morbidity. A less extensive primary treatment approach may potentially be considered for anastomotic leak. Future studies are needed to confirm current findings and guide optimal treatment of anastomotic leak after oesophagectomy.

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Introduction

Oesophagectomy is a crucial component of multimodal treatment of patients with curable oesophageal cancer[1,2]. However, oesophagectomy is associated with considerable morbidity and risk of complications[3–5]. Anastomotic leak (AL) is a severe and potentially life-threatening complication after oesophagectomy. AL occurs in up to 30 per cent of patients and annually 20 000 patients develop AL after oesophagectomy worldwide[3–8]. AL is a main contributor to postoperative morbidity and mortality after oesophagectomy and is associated with poor oncological survival and decreased quality of life[4,9–14]. Although various treatment strategies have been described[10,15,16], the optimal treatment strategy for patients with AL is unknown[5,17–19].

The arsenal for treatment of AL includes an array of supportive, radiological, endoscopic, and surgical interventions. Several studies have reported outcomes of a single modality, such as endoscopic vacuum-assisted closure (EVAC)[20–22]. However, recent systematic reviews have concluded that evidence to support a specific treatment of AL is currently lacking, as most studies are small, descriptive studies, lacking comparative analyses, and do not consider leak severity or clinical manifestation of AL[17,18]. The clinical presentation of AL is diverse and, in clinical practice, the treatment strategy is generally determined by the presence of intrathoracic fluid collections and the vitality of the conduit[19]. Consequently, investigating the optimal treatment should be guided by these findings. Furthermore, instead of evaluating the outcomes of a single intervention, identifying a treatment strategy based on treatment principles may have more clinical relevance. Different principles of AL treatment have been identified: supportive interventions (for example antibiotics and feeding support); drainage of fluid collections; closing the defect to prevent further leakage (for example stent or EVAC); and oesophageal diversion (that is resection of the conduit and diversion using an oesophagostomy)[19].

Gaining insight into the efficacy of treatment strategies for AL is crucial, in order to provide effective care and improve clinical outcomes. The aim of this study was to investigate the efficacy of different treatment strategies for different manifestations of AL after oesophagectomy.

Methods

Study design

The TENTACLE—Esophagus study is an international retrospective cohort study in 71 centres across 20 countries. Details of the TENTACLE—Esophagus study have been published previously (NCT03829098)[23]. Characteristics of the participating centres can be found in *Table S1*. Data quality validation by independent local validators showed a data accuracy of 96.5 per cent[23]. The protocol was approved by the institutional review board of Radboud University Medical Centre (review file 2018-4585) and by local ethical committees if needed. The need for individual informed consent was waived by the institutional review board due to the retrospective study design and pseudonymous data collection. This study was conducted in accordance with STROBE guidelines[24].

Population

Consecutive patients with AL after oesophagectomy with gastric tube reconstruction for resectable oesophageal or gastro-oesophageal junction (GOJ) carcinoma (cT1–4a N0–3 M0) between January 2011 and June 2019 were included. AL was defined according to the Esophagectomy Complications Consensus Group (ECCG) definition: 'a full thickness gastrointestinal defect involving oesophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification'[25]. Patients were excluded if they underwent extended gastrectomy or emergency resection, or if they died before treatment for AL was started.

Based on a recent mixed-methods study, consisting of an international survey and expert discussions, three different manifestations of AL were distinguished: (1) patients with local manifestations (that is confirmed leak without mediastinal/pleural fluid collections; well perfused conduit); (2) patients with intrathoracic manifestations (that is mediastinal and/or pleural collections; well perfused conduit); and (3) patients with overall ischaemia/necrosis of the gastric conduit[19].

Treatment strategies

In line with recommendations of the mixed-methods study mentioned above, the current analysis focused on treatment principles rather than individual modalities, and four main treatment principles were defined: supportive care; drainage; defect closure; and oesophageal diversion[19]. Supportive care was defined as treatment that aimed to support the patient and that was not directed at the leak itself. This included antibiotic treatment and feeding interventions (for example feeding tube placement or jejunostomy). Drainage included any method to drain infectious fluids: chest tube placement; radiological drain placement; endoscopic drainage (that is nasogastric tube with suction or drain placement through the defect); EVAC; or surgical drainage via reoperation. Defect closure was defined as closure or covering the anastomotic defect using endoscopic techniques (that is EVAC, stent placement, or clipping) or surgical techniques (that is suturing, resection, and re-anastomosis, covering with muscle flap or other tissue). Oesophageal diversion was defined as resection of the conduit and diversion with cervical oesophagostomy.

This study focused on the efficacy of primary treatment strategies and primary treatment was defined as treatment within 48 h after diagnosis of AL. Any treatment initiated greater than or equal to 48 h after diagnosis or after failure of primary treatment was considered secondary treatment. For each manifestation of AL, two common primary treatment strategies were identified based on previous literature. In patients with local manifestations, outcomes of a primary interventional strategy were compared with primary supportive-only treatment[19]. In patients with intrathoracic manifestations, the outcomes of drainage and defect closure (for example EVAC or stent combined with drainage) during primary treatment were compared with drainage only[18,19,26,27]. In patients with conduit ischaemia/necrosis, outcomes of primary oesophageal diversion were compared with 'continuity-preserving' treatment (that is no oesophageal diversion)[19,28]. An overview of the three manifestations of AL and compared primary treatment strategies is presented in *Fig. 1*. Patients were included in only one comparative analysis, in line with the defined manifestations and investigated treatment strategies. Patients who underwent different, uncommon primary treatment (for example oesophageal diversion for local manifestations) were not included in comparative analyses.

Outcomes

The primary outcome was 90-day mortality, defined as overall mortality within 90 days after oesophagectomy. Secondary

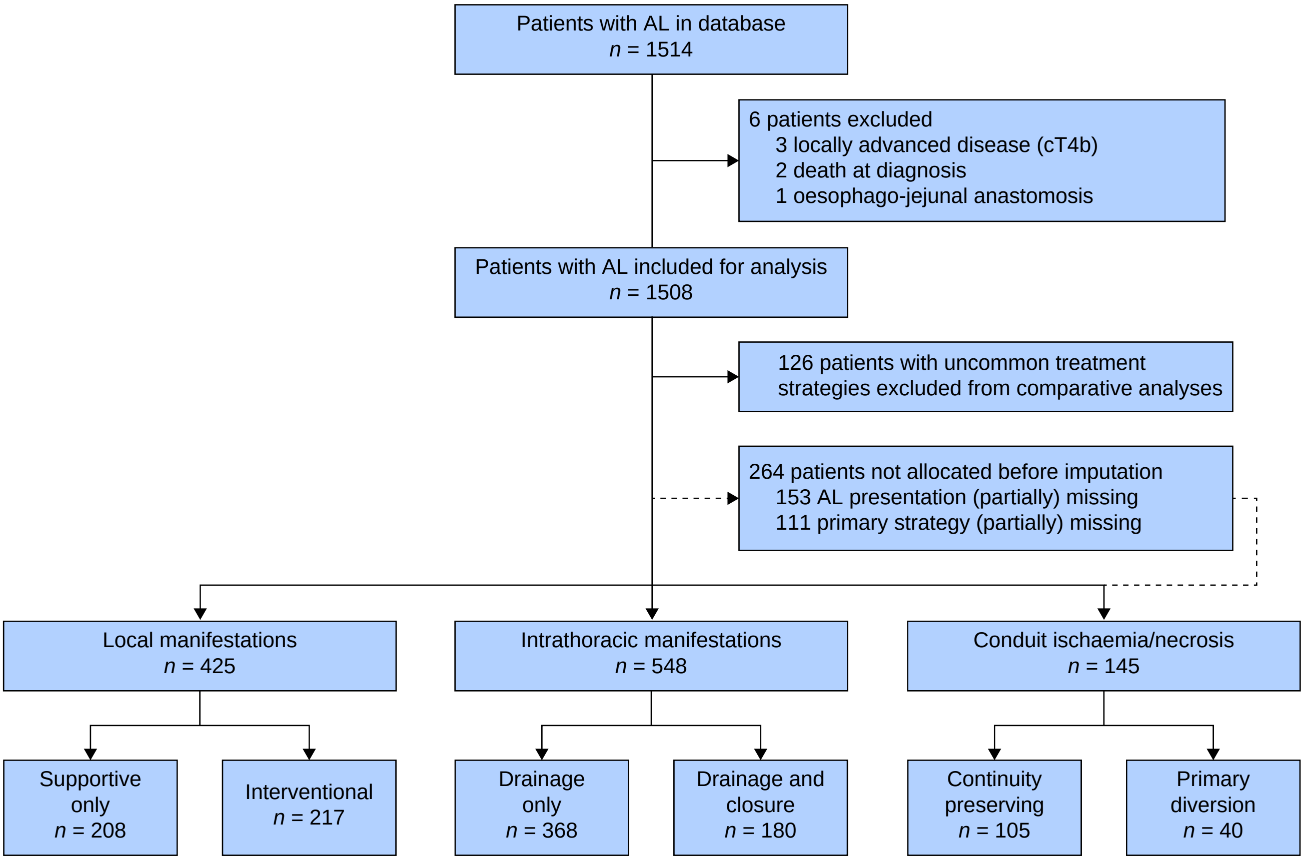

Fig. 1 Distribution of patients per manifestation and treatment strategy

Broken lines represent patients who could not be allocated before multiple imputation owing to missing data. These patients have been allocated after multiple imputation and are not included in the number of cases per clinical manifestation presented. AL, anastomotic leak.

outcomes included length of stay in hospital and on ICU, leak healing time (assessed by imaging or clinical confirmation by resuming a non-clear liquid diet), and comprehensive complication index (CCI). The CCI expresses overall patient morbidity, ranging from 0 to 100, by combining the severity of all postoperative complications[29]. No detailed sample size calculation was performed for the evaluation of treatment efficacy within the manifestations of AL, due to the explorative character of the study.

Statistical analysis

Missing data were assumed 'missing at random' and multiple imputation using chained equations was used to avoid bias during analysis[30]. Additional information on the handling of missing data is presented in *Methods S1*. Patient, leak-related, and treatment characteristics are described as count (percentage) or median (interquartile range (i.q.r.)), as appropriate.

Propensity score matching (PSM) was performed to minimize confounding bias in comparative analyses (*Methods S2*)[31]. PSM was performed separately per AL manifestation using multivariable logistic regression including known confounders: age; co-morbidity; performance status; tumour histology; postoperative day (POD) of diagnosis; level of care at diagnosis; diet at diagnosis; organ failure (that is respiratory failure, haemodynamic failure, renal failure, and quick sequential organ failure assessment (qSOFA) score); leucocyte count; intrathoracic fluid collections; defect circumference; hospital volume; and year of surgery. Cases were matched using nearest-neighbour matching, with a caliper of 0.2 and 2 : 1 ratio[32,33]. Standardized mean difference (SMD) was calculated to assess covariate balance between treatment groups before and after PSM, and an SMD less than 0.1 was considered to indicate sufficient balance[34]. Differences regarding primary (that is 90-day mortality) and secondary outcomes between treatment strategies were assessed using logistic regression for binary outcomes or linear regression for continuous outcomes and expressed as risk difference (RD) and OR with 95 per cent c.i. and absolute difference with 95 per cent c.i. respectively.

Multiple sensitivity analyses were performed to assess the robustness of the findings. First, in patients with local manifestations and intrathoracic manifestations, treatment efficacy was assessed separately for patients with either cervical or intrathoracic anastomosis after PSM, as previous studies have suggested that treatment may depend on the location of the anastomosis[28,35]. Second, to assess whether it is safe to start less extensive primary treatment and reserve more extensive interventions for secondary treatment if needed, outcomes of patients undergoing secondary treatment after less extensive primary treatment were compared with patients undergoing more extensive primary treatment (for example secondary treatment after drainage only *versus* primary drainage and defect closure for intrathoracic manifestations) after PSM. Third, as variation has been found in the treatment of AL related to annual resection volume, treatment efficacy was assessed in patients treated in middle- or high-volume centres (greater than or equal to 20 resections annually) and compared with findings in the entire cohort after PSM[36,37]. Finally, treatment success and other outcomes of different treatment modalities were assessed. Treatment success was defined as avoidance of 90-day mortality, secondary ICU readmission, and secondary oesophagostomy. No PSM was performed in this analysis due to small groups of patients.

PSM and comparative analyses were performed in each data set and results were pooled subsequently using Rubin's rule. Statistical analysis was performed in R (version 3.6.2) with packages 'mice' and 'matchit'.

Results

In total, 1514 patients were recorded in the database, of which 1508 patients were included in the current study. Six patients were excluded from the analysis; four patients because they did not meet the inclusion criteria (locally advanced diseases, three patients; and oesophago-jejunal anastomosis, one patient) and two patients because of death before treatment could be started. *Figure 1* shows the flow chart of the study. Of 1508 patients, 425 patients (28.2 per cent) had local manifestations, 548 patients (36.3 per cent), had intrathoracic manifestations and 145 patients (9.6 per cent) had overall conduit ischaemia/necrosis (*Table S2* and *Table S3*); 126 patients (8.4 per cent) were excluded from comparative analyses, as these patients were not treated in line with the predefined investigated treatment strategies, and 264 patients (17.5 per cent) could not be allocated before imputation due to missing data and were allocated after multiple imputation. Treatment and outcomes of patients with local manifestations, intrathoracic manifestations, and overall conduit ischaemia/necrosis before PSM are shown in *Table 1*, *Table 2*, and *Table 3* respectively. In addition, *Fig. 2* provides a graphical representation of primary treatment, secondary treatment, and outcome of different leak treatments per manifestation of AL.

Local manifestations

Of 425 patients with local manifestations, 217 patients (51.1 per cent) underwent primary interventional treatment and 208 patients (48.9 per cent) underwent supportive-only treatment (*Table 1*). After PSM, a good balance was achieved between the interventional and supportive-only treatment groups (*Table S4*). There was no statistically significant difference in 90-day mortality after interventional *versus* supportive-only primary treatment (RD 3.2 per cent, 95 per cent c.i. −1.8 to 8.2 per cent). After primary interventional treatment, length of stay in hospital and on ICU were statistically significantly longer (hospital 8 days, 95 per cent c.i. 6 to 10 days; ICU 3 days, 95 per cent c.i. 1 to 4 days) and CCI was higher (9.0, 95 per cent c.i. 6.7 to 11.3) compared with supportive-only treatment (*Table 4*).

Intrathoracic manifestations

Of 548 patients with intrathoracic manifestations, 368 patients (67.2 per cent) underwent primary drainage only and 180 patients (32.8 per cent) underwent primary drainage and defect closure (*Table 2*). After PSM, covariates were appropriately balanced between the two groups (*Table S5*). No statistically significant difference in 90-day mortality was found after primary drainage and defect closure *versus* drainage only (RD 5.8 per cent, 95 per cent c.i. −1.2 to 12.8 per cent). After drainage and defect closure, length of stay in hospital and on ICU (hospital 6 days, 95 per cent c.i. 4 to 8 days; ICU 5 days, 95 per cent c.i. 4 to 7 days) and healing time (5 days, 95 per cent c.i. 2 to 9 days) were statistically significantly longer and CCI was higher (6.2, 95 per cent c.i. 4.0 to 8.4) compared with drainage only (*Table 4*).

Table 1 Local manifestations before propensity score matching

Parameter	Supportive only	Intervention
Patients, *n*	208	217
Age (years), median (i.q.r.)	65 (57–71)	67 (62–72)
Co-morbidity*		
ASA I	28 (13.5)	14 (6.5)
ASA II	125 (60.1)	113 (52.1)
ASA ≥III	54 (26.0)	88 (40.6)
Performance status*		
ECOG 0	99 (47.6)	90 (41.5)
ECOG 1	62 (29.8)	68 (31.3)
ECOG ≥2	16 (7.7)	13 (6.0)
Resection type*		
TTO-CA	79 (38.0)	73 (33.6)
TTO-IA	57 (27.4)	110 (50.7)
THO-CA	71 (34.1)	34 (15.7)
POD of diagnosis, median (i.q.r.)	7 (6–9)	7 (6–10)
Level of care*		
Surgical ward	153 (73.6)	132 (60.8)
ICU/HC/MC/PACU	43 (20.7)	73 (33.6)
ED/other	9 (4.3)	10 (4.6)
Leucocyte count (×10^9/L), median (i.q.r.)	10.5 (8.3–13.7)	11.9 (9.1–15.4)
qSOFA score, median (i.q.r.)	0 (0–0)	0 (0–1)
Respiratory failure	9 (4.3)	33 (15.2)
Haemodynamic failure	1 (0.5)	10 (4.6)
Renal failure	4 (1.9)	10 (4.6)
Defect circumference ≥25%	9 (4.3)	22 (10.1)
Primary treatment		
Primary strategy		
Supportive only	208 (100.0)	0 (0.0)
Drainage	0 (0.0)	142 (65.4)
Defect closure	0 (0.0)	19 (8.8)
Drainage and defect closure	0 (0.0)	56 (25.8)
Feeding intervention	25 (12.0)	32 (15.7)
Endoscopic drainage	0 (0.0)	50 (23.0)
Stent placement	0 (0.0)	47 (21.7)
EVAC	0 (0.0)	16 (7.4)
Reoperation	3 (1.4)	51 (23.5)
ICU/HC/MC readmission	11 (5.3)	61 (28.1)
Secondary treatment		
Need for secondary treatment	78 (37.5)	123 (56.7)
Secondary strategy		
Supportive only	52 (25.0)	50 (23.0)
Drainage	7 (3.4)	23 (10.6)
Defect closure	12 (5.8)	19 (8.8)
Drainage and defect closure	4 (1.9)	25 (11.5)
Missing	2 (1.0)	2 (0.9)
Stent placement	15 (7.2)	28 (12.9)
EVAC	0 (0.0)	9 (4.1)
Reoperation	7 (3.4)	24 (11.1)
ICU/HC/MC readmission	9 (4.3)	21 (9.7)
Outcomes		
90-day mortality	9 (4.3)	23 (10.6)
LOS, hospital (days), median (i.q.r.)	20 (15–28)	28 (20–42)
LOS, ICU (days), median (i.q.r.)	2 (1–5)	5 (2–12)
Healing time (days), median (i.q.r.)	19 (10–29)	21.50 (9–37)
CCI, median (i.q.r.)	31 (21–50)	43 (32–65)

Values are *n* (%) unless otherwise indicated. *Percentages may not add up to 100% due to missing data. i.q.r., interquartile range; ECOG, Eastern Collaborative Oncology Group; TTO, transthoracic oesophagectomy; CA, cervical anastomosis; IA, intrathoracic anastomosis; THO, transhiatal oesophagectomy; POD, postoperative day; HC, high care; MC, medium care; PACU, post-anaesthesia care unit; ED, emergency department; qSOFA, quick sequential organ failure assessment; EVAC, endoscopic vacuum-assisted closure; LOS, length of stay; CCI, comprehensive complication index.

Overall conduit ischaemia/necrosis

Of 145 patients with overall conduit ischaemia/necrosis, 40 patients (27.6 per cent) underwent primary oesophageal diversion and 105 patients (72.4 per cent) underwent continuity-preserving

Table 2 Intrathoracic manifestations before propensity score matching

Parameter	Drainage only	Drainage and defect closure
Patients, *n*	368	180
Age (years), median (i.q.r.)	65 (58–71)	65 (59–71)
Co-morbidity*		
ASA I	35 (9.5)	16 (8.9)
ASA II	213 (57.9)	97 (53.9)
ASA ≥III	116 (31.5)	62 (34.4)
Performance status*		
ECOG 0	172 (46.7)	74 (41.1)
ECOG 1	96 (26.1)	57 (31.7)
ECOG ≥2	30 (8.2)	5 (2.8)
Resection type*		
TTO-CA	79 (21.5)	21 (11.7)
TTO-IA	257 (69.8)	156 (86.7)
THO-CA	29 (7.9)	3 (1.7)
POD of diagnosis, median (i.q.r.)	8 (6–11)	8 (5–11)
Level of care*		
Surgical ward	206 (56.0)	83 (46.1)
ICU/HC/MC/PACU	140 (38.0)	90 (50.0)
ED/other	12 (3.3)	6 (3.3)
Leucocyte count (×10^9/L), median (i.q.r.)	13.6 (10.3–17.6)	14.2 (11.0–18.6)
qSOFA score, median (i.q.r.)	0 (0–1)	1 (0–1)
Respiratory failure	69 (18.8)	51 (28.3)
Haemodynamic failure	40 (11.7)	29 (17.8)
Renal failure	40 (10.9)	29 (16.1)
Defect circumference ≥25%	38 (10.3)	49 (27.2)
Primary treatment		
Primary strategy		
Drainage	368 (100.0)	0 (0.0)
Drainage and defect closure	0 (0.0)	180 (100.0)
Radiological drainage	109 (29.6)	21 (11.7)
Chest tube drainage	85 (23.1)	38 (21.1)
Endoscopic drainage	132 (35.9)	53 (29.4)
Stent placement	0 (0.0)	104 (57.8)
EVAC	0 (0.0)	27 (15.0)
Reoperation	99 (26.9)	80 (44.4)
ICU/HC/MC readmission	153 (41.6)	110 (61.1)
Secondary treatment		
Need for secondary treatment	263 (71.5)	138 (76.7)
Secondary strategy		
Supportive only	63 (17.1)	20 (11.1)
Drainage	110 (29.9)	33 (18.3)
Defect closure	20 (5.4)	24 (13.3)
Drainage and defect closure	56 (15.2)	42 (23.3)
Oesophageal diversion	3 (0.8)	12 (6.7)
Missing	11 (3.0)	8 (4.4)
Stent placement	59 (16.0)	54 (30.0)
EVAC	10 (2.7)	21 (11.7)
Reoperation	55 (14.9)	38 (21.1)
ICU/HC/MC readmission	74 (20.1)	46 (25.6)
Outcomes		
90-day mortality	42 (11.4)	34 (18.9)
LOS, hospital (days), median (i.q.r.)	37 (26–56)	41 (28–65)
LOS, ICU (days), median (i.q.r.)	8 (3, 18)	11 (5–25)
Healing time (days), median (i.q.r.)	31 (18–50)	34 (18–58)
CCI, median (i.q.r.)	50 (36–66)	50 (35–69)

Values are *n* (%) unless otherwise indicated. *Percentages may not add up to 100% due to missing data. i.q.r., interquartile range; ECOG, Eastern Collaborative Oncology Group; TTO, transthoracic oesophagectomy; CA, cervical anastomosis; IA, intrathoracic anastomosis; THO, transhiatal oesophagectomy; POD, postoperative day; HC, high care; MC, medium care; PACU, post-anaesthesia care unit; ED, emergency department; qSOFA, quick sequential organ failure assessment; EVAC, endoscopic vacuum-assisted closure; LOS, length of stay; CCI, comprehensive complication index.

treatment (*Table 3*). Only five patients (4.8 per cent) underwent secondary oesophageal diversion after primary continuity-preserving treatment. After PSM, covariate balance was achieved (*Table S6*). No statistically significant difference in 90-day mortality was found between the two treatments (RD 0.1 per cent, 95 per cent c.i. −21.4 to 21.6 per cent). After primary oesophageal diversion, length of stay in hospital and on ICU were shorter (1 day (95 per cent c.i. −10 to 7) and 2 days (95 per cent c.i. −8 to 4) respectively) and CCI was higher (6.2, 95 per cent c.i. −2.1 to 14.5), but not statistically significant (*Table 4*).

Sensitivity analyses

Adjusted outcomes of either cervical or intrathoracic AL in patients with local manifestations and intrathoracic manifestations are presented in *Table S7*. In patients with intrathoracic manifestations, differences between drainage only *versus* drainage and defect closure were larger in cervical leaks than in intrathoracic leaks. For example there was a larger difference in duration of ICU care; 19 days (95 per cent c.i. 13 to 25 days) longer after drainage and defect closure in cervical leaks

Table 3 Overall conduit ischaemia/necrosis before propensity score matching

Parameter	Continuity preserving	Oesophageal diversion
Patients, *n*	105	40
Age (years), median (i.q.r.)	66 (60–72)	67 (61–73)
Co-morbidity*		
ASA I	8 (7.6)	5 (13)
ASA II	52 (49.5)	18 (45)
ASA ≥III	38 (36.2)	17 (42)
Performance status*		
ECOG 0	32 (30.5)	19 (48)
ECOG 1	24 (22.9)	15 (38)
ECOG ≥2	10 (9.5)	5 (13)
Resection type*		
TTO-CA	36 (34.3)	15 (38)
TTO-IA	49 (46.7)	21 (53)
THO-CA	20 (19.0)	1 (3)
POD of diagnosis, median (i.q.r.)	7 (5–11)	6 (4–9)
Level of care*		
Surgical ward	42 (40.0)	13 (32.5)
ICU/HC/MC/PACU	57 (54.3)	25 (62.5)
ED/other	5 (4.8)	0 (0)
Leucocyte count ($\times 10^9$/L), median (i.q.r.)	11.4 (8.7–18.6)	12.7 (8.2–19.9)
qSOFA score, median (i.q.r.)	1 (0–2)	1 (0–2)
Respiratory failure	34 (32.4)	11 (28)
Haemodynamic failure	23 (21.9)	8 (20)
Renal failure	5 (4.8)	5 (13)
Defect circumference ≥25%	24 (22.9)	22 (55)
Primary treatment		
Primary strategy		
Supportive only	12 (11.4)	0 (0)
Drainage	32 (30.5)	0 (0)
Defect closure	12 (11.4)	0 (0)
Drainage and defect closure	35 (33.3)	0 (0)
Oesophageal diversion	0 (0.0)	40 (100)
Radiological drainage	7 (6.7)	2 (5)
Chest tube drainage	14 (13.3)	2 (5)
Endoscopic drainage	24 (22.9)	3 (8)
Stent placement	30 (28.6)	0 (0)
EVAC	5 (4.8)	0 (0)
Reoperation	41 (39.0)	40 (100)
ICU/HC/MC readmission	39 (37.1)	27 (68)
Secondary treatment		
Need for secondary treatment	69 (65.7)	24 (60)
Secondary strategy		
Supportive only	14 (13.3)	8 (20)
Drainage	19 (18.1)	6 (15)
Defect closure	4 (3.8)	0 (0)
Drainage and defect closure	20 (19.0)	1 (3)
Oesophageal diversion	5 (4.8)	0 (0)
Missing	7 (6.7)	9 (23)
Stent placement	17 (16.2)	0 (0)
EVAC	2 (1.9)	0 (0)
Reoperation	25 (23.8)	5 (13)
ICU/HC/MC readmission	24 (22.9)	6 (15)
Outcomes		
90-day mortality	20 (19.0)	11 (28)
LOS, hospital (days), median (i.q.r.)	43 (27–61)	42 (28–72)
LOS, ICU (days), median (i.q.r.)	12 (3–29)	17 (7–30)
Healing time (days), median (i.q.r.)	32 (13–54)	24 (24–26)
CCI, median (i.q.r.)	49 (34–63)	56 (40–69)

Values are *n* (%) unless otherwise indicated. *Percentages may not add up to 100 per cent due to missing data. i.q.r., interquartile range; ECOG, Eastern Collaborative Oncology Group; TTO, transthoracic oesophagectomy; CA, cervical anastomosis; IA, intrathoracic anastomosis; THO, transhiatal oesophagectomy; POD, postoperative day; HC, high care; MC, medium care; PACU, post-anaesthesia care unit; ED, emergency department; qSOFA, quick sequential organ failure assessment; EVAC, endoscopic vacuum-assisted closure; LOS, length of stay; CCI, comprehensive complication index.

versus 3 days (95 per cent c.i. 2 to 4 days) longer after drainage and defect closure in intrathoracic leaks. However, only 28 patients with cervical leaks underwent drainage and defect closure.

In all manifestations of AL, patients who underwent secondary treatment after (failure of) less extensive primary treatment did not have poorer outcomes than patients who primarily underwent more extensive treatment (*Table S8*). Treatment outcomes of patients treated in middle- and high-volume centres are presented in *Table S9*, and showed no substantial differences compared with treatment outcomes in all centres. Details on the primary treatment modalities per manifestation of AL and consequent outcomes are presented in *Table S10*.

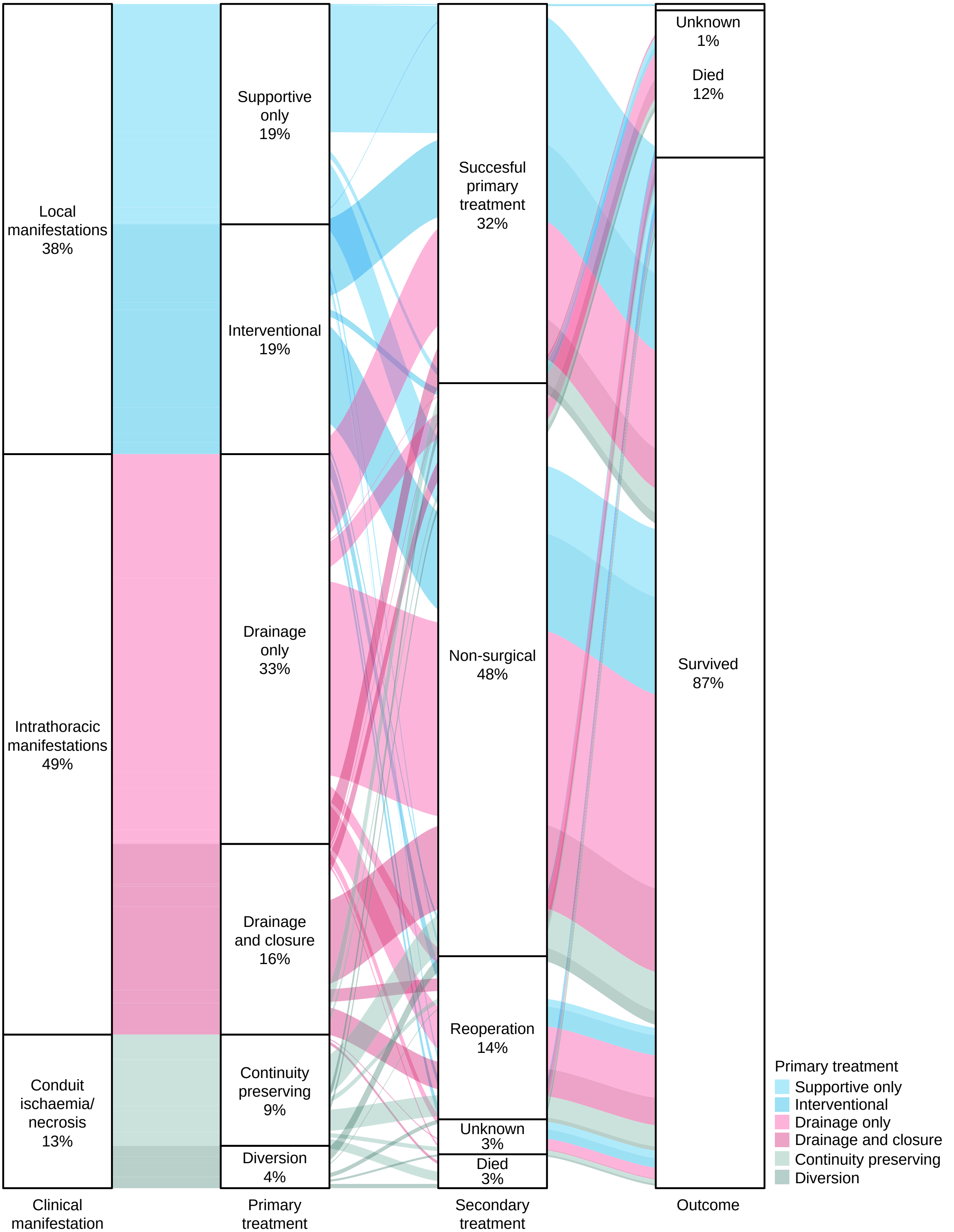

Fig. 2 Alluvial diagram on primary treatment, secondary treatment, and outcome of patients with anastomotic leak

Table 4 Outcomes of leak treatment after propensity score matching

Outcome	Local manifestations (interventional *versus* supportive only (reference))	Intrathoracic manifestations (drainage and defect closure *versus* drainage only (reference))	Conduit ischaemia/necrosis (oesophageal diversion *versus* continuity-preserving (reference))
90-day mortality			
Risk difference (95% c.i.)	3.2% (−1.8%,8.2%)	5.8% (−1.2%,12.8%)	0.1% (−21.4%,21.6%)
OR (95% c.i.)	1.96 (0.72,5.39)	1.58 (0.92,2.71)	1.01 (0.29,3.43)
LOS in hospital in days (95% c.i.)	8 (6,10)	6 (4,8)	−1 (−10,7)
LOS on ICU in days (95% c.i.)	3 (1,4)	5 (4,7)	−2 (−8,4)
Healing time in days (95% c.i.)	2 (−1,6)	5 (2,9)	−12 (−30,7)*
CCI (95% c.i.)	9.0 (6.7,11.3)	6.2 (4.0,8.4)	6.2 (−2.1,14.5)

*Not available for most patients who underwent oesophageal diversion. LOS, length of stay; CCI, comprehensive complication index.

Discussion

This large, collaborative cohort study investigated the efficacy of primary treatment strategies for different manifestations of AL after oesophagectomy. Across the three manifestations of AL, patients who underwent less extensive primary treatment had better outcomes and reduced morbidity compared with patients who underwent more extensive treatment. These findings suggest that a less extensive approach to primary treatment of AL may potentially lead to better clinical outcomes.

Previous studies were hampered by limited numbers of patients, lack of detailed data, confounding bias, and heterogeneity[17]. To the best of our knowledge, the current study has been the first to perform robust comparative analyses on the efficacy of treatment strategies in a large, detailed cohort of patients with AL. Furthermore, the manifestations of AL and treatment strategies investigated were based on a recent mixed-methods study, which conducted a survey and expert discussions, and thus represent treatment dilemmas of current clinical practice[19].

Some limitations need to be discussed. First, confounding and missing data were potential sources of bias. Confounding bias (for example more severe leaks could be treated more aggressively) was minimized through defining different manifestations of AL and through propensity score matching[31]. Whereas subtle differences may still have been present, an appropriate balance was achieved in comparative analyses. Although residual confounding and selection cannot be ruled out, all well known patient-related and leak-related confounders were included during propensity score matching. Missing data in different leak-related and treatment parameters were anticipated during study initiation and meticulous data registration and data quality validation was performed to optimize data quality[23]. In addition, multiple imputation was performed to avoid bias due to missing data during analysis[30]. Second, the large number of participating centres led to a heterogeneous cohort. Previous studies have found substantial differences between centres, including differences in patient parameters, leak severity at diagnosis, and treatment of AL[19,28,36,37]. In addition, differences in leak management and outcomes of patients with AL were associated with annual resection volume[36–39]. In the current study, characteristics of participating centres have been reported transparently. Hospital volume was included in propensity score matching to correct for variation between centres where possible. Furthermore, a sensitivity analysis was performed in patients treated in middle-/high-volume centres to evaluate findings in these centres. As the outcomes of this analysis were largely similar to the overall analysis, findings appear to be robust. Third, current analysis focused on primary leak treatment and did not fully take into account secondary treatment. Although secondary treatment may affect outcomes, it was not possible to further investigate the impact of secondary treatments, as this would have resulted in patient groups that were too small and data regarding the indications and timing of secondary treatment were not available. Moreover, the current focus on primary treatment prevents unjustified selection of patients. Fourth, the comparative analysis did not consider the location of the anastomosis. It has been much debated whether treatment of AL is fundamentally different for cervical and intrathoracic anastomosis[19,28,35]. A sensitivity analysis in the current study showed differences between cervical and intrathoracic leaks in patients with intrathoracic manifestations, but groups were of a limited size. Finally, data on health-related quality of life (HRQOL) and long-term survival were not available. Next to mortality, HRQOL may be an important outcome measure to evaluate different treatments of AL.

In line with previous studies, the overall 90-day mortality rate was 11.7 per cent and large differences in mortality were observed between different manifestations of AL[5]. In patients with local manifestations, many surgeons intervene using drain placement and/or defect closure to promote recovery and prevent formation of fluid collections, whereas others rely solely on supportive treatment such as antibiotics and feeding support[19]. Current findings showed no benefit of intervening in these patients; supportively-only treatment was safe and resulted in less morbidity. Antibiotics may be indicated for any signs of systemic infection and supporting feeding is important to promote recovery[5,40,41]. In patients with intrathoracic manifestations, no benefit was found for performing defect closure in addition to drainage of fluid collections; overall morbidity was higher and closing the defect did not reduce the leak healing time. These findings contrast with multiple recent studies, which (although often lacking comparative analyses) have propagated the possible benefits of defect closure in addition to drainage, for example using stent and EVAC[20,21,42–45]. Patients with conduit ischaemia/necrosis had the highest postoperative mortality, in line with a previous study[5]. Interestingly, most patients with ischaemia/necrosis were treated with a continuity-preserving approach and, in this group, secondary diversion was only needed in 5 per cent of patients. Even though the number of patients with conduit ischaemia/necrosis was limited and no detailed data on the extent of ischaemia/necrosis were available, current findings indicate that a continuity-preserving treatment strategy may be feasible and secondary diversion is rarely needed. More generally, our findings indicate that, in current clinical practice, AL rarely results in oesophageal diversion with oesophagostomy, which aligns with current beliefs regarding oesophageal diversion[19,46,47].

This study could provide guidance for treatment of AL in clinical practice. Across the different manifestations, less extensive primary treatment strategies showed at least similar mortality rates and resulted in lower morbidity. Although a substantial number of patients required secondary (invasive) treatment after less extensive primary treatment, these patients did not have poorer outcomes than patients who underwent more extensive treatment directly at diagnosis. Consequently, if confronted with a treatment dilemma in clinical practice, clinicians may potentially choose the less extensive strategy for primary treatment and reserve more extensive treatment for secondary step-up if needed. This less extensive approach to primary treatment of AL also underscores the need for adequate monitoring of patients. Knowing when and how to intervene is of great importance and may contribute to lower failure to rescue[36].

To further progress evidence-based treatment of AL, prospective studies and ideally randomized trials are warranted. The benefits of a less extensive approach to primary treatment of AL found in the current study should be confirmed in future studies evaluating treatment strategies for AL. In addition, future studies (both quantitative and qualitative) should investigate the indications, timing, and strategy of secondary treatment, in order to provide further support regarding the treatment of AL. Prospective data provide insight into contemporary management of AL, in which the use of advanced techniques (for example EVAC) may have become more widespread. In addition, prospective registries offer the opportunity to standardize the recording of leak characteristics and treatment. Currently, different prospective initiatives investigate specific modalities for management of AL; the VAC-Stent Registry (NCT03962179) and the Eso-Sponge Registry (NCT02662777) may provide high-quality data on the use of these techniques and may promote standardization[45]. However, these studies will not perform comparative analyses, which are needed to further identify optimal treatment strategies for AL. Despite the fact that conducting large prospective or randomized studies will be hugely challenging, there are examples of successful clinical trials and innovative study designs in rare surgical conditions[48,49]. Whilst awaiting further evidence for optimal treatment of AL, clinical guidance for management of AL is much needed[19,28]. Although an evidence-based guideline may require more support than is provided by this study, the current findings may inform the development of a clinical consensus statement. Developing a consensus statement on the management of AL is one of the future projects of the TENTACLE—Esophagus Study Group and may guide clinical practice, promote standardization, and improve outcomes of patients with anastomotic leak after oesophagectomy.

Conclusion

In conclusion, in all different manifestations of AL, patients who underwent less extensive primary treatment were found to have less morbidity compared with more extensive primary treatment of AL. Potentially, a less extensive primary treatment strategy may lead to better outcomes and more extensive treatment may be reserved for secondary step-up if needed. However, current findings may be affected by selection and thus, future studies are needed to confirm our findings. More scientific evidence is needed to progress treatment of AL and ultimately improve clinical outcomes.

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Supplementary material

Supplementary material is available at *BJS* online.

Data availability

Study data are not openly available. The authors are willing to share data upon reasonable request to the corresponding author.

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