European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Practice variation in anastomotic leak after esophagectomy: Unravelling differences in failure to rescue

Sander Ubels [a,], Eric Matthée [a,b], Moniek Verstegen [a], Bastiaan Klarenbeek [a], Stefan Bouwense [c], Mark I. van Berge Henegouwen [d,e], Freek Daams [f], Jan Willem T. Dekker [g], Marc J. van Det [h], Stijn van Esser [g], Ewen A. Griffiths [i], Jan Willem Haveman [j], Grard Nieuwenhuijzen [k], Peter D. Siersema [l], Bas Wijnhoven [m], Gerjon Hannink [n], Frans van Workum [a,b], Camiel Rosman [a], the TENTACLE – Esophagus collaborative group, Writing Committee, Joos Heisterkamp [o], Fatih Polat [p], Jeroen Schouten [q], Pritam Singh [r], Study collaborators

[a] Department of Surgery, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[b] Department of Surgery, Canisius-Wilhelmina Hospital, Nijmegen, the Netherlands
[c] Department of Surgery, Maastricht University Medical Center+, Maastricht, the Netherlands
[d] Department of Surgery, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
[e] Cancer Center Amsterdam, Amsterdam, the Netherlands
[f] Department of Surgery, Amsterdam UMC, Location Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[g] Department of Surgery, Reinier de Graaf Gasthuis, Delft, the Netherlands
[h] Department of Surgery, ZGT Hospital Group, Almelo, the Netherlands
[i] Department of Upper Gastrointestinal Surgery, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom
[j] Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[k] Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands
[l] Department of Gastroenterology and Hepatology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[m] Department of Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands
[n] Department of Operating Rooms, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[o] Elisabeth-Tweesteden Ziekenhuis, Tilburg, the Netherlands
[p] Canisius-Wilhelmina Ziekenhuis, Nijmegen, the Netherlands
[q] Radboud University Medical Center, Nijmegen, the Netherlands
[r] Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom

ARTICLE INFO

Article history:
Received 29 September 2022
Received in revised form
20 December 2022
Accepted 11 January 2023
Available online xxx

Keywords:
Failure to rescue
Esophagectomy
Complications
Anastomotic leak
Practice variation

ABSTRACT

Introduction: Failure to rescue (FTR) is an important outcome measure after esophagectomy and reflects mortality after postoperative complications. Differences in FTR have been associated with hospital resection volume. However, insight into how centers manage complications and achieve their outcomes is lacking. Anastomotic leak (AL) is a main contributor to FTR. This study aimed to assess differences in FTR after AL between centers, and to identify factors that explain these differences.
Methods: TENTACLE – Esophagus is a multicenter, retrospective cohort study, which included 1509 patients with AL after esophagectomy. Differences in FTR were assessed between low-volume (<20 resections), middle-volume (20–60 resections) and high-volume centers (≥60 resections). Mediation analysis was performed using logistic regression, including possible mediators for FTR: case-mix, hospital resources, leak severity and treatment.
Results: FTR after AL was 11.7%. After adjustment for confounders, FTR was lower in high-volume vs. low-volume (OR 0.44, 95%CI 0.2–0.8), but not versus middle-volume centers (OR 0.67, 95%CI 0.5–1.0). After mediation analysis, differences in FTR were found to be explained by lower leak severity, lower

Abbreviations: AL, Anastomotic Leak; FTR, Failure to Rescue; ICU, Intensive Care Unit; SEAL, Severity of Esophageal Anastomotic Leak.

Corresponding author. Radboud university medical center, P.O. Box 9101, 6500, HB, Nijmegen, the Netherlands.
E-mail address: Sander.Ubels@radboudumc.nl (S. Ubels).

https://doi.org/10.1016/j.ejso.2023.01.010

secondary ICU readmission rate and higher availability of therapeutic modalities in high-volume centers. No statistically significant direct effect of hospital volume was found: high-volume vs. low-volume 0.86 (95%CI 0.4–1.7), high-volume vs. middle-volume OR 0.86 (95%CI 0.5–1.4).

Conclusion: Lower FTR in high-volume compared with low-volume centers was explained by lower leak severity, less secondary ICU readmissions and higher availability of therapeutic modalities. To reduce FTR after AL, future studies should investigate effective strategies to reduce leak severity and prevent secondary ICU readmission.

1. Introduction

In patients with curable esophageal cancer, surgery is an important component of multimodal treatment [1,2]. Despite advancements in surgical technique and perioperative care, esophagectomy is associated with substantial postoperative morbidity and mortality [3–5]. Differences in postoperative mortality rates between centers have been found to be related to hospital volume [6,7]. Previous studies have suggested that differences in postoperative mortality between centers are not related to the incidence of complications, but rather to *failure to rescue* (FTR), i.e., patients dying after postoperative complications [7–9]. High-volume centers have been found to have lower FTR rates possibly due to earlier recognition and adequate treatment of complications [10–12].

Although these observations have been used as an argument for centralization of complex surgery in high-volume centers, centralization is not feasible in every health care system [6,13,14]. Therefore, investigating how centers manage complications and rescue patients can provide important insights to reduce FTR and improve outcomes on a global scale. Hypothetically, the association between FTR and hospital volume could be explained by differences in management of complications, differences in patient selection and/or differences in available hospital resources. However, detailed insight into how centers manage complications and achieve their outcomes is lacking [15,16].

Anastomotic leak (AL) is a common complication contributing to postoperative mortality after esophagectomy [3,17]. Previous studies have reported differences in diagnosis and treatment of patients with AL in relation to hospital volume [18–20]. However, the association between these differences and FTR has not been studied. The aim of this study was to evaluate the association of hospital volume with FTR in patients with AL after esophagectomy, and to identify factors that explain differences in FTR between centers.

2. Methods

This study was performed in the cohort of the TENTACLE – Esophagus study (NCT03829098), an international retrospective cohort study in 71 centers from Asia, Africa, Europe, South America and Oceania. Details regarding the study design and data collection were published previously [21]. In addition, data quality validation was performed by independent validators and showed a data accuracy of 96.5% [21]. The current analysis included 1509 patients with AL after esophagectomy between January 1st, 2011 until June 30th, 2019 enrolled consecutively in the TENTACLE – Esophagus study. AL was defined as a “full thickness gastrointestinal defect involving esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification” [22].

2.1. Hospital volume

Differences in FTR were assessed according to annual hospital volume. The annual hospital volume of centers and other site characteristics were recorded in a survey during data collection of the TENTACLE – Esophagus study (Supplementary Methods 1). Centers were stratified into three groups based on their annual resection volume: low-volume centers performing <20 resections, middle-volume centers performing 20–59 resections and high-volume centers performing ≥60 resections per year. Although various volume cut-offs have been used, these cut-offs are generally accepted in current literature and have been used as cut-offs for policies in different countries [12–14,18,23].

2.2. Outcome parameters

The primary outcome was FTR, which was defined as mortality in patients with AL within 90-days after esophagectomy. The 90-day interval has been found to be the most reliable measure of mortality due to complications without including non-complication mortality (e.g., cancer recurrence) [24–26]. Secondary outcome parameters included length of hospital stay, intensive care unit (ICU) stay and leak healing (i.e., time to confirmed healing or non-clear liquid diet), and comprehensive complication index (CCI). The CCI is a scale ranging from 0 (no complications) to 100 (death) and represents the severity of all complications in a patient [27].

2.3. Statistical analysis

Center characteristics (e.g., availability of therapeutic techniques), case-mix parameters, leak parameters, treatment parameters and outcomes were described stratified by hospital volume. Differences between patients in low-, middle- and high-volume centers were assessed using Chi-square test or Fisher's exact test, and one-way ANOVA or Kruskal-Wallis test where appropriate.

The association between hospital volume and FTR found by previous studies resembles the total effect of hospital volume on FTR [10–12]. This total effect may consist of a direct effect of hospital volume and may also be explained by indirect effects (i.e., mediators): differences in parameters along the causal pathway between hospital volume and FTR [28]. For example, high-volume centers may treat complications differently, and may thus have different FTR rates. Mediation analysis is used to open the ‘black box’ of the total effect and gain insight into the underlying mechanism(s) of a total effect [29,30]. In current study, mediation analysis was performed to identify mediators explaining the relationship between hospital volume and FTR. Possible mediators for the association between hospital volume and FTR included differences in case-mix parameters, leak severity, treatment of AL and available hospital resources. The assumed causal pathways between hospital volume, possible mediators and FTR were visualized using a Directed Acyclic Graph (Fig. 1).

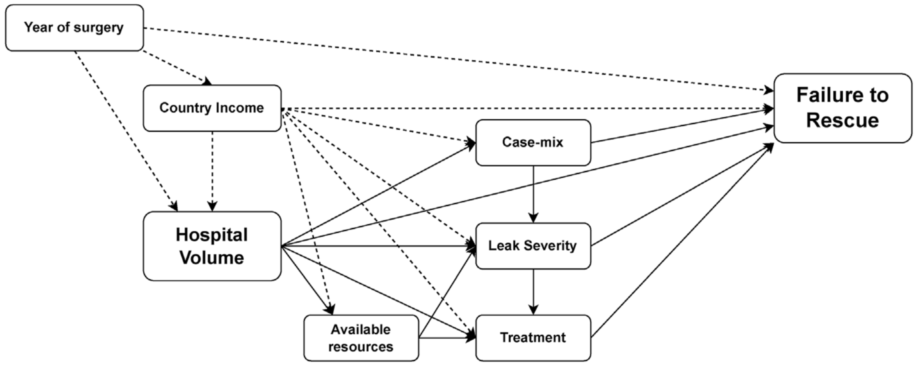

Fig. 1. Assumed relationships between hospital volume, possible mediators and Failure to Rescue.

The continuous lines together represent the total effect of hospital volume on failure to rescue (FTR). The continuous line from hospital volume to FTR represents the possible direct effect of hospital volume on FTR. The continuous lines that connect hospital volume with FTR via case-mix, leak severity, available resources and treatment resemble possible indirect effects (i.e., mediators) which explain the total effect of hospital volume on FTR. The dotted lines represent possible confounding of year of surgery and country income on hospital volume and FTR. Case-mix parameters include age, comorbidity (i.e., ASA-classification), performance status (i.e., ECOG score) and tumor histology. Hospital resources include available diagnostic and therapeutic modalities. Leak severity is measured by the Severity of Esophageal Anastomotic Leak (SEAL) score, a score combining 12 clinical parameters at diagnosis into four classes of leak severity (i.e., mild, moderate, severe, critical). Treatment parameters include primary treatment strategy, primary reoperation, primary intensive care unit (ICU) readmission, secondary treatment, secondary reoperation and secondary ICU readmission.

The total effect of hospital volume on FTR in patients with AL was assessed using multiple logistic regression, adjusting for relevant confounders: year of surgery and country income [18]. Country income was dichotomized into low-/middle-income countries (LMIC) and high-income countries (HIC) based on the list published by the World bank [31]. Mediation analysis was performed using multiple logistic regression including relevant confounders (i.e., year of surgery, country income) and possible mediators: case-mix parameters, leak severity, AL treatment and available hospital resources. Case-mix parameters included age, comorbidity (i.e., American Society of Anesthesiologists (ASA) classification), performance status (i.e., Eastern Cooperative Oncology Group (ECOG) score) and tumor histology [10,16,21]. Leak severity at diagnosis was measured using the recently developed Severity of Esophageal Anastomotic Leak (SEAL) score [21]. This internally validated tool combines 12 clinical parameters at diagnosis (e.g., organ failure, circumference of the anastomotic defect) and differentiates four classes of leak severity (i.e., mild, moderate, severe and critical). The primary treatment strategy (i.e., within 48 h after diagnosis) was categorized according to the treatment principle: drainage of fluid collections, closure of the anastomotic defect (e.g., endoscopic stent, surgical closure), esophageal diversion and only supportive treatment [20]. Primary reoperation and ICU readmission were included as measures for invasiveness of primary treatment. Secondary treatment (i.e., treatment due to failure of primary treatment or >48 h after diagnosis), secondary reoperation and secondary ICU readmission were included as measures for failure of primary treatment. The number of available diagnostic and therapeutic modalities were included (i.e., all available, 1 modality unavailable, $\geq$2 modalities unavailable).

Estimates of the impact of hospital volume on FTR were expressed as odds ratios (OR) with 95% confidence interval (CI). A p-value <0.05 was considered statistically significant. Multiple imputation with chained equations was used to avoid bias due to missing data [32]. Analyses were performed in each imputed dataset and pooled according to Rubin's rule, using R version 3.6.2 with packages ‘rms’ and ‘mice’ [33].

3. Results

In total, 1509 patients with AL after esophagectomy were included by 71 centers in 20 countries. Of the 1509 included patients, 139 patients (9%) were included by 19 low-volume centers, 959 patients (64%) by 38 middle-volume and 411 patients (27%) by 14 high-volume centers (Supplementary Table 1).

3.1. Hospital volume

Patients with AL in middle- and high-volume centers had less comorbidity and a higher incidence of adenocarcinoma than patients in low-volume centers (Table 1). Availability of computed tomography (CT) guided drainage and endoscopic vacuum assisted closure (endoVAC) was lower in low-volume centers compared with middle- and high-volume centers. The FTR rate was lower in middle- and high-volume centers (low-volume 20% vs. middle-volume 12% vs. high-volume 8%, $p = 0.001$) (Table 2).

3.2. Diagnosis and management of AL

Table 3 presents clinical parameters and AL treatment of patients in low-, middle- and high-volume centers. High-volume centers confirmed AL one postoperative day (POD) later than low- and middle-volume centers (median POD low-volume 7, middle-volume, high-volume 8). Leak severity at diagnosis was the lowest in high-volume centers, as more patients had a mild or moderate leak as measured by the SEAL score (low-volume 68% vs. middle-volume 76% vs. high-volume 80%, $p = 0.001$). Patients in high-volume centers less frequently had hemodynamic or pulmonary organ failure compared with low- and middle-volume centers.

The primary treatment strategy differed between low-, middle- and high-volume centers: more patients in high-volume centers were only treated supportively, whereas defect closure was performed more often in low-volume centers. The primary ICU readmission rate was higher in low-volume centers compared with middle- and high-volume centers. Although, a similar percentage

Table 1
Center and patient characteristics.

Parameters	Low-volume	Middle-volume	High-volume	P-value
Center characteristics				
Centers (%)	19 (27)	38 (54)	14 (20)	
Country Income (%)				
LMIC	6 (32)	2 (5)	1 (7)	0.023
HIC	13 (68)	36 (95)	13 (93)	
Hospital type (%)				
General hospital	7 (37)	14 (37)	0 (0)	0.042
University hospital	11 (58)	20 (53)	12 (86)	
Cancer center	1 (5)	4 (11)	2 (14)	
Preferred anastomosis location (%)				
Intrathoracic	16 (84)	25 (66)	13 (93)	0.087
Cervical	3 (16)	13 (34)	1 (7)	
Availability of diagnostic tests (%)				
Clinical leak test, Methylene blue	17 (90)	36 (95)	13 (93)	0.828
X-ray swallow	18 (95)	36 (95)	14 (100)	1.000
CT-scan	19 (100)	38 (100)	14 (100)	–
CT-scan, oral contrast	17 (90)	38 (100)	14 (100)	0.105
Endoscopy	18 (95)	38 (100)	14 (100)	0.465
Availability of treatment (%)				
Ultrasound-guided drainage	19 (100)	38 (100)	14 (100)	–
CT-guided drainage	15 (79)	38 (100)	14 (100)	0.005
Endoscopic drainage	18 (95)	37 (97)	14 (100)	1.000
Stent	17 (90)	38 (100)	14 (100)	0.105
EndoVAC	7 (37)	33 (87)	11 (79)	<0.001
Endoclip	17 (90)	37 (97)	14 (100)	0.270
Thoracoscopy/VATS	16 (84)	35 (92)	14 (100)	0.332
Laparoscopy	18 (95)	38 (100)	14 (100)	0.465
Patient characteristics				
Patients	139 (9)	959 (64)	411 (27)	
Year of surgery (median [IQR])	2015 ['13, '17]	2015 ['13, '17]	2015 ['14, '18]	<0.001
Age (median [IQR])	66 [59, 71]	66 [59, 72]	66 [58, 71]	0.512
Comorbidity (%)				
ASA I	3 (2)	111 (12)	29 (7)	<0.001
ASA II	60 (44)	539 (58)	246 (60)	
≥ASA III	75 (54)	277 (30)	136 (33)	
Missing	1 (1)	32 (3)	0 (0)	
Performance status (%)				
ECOG 0	59 (42)	435 (45)	172 (42)	0.053
ECOG 1	61 (44)	259 (27)	105 (26)	
≥ECOG 2	13 (9)	57 (6)	29 (7)	
Missing	6 (4)	208 (22)	105 (26)	
Tumor histology (%)				
Adenocarcinoma	84 (60)	705 (74)	299 (73)	0.022
Squamous cell carcinoma	51 (37)	228 (24)	98 (24)	
Other	3 (2)	24 (3)	11 (3)	
Missing	1 (1)	2 (0.2)	3 (1)	

Abbreviations: LMIC, low-/middle-income country; HIC, high-income country; CT, computed tomography; VATS, video-assisted thoracoscopic surgery ASA, American Society of Anesthesiologists; ECOG, Eastern Collaborative Oncology Group.

of patients underwent secondary treatment (i.e., treatment due to failure of primary treatment or >48 h after diagnosis) in low-, middle- and high-volume centers, in low-volume centers the secondary ICU readmission rate was higher, and more patients underwent secondary reoperation.

3.3. Regression analyses

After adjusting for confounders, lower FTR was found in high-volume centers vs. low-volume centers (OR 0.44, 95%CI 0.2–0.8), but no statistically significant differences in FTR were found between high-volume vs. middle-volume centers (OR 0.67, 95%CI 0.5–1.0) (Table 4).

Table 2
Outcomes of patients with AL in low-, middle- and high-volume centers.

Parameters	Low-volume	Middle-volume	High-volume	P-value
Patients	139	959	411	
Failure to rescue (%)	27 (19.4)	115 (12.0)	34 (8.3)	0.001
LOS, hospital (days, median [IQR])	32 [20, 52]	30 [19, 48]	31 [21, 51]	0.087
LOS, ICU (days, median [IQR])	7 [3, 18]	5 [2, 15]	6 [3, 14]	0.008
Healing time (days, median [IQR])	17 [8, 33]	28 [15, 48]	23 [12, 40]	<0.001
CCI (median [IQR])	45 [34, 72]	43 [30, 62]	45 [34, 66]	0.083

Abbreviations: LOS, length of stay; ICU, intensive care unit; IQR, interquartile range; CCI, comprehensive complication index; LMIC, low-/middle-income countries; HIC, high-income countries.

Table 3
Clinical parameters at diagnosis and treatment of patients with AL per hospital volume.

Parameters	Low-volume	Middle-volume	High-volume	P-value
Patients	139 (9)	959 (64)	411 (27)	
Resection type (%)				
TTE-CA	43 (31)	233 (24)	131 (32)	<0.001
TTE-IA	65 (47)	558 (58)	226 (55)	
THE-CA	27 (19)	161 (17)	53 (13)	
Missing	4 (3)	7 (1)	1 (0.2)	
POD of diagnosis (median [IQR])	7 [5, 10]	7 [5, 11]	8 [6, 11]	0.002
Missing (%)	13 (9)	52 (5)	75 (18)	
Modality confirming AL (%)				
Endoscopy	13 (9)	129 (13)	40 (10)	<0.001
Esophagram	32 (23)	99 (10)	74 (18)	
CT	66 (48)	451 (47)	226 (55)	
Drain	21 (15)	208 (22)	31 (8)	
Reoperation	1 (1)	20 (2)	2 (0.4)	
Other	4 (3)	41 (4)	9 (2)	
None	0 (0)	3 (0.3)	11 (3)	
Missing	2 (1)	8 (1)	18 (4)	
Number of different assessments in 48 h before diagnosis (%)				
0	62 (45)	304 (32)	161 (39)	<0.001
1	70 (50)	494 (52)	146 (36)	
≥2	7 (5)	133 (14)	33 (8)	
Missing (%)	0	28 (3)	71 (17)	
Leak severity, SEAL score (%)				
Mild	20 (14)	239 (25)	85 (21)	0.001
Moderate	74 (53)	494 (52)	243 (59)	
Severe	29 (21)	119 (12)	54 (13)	
Critical	16 (12)	107 (11)	29 (7)	
Ward at diagnosis (%)				
Ward	62 (45)	551 (58)	249 (61)	0.002
ICU/MC/HC/PACU	68 (49)	342 (36)	133 (32)	
ED/Other	6 (4)	46 (5)	9 (2)	
Missing	3 (2)	20 (2)	20 (5)	
Diet at diagnosis (%)				
No restrictions	16 (12)	113 (12)	39 (9)	0.350
Liquid	37 (27)	255 (26)	79 (19)	
Water	10 (7)	102 (11)	46 (11)	
Nil per mouth	66 (47)	391 (41)	155 (38)	
Missing	10 (7)	98 (10)	92 (22)	
Antibiotics prescribed before diagnosis (%)	79 (57)	445 (46)	187 (46)	0.089
Leukocyte count at diagnosis (median [IQR])	12.7 [8.6, 16]	12.3 [9.4, 16]	12.5 [9.4, 17]	0.937
qSOFA score (mean (SD))	0.7 (0.9)	0.5 (0.8)	0.4 (0.8)	0.030
Missing (%)	20 (14)	246 (26)	150 (37)	
Pulmonary failure (%)	30 (22)	176 (18)	49 (12)	0.051
Missing (%)	6 (4)	46 (5)	67 (16)	
Hemodynamic failure (%)	22 (16)	89 (9)	26 (6)	0.009
Missing (%)	10 (7)	71 (7)	65 (16)	
Renal failure (%)	11 (8)	26 (3)	18 (4)	0.009
Missing (%)	6 (4)	84 (9)	35 (9)	
Intrathoracic fluid collections (%)				
None	43 (31)	330 (34)	146 (36)	0.046
Drained	21 (15)	84 (9)	34 (8)	
Undrained	74 (53)	395 (41)	217 (53)	
Missing	1 (1)	150 (16)	14 (3)	
Defect circumference (%)				
< 25%	72 (52)	322 (34)	176 (43)	0.797
≥ 25%	28 (20)	106 (11)	59 (14)	
Not available	39 (28)	531 (55)	176 (43)	
Missing	0 (0)	1 (0.1)	0 (0)	
Overall tube condition (%)				
Viable	104 (75)	683 (71)	297 (72)	0.293
Ischemic/necrotic	12 (9)	103 (11)	33 (8)	
Missing	23 (17)	173 (18)	81 (20)	
Primary treatment				
Primary strategy (%)				
Supportive only	28 (20)	203 (21)	104 (25)	0.006
Drainage	54 (39)	380 (40)	156 (38)	
Defect closure	15 (11)	45 (5)	8 (2)	
Drainage and defect closure	30 (22)	184 (19)	75 (18)	
Esophageal Diversion	6 (4)	32 (3)	19 (5)	
Stent placement (%)	35 (25)	187 (19)	41 (10)	<0.001
EndoVAC (%)	5 (4)	21 (2)	22 (5)	0.009
Primary Reoperation (%)	30 (22)	248 (26)	87 (21)	0.130
Antibiotics (%)	129 (93)	751 (78)	385 (94)	<0.001

(continued on next page)

Table 3 (*continued*)

Parameters	Low-volume	Middle-volume	High-volume	P-value
Feeding support (%)	17 (12)	140 (15)	64 (16)	0.673
Primary ICU readmission (%)	61 (44)	295 (31)	128 (31)	0.005
Secondary treatment				
Need for secondary treatment (%)	86 (62)	554 (58)	248 (60)	0.755
Secondary ICU readmission (%)	30 (22)	137 (14)	49 (12)	0.015
Secondary reoperation (%)	24 (17)	123 (13)	49 (12)	0.245

Abbreviations: AL; anastomotic leak TTE, transthoracic esophagectomy; CA, cervical anastomosis; IA, intrathoracic anastomosis; THE, transhiatal esophagectomy; POD, postoperative day; IQR, interquartile range; SD, standard deviation; CT, computed tomography; SEAL, severity of esophageal anastomotic leak; ICU, intensive care unit; MC, medium care; HC, high care; PACU, post anesthesia care unit; ED, emergency department; qSOFA, quick sequential organ failure assessment; EndoVAC, endoscopic vacuum assisted closure.

Table 4
Multivariable regression identifying parameters underlying differences in FTR.

Parameters	*Total effect*[a] **OR (95%CI)**	*Mediation analysis*[b] **OR (95%CI)**
Hospital volume		
Low	1	1
Middle	0.64 (0.4–1.0)	1.01 (0.6–1.8)
High	0.44 (0.2–0.8)	0.86 (0.4–1.7)
Country income status		
Low/Middle	1	1
High	0.27 (0.1–0.5)	0.28 (0.1–0.7)
Year of surgery		
2011–2013	1	1
2014–2016	1.05 (0.7–1.6)	1.19 (0.8–1.9)
2017–2019	0.83 (0.6–1.3)	0.90 (0.6–1.5)
Available diagnostic modalities[c]		
All modalities available		1
1 unavailable		1.30 (0.6–2.8)
≥ 2 unavailable		1.25 (0.5–3.3)
Available treatment modalities[c]		
All modalities available		1
1 unavailable		1.27 (0.8–2.1)
≥ 2 unavailable		2.59 (1.2–5.8)
Age[c]		1.42 (1.1–1.9)
Comorbidity		
ASA I		1
ASA II		1.67 (0.6–4.5)
≥ASA III		1.77 (0.6–4.9)
Performance status		
ECOG 0		1
ECOG 1		1.57 (1.0–2.5)
≥ECOG 2		2.00 (1.0–3.9)
Tumor histology		
Adenocarcinoma		1
Squamous cell carcinoma		1.44 (1.0–2.1)
Other		0.41 (0.1–2.0)
Leak severity, SEAL score		
Mild		1
Moderate		2.44 (1.2–4.9)
Severe		6.13 (2.8–13.4)
Critical		10.66 (5.0–22.6)
Primary strategy		
Supportive only		1
Drainage		1.15 (0.6–2.1)
Defect closure		0.98 (0.4–2.4)
Drainage & defect closure		1.53 (0.8–3.0)
Esophageal diversion		1.32 (0.5–3.5)
Primary reoperation		1.24 (0.8–2.0)
Primary ICU readmission		1.05 (0.7–1.6)
Secondary treatment		1.04 (0.6–1.7)
Secondary reoperation		1.44 (0.9–2.3)
Secondary ICU readmission		3.43 (2.1–5.5)

Abbreviations: FTR, failure to rescue; LMIC, low-/middle-income countries; HIC, high-income countries; AL, anastomotic leak; OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; ECOG, Eastern Collaborative Oncology Group; SEAL, severity of esophageal anastomotic leak; ICU, intensive care unit.
Recorded diagnostic modalities are methylene blue, swallow X-ray, computed tomography (CT), contract CT) and endoscopy; Recorded therapeutic modalities are ultrasound-guided drainage, CT-guided drainage, endoscopic drainage, stent treatment, endoscopic vacuum-assisted closure (endoVAC), endoscopic clipping (endoclip), video-assisted thoracoscopic surgery (VATS) and laparoscopy.

[a] Hospital volume was corrected for confounders: year of surgery, country income.
[b] OR of parameters other than hospital volume should be interpreted with caution due to the 'Table 2 fallacy'. (Westreich & Greenland, 2013).
[c] Interquartile odds ratio, interquartile range: 59–71 years.

During mediation analysis, three parameters were found to mediate the total effect of hospital volume on FTR: leak severity as measured by the SEAL score (moderate OR 2.4, 95%CI 1.2–4.9; severe OR 6.1, 95%CI 2.8–13.4; critical OR 10.7, 95%CI 5.0–22.6), secondary ICU readmission (OR 3.4, 95%CI 2.1–5.5) and availability of therapeutic modalities (one modality unavailable vs. all modalities available: OR 1.3, 95%CI 0.8–2.1; two or more modalities unavailable vs. all modalities available: OR 2.6, 95%CI 1.2–5.8). The primary treatment strategy had no statistically significant impact on FTR. In addition, no statistically significant direct effect was found between hospital volume and FTR: high-volume vs. low-volume 0.86 (95%CI 0.4–1.7), high-volume vs. middle-volume OR 0.86 (95%CI 0.5–1.4). This indicates the lower FTR rate in high-volume centers compared with low-volume centers was explained by lower leak severity, lower secondary ICU readmission rates and higher availability of therapeutic modalities in high-volume centers.

4. Discussion

This large retrospective study has explored differences FTR between centers in patients with AL after esophagectomy. A lower FTR rate was found in high-volume centers compared with low-volume centers, but not compared with middle-volume centers. The higher FTR in low-volume centers was found to be explained by higher leak severity at diagnosis of AL, higher ICU readmission rate during secondary treatment and lower availability of therapeutic modalities.

In line with other studies, the current study observed an 11.7% FTR rate in patients with AL and found substantial differences in FTR related to hospital volume [15,16]. Patients in high-volume centers were found to have less comorbidity and better performance status, corroborating previous findings [16,34]. Potentially, this may be related to differences in patient selection between different centers. In addition, it has to be considered that more patients treated in low-volume centers were from low-/middle-income countries, which may contribute to differences in comorbidity and performance status. However, these explanations could not be substantiated in current data as this was not the topic of the TENTACLE – Esophagus study and the study did not include patients undergoing esophagectomy that did not develop AL.

Besides case-mix parameters, previous studies have not further investigated factors that underly differences in FTR related to hospital volume. We found that differences in FTR were explained by lower leak severity at diagnosis in high-volume centers, especially due to lower incidence of organ failure and ICU admission at diagnosis. From a theoretical perspective, the lower leak severity may be related to earlier diagnosis of AL or more standardized postoperative care, as suggested by a previous study [18]. However, current data did not support this hypothesis: rather than earlier, AL was diagnosed one day later in high-volume centers compared with low- and medium-volume centers. Furthermore, there was no difference in proportion of patients already prescribed antibiotics before diagnosis (i.e., during suspicion of AL). Unfortunately, data on the events before diagnosis of AL were not available. Therefore, differences in leak severity between centers could not be fully explained and should be further investigated.

Regarding treatment of AL, although there was a difference in the primary treatment strategy between low-, middle- and high-volume centers, this difference was not found to explain differences in FTR. In addition, there was no difference in the overall proportion of patients that underwent secondary treatment between low-, middle- and high-volume centers. However, the rate of ICU readmission and reoperation during secondary treatment was lower in middle- and high-volume centers compared with low-volume centers, and secondary ICU readmission was identified as a factor explaining differences in FTR between centers. These findings indicate that middle- and high-volume centers may monitor the course of treatment more effectively and change their treatment strategy more effectively.

Corroborating previous findings, the availability of therapeutic modalities (i.e., endoVAC and CT-guided drainage) was lower in low-volume centers compared with middle- and high-volume centers [18]. The availability of therapeutic modalities was identified as a factor explaining the differences in FTR between centers. Extending availability of therapeutic resources could improve outcomes, however, new modalities should be carefully introduced, and implementation requires broad expertise of surgeons, gastroenterologists and radiologists. Moreover, whereas endoVAC was the modality with the largest differences in availability, this modality was scarcely used across all centers. Consequently, it may be questioned whether the mediating effect is truly attributable to the availability of treatment modalities or whether it reflects a higher level of specialized care in middle- and high-volume centers such as on-call esophageal teams and interventional radiology services [18].

Differences in postoperative outcomes in relation to hospital volume have been an argument for centralization of esophageal surgery [6,13,14]. However, centralization may not be possible in every setting or country. Therefore, our study investigated what factors underly differences in FTR and found that differences in FTR in relation to hospital volume are attributable to leak severity at diagnosis, secondary ICU readmission and available therapeutic resources. Although leak severity and secondary ICU admission rates are not directly modifiable, strategies to reduce leak severity and prevent secondary ICU readmission should be further explored to improve outcomes. Standardization of diagnostic and therapeutic strategies may be an important tool to improve outcomes and recently standardization of post-operative care after pancreatic surgery led to a substantial reduction in postoperative morbidity and mortality [35]. However, high-quality evidence to support guidelines for diagnosis and treatment of AL after esophagectomy is still lacking [19,36]. In absence of high-quality evidence, qualitative approaches may be useful and centers may engage in sharing experiences to identify best practices in diagnosis and management of AL [16,20].

The main strength of this study is the detailed data on clinical parameters, treatment and outcome of AL in combination with data on hospital volume. Previous studies were not able to investigate practice variation in relation to outcomes due to the lack of detailed data [15,18]. Our study identified explanations for differences in FTR, which can be further explored to improve outcomes of AL after esophagectomy. Some limitations of this study need to be addressed. First, as the current study only included patients with AL, differences in overall postoperative mortality and incidence of AL could not be assessed. Although differences in incidence of AL related to hospital volume have been reported, other studies have found that differences in postoperative mortality were not related to incidence of complications but to FTR [7,8,37]. Second, there is large variation in diagnosis and treatment of AL and management of AL may have changed during the 8.5-year study period [18,19]. Differences in treatment of AL related to country income have been previously reported [18]. Although analysis on the relationship between country income and FTR could have been insightful, no detailed analysis could be performed as current cohort only included 41 patients from low/middle-income countries. Nonetheless, analyses on hospital volume were corrected for country income and year of surgery, bias due to temporal and geographic variation was minimized. Third, previous studies have suggested that micro-level factors such as teamwork, and leadership are associated with FTR [38,39]. In addition, organizational factors may also affect FTR and high-volume centers have been found to use perioperative protocols more often and have a higher availability of specialized on-call teams [18]. The impact of micro-level and organizational factors on FTR could not be assessed as these data were not available from the current study. Future research may evaluate the impact of organizational and micro-level factors on outcomes of care.

In conclusion, substantial differences were found in the FTR rates related to hospital volume in patients with AL after esophagectomy. Lower FTR rate in high-volume centers compared with low-volume centers was explained by lower leak severity, lower secondary ICU readmission rate and higher availability of therapeutic modalities. Future studies should identify effective strategies to reduce leak severity and prevent secondary ICU readmission in order to improve outcomes of patients with AL after esophagectomy globally.

Funding

The TENTACLE – Esophagus study received funding from Medtronic company. The study was performed independently, and Medtronic had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit to manuscript.

Ethical approval

TENTACLE – Esophagus was approved by the institutional review board of Radboud university medical center (reference number 2018–4585).

CRediT authorship contribution statement

Sander Ubels: Funding acquisition, Formal analysis, Data curation, Writing – original draft, or interpretation of data: Drafting of the manuscript: Critical revision of the manuscript for important intellectual content: Statistical analysis: Administrative, technical or material support. **Eric Matthée:** Funding acquisition, Formal analysis, Data curation, Writing – original draft, Acquisition, analysis or interpretation of data: Drafting of the manuscript: Critical revision of the manuscript for important intellectual content: Administrative, technical or material support. **Moniek Verstegen:** Funding acquisition, Formal analysis, Data curation, Writing – original draft, Acquisition, analysis or interpretation of data: Drafting of the manuscript: Critical revision of the manuscript for important intellectual content: Concept and design: Obtained funding. **Bastiaan Klarenbeek:** Funding acquisition, Formal analysis, Writing – original draft, Conceptualization, and design: Drafting of the manuscript: Critical revision of the manuscript for important intellectual content: Statistical analysis: Obtained funding, Supervision. **Stefan Bouwense:** Funding acquisition, Conceptualization, and design: Critical revision of the manuscript for important intellectual content: Obtained funding. **Mark I. van Berge Henegouwen:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis or interpretation of data: Critical revision of the manuscript for important intellectual content, Conceptualization, and design. **Freek Daams:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis or interpretation of data: Critical revision of the manuscript for important intellectual content, Conceptualization, and design. **Jan Willem T. Dekker:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis or interpretation of data: Critical revision of the manuscript for important intellectual content. **Marc J. van Det:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis or interpretation of data: Critical revision of the manuscript for important intellectual content, Conceptualization, and design. **Stijn van Esser:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis or interpretation of data: Critical revision of the manuscript for important intellectual content. **Ewen A. Griffiths:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis or interpretation of data: Critical revision of the manuscript for important intellectual content, Conceptualization, and design. **Jan Willem Haveman:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis or interpretation of data: Critical revision of the manuscript for important intellectual content, Conceptualization, and design. **Grard Nieuwenhuijzen:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis or interpretation of data: Critical revision of the manuscript for important intellectual content, Conceptualization, and design. **Peter D. Siersema:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis or interpretation of data: Critical revision of the manuscript for important intellectual content, Conceptualization, and design. **Bas Wijnhoven:** Funding acquisition, Formal analysis, Data curation, Acquisition, analysis or interpretation of data: Critical revision of the manuscript for important intellectual content: Obtained funding, Conceptualization, and design. **Gerjon Hannink:** Funding acquisition, Formal analysis, Data curation, Writing – original draft, Acquisition, analysis or interpretation of data: Drafting of the manuscript: Critical revision of the manuscript for important intellectual content: Statistical analysis: Administrative, technical or material support, Supervision, Conceptualization, and design. **Frans van Workum:** Funding acquisition, Formal analysis, Data curation, Writing – original draft, Acquisition, analysis or interpretation of data: Drafting of the manuscript: Critical revision of the manuscript for important intellectual content: Statistical analysis: Obtained funding: Administrative, technical or material support, Supervision, Conceptualization, and design. **Camiel Rosman:** Funding acquisition, Formal analysis, Data curation, Writing – original draft, Acquisition, analysis or interpretation of data: Drafting of the manuscript: Critical revision of the manuscript for important intellectual content: Statistical analysis: Obtained funding, Supervision, Conceptualization, and design.

Declaration of competing interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare funding by Medtronic for the submitted work. PS reports grants from The Enose Company, grants and other from Motus GI, grants from Pentax, grants from Micro-Tech, other from Boston Scientific outside the submitted work; BK reports grants from Medtronic, grants from ZonMw, outside the submitted work; MIvBH reports other from Mylan, other from Alesi Surgical, other from Johnson and Johnson, other from BBraun, other from Medtronic, grants from Olympus, grants from Stryker, outside the submitted work; all fees unrelated to submitted work, paid to institution.

Acknowledgments

We thank all people involved in the TENTACLE – Esophagus study for their contribution to this large international study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.01.010.

References

[1] van Hagen P, Hulshof MCCM, van Lanschot Jjb, Steyerberg EW, MivB Henegouwen, Wijnhoven BPL, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366(22):2074–84.
[2] Al-Batran S-E, Homann N, Schmalenberg H, Kopp H-G, Haag GM, Luley KB, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial. J Clin Oncol 2017;35(15_suppl):4004.
[3] Goense L, Meziani J, Ruurda JP, van Hillegersberg R. Impact of postoperative complications on outcomes after oesophagectomy for cancer. Br J Surg 2019;106(1):111–9.
[4] van Workum F, Verstegen MHP, Klarenbeek BR, Bouwense SAW, van Berge Henegouwen MI, Daams F, et al. Intrathoracic vs cervical anastomosis after totally or hybrid minimally invasive esophagectomy for esophageal cancer: a randomized clinical trial. JAMA Surg 2021;156(7):601–10.
[5] Puccetti F, Wijnhoven BPL, Kuppusamy M, Hubka M, Low DE. Impact of standardized clinical pathways on esophagectomy: a systematic review and meta-analysis. Dis Esophagus 2022;35(2).
[6] Markar SR, Karthikesalingam A, Thrumurthy S, Low DE. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000-2011. J Gastrointest Surg 2012;16(5):1055–63.
[7] Oesophago-Gastric Anastomotic Audit (OGAA) Collaborative. Mortality from esophagectomy for esophageal cancer across low, middle, and high-income countries: an international cohort study. Eur J Surg Oncol 2021;47(6):1481–8.
[8] Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009;361(14):1368–75.
[9] Ghaferi AA, Birkmeyer JD, Dimick JB. Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. Ann Surg 2009;250(6):1029–34.
[10] Liou DZ, Serna-Gallegos D, Mirocha J, Bairamian V, Alban RF, Soukiasian HJ. Predictors of failure to rescue after esophagectomy. Ann Thorac Surg 2018;105(3):871–8.
[11] Ghaferi AA, Birkmeyer JD, Dimick JB. Hospital volume and failure to rescue with high-risk surgery. Med Care 2011;49(12):1076–81.
[12] Henneman D, Dikken JL, Putter H, Lemmens VE, Van der Geest LG, van Hillegersberg R, et al. Centralization of esophagectomy: how far should we go? Ann Surg Oncol 2014;21(13):4068–74.
[13] Brusselaers N, Mattsson F, Lagergren J. Hospital and surgeon volume in relation to long-term survival after oesophagectomy: systematic review and meta-analysis. Gut 2014;63(9):1393–400.
[14] van Lanschot JJ, Hulscher JB, Buskens CJ, Tilanus HW, ten Kate FJ, Obertop H. Hospital volume and hospital mortality for esophagectomy. Cancer 2001;91(8):1574–8.
[15] Busweiler LA, Henneman D, Dikken JL, Fiocco M, van Berge Henegouwen MI, Wijnhoven BP, et al. Failure-to-rescue in patients undergoing surgery for esophageal or gastric cancer. Eur J Surg Oncol 2017;43(10):1962–9.
[16] Abdelsattar ZM, Habermann E, Borah BJ, Moriarty JP, Rojas RL, Blackmon SH. Understanding failure to rescue after esophagectomy in the United States. Ann Thorac Surg 2020;109(3):865–71.
[17] Oesophago-Gastric Anastomosis Study Group on behalf of the West Midlands Research C. Rates of anastomotic complications and their management following esophagectomy: results of the oesophago-gastric anastomosis audit (OGAA). Ann Surg 2022;275(2):e382–91.
[18] Oesophago-Gastric Anastomosis Study Group on behalf of the West Midlands Research Collaborative. International variation in surgical practices in units performing oesophagectomy for oesophageal cancer: a unit survey from the oesophago-gastric anastomosis audit (OGAA). World J Surg 2019;43(11):2874–84.
[19] Hagens ERC, Anderegg MCJ, van Berge Henegouwen MI, Gisbertz SS. International survey on the management of anastomotic leakage after esophageal resection. Ann Thorac Surg 2018;106(6):1702–8.
[20] Ubels S, Lubbers M, Verstegen MHP, Bouwense SAW, van Daele E, Ferri L, et al. Treatment of anastomotic leak after esophagectomy: insights of an international case vignette survey and expert discussions. Diseases of the Esophagus; 2022.
[21] Ubels S, Verstegen M, Klarenbeek B, Bouwense S, van Berge Henegouwen M, Daams F, et al. Severity of oEsophageal Anastomotic Leak in patients after oesophagectomy: the SEAL score. Br J Surg 2022;109(9):864–71.
[22] Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'Journo XB, et al. International consensus on standardization of data collection for complications associated with esophagectomy: esophagectomy complications consensus group (ECCG). Ann Surg 2015;262(2):286–94.
[23] van der Werf LR, Busweiler LAD, van Sandick JW, van Berge Henegouwen MI, Wijnhoven BPL. Reporting national outcomes after esophagectomy and gastrectomy according to the esophageal complications consensus group (ECCG). Ann Surg 2020;271(6):1095–101.
[24] Damhuis RA, Wijnhoven BP, Plaisier PW, Kirkels WJ, Kranse R, van Lanschot JJ. Comparison of 30-day, 90-day and in-hospital postoperative mortality for eight different cancer types. Br J Surg 2012;99(8):1149–54.
[25] Talsma AK, Lingsma HF, Steyerberg EW, Wijnhoven BP, Van Lanschot JJ. The 30-day versus in-hospital and 90-day mortality after esophagectomy as indicators for quality of care. Ann Surg 2014;260(2):267–73.
[26] In H, Palis BE, Merkow RP, Posner MC, Ferguson MK, Winchester DP, et al. Doubling of 30-day mortality by 90 Days after esophagectomy: a critical measure of outcomes for quality improvement. Ann Surg 2016;263(2):286–91.
[27] Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258(1):1–7.
[28] Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. Int J Epidemiol 2013;42(5):1511–9.
[29] Cohen P, West SG, Aiken LS. Applied multiple regression/correlation analysis for the behavioral sciences. Psychology press; 2014.
[30] Hafeman DM, Schwartz S. Opening the Black Box: a motivation for the assessment of mediation. Int J Epidemiol 2009;38(3):838–45.
[31] The World Bank. Low and middle income | Data 2022. The World Bank; 2022 [Available from: https://data.worldbank.org/income-level/low-and-middle-income.
[32] van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. J Stat Software 2010:1–68.
[33] Wood AM, Royston P, White IR. The estimation and use of predictions for the assessment of model performance using large samples with multiply imputed data. Biom J 2015;57(4):614–32.
[34] Dikken JL, Dassen AE, Lemmens VE, Putter H, Krijnen P, van der Geest L, et al. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in The Netherlands between 1989 and 2009. Eur J Cancer 2012;48(7):1004–13.
[35] Smits FJ, Henry AC, Besselink MG, Busch OR, van Eijck CH, Arntz M, et al. Algorithm-based care versus usual care for the early recognition and management of complications after pancreatic resection in The Netherlands: an open-label, nationwide, stepped-wedge cluster-randomised trial. Lancet 2022;399(10338):1867–75.
[36] Verstegen MHP, Bouwense SAW, van Workum F, Ten Broek R, Siersema PD, Rovers M, et al. Management of intrathoracic and cervical anastomotic leakage after esophagectomy for esophageal cancer: a systematic review. World J Emerg Surg 2019;14:17.
[37] Voeten DM, Gisbertz SS, Ruurda JP, Wilschut JA, Ferri LE, van Hillegersberg R, et al. Overall volume trends in esophageal cancer surgery results from the Dutch upper gastrointestinal cancer audit. Ann Surg 2021;274(3):449–58.
[38] Ghaferi AA, Dimick JB. Importance of teamwork, communication and culture on failure-to-rescue in the elderly. Br J Surg 2015;103(2):e47–51.
[39] Johnston MJ, Arora S, King D, Bouras G, Almoudaris AM, Davis R, et al. A systematic review to identify the factors that affect failure to rescue and escalation of care in surgery. Surgery 2015;157(4):752–63.